IntechOpen

Current Topics in Functional Food

Edited by Naofumi Shiomi and Anna Savitskaya

Current Topics in Functional Food

Edited by Naofumi Shiomi and Anna Savitskaya

Published in London, United Kingdom

Current Topics in Functional Food
http://dx.doi.org/10.5772/intechopen.98161
Edited by Naofumi Shiomi and Anna Savitskaya

Contributors
Ahmed M. Saad, Mahmoud Z. Sitohy, Belal A. Omar, Mohamed T. El-Saadony, Basel Sitohy, Kohei Suruga, Tsuyoshi Tomita, Kazunari Kadokura, Saijuddin Shaikh, Pilar Zafrilla, Begoña Cerdá, Javier Marhuenda, Raúl Arcusa, Débora Villaño, Purificación Ballester, Shakira Ghazanfar, Ghulam Muhammad Ali, Mohammad Mohammad K Okla, Saud S. AL-amri, Yasmeen A. Alwasel, Arshad Farid, Nosheen Akhtar, Yasir Hameed, Rameesha Abid, Nahid Akhtar Batool, Sharjeel Khalid, Nilay Seyidoglu, Cenk Aydin, Alejandro Galindo, Amy L. Stockert, Sean Mild, Premagowri Balakrishnan, Sakhawat Riaz, Rimsha Farooq, Munir Ahmed, Muhammad Shaheryar, Muneer Hussain, Arslan Ahmad, Charles Ntungwen Fokunang, John Dobgima Fomnboh, Mbong Grace Annih, Manju Evelyn Bih, Estella Tembe Fokunang, Lem Edith Abongwa, Tchadji Mayoudom Vanessa, Najaf Allahyari Fard, Arezu Heydari, Farshid Parvinin, Anvi Rana, Fatemeh Hosseini, Mohammad Reza Sanjabi, Mehran Kazemi, Nasim Ghaemian

First published in London, United Kingdom, 2022 by IntechOpen
IntechOpen is the global imprint of INTECHOPEN LIMITED, registered in England and Wales, registration number: 11086078, 5 Princes Gate Court, London, SW7 2QJ, United Kingdom

British Library Cataloguing-in-Publication Data
A catalogue record for this book is available from the British Library

Additional hard and PDF copies can be obtained from orders@intechopen.com

Current Topics in Functional Food
Edited by Naofumi Shiomi and Anna Savitskaya
p. cm.
Print ISBN 978-1-80355-792-2
Online ISBN 978-1-80355-793-9
eBook (PDF) ISBN 978-1-80355-794-6

Meet the editors

Dr. Naofumi Shiomi studied the use of recombinant yeast as a researcher at the Laboratory of Production Technology of Kaneka Corporation for 15 years until 1998. He earned his Ph.D. in Engineering from Kyoto University, Japan. He now works as a professor at the School of Human Sciences, Kobe College, Japan, where he teaches applied microbiology, biotechnology, and life science and studies at "Applied Life Science" laboratories. He has studied bioremediation for 20 years at Kobe College. His recent research has focused on the prevention of obesity and aging.

Anna Savitskaya, a researcher from Russia, graduated from Siberian State University of Sciences and Technologies, Russia. Her field of research is microorganisms, both fungi and bacteria. She received her Ph.D. from the School of Medical Sciences, Niigata University, Japan. Her Ph.D. work investigated the effect of the C-terminal domain on mycobacterial histone-like protein on bacterial life cycle and resistance to treatment. Currently, Dr. Savitskaya has a postdoc position at the Shemyakin and Ovchinnikov Institute of Bioorganic Chemistry, Russia.

Contents

Preface

Functional foods are defined as food products containing several health-related functional compounds. Superfoods can be included in this broad definition. The importance of the daily consumption of functional foods in maintaining health has become gradually accepted worldwide, and the market for functional foods has steadily increased. Data from Report Ocean shows that the global food market for health was approximately 180 billion dollars in 2020, with a 6.7% increase predicted until 2027. North America is expected to be the region with the highest growth rate because of changes in diet. The Asia-Pacific area will also experience high growth rates because of the increased variety of available healthy foods.

Recent studies have clarified that novel functional compounds contained in foods are effective in preventing and reducing the risk of diseases. Several novel supplements and food products have been developed. Moreover, many foods that enhance functional compounds have been developed using gene manipulation and gene-editing technologies. Gene-editing technology based on CRISPR/Cas9 is being applied to foods and such foods will soon become commercially available.

This book presents a comprehensive overview of current topics in functional foods. It discusses the categories and characteristics of functional foods, foods containing effective ingredients for health, and novel types of functional foods including gene-edited plants. It also examines the effects of functional foods such as ginger, fermented foods, and the "MIND diet," on health. Finally, the book highlights the characteristics and medicinal properties of mushrooms. This text offers new ideas for the production of novel functional foods and health management through daily diet.

I would like to thank Ms. Elena Vracaric and the publishing managers at IntechOpen for their support and assistance throughout the writing and publication of this book.

Naofumi Shiomi
Kobe College,
Kobe, Japan

Anna Savitskaya
Institute of Bioorganic Chemistry of Russian Academy of Science,
Moscow, Russian Federation

Chapter 1

Sources and Health Benefits of Functional Food Components

Saijuddin Shaikh

Abstract

Functional foods are the foods claimed that have additional health benefits beyond their basic nutritional values, and functional food components are bioactive, potentially beneficial compounds that are found either naturally in foods or added to them as functional ingredients. Some important functional food components are carotenoids, isothiocyanates, soluble and insoluble dietary fiber, phenolic acids, fatty acids, plant stanols and sterols, flavonoids, polyols, soy protein, prebiotics and probiotics, phytoestrogens, vitamins, and minerals. Most of the functional food components occur mainly in plant foods (whole grains, fruits, and vegetables), however, few functional foods components, such as omega-3, -6, and -9 polyunsaturated fatty acids are also found in animal products (e.g. milk, fermented milk products, and cold-water fish). Evidence suggested that there is a relationship between functional food components and health benefits. Functional food components can be used for the treatment and prevention of different diseases. Biologically active functional food components can reduce the risk of certain non-communicable diseases, such as cancer, type II diabetes, cardiovascular diseases, osteoporosis, inflammation, and lowering of blood cholesterol. Thus, people should consume a wide variety of foods to assure the ingestion of functional food components in their body, such as fatty acids, fiber, carotenoids, flavonoids, prebiotics and probiotics, vitamins, and mineral.

Keywords: functional food, components, nutritional, physiological

1. Introduction

1.1 What are functional foods?

Functional foods are such types of foods that are highly nutritious and have a potential health benefits besides their basic nutritional values. Functional foods contain either supplements or other additional ingredients designed to improve the health of the general population. Foods are being examined and improved which may reduce chronic disease risk and optimize health. Japanese has first developed the concept of functional foods in 1980. At that time, their health care costs were escalating and the Ministry of Health and Welfare initiated to approve some foods which were documented with their health benefits and used for improving the health of the aging population [1].

1.2 Functional food components

Functional food components are bioactive compounds used in the manufacture of functional foods. They are potentially beneficial compounds found either naturally in foods or added to them as functional ingredients. The functional food components are carotenoids, isothiocyanates, dietary fiber, phenolic acids, fatty acids, plant stanols and sterols, flavonoids, polyols, soy protein, prebiotics and probiotics, phytoestrogens, vitamins, and minerals. Research-based evidence suggested that there is a relationship between functional food components, health, and well-being [2]. Therefore, functional food components can be used in the treatment and prevention of diseases, as they have health-promoting roles at various stages of disease control. Phytochemicals are plant-derived, non-nutritive, and biologically active functional food components that function in the body to prevent certain non-communicable diseases [3]. About 900 phytochemicals are found in foods and 120 g of foods or vegetables may have around 100 different types of phytochemicals [4]. The earlier concept was that functional food components occur mainly in plant foods, such as whole grain, fruits, and vegetables. However, functional food components are also found in animal products; these are milk, fermented milk products, and cold-water fish. These animal source food components are probiotics, prebiotics, symbiotic, conjugated linolenic acid, long-chain omega-3, -6, and -9 polyunsaturated fatty acids, etc.

1.3 Production of functional foods

Functional foods can be made by different approaches, such as (1) eliminating harmful components from the food (e.g. allergic protein), (2) increasing the concentration of a component in the food by fortification with micronutrients or any other ingredient, (3) eliminating excessive component mainly a macronutrient like fats and producing a beneficial component such as chicory inulin, (4) increasing stability or bioavailability of a component to produce a functional effect or to reduce the disease risk, and (5) adding a new component in the foods which has the beneficial effect, e.g. antioxidant.

In this chapter, functional food ingredients, including their sources and physiological functions, are discussed.

2. Sources and health benefits of functional food components

2.1 Carotenoids

The carotenoids are the most widespread and important fat-soluble pigments in nature and they have varied health functions. Most carotenoids consumed foods are beta-carotene, alpha-carotene, gamma-carotene, lycopene, lutein, beta-cryptoxanthin, zeaxanthin, and astaxanthin.

2.1.1 Sources

Carotenoids are available in plants, fruits, flowers, algae, and photosynthetic bacteria. The other sources of carotenoids are non-photosynthetic bacteria, yeasts, and molds.

2.1.2 Function

Carotenoids are used as antioxidants in dietary supplements. They are also used as colors in foods and beverages and as pigments in poultry and fish farm, and as food ingredients. Carotenoids have an important role in human health. The main dietary source of vitamin A is beta-carotene. Protective effects of carotenoids have been identified against serious disorders, such as cancer [5], heart disease [6], and degenerative eye disease [7]. The role of carotenoids as antioxidants and as regulators of the immune response system is also recognized.

2.2 Dietary fibers

Dietary fibers are the portion of plant-derived foods. They cannot be fully fragmented by human digestive enzymes. Fibers are non-starch polysaccharides, such as cellulose, hemicellulose, galactooligosaccharides, polyfructose, gums, mucilages, pectins, and lignin. These are soluble or insoluble fibers that pass through the stomach and small intestine undigested, but they are fermented by bacteria in the colon when they reach the large intestine.

2.2.1 Sources

Beans, whole grains, brown rice, popcorn, nuts, baked potato with skin, berries, bran cereal, oatmeal, and vegetables are the sources of dietary fibers.

2.2.2 Function

Fibers are fermented and produced short-chain fatty acids in the colon that provide important health benefits. Some fibers are manufactured and added to food products to provide similar health benefits without adding calories called functional fibers. These are cellulose, polydextrose, maltodextrin, and inulin. There are several potential health benefits of the consumption of dietary and functional fibers. Fibers reduce the incidence of constipation [8], irritable bowel syndrome [9], lower cholesterol, and reduce the incidence of coronary and cardiovascular heart diseases [10], prevent obesity [11] and diabetes [12], avoid colon cancer [13], and increase survival in breast cancer [14]. However, there are some adverse effects of excessive intake of dietary fiber, such as intestinal obstruction (in susceptible individuals), dehydration (due to a fluid imbalance), increase in intestinal gas, resulting in distention and flatulence, and reduced absorption of vitamins, minerals, proteins, and calories from the gut [15].

3. Essential fatty acids

Essential fatty acids (EFAs) cannot be synthesized by the human body but the body requires them for good health and therefore, they must be obtained through diet. Essential fatty acids are long-chain polyunsaturated fatty acids. They are called "good fats" and they increase the levels of high-density lipoprotein (HDL) and decrease the levels of low-density lipoprotein (LDL). Alpha linoleic acid and linolenic acid are the primary essential fatty acids in the human body.

3.1 Sources

Sources of essential fatty acids are mackerel, salmon, cod liver oil, herring, oysters, soybeans, sardines, flax seeds, anchovies, caviar, walnuts, chia seeds, and canola oils.

3.2 Function

Essential fatty acids help in the absorption of important nutrients and expelling of harmful waste products that support the reproductive, cardiovascular, nervous systems, and immune. They are also important for proper growth, neural development, and maturation of sensory systems in children. Other important roles of EFAs are to increase the production of prostaglandins that regulate body functions, such as blood pressure, heart rate, blood clotting, conception, and fertility. EFAs also play an important role in immune function by regulating inflammation and encouraging the body to fight infection [16]. Essential fatty acids are beneficial for those suffering from rheumatoid arthritis [17] and reduce tenderness in joints, swelling, and diminish morning stiffness. It has also been observed that EFAs are important elements for asthma [18], depression [19], bipolar disorder schizophrenia [20], hypertension [21], heart diseases [22], burns [23], photodermatitis, acne or psoriasis [24], cholesterol [25], obesity [26], insulin sensitivity [27], osteoporosis [28], attention deficit disorder or attention deficit hyperactivity disorder [29], age-related macular degeneration [30], dry-eye conditions, such as Sjögren's syndrome [31]. Consumption of sufficient amounts of foods rich in omega-3 fatty acids reduces the risk of colorectal [32], breast cancer [33], and prostate cancer [34].

4. Isothiocyanates

Isothiocyanates are compounds produced by hydrolysis of glucosinolates that are precursors of cruciferous vegetables. Some isothiocyanates are volatile and evaporated below the boiling point. Isothiocyanates hydrolyze at higher cooking temperatures and their bioavailability is affected by microwaving at high power [35].

4.1 Sources

Good sources of isothiocyanates are cruciferous vegetables, such as broccoli, brussels sprouts, watercress, Japanese radish, cabbage, cauliflower, and kale.

4.2 Function

Several studies revealed that isothiocyanates and their metabolites decrease the risk of developing different types of cancer, such as stomach, breast, liver, esophagus, lung, small intestine, and colon [36, 37]. Isothiocyanates effect *Helicobacter pylori* and reduce the risk of developing gastric cancer. On the other hand, sulforaphane inhibits the growth of multiple strains of bacteria [38] and there is a role in eradication in some cases [39]. People who consume isothiocyanates-rich vegetables have a lower incidence or severity of cardiovascular disease [40].

5. Flavonoids

Flavonoids are pigments synthesized by plants and there are many different subclasses, each comprising many different compounds, such as isoflavones (biochanin A, daidzin, daidzein, formononetin, glycitein, genistein); flavononols (astilbin, genistin, taxifolin, engeletin); anthocyanidins (cyanidin, malvidin, delphinidin, apigenin, peonidin, pelargonidin, petunidin); chalcones (okanin, butein); flavonols (isorhamnetin, quercetin, kaempferol, myricetin); flavanols (positive-catechin, negative-epicatechin, positive-gallocatechin, negative-epigallocatechin, negative-epicatechin gallate); flavones (apigenin, luteolin, chrysin, rutin); flavanones (eriodictyol, isosakuranetin, hesperidin, naringin, naringenin, taxifolin) [41].

5.1 Sources

Sources of flavonoids are fresh capers, elderberry juice, dried parsley, sorrel, red onions, rocket lettuce, fresh cranberries, goji berries, cooked asparagus, blackcurrants, dried oregano, grapefruit, lemons, orange juice, limes, oranges, grapefruit juice, artichokes, green tea, black tea, dried cocoa, dark chocolate, blackberries, cooked broad beans, pecan nuts, red table wine, apples, peaches, dried parsley, aronia, green pepper, bilberries, chickpeas, black currants, American bilberries, red cabbage, red currants, raspberries, and strawberries.

5.2 Function

There are several health benefits of flavonoids, including antiallergic, antioxidant activities, antiviral [42], antitoxic, antifungal [43], antibacterial [44] and anti-inflammatory [45]. Recent researches identified the many defensive roles of flavonoids, these are eye diseases [46], heart diseases [47], hemorrhoids [48], diabetes [49], neurodegenerative diseases, such as Alzheimer's or Parkinson's [50], gout [51] and periodontal disease [52]. Flavonoids are also used for the prevention and treatment of different types of cancer, such as prostate [53], ovarian [54], pancreatic, colon, breast [55], leukemia, lung [56], esophageal [57], hepatocellular carcinoma [58], and renal cell carcinoma [59].

6. Phenolic acids

Phenolic acids contain a phenolic ring and a carboxyl functional group. Some examples of phenolic acids are protocatechuic acid, vanillic acid, p-hydroxybenzoic acid, ferulic acid, caffeic acid, p-coumaric acid, sinapinic acid, and syringic acid. Phenolic acids are absorbed through the walls of the intestine and serve beneficial roles, such as antioxidants and protect cellular damage by free-radical oxidation reactions.

6.1 Sources

Sources of phenolic acids are cereals, oilseeds, legumes, vegetables, fruits, beverages, and herbs. Besides these sources, they are also found in all food groups.

6.2 Function

Phenolic acids have several health benefits, such as intake of phenolic acids decrease the risk of cardiovascular diseases, certain cancers, type II diabetes, and neurodegenerative disorders [60–62], through multiple putative mechanisms of actions, including antioxidation, glucoregulation, anti-inflammation, antiproliferation, and microbial modulation. Russo et al. [63] found a negative relationship between dietary intake phenolic acids (e.g. ferulic acid and caffeic acid) and prostate cancer and they showed that both phenolic acids are associated with reduced prostate cancer. Also, immunoregulation diseases, asthma, and allergic reactions are protected by caffeic acid which is phenolic acid. Caffeic acid has a positive role against colon cancer [64] and it has inhibitor properties of HIV-1 that act as a potential antiviral therapy [65]. It is also found that a higher intake of phenolic acids is significant lower mean systolic and diastolic blood pressure compared to a lower intake of phenolic acids [66].

7. Plant stanols and sterols

Plant stanols and sterols are a group of substances made in the plant. The most important and ample of plant sterol is sitosterol. However, campesterol and stigmasterol are also significant quantitative of sterol. They reduce the absorption of cholesterol in the intestine and help to lower low-density lipoprotein (LDL) cholesterol levels in the blood without affecting high-density lipoprotein (HLD) cholesterol levels.

7.1 Sources

Sterols and stanols are found in the highest amount in foods, such as fruits, vegetables, seeds, nuts, legumes, cereals, and vegetable oils.

7.2 Function

Plant sterols work as an anti-inflammatory, antioxidant [67], and antiatherosclerosis. Phytosterols have antifungal activity and protect against ulcers [68]. The intake of plant sterols can prevent different types of cancer, such as the esophagus, prostate [69], lung [70], breast [71], ovary [72], stomach, and endometrial [73]. LDL-cholesterol is a risk factor for cardiovascular diseases. Plant sterols or stanols prevent absorption of LDL cholesterol from the gut, as a result, serum levels of LDL are lower, and assumed that lowering LDL-cholesterol is expected to lower cardiovascular diseases.

8. Polyols

Polyol is an organic compound and low-calorie carbohydrate-based sweetener. It is a hydrogenated version of carbohydrates. Its taste and texture are like sugar with half the calories. Polyols are used as sugar-free and low-calorie ingredients in many foods. There are various types of polyols, such as erythritol, isomalt, polyglucitol, lactitol, polyglycitol, mannitol, sorbitol, maltitol, and xylitol.

8.1 Sources

Polyols are found in some fruits, vegetables, and mushrooms.

8.2 Function

Polyols are used in different industries for making foods, such as ice cream, chewing gums, frozen desserts, candies, and baked goods [74]. They are also used for frostings, canned fruits, beverages, yogurt, and tabletop sweeteners. Polyols have some important health benefits and they maintain good oral health [75]. They are also used for weight control and reduction of dietary glycemic load [74]. Polyols may play an important role in the maintenance of human digestive health as these are low digestible carbohydrates [76]. Sometimes overconsumption of polyol-containing foods may have laxative effects [74].

9. Soy protein

Soy protein is extracted from soybean and hence, it is a complete plant-based protein and it contains adequate amounts of all the essential amino acids. Health benefits of soy protein depend on consumption per day. Per person need to consume 25 g of soy protein or more every day to get results.

9.1 Sources

Whole soybeans are the source of soy protein and dietary fiber. Some selected soy food products are soya sauce (2 g protein of 18 g soy sauce), cooked and fermented soy (5 g protein of 28 g cooked and fermented soy), soybean curd (6 g protein of 84 g soybean curd), and soy veggie burger (11 g protein of 70 g soy veggie burger).

9.2 Function

Soy protein has many potential health benefits. Beneficial effects of soy protein products on women are improvement of diet and cardiovascular status, prevention of certain types of cancer, health improvement following menopause, and obesity prevention [77]. Xiao et al. [78] have shown some chemopreventive activity of soy protein. The potential role of consumption of soy protein is reducing body weight and fat mass which reduces plasma cholesterol and triglycerides [79]. Soy protein may reduce the risk of cardiovascular disease, stroke, and coronary heath disease.

10. Phytoestrogens

Phytoestrogens (PEs) are the compounds found in plans and they are not generated within the endocrine system in the human body and are consumed by eating phytoestrogenic plants. They have roles in the metabolism of proteins, carbohydrates, fats, and minerals in the human body and they act as estrogen hormone in the reproductive cycle in women [80]. There are three types of phytoestrogens, such as lignans (enterolactone or enterodiol), coumestans (coumestrol), and isoflavones (genistein, daidzein, glycitein).

10.1 Sources

The greater sources of phytoestrogens are soybeans, soy beverages, tofu, tempeh, linseed (flax), wheat, berries, sesame seeds, oats, barley, lentils, dried beans, rice, alfalfa, mung beans, apples, wheat germ, carrots, rice bran, and soy-linseed bread.

10.2 Function

There are several health benefits of phytoestrogens. They affect the cardiovascular system [80] and skeleton and reduce the incidence of osteoporosis [81] and menopausal symptoms [82]. Phytoestrogens have cell proliferation inhibiting factors that prevent cancer. They have positive effect on prostate cancer [83], breast cancer [84], thyroid cancer [85], colorectal cancer [86], skin cancer [87] and endometrial cancer [88]. Soy foods containing PEs improve control of blood glucose and insulin levels [89]. There are antibacterial and fungistatic activities in some phytoestrogens which play an antiviral role [90].

11. Probiotics

There are two types of bacteria in our body, such as good bacteria and bad bacteria. Probiotics are living bacteria that provide health benefits by improvement of the balance of the intestinal microflora [91] when ingested in an adequate amount. Some yeasts also work as probiotics. There are so many types of probiotics, but *Bifidobacterium*, *Lactobacillus (or lactic acid bacteria—LAB)*, *Lactococcus*, *Saccharomyces*, *Streptococcus thermophilus,* and *Enterococcus* are common probiotics. Of them, *Saccharomyces boulardii* is a probiotic yeast and others are bacteria.

11.1 Sources

Some best probiotic foods are yogurt, traditional buttermilk, pickles, kombucha, kimchi, sauerkraut, cheese, and kefir.

11.2 Function

Probiotic is used for the treatment of diarrhea [92], *Lactobacillus* has probiotic action on infectious diarrhea and gastroenteritis in infants and children, and probiotic is used for the treatment of constipation. Probiotics therapy may help for irritable bowel syndrome treatment and inflammatory bowel disease [93]. Probiotic therapy is used for control other diseases, such as hypertension [94], lactose intolerance [95], hepatic encephalopathy [96], immune system [97], cancer [94], vaginal infections [98], *H. pylori* [99], kidney stones [100], cholesterol [101], allergies, and eczema [102]. Probiotics may reduce necrotizing enterocolitis and mortality in low-birthweight infants [103].

12. Prebiotics

Prebiotics are non-digestible fibers present in plants and help healthy bacteria to grow in the gut and make the human digestive system work better. Most of the

prebiotics are oligosaccharides that stimulate selectively the growth of *bifidobacteria*. Some prebiotics are fructooligosaccharides, lactosucrose, inulins, lactilol, isomalto-oligosaccharides, lactulose, soy oligosaccharides, pyrodextrins, transgalacto-oligosaccharides, and xylo-oligosaccharides.

12.1 Sources

Main sources of prebiotics are fruits, vegetables, and whole grains, such as apples, artichokes, asparagus, bananas, barley, berries, chicory, cocoa, dandelion greens, flaxseed, garlic, green vegetables, leeks, konjac root, legumes, oats, tomatoes, onions, soybeans, wheat, and yacon root. Also, some foods are fortified with prebiotics, for example, baby formula, bread, cereal, cookies, and yogurt.

12.2 Function

Prebiotics work as anticarcinogenic, antimicrobial, and antiosteoporotic activities. Prebiotics are also used for the treatment of constipation, hepatic encephalopathy, and inflammatory bowel disease. There is a beneficial role of prebiotics in diabetes mellitus. Prebiotics also have an important role in improving mineral absorption and balance and enhancing the colonic absorption of some minerals. Prebiotics also ferment foods faster in the intestine and prevent constipation. Prebiotics reduce sepsis and mortality in premature and low-birth-weight infants [104].

13. Synbiotics

Synbiotics are the combined products of both probiotics and prebiotics. The advantage of the combination of beneficial bacteria is the encouragement of beneficial bacterial growth. Synbiotics are produced by combinations of *lactobacillus* GG and inulins, *bifidobacteria* and fructooligosaccharides (FOS), and bifidobacteria and lactobacilli with FOS or inulins.

13.1 Sources

As symbiotics are the combined products of prebiotics and probiotics, so the sources of symbiotics are the same as probiotics and prebiotics. However, this combination is produced commercially.

13.2 Function

Evidence suggested that symbiotics can reduce sepsis, lower respiratory tract infection, and mortality among low-birth-weight infants [105].

14. Vitamins

Vitamins are organic molecules and essential for the proper functioning of the human body. Vitamins are required in small amounts obtained from a correct diet. There are two types of vitamins such as fat-soluble vitamins and water-soluble vitamins. Fat-soluble vitamins are A, D, E, and K and they can be stored in the body.

On the other hand, water-soluble vitamins are C and B-complex, such as vitamins B6, B12, niacin (B3), riboflavin (B2), biotin (B7), thiamine (B1), pantothenic acid (B5), and folic acid (B9). They cannot be stored in the body because the excess ingested is eliminated through human fluids, such as urine and transpiration, and hence necessary to ingest a daily amount of these vitamins [106].

14.1 Vitamin A

There are different forms of vitamin A, such as retinol, retinal, retinoic acid, and all known as retinoids.

14.1.1 Sources

The best sources of vitamin A are beef liver, cod liver oil, spinach, sweet potato, carrots, broccoli, black-eyed peas, mango, sweet red pepper, cantaloupe, dried apricots, pumpkin pie, tomato juice, and herring.

14.1.2 Function

Vitamin A plays an important role in many processes in the body, including immune function, reproduction, healthy vision, proper functioning of the heart, kidneys, lungs, and other organs, skink health and growth development. Vitamin A also helps to prevent lung and breast cancer [107]. Vitamin A can be used for the treatment of leukemia [108], skin disorders, and retinitis pigmentosa [109].

14.2 Vitamin B-complex

Vitamin B-complex is a product that is composed of B vitamins, such as thiamine (B1), riboflavin (B2), niacin (B3), pantothenic acid (B5), vitamins B6, biotin (B7), folic acid (B9), and B12.

14.2.1 Sources

Adequate amount of vitamins B sources are milk, cheese, eggs, liver and kidney, meat (chicken and red meat), fish (tuna, mackerel, and salmon), shellfish (oysters and clams), and dark green vegetables (spinach and kale).

14.2.2 Function

Vitamin B-complex has several health benefits:

Thiamin/thiamine (B1) is used for the treatment of Alzheimer's disease [110], congestive heart failure [111], and cancer [112].

Riboflavin (vitamin B2) is used to prevent cataracts [113] and migraine headaches [114].

Niacin (B3) is used to prevent insulin-dependent diabetes mellitus [115]. It has a significant role to treat high cholesterol and cardiovascular disease [116].

Pantothenic acid (B5) can help in wound healing [117] and play an important role to maintain cholesterol levels [118].

Vitamin B6 has a vital role to prevent cardiovascular disease [119], kidney stones, and immune and cognitive functions [120]. It is also used for the treatment

of premenstrual syndrome [121]. Vitamin B6 can protect from side effects of oral contraceptives, nausea, and vomiting in pregnancy [122] and reduce depression.

Biotin (B7) is used for the treatment of diabetes [123] and in the prevention of some birth defects [124]. It plays a vital role in the treatment of cholesterol [125], brittle fingernails [126], seborrheic dermatitis [127], and hair loss.

Folic acid (B9) is used to prevent some pregnancy complications, such as fetal neural tube defects [128]. It may be used to prevent certain heart defects and limb malformations [129] and birth defects [130]. Folic acid is used to prevent colorectal and breast cancer [131], heart diseases [132], Alzheimer's disease, and cognitive impairment [133].

Vitamin B12 plays an important role in the prevention of neural tube defects, cancer [134], cardiovascular disease [135], depression, Alzheimer's disease, and dementia [136].

14.3 Vitamin C

Vitamin C (ascorbic acid) is a very effective nutrient and the main sources of vitamin C are citrus fruit (oranges and orange juice), strawberries, peppers, broccoli, blackcurrants, brussels sprouts, and potatoes. It plays an important role against immune system deficiencies, cardiovascular disease [137], prenatal health problems, eye disease, and skin wrinkling. Vitamin C works as an antioxidant and can prevent scurvy, lead toxicity, and cancer [138].

14.4 Vitamin D

Vitamin D is a combination of calciferol (*vitamin* D_2) and cholecalciferol (*vitamin* D_3). Vital sources of vitamin D are liver, egg yolks, red meat, fortified foods (e.g. fat spreads and breakfast cereals), and oily fish (sardines, salmon, herring, and mackerel). Several functions of vitamin D exist in the human body. Vitamin D promotes healthy bones and teeth, supports immune, brain and nervous health, and manages diabetes by regulating insulin levels. It has also a beneficial role in lung function and cardiovascular health and influences the expression of genes involved in cancer development.

14.5 Vitamin E

Vitamin E has several forms and the human body can use only alpha-tocopherol form. Good sources of vitamin E are plant-based oil (e.g. sunflower, soya, corn, and olive oil), nuts, seeds, fruits, and vegetables. The potential health benefits are moisturizing skin, wound healing, preventing cancer [139], reducing skin itching and eczema, psoriasis, preventing and minimizing the appearance of scars, uses for treatment of wrinkles, preventing sunburn, promoting nail health and enhance immune response [140]. Vitamin E is also used for the treatment of diabetes and dementia [141].

14.6 Vitamin K

Vitamin K is a group of compounds and of them, the main are vitamin K1 and vitamin K2. The main sources of vitamin K1 are leafy greens vegetables and other vegetables (brussels sprouts, broccoli, cauliflower, and cabbage). However, sources of

vitamin K2 are meats, fish, liver, cheeses, and eggs. Vitamin K plays an important role to prevent osteoporosis [142], vascular calcification [143], and cardiovascular disease. Besides these, it has other health benefit roles, such as bone health, cognitive health, and heart health.

15. Minerals

Minerals are inorganic elements present in the soil and water and are important for the body to stay healthy. According to the human body demands, dietary minerals are two types, such as macro-minerals those are required in large amounts (e.g. calcium, phosphorus, magnesium, sodium, potassium, and sulfur), and micro- or trace-minerals those are required very small amounts (e.g. chromium, copper, cobalt, iron, fluorine, manganese, iodine, molybdenum, zinc, and selenium) [144].

15.1 Calcium

Calcium is a nutrient that all living organisms need and it is the most common mineral in the human body.

15.1.1 Sources

The main sources of calcium are milk, cheese, yogurt and other dairy products, green leafy vegetables (curly kale and okra), soya drinks with added calcium, and bread made with fortified flowers.

15.1.2 Function

Calcium has an important role in the human body. It is essential for the development of growth and maintain bone and reduces osteoporosis, helps regulation of muscle contraction, and maintains blood pressure. Calcium also prevents colorectal cancer [145] and preeclampsia [146].

15.2 Magnesium

Magnesium is one of the most important macro-nutrients for the human body.

15.2.1 Sources

Main sources of magnesium are avocados, legumes, nuts, seeds, tofu, whole grains, some fatty fish, dark chocolate, bananas, and leafy greens.

15.2.2 Function

Magnesium plays an important role in bone health and cardiovascular health, prevents diabetes and migraine headaches [147], premenstrual syndrome, and anxiety.

15.3 Potassium

Potassium is an important and necessary nutrient for the human body.

15.3.1 Sources

Potassium-rich foods are bananas, oranges, cantaloupe, honeydew, apricots, grapefruit, dried fruits, such as prunes, raisins and dates, cooked spinach and broccoli, potatoes, sweet potatoes, mushrooms, peas, cucumbers, and seafood. Milk, meat, yogurt, and nuts are also good sources of potassium.

15.3.2 Function

An adequate amount of potassium intake may prevent high blood pressure [148] that may reduce cardiovascular disease and stroke [149]. People who eat potassium-containing fruits and vegetables may have higher bone mineral density and it also helps to preserve muscle mass. High potassium may help kidneys' ability to reabsorb calcium and reduce kidney stones [150].

15.4 Chromium

Chromium is an essential trace element that the human body needs in very small quantities to properly maintain some health functions.

15.4.1 Sources

The good sources of chromium are grape juice, whole wheat flour, brewer's yeast, orange juice, beef, tomato juice, apples, and green beans.

15.4.2 Function

Some important health benefits of chromium are it may be helpful for type II diabetic patients. It can decrease glucose levels and improve insulin sensitivity. Chromium supplements can be used to build muscle or trigger weight loss. Some side effects including watery stool, vertigo, headaches, and hives are reported for taking chromium supplements.

15.5 Copper

Copper is required in small quantities but it is an essential nutrient for the body.

15.5.1 Sources

Main sources of copper are organ meats (liver and kidneys), oysters, spirulina, shiitake mushrooms, nuts and seeds, lobster, dark leafy greens, whole grains, dried fruits (prunes, cocoa, and black pepper), and dark chocolate.

15.5.2 Function

Copper helps to produce red blood cells, regulates heart rate and blood pressure, the absorption of iron, prevents inflammation of the prostate, in development and maintenance of bone, brain, and heart, and activates the immune system [151].

15.6 Iodine

Iodine is an essential trace element and is required for the human body.

15.6.1 Sources

The important sources of iodine are fish (cod and tuna), shrimp, and other seafood. Dairy products (milk, yogurt, and cheese), eggs, prunes, lima beans, and iodized salt.

15.6.2 Function

Iodine is essential for the synthesis of thyroid hormone that is required for metabolism. The deficiency of thyroid hormone is called hypothyroidism can lead to issues with fatigue, joint pain, and fertility problems. Iodine plays an important role in proper bone and brain development.

15.7 Iron

Iron deficiency is associated with several health impairments.

15.7.1 Sources

Good sources of iron are organ meats, red meat, turkey, shellfish, white beans, pumpkin seeds, quinoa, nuts, dark chocolate, dried fruits, soybean flour, lentils, tofu, sardines, spinach, broccoli, cooked oysters, and fortified breakfast cereals.

15.7.2 Function

Iron is helpful for the treatment of anemia; it may reduce fatigue and improves muscle endurance. It has an important role in strengthening the immunity system. Iron improves cognitive function [152] and reduces bruising.

15.8 Selenium

Selenium is an important macromineral and essential for the human body. Selenium deficiency is common in a certain part of the world as it can be affected by pH.

15.8.1 Sources

The sources of selenium are Brazil nuts, fish, ham, enriched foods, pork, beef, turkey, chicken, cottage cheese, eggs, brown rice, sunflower seeds, baked beans, mushrooms, oatmeal, spinach, milk and yogurt, lentils, cashews, and bananas.

15.8.2 Function

Selenium has several health benefits, such as acts as a powerful antioxidant, may reduce the risk of certain cancers-lung [153], prostate [154], liver, colon [155], esophageal, and gastric [156]. It may protect against heart disease and prevents

mental decline. Selenium is important for maintaining thyroid health, helping to boost the immune system, and reducing asthma symptoms.

15.9 Zinc

Zinc is a vital and second-most-abundant and essential mineral for the human body.

15.9.1 Sources

The best sources of zinc are meat, shellfish, legumes, hemp seeds, nuts, dairy, eggs, whole grains, some vegetables, and dark chocolate.

15.9.2 Function

Zinc is important for various functions in the body, such as helps to increase the immune system, uses in treating diarrhea, wound healing, works as an antioxidant and reduces chronic diseases, prevents age-related macular degeneration [157], improves sexual health, prevents osteoporosis, reduces neurological symptoms, protects from the common cold, boosts cognitive function, and increase learning and memory.

16. Conclusion

Functional food components are important compounds available in a variety of fruits, vegetables, and some animal products. They are also manufactured commercially. They have several health benefits for the human body. Many functional food components are antioxidants rich and help to neutralize free radicals, prevent cell damage, and reduce non-communicable diseases, such as cancer, diabetes, heart diseases and maintain health properly. To optimize health benefits and bioavailability of functional food components in the human body are critical factors. To maintain the levels required in the human body need an adequate amount of these components. Recent information in this regard is not sufficient. Therefore, need to provide more information to consumers to guide them effectively so that they can choose diets that contain adequate levels of health-promoting functional food components.

Conflict of interest

The author declares that there is no conflict of interest.

Notes/thanks/other declarations

None.

Author details

Saijuddin Shaikh
Department of International Health, Johns Hopkins University, Baltimore, MD, USA

*Address all correspondence to: saiju60@hotmail.com

IntechOpen

References

[1] Arai S. Studies on functional foods in Japan—State of the art. Bioscience, Biotechnology, and Biochemistry. 1996;**60**:9-15

[2] Shibamoto T, Kanazawa K, Shahidi F, Ho Chi-Tang. Functional food health: An overview. ACS Symposium. Vol. 993. Washington, DC: American Chemical Society; 2008

[3] Murano PS. Phytochemicals and Phytonutrients in Understanding Food Science & Technology. Bemont: Wadsworth; 2003. pp. 51-56

[4] Srividya AR, Nagasamy V, Vishnuvarthan VJ. Nutraceutical as medicine: A review. Pharmanest. 2010;**1**(2):132-145

[5] Kantoff P. Prevention, complementary therapies, and new scientific developments in the field of prostate cancer. Revista de Urología. 2006;**8**(Suppl. 2):S9-S14

[6] Sesso HD, Liu S, Gaziano JM, Buring JE. Dietary lycopene, tomato-based food products and cardiovascular disease in women. The Journal of Nutrition. 2003;**133**:2336-2341

[7] Mozaffarieh M, Sacu S, Wedrich A. The role of the carotenoids, lutein and zeaxanthin, in protecting against age-related macular degeneration: A review based on controversial evidence. Nutrition Journal. 2003;**2**:20

[8] Castillejo G, Bullo M, Anguera A, Escribano J, Salas-Salvado J. A controlled, randomized, double-blind trial to evaluate the effect of a supplement of cocoa husk that is rich in dietary fiber on colonic transit in constipated Pediatric patients. Pediatrics. 2006;**118**(3):e641-ee48

[9] Malhotra S, Rana SV, Sinha SK, Khurana S. Dietary fiber assessment of patients with irritable bowel syndrome from northern India. Indian Journal of Gastroenterology. 2004;**23**(6):217-218

[10] Van Rosendaal GMA, Shaffer EA, Edwards AL, Brant R. Effect of time of administration on cholesterol-lowering by psyllium: A randomized cross-over study in normocholesterolemic or slightly hypercholesterolemic subjects. Nutrition Journal. 2004;**3**:17

[11] Murakami K, Sasaki S, Okubo H, Takahashi Y, Hosoi Y, Itabashi M. Dietary fiber intake, dietary glycemic index and load, and body mass index: A cross-sectional study of 3931 Japanese women aged 18-20 years. European Journal of Clinical Nutrition. 2007;**61**:986-995

[12] Hannan JM, Ali L, Rokeya B, Khaleque J, Akhter M, Flatt PR, et al. Soluble dietary fibre fraction of Trigonella foenum-graecum (fenugreek) seed improves glucose homeostasis in animal models of type 1 and type 2 diabetes by delaying carbohydrate digestion and absorption, and enhancing insulin action. The British Journal of Nutrition. 2007;**97**:514-521

[13] Wakai K, Date C, Fukui M, Tamakoshi K, Watanabe Y, Hayakawa N, et al. Dietary fiber and risk of colorectal cancer in the Japan collaborative cohort study. Cancer Epidemiology, Biomarkers & Prevention. 2007;**16**:668-675

[14] McEligot AJ, Largent J, Ziogas A, Peel D, Anton-Culver H. Dietary fat, fiber, vegetable, and micronutrients are associated with overall survival in postmenopausal women diagnosed with breast cancer. Nutrition and Cancer. 2006;**55**:132-140

[15] Slavin JL, Greenberg NA. Partially hydrolyzed guar gum. Clinical nutrition uses. Nutrition. 2003;**19**:549-552

[16] Vanek C, Connor WE. Do n–3 fatty acids prevent osteoporosis? The American Journal of Clinical Nutrition. 2007;**85**:647-648

[17] Calder PC, Zurier RB. Polyunsaturated fatty acids and rheumatoid arthritis. Current Opinion in Clinical Nutrition and Metabolic Care. 2001;**4**:115-121

[18] Oddy W, de Klerk N, Kendall G, Mihrshahi S, Peat J. Ratio of Omega-6 to Omega-3 fatty acids and childhood asthma. The Journal of Asthma. 2004;**41**:319-326

[19] Logan AC. Omega-3 fatty acids and major depression: A primer for the mental health professional. Lipids in Health and Disease. 2004;**3**:25

[20] Sagduyu K, Dokucu ME, Eddy BA, Craigen G, Baldassano CF, Yildiz A. Omega-3 fatty acids decreased irritability of patients with bipolar disorder in an add-on, open label study. Nutrition Journal. 2005;**4**:6

[21] Schwalfenberg G. Omega-3 fatty acids: Their beneficial role in cardiovascular health. Canadian Family Physician. 2006;**52**:734-740

[22] Martirosyan DM, Miroshnichenko LA, Kulakova SN, Pogojeva AV, Zoloedov VI. Amaranth oil application for coronary heart disease and hypertension. Lipids in Health and Disease. 2007;**6**:1-12

[23] Pratt VC, Tredget EE, Clandinin MT, Field CJ. Fatty acid content of plasma lipids and erythrocyte phospholipids are altered following burn injury. Lipids. 2001;**36**:675-682

[24] Mayser P, Mrowietz U, Arenberger P, Bartak P, Buchvald J, Christophers E, et al. Omega-3 fatty acid-based lipid infusion in patients with chronic plaque psoriasis: Results of a double-blind, randomized, placebo-controlled, multicenter trial. Journal of the American Academy of Dermatology. 1998;**38**:539-547

[25] Calabresi L, Villa N, Canavesi M, Sirtori CR, James RW, Bernini F, et al. An Omega-3 polyunsaturated fatty acid concentrate increases plasma high-density lipoprotein 2 cholesterol and paraoxonase levels in patients with familial combined hyperlipidemia. Metabolism. 2004;**53**:153-158

[26] Hirsch J. The search for new ways to treat obesity. Proceedings of the National Academy of Sciences of the United States of America. 2002;**99**:9096-9097

[27] Brown JM, McIntosh MK. Conjugated linoleic acid in humans: Regulation of adiposity and insulin sensitivity. The Journal of Nutrition. 2005;**133**:3041-3046

[28] Griel AE, Kris-Etherton PM, Hilpert KF, Zhao G, West SG, Corwin RL. An increase in dietary n-3 fatty acids decreases a marker of bone resorption in humans. Nutrition Journal. 2007;**6**:1-8

[29] Sinn N, Bryan J. Effect of supplementation with polyunsaturated fatty acids and micronutrients on learning and behavior problems associated with child ADHD. Journal of Developmental and Behavioral Pediatrics. 2007;**28**:82-91

[30] Cangemi FE. TOZAL study: An open case control study of an oral antioxidant and Omega-3 supplement for dry AMD. BMC Ophthalmology. 2007;**7**:1-10

[31] Aragona P, Bucolo C, Spinella R, Giuffrida S, Ferreri G. Systemic Omega-6

essential fatty acid treatment and PGE1 tear content in Sjögren's syndrome patients. Investigative Ophthalmology & Visual Science. 2005;**46**:4474-4479

[32] Chapkin RS, McMurray DN, Lupton JR. Colon cancer, fatty acids and anti-inflammatory compounds. Current Opinion in Gastroenterology. 2007;**23**:48-54

[33] Shannon J, King IB, Moshofsky R, Lampe JW, Gao DL, Ray RM, et al. Erythrocyte fatty acids and breast cancer risk: A case-control study in Shanghai, China. American Journal of Clinical Nutrition. 2007;**85**:1090-1097

[34] Kelavkar UP, Hutzley J, Dhir R, Kim P, Allen KGD, McHugh K. Prostate tumor growth and recurrence can be modulated by the ω-6:ω-3 ratio in diet: Athymic mouse xenograft model simulating radical prostatectomy. Neoplasia. 2006;**8**:112-124

[35] Rouzaud G, Young SA, Duncan AJ. Hydrolysis of glucosinolates to isothiocyanates after ingestion of raw or microwaved cabbage by human volunteers. Cancer Epidemiology, Biomarkers & Prevention. 2004;**13**:25-31

[36] Johnson IT. Cruciferous vegetables and risk of cancers of the gastrointestinal tract. Molecular Nutrition & Food Research. 2018;**62**:1701000

[37] Zhang Z, Bergan R, Shannon J, Slatore CG, Bobe G, Takata Y. The role of cruciferous vegetables and isothiocyanates for lung cancer prevention: Current status, challenges, and future research directions. Molecular Nutrition & Food Research. 2018;**62**:1700936

[38] Fahey JW, Haristoy X, Dolan PM, Kensler TW, Scholtus I, Stephenson KK, et al. Sulforaphane inhibits extracellular, intracellular, and antibiotic-resistant strains of *Helicobacter pylori* and prevents benzo[a]pyrene-induced stomach tumors. Proceedings of the National Academy of Sciences of the United States of America. 2002;**99**:7610-7615

[39] Haristoy X, Angioi-Duprez K, Duprez A, Lozniewski A. Efficacy of sulforaphane in eradicating helicobacter pylori in human gastric xenografts implanted in nude mice. Antimicrobial Agents and Chemotherapy. 2003;**47**: 3982-3984

[40] Blekkenhorst LC, Bondonno CP, Lewis JR, Devine A, Zhu K, Lim WH, et al. Cruciferous and total vegetable intakes are inversely associated with subclinical atherosclerosis in older adult women. Journal of the American Heart Association. 2018;**7**(8):e008391

[41] Beecher GR. Overview of dietary flavonoids: Nomenclature, occurrence and intake. The Journal of Nutrition. 2003;**133**:3248S-3254S

[42] Kanerva A, Raki M, Ranki T, Sarkioja M, Koponen J, Desmond RA, et al. Chlorpromazine and apigenin reduce adenovirus replication and decrease replication associated toxicity. The Journal of Gene Medicine. 2007;**9**:3-9

[43] Friedman M. Overview of antibacterial, antitoxin, antiviral, and antifungal activities of tea flavonoids and teas. Molecular Nutrition & Food Research. 2007;**51**:116-134

[44] Zhou L, Li D, Wang J, Liu Y, Wu J. Antibacterial phenolic compounds from the spines of Gleditsia Sinensis lam. Natural Product Research. 2007;**21**:283-291

[45] Nowakowska Z. A review of anti-infective and anti-inflammatory

chalcones. European Journal of Medicinal Chemistry. 2007;**42**:125-137

[46] Zhang B, Osborne NN. Oxidative-induced retinal degeneration is attenuated by epigallocatechin gallate. Brain Research. 2006;**1124**:176-187

[47] Mink PJ, Scrafford CG, Barraj LM, Harnack L, Hong CP, Nettleton JA, et al. Flavonoid intake and cardiovascular disease mortality: A prospective study in postmenopausal women. The American Journal of Clinical Nutrition. 2007;**85**:895-909

[48] Jiang ZM, Cao JD. The impact of micronized purified flavonoid fraction on the treatment of acute haemorrhoidal episodes. Current Medical Research and Opinion. 2006;**22**:1141-1147

[49] Li T, Liu J, Zhang X, Ji G. Antidiabetic activity of lipophilic (−)-epigallocatechin-3-gallate derivative under its role of alphaglucosidase inhibition. Biomedicine & Pharmacotherapy. 2007;**61**:91-96

[50] Hirohata M, Hasegawa K, Tsutsumi-Yasuhara S, Ohhashi Y, Ookoshi T, Ono K, et al. The antiamyloidogenic effect is exerted against Alzheimer's beta-amyloid fibrils in vitro by preferential and reversible binding of flavonoids to the amyloid fibril structure. Biochemistry. 2007;**46**:1888-1899

[51] Zhu JX, Wang Y, Kong LD, Yang C, Zhang X. Effects of biota orientalis extract and its flavonoid constituents, quercetin and rutin on serum uric acid levels in oxonate-induced mice and xanthine dehydrogenase and xanthine oxidase activities in mouse liver. Journal of Ethnopharmacology. 2004;**93**:133-140

[52] Zhu G, Li C, Cao Z. Inhibitory effect of flavonoid baicalin on degranulation of human polymorphonuclear leukocytes induced by interleukin-8: Potential role in periodontal diseases. Journal of Ethnopharmacology. 2007;**109**:325-330

[53] Kurahashi N, Iwasaki M, Sasazuki S, Otani T, Inoue M, Tsugane S. Soy product and isoflavone consumption in relation to prostate cancer in Japanese men. Cancer Epidemiology, Biomarkers & Prevention. 2007;**16**:538-545

[54] Gates MA, Tworoger SS, Hecht JL, De Vivo I, Rosner B, Hankinson SE. A prospective study of dietary flavonoid intake and incidence of epithelial ovarian cancer. International Journal of Cancer. 2007;**121**:2225-2232

[55] Fink BN, Steck SE, Wolff MS, Britton JA, Kabat GC, Schroeder JC, et al. Dietary flavonoid intake and breast cancer risk among women on Long Island. American Journal of Epidemiology. 2007;**165**:514-523

[56] Hostanska K, Jurgenliemk G, Abel G, Nahrstedt A, Saller R. Willow bark extract (BNO1455) and its fractions suppress growth and induce apoptosis in human colon and lung cancer cells. Cancer Detection and Prevention. 2007;**31**:129-139

[57] Rossi M, Garavello W, Talamini R, La Vecchia C, Franceschi S, Lagiou P, et al. Flavonoids and risk of squamous cell esophageal cancer. International Journal of Cancer. 2007;**120**:1560-1564

[58] Yeh TC, Chiang PC, Li TK, Hsu JL, Lin CJ, Wang SW, et al. Genistein induces apoptosis in human hepatocellular carcinomas via interaction of endoplasmic reticulum stress and mitochondrial insult. Biochemical Pharmacology. 2007;**73**:782-792

[59] Bosetti C, Rossi M, McLaughlin JK, Negri E, Talamini R, Lagiou P, et al.

Flavonoids and the risk of renal cell carcinoma. Cancer Epidemiology, Biomarkers & Prevention. 2007;**16**:98-101

[60] De Munter JS, Hu FB, Spiegelman D, Franz M, van Dam RM. Whole grain, bran, and germ intake and risk of type 2 diabetes: A prospective cohort study and systematic review. PLoS Medicine. 2007;**4**(8):e261

[61] Hollman PC, Geelen A, Kromhout D. Dietary flavonol intake may lower stroke risk in men and women. The Journal of Nutrition. 2010;**140**:600-604

[62] Sun Q, Wedick NM, Tworoger SS, Pan A, Townsend MK, Cassidy A, et al. Urinary excretion of select dietary polyphenol metabolites is associated with a lower risk of type 2 diabetes in proximate but not remote follow-up in a prospective investigation in 2 cohorts of US women. The Journal of Nutrition. 2015;**145**:1280-1288

[63] Russo GI, Campisi D, Mauro MD, Regis F, Reale G, Marranzano M, et al. Dietary consumption of phenolic acids and prostate cancer: A case-control study in Sicily, Southern Italy. Molecules. 2017;**22**:2159

[64] Xiang D, Wang D, He Y, Xie J, Zhong Z, Li Z, et al. Caffeic acid phenethyl ester induces growth arrest and apoptosis of colon cancer cells via the beta-catenin/T-cell factor signaling. Anti-Cancer Drugs. 2006;**17**:753-762

[65] Bailly F, Cotelle P. Anti-HIV activities of natural antioxidant caffeic acid derivatives: Toward an antiviral supplementation diet. Review. Current Medicinal Chemistry. 2005;**12**:1811-1818

[66] Godos J, Sinatra D, Blanco I, Mulè S, La Verde M, Marranzano M. Association between dietary phenolic acids and hypertension in a Mediterranean cohort. Nutrients. 2017;**9**:1069

[67] Homma Y, Ikeda I, Ishikawa T, Tateno M, Sugano M, Nakamura H. A randomized, placebo-controlled trial: Decrease in plasma low-density lipoprotein cholesterol, apolipoprotein B, cholesteryl ester transfer protein, and oxidized low-density lipoprotein by plant ptanol pster-containing spread. Nutrition. 2003;**19**:369-374

[68] Jayaraj PA, Tovey FI, Hobsley M. Duodenal ulcer prevalence: Research into the nature of possible protective dietary lipids. Phytotherapy Research. 2003;**17**:391-398

[69] Bennani H, Drissi A, Giton F, Kheuang L, Fiet J, Adlouni A. Antiproliferative effect of polyphenols and sterols of virgin argan oil on human prostate cancer cell lines. Cancer Detection and Prevention. 2007;**31**:64-69

[70] Schabath MB, Hernandez LM, Wu X, Pillow PC, Spitz MR. Dietary phytoestrogens and lung cancer risk. JAMA. 2005;**294**:1493-1504

[71] Awad AB, Roy R, Fink CS. ß-sitosterol, a plant sterol, induces apoptosis and activates key caspases in MDA-MB-231 human breast cancer cells. Oncology Reports. 2003;**10**:497-500

[72] Mccann SE, Freudenheim JL, Marshall JR, Graham S. Risk of human ovarian cancer is related to dietary intake of selected nutrients, Phytochemicals and Food Groups. Journal of Nutrition. 2003;**133**:1937-1942

[73] Mccann SE, Freudenheim JL, Marshall JR, Brasure JR, Swanson MK, Graham S. Diet in the epidemiology of endometrial cancer in Western New York (United States). Cancer Causes & Control. 2000;**11**:965-974

[74] Wolever TMS, Piekarz A, Hollands M, Younker K. Sugar alcohols and diabetes; a review. Canadian Journal of Diabetes. 2002;**26**:356-362

[75] Hayes C. The effect of non-cariogenic sweeteners on the prevention of dental caries: A review of the evidence. Journal of Dental Education. 2001;**65**:1106-1109

[76] Scheppach W, Luehrs H, Menzel T. Beneficial health effects of low-digestible carbohydrate consumption. The British Journal of Nutrition. 2001;**85**:S23-S30

[77] Montgomery KS. Soy protein. Journal of Perinatal Education. 2003;**12**:42-45

[78] Xiao R, Badger TM, Simmen FA. Dietary exposure to soy or whey proteins alters colonic global gene expression profiles during rat colon tumorigenesis. Molecular Cancer. 2005;**4**:1

[79] Velasquez MT, Bhathena SJ. Role of dietary soy protein in obesity. Review. International Journal of Medical Sciences. 2007;**4**:72-82

[80] Gardiner T, Ramberg J. Plant estrogens: Importance in health and disease. Glycoscience &. Nutrition. 2001;**2**:2-12

[81] Roudsari AH, Tahbaz F, Hossein-Nezhad A, Arjmandi B, Larijani B, Kimiagar SM. Assessment of soy phytoestrogens' effects on bone turnover indicators in menopausal women with osteopenia in Iran: A before and after clinical trial. Nutrition Journal. 2005;**4**:30

[82] Kronenberg F, Fugh-Berman A. Complementary and alternative medicine for menopausal symptoms: A review of randomized, controlled trials. Annals of Internal Medicine. 2002;**137**:805-813

[83] Bosland MC. The role of estrogens in prostate carcinogenesis: A rationale for chemoprevention. Revista de Urología. 2005;**7**:S4-S10

[84] Ziegler RG. Phytoestrogens and breast cancer. The American Journal of Clinical Nutrition. 2004;**79**:183-184

[85] Horn-Ross PL, Hoggatt KJ, Lee MM. Phytoestrogens and thyroid cancer risk. The San Francisco Bay Area thyroid cancer study. Cancer Epidemiology, Biomarkers & Prevention. 2002;**11**:43-49

[86] Cotterchio M, Boucher BA, Manno M, Gallinger S, Okey A, Harper P. Dietary phytoestrogen intake is associated with reduced colorectal cancer risk. The Journal of Nutrition. 2006;**136**:3046-3053

[87] Widyarini S, Domanski D, Painter N, Reeve VE. Estrogen receptor signaling protects against immune suppression by UV radiation exposure. Proceedings of the National Academy of Sciences of the United States of America. 2006;**103**:12837-12842

[88] Sexton E, Van Themsche C, Leblanc K, Parent S, Lemoine P, Asselin E. Resveratrol interferes with AKT activity and triggers apoptosis in human uterine cancer cells. Molecular Cancer. 2006;**5**:45

[89] Blair RM, Henley EC, Tabor A. Soy foods have low glycemic and insulin response indices in normal weight subjects. Nutrition Journal. 2006;**5**:35

[90] Konigheim BS, Goleniowski ME, Contigiani MS. Cytotoxicity and antiviral activity of a lignan extracted from Larrea divaricata. Drug Design Reviews. 2005;**2**:81-83

[91] Morelli L, Zonenschain D, Callegari ML, Grossi E, Maisano F,

Fusillo M. Assessment of a new synbiotic preparation in healthy volunteers: Survival, persistence of probiotic strains and its effect on the indigenous flora. Nutrition Journal. 2003;**2**:11

[92] Weizman Z, Asli G, Alsheikh A. Effect of a probiotic infant formula on infections in child care centers: Comparison of two probiotic agents. Pediatrics. 2005;**115**:5-9

[93] Penner RM, Fedorak RN. Probiotics in the management of inflammatory bowel disease. Medscape General Medicine. 2005;**7**:19

[94] Parvez S, Malik KA, Kang SA, Kim HY. Probiotics and their fermented food products are beneficial for health. Journal of Applied Microbiology. 2006;**100**:1171-1185

[95] Pelletier X, Laure-Boussuge S, Donazzolo Y. Hydrogen excretion upon ingestion of dairy products in lactose-intolerant male subjects: Importance of the live flora. European Journal of Clinical Nutrition. 2001;**55**:509-512

[96] Solga SF. Probiotics can treat hepatic encephalopathy. Medical Hypotheses. 2003;**61**:307-313

[97] Galdeano CM, Perdigón G. The probiotic bacterium *Lactobacillus casei* induces activation of the gut mucosal immune system through innate immunity. Clinical and Vaccine Immunology. 2006;**13**:219-226

[98] Brown AC, Valiere A. Probiotics and medical nutrition therapy. Nutrition in Clinical Care. 2004;**7**:56-68

[99] Sgouras D, Maragkoudakis P, Petraki K, Martinez-Gonzalez B, Eriotou E, Michopoulos S, et al. In vitro and in vivo inhibition of *Helicobacter pylori* by *Lactobacillus casei* Strain Shirota. Applied and Environmental Microbiology. 2004;**70**:518-526

[100] Azcarate-Peril MA, Bruno-Bárcena JM, Hassan HM, Klaenhammer TR. Transcriptional and functional analysis of oxalyl-coenzyme a (CoA) decarboxylase and formyl-CoA transferase genes from *Lactobacillus acidophilus*. Applied and Environmental Microbiology. 2006;**72**:1891-1899

[101] Liong MT, Shah NP. Optimization of cholesterol removal by probiotics in the presence of prebiotics by using a response surface method. Applied and Environmental Microbiology. 2005;**71**:1745-1753

[102] Pohjavuori E, Viljanen M, Korpela R, Kuitunen M, Tiittanen M, Vaarala O, et al. *Lactobacillus* GG effect in increasing IFN-gamma production in infants with Cow's milk allergy. The Journal of Allergy and Clinical Immunology. 2004;**114**:131-136

[103] Sharif S, Meader N, Oddie SJ, Rojas-Reyes MX, McGuire W. Probiotics to prevent necrotising enterocolitis in very preterm or very low birth weight infants. Cochrane Database of Systematic Reviews. 2020;(10): Art. No.: CD005496

[104] Chi C, Buys N, Li C, Sun J, Yin C. Effects of prebiotics on sepsis, necrotizing enterocolitis, mortality, feeding intolerance, time to full enteral feeding, length of hospital stay, and stool frequency in preterm infants: A meta-analysis. European Journal of Clinical Nutrition. 2019;**73**:657-670

[105] Panigrahi P, Parida S, Nanda NC, Satpathy R, Pradhan L, Chandel DS, et al. A randomized synbiotic trial to prevent sepsis among infants in rural India. Nature. 2017;**548**:407-411

[106] Ball G. Vitamins. Their Role in the Human Body. New York: Blackwell Publishing; 2004

[107] Prakash P, Krinsky NI, Russell RM. Retinoids, carotenoids, and human breast cancer cell cultures: A review of differential effects. Nutrition Reviews. 2000;**58**:170-176

[108] Rego EM, He LZ, Warrell RP Jr, Wang ZG, Pandolfi PP. Retinoic acid (RA) and As_2O_3 treatment in transgenic models of acute promyelocytic leukemia (APL) unravel the distinct nature of the leukemogenic process induced by the PML-RNAα and PLZF-RNAα oncoproteins. Proceedings of the National Academy of Sciences of the United States of America. 2000;**97**:10173-10178

[109] Berson EL, Rosner B, Sandberg MA, Hayes KC, Nicholson BW, Weigel-DiFranco C, et al. A randomized trial of vitamin A and vitamin E supplementation for retinitis pigmentosa. Archives of Ophthalmology. 1993;**111**:761-772

[110] Meador K, Loring D, Nichols M, Zamrini E, Rivner M, Posas H, et al. Preliminary findings of high dose thiamine in dementia of Alzheimer's type. Journal of Geriatric Psychiatry and Neurology. 1993;**6**:222-229

[111] Mendoza CE, Rodriguez F, Rosenberg DG. Reversal of refractory congestive heart failure after thiamine supplementation: Report of a case and review of literature. Journal of Cardiovascular Pharmacology and Therapeutics. 2003;**8**:313-316

[112] Comin-Anduix B, Boren J, Martinez S, Moro C, Centelles JJ, Trebukhina R, et al. The effect of thiamine supplementation on tumour proliferation. A metabolic control analysis study. European Journal of Biochemistry. 2001;**268**:4177-4182

[113] Kuzniarz M, Mitchell P, Cumming RG, Flood VM. Use of vitamin supplements and cataract: The Blue Mountains eye study. American Journal of Ophthalmology. 2001;**132**:19-26

[114] Schoenen J, Lenaerts M, Bastings E. High-dose riboflavin as a prophylactic treatment of migraine: Results of an open pilot study. Cephalalgia. 1994;**14**:328-329

[115] Hannan F, Davoren P. Use of nicotinic acid in the management of recurrent hypoglycemic episodes in diabetes. Diabetes Care. 2001;**24**(7):1301

[116] Canner PL, Berge KG, Wenger NK, Stamler J, Friedman L, Prineas RJ, et al. Fifteen year mortality in coronary drug project patients: Long-term benefit with niacin. Journal of the American College of Cardiology. 1986;**8**:1245-1255

[117] Vaxman F, Chalkiadakis G, Olender S, Maldonado H, Aprahamian M, Bruch JF, et al. Improvement in the healing of colonic anastomoses by vitamin B5 and C supplements. Experimental study in the rabbit. Annales de Chirurgie. 1990;**44**:512-520

[118] Naruta E, Buko V. Hypolipidemic effect of pantothenic acid derivatives in mice with hypothalamic obesity induced by aurothioglucose. Experimental and Toxicologic Pathology. 2001;**53**:393-398

[119] Fakhrzadeh H, Ghotbi S, Pourebrahim R, Nouri M, Heshmat R, Bandarian F, et al. Total plasma homocysteine, folate, and vitamin B12 status in healthy Iranian adults: The Tehran Homocysteine Survey (2003-2004)/a cross–sectional population based study. BMC Public Health. 2006;**6**:29

[120] Selhub J, Bagley LC, Miller J, Rosenberg IH. B Vitamins, homocysteine, and neurocognitive function in the elderly. The American Journal of Clinical Nutrition. 2000;**71**:614S-620S

[121] Wyatt KM, Dimmock PW, Jones PW, O'Brien PMS. Efficacy of vitamin B-6 in the treatment of premenstrual syndrome: Systematic review. BMJ. 1999;**318**:1375-1381

[122] Jewell D, Young G. Interventions for nausea and vomiting in early pregnancy. (Cochrane Review). In: The Cochrane Library, Issue 4. Chichester, UK: John Wiley & Sons, Ltd; 2003

[123] Fuhr JP, He H, Goldfarb N, Nash DB. Use of chromium picolinate and biotin in the management of Type 2 diabetes: An economic analysis. Disease Management. 2005;**8**:265-275

[124] Zempleni J, Mock DM. Marginal biotin deficiency is teratogenic. Proceedings of the Society for Experimental Biology and Medicine. 2000;**223**:14-21

[125] Geohas J, Daly A, Juturu V, Finch M, Komorowski J. Chromium picolinate and biotin combination reduces atherogenic index of plasma in patients with type 2 diabetes mellitus: A placebo-controlled, double-blinded, randomized clinical trial. The American Journal of the Medical Sciences. 2007;**333**:145-153

[126] Iorizzo M, Pazzaglia M, Piraccini BM, Tullo S, Tosti A. Brittle nails. Journal of Cosmetic Dermatology. 2004;**3**:138-144

[127] Schulpis KH, Nyalala JH, Papakonstantinou ED, Leondiadis L, Livaniou E, Ithakisios D, et al. Biotin recycling impairment in phenylketonuric children with seborrheic dermatitis. International Journal of Dermatology. 1998;**37**:918-921

[128] Scholl TO, Johnson WG. Folic acid: Influence on the outcome of pregnancy. The American Journal of Clinical Nutrition. 2000;**71**:1295S-1303S

[129] Oakley GP. Global prevention of all folic acid-preventable spina bifida and anencephaly by 2010. Community Genetics. 2002;**5**:70-77

[130] Rao KA, Pillai JR. Recurrent pregnancy loss. Journal of the Indian Medical Association. 2006;**104**:458-461

[131] van den Donk M, van Engeland M, Pellis L, Witteman BJ, Kok FJ, Keijer J, et al. Dietary folate intake in combination with MTHFR C677T genotype and promoter methylation of tumor suppressor and DNA repair genes in sporadic colorectal adenomas. Cancer Epidemiology, Biomarkers & Prevention. 2007;**16**:327-333

[132] Shirodaria C, Antoniades C, Lee J, Jackson CE, Robson MD, Francis JM, et al. Global improvement of vascular function and redox state with low-dose folic acid. Implications for folate therapy in patients with coronary artery disease. Circulation. 2007;**115**:2262-2270

[133] Tettamanti M, Garri MT, Nobili A, Riva E, Lucca U. Low folate and the risk of cognitive and functional deficits in the very old: The Monzino 80-plus study. Journal of the American College of Nutrition. 2006;**25**:502-508

[134] Donaldson MS. Nutrition and cancer: A review of the evidence for an anti-cancer diet. Nutrition Journal. 2004;**3**:19

[135] Quinlivan EP, McPartlin J, McNulty H, Ward M, Strain JJ, Weir DG,

et al. Importance of both folic acid and vitamin B12 in reduction of risk of vascular disease. Lancet. 2002;**359**:227-228

[136] Clarke R, Smith AD, Jobst KA, Refsum H, Sutton L, Ueland PM. Folate, vitamin B12, and serum total homocysteine levels in confirmed Alzheimer disease. Archives of Neurology. 1998;**55**:1449-1455

[137] Huang J, Agus DB, Winfree CJ, Kiss S, Mack WJ, McTaggart RA, et al. Dehydroascorbic acid, a blood–brain barrier transportable form of vitamin C, mediates potent cerebroprotection in experimental stroke. Proceedings of the National Academy of Sciences of the United States of America. 2001;**98**:11720-11724

[138] Michels KB, Holmberg L, Bergkvist L, Ljung H, Bruce A, Wolk A. Dietary antioxidant vitamins, retinol, and breast cancer incidence in a cohort of Swedish women. International Journal of Cancer. 2001;**91**:563-567

[139] Zhang Y, Ni J, Messing EM, Chang E, Yang CR, Yeh S. Vitamin E succinate inhibits the function of androgen receptor and the expression of prostate-specific antigen in prostate cancer cells. Proceedings of the National Academy of Sciences of the United States of America. 2002;**99**:7408-7413

[140] Wang XL, Rainwater DL, Mahaney MC, Stocker R. Supplementation with vitamin E and coenzyme Q10 reduces circulating markers of inflammation in baboons. The American Journal of Clinical Nutrition. 2004;**80**:649-655

[141] Khanna S, Roy S, Slivka A, Craft TK, Chaki S, Rink C, et al. Neuroprotective properties of the natural vitamin E α-Tocotrienol. Stroke. 2005;**36**:2258-2264

[142] Vermeer C, Knapen MH, Schurgers LJ. Vitamin K and metabolic bone disease. Journal of Clinical Pathology. 1998;**51**:424-426

[143] Schurgers LJ, Dissel PE, Spronk HM, Soute BA, Dhore CR, Cleutjens JP, et al. Role of vitamin K and vitamin K dependent proteins in vascular calcification. Zeitschrift für Kardiologie. 2001;**90**:57-63

[144] Lieberman S, Brunning N. Real Vitamin and Mineral Book. New York: Penguin Books; 2003

[145] Peters U, Chatterjee N, McGlynn KA, Schoen RE, Church TR, Bresalier RS, et al. Calcium intake and colorectal adenoma in a US colorectal cancer early detection program. The American Journal of Clinical Nutrition. 2004;**80**:1358-1365

[146] Kulier R, de Onis M, Gulmezoglu AM, Villar J. Nutritional interventions for the prevention of maternal morbidity. International Journal of Gynaecology and Obstetrics. 1998;**63**:231-246

[147] Mauskop A, Altura BM. Role of magnesium in the pathogenesis and treatment of migraines. Clinical Neuroscience. 1998;**5**:24-27

[148] Barri YM, Wingo CS. The effects of potassium depletion and supplementation on blood pressure: A clinical review. The American Journal of the Medical Sciences. 1997;**314**:37-40

[149] Bazzano LA, He J, Ogden LG, Loria C, Vupputuri S, Myers L, et al. Dietary potassium intake and risk of stroke in US men and women. Stroke. 2001;**32**:1473-1480

[150] Curhan GC, Willett WC, Speizer FE, Spiegelman D, Stampfer MJ. Comparison

of dietary calcium with supplemental calcium and other nutrients as factors affecting the risk for kidney stones in women. Annals of Internal Medicine. 1997;**126**:497-504

[151] Eaton-Evans J, Mellwrath EM, Jackson WE, McCartney H, Strain JJ. Copper supplementation and the maintenance of bone mineral density in middle-aged women. Journal of Trace Elements in Experimental Medicine. 1996;**9**:87-94

[152] Grantham-Mcgregor S, Ani C. A review of studies on the effect of iron deficiency on cognitive development in children. The Journal of Nutrition. 2001;**131**:649S-666S

[153] Reid ME, Duffield-Lillico AJ, Garland L, Turnbull BW, Clark LC, Marshall JR. selenium supplementation and lung cancer incidence: An update of the nutritional prevention of cancer trial. Cancer Epidemiology, Biomarkers & Prevention. 2002;**11**:1285-1291

[154] Brooks JD, Metter EJ, Chan DW, Sokoll LJ, Landis P, Nelson WG, et al. Plasma selenium level before diagnosis and the risk of prostate cancer development. The Journal of Urology. 2001;**166**:2034-2038

[155] Ghadirian P, Maisonneuve P, Perret C, Kennedy G, Boyle P, Krewski D, et al. A case-control study of toenail selenium and cancer of the breast, colon, and prostate. Cancer Detection and Prevention. 2000;**24**:305-313

[156] Mark SD, Qiao YL, Dawsey SM, Wu YP, Katki H, Gunter EW, et al. Prospective study of serum selenium levels and incident esophageal and gastric cancers. Journal of the National Cancer Institute. 2000;**92**:1753-1763

[157] Clemons TE, Kurinij N, Sperduto RD. AREDS research group. Associations of mortality with ocular disorders and an intervention of high-dose antioxidants and zinc in the age-related eye disease study: AREDS report No.13. Archives of Ophthalmology. 2004;**122**:716-726

Chapter 2

Categories and Management of Functional Food

Anvi Rana

Abstract

Functional foods are any whole, fortified, enhanced, or improved foods that provide health benefits beyond the availability of fundamental components when consumed in effective amounts as part of a varied diet regularly (e.g., minerals and vitamins). Based on the type of evidence, this review segregates a range of functional foods. Furthermore, not even all foods labeled as functional foods on the market today are backed up by enough data to substantiate such claims. In the food and nutrition sciences, functional foods are presently one of the most thoroughly researched and encouraged fields. This topic evaluates the complex nature of trying to define functional foods, and also the categorizations of food products introduced to the market as functional, legislation of functional foods, science-based supporting evidence and development of functional ingredients investigation, and a statement to registered dietitians and dieticians specialists on how to keep up to date on nutritional and functional investigation and its interpretation to buyers.

Keywords: functional food, food ingredient, health, food security

1. Introduction

Food that is useful when taken as part of a diverse diet on a routine basis, whole foods, and fortified, enhanced, or improved foods can improve health, and they are an exciting contemporary development in the food and nutrition sector [1]. The significant research acceptance level of proof should be used to support health claims on food items, particularly functional foods. The fast-developing trend of functional foods raises a slew of new concerns and opportunities for public health, particularly in terms of giving truthful data [2]. Nutritional study advanced slowly until the 1940s when several deficiency disorders and the nutrients that may "treat" them became the focus. Top Scientists and others found nutrients that were important for many existing disease illnesses during this golden period of biochemistry [3].

Companies that make functional foods and dietary supplements began to clash with scientists who demanded scientific proof to increase their profitability. Organic food shops expanded in quantity and power to the point that they produced major chain stores that competed with regular supermarkets [4]. The National Center for Complementary and Alternative Medicine, which sponsored university-affiliated research institutions, was established inside the National Institutes of Health in 1998,

further cementing government acknowledgment of the unconventional proactive health approach advocated by functional foods [5]. This time of life Hippocrates phrase, "Let food be thy medicine, and medicine be thy food," is the credo of today's modern health-conscious populace. Following that, Metchnikoff's "Law of Longevity" was linked to extended youth and healthful old age, as seen mostly in the Russian population. Commoners in the Balkans at the time consumed cultured kinds of milk [6].

Since that day, researchers have been working to better understand the impact of a variety of food components and nutrients in improving health and avoiding chronic illnesses. Functional foods are the product of this field's study, which has culminated in a slew of new brands for foods that have been linked to certain health advantages [7]. The notion of functional ingredients stresses that food is important not only for sustenance but also for preventing and reducing potential risks for a spectrum of ailments, as well as increasing some critical physiological activities. Functional foods also supply the body with essential nutrients, lipids, proteins, carbs, and other nutrients. Now we'll delve deeper into the topic of Functional Foods [8].

Registered dietitians obey Hippocrates' lead by advocating food as medical nutrition treatment to cure a variety of illnesses and/or to protect, recover, and enhance wellness and health. As a consequence, understanding and incorporating functional foods within their treatment is crucial. They serve as a link between scientific proof studies and overall wellness for consumers. The number of functional food items on the market will keep growing. RDs must know how these foods get to market and how they are marketed [9].

2. Interpretation of functional food

Functional foods became initially coined in Japan in the early 1980s, and they allude to manufactured meals that incorporate components that, in conjunction with just being nutritious, enhance various biological processes. Japan is currently the only country that has established a governmental authorization for functional foods [10].

Concepts	Organization
1. Complete foods and fortified, enhanced, or boosted foods, have a theoretically positive impact on health when taken regularly in optimum amounts as a component of a diversified meal.	The Academy of Nutrition and Dietetics - (AND)
2. A diet that, despite appropriate nutritional benefits, has a good effect solely on a single or maybe more target functions in the body in ways that is pertinent either to better health status and well-being or a reduced risk of illness." It's part of the regular eating routine. It is not a tablet, a pill, or any other type of vitamin supplement.	The Commission of the European (EC)
3. A serving of functional food resembles but is not identical to, a traditional meal is taken as part of a regular meal, and has been shown to offer physiological advantages and/or lower the risk of a chronic condition in addition to fundamental nutritious requirements.	Canada's Department of Health (CDH)
4. Foods or food supplements may give health benefits beyond basic nutrition, such as lowering or reducing the risk of certain illnesses and other health complications.	Food Information Council of the United Nations (FICUN)

Table 1.
Versions of the word "functional foods" that are currently in use.

Certain foods, known as Foods for Specified Health Use (FOSHU), are qualifying for the Japanese Ministry of Health and Welfare's mark of approval. Functional foods are referred to as nutritional supplements, designer foodstuffs, crucial foods, pharma-foods, medicine types of food, medical foods in the United States and Europe. A plant-based diet can lower the incidence of chronic illnesses, according to mounting evidence from epidemiology, in vivo, in vitro, and clinical study evidence [11].

The Food and Nutrition Board (FNB) of the US National Institute Of health (NHS) defined functional foods as "every food or food component which may provide a medical benefit far beyond typical nutrients it provides" in 1995 [12].

Table 1 shows an overview of the characteristics of functional food in several organizations as shown below [13].

3. Categories of functional food

Food companies can now use four different types of cases on labeling to transmit medical messages to consumers [14]. As indicated in **Table 2**, these categories include improved commodities, modified and unmodified products, enhanced products, and fortified products [15]:

The understanding that the outcomes of this research knowledge support "assertions," which will be transformed into communications to users, is an apparent inference of investigation and progress in the field of food products. Furthermore, assertions are critical to the creation of functional foods, and there are two types of depictions that are particularly important, Type A and Type B [16].

1. **Type A** - Benefits for improved function:

An enhanced statement (type A) references the good connection between a healthy food pattern and particular physical duties without even implying a direct relationship to a reduction in illness risk. One use of antioxidants is to prevent oxidative stress [17].

2. **Type B** - Appeals for lower disease risk:

An illness risk mitigation claim (type B) refers to the possibility of illness being reduced by ingesting a single or a combination of specified dietary components or food products. The lowering of the risk of cardiovascular disease or cancer is an instance of these assertions. Although it may vary depending on the disease that functional food promised the decreased the risk, demonstrating such benefits remained a tough challenge that may need lengthy tests based on strong hypotheses backed by decent knowledge on the understanding the mechanisms of the impact to be predicted [18].

Those now deployed in clinical trials for medication creation will be required to demonstrate an impact to substantiate claims for humans. Undoubtedly, the majority of this nutrient based on the researchers' key populations are "healthy people" or "ostensibly healthy people," for whom the "usual" (ideally stable) diet will be altered in order to assert a (statically significant, but more pertinently, biologically) significant change in criteria reflective of a state of "excellent health." These paradismfood iseters/ (bio) markers were being identified and, most importantly, verified in the great majority of instances [19].

The specialty of functional food	Description	Examples
Improved commodities	food that has been supplemented with new minerals or ingredients that are not ordinarily found in that food	Prebiotics, probiotics, and plant sterol esters margarine
Modified and Unmodified products	**Modified** - Foods that have had dangerous chemicals eliminated, decreased, or replaced with a chemical that has positive benefits **Unmodified** - Foods that have extremely high levels of minerals or elements	**In modified** - In meat and ice cream, fiber acts as a lipid reliever. **In Unmodified** - Fish products (LCn-3 PUFA)
Enhanced products	Foods that have had one constituent organically boosted through unique producing circumstances, foods that have a new composition, foods that have been genetically changed, or foods that have been transformed in various ways.	Eggs with a higher omega-3 concentration as a result of a change in chicken feed
Fortified products	Food that has been supplemented with extra nutrients	vitamin C-fortified fruit juice

Table 2.
Functional foods are divided into several categories.

4. Functional foods scientific advancement

The content and morphology of a meal typically referred to as the feed solution, has been proven to influence the digestibility of minerals within that nourishment [20]. Numerous research looking into the development of flexible meals have discovered that interaction between micronutrients and non-nutrient within the food matrix can be multiplicative, complementary, or negating. Vitamin C, for instance, rejuvenates vitamin E and boosts the antioxidant effects of carotenoid molecules. In vitro studies have also shown that flavonoids, a subclass of phenolic phytochemicals, work in tandem with vitamin E to inhibit the oxidation of low-density lipoproteins. Given the different relationships between nutritional and non-nutrient components, the correlation coefficients of such components must always be completely explained to design functional meals with the greatest potential to benefit people's health synergistically [21].

5. Functional food management

Country management of functional food is important for effectiveness and safety, but it varies in each country. Japan has been a pioneer in the field of multi-functional food standards. The Ministry of Health, Labor, and Welfare of Japan, for instance, was the first regulatory agency to designate food products as a distinct food section as discussed before in the above topic [22]. The Food for Specified Health Uses (FOSHU) program, which launched in 1991, was the first one to enable health decisions for functional foods backed by scientific data. The Food for Specified Health Uses (FOSHU) seal of approval may be used on the labeling of commodities that have been acknowledged as FOSHU [23]. The volume of Food for Specified Health Uses (FOSHU) approved foods has continuously increased to around 950 as of 2011 [24].

A nutritional element	Source of competence	Health claim wording that is justified
1. Vitamin B6, vitamin B12, and folic acid	vitamin B6, vitamin B12, and nutritional support	Cholesterol, folic acid, and vitamins B6 and 12 may mitigate the chances of vascular disease when consumed in conjunction with a well-balanced, low-saturated-fat diet. Although it is well established that foods reduced in saturated fat and cholesterol lower the incidence of heart disease and other vascular disorders, the FDA considered the data supporting that statement to be unclear.
2. Omega 3 fatty acids	Supplements, fish, and other traditional meals	Consumption of EPA and DHA n-3 fatty acids may lower the incidence of Coronary Heart Disease (CHD), according to a preliminary but no definitive study.
3. Walnuts	Walnuts, in whole diced	Findings suggest that consuming 1.5 ounces of walnuts each day, as half of a reduced saturated fat, low cholesterol regimen that does not result in higher calorie consumption, may lower the risk of Coronary Heart Disease (CHD).
4. Canola oil contains unsaturated fats.	Canola oil, vegetable oil mixes, condiments, shortenings, and items incorporating canola oil	According to the unsaturated fatty acids of canola oil, modest and inconclusive scientific data shows that ingesting roughly 11 /2 tbsp. (19 g) of canola oil, every day may lower the risk of Coronary Heart Disease (CHD). To obtain this potential advantage, canola oil should be used to replace a similar quantity of saturated fat without increasing your daily calorie intake.
5. Olive oil contains mono-unsaturated fats.	Dressings for salads, vegetable oil, foods incorporating olive oil, and shortenings	According to the monounsaturated fat in olive oil, modest and inconclusive scientific data shows that ingesting roughly 2 tsp. (23 g) of olive oil, every day might lower the incidence of Coronary Heart Disease (CHD). To obtain this potential advantage, olive oil should be used to substitute an equivalent circuit of saturated fat without increasing your daily calorie intake.

Table 3.
Cardiovascular disease trained healthcare benefits in terms of dietary element, qualifying authority, region, and claim levels.

Food is governed in the United States by the Food and drug administration (FDA), Drug, and Cosmetic Act of 1938, which does not include a description of functional foods. This seems to be due to the belief that there are currently sufficient rules regarding the use of food ingredients to cover functional food elements. The main determinant of changes in the laws, as per the Food and Drug Administration (FDA), is the original function of food, and foods in their basic way are regulated. The Nutritional Labeling and Education Act of 1990 covers equally common goods and products for certain health purposes [25].

However, food companies can now make four types of claims on labeling to transmit health messages to consumers. These are some of the subgroups [26]:

1. Claims about the nutritional content

2. Assertions about the framework

3. Claims about the health

4. Trained healthcare claims

On functional labeling requirements, all four kinds of assertions are permitted if they match the established requirements for each benefit to the customers [27]. The FDA webpage has further information concerning the sorts of decisions that can be made on functional foods in the United States. After a rigorous assessment of scientific data submitted to the FDA, food is permitted to bear a health benefit, as per the Nutritional Labeling and Education Act. Extraordinary statements are allowed if there is sufficient scientific consensus or if a single expert of the US government or the National Academy of Sciences issues an acceptable declaration. Whether they may be used on food labels, health claims must always be approved by the FDA. There are now 12 health claims that achieve this important scientific requirement, as well as health claims that are backed up by authoritative statements. The FDA webpage highlights these health decisions [28].

Whenever the statistical backing for a statement has not achieved the greatest degree of scientific proof, trained healthcare claims are used to give details about the diet-disease association [29]. Dermatitis risk, cancer risk, cardiovascular disease risk, cognitive function, diabetes, and hypertension are among the six illness areas for which qualifying health claims are now permitted. **Table 3** lists the dietary components that can be used to make a trained healthcare statement for cardiovascular disease, as well as the statement's particular wording and degree of scientific proof [30].

6. Consequences

As a consequence of recent progress in science and technology, the functional food industry has risen dramatically, and the panorama of the food and nutrition area continues to evolve.

People's interest in the medical benefits of foods or food ingredients is also at some all peak and is expected to continue to increase. Registered Dietitians (RD) are particularly suited to convert research discoveries on functional foods into pragmatic dietary applications for consumers, other healthcare providers, legislators, and the press. As a result, they should proactively stay up with new studies on functional foods and their functions in human health, as well as communicate what they have learned.

Conflict of interest

The authors declare no conflict of interest.

DOI: http://dx.doi.org/10.5772/intechopen.104664

Author details

Anvi Rana
Lovely Professional University, Phagwara, Punjab, India

*Address all correspondence to: anvirana001@gmail.com

References

[1] Crowe KM, Francis C. Position of the academy of nutrition and dietetics: Functional foods. Journal of the Academy of Nutrition and Dietetics. 2013;**113**(8):1096-1103

[2] Tuorila H, Cardello AV. Consumer responses to an off-flavor in juice in the presence of specific health claims. Food Quality and Preference. 2002;**13**(7-8):561-569

[3] Siró I, Kápolna E, Kápolna B, Lugasi A. Functional food. Product development, marketing and consumer acceptance—A review. Appetite. 2008;**51**(3):456-467

[4] Roe B, Levy AS, Derby BM. The impact of health claims on consumer search and product evaluation outcomes: Results from FDA experimental data. Journal of Public Policy & Marketing. 1999;**18**(1):89-105

[5] Roberfroid MB. Global view on functional foods: European perspectives. British Journal of Nutrition. 2002;**88**(S2):S133-S138

[6] Van Trijp HC, Van der Lans IA. Consumer perceptions of nutrition and health claims. Appetite. 2007;**48**(3):305-324

[7] Schieber A. Functional foods and nutraceuticals. Food Research International. 2012;**2**(46):437

[8] Verbeke W. Consumer acceptance of functional foods: Socio-demographic, cognitive and attitudinal determinants. Food Quality and Preference. 2005;**16**(1):45-57

[9] Verbeke W. Functional foods: Consumer willingness to compromise on taste for health? Food Quality and Preference. 2006;**17**(1-2):126-131

[10] Van Kleef E, van Trijp HC, Luning P. Functional foods: Health claim-food product compatibility and the impact of health claim framing on consumer evaluation. Appetite. 2005;**44**(3):299-308

[11] Bell SJ, Goodrick GK. A functional food product for the management of weight. Critical Reviews in Food Science and Nutrition. 2002;**42**(2):163-178

[12] Baboota RK, Bishnoi M, Ambalam P, Kondepudi KK, Sarma SM, Boparai RK, et al. Functional food ingredients for the management of obesity and associated co-morbidities–a review. Journal of Functional Foods. 2013;**5**(3):997-1012

[13] Shegelman IR, Kirilina VM, Vasilev AS, Blazhevich LE, Smirnova OE. Supply chain management application in functional food industry. International Journal of Supply Chain Management. 2020;**3**(3):537

[14] Hilton J. Growth patterns and emerging opportunities in nutraceutical and functional food categories: Market overview. In: Developing New Functional Food and Nutraceutical Products. Science direct. United States: Academic Press; 2017. pp. 1-28

[15] Burdock GA, Carabin IG, Griffiths JC. The importance of GRAS to the functional food and nutraceutical industries. Toxicology. 2006;**221**(1):17-27

[16] Hilliam M. The market for functional foods. International Dairy Journal. 1998;**8**(5-6):349-353

[17] Jago D. Functional foods, market trends. In: Functional Foods Symposium.

Food Products Evolution: Innovation Drivers and Market Trends Up. Amsterdam: Springer; 2009

[18] Jones PJ, Jew S. Functional food development: Concept to reality. Trends in Food Science & Technology. 2007;**18**(7):387-390

[19] Krygier K, Florowska A. Functional foods in Poland. In: Proceedings of the Fourth International FFNet Meeting on Functional Foods. The American Journal of Clinical Nutrition; 2007

[20] Shi J, Ho CT, Shahidi F, editors. Functional Foods of the East. Journal of Food Lipids and Journal of Functional Foods. CRC press; 2010

[21] Hasler CM. The changing face of functional foods. Journal of the American College of Nutrition. 2000;**19**(suppl. 5):499S-506S

[22] Khan RS, Grigor J, Winger R, Win A. Functional food product development–opportunities and challenges for food manufacturers. Trends in Food Science & Technology. 2013;**30**(1):27-37

[23] Choudhary M, Grover K. Development of functional food products in relation to obesity. Functional Foods in Health and Disease. 2012;**2**(6):188-197

[24] Martirosyan DM, Singh J. A new definition of functional food by FFC: What makes a new definition unique? Functional foods in Health and Disease. 2015;**5**(6):209-223

[25] Goetzke BI, Spiller A. Health-improving lifestyles of organic and functional food consumers. British Food Journal. 2014;**116**(3)

[26] Goetzke B, Nitzko S, Spiller A. Consumption of organic and functional food. A matter of well-being and health? Appetite. 2014;**77**:96-105

[27] Alongi M, Anese M. Re-thinking functional food development through a holistic approach. Journal of Functional Foods. 2021;**81**:104466

[28] Monro JA. Virtual food components: Functional food effects expressed as food components. European Journal of Clinical Nutrition. 2004;**58**(2):219-230

[29] Urala N, Lahteenmaki L. Reasons behind consumers' functional food choices. Nutrition & Food Science. 2003;**33**:148-158

[30] Patel S. Functional food relevance of whey protein: A review of recent findings and scopes ahead. Journal of Functional Foods. 2015;**19**:308-319

Chapter 3

Bioactive Ingredients in Functional Foods: Current Status and Future Trends

Fatemeh Hosseini, Mohammad Reza Sanjabi, Mehran Kazemi and Nasim Ghaemian

Abstract

Bioactive ingredients (BI) bestow various health-promoting outcomes on consumers, including treating or preventing diabetes, obesity, cancer, coronary heart diseases, and so on. Several BI have been found in nature, such as flavonoids, carotenoids, polyphenols, curcumin, phytosterols, probiotics, bioactive peptide, minerals, and nano-bio minerals, which can be incorporated into foodstuffs to improve their nutritional values. The foods containing BI are considered functional food. This review shed light on the health benefits of various BI for consumers. Due to the growing rate of population and surging demands for healthy foods in the future, it is pivotal to use affordable natural sources of BI to provide functional foods for a vast majority of people. Thus, in this review article, some potent by-products are addressed as alternative sources of BI.

Keywords: bioactive ingredients, functional food, nutrients

1. Introduction

Nutrients are classified into two major groups, including essential and nonessential nutrients. Essential nutrients can be synthesized by the human body, while nonessential nutrients cannot be made in the body. The former provides normal cellular function, and the latter is not required for life yet brings about health-promoting outcomes for consumers [1]. Our body is not capable of synthesizing nonessential nutrients. Thus, it is crucial to ingest these vital constituents in the form of dietary supplements or foods. In this regard, the foods containing these beneficial substances that are considered bioactive ingredients (BI), are called functional foods. Functional foods confer a broad spectrum of physiological benefits, including the prevention of cardiovascular disorders, obesity, diabetes, cancers, stress, Parkinson's and Alzheimer's diseases, neurological diseases, and pulmonary and respiratory disorder [2].

Generally, functional foods can be available in two forms. One of the forms is those that possess indigenous BI intrinsicality (such as fruits and vegetables), and the

other forms are ones that are fortified by BI extracted from available sources (such as snacks fortified by carotenoids) [3]. As the amount of indigenous BI in various sources might not be enough to provide health benefits, the purified BI are incorporated in foods to increase their nutritional values.

Phytochemicals are plant-produced substances that represent unique features, some of which could be utilized in maintaining human health and strengthening the body's defense shield against diseases. Phytochemicals can be classified based on the chemical structure or their properties: flavonoids, carotenoids, polyphenols, curcumin, and phytosterols are the noteworthy groups [4].

WHO defines probiotics as "live microorganisms that, when administered in adequate amounts, confer a health benefit on the host". They might be available in different forms of products, from fortified foods to supplements and drugs formulated with colony-forming units per gram (CFU/g) of probiotic strains of bacteria. Prebiotics, on the other hand, are a group of carbohydrates found in food, which the human body enzymes are incapable of digesting. Probiotic bacteria and some strains of gut microflora can break down these molecules and allow the body to gain nutritional benefits. The products that contain both probiotics and prebiotics are referred to as symbiotics [5]. Various functions in the body are carried out by interactions between proteins. Peptides are counted as the builder blocks of the proteins thus they also play a crucial part in the regulation of many functions in the body. Bioactive peptides have shown advantageous qualities such as immune system booster, cardioprotection, and neuroprotection [6]. For decades, the food industry strived to enrich the food with vitamins and minerals. Fortification of margarine with vitamin A, wheat with folic acid, cereals with vitamin B1, B2, and B3, and adding iodine to salt are among the processes that were done to produce more nutritious foods in the past. In recent years, encapsulating fat-soluble vitamins has been employed in order to increase their bioavailability [7].

Bio-mineralization is attributed to the formation of mineral complexes through living organisms, like bacteria. It can happen through two paths: (a) the metal complexes are formed due to electrostatic interactions between the negatively charged functional groups like COOH groups on the surface of the bacteria and positively charged ions, (b) the other path happens inside the bacteria and the microorganism synthesizes mineral biogenic, also called bio-mineral [8].

Among a myriad of BI, which play a substantial role in human health, we seek to address some of the most prominent ones, such as phytochemicals, prebiotics, probiotics, bioactive peptides, vitamins, minerals, and nano-bio mineral. Future trends: probiotics and bioactive.

2. Components of functional foods

Many definitions have been provided for functional foods by different organizations and since it is not legally accepted in any country except Japan, they are not unified. What is identical in all of them is that functional foods are food substances that have been modified in a way so that they have health-related benefits, and may subside the risk of some diseases. They may come from various sources: plants, fruits and vegetables, animals, probiotics, prebiotics, etc. Functional food components can be classified based on the product and the ingredients they contain.

2.1 Animal-based products

Meat is a key supply of amino acids, (e.g. cysteine, methionine, glycine, etc.) [9], and vitamins such as linolic acid, taurine, and creatine. By exerting some modifications on meat products, such as reducing the content of sodium chloride and the addition of nutrients like fish oil, natural extracts, and fiber from nuts, meat products can be a precious source of functional food. Moreover, chondroitin sulfate and glucosamine are ingredients that can be extracted from bovine skin and employed in the process of making functional beverages that promote joint health.

Egg also is one of the products that is being used largely in the market and its modification can diminish the risk of ischemic heart diseases. One of the strategies used to produce functional egg is enriching them by omerga-3. For accomplishing this, there are two approaches, in the first one, linseed or flaxseed that contains large amounts of linolic acid would be added to the hen's diet, as a result of which the linolic acid would be incorporated in the egg. However, the health-promoting effects of n-3 are mainly linked to the DHA (docosahexaenoic acid) and the conversion of linolic acid to DHA does not occur sufficiently in the human body. In this case, the second way of enhancing of n-3 level plays a significant role. It carries out via fortifying hen's food with fish oil. Nonetheless, this strategy can lead to an undesirable fishy taste in the egg yolk, which is considered an undesirable characterization [10].

2.2 Dairy products

Proteins, vitamins, and minerals are the main functional components of dairy products along with hormones, cytokines, and immunoglobulins. The amino acid sequences of the peptides and proteins in the dairy-based products can promote health benefits by reducing cardiovascular diseases, e.g., hypertension, myocardial infarction, stroke, which are the leading causes of death globally. There are some products that have been modified by adding a number of functional Peptides with the sequences of VPP (valine-proline-proline) and IPP (isoleucine-proline-proline), with lowering blood pressure properties, beta-lactoglobulin, and glycomacropeptide (GMP) with the same quality along with increased protection against viral and bacterial infections [11].

2.3 Herbal products

For years ago, herbs have been used in various forms to treat several pathological conditions, some examples are polyphenols (quercetin, catechins, caffeic, and tannuic acid), which can chelate iron consequently, this can mitigate neurodegenerative diseases like Alzheimer's disease since the iron build-up is one of the causes of neuronal damage [12]. A study conducted by Chopra et al. showed that propolis can have protective effects against myocardial injuries due to its free radical scavenging effect [13]. Curcumin has shown neuroprotective properties by modifying the expression of inflammatory cytokines, reducing the oxidized protein, and increasing interleukin-1ß. Curcumin also interacts with iron and copper ions and chelates these metals and suppresses oxidative damage, inflammation, and cognitive deficits in neurons [14]. Thus, the use of herbal extracts in different food products can have disease prevention and health-promoting advantages.

2.4 Fruits and vegetables

Fruits and vegetables contain a wide range of substances, which have health-promoting effects and can reduce the risk of various diseases with their antioxidant, anti-inflammatory, and cardioprotective properties. A variety of polyphenols, in which anthocyanins, flavanols, and catechins, phenolic acids like hydroxycinnamic acids, and tannins like proanthocyanins and ellagitannins are among the more important ones due to their disease preventive effects are substances that mainly exist in berry fruit [15]. Resveratrol, which is the phytochemical present in red grapes has shown lipid-modifying and antioxidant effects [16]. Lycopene is a carotenoid that majorly is known for existing in tomatoes and it is valuable as a functional food component Because it inhibits oxidative stress, hypertension, and atherosclerosis [17].

2.5 Marine products

Marine world has incredible biodiversity which includes marine plants, microorganisms, sponges, fish, etc. Therefore, the aquatic environment offers a vast array of functional compounds including omega 3 (ω3)-polyunsaturated fatty acids (PUFA), chitosan, chitosan oligosaccharides, glucosamine, carotenoids and xanthophylls, marine enzymes, and protein hydrolysates [18].

2.6 Probiotics and prebiotics

Probiotics are live microorganisms, commonly bacteria, that consuming an adequate amount of them can benefit the host. Prebiotics are oligosaccharides that the human body's enzymes cannot digest, but are used by limited strains of bacteria, mainly microflora (intestinal bacteria), and promote their growth and again have advantages for the host's health [19]. *Lactobacillus* and *Bifidobacteria* are the common strains of probiotics that have been investigated in research and used in functional foods [15, 20].

3. Bioactive compounds from vegetables and fruits by-product

According to WHO (world health organization), a healthy diet consists of 5 servings of different fruits and vegetables or 400 g of them on a daily basis. People's diet varies in different countries, but in recent years many individuals consume more packaged food rather than fresh vegetables, which indicates the need for producing healthier food products. This can be achieved through producing bioactive compounds from vegetables and fruits by-products and adding them to conventional food [21].

Bioactive compounds are molecules that are produced in natural procedures, many of them are plant-based and can portray beneficial effects on human health. Commonly, fresh parts of fruits and vegetables are consumed, however, a huge part of phytochemicals exist in the seeds, shells, peels, bran, bagasse, and trimming, which are the by-products of the fruits and vegetables [22]. Tomato by-products (paste waste, skins, and seeds) can be used for the extraction of carotenoids, which regard as a lycopene source. Apple pomace contains phenolic compounds such as naringin and phlorizin. Phlorizin could be used in the synthesis of a new generation of antidiabetic drugs with the mechanism of inhibiting the sodium-glucose co-transporter 2.

Grapes skins and other by-products including seed, stem, skin, and pomace are also rich in polyphenols namely resveratrol. White grape seeds could be used to extract gallic acid, catechin, and epicatechin [22]. Avocado's seed and peel are rich sources of carbohydrates, they also contain, lipids, proteins, fibers, and minerals. These by-products contain terpenoids, alkaloids, saponins, and acetogenins [23].

4. Bioactive compounds from diverse plant, microbial, and marine sources

Plant-based bioactive compounds, which are called phytochemicals, are the secondary metabolites of the plant that normally are produced to protect the plant against insects and animals. In the human body, however, they can prevent and reduce the risk of some types of cancer or chronic diseases such as diabetes. Phytochemicals' favorable properties have brought researchers' interest towards them and resulted in isolating and identifying thousands of plant-based bioactive compounds. Vitamin C, folate, provitamin A, potassium, calcium, magnesium, flavonoids, phenolics acids, alkaloids, carotenoids, and fibers are among the outstanding ones that could be mentioned [24]. Here, some of the plants that are sources of phytochemicals are mentioned. The *Origanum Spp*. has different terpene derivatives and phenolic compounds. These compounds exist in the essential oil extracted from the plant and have shown antibacterial, antioxidant, and anti-inflammatory activities. The *Thymus spp*., especially the flowers are rich in terpenes, terpene alcohols, phenolic derivatives, ketones, aldehydes, ethers, and esters. Although the chemical composition highly depends on the species. *Salvia Spp.* has terpenic, flavonoid, phenolic acid, and steroid structures and therefore can be utilized to extract anti-microbial and anti-oxidant phytoconstituents [25].

There are various microbes such as bacteria, fungi, and cyanobacteria that produce bioactive compounds through their metabolic pathways [26].

Cyanobacteria are microorganisms with characteristics similar to bacteria and fungi, they have 2000 species and are a great bioresource of pigments. During screening programs in search of bioactive compounds, cyanobacterial metabolites are with potential use in fluorescent probes have been found. Cyanobacteria consist of phycobiliproteins, molecules valuable as sensing elements in biosensors for light characterization [27].

Probiotics are a vast source of beneficial bioactive materials, among them *Lactobacillus spp., Bifidobacterium spp., Clostridium spp*., and, Enterobacteriaceae are known for producing metabolites with health benefits such as amino acids, vitamins, and folates [28].

There are two major groups of marine algae: (A) Microalgae that is divided into 4 types *Chlorophyta* (green algae); *Chrysophyta* (golden-brown, yellow algae, and diatoms); *Pyrrhophyta* (dinoflagellates); *Euglenophyta.* They produce a type of toxin called dinoflagellate and could be used in studying cellular processes. (B) Macroalgae that consists of seaweeds and marine vegetables, they are a resource for hydrocolloids and phycocolloids, these two are being used as gelling substances, emulsifying agents, and wound dressing [29].

5. Recent advances in production of bioactive compounds

Fermentation by probiotic bacteria is an approach used to the preservation of food for a long time. Fermented commodity contains bioactive compounds owing

to the activity of probiotics in foodstuffs. The bioactive substances produced by probiotics in functional foods prompt beneficial outcomes for consumers [30]. In this regard, *Enterococcus sps, streptococcus sps, Bacillus sps* have the ability to synthesize amino acids, such as tryptophan and tyrosine, which are claimed to be advantageous to the function of the male and female reproductive system. Not only that, some probiotics are capable of yielding vitamin B groups. For instance, *Lactococcus lactis*, *Bifidobacterium sps.*, *Lactococcus fermentum* CECT 5716, *Lactobacillus reuteri* JCM1112 and could take part in the production of vitamin B2 (responsible for energy metabolism), B6 (responsible for amino acid metabolism), B9 (responsible for energy metabolism), and B12 (responsible for helping red blood cell formation and making DNA), respectively. For producing bioactive in protein-based foods (such as meat products, dairy products, soy milk, etc.), lactic acid bacteria are considered nontrivial. Besides, fungal fermentation of foods is employed to produce bioactive peptides in both plant and animal sources. In this regard, proteolyze activity of *Aspergillus oryzae* and *Aspergillus flavipes* in goat milk brought about the generation of peptides with antimicrobial/antioxidant nature [30]. Another conventional method used for the generation of bioactive peptides is the enzymatic hydrolysis of protein, by which one or more peptidases are added to a reactor containing deionized water and concentrated protein and controlling the temperature and pH throughout the process [31]. In addition to these conventional techniques, there are also innovative technologies, such as ultrasound-assisted and subcritical water extraction, which have been operated to produce bioactive peptides. Ultrasound-assisted extraction is a non-thermal and green technology that works based upon mechanical waves with frequencies of higher than 20 kHz, which traverses through a medium. Ultrasound waves give rise to strong forces at a microscopic scale in form of vibrations with large amplitudes in the medium, which then cause physical or chemical changes in foods [30]. This technique can be performed along with enzymatic hydrolysis in order to accelerate the process. Liang et al. [32] utilized low-frequency ultrasound with powers between 45 and 65 W/L on the enzymolysis of corn protein, which resulted in the production of short-chain peptides with a molecular weight of 200–1000 Da (11.84%) and 1000–3000 Da (21.29%) at optimal condition. In another study with a similar approach, Guerra-Almonacid et al. [33] used ultrasonic pre-treatment with a frequency of 80 kHz and an amplitude of 100% for 10 min prior to enzymatic hydrolysis of the plant protein. They reported that this procedure produced hydrolysates that possessed molecular weight ranging from 8 to 20 kDa. Subcritical water is liquid water at temperatures from 100 to 374°C under pressure less than 22 MPa (below the critical point of water). Once the dissociation constant (K_w) of subcritical water escalates as a function of temperature, subcritical water behaves as an acid or base catalyst [30]. Espinoza et al. [34] stated that the optimal condition regarding hydrolysis of whey protein isolate using subcritical water was at 300°C for 40 min, in which the free amino acids generation, especially lysin, was the highest.

6. Food technology and its impact on functional food development

Several strategies and technologies have been adopted for fortifying foodstuffs and increasing their nutritional value. Recently, vacuum impregnation as an emerging technology has captivated a lot of attention in food science and technology. This technique is an operation whereby a liquid medium containing bioactive compounds enters the solid porous food in favor of internal gas through capillary pressure [35]. In

this regard, numerous studies conducted to enhance the nutritional quality of foods via this method, such as enriching ready-to-eat sweet potatoes with polyphenols [36], enriching potato tuber with ascorbic acid [37], fortifying potato snacks with calcium, vitamin C, and E [38], and incorporating *Lactobacillus casei* into apple cylinders [39].

High-pressure processing is a widely applied technology by which 10–1000 MP is exerted on foods at mild temperatures. This technique influences non-covalent bonds, including hydrogen, ionic, hydrophobic bonds. As this approach excludes heat treatment, it is tailored for the sterilization of foods containing thermo-sensitive BI [40]. Aguayo et al. [41] evaluated bioactive stability under two processes, including the high-pressure homogenization (HPH) treatments (80 and 120 MPa) versus thermal treatment (80 °C, atmospheric pressure). They reported that the high-pressure process was a better alternative for the retention of heat-sensitive compounds such as vitamin C, vitamin A, and unsaturated fatty acids (10-hydroxy-2-decenoic acid). Not only might high-pressure processing averting loss of BI, in some cases, it could improve the nutritional value. In this regard, Saricaoglu et al. [42] claimed that high pressure homogenized rosehip nectars showed more antioxidant capacity after treatment owing to an increase in total carotenoid content.

Bioactive ingredients are usually susceptible to detrimental conditions such as low pH, and gastrointestinal conditions. Hence, encapsulation is a practical approach whereby bioactive compounds are protected from various deteriorative conditions by entrapping them in various non-toxic materials [43]. The most common materials exploited for encapsulation in food science are proteins [44], polysaccharides [45, 46], lipids [47], hydrogels [48], and metal-organic frameworks [49, 50] or a proper mixture of them for controlled release. A wide array of novel technologies has been utilized for the encapsulation of bioactive, some of the recent and intriguing ones are spray chilling [51], electrospinning [52], supercritical fluid [53], and microfluidic [54, 55]. The size of carriers is divided mainly into nano- or microcarriers [56]. The former has been used for most of the bioactive compounds [47], and the latter is suited for both bioactive and probiotics [52].

7. Future trends

Bioactive peptides (BP) are short sequences of amino acids, which in most cases are composed of 2–20 hydrophobic amino acids in the peptide chain. Nonetheless, longer sequences of BP have been reported, such as Linasin, which is a soy-derived peptide wherein 43 amino acid residues exist [30]. BP can be utilized in foodstuffs to produce functional foods due to the numerous health-promoting outcomes that they bestow on consumers [57], such as imparting antihypertension, antithrombotic, anti-cancer, antimicrobial, antioxidant, and immunomodulatory to the human body. Several natural sources of BP are exploitable, including soybean, cereals germ, potato, nuts, dairy products, egg, and meat proteins [58]. Moreover, marine microorganisms, for instance, microalgae, recently captivated increasing attention as a source of BP [59]. BP does not display biological activities unless they become activated through enzymatic, chemical, and microbial hydrolysis [58]. For the production of BP, enzymatic hydrolysis and fermentation are preferable to the chemical approaches [31]. The BP production via an enzymatic procedure possesses the advantage of complete control over the process [57]. However, in comparison to the enzymatic manner, fermentation is considered a more cost-effective strategy to obtain BP [31]. Moreover, novel technologies employed to produce BP in foods are

Category	Name	Website
Protein database	NCBI Protein	http://www.ncbi.nlm.nih.gov/protein
	BIOPEP	http://www.uwm.edu.pl/biochemia
	PepBank	http://pepbank.mgh.harvard.edu
	UniProtKB	http://www.uniprot.org
	PeptideDB	http://www.peptides.be
	RCSB	https://www.rcsb.org/pdb/home/home.do
Bioactive peptide protentional	PeptideLocator	http://bioware.ucd.ie
	BIOPEP	http://www.uwm.edu.pl/biochemia/index.php/en/biopep
	PeptideRanke	http://bioware.ucd.ie/~compass/biowareweb
	AntiBP2	http://www.imtech.res.in/raghava/antibp2
	BitterDB	https://bitterdb.agri.huji.ac.il/dbbitter.php
	EROP-Moscow	http://erop.inbi.ras.ru
	APD	https://aps.unmc.edu/prediction

Table 1.
Bioinformatic database.

subcritical water extraction, ohmic heating, pulsed electric fields, and high hydrostatic pressure [30]. Since all peptides are not regarded as BP, it is pivotal to identify the BP among various other peptides. In this regard, bioinformatics and peptidomics are promising approaches proposed to discover BP effectively.

Peptidomics is the quantitative and qualitative analysis of a vast array of peptides in biological samples throughout protein hydrolysis, in which High-performance liquid chromatography (HPLC) and mass spectrometry (MS) are performed to discover or identify peptides, even in complex matrices [60–62]. Fermented foods contain probiotics that possess proteolytic activity. These probiotics can be able to release BP enzymatically in foods containing proteins as a result of fermentation. In this regard, *Lactobacillus* bacteria is the epitome of BP production in fermented dairy products [60]. Gu et al. [63] identified a novel BP (NENLLRFF) using UPLC-MS/MS, which was produced by multi-species probiotics in yogurt. Those authors claimed that the newly found BP might have angiotensin-I converting enzyme inhibitory, antioxidative, hypotensive, and stimulating properties. Peptidomics has advantages, such as it can accelerate peptide identification and does not require complete peptide separation [64]. Nevertheless, the main restriction associated with peptidomics is the difficulty or impossibility with regard to the identification of very short peptides (<5 amino acids), large-sized polypeptides, and disulfide cross-linked hetero-oligomers [60]. Employing appropriate tools to analyze and interpret the obtained peptidomics data is crucial, and bioinformatics, as a practical approach, provides a great opportunity for *in silico* analysis of biological data via various software (such as GalaxyPepDock) and database (which some of them are represented in **Table 1**).

8. Conclusion

Bioactive ingredients (BI) play a substantial role in health, and consuming foods possessing these beneficial substances, which are called functional foods, can

therefore enhance human well-being. BI are abundant in various natural sources, including animal-based products, marine products, fruits, vegetables, and herbs. Probiotics can increase the nutritional value of these commodities via their enzymatic activity, which may lead to producing a vast array of BI in foods, such as vitamins, bioactive peptides, and folates. In addition to fermentation, there are other novel technologies that have been employed for the generation of BI in foods, like subcritical water extraction, ohmic heating, pulsed electric fields, and high hydrostatic pressure. In this regard, peptidomics and bioinformatics are two robust approaches to identify and discover the bioactive peptides formed in functional foods.

Conflict of interest

The authors declare no conflict of interest.

Author details

Fatemeh Hosseini[1*], Mohammad Reza Sanjabi[2], Mehran Kazemi[3] and Nasim Ghaemian[4]

1 Department of Biotechnology, Iranian Research Organization for Science and Technology, Tehran, Iran

2 Agriculture Research Institute, Iranian Research Organization for Science and Technology (IROST), Iran

3 Faculty of Agriculture, Department of Food Science and Technology, Ferdowsi University of Mashhad, Mashhad, Iran

4 Department of Pharmaceutics, School of Pharmacy, Shahid Beheshti University of Medical Sciences, Tehran, Iran

*Address all correspondence to: zinolife2014@gmail.com

References

[1] Watson RR, Ronald R, Preedy VR. Bioactive Foods in Promoting Health: Fruits and Vegetables. 2010. p. 737

[2] Keservani RK, Kesharwani RK, Sharma AK, Gautam SP, Verma SK. Nutraceutical formulations and challenges. In: Developing New Functional Food and Nutraceutical Products. Elsevier Inc; 2017. pp. 161-177

[3] McClements DJ. Future Foods: How Modern Science is Transforming the Way We Eat. 2019. p. 1-392

[4] Leitzmann C. Characteristics and health benefits of phytochemicals. Forschende Komplementärmedizin. 2016;**23**(2):69-74

[5] Guarner F, Khan A, Garisch J, et al. World gastroenterology organisation global guidelines: Probiotics and prebiotics. Journal of Clinical Gastroenterology. 2012;**46**(6):468-481

[6] Daliri EBM, Oh DH, Lee BH. Bioactive peptides. Food. 2017;**6**(5):1-21

[7] Betoret E, Betoret N, Vidal D, Fito P. Functional foods development: Trends and technologies. Trends in Food Science and Technology. 2011;**22**(9):498-508

[8] Bäuerlein E. Biomineralization of unicellular organisms: An unusual membrane biochemistry for the production of inorganic nano- and microstructures. Angewandte Chemie, International Edition. 2003;**42**(6):614-641

[9] Górska-Warsewicz H, Laskowski W, Kulykovets O, Kudlińska-Chylak A, Czeczotko M, Rejman K. Food products as sources of protein and amino acids—The ca se of Poland. Nutrients. 2018;**10**(12):1977

[10] Surai PF, Sparks NHC. Designer eggs: From improvement of egg composition to functional food. Trends in Food Science and Technology. 2001;**12**(1):7-16

[11] Hosseini-Zare MS, Sarhadi M, Zarei M, Thilagavathi R, Selvam C. Synergistic effects of curcumin and its analogs with other bioactive compounds: A comprehensive review. European Journal of Medical Chemistry. 2021;**210**:113072

[12] Ferrari CKB. Functional foods, herbs and nutraceuticals: Towards biochemical mechanisms of healthy aging. Biogerontology. 2004;**5**(5):275-289

[13] Chopra S, Pillai KK, Husain SZ, Girl DK. Propolis protects against doxorubicin-induced myocardiopathy in rats. Experimental and Molecular Pathology. 1995;**62**(3):190-198

[14] Aggarwal BB, Harikumar KB. Potential therapeutic effects of curcumin, the anti-inflammatory agent, against neurodegenerative, cardiovascular, pulmonary, metabolic, autoimmune and neoplastic diseases. The International Journal of Biochemistry & Cell Biology. 2009;**41**(1):40-59

[15] Kaur S, Das M. Functional foods: An overview. Food Science and Biotechnology. 2011;**20**(4):861-875

[16] Dellagli M. Vascular effects of wine polyphenols. Cardiovascular Research. 2004;**63**(4):593-602

[17] Kong K-W, Khoo H-E, Prasad KN, Ismail A, Tan C-P, Rajab NF. Revealing the power of the natural red pigment lycopene. Molecules. 2010;**15**(2):959-987

[18] Shahidi F, Ambigaipalan P. Novel functional food ingredients from marine

sources. Current Opinion in Food Science. 2015;**2**:123-129

[19] Stanton C, Ross RP, Fitzgerald GF, Van Sinderen D. Fermented functional foods based on probiotics and their biogenic metabolites. Current Opinion in Biotechnology. 2005;**16**(2):198-203

[20] Rincón-León F. Encyclopedia Food Science Nutrition. 2003;2827-2832.

[21] Ruiz Rodríguez LG, Zamora Gasga VM, Pescuma M, Van Nieuwenhove C, Mozzi F, Sánchez Burgos JA. Fruits and fruit by-products as sources of bioactive compounds. Benefits and trends of lactic acid fermentation in the development of novel fruit-based functional beverages. Food Research International. 2021;**140**:109854

[22] Bharat Helkar P, Sahoo A. Review: Food industry by-products used as a functional food ingredients. International Journal of Waste Resources. 2016;**6**(3):1-6

[23] Salazar-López NJ, Domínguez-Avila JA, Yahia EM, Belmonte-Herrera BH, Wall-Medrano A, Montalvo-González E, et al. Avocado fruit and by-products as potential sources of bioactive compounds. Food Research International. 2020;**138**:109774

[24] de Rivero-Montejo J, Vargas-Hernandez M, Torres-Pacheco I. Nanoparticles as novel elicitors to improve bioactive compounds in plants. Agriculture. 2021;**11**(2):134

[25] Fierascu RC, Fierascu I, Baroi AM, Ortan A. Selected aspects related to medicinal and aromatic plants as alternative sources of bioactive compounds. International Journal of Molecular Sciences. 2021;**22**(4):1521

[26] Iwai Y, Takahashi Y. Selection of microbial sources of bioactive compounds. 1992. p. 281-302

[27] Prasanna R, Sood A, Jaiswal P, Nayak S, Gupta V, Chaudhary V, et al. Rediscovering cyanobacteria as valuable sources of bioactive compounds (review). Applied Biochemistry and Microbiology. 2010;**46**(2):119-134

[28] Indira M, Venkateswarulu TC, Abraham Peele K, Nazneen Bobby M, Krupanidhi S. Bioactive molecules of probiotic bacteria and their mechanism of action: A review. 3 Biotech. 2019;**9**(8):1-11

[29] Kiuru P, Dauria M, Muller C, Tammela P, Vuorela H, Yli-Kauhaluoma J. Exploring marine resources for bioactive compounds. Planta Medica. 2014;**80**(14):1234-1246

[30] Ulug SK, Jahandideh F, Wu J. Novel technologies for the production of bioactive peptides. Trends in Food Science and Technology. 2021;**108**:27-39

[31] Tadesse SA, Emire SA. Production and processing of antioxidant bioactive peptides: A driving force for the functional food market. Heliyon. 2020;**6**:e04765

[32] Liang Q, Ren X, Ma H, Li S, Xu K, Oladejo AO. Effect of low-frequency ultrasonic-assisted enzymolysis on the physicochemical and antioxidant properties of corn protein hydrolysates. Journal of Food Quality. 2017;**2017**:1-10

[33] Guerra-Almonacid CM, Torruco-Uco JG, Jonh Jairo Méndez-Arteaga WM-A, Rodríguez-Miranda J. Effect of ultrasound pretreatment on the antioxidant capacity and antihypertensive activity of bioactive peptides obtained from the protein hydrolysates of *Erythrina edulis*. Emirates Journal of Food Agriculture. 2019;**288**:288-296

[34] Espinoza AD, Morawicki RO, Hager T. Hydrolysis of whey protein

isolate using subcritical water. Journal of Food Science. 2012;**77**(1):C20-C26

[35] Betoret E, Betoret N, Rocculi P, Dalla RM. Strategies to improve food functionality: Structure–property relationships on high pressures homogenization, vacuum impregnation and drying technologies. Trends in Food Science and Technology. 2015;**46**(1):1-12

[36] Abalos RA, Naef EF, Aviles MV, Gómez MB. Vacuum impregnation: A methodology for the preparation of a ready-to-eat sweet potato enriched in polyphenols. LWT. 2020;**131**:109773

[37] Hironaka K, Kikuchi M, Koaze H, Sato T, Kojima M, Yamamoto K, et al. Ascorbic acid enrichment of whole potato tuber by vacuum-impregnation. Food Chemistry. 2011;**127**(3):1114-1118

[38] Duarte-Correa Y, Granda-Restrepo D, Cortés M, Vega-Castro O. Potato snacks added with active components: Effects of the vacuum impregnation and drying processes. Journal of Food Science and Technology. 2020;**57**(4):1523-1534

[39] Betoret N, Puente L, Diaz M, Pagan M, Garcia M, Gras M, et al. Development of probiotic-enriched dried fruits by vacuum impregnation. Journal of Food Engineering. 2003;**56**(2-3):273-277

[40] Ofori JA, Peggy Y-H. Novel technologies for the production of functional foods. In: Bio-Nanotechnology. Oxford, UK: Blackwell Publishing Ltd.; 2013. pp. 141-162

[41] Aguayo E, Tarazona-Díaz MP, Martínez-Sánchez A, García-González A. Influence of moderate high-pressure homogenization on quality of bioactive compounds of functional food supplements. Journal of Food Quality. 2017;**2017**:1-11

[42] Saricaoglu FT, Atalar I, Yilmaz VA, Odabas HI, Gul O. Application of multi pass high pressure homogenization to improve stability, physical and bioactive properties of rosehip (*Rosa canina* L.) nectar. Food Chemistry. 2019;**282**:67-75

[43] Champagne CP, Fustier P. Microencapsulation for Delivery of Probiotics and Other Ingredients in Functional Dairy Products. 2nd ed. Sawston, Cambridge: Woodhead Publishing Limited; 2007. pp. 404-426

[44] Burgain J, Corgneau M, Scher J, Gaiani C. Encapsulation of probiotics in milk protein microcapsules. In: Microencapsulation and Microspheres for Food Applications. 2015. pp. 391-406

[45] Akbari-Alavijeh S, Shaddel R, Jafari SM. Encapsulation of food bioactives and nutraceuticals by various chitosan-based nanocarriers. Food Hydrology. 2020;**105**:105774

[46] Taheri A, Jafari SM. Gum-based nanocarriers for the protection and delivery of food bioactive compounds. Advanced Colloid Interface Science. 2019;**269**:277-295

[47] Katouzian I, Faridi Esfanjani A, Jafari SM, Akhavan S. Formulation and application of a new generation of lipid nano-carriers for the food bioactive ingredients. Trends in Food Science and Technology. 2017;**68**:14-25

[48] Hennink W, van Nostrum C. Novel crosslinking methods to design hydrogels. Advanced Drug Delivery Review [Internet]. 2002;**54**(1):13-36

[49] Moussa Z, Hmadeh M, Abiad MG, Dib OH, Patra D. Encapsulation of curcumin in cyclodextrin-metal organic frameworks: Dissociation of loaded CD-MOFs enhances stability of curcumin. Food Chemistry. 2016;**212**(2016):485-494

[50] Chen Y, Tai K, Ma P, Su J, Dong W, Gao Y, et al. Novel γ-cyclodextrin-metal–organic frameworks for encapsulation of curcumin with improved loading capacity, physicochemical stability and controlled release properties. Food Chemistry. 2021;**347**(17):128978

[51] de Figueiredo J, de Silva P, Souza Oliveira MF, Norcino LB, Campelo PH, Botrel DA, et al. Microencapsulation by spray chilling in the food industry: Opportunities, challenges, and innovations. Trends Food Science Technology. 2022;**120**:274-287

[52] Martín MJ, Lara-Villoslada F, Ruiz MA, Morales ME. Microencapsulation of bacteria: A review of different technologies and their impact on the probiotic effects. Innovative Food Science and Emerging Technologies. 2015;**27**:15-25

[53] Klettenhammer S, Ferrentino G, Morozova K, Scampicchio M. Novel technologies based on supercritical fluids for the encapsulation of food grade bioactive compounds. Foods. 2020;**9**:1395

[54] Fonseca LR, Santos TP, Czaikoski A, Cunha RL. Microfluidics-based production of chitosan-gellan nanocomplexes encapsulating caffeine. Food Res Int [Internet]. Jan 2022; **151**:110885

[55] Logesh D, Vallikkadan MS, Leena MM, Moses JA, Anandharamakrishnan C. Advances in microfluidic systems for the delivery of nutraceutical ingredients. Trends in Food Science and Technology. 2021;**116**:501-524

[56] McClements DJ. Delivery by Design (DbD): A standardized approach to the development of efficacious nanoparticle- and microparticle-based delivery systems. Comprehensive Reviews in Food Science and Food Safety. 2018;**17**(1):200-219

[57] Lafarga T, Sánchez-Zurano A, Villaró S, Morillas-España A, Acién G. Industrial production of spirulina as a protein source for bioactive peptide generation. Trends in Food Science and Technology. 2021;**116**(June):176-185

[58] Peighambardoust SH, Karami Z, Pateiro M, Lorenzo JM. A review on health-promoting, biological, and functional aspects of bioactive peptides in food applications. Biomolecules. 2021;**11**(5):1-21

[59] Abarca RM. Functional ingredients from algae for foods and nutraceuticals. Nuevos sistemas de comunicación e información. 2021:2013-2015

[60] Martini S, Solieri L, Tagliazucchi D. Peptidomics: New trends in food science. Current Opinion in Food Science. 2021;**39**:51-59

[61] Dallas DC, Guerrero A, Parker EA, Robinson RC, Gan J, German JB, et al. Current peptidomics: Applications, purification, identification, quantification, and functional analysis. Proteomics. 2015;**15**(5-6):1026-1038

[62] Schrader M. Origins, technological development, and applications of peptidomics. Methods in Molecular Biology. 2018:3-39

[63] Gu Y, Li X, Liu H, Li Q, Xiao R, Dudu OE, et al. The impact of multiple-species starters on the peptide profiles

of yoghurts. International Dairy Journal. 2020;**106**:104684

[64] Agyei D, Tsopmo A, Udenigwe CC. Bioinformatics and peptidomics approaches to the discovery and analysis of food-derived bioactive peptides. Analytical and Bioanalytical Chemistry. 2018;**410**:3463-3472

Chapter 4

Functional Foods and Antioxidant Effects: Emphasizing the Role of Probiotics

Arezu Heydari, Farshid Parvini and Najaf Allahyari Fard

Abstract

Probiotics are host-compatible microorganisms that can optimally alter the balance of intestinal microflora, inhibit the growth of harmful bacteria, improve digestion, and increase the body's resistance by strengthening the immune system. Studies show that probiotics have antioxidant properties. Antioxidants are compounds that reduce the risk of various cancers and diseases. These compounds, in fact, inhibit the activity of free radicals and prevent their oxidation. By inactivation of free radicals, the body cells are protected from the destructive effects of these compounds. Oxidative stress is a condition that occurs as a result of disturbing the antioxidant-prooxidant balance in the cell, which eventually leads to apoptosis and cell death. Consumption of probiotic strains with antioxidant activity can benefit human health by reducing oxidative damage. Since the use of probiotics helps hemostasis, improves immune responses, and prevents many disorders caused by oxidation in the host, in this chapter, we discuss the antioxidant effects of probiotics as functional foods.

Keywords: functional foods, antioxidant effects, probiotics

1. Introduction

Oxidative stress is a process that leads to an increase in the level of oxygen radicals within the cell, which in turn causes damage to vital macromolecules (such as lipids, proteins, and nucleic acids) in the body [1]. Reactive oxygen species (ROS) are reactive molecules that contain superoxide anion radicals, hydroxyl radicals, and hydrogen peroxide. By contrast, natural antioxidants contain enzymatic antioxidants, such as superoxide dismutase (SOD), glutathione reductase (GR), and glutathione peroxidase (GPx), as well as non-enzymatic antioxidants, such as various types of vitamins, glutathione, and carotenoids, which have been formed during the evolution of organisms to prevent damage caused by oxidative stress [2]. Synthetic antioxidant additives can be used to prevent the oxidation of cellular compounds and thus prevent damage due to oxidative stress. The use of synthetic antioxidants has been questioned due to some reported side effects. Therefore, the preparation and use of natural antioxidants instead of synthetic antioxidants have attracted much attention [3, 4]. Probiotics are non-pathogenic microorganisms so sufficient consumption of them is beneficial for gastrointestinal health [4]. They also show antioxidant properties in various ways [5–8].

2. Reactive oxygen species

In all animals and plants, maintaining a normal oxygen concentration is essential. In contrast, an imbalance in oxygen concentration will lead to consequences, such as hypoxia (low oxygen) and oxidative stress (high oxygen), which can lead to tissue damage and even cell death. Cigarettes, herbicides, nitrogen oxide, ozone, radiation, and some metals affect oxygen concentration and oxidative stress conditions [9].

ROS originates from the metabolic process of oxygen used to induce oxidative stress [10]. The sources of ROS production are divided into exogenous and endogenous. Vital molecule changes due to reaction with ROS can be associated with various chronic diseases, such as atherosclerosis, osteoarthritis, diabetes, Alzheimer's disease, degenerative neurological diseases, and cardiovascular disease (**Figure 1**) [11–16]. ROS concentration determines their role; so that in equilibrium, they can play a role as the second cellular messenger and regulator of biological processes, but an excessive increase of ROS concentration causes oxidative stress [17, 18].

In 1991, the relationship between the induction of oxidants (ionizing radiation) and the activation of transcription factors was identified [19]. ROS affects the redox-sensitive elements of some transcription factors, such as hypoxia-inducible factors (HIFs) and kinases like phosphatidylinositol 3-kinase (PI3K); thus, it is possible to regulate these factors by oxygen free radicals [1, 20]. It is not easy to use antioxidants, because the body needs a sufficient concentration of ROS for specific purposes, but antioxidants alter the redox biology and interfere with the body's normal functioning.

3. Probiotics and antioxidant properties

According to researches, in metabolic diseases (such as obesity and diabetes), there is an imbalance in the intestinal microbiota, so people's health is associated with the intestinal microbiota. As a result, by balancing the altered microbial flora by consuming some cloning probiotics, the health status of individuals can be improved [21–23]. In addition, reducing undesirable metabolites and precancerous enzymes and

Figure 1.
Reactive oxygen species (ROS) and associated diseases.

stimulating the immune system (cellular and humoral) are other beneficial effects of probiotics to improve the gastrointestinal status and prevent colorectal cancer [2].

In the pharmaceutical and food industries, lactic acid bacteria (LAB) strains are widely used probiotics [24]. One of the beneficial effects of these probiotics on the body of patients is the improvement of the condition in metabolic diseases [22, 25] and ulcerative colitis (UC) [26–28]. Also, based on research on fish, improvement of oxidative status and promotion of immunity with probiotics, such as *Lactobacillus lactis* and *Lactobacillus rhamnosus*, are observed [29, 30].

Bifidobacteria are an example of another common bacterial probiotic. The beneficial effects of these probiotics include improving women with irritable bowel syndrome [31] and strengthening the immune system against tumors [32]. The presence of characteristics in *Bacillus* species has made them one of the most widely used probiotics in the food industry. One of these characteristics is the ability to produce protease, amylase, and lipase enzymes [33].

Based on the evidence, LAB strains are resistant to various types of ROS, such as superoxide anions, peroxide radicals, and hydroxyl radicals [34, 35]. Studies in recent decades show the antioxidant potential of probiotics; for example, the probiotic *Bifidobacterium animalis 01* eliminates free radicals (such as hydroxyl and anion peroxide) *in vitro* and increases antioxidant activity in mice [6]. In addition, improving the state of oxidative stress by multivitamin probiotics in people with type 2 diabetes [36] and increasing the level of antioxidants and neutralizing the effects of ROS by *Lactobacillus rhamnosus* in athletes who expose their bodies to oxidative stress [37]. Some of the studies on the relationship between probiotics and various diseases are listed in **Table 1**.

Probiotics	Results	References
Lactobacillus plantarum PBS067, *Lactobacillus reuteri* PBS072 and *Lactobacillus rhamnosus* LRH020	Improving levels of inflammatory markers in patients with atopic dermatitis.	[38]
Lactobacillus acidophilus La-14, *Lactobacillus casei* Lc-11, *Lactococcus lactis* Ll-23, *Bifidobacterium lactis* Bl-04, and *B. bifidum* Bb-06	Reducing inflammatory biomarkers and improving the oxidative/nitrosative profile in people with rheumatoid arthritis.	[39]
Lactobacillus casei Shirota	Improving cytokine profile toward an anti-inflammatory phenotype in stable cirrhotic patients.	[40]
Lactobacillus acidophilus LA-5, *Bifidobacterium* BB-12, *Streptococcus Thermophilus* STY-31, and *Lactobacillus delbrueckii bulgaricus* LBY-27	Improving several inflammations and oxidative stress biomarkers in women with gestational diabetes mellitus.	[41]
Lactobacillus acidophilus, Lactobacillus casei and *Bifidobacterium bifidum*	Reducing inflammatory biomarkers in patients with major depressive disorder.	[42]
Lactobacillus plantarum DR7	Improving upper respiratory tract infections via enhancing immune and inflammatory parameters.	[43]
Streptococcus thermophilus	Reducing biomarkers of oxidative stress and cardiovascular disease.	[44]

Table 1.
Relationship between probiotic consumption and treatment of various diseases.

4. The mechanisms of action of probiotics in antioxidation

There are different types of probiotics, so a variety of resistance mechanisms in different probiotic strains to cope with oxidative stress can be expected (**Figure 2**).

4.1 Metal chelating ability

Some probiotics exert their antioxidant potential by preventing metal ions from oxidizing. They use chelators to trap metal ions. These chelators include bathophenanthroline disulfonic acid (BPS), desferrioxamine, and ethylene diamine tetraacetic acid (EDTA) [45].

Different strains of probiotic bacteria were studied for this antioxidant mechanism; for example, among the various strains capable of chelating iron (II) or copper (II), the strains of *Lactobacillus casei* KCTC 3260 and *Streptococcus thermophilus* 821 have a much higher ability to chelate iron (II) and copper (II) [46]. Also, the high potency of *Lactobacillus helveticus* CD6 intracellular cell-free extraction in chelating iron (II) ions can be mentioned [47].

These chelating agents are not fully understood in probiotic bacteria. However, studies have shown their role in inhibiting phosphate ester displacement enzymatic reactions, as well as the production of radicals (such as peroxyl radical and alkoxyl radical) due to the decomposition of hydroperoxide compounds [48].

4.2 Antioxidant enzymes system

Mitochondria are sources of superoxide production. Superoxide is one of the most prevalent ROS. To reduce the risk of this compound, an enzyme called superoxide dismutase (SOD), as one of the essential enzymes in antioxidant enzyme systems, is needed. This enzyme breaks down the high-risk compound superoxide and converts it into less dangerous compounds, such as hydrogen peroxide and water. Therefore, it can be said that SOD in animals and also in prokaryotes plays an important role in regulating ROS [49].

Types of SOD enzymes have been identified in mammals and bacteria, which are used against oxidative stress. Fe-SOD and Mn-SOD have been observed in bacteria [50]; for example, the Mn-SOD in *Lactobacillus fermentum* E-3 and E-18 was reported by Kalisar et al. [35]. While cytoplasmic and extracellular Zn-SOD and mitochondrial Mn-SOD have been observed in mammals [50].

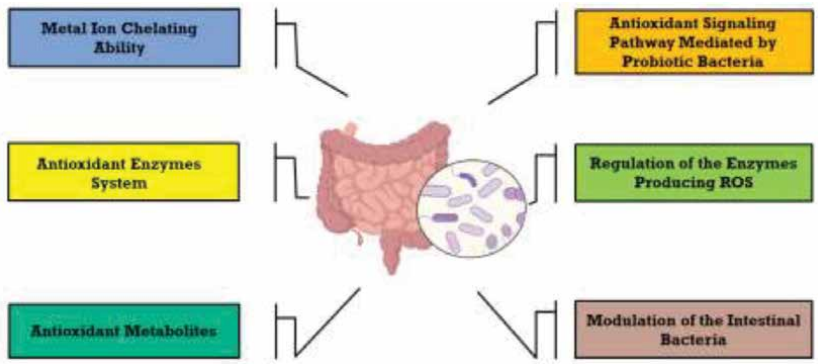

Figure 2.
The action modes of probiotic bacteria in antioxidation.

SOD enzymes need suitable transporters, that can be used in the local delivery of these enzymes [51] because despite its antioxidant activity [52–54], the limited bioavailability of SOD (due to its short half-life in the circulating) has questioned its therapeutic application. The use of probiotic bacteria for this purpose led to successful results; for example, the use of probiotic bacteria as a transporter for topical delivery of SOD was effective in counteracting the oxidative stress induced by ROS in people with intestinal diseases. Also, according to a study, engineered strains of *Lactobacillus casei* BL23 (capable of producing SOD) improved the inflammatory status and increased enzymatic activity of mice with Crohn's disease, which shows the beneficial effect of using probiotic bacteria as a carrier [51].

Another enzyme that can be found in probiotic bacteria (except LAB) is called catalase (CAT), Which acts as an antioxidant under oxidative stress. CAT is involved in a reaction known as Fenton. In this reaction, CAT inhibits the production of hydroxyl radicals by the decomposition of hydrogen peroxide, in this way, exerts its antioxidant role [55]. To determine the antioxidant effect of the enzyme CAT, studies have been performed on bacteria that contain this enzyme. CAT-producing probiotic bacteria include *Lactococcus lactis* and the engineered strains of *Lactobacillus casei* BL23 [56].

Another action of probiotics inside the host is to enhance antioxidant activity by increasing the levels and activity of several enzymes. For example, according to studies, the probiotic *Lactobacillus fermentum* increases the levels of SOD, GPx, CAT and Cu, and Zn-SOD enzymes [57], yeast probiotics increase the activity of GPx enzyme [58], and *Bacillus amyloliquefaciens* SC06 probiotic increases the expression of genes such as *CAT* and glutathione S-transferase (GST) in the studied animals [7]. In addition, people with type 2 diabetes show increased antioxidant activity by taking the probiotics *Lactobacillus acidophilus* La5 and *Bifidobacterium lactis* Bb12, which is due to increased activity of antioxidant enzymes such as SOD and GPx in red blood cells [59].

4.3 Antioxidant metabolites

Probiotics can exert their antioxidant power in other ways, **for example, they** produce various metabolites with antioxidant properties. These metabolites include glutathione (GSH), butyrate, and folate.

The properties of folate include the acceptance of mono carbon units, its use in various metabolic pathways, and its necessity in DNA synthesis and regeneration, DNA methylation, and cell division [60].

Studies showed an increase in folate levels in the body of rats and humans after treatment with *bifidobacteria* [61, 62] and an increase in the level of this metabolite and vitamin B12 in people treated with the probiotic *Lactobacillus acidophilus* La1 [63]. Evidence also showed that patients with type 2 diabetes experience oxidative stress, and in the absence of metabolites, such as folate and vitamin B12, this condition is exacerbated. Therefore, host treatment with these types of probiotics can increase the levels of these antioxidant metabolites in patients [64]. In addition, according to the study, intact cells of *Lactobacillus helveticus* CD6 producing folate and intracellular cell-free extract of this probiotic have similar antioxidant power [47]. Vitamins, such as vitamin B1, can make cells more resistant to oxidative stress. According to research, consumption of some probiotics can lead to increased absorption of this vitamin in individuals, which helps protect cells against oxidative stress [65–67].

GSH is another example of a non-enzymatic antioxidant, which is involved in the removal of radicals (such as hydrogen peroxides, hydroxyl radicals, and peroxynitrite). GSH works in conjunction with the selenium-dependent enzyme glutathione peroxidase [68]. Probiotics may contain GSH, and have antioxidant properties under oxidative stress. According to studies, *Lactobacillus fermentum* E-3, E-18, and ME-3 are among the probiotics with large amounts of GSH [35, 69].

During the fermentation of a series of indigestible substances, the microbiota makes a short-chain fatty acid (SCFA) called butyrate [70]. Butyrate has an antioxidant role under oxidative stress by inducing antioxidants. Some probiotics can produce butyrate; for example, based on evidence, MIYAIRI 588 strain of *Clostridium butyricum* with the production of butyrate has been able to improve rats with non-alcoholic fatty liver and exposed to oxidative stress [71].

4.4 Antioxidant signaling pathway mediated by probiotic bacteria

4.4.1 Nrf2-Keap1-ARE

Under oxidative stress, the expression of genes involved in the detoxification of ROS can be mediated through a pathway called Nrf2-Keap1-ARE (**Figure 3**) [72, 73]. In this pathway, the binding of Nrf2 to the antioxidant response element (ARE) sequences in the nucleus leads to the expression of factors related to the detoxification of ROS [74–76]. The activation or inhibition of Nrf2 depends on the amount of ROS. When the amount of ROS is low, the cytoplasmic inhibitor Keap1 binds to Nrf2, causing its proteasome degradation by polyubiquitination [77]; however, under oxidative stress, the functional structure of Keap1 changes due to the influence of the amino acid cysteine, which leads to the activation of Nrf2 and its entry into the nucleus and binding to the ARE sequences [74–76, 78].

Probiotics can exert their antioxidant effects by regulating the Nrf2-Keap1-ARE pathway. According to research, probiotics such as *Lactobacillus Plantarum* FC225, *Lactobacillus Plantarum* CA16, and *Lactobacillus Plantarum* SC4 can increase the level of Nrf2 in the liver cells of hypertensive mice [79, 80]. The effect of *Clostridium butyricium* MIYAIRI 588 [71] and *Bacillus amyloliquefaciens* SC06 on increasing the level and regulation of Nrf2 expression in the studied animals has been shown [7].

4.4.2 NFκB

In inflammatory conditions, the expression of inflammatory cytokines is mediated by the transcription factor NFκB. This factor is activated by ROS. It can be said that NFκB is the first transcription factor that responds to oxidative stress [19]. Evidence suggests that probiotics may inhibit NFκB by their antioxidant power, and thus play a role in preventing inflammation. Inhibition of NFκB and stimulation of heat shock proteins (Hsps) in colon epithelial cells by probiotic mixture VSL # 3 and also the effect of *Bacillus* sp. strain LBP32 in the prevention of inflammation in RAW 264.7 macrophages are examples of the antioxidant effect of probiotics by inhibiting NFκB [81, 82].

4.4.3 MAPK

Among the four subfamilies of mitogen-activated protein kinases (MAPKs), c-jun N-terminal kinase (JNKs) and p38-MAPK are key enzymes involved in response to various stresses (UV irradiation and osmotic shock), and extracellular regulated

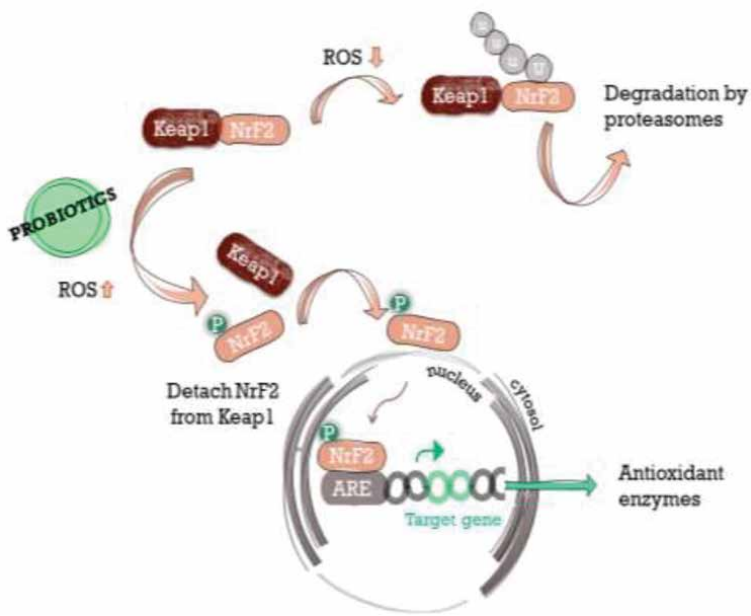

Figure 3.
Nrf2-keap1-ARE pathway mediated by probiotics.

protein kinases (ERKs) have an important role in anabolic metabolisms [83, 84]. These are the best-known mitogen-activated protein kinases [85].

Based on studies, some probiotics, such as *Lactobacillus* GG, can activate MAPK in the young adult mouse colon (YAMC) cells. Soluble agents in the conditioned media from the probiotic *Lactobacillus* GG (*Lactobacillus* GG-CM) in these cells stimulate Hsp25 and Hsp72. MAPK signaling pathways are involved in the expression and stimulation of Hsps in treated cells, so inhibition of p38 and JNK in the YAMC and then treatment with the probiotic *Lactobacillus* GG-CM stops the expression of Hsp72 [86]. In addition, the soluble proteins p40 and p75 produced by the probiotic *Lactobacillus rhamnosus* GG via the MAPK pathway can correct the dysfunction of epithelial cell barriers caused by a potent oxidant [85].

4.4.4 PKC

The control of the phosphorylation function of hydroxyl groups of serine and threonine residues in proteins is associated with Protein kinase C (PKC). PKC is also cellular messenger molecule that plays a role in various pathways, including regulation of cell growth and death and response to stresses. This molecule is very sensitive to redox modification, as well [87–89]. On the other hand, some probiotics can affect PKC activity. Corresponding to the previous report (Seth et al., 2008), inhibition of Ro-32-0432 (PKC inhibitor) by soluble proteins p40 and p75 produced by *L. rhamnosus* GG improves H2O2-induced epithelial barrier disorder [85].

4.5 Regulation of the ROS producing enzymes

Production of ROS through enzymatic reactions and various chemical processes in the host body is essential [90]; because they play an important role in defense

and messaging functions [91]. The human NADPH oxidase (NOX) complex, as the main source of reactive oxygen species [92–94], has seven homologs (NOX1–5, dual oxidase 1 (DUOX1), and DUOX2) [91]. Membrane-bound NOX2 catalytic subunits and p22phox in combination with cytosolic agents (e.g., p40phox, p47phox, p67phox, and small GTPase RAC1, called by neutrophils) cause a respiratory burst (**Figure 4**) [95, 96]. However, oxidative stress occurs if there is an imbalance in the production of ROS or a decrease in the level of oxygen-scavenging proteins, which leads to tissue damage and cell death [93].

Probiotics are able to affect the production of ROS by the NOX complex. Based on researches, the probiotic *Bacillus amyloliquefaciens* SC06 reduces the activity of NOX and expression of p47phox (H2O2-induced IPEC-1) and the probiotics *Lactobacillus fermentum* CECT5716, *Lactobacillus coryniformis* CECT5711 (K8) and *Lactobacillus gasseri* CECT5714 (LC9) reduce NOX activity and decrease the mRNA expression of NOX-1 and NOX-4 enzymes (in hypertensive rats), as a result, they reduce the production level of ROS [7, 97].

On the other hand, ROS can be produced during prostaglandin biosynthesis. For example, cyclo-oxygenase (COX) participates in process of prostaglandin biosynthesis [98]. In some diseases, such as atherosclerosis, COX-2 expression is increased [99]. Therefore, it can be said that the production of vascular prostanoids is caused by overexpression of the COX-2 enzyme [100]. Studies have shown that some probiotics can reduce the expression of COX-2 in the host; for example, the commercial probiotic Lacidofil, when used in mice infected with Helicobacter pylori [101]. Furthermore, it has been established that the expression of COX-2 is reduced by *Lactobacillus acidophilus* in Catla thymus macrophages [102].

Improper functioning of cytochrome P450 (CYP) enzymes is associated with overproduction of ROS and oxidative stress conditions [103]; because they are involved in the metabolism of xenobiotic substances [104]. Some probiotics reduce the expression of these enzymes. Matuskova et al. reported *Lactobacillus casei* is involved in reducing the expression of CYP1A1 enzyme in the intestines of male rats [105].

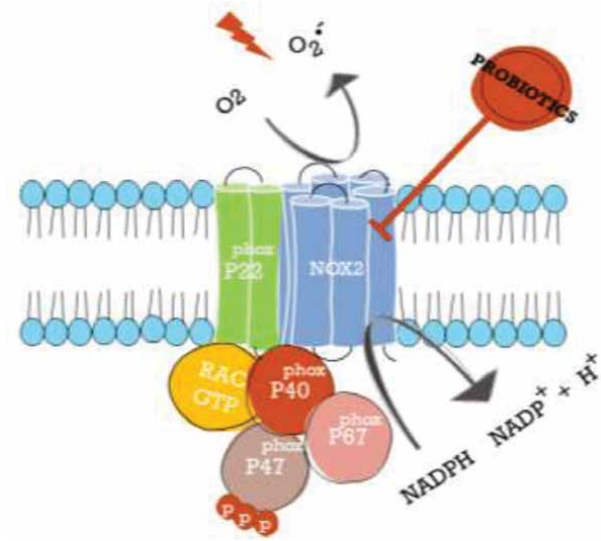

Figure 4.
NADPH oxidase (NOX) complex regulated by probiotics.

4.6 Modulation of the intestinal microbiota

Studies have shown that some probiotics can be used to treat intestinal diseases [106, 107] because they have the ability to improve the oxidative stress created by changing the composition of the microbiota. In fact, probiotics show their antioxidant properties by settling in the gastrointestinal tract [108, 109] to regulate the altered microbiota composition and prevent the proliferation of harmful bacteria. Based on researches, *Lactobacillus* and *Bifidobacterium* are among the probiotics that prevent the growth of pathogenic bacteria by lowering the pH of the intestine; as a result, a balance is established in the composition of the microbiota [110, 111]. In addition, some probiotics produce toxic compounds (such as organic acids, bactericides, and biosurfactants) against pathogenic microorganisms [112]. For example, *Lactobacillus rhamnosus* GG, suppresses different bacteria by producing antimicrobial compounds [113]. As previously mentioned, the use of probiotics leads to improving oxidative stress by modulating the composition of gut microbiota and reducing the abundance of harmful bacteria.

5. Conclusion

Probiotics are microorganisms, when consumed in appropriate doses, can be beneficial to humans in a variety of biological manners. In the last few years, probiotics with antioxidant potential that have the ability to cope with oxidative stress have received much attention. Therefore, extensive studies have shown that the use of these probiotics can improve health in patients who experience different oxidative stress conditions. Known mechanisms that probiotics use to counteract with reactive oxygen species include chelating metal ions, affecting enzymes, metabolites, antioxidant signaling pathways, and modulating intestinal microbial composition. However, more research is required on the type of probiotics and their dosage. Ultimately, probiotics can regard as the therapeutic potential for inflammatory disease.

Acknowledgements

The authors thank the National Institute of Genetic Engineering and Biotechnology (NIGEB) and Semnan University for their facilities and cooperation.

This section of your manuscript may also include funding information.

Conflict of interest

The authors declare no conflict of interest.

Author details

Arezu Heydari[1], Farshid Parvini[1] and Najaf Allahyari Fard[2*]

1 Semnan University, Semnan, Iran

2 National Institute of Genetic Engineering and Biotechnology, Tehran, Iran

*Address all correspondence to: allahyar@nigeb.ac.ir

IntechOpen

References

[1] Schieber M, Chandel NS. ROS function in redox signaling and oxidative stress. Current Biology. 2014;**24**(10): R453-R462

[2] Mishra V, Shah C, Mokashe N, Chavan R, Yadav H, Prajapati J. Probiotics as potential antioxidants: A systematic review. Journal of Agricultural and Food Chemistry. 2015;**63**(14):3615-3626

[3] Luo D, Fang B. Structural identification of ginseng polysaccharides and testing of their antioxidant activities. Carbohydrate Polymers. 2008;**72**(3):376-381

[4] Williams NT. Probiotics. American Journal of Health Pharmacy. 2010;**67**(6): 449-458

[5] Lin MY, Yen CL. Antioxidative ability of lactic acid bacteria. Journal of Agricultural and Food Chemistry. 1999;**47**(4):1460-1466

[6] Shen Q, Shang N, Li P. In vitro and in vivo antioxidant activity of bifidobacterium animalis 01 isolated from centenarians. Current Microbiology. 2011;**62**(4):1097-1103

[7] Wang Y, Wu Y, Wang Y, Fu A, Gong L, Li W, et al. Bacillus amyloliquefaciens SC06 alleviates the oxidative stress of IPEC-1 via modulating Nrf2/Keap1 signaling pathway and decreasing ROS production. Applied Microbiology and Biotechnology. 2017;**101**(7):3015-3026

[8] Persichetti E, De Michele A, Codini M, Traina G. Antioxidative capacity of Lactobacillus fermentum LF31 evaluated invitro by oxygen radical absorbance capacity assay. Nutrition. 2014;**30**(7-8):936-938

[9] Halliwell B, Cross CE. Oxygen-derived species: Their relation to human disease and environmental stress. Environmental Health Perspectives. 1994;**102**(Suppl. 10):5-12

[10] Cross CE, Halliwell B, Borish ET, Pryor WA, Ames BN, Saul RL, et al. Oxygen radicals and human disease. Annals of International Medicine. 1987;**107**(4):526-545

[11] Ames BN, Shigenaga MK, Hagen TM. Oxidants, antioxidants, and the degenerative diseases of aging. Proceedings of the National Academy of Sciences of the United States of America. 1993;**90**(17):7915-7922

[12] Eftekharzadeh B, Maghsoudi N, Khodagholi F. Stabilization of transcription factor Nrf2 by tBHQ prevents oxidative stress-induced amyloid β formation in NT2N neurons. Biochimie. 2010;**92**(3):245-253

[13] Harrison D, Griendling KK, Landmesser U, Hornig B, Drexler H. Role of oxidative stress in atherosclerosis. The American Journal of Cardiology. 2003;**91**(3):7-11

[14] Ostrakhovitch EA, Afanas'ev IB. Oxidative stress in rheumatoid arthritis leukocytes: Suppression by rutin and other antioxidants and chelators. Biochemical Pharmacology. 2001;**62**(6):743-746

[15] Griendling KK, FitzGerald GA. Oxidative stress and cardiovascular injury Part I: Basic mechanisms and in vivo monitoring of ROS. Circulation. 2003;**108**(16):1912-1916

[16] Ceriello A, Motz E. Is oxidative stress the pathogenic mechanism underlying

insulin resistance, diabetes, and cardiovascular disease? The common soil hypothesis revisited. Arteriosclerosis, Thrombosis, and Vascular Biology. 2004;**24**(5):816-823

[17] Morrell CN. Reactive oxygen species: Finding the right balance. Circulation Research. 2008;**103**(6):571-572

[18] Finkel T. Signal transduction by reactive oxygen species. The Journal of Cell Biology. 2011;**194**(1):7-15

[19] Schreck R, Rieber P, Baeuerle PA. Reactive oxygen intermediates as apparently widely used messengers in the activation of the NF-kappa B transcription factor and HIV-1. The EMBO Journal. 1991;**10**(8):2247-2258

[20] Hensley K, Robinson KA, Gabbita SP, Salsman S, Floyd RA. Reactive oxygen species, cell signaling, and cell injury. Free Radical Biology & Medicine. 2000;**28**(10):1456-1462

[21] Wang J, Tang H, Zhang C, Zhao Y, Derrien M, Rocher E, et al. Modulation of gut microbiota during probiotic-mediated attenuation of metabolic syndrome in high fat diet-fed mice. ISME Journal. 2015;**9**(1):1-15

[22] Homayouni-Rad A, Soroush AR, Khalili L, Norouzi-Panahi L, Kasaie Z, Ejtahed HS. Diabetes management by probiotics: current knowledge and future pespective. International Journal Vitamin Nutrition Research. 2017;**1**(1):1-3

[23] Gomes AC, Bueno AA, De Souza RGMH, Mota JF. Gut microbiota, probiotics and diabetes. Nutrition Journal. 2014;**13**(1):1-13

[24] Holzapfel WH, Schillinger U. Introduction to pre- and probiotics. Food Research International. 2002;**35**(2-3):109-116

[25] Huang HY, Korivi M, Tsai CH, Yang JH, Tsai YC. Supplementation of lactobacillus plantarum K68 and fruit-vegetable ferment along with high fat-fructose diet attenuates metabolic syndrome in rats with insulin resistance. Evidence-based Complementary and Alternative Medicine. 2013;**2013**

[26] Zocco MA, Dal Verme LZ, Cremonini F, Piscaglia AC, Nista EC, Candelli M, et al. Efficacy of *Lactobacillus* GG in maintaining remission of ulcerative colitis. Alimentary Pharmacology & Therapeutics. 2006;**23**(11):1567-1574

[27] Saez-Lara MJ, Gomez-Llorente C, Plaza-Diaz J, Gil A. The role of probiotic lactic acid bacteria and bifidobacteria in the prevention and treatment of inflammatory bowel disease and other related diseases: A systematic review of randomized human clinical trials. BioMed Research International. 2015;**22**

[28] Liu YW, Su YW, Ong WK, Cheng TH, Tsai YC. Oral administration of Lactobacillus plantarum K68 ameliorates DSS-induced ulcerative colitis in BALB/c mice via the anti-inflammatory and immunomodulatory activities. International Immunopharmacology. 2011;**11**(12):2159-2166

[29] Dawood MAO, Koshio S, Ishikawa M, Yokoyama S, El Basuini MF, Hossain MS, et al. Effects of dietary supplementation of Lactobacillus rhamnosus or/and *Lactococcus lactis* on the growth, gut microbiota and immune responses of red sea bream, Pagrus major. Fish Shellfish Immunology. 2016;**49**:275-285

[30] Dawood MAO, Koshio S, Ishikawa M, El-Sabagh M, Esteban MA, Zaineldin AI. Probiotics as an environment-friendly approach to enhance red sea bream, Pagrus major growth, immune response

and oxidative status. Fish & Shellfish Immunology. 2016;**57**:170-178

[31] Whorwell PJ, Altringer L, Morel J, Bond Y, Charbonneau D, O'Mahony L, et al. Efficacy of an encapsulated probiotic Bifidobacterium infantis 35624 in women with irritable bowel syndrome. The American Journal of Gastroenterology. 2006;**101**(7):1581-1590

[32] Sivan A, Corrales L, Hubert N, Williams JB, Aquino-Michaels K, Earley ZM, et al. Commensal Bifidobacterium promotes antitumor immunity and facilitates anti-PD-L1 efficacy. Science (80-). 2015;**350**(6264):1084-1089

[33] Lei K, Li YL, Yu DY, Rajput IR, Li WF. Influence of dietary inclusion of Bacillus licheniformis on laying performance, egg quality, antioxidant enzyme activities, and intestinal barrier function of laying hens. Poultry Science. 2013;**92**(9):2389-2395

[34] Stecchini ML, Del Torre M, Munari M. Determination of peroxy radical-scavenging of lactic acid bacteria. International Journal of Food Microbiology. 2001;**64**(1-2):183-188

[35] Kullisaar T, Zilmer M, Mikelsaar M, Vihalemm T, Annuk H, Kairane C, et al. Two antioxidative lactobacilli strains as promising probiotics. International Journal of Food Microbiology. 2002;**72**(3):215-224

[36] Asemi Z, Zare Z, Shakeri H, Sabihi SS, Esmaillzadeh A. Effect of multispecies probiotic supplements on metabolic profiles, hs-CRP, and oxidative stress in patients with Type 2 Diabetes. Annals of Nutrition & Metabolism. 2013;**63**(1-2):1-9

[37] Martarelli D, Verdenelli MC, Scuri S, Cocchioni M, Silvi S, Cecchini C, et al. Effect of a probiotic intake on oxidant and antioxidant parameters in plasma of athletes during intense exercise training. Current Microbiology. 2011;**62**(6):1689-1696

[38] Michelotti A, Cestone E, De Ponti I, Giardina S, Pisati M, Spartà E, et al. Efficacy of a probiotic supplement in patients with atopic dermatitis: A randomized, double-blind, placebo-controlled clinical trial. European Journal of Dermatology. 2021;**31**(2):225-232

[39] Cannarella LAT, Mari NL, Alcântara CC, Iryioda TMV, Costa NT, Oliveira SR, et al. Mixture of probiotics reduces inflammatory biomarkers and improves the oxidative/nitrosative profile in people with rheumatoid arthritis. Nutrition. 2021;**1**:89

[40] Macnaughtan J, Figorilli F, García-López E, Lu H, Jones H, Sawhney R, et al. A double-blind, Randomized Placebo-controlled trial of probiotic lactobacillus casei shirota in stable cirrhotic patients. Nutrients. 2020;**12**:6

[41] Hajifaraji M, Jahanjou F, Abbasalizadeh F, Aghamohammad zadeh N, Abbasi MM, Dolatkhah N. Effect of probiotic supplements in women with gestational diabetes mellitus on inflammation and oxidative stress biomarkers: A randomized clinical trial. Asia Pacific Journal of Clinical Nutrition. 2018;**27**(3):581-591

[42] Akkasheh G, Kashani-Poor Z, Tajabadi-Ebrahimi M, Jafari P, Akbari H, Taghizadeh M, et al. Clinical and metabolic response to probiotic administration in patients with major depressive disorder: A randomized, double-blind, placebo-controlled trial. Nutrition. 2016;**32**(3):315-320

[43] Chong HX, Yusoff NAA, Hor YY, Lew LC, Jaafar MH, Choi SB, et al. Lactobacillus plantarum DR7 improved upper respiratory tract infections via enhancing immune and inflammatory parameters: A randomized, double-blind, placebo-controlled study. Journal of Dairy Science. 2019;**102**(6):4783-4797

[44] Ito M, Kusuhara S, Yokoi W, Sato T, Ishiki H, Miida S, et al. Streptococcus thermophilus fermented milk reduces serum MDA-LDL and blood pressure in healthy and mildly hypercholesterolaemic adults. Beneficial Microbes. 2017;**8**(2):171-178

[45] Gutteridge JMC, Richmond R, Halliwell B. Inhibition of the iron-catalysed formation of hydroxyl radicals from superoxide and of lipid peroxidation by desferrioxamine. The Biochemical Journal. 1979;**184**(2): 469-472

[46] Lee J, Hwang KT, Chung MY, Cho DH, Park CS. Resistance of Lactobacillus casei KCTC 3260 to Reactive Oxygen Species (ROS): Role for a Metal Ion Chelating Effect. Journal of Food Science. 2005;**70**(8):m388-m391

[47] Ahire JJ, Mokashe NU, Patil HJ, Chaudhari BL. Antioxidative potential of folate producing probiotic Lactobacillus helveticus CD6. Journal of Food Science and Technology. 2011;**50**(1):26-34

[48] Halliwell B, Murcia MA, Chirico S, Aruoma OI. Free radicals and antioxidants in food and in vivo: What they do and how they work. Critical Reviews in Food Science & Nutrition. 1 Jan 1995;**35**(1-2):7-20

[49] Landis GN, Tower J. Superoxide dismutase evolution and life span regulation. Mechanisms of Ageing and Development. 2005;**126**(3):365-379

[50] Davies K. Oxidative stress, antioxidant defenses, and damage removal, repair, and replacement systems. IUBMB Life. 2000;**50**(4-5):279-289

[51] LeBlanc JG, del Carmen S, Miyoshi A, Azevedo V, Sesma F, Langella P, et al. Use of superoxide dismutase and catalase producing lactic acid bacteria in TNBS induced Crohn's disease in mice. Journal of Biotechnology. 2011;**151**(3):287-293

[52] Koc M, Taysi S, Buyukokuroglu ME, Bakan N. Melatonin protects rat liver against irradiation-induced oxidative injury. Journal of Radiation Research. 2003;**44**(3):211-215

[53] Seguí J, Gironella M, Sans M, Granell S, Gil F, Gimeno M, et al. Superoxide dismutase ameliorates TNBS-induced colitis by reducing oxidative stress, adhesion molecule expression, and leukocyte recruitment into the inflamed intestine. Journal of Leukocyte Biology. 2004;**76**(3):537-544

[54] Mollà M, Gironella M, Salas A, Closa D, Biete A, Gimeno M, et al. Protective effect of superoxide dismutase in radiation-induced intestinal inflammation. International Journal of Radiation Oncology, Biology, Physics. 2005;**61**(4):1159-1166

[55] Ho YS, Xiong Y, Ma W, Spector A, Ho DS. Mice lacking catalase develop normally but show differential sensitivity to oxidant tissue injury *. The Journal of Biological Chemistry. 2004;**279**(31):32804-32812

[56] De Moreno De LeBlanc A, LeBlanc JG, Perdigón G, Miyoshi A, Langella P, Azevedo V, et al. Oral administration of a catalase-producing Lactococcus lactis can prevent a chemically induced colon cancer in

mice. Journal of Medical Microbiology. 2008;**57**(1):100-105

[57] Wang AN, Yi XW, Yu HF, Dong B, Qiao SY. Free radical scavenging activity of Lactobacillus fermentum in vitro and its antioxidative effect on growing–finishing pigs. Journal of Applied Microbiology. 2009;**107**(4):1140-1148

[58] Aluwong T, Kawu M, Raji M, Dzenda T, Govwang F, Sinkalu V, et al. Effect of yeast probiotic on growth, antioxidant enzyme activities and malondialdehyde concentration of broiler chickens. Antioxidants. 2013;**2**(4):326-339

[59] Ejtahed HS, Mohtadi-Nia J, Homayouni-Rad A, Niafar M, Asghari-Jafarabadi M, Mofid V. Probiotic yogurt improves antioxidant status in type 2 diabetic patients. Nutrition. 2012;**28**(5):539-543

[60] Pompei A, Cordisco L, Amaretti A, Zanoni S, Matteuzzi D, Rossi M. Folate production by bifidobacteria as a potential probiotic property. Applied and Environmental Microbiology. 2007;**73**(1):179-185

[61] Pompei A, Cordisco L, Amaretti A, Zanoni S, Raimondi S, Matteuzzi D, et al. Administration of folate-producing bifidobacteria enhances folate status in Wistar rats. The Journal of Nutrition. 2007;**137**(12):2742-2746

[62] Strozzi GP, Mogna L. Quantification of folic acid in human feces after administration of Bifidobacterium probiotic strains. Journal of Clinical Gastroenterology. 2008;**42**(Suppl. 3):2

[63] Mohammad MA, Molloy A, Scott J, Hussein L. Plasma cobalamin and folate and their metabolic markers methylmalonic acid and total homocysteine among Egyptian children before and after nutritional supplementation with the probiotic bacteria *Lactobacillus acidophilus* in yoghurt matrix. International Journal of Food Sciences and Nutrition. 1 Jan 2006;**57**(7-8):470-480

[64] Al-Maskari MY, Waly MI, Ali A, Al-Shuaibi YS, Ouhtit A. Folate and vitamin B12 deficiency and hyperhomocysteinemia promote oxidative stress in adult type 2 diabetes. Nutrition. 2012;**28**(7-8):e23-e26

[65] Nandi D, Patra RC, Swarup D. Effect of cysteine, methionine, ascorbic acid and thiamine on arsenic-induced oxidative stress and biochemical alterations in rats. Toxicology. 2005;**211**(1-2):26-35

[66] Mehta R, Dedina L, O'Brien PJ. Rescuing hepatocytes from iron-catalyzed oxidative stress using vitamins B1 and B6. Toxicology in Vitro. 2011;**25**(5):1114-1122

[67] Fabian E, Majchrzak D, Dieminger B, Meyer E, Elmadfa I. Influence of probiotic and conventional yoghurt on the status of vitamins B1, B2 and B6 in young healthy women. Annals of Nutrition & Metabolism. 2008;**52**(1):29-36

[68] Zilmer M, Soomets U, Rehema A, Langel Ü. The glutathione system as an attractive therapeutic target. Drug Design Review Online. 2005;**2**(2):121-127

[69] Kullisaar T, Songisepp E, Aunapuu M, Kilk K, Arend A, Mikelsaar M, et al. Complete glutathione system in probiotic Lactobacillus fermentum ME-3. Applied Biochemical Microbiology. 2010;**46**(5):481-486

[70] Kau AL, Ahern PP, Griffin NW, Goodman AL, Gordon JI. Human nutrition, the gut microbiome and the immune system. Nature. 2011;**474**(7351):327-336

[71] Endo H, Niioka M, Kobayashi N, Tanaka M, Watanabe T. Butyrate-producing probiotics reduce nonalcoholic fatty liver disease progression in rats: New insight into the probiotics for the gut-liver axis. PLoS One. 2013;**8**(5):e63388

[72] Kobayashi M, Li L, Iwamoto N, Nakajima-Takagi Y, Kaneko H, Nakayama Y, et al. The antioxidant defense system Keap1-Nrf2 comprises a multiple sensing mechanism for responding to a wide range of chemical compounds. Molecular and Cellular Biology. 2009;**29**(2):493-502

[73] Jones RM, Desai C, Darby TM, Luo L, Wolfarth AA, Scharer CD, et al. Lactobacilli modulate epithelial cytoprotection through the Nrf2 pathway. Cell Reports. 2015;**12**(8):1217-1225

[74] Zhang DD. Mechanistic studies of the Nrf2-Keap1 signaling pathway. Drug Metabolism Reviews. 1 Jan 2006;**38**(4):769-789

[75] Klaassen CD, Reisman SA. Nrf2 the rescue: Effects of the antioxidative/electrophilic response on the liver. Toxicology and Applied Pharmacology. 2010;**244**(1):57-65

[76] Maher J, Yamamoto M. The rise of antioxidant signaling—The evolution and hormetic actions of Nrf2. Toxicology and Applied Pharmacology. 2010;**244**(1):4-15

[77] Zhang DD, Lo S-C, Cross JV, Templeton DJ, Hannink M. Keap1 is a redox-regulated substrate adaptor protein for a Cul3-dependent ubiquitin ligase complex. Molecular and Cellular Biology. 2004;**24**(24):10941-10953

[78] Motohashi H, Yamamoto M. Nrf2–Keap1 defines a physiologically important stress response mechanism. Trends in Molecular Medicine. 2004;**10**(11):549-557

[79] Wang LX, Liu K, Gao DW, Hao JK. Protective effects of two Lactobacillus plantarum strains in hyperlipidemic mice. World Journal of Gastroenterology. 2013;**19**(20):3150-3156

[80] Gao D, Gao Z, Zhu G. Antioxidant effects of Lactobacillus plantarum via activation of transcription factor Nrf2. Food & Function. 2013;**4**(6):982-989

[81] Diao Y, Xin Y, Zhou Y, Li N, Pan X, Qi S, et al. Extracellular polysaccharide from Bacillus sp. strain LBP32 prevents LPS-induced inflammation in RAW 264.7 macrophages by inhibiting NF-κB and MAPKs activation and ROS production. International Immunopharmacology. 2014;**18**(1):12-19

[82] Petrof EO, Kojima K, Ropeleski MJ, Musch MW, Tao Y, De Simone C, et al. Probiotics inhibit nuclear factor-κB and induce heat shock proteins in colonic epithelial cells through proteasome inhibition. Gastroenterology. 2004; **127**(5):1474-1487

[83] Widmann C, Gibson S, Jarpe MB, Johnson GL. Mitogen-activated protein kinase: Conservation of a three-kinase module from yeast to human. Physiological Reviews. 1999;**79**(1):143-180

[84] Kyriakis JM, Avruch J. Mammalian mitogen-activated protein kinase signal transduction pathways activated by stress and inflammation. Physiological Reviews. 2001;**81**(2):807-869

[85] Seth A, Yan F, Polk DB, Rao RK. Probiotics ameliorate the hydrogen peroxide-induced epithelial barrier disruption by a PKC-and MAP kinase-dependent mechanism. American Journal of Physiology-Gastrointestinal and Liver Physiology. Apr 2008;**294**(4):G1060-9

[86] Tao Y, Drabik KA, Waypa TS, Musch MW, Alverdy JC, Schneewind O, et al. Soluble factors from Lactobacillus GG activate MAPKs and induce cytoprotective heat shock proteins in intestinal epithelial cells. American Journal of Physiology-Cell Physiology. Apr 2006;**290**(4):C1018-30

[87] Blumberg PM. Complexities of the protein kinase C pathway. Molecular Carcinogenesis. 1991;**4**(5):339-344

[88] Stabel S, Parker PJ. Protein kinase C. Pharmacology & Therapeutics. 1991;**51**(1):71-95

[89] Gopalakrishna R, Chen ZH, Gundimeda U. Modifications of cysteine-rich regions in protein kinase C induced by oxidant tumor promoters and enzyme-specific inhibitors. Methods in Enzymology. 1995;**252**(C):132-146

[90] Lin CC, Hsieh HL, Shih RH, Chi PL, Cheng SE, Chen JC, et al. NADPH oxidase 2-derived reactive oxygen species signal contributes to bradykinin-induced matrix metalloproteinase-9 expression and cell migration in brain astrocytes. Cell Communication and Signaling. Dec 2012;**10**(1):1-5

[91] Aguirre J, Lambeth JD. Nox enzymes from fungus to fly to fish and what they tell us about Nox function in mammals. Free Radical Biology & Medicine. 2010;**49**(9):1342-1353

[92] Rahman I, Biswas SK, Kode A. Oxidant and antioxidant balance in the airways and airway diseases. European Journal of Pharmacology. 2006;**533**(1-3):222-239

[93] Lin CC, Yang CC, Wang CY, Tseng HC, Pan CS, Hsiao LD, et al. NADPH oxidase/ROS-dependent VCAM-1 induction on TNF-α-challenged human cardiac fibroblasts enhances monocyte adhesion. Frontier in Pharmacology. 28 Jan 2016;**6**:310

[94] Lee IT, Yang CM. Inflammatory signalings involved in airway and pulmonary diseases. Mediators of Inflammation. 2013;**2013**

[95] Holmström KM, Finkel T. Cellular mechanisms and physiological consequences of redox-dependent signalling. Nature Reviews. Molecular Cell Biology. 2014;**15**(6):411-421

[96] Bedard K, Krause KH. The NOX family of ROS-generating NADPH oxidases: Physiology and pathophysiology. Physiological Reviews. 2007;**87**(1):245-313

[97] Gómez-Guzmán M, Toral M, Romero M, Jiménez R, Galindo P, Sánchez M, et al. Antihypertensive effects of probiotics Lactobacillus strains in spontaneously hypertensive rats. Molecular Nutrition & Food Research. 2015;**59**(11):2326-2336

[98] Hussain T, Gupta S, Mukhtar H. Cyclooxygenase-2 and prostate carcinogenesis. Cancer Letters. 2003;**191**(2):125-135

[99] Schonbeck U, Sukhova GK, Graber P, Coulter S, Libby P. Augmented expression of cyclooxygenase-2 in human atherosclerotic lesions. The American Journal of Pathology. 1999;**155**(4):1281-1291

[100] Belton O, Byrne D, Kearney D, Leahy A, Fitzgerald DJ. Cyclooxygenase-1 and -2-dependent prostacyclin formation in patients with atherosclerosis. Circulation. 2000;**102**(8):840-845

[101] Brzozowski T, Konturek PC, Mierzwa M, Drozdowicz D, Bielanski W, Kwiecien S, et al. Effect of probiotics and triple eradication therapy on the

cyclooxygenase (COX)-2 expression, apoptosis, and functional gastric mucosal impairment in Helicobacter pylori-infected Mongolian gerbils. Helicobacter. 2006;**11**(1):10-20

[102] Patel B, Kumar P, Banerjee R, Basu M, Pal A, Samanta M, et al. Lactobacillus acidophilus attenuates Aeromonas hydrophila induced cytotoxicity in catla thymus macrophages by modulating oxidative stress and inflammation. Molecular Immunology. 2016;**75**:69-83

[103] Zangar RC, Davydov DR, Verma S. Mechanisms that regulate production of reactive oxygen species by cytochrome P450. Toxicology and Applied Pharmacology. 2004;**199**(3):316-331

[104] Bondy SC, Naderi S. Contribution of hepatic cytochrome P450 systems to the generation of reactive oxygen species. Biochemical Pharmacology. 1994;**48**(1):155-159

[105] Matušková Z, Šiller M, Tunková A, Anzenbacherová E, Zachařová A, Hogenová HT, et al. Effects of Lactobacillus casei on the expression and the activity of cytochromes P450 and on the CYP mRNA level in the intestine and the liver of male rats. Neuroendocrinology Letters. 2011;**32**(1):22167211

[106] O'Toole PW, Cooney JC. Probiotic bacteria influence the composition and function of the intestinal microbiota. Interdisciplinary Perspectives on Infectious Diseases. 2008;**2008**:1-9

[107] Butel MJ. Probiotics, gut microbiota and health. Médecine et Maladies Infectieuses. 2014;**44**(1):1-8

[108] Bhardwaj A, Kaur G, Gupta H, Vij S, Malik RK. Interspecies diversity, safety and probiotic potential of bacteriocinogenic Enterococcus faecium isolated from dairy food and human faeces. World Journal of Microbiology and Biotechnology. 2010;**27**(3):591-602

[109] Bhardwaj A, Malik RK, Chauhan P. Functional and safety aspects of enterococci in dairy foods. Indian Journal of Microbiology. 2008;**48**(3):317-325

[110] Doron S, Gorbach SL. Probiotics: Their role in the treatment and prevention of disease. Expert Review of Anti-Infective Therapy. 2006;**4**(2):261-275

[111] Alvarez-Olmos MI, Oberhelman RA. Probiotic agents and infectious diseases: A modern perspective on a traditional therapy. Clinical Infectious Diseases. 2001;**32**(11):1567-1576

[112] Vanderhoof JA, Young RJ. Current and potential uses of probiotics. Annals of Allergy, Asthma & Immunology. 2004;**93**(5):S33-S37

[113] Silva M, Jacobus NV, Deneke C, Gorbach SL. Antimicrobial substance from a human Lactobacillus strain. Antimicrobial Agents and Chemotherapy. 1987;**31**(8):1231

Chapter 5

Is There Still Room to Improve Medicinal Herbs (Functional Herbs) by Gene Editing for Health?

Nilay Seyidoglu and Cenk Aydin

Abstract

Herbs have a wide variety of chemical compounds that can support food quality, medicines, and biotechnology approaches. Over the years, extensive research has been carried out in genetic engineering of foods, including improving the feasibility of herbs. The story behind the herbal genetic technology relates to food allergy, the pharmaceutical industry, and of course, the growing food shortage that is the biggest nutritional issue of this century. Researchers have highlighted that in genome editing, creating synthetic biology is a good strategy. Furthermore, the production of secondary metabolites in herbs may be enhanced through genetic methods. The researchers investigated the plants' secondary metabolic pathways as well as their genetic alterations. Yet there are some herbal remedies used in genetic engineering. This chapter begins with a discussion of our studies of functional foods and their effects on human and animal health. Next, we will highlight the importance of genome editing in herbs and methodologies. Additionally, the differences between natural functional foods and genome editing herbs will try to prove efficacy on humans and animals. Consequently, we will attempt to reveal if genomic foods have protective effects on health and particularly on pandemic diseases.

Keywords: gene editing, herbal remedies, health, pandemic diseases, food shortage

1. Introduction

Genetic engineering, which is a branch of biotechnology, is the most important innovation in the present century. Since the 1990s, this technology has provided genetic and biological research to several novelties for human, animal, plant, health, agriculture, and nutrition (**Figure 1**). However, researchers are still interested in exciting new approaches to improving the technology.

Global population is expected to grow by 10 billion in the coming decades, along with climate change and drought. In addition to the shortage of crops, vegetables, and fruits, it is inevitable to increase inadequate nutrition and malnutrition. Following this problem, biotechnology approaches based on genome modification have been highlighted. In particular, editing the plant genome may be the most significant innovation for this purpose.

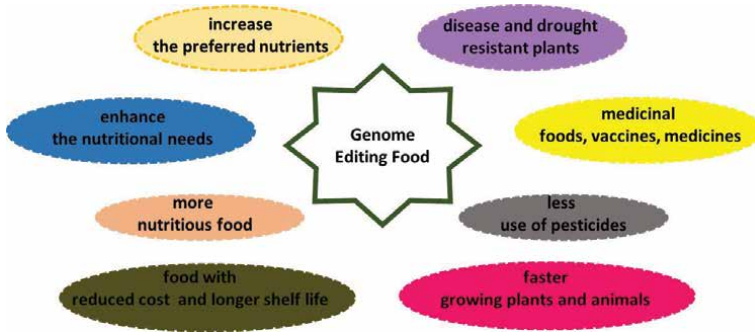

Figure 1.
The possible benefits of genomic editing technologies.

New genome editing technologies make it possible for researchers to know exactly and quickly the desired characteristics of the plant. These technologies could be a model of effectiveness that could change and enhance genes in crop production. In order to achieve this goal, several tasks are required between many disciplines, including plant breeders, molecular biologists, nutritionists, and even social scientists. Most authorities focus on global food security as well as malnutrition. In this chapter, we will attempt to present the importance of genome modification in herbs, methodologies, and correlation with health.

2. Is an herb a savior as a medicine for health?

Being part of the new global strategies on agricultural challenges and diseases, improving food products, quality of herbs and herbal medicines are very important. In particular, nowadays in pandemic diseases, herbs, natural foods, phytogenic ingredients, essential oils, and antioxidants have been studied by researchers in human and animal health [1].

It's well known that the use of natural foods or natural additives is good for health as well as life quality. Among these additives, algae, spirulina, ginger, thyme, yeasts, Echinacea, sage tea, and green tea are the most interested ones. As a matter of fact, the relationship between natural herbs and health is evaluated on their ingredients. The most known compounds are polyphenols, flavonoids, phycocyanin, vitamins, carotene, and glutathione. These compounds have a broad range of health effects, such as antioxidants, anticancer, immunomodulatory, antivirals, and others [2–7].

Natural foods may alternate several processes in the body, especially oxidative balance, inflammation, genetic changes, immune stimulation, and growth factors. Along with literatures, especially class of antioxidant compounds has radical scavenging properties. Flavonoids, flavones and anthocyanins, the most important antioxidant compounds, are enormously aware of the health benefits. They are all health-oriented and promote efficacy and functional activity against diseases due to the presence of multiple hydroxyl groups [1, 8–10]. What is more, certain nutraceuticals, such as phenylpropanoids, would have a role against environmental stress. However, certain important herbs can maintain homeostasis by reducing high fever [11, 12], may have metabolic effects through inhibition of cancer cell proliferation [13, 14], or act as a chemical quench [15]. Nonetheless, scientific studies have been investigated that

several herbs and compounds are used to enhance immunity by inhibiting activation of specific cytokines [1, 10, 16–18]. In addition, certain herbs and their compounds have antiviral effects that are dependent on the inhibition of viral protein synthesis and viral replication [19].

Previously, the preventive role of the health and quality of life of herbs and their compounds were assessed. In addition, the association between these herbs and the target mechanism in humans and animals has been sought to identify. Several natural foods and their components have been used over the years. Especially nowadays, people try to protect their health in a natural way that is natural foods or their compounds, even if it is a natural medication or natural supplement. In fact, there is enormous complexity about this use knowingly or unknowingly. Thus, the use of traditional herbs and their effects have been researched over the years. In addition, new strategies have been identified for natural foods and their health-enhancing compounds.

3. In the near future: the importance of genome editing in herbs and the methodologies

Genome editing technologies have potential for nutrition due to climate change, reduced agricultural fields, and increased plant stressors. New global agriculture and food production strategies indicate that the revision of the food genome has been important. Actually, the history of genome editing was established over the 1980s as plant breeding. This innovation has supported both nutrition and the food and pharmaceutical industries.

Genome editing technology is a type of genetic engineering in which DNA is inserted, suppressed, altered, or replaced in the genome of a living organism. Genetic material is randomly inserted into the genome of a host by focusing on specific locations. However, it has been reported that random insertion of DNA into the host genome is a disadvantage of this technology because of disruption or alteration of other genes in the organism [20]. So, there was a concern about genetically modified products. Nevertheless, in the 2000s, genome editing has been successfully accomplished for both animal and plant systems with the use of artificial or natural region-specific nucleases and genome editing technologies. Genome editing technology has become a powerful method for functional genomics and crop selection studies in comparison with the randomized method [21].

Some plant transformation techniques are used for genome editing; administration of polyethylene glycol in protoplasts [22], microparticle bombardment [23], WHISKERS™ [24], and Agrobacterium [25]. They can deliver these genome editing reagents to plant cells [26, 27]. More recently, genome editing methods have started to be used to improve our understanding of plant gene functions and the alteration and enhancement of plant genes. The genome editing allows the addition, removal, or modification of the desired genes in the genome by creating double-strand breaks (DSBs) with the specific nucleases of the region. There are four ways to accomplish this: 1. Meganucleases; 2. Zinc finger nucleases (ZFNs); 3. Transcription activator-like effector nucleases (TALENs) and 4. Clustered regularly interspaced short palindromic repeats (CRISPR).

Meganucleases are regarded as the most specific naturally occurring restriction enzymes that are also mobile genetic compounds. They are synthesized in mitochondrial and chloroplast genomes. Despite the identification of several meganucleases, it

is naturally impossible to find a suitable enzyme for each region. A new enzyme model is needed for each study. Meganucleases have been successfully used to target DNA insertions in various plants, such as maize, tobacco, and *Arabidopsis* species [28].

Zinc finger nucleases (ZFNs) are artificial restriction enzymes generated by merging a DNA-binding domain from a zinc finger to a DNA cleavage domain. ZFNs are synthetic nucleases, which were first discovered in TFIIIA from *Xenopus laevis* frogs. The zinc finger protein motif encounters transcribing factors and recognizes the DNA sequences. In fact, ZFNs can be designed to bind and divide any of the DNA sequences. However, for each region of the genome, ZFN must be regenerated. This increases costs and is time-consuming. Several studies have been carried out on plant genome modification using ZFNs, in particular *Arabidopsis* plants, tobacco, maize, and soybeans [29–32]. Additionally, genome editing in microalgae with ZFNs was first reported for *Chlamydomonas reinhardtii*, which was the adapted model strain [33, 34].

Transcription activator-like effector nucleases (TALENs) are similar to those in ZFN. The targeting strategy is delivered by linking pairs to two tightly spaced DNA sequences in both systems. The TALEN proteins were obtained from the phytopathogenic bacterium Xanthomonas. The TALENs method was considered to be successful for Arabidopsis, rice, tobacco, barley, Brachypodium, and corn [35]. Nonetheless, the microalgae *Phaeodactylum tricornutum* was highlighted by the TALENs method to improve lipid accumulation [36]. It was also reported that genome editing in *P. tricornutum* and *Chlamydomonas* has been established by TALENs [37, 38].

Clustered regularly interspaced short palindromic repeat (CRISPR) is the most important method for plant biotechnology whose working principle is based on RNA-mediated nucleases [39]. This is a system discovered from *Streptococcus pygonese* and named CRISPR/Cas9 system. Clustered regularly interspaced short palindromic repeats (CRISPRs)-case-mediated immunity in bacteria provides bacterial populations with protection from pathogens. However, they are also exposed to the dangers of autoimmunity by developing protection that targets their own genomes. CRISPR/Cas vectors have a replication origin and marker gene and also have a power promotor with Cas genes. This makes it possible to target several genes, and consequently, this technology costs less than others. The scientists reported that the Cas9 system could be used to modify the human genome as well as the plant genome [39, 40]. There are two main strategies: using RNA as vectors or transferring a functional nuclease directly into the cells of plants.

Besides its applicability in plant biology, the main focus of CRISPR/Cas system is producing heritable mutations within NHEJ-mediated (NHEJ: nonhomologous end joining) in many species. Also, it's possible to add a DNA fragment via HDR (HDR: homology directed recombination) to a desired region in the plant genome with the CRISPR system; however, a few number of studies have been conducted [41, 42]. Several plant genomes have been modified with CRISPR technology: rice, wheat, corn, tomato, potatoes, cucumber, orange, soybean, tobacco, lemon, and microalgae [32, 43]. The studies provided comparative data, including mutagenesis, efficiency, truncation specifications, potential for generating chromosomal deletions, or adding CRISPR genes [39, 44]. Also, it was reported that there have been several studies; nontoxicity mutation with mediated-CRISPR such as microalgae [45], basic biological studies such as on the opium poppy [46], and improving the quality of products such as tomatoes [47]. The CRISPR system is a multiplex engineering of the genome, which means that multiple genes may be targeted.

In addition, the main advantage of the CRISPR system is that it prevents the gene from moving between organisms and problems related to gene transporting. Also, no

difference occurs in the next generation of organism, biallelic may be provided, and heterozygous and homozygous mutations may be generated [48]. Svitashev et al. [49] and Woo et al. [50] have conducted studies with lettuce, rice, and corn to get successful mutations and modified fields with no alien DNA and marker. In addition, some microalgae, namely *C. reinhardtii*, *Chlamydomonas*, and *P. tricornutum*, have been edited successfully without cytotoxic effects [45, 51, 52]. According to the literature, genome editing with CRISPR/Cas engineering for single nucleotide resolution editing, multiple gene editing, transcriptional regulation, and genome-wide modifications of *Saccharomyces cerevisiae* have been shown [53, 54]. *S. cerevisiae* is an important eukaryotic yeast for the biosynthesis and biofuels [55, 56]. However, there are still some limitations and challenges, in particular the application of CRISPR could limit the effectiveness of yeast processing.

All these technologies have been reported for improving plant micronutrients, such as flavonoids, phenols, saponins, tannins, etc. [57]. These are bioactive compounds known as medicines that are important to health. In particular, the CRISPR/

Plants	**Methods**	**Improved trait**
Rice	*TALENs*	Increased fragrance content
Rice	*CRISPR/Cas9*	Functional metabolites (amylose, Proanthocyanidins, anthocyanidins, beta carotene)
Wheat	*CRISPR/Cas9*	Increased protein (reduce gliadins)
Corn	*ZFNs*	Antinutrient (reduce the phytic acid content)
Corn	*TALEN*	Antinutrient (reduce the phytic acid content)
Corn	*CRISPR/Cas9*	Protein (reduce zein protein)
Potato	*TALEN*	Reduced browning, antinutrient (reduce steroidal glycoalkaloids) Toxic substance (reduce sugar and acrylamide)
Potato	*CRISPR/Cas9*	Reduced browning, starch (amylose), anti-nutrient (absence of steroidal glycoalkaloids)
Oilseed	*CRISPR/Cas9* *TALEN*	Reduced oil content, Reduced polyunsaturated fatty acids,
Tobacco	*Meganuclease*	Reduced nicotine levels
Tomato	*TALEN*	Functional metabolite (increased anthocyanin)
Tomato	*CRISPR/Cas9*	Functional metabolite (increased anthocyanin, aminobutyric acid content)
Tomato	*ZFN*	Antinutrient (reduced anti-nutrient oxalic acid)
Grape	*CRISPR/Cas9*	Antinutrient (reduced tartaric acid level)
Sage (Salvia miltiorrhiza)	*CRISPR/Cas9*	Decreased phenolic acid contents
Pomegranate	*CRISPR/Cas9*	Changes the galloyl-glucose conjugates
Grapevine	*CRISPR/Cas9*	Lack of pigments phenotypes
Papaver	*CRISPR/Cas9*	Biosynthesis flux of morphine, thebaine, etc.
Banana	*CRISPR/Cas9*	Functional metabolites (Beta carotene)

Table 1.
Some nutritional quality-improved foods by gene-editing technologies (Prepared according to literatures; Ku and Ha [64], Scarano et al. [65], Dey et al. [66]).

Cas9 technology can be used to target genes in medicinal plants and their compounds. In addition, this technology can tolerate environmental stress along with quality and performance. There have been successful studies about plant biosynthetic pathways with CRISPR/Cas9, such as tomato for gamma-aminobutyric acid, banana, and rice for beta carotene [58–61]. Also, CRISPR/Cas9 is an effectible technology for bacterial resistance of herbs and plant-derived products and against climate changes [62, 63]. Genome editing technology involves more controlled mutations, and genetic improvement is less time-consuming.

Biotechnology approaches have been interpreted in the context of genome editing technologies over the years. Secondary plant metabolites that belong to genome technology are pharmacologically important as well as nutritional (**Table 1**). However, the editing of the genome is still in its beginnings in plants and their contents. As new and interesting results are obtained in this field, new technologies will emerge.

4. The differences between functional foods and herbs with edited genomes

Scientific evidence shows a great relationship between functional foods and improvement of physiological condition. It is also important to achieve health-related results, particularly in the case of chronic diseases and pandemics. Several studies and clinical trials for herbal nutrition exist. In fact, functional foods have been accepted as mainstream medicine for generations. Based on the literature review, it may be suggested that functional foods are safe to use. They have several health benefits such as preventing adverse effects, increasing the beneficial effect on health, and improving health status [1, 2, 9, 10, 15].

Genome editing of herbs is an exciting innovation for agricultural, nutritional, and pharmacological areas. Some foods designed to modify the genome have been in use for 25 years. This technology is addressed in the cultivation of first-generation transgenic crops, and it permits gene deletion, insertion, silencing, and gene knock-out. The main problem in genome editing is off-target effect. The off-target effect results in inadequacy and typing error, and undesired mutations occur. These off-target activities may change in organisms. However, any such mismatches can be guessed through computer programs [67]. There have been several studies to decrease these effects [68, 69].

Unlike random recombinant methods, CRISPR/Cas9 editing technology is accepted as target-specific. On the contrary, especially in rice, the off-target sites of CRISPR/Cas9 editing are still unknown [70]. However, studies have shown that there are no nontarget DNA changes in rice mutants generated by CRISPR/Cas9, which should be important for the regulation of gene-modified breeding [71, 72]. In addition, it was reported that besides rice, *Arabidopsis*, cotton, and tobacco have indicated off-target mutations rarely [73]. However, some studies have indicated that off-target mutations are possible. Thus, genome editing still leaves room for improvement for the future.

5. Future perspectives: genomic foods have protective effects on health or not?

Most national authorities consider the need for a specific evaluation of genetically modified foods. Certain specific systems for assessing foods intended to modify genes for humans and the environment have been improved. Therefore, the World Health

Organization's (WHO's) The Department of Food Safety and Zoonoses requests national authorities to implement risk assessment procedures and recommend safety assessment approaches.

Theoretical discussions were raised regarding the effectiveness of editing the food genome. However, discussing the potentials for stimulating allergenicity, gene transfer and outcrossing are the fact of the matter. For allergenicity, The Food and Agriculture Organization of the United Nations (FAO) and WHO have evaluated the protocols for testing of genome editing of foods, and no allergic effects were found right now on marketing. It was reported that plant breeding could cause high toxins and allergen concentration in plants. Also, a number of food poisoning could be done due to new varieties into food chain [74]. Gene transfer technology is encouraged with antibiotic resistance genes because of the concern of transferred genetic material from genome-edited foods to humans. Outcrossing is the migration of genes from genome editing plants into conventional crops, which is also mixing of crops from conventional seeds with genome editing crops. This has an indirect effect on food security. There are studies reporting that genome modification cultures for animal feed have been determined to products for humans in a low value. In this way, several countries have adopted major strategies aimed at reducing the mixing and separation of fields where genome editing and conventional crops are grown.

In addition, antibiotic resistance, immunosuppression, cancer, and loss of nutrition can also be counted for unexpected effects and health risks of genome editing technology. It can be said that all genome-edited foods contain antibiotic resistance markers to help identify the transferring of new genetic material into host food. Food and Drug Administration (FDA) introduces these antibiotic markers into the food on a widespread basis. Because of this, some important antibiotics against human illnesses could be made unnecessary. Even though the FDA ignored the issue, the British Medical Association (BMA) has concluded that antibiotic marker genes in the modification of the food genome should constitute a risk to human health and the development of microorganisms is going to be a very important issue in the twenty-first century. In addition, some researchers have shown that changes in the potato genome have significant negative effects on immunity and organ development in rats. They found a valid link between changing the food's genome and immunosuppression [75]. Also, in 1993, a study about engineering recombinant bovine growth hormone (rBGH) resulted in concerns. Researchers showed that levels of hormone called insulin-like growth factor-1 (IGF-1) are increased in dairy cows treated with rBGH. This hormone, IGF-1, is an important factor for breast cancer, colon cancer, or prostate cancer [76]. Another concern was that modifying the genome may alter the nutritional value of foods. Researchers reported that some foods are in "undesirable alteration in the level of nutrients" and noted the nutritional changes. However, these findings were not considered by the FDA in their studies. Nevertheless, the WHO has pointed out that the modification of the genome of foods currently available on the international market is safe and does not pose a risk to human health. In addition, it was indicated that the principles of Codex Alimentarius must be applied on an ongoing basis and that post-market monitoring should ensure the safety of foods for genome editing [77].

6. Conclusion

Introducing new genetic material from a plant may produce certain chemicals. New technologies are necessary to test toxicity with safe boundaries. This means that

risk assessment and food safety are important. There is a need to provide food safety, biological severity, feed, renewable resources for fuel and the environment. Genome editing technologies may improve the ability of these objectives. In this regard, some countries have regulatory policies restricting the editing of the food genome; in particular, about the traceability of plants or food with technologies, or resistance to genetic transformations.

The state of being natural for food is important for health, life, and the environment. There are several points about genetically modified foods. Researchers continue to investigate these and new technologies. But everyone agrees that there is still work to be done.

Conflict of interest

"The authors declare no conflict of interest."

Acronymes and abbreviations

DNA	deoxyribonucleic acid
RNA	ribonucleic acid
ZFNs	zinc finger nucleases
TALENs	transcription activator-like effector nucleases
CRISPR	clustered regularly interspaced short palindromic repeats
TFIIIA	transcription factor IIIA
Cas9	a protein plays a vital role in the immunological defense of certain bacteria against DNA viruses and plasmids
NHEJ	nonhomologous end joining
HDR	homology directed recombination
WHO	the World Health Organization
FAO	the Food and Agriculture Organization of the United Nations
FDA	Food and Drug Administration
BMA	British Medical Association
rBGH	recombinant bovine growth hormone
IGF-1	insulin-like growth factor-1

Appendices and nomenclature

Antioxidants	proanthocyanidins, anthocyanidins, beta carotene, phenolic acid
Microalgae	Spirulina
Algae	*Phaeodactylum tricornutum*
Algae	*Chlamydomonas reinhardtii*
Yeast	*Saccharomyces cerevisiae*
Agrobacterium	plant bacteria
Bacteria	*Streptococcus pygonese*

Author details

Nilay Seyidoglu[1*] and Cenk Aydin[2]

1 Faculty of Veterinary Medicine, Department of Physiology, Tekirdag Namik Kemal University, Tekirdag, Turkey

2 Faculty of Veterinary Medicine, Department of Physiology, Bursa Uludag University, Bursa, Turkey

*Address all correspondence to: nseyidoglu@nku.edu.tr

References

[1] Aydin C, Seyidoglu N. Natural antioxidants to the rescue? In: Waisundara VY, editor. Antioxidants—Benefits, Sources, Mechanisms of Action. London: IntechOpen; 2021. pp. 131-149. DOI: 10.5772/intechopen.96132

[2] Chehue Romero A, Olvera Hernández EG, Flores Cerón T, Álvarez-Chávez A. The exogenous antioxidants. In: Morales-González JA, editor. Oxidative Stress and Chronic Degenerative Diseases—A Role for Antioxidants. Croatia: InTechOpen; 2013. p. 33. DOI: 10.5772/52490

[3] Seyidoglu N, Galip N, Budak F, Uzabaci E. The effects of *Spirulina platensis* and *Saccharomyces cerevisiae* on the distribution and cytokine production of CD4+ And CD8+ T-Lymphocytes in rabbits. Austral Journal of Veterinary Sciences. 2017;**49**(3):185-190. DOI: 10.4067/S071981322017000300185

[4] Seyidoglu N. Algae. Turkiye Klinikleri Journal of Animal Nutrition and Nutritional Diseases Special Topics. 2017;**3**(1):1-7

[5] Seyidoglu N, Gurbanli R, Koseli E, Cengiz F, Aydin C. The effects of Spirulina (Arthrospira) platensis on morphological and hematological parameters evoked by social stress in male rats. Journal of Istanbul Veterinary Sciences. 2019;**3**(1):21-27. DOI: 10.30704/http-www-jivs-net.544154

[6] Seyidoğlu N, Köşeli E, Gurbanlı R, Aydın C. Role of essential oils in antioxidant capacity and immunity in a rat model of mixed stress. South African Journal of Animal Science. 2021;**51**(4):426-436. DOI: 10.4314/sajas.v51i4.2

[7] Seyidoğlu N, Köşeli E, Gurbanlı R, Aydın C. The preventive role of Spirulina platensis (*Arthrospira platensis*) in immune and oxidative insults in a stress-induced rat model. Journal of Veterinary Research. 2021;**65**:193-200. DOI: 10.2478/jvetres-2021-0033

[8] Yashin A, Yashin Y, Xia X, Nemzer B. Antioxidant activity of spices and their impact on human health: A review. Antioxidants (Basel). 2017;**6**(3):70. DOI: 10.3390/antiox6030070

[9] D'Amelia V, Aversano R, Chiaiese P, Carputo D. The antioxidant properties of plant flavonoids: Their exploitation by molecular plant breeding. Phytochemistry Reviews. 2018;**17**:611-625. DOI: 10.1007/s11101-018-9568-y

[10] Seyidoglu N, Aydin C. Stress, natural antioxidants and future perspectives. In: Salant LC, editor. The Health Benefits of Foods—Current Knowledge and Further Development. London: IntechOpen; 2020. pp. 149-165. DOI: 10.5772/intechopen.91167

[11] Ippoushi K, Azuma K, Ito H, Horie H, Higashio H. [6]-Gingerol inhibits nitric oxide synthesis inactivated J774.1 mouse macrophages and prevents peroxynitrite-induced oxidation and nitration reactions. Life Sciences. 2003;**73**(26):3427-3437

[12] Rahmani AH, Al Sharbrmi FM, Aly SM. Active ingredients of ginger as potential candidates in the prevention and treatment of diseases via modulation of biological activities. International Journal of Physiology, Pathophysiology and Pharmacology. 2014;**6**(2):125-136. DOI: PMCID: PMC4106649

[13] Han DH, Lee MJ, Kim JH. Antioxidant and apoptosis-inducing

activities of ellagic acid. Anticancer Research. 2006;**26**:3601-3606. DOI: 10.1007/s11356-019-07352-8

[14] Duan J, Zhan JC, Wang GZ, Zhao XC, Huang WD, Zhou GB. The red wine component ellagic acid induces autophagy and exhibits anti-lung cancer activity in vitro and in vivo. Journal of Cellular and Molecular Medicine. 2018;**23**(1):143-154. DOI: 10.1111/jcmm.13899

[15] Fiedor J, Burda K. Potential role of carotenoids as antioxidants in human health and disease. Nutrients. 2014;**6**:466-488. DOI: 10.3390/nu6020466

[16] Babich O, Sukhikh S, Prosekov A, Asyakina L, Ivanova S. Medicinal plants to strengthen immunity during a pandemic. Pharmaceuticals. 2020;**13**:313. DOI: 10.3390/ph13100313

[17] Kyo E, Uda N, Kasuga S, Itakura Y. Immunmodulator effects of aged garlic extract. The Journal of Nutrition. 2001;**131**(3s):1075-1079. DOI: 10.1093/jn/131.3.1075S

[18] Zhang XL, Guo YS, Wang CH, Li GQ, Xu JJ, Chung HY, et al. Phenolic compounds from Origanum vulgare and their antioxidant and antiviral activities. Food Chemistry. 2014;**152**:300-306. DOI: 10.1016/j. foodchem.2013.11.153

[19] Oladele JO, Ajayi EI, Oyeleke OM, Oladele OT, Olowookere BD, Adeniyi BM, et al. A systematic review on COVID-19 pandemic with special emphasis on curative potentials of Nigeria based medicinal plants. Heliyon. 2020;**6**(9):e04897. DOI: 10.1016/j.heliyon.2020.e04897

[20] Woolf TM. Therapeutic repair of mutated nucleic acid sequences. Nature Biotechnology. 1998;**16**(4):341-344. DOI: 10.1038/nbt0498-341

[21] Durai S, Mani M, Kandavelou K, Wu J, Porteus MH, Chandrasegaran S. Zinc finger nucleases: Custom-designed molecular scissors for genome engineering of plant and mammalian cells. Nucleic Acids Research. 2005;**2005**(33):5978-5990. DOI: 10.1093/nar/gki912

[22] Townsend JA, Wright DA, Winfrey RJ, Fu F, Maeder ML, Joung JK, et al. High-frequency modification of plant genes using engineered zinc-finger nucleases. Nature. 2009;**459**:442-445. DOI: 10.1038/nature07845

[23] Ainley WM, Sastry-Dent L, Welter ME, Murray MG, Zeitler B, Amora R, et al. Trait stacking via targeted genome editing. Plant Biotechnology Journal. 2013;**11**(9):1126-1134. DOI: 10.1111/pbi.12107

[24] Shukla VK, Doyon Y, Miller JC, DeKelver RC, Moehle EA, Worden SE, Mitchell JC, Arnold NL, Gopalan S, Meng X, Choi VM, Rock JM, Wu YY, Katibah GE, Zhifang G, McCaskill D, Simpson MA, Blakeslee B, Greenwalt SA, Butler HJ, Hinkley SJ, Zhang L, Rabar EJ, Gregory PD, urnov FD. Precise genome modification in the crop species Zea mays using zinc-finger nucleases. Nature 2009;459:437-441. DOI: https://doi.org/10.1038/nature07992

[25] de Pater S, Pinas JE, Hooykaas PJ, van der Zaal BJ. ZFN-mediated gene targeting of the Arabidopsis protoporphyrinogen oxidase gene through Agrobacterium-mediated floral dip transformation. Plant Biotechnology Journal. 2013;**11**:510-515. DOI: 10.1111/pbi.12040

[26] Vainstein A, Marton I, Zuker A, Danziger M, Tzfira T. Permanent genome modifications in plant cells by transient viral vectors. Trends in Biotechnology. 2011;**29**(8):363-369. DOI: 10.1016/j.tibtech.2011.03.007

[27] Baltes NJ, Gil-Humanes J, Cermak T, Atkins PA, Voytas DF. DNA replicons for plant genome engineering. The Plant Cell. 2014;**26**:151-163. DOI: 10.1105/tpc.113.119792

[28] Rinaldo AR, Ayliffe M. Gene targeting and editing in crop plants: A new era of precision opportunities. Molecular Breeding. 2015;**35**(1):40. DOI: 10.1007/s11032-015-0210-z

[29] Weinthal D, Tovkach A, Zeevi V, Tzfira T. Genome editing in plant cells by zinc finger nucleases, feature review. Trends in Plant Science. 2010;**2010**(15):308-321. DOI: 10.1016/j.tplants.2010.03.001

[30] Zhang F, Voytas DF. Targeted mutagenesis in arabidopsis using zinc-finger nucleases. In: Birchler J, editor. Plant Chromosome Engineering. Methods in Molecular Biology (Methods and Protocols). Totowa, NJ: Humana Press; 2011. pp. 167-177. DOI: 10.1007/978-1-61737-957-4_9

[31] Petolino JF. Genome editing in plants via designed zinc finger nucleases. In Vitro Cellular & Developmental Biology. Plant. 2015;**51**(1):1-8. DOI: 10.1016/j.cell.2013.02.022

[32] Akbudak MA, Kontay K. New generation genome editing techniques: ZFNs, TALENs, CRISPRs and their use in plant research review. Journal of Central Research Institute for Field Crops. 2017;**26**(1):111-126. DOI: 10.21566/tarbitderg.323614

[33] Sizova I, Greiner A, Awasthi M, Kateriya S, Hegemann P. Nuclear gene targeting in Chlamydomonas using engineered zinc-finger nucleases. The Plant Journal. 2013;**73**:873-882. DOI: 10.1111/tpj.12066

[34] Greiner A, Kelterborn S, Evers H, Kreimer G, Sizova I, Hegemann P. Targeting of photoreceptor genes in Chlamydomonas reinhardtii via zinc-finger nucleases and CRISPR/Cas9. The Plant Cell. 2017;**29**:2498-2518. DOI: 10.1105/tpc.17.00659

[35] Keles NA, Tufan F. Genom düzenleme teknolojileri ve bitkilerdeki uygulamaları. Haliç Üniversitesi Fen Bilimleri Dergisi. 2019;**2**(1):113-133

[36] Daboussi F, Leduc S, Maréchal A, Dubois G, Guyot V, Perez-Michaut C, et al. Genome engineering empowers the diatom Phaeodactylum tricornutum for biotechnology. Nature Communications. 2014;**29**(5):3831. DOI: 10.1038/ncomms4831

[37] Gao H, Wright DA, Li T, Wang Y, Horken K, Weeks DP, et al. TALE activation of endogenous genes in Chlamydomonas reinhardtii. Algal Research. 2014;**5**:52-60. DOI: 10.1016/j.algal.2014.05.003

[38] Weyman PD, Beeri K, Lefebvre SC, Rivera J, McCarthy JK, Heuberger AL, et al. Inactivation of Phaeodactylum tricornutum urease gene using transcription activator-like effector nuclease-based targeted mutagenesis. Plant Biotechnology Journal. 2015;**13**(4):460-470. DOI: 10.1111/pbi.12254

[39] Bortesi L, Fischer R. The CRISPR/Cas9 system for plant genome editing and beyond. Biotechnology Advances. 2015;**33**(1):41-52. DOI: 10.1016/j.biotechadv.2014.12.006

[40] Schiml S, Puchta H. Revolutionizing plant biology: Multiple ways of genome engineering by CRISPR/Cas. Plant Methods. 2016;**12**:8. DOI: 10.1186/s13007-016-0103-0

[41] Schiml S, Fauser F, Puchta H. The CRISPR/Cas system can be used as

nuclease for in planta gene targeting and as paired nickases for directed mutagenesis in Arabidopsis resulting in heritable progeny. The Plant Journal. 2014;**80**(6):1139-1150. DOI: 10.1111/tpj.12704

[42] Ma X, Zhu Q, Chen Y, Liu YG. CRISPR/Cas9 platforms for genome editing in plants: Developments and applications. Molecular Plant. 2016;**9**(7):961-974

[43] Kumar G, Shekh A, Jakhu S, Sharma Y, Kapoor R, Sharma TR. Bioengineering of microalgae: Recent advances, perspectives, and regulatory challenges for industrial application. Frontiers in Bioengineering and Biotechnology. 2020;**8**:914. DOI: 10.3389/fbioe.2020.00914

[44] Zhou H, Liu B, Weeks DP, Spalding MH, Yang B. Large chromosomal deletions and heritable small genetic changes induced by CRISPR/Cas9 in rice. Nucleic Acids Research. 2014;**42**(17):10903-10914. DOI: 10.1093/nar/gku806

[45] Shin SE, Lim JM, Koh HG, Kim EK, Kang NK, Jeon S, et al. CRISPR/Cas9-induced knockout and knock-in mutations in Chlamydomonas reinhardtii. Scientific Reports. 2016;**6**:27810. DOI: 10.1038/srep27810

[46] Alagoz Y, Gurkok T, Zhang BH, Unver T. Manipulating the biosynthesis of bioactive compound alkaloids for next-generation metabolic engineering in opium poppy using CRISPR-Cas 9 genome editing technology. Scientific Reports. 2016;**6**(1):30910. DOI: 10.1038/srep30910

[47] Ito Y, Nishizawa-Yokoi A, Endo M, Mikami M, Toki S. CRISPR/Cas9-mediated mutagenesis of the RIN locus that regulates tomato fruit ripening. Biochemical and Biophysical Research Communications. 2015;**467**(1):76-82. DOI: 10.1016/j.bbrc.2015.09.117

[48] Zhang Y, Liang Z, Zong Y, Wang Y, Liu J, Chen K, et al. Efficient and transgene-free genome editing in wheat through transient expression of CRISPR/Cas9 DNA or RNA. Nature Communications. 2016;**7**:12617. DOI: 10.1038/ncomms12617

[49] Svitashev S, Schwartz C, Lenderts B, Young JK, Cigan AM. Genome editing in maize directed by CRISPRCas9 ribonucleoprotein complexes. Nature Communications. 2016;**7**:13274. DOI: 10.1038/ncomms13274

[50] Woo JW, Kim J, Kwon S, Corvalán C, Cho SW, Kim H, et al. DNA-free genome editing in plants with preassembled CRISPR-Cas9ribonucleoproteins. Nature Biotechnology. 2015;**33**(11):1162-1164. DOI: 10.1038/nbt.3389

[51] Nymark M, Sharma AK, Sparstad T, Bones AM, Winge P. A CRISPR / Cas9 system adapted for gene editing in marine algae. Nature Publications. 2016;**6**:24951. DOI: 10.1038/srep24951

[52] Ng I, Keskin BB, Tan S. A critical review of genome editing and synthetic biology applications in metabolic engineering of microalgae and cyanobacteria. Biotechnology Journal. 2020;**15**:1900228. DOI: 10.1002/biot.201900228

[53] DiCarlo JE, Norville JE, Mali P, Rios X, Aach J, Church GM. Genome engineering in Saccharomyces cerevisiae using CRISPR-Cas systems. Nucleic Acids Research. 2013;**41**:4336-4343. DOI: 10.1093/nar/gkt135

[54] Generoso WC, Gottardi M, Oreb M, Boles E. Simplified CRISPR-Cas genome editing for Saccharomyces cerevisiae.

Journal of Microbiological Methods. 2016;**127**:203-205. DOI: 10.1016/j.mimet.2016.06.020

[55] Meng J, Qiu Y, Shi S. CRISPR/Cas9 Systems for the development of Saccharomyces cerevisiae cell factories. Frontiers in Bioengineering and Biotechnology. 2020;**8**:594347. DOI: 10.3389/fbioe.2020.594347

[56] Yu T, Zhou YJ, Wenning L, Liu Q, Krivoruchko A, Siewers V, et al. Metabolic engineering of Saccharomyces cerevisiae for production of very long chain fatty acid-derived chemicals. Nature Communications. 2017;**8**:15587. DOI: 10.1038/ncomms15587

[57] Pillay M. Genome editing technologies for crop improvement. In: Kang M, editor. Quantitative Genetics, Genomics and Plant Breeding, 2nd ed.; CABI; USA: 2020. p. 33-44. DOI: https://doi.org/10.3920/978-90-8686-885-8

[58] Kaur N, Alok A, Shivani KP, Kaur N, Awasthi P, Chaturvedi S, et al. CRISPR/Cas9 directed editing of lycopene epsilon-cyclase modulates metabolic flux for β-carotene biosynthesis in banana fruit. Metabolic Engineering. 2020;**59**:76-86. DOI: 10.1016/j.ymben.2020.01.008

[59] Li R, Li R, Li X, Fu D, Zhu B, Tian H, et al. Multiplexed CRISPR/Cas9-mediated metabolic engineering of γ-aminobutyric acid levels in Solanum lycopersicum. Plant Biotechnology Journal. 2018;**16**(2):415-427. DOI: 10.1111/pbi.12781

[60] Butt H, Jamil M, Wang JY, Al-Babili S, Mahfouz M. Engineering plant architecture via CRISPR/Cas9-mediated alteration of strigolactone biosynthesis. BMC Plant Biology. 2018;**18**(174):1-9. DOI: 10.1186/s12870-018-1387-1

[61] Feng Z, Mao Y, Xu N, Zhang B, Wei P, Yang DL, et al. Multigeneration analysis reveals the inheritance, specificity, and patterns of CRISPR/Cas-induced gene modifications in Arabidopsis. Proceedings of the National Academy of Sciences. 2014;**111**(12):4632-4637. DOI: 10.1073/pnas.1400822111

[62] Hilary VE, Ceasar SA. Aplication of CRISPR/Cas9 genome editing system in cereal crops. The Open Biotechnology Journal. 2019;**13**(1):173-179. DOI: 10.2174/1874070701913010173

[63] Wang F, Wang C, Liu P, Lei C, Hao W, Gao Y, et al. Enhanced rice blast resistance by CRISPR/Cas9-targeted mutagenesis of the erf transcription factor gene OsERF922. PLoS One. 2016;**11**(4):e0154027. DOI: 10.1371/journal.pone.0154027

[64] Ku HK, Ha SH. Improving nutritional and functional quality by genome editing of crops: Status and perspectives. Frontiers in Plant Science. 2020;**23**(11):577313. DOI: 10.3389/fpls.2020.577313

[65] Scarano A, Chieppa M, Santino A. Plant polyphenols-biofortified foods as a novel tool for the prevention of human gut diseases. Antioxidants (Basel). 2020;**9**(12):1225. DOI: 10.3390/antiox9121225

[66] Dey A. CRISPR/Cas genome editing to optimize pharmalogically active plant natural products. Pharmacological Research. 2021;**2021**(164):10359. DOI: 10.1016/j.phrs.2020.105359

[67] Zhang B, Yang X, Yang CP, Li MY, Guo YL. Exploiting the CRISPR/Cas9 System for targeted genome mutagenesis in petunia. Scientific Reports. 2016;**6**: 20315. DOI: 10.1038/srep20315

[68] Pan C, Ye L, Qin L, Liu X, He YJ, Wang J, et al. CRISPR/Cas9- mediated

efficient and heritable targeted mutagenesis in tomato plants in the first and later generations. Scientific Reports. 2016;**6**:24765. DOI: 10.1038/srep24765

[69] Paul JW, Qi Y. CRISPR/Cas9 for plant genome editing: Accomplishments, problems and prospects. Plant Cell Reports. 2016;**35**(7):1417-1427. DOI: 10.1007/s00299-016-1985-z

[70] Tang X, Liu G, Zhou J, Ren Q, You Q, Tian L, et al. A large-scale whole-genome sequencing analysis reveals highly specific genome editing by both Cas9 and Cpf1 (Cas12a) nucleases in rice. Genome Biology. 2018;**19**:84. DOI: 10.1186/s13059-018-1458-5

[71] Araki M, Ishii T. Towards social acceptance of plant breeding by genome editing. Trends in Plant Science 2015;20:145e149. DOI: 10.1016/j.tplants.2015.01.010

[72] Schaeffer SM, Nakata PA. CRISPR/Cas9-mediated genome editing and gene replacement in plants: Transitioning from lab to field. Plant Science. 2015;**240**:130-142. DOI: 10.1016/j.plantsci.2015.09.011

[73] Feng S, Song W, Fu R, Zhang H, Xu A, Li J. Application of the CRISPR/Cas9 system in Dioscorea zingiberensis. Plant Cell Tissue Organ Culture. 2018;**135**(1):133-141

[74] Louwaars N. Food safety and plant breeding: Why are there no problems in practice? In: Urazbaeva A, Szajkowska A, Wernaart B, Tilkin Franssens N, Spirovska Vaskoska R, editors. The Functional Field of Food Law: Reconciling the Market and Human Rights. Netherlands: Wageningen Academic; 2019. pp. 89-101. DOI: 10.3920/978-90-8686-885-8_5

[75] Ewen SW, Pusztai A. Effect of diets containing genetically modified potatoes expressing Galanthus nivalis lectin on rat small intestine. Lancet. 1999;**354**(9187):1353-1354

[76] American Cancer Society. cancer.org | 1.800.227.2345 [Internet]. 2014. Available from: https://www.cancer.org/content/dam/CRC/PDF/Public/622.00.pdf [Accessed: January 02, 2022]

[77] WHO. Food, Genetically modified. In: Food Safety, Fact Sheet [Internet]. 2020. Available from: https://www.who.int/news-room/questions-and-answers/item/food-genetically-modified. [Accessed: January 02, 2022]

Chapter 6

Food-Based PPARγ Ligands

Amy L. Stockert and Sean Mild

Abstract

Foods and herbs have long been used medicinally and the interest in natural product therapies have returned in the recent decades. PPARγ is a transcription factor that regulates expression of a variety of metabolic genes. The discovery of full activators of PPARγ have been useful in the treatment of diabetes but are not without side effects. The discovery of food based PPARγ ligands have allowed the exploration of natural treatment of a variety of diseases with potentially fewer side effects due to the ligand based activation rather than full activation. Here we present background on the PPARγ transcription factors and summarize several compounds and the food sources that have demonstrated therapeutic potential for disease states including diabetes, cancer, and cardiovascular disease.

Keywords: PPARγ, peroxisome proliferator-activated receptor gamma, nutraceuticals, cinnamon, diabetes, inflammation

1. Introduction

Peroxisome proliferator-activated receptor gamma (PPARγ) is a transcription factor that is activated by ligand binding as well as via ligand-independent activation. PPARγ plays an active role in regulation of glucose and lipid metabolism but more recently has been examined for its role in numerous disease states including: diabetes, cardiovascular disease, cancer, inflammation, angiogenesis and metastasis [1–6]. Some research also suggests it provides potential for anti-aging activity [7]. Prior to the discovery of the thiazolidinedione (TZD) drugs used for treatment of diabetes, the general consensus was that PPARγ was subject only to ligand-independent activation [8]. It was the discovery of these drugs that suggested that PPARγ was also sensitive to ligand-dependent activation [8–11]. The goal of the first generation TZDs was to target insulin sensitivity and although the drugs were successful with this they were not without toxicity concerns. The focus more recently has looked to natural methods to accomplish therapeutic level results and PPARγ provides a viable target with multiple mechanisms available for activation and a variety of functional food sources for PPARγ ligands.

PPARγ is a member of the nuclear receptors gene subfamily and is found on chromosome 3. Other members of the gene family include PPARα and PPARβ/δ. In addition due to alternative splicing, there are multiple isoforms of PPARγ, known as PPARγ1 and PPARγ2 [12, 13]. PPARγ1 is expressed at high levels in white and brown adipose tissue, however, lower levels of expression of PPARγ1 are found in all tissues as well as the immune cells. PPARγ2 is expressed only in white and brown adipose

tissue [14]. Although disease states are sometimes related to changes in expression of these isoforms and inefficient signaling associated with the pathway, some research has demonstrated that specific variants have been linked to early onset type 2 diabetes. Nearly half of these patients had a variant in PPARγ2 resulting in an amino acid substitution of tyrosine to cysteine in the activation function domain 1 (AF1). Of note is also that of these patients, 83% also had diabetic kidney disease [15]. Another study demonstrated that loss of function mutation of arginine 288 to histidine in the ligand-binding domain (LBD) resulted in significant conformational changes in the protein that lead to blunting of the activation via prostaglandins [16].

Mouse studies have shown that knockout of PPARγ2 results in insulin resistance [13]. In contrast, it was demonstrated that activation of PPARγ in mouse adipocytes improves insulin sensitivity [17]. Together these studies support the effects of PPARγ activity on insulin resistance and type 2 diabetes in addition to its known role in adipocyte differentiation [12, 18]. PPARγ also controls the expression of the skeletal muscle and adipose glucose transporter (GLUT4), and adipose tissue based hormones adiponectin, resistin and leptin [19–21]. It is clear from these studies that modulation of PPARγ activity plays a significant role in patient wellness considering the effects of activation on glucose homeostasis, lipid metabolism and adipocyte differentiation. These effects strongly suggest that activation of PPARγ in a controlled fashion provide strong potential for improvement of patient quality of life. Nutraceuticals offer this type of low level controlled activation that may benefit the patient even beyond the potential for the synthetic drugs targeting PPARγ activation.

The structure of PPARγ contains multiple protein domains of importance as shown in **Figure 1**. The individual domains are separated based on function and can themselves be modified in most cases. The activation function domain 1 (AF1) is on the N-terminus and is subject to phosphorylation, and small ubiquitin like modifiers (SUMOylation). In general SUMOylation leads to suppression of transcriptional activity while ubiquitination increase transcriptional activity. Phosphorylation can increase or decrease transcriptional activity depending on the site of phosphorylation and the enzyme catalyzing the phosphorylation event. In general deacetylation by Sirt-1, the histone deacetylase leads to dissociation of the nuclear receptor corepressor (NCoR) and increased transcriptional activity [22]. The next domain is the DNA binding domain (DBD) responsible for interacting with the DNA in conjunction with the retinoid c receptor (RXR). RXR houses a binding site for 9-cis-retinoic acid, which when bound allows RXR to complex with the PPARγ complex and interaction with DNA [23]. The HD domain is a regulatory domain named due to the histidine

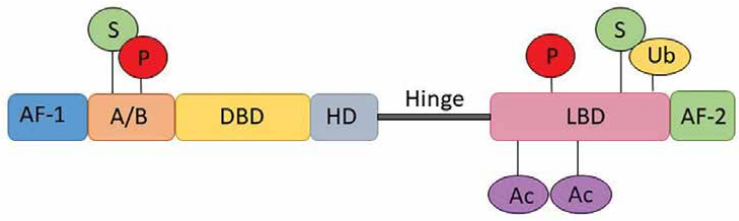

Figure 1.
The structure of PPARγ. AF-1 is the activated function 1 domain. A/B houses a SUMOylation (S) and phosphorylation (P) site. DBD is the DNA binding domain. HD is the conserved protein domain with histidine and aspartate that interacts with the coactivator PGC-1α. The ligand binding domain (LBD) is attached via a hinge region and houses a SUMOylation, phosphorylation, ubiquitination (Ub) and two acetylation (Ac) sites. AF-2 is the activated function.

(H)-aspartate (D) amino acids conserved in the region. The HD domain interacts with either the coactivator, peroxisome proliferator-activated receptor gamma coactivator (PGC-1α) or the corepressors NCoR and silencing mediator of retinoid and thyroid hormone receptors (SMRT) [24]. On the C-terminal end is the ligand binding domain (LBD) that when ligand bound by an activator, stimulates transcription. When no ligand is bound, and the corepressor is bound, transcription is limited. The LBD is also subject to phosphorylation, ubiquitination, SUMOylation and acetylation. Each of these affect the likelihood of ligand activation. Of interest are the histone deacetylase enzyme (HDAC) which deacetylate the ligand binding domain. Inhibition of this HDAC, limits deacetylation of the LBD and leads towards PPARγ activation via the ligand independent pathway [25].

The PPARγ pathway involves several overlapping cellular functions. Activation of PPARγ, either ligand-independent or ligand dependent, leads to change in the immune system, metabolic organs including skeletal muscle and adipose tissue [26–28]. For example in the immune system macrophages and regular T cells, activation of PPARγ in general will decrease inflammation. Inflammation is decreased in the heart and brain but lipid storage is increased in the heart as well as growth. In white adipose tissue lipid metabolism and glucose homeostasis is improved with activation. Of particular interest is the fact that activation of PPARγ increases remodeling and browning of white adipose tissue, a benefit that will likely lead to better ability for patients to manage weight (ref). It is clear that there are strong benefits to PPARγ activation, but potential side effects such as lipid storage in the heart, sodium and fluid retention and increased desire for food can also result in unwanted effects [22].

It is important to consider how PPARγ activation can be achieved while minimizing the potentially harmful side effects. A benefit also exists to activate PPARγ in a ligand dependent fashion versus the ligand independent activation. Endogenous ligands to PPARγ are typically fairly weak agonists while the TZDs are strong agonists [8, 29]. The first generation TZD troglitazone was pulled from the market in the US approximately 3 years after first becoming available because it resulted in severe or fatal hepatotoxicity in numerous cases [30–34]. Other TZDs were taken off the European market and restricted in the US markets due to potentially dangerous side effects including myocardial infarction, heart failure, hepatic failure [35–38]. It is still currently believed that these side effects resulted in part to the full PPARγ activation rather than the moderate activation offered by the weaker ligand agonists [29]. Gene expression, especially expression of genes involved in metabolic process that are sensitive to endogenous ligands as well, should be tightly controlled with an effective regulatory method that allows frequent adjustment of expression levels in response to the environment. Altering expression of genes fully by fully activating PPARγ poses several concerns, especially since there is so much overlap within the PPARγ activation pathway. Thus, an increased emphasis on natural and less specific activators is warranted. Natural ligands are particularly useful in this situation because the full and permanent activation is not desired. Given the range of disease state linked to PPARγ signaling, exploring the potential natural food based ligands is an essential tool in moving patient wellness forward.

2. Food sources and therapeutic potential

Several herbs and foods have been used medicinally for centuries, although mechanism of action was not known and in some cases remains unclear. Many of the

compounds found in common herbs and foods have been discovered to be ligands of the nuclear receptors such as PPARγ. A variety of studies presented summarize the compound identified to harbor therapeutic potential as a PPARγ ligand resulting in partial activation of the transcription factor and expression of a variety of metabolic and growth genes. Many of these compounds are found in overlapping herbs or spices. For example, cinnamon contains numerous compounds that are demonstrated ligands including: 2-hydroxychalcone, cinnamaldehyde, catechin, eugenol, ethylcinnamate, epicatechin, and cinnaminc acid. As expected, cinnamon has been used medicinally to treat digestive disorders and metabolic problems for decades.

Given the large number of compounds that function as PPARγ ligands, detailed discussion of each is warranted, but an overall summary is also important. **Table 1** identifies several of the compounds of interest, their food sources and conveniently lists references that pertain to the studies. Apigenin acts as a partial agonist for PPARγ, inducing an effect of agonism in the absence of a full agonist, and antagonism in the presence of a full agonist. This is due to the low binding affinity that apigenin has for PPARγ itself [6, 39]. However, even with this low binding affinity, it has shown to still produce beneficial effects through this pathway. Due to its interactions with PPARγ, apigenin has anti-inflammatory effects, and has been used for treatment of colitis, or inflammation of the intestines. However, beyond its interactions with PPARγ, apigenin has also been shown to decrease food-intake, and help with weight loss [39]. Apigenin has a lot of potential clinical use and application, and can be found in marjoram, sage, thyme, holy basil, parsley, and alfalfa [6, 39].

2-Hydroxychalcone is another example of a partial agonist for PPARγ. Similar to apigenin, this partial agonism of PPARγ leads to anti-inflammatory effects induced by 2-Hydroxychalcone. Although the pathways for these effects are not yet understood in the case of 2-Hydroxychalcone, it is an example of a PPARγ ligand that has shown anti-inflammatory effects [4, 6, 39]. As for food sources of 2-Hydroxychalcone, it is primarily found in cinnamon [6, 39].

PPARγ agonists	**Food Sources**	**References**
Apigenin	Marjoram, sage, thyme, holy basil, parsley, alfalfa	[6, 39]
2-Hydroxychalcone	Cinnamon	[6, 39]
Luteolin	Marjoram, sage, rosemary, tarragon, thyme, parsley, alfalfa	[6, 39]
Rosmarinic Acid	Marjoram, sage, rosemary, lavender, thyme, oregano	[6, 39]
Cinnamaldehyde, Cinnamic Acid	Cinnamon, clove	[6, 39]
Resveratrol	Bilberries (European blueberries), peanuts, grapes, wine	[5, 6, 32]
Quercetin	Dill, bay leaves, oregano, pomegranate fruit, apples, tarragon, parsley, chive, lovage	[6, 39]
Catechin	Apples, marjoram, sage, rosemary, cinnamon, pomegranate fruit, cacao, green tea, grapes, apricots, cherries	[4, 6, 40, 41]
Eugenol	Cinnamon, clove	[6, 39]
Epicatechin	Cacao, tea, cinnamon, thyme, apples, grapes	[6, 42, 43]

Table 1.
Select compounds that function as PPARγ agonists and the food sources.

Luteolin acts as a partial agonist for PPARγ, thus affecting PPARγ-dependent gene expression and causing agonism, or an increase in gene expression in the absence of a full agonist, and causing antagonism, or a decrease in gene expression in the presence of a full agonist. However, luteolin uniquely acts as a full agonist for the gene expression of insulin dependent glucose transporters (GLUT-4) in the 3 T3-L1 mouse cell model [4]. Currently it is unclear if this effect is also seen in humans, however it is a potential target for future research. Luteolin also has an effect on inflammation through its effect on proinflammatory cytokines such as interleukin-8 (IL-8) [4]. Although the clinical implications are still unclear for luteolin, recent studies have started to uncover some of the potential beneficial effects it may have. In an in vitro study in human intestinal cells, luteolin has shown to prevent the damage caused by chemotherapeutic treatment. As for the sources of luteolin, luteolin has been shown to be present in marjoram, sage, rosemary, tarragon, thyme, parsley, and alfalfa [6, 39].

Similar to luteolin, rosmarinic acid also acts as a partial agonist for PPARγ, allowing for weak agonism in the absence of a full agonist, and antagonism in the presence of a full agonist [6]. Rosmarinic acid has shown to have anti-inflammatory activity in cell culture assays, however its clinical applications should still be further explored and elaborated on. Rosmarinic acid does however have a poor bioavailability, so its application in humans may be limited regardless of its ability to bind to PPARγ [39]. It still has shown activity as a PPARγ ligand though, so it may be worth further investigation. As far as where rosmarinic acid can be found, it is seen in marjoram, oregano, rosemary, sage, thyme, and lavender [6, 39].

Cinnamic acid and cinnamaldehyde work very similarly. Cinnamaldehyde acts as a partial agonist for PPARγ, allowing for weak agonism in the absence of a full agonist, and antagonism in the presence of a full agonist. Cinnamic acid functions in a similar way, but with a much higher binding affinity for PPARγ [6, 44]. They have both shown a plethora of beneficial effects related to its effect on PPARγ. These include, but are not limited to reducing amyloid-β plaques in Alzheimer's disease, anti-inflammatory effects, as well as improving glucose and lipid levels as well as insulin sensitivity in Diabetes [39, 44, 45]. Although not all of these effects have been shown in humans yet, some have, and there is great potential for clinical application of cinnamaldehyde. As far as the sources of cinnamaldehyde and cinnamic acid, they can both be found in cinnamon as well as clove [6, 39].

Similar to luteolin, resveratrol also acts as a partial agonist for PPARγ-dependent gene expression, which leads to slight agonism in the absence of a full agonist, and antagonism in the presence of a full agonist. Resveratrol affects both glucose and lipid metabolism, and can also have an effect on inflammation in animal models. Resveratrol has also been shown to improve insulin sensitivity in human patients, which is a contributing factor for Type 2 Diabetes, and can help in control of that disease state beyond metabolism of foods consumed. These mechanisms indicate Resveratrol as potentially beneficial in patients with Type 2 Diabetes, as it can help with glucose metabolism, insulin action, and the storage of fat, potentially lowering their risk of cardiovascular events associated with fats [4]. As for the sources of resveratrol, resveratrol has been shown to be present in foods such as bilberries (European blueberries), grapes, wines, and peanuts [5, 6].

Quercetin acts as a partial agonist for PPARγ-dependent gene expression, causing agonism, or an increase in gene expression in the absence of a full agonist, and causing antagonism, or a decrease in gene expression in the presence of a full agonist [4, 6]. Quercetin has also been shown in a mouse fibroblast cell model (3 T3-L1), that it promotes glucose uptake through insulin-dependent glucose transporters (GLUT-4),

however does not affect the production of lipid stores through adipogenesis [4]. Additionally quercetin has shown anti-inflammatory effects in vivo, and is very similar in this regard to resveratrol [4, 39, 46, 47]. Quercetin is also fairly abundant in food sources, and can be found in dill, bay leaves, oregano, pomegranate fruit, apples, tarragon, parsley, chive, and lovage [6, 39].

Catechin too binds to PPARγ, however unlike the previous compounds mentioned, catechin acts as a full agonist for PPARγ-dependent gene expression, and as such does not provide antagonism [4]. This being said, the effects of catechin are expected to differ from the other compounds mentioned previously. One of these differences seen is that the negative enantiomer of catechin promotes the differentiation of mesenchymal stem cells into adipocytes, or fat cells [40]. Alternatively, the positive enantiomer of catechin has anti-inflammatory properties, similar to those previously mentioned [41]. Altogether, both enantiomers of catechin appear to have beneficial effects in terms of health, and both appear to affect the PPARγ pathways. Additionally, the sources of catechin are plentiful, as it can be found in apples, marjoram, sage, rosemary, cinnamon, pomegranate fruit, cacao, green tea, grapes, apricots, and cherries [4, 6, 40, 41].

Although the activities of eugenol through PPARγ are not yet well-defined, it is known to bind to PPARγ with a greater affinity than that of catechin, which acts as a full agonist [4, 6]. Eugenol is also a compound that has been demonstrated to increase insulin sensitivity, and has seen use in essential oils for that purpose [39]. Eugenol has also shown anti-inflammatory effects, like all of the other compounds discussed in this chapter [39]. As for where eugenol is found though, it is seen mostly in clove and cinnamon [6, 39].

Ethyl cinnamate is very similar to cinnamic acid and cinnamaldehyde. It too works similarly in terms of agonism, but has a binding affinity more similar to that of cinnamic acid as opposed to cinnamaldehyde [6]. Additionally, as a PPARγ agonist, it shows the same anti-inflammatory effects that all of the other compounds previously mentioned exhibit [39]. In terms of food sources for ethyl cinnamate though, it is seen in mainly cinnamon and clove [6, 39].

Epicatechin is very similar to the compound discussed earlier, catechin. They both have great binding affinities for PPARγ, and have very similar effects [6]. Like catechin, epicatechin has anti-inflammatory properties. However unlike catechin, epicatechin has also been shown to inhibit PPARγ signaling as well as adipogenesis, or the development of fat stores. Altogether, epicatechin has many positive effects, whether related to its actions on PPARγ, or it's other bioactivities, and has great promise for medicinal application [42, 43]. In terms of sources of epicatechin, it can be found most prominently in cacao, but also in tea, cinnamon, thyme, apples, grapes, and many other fruits and vegetables [6, 42, 43].

3. Conclusion

As presented there are several natural sources of PPARγ ligands found in spices and food that are commonly consumed. The degree of activation varies on whether the ligand acts as a full agonist or simply as a partial agonist. Molecules that demonstrate a low binding affinity, less than 100 μM, include apigenin, 2-hydoxylchalcone, luteolin, rosmarinic acid, cinnamaldehyde and cinnamic acid, resveratrol and quercetin. Those with moderate binding affinities of 100 to 500 μM, are catechin and eugenol. Those with higher binding affinities include ethylcinnamate and

epicatechin. It is important to note that many of these compounds have also been shown to interact in other signaling pathways in the body that could lead to an altered therapeutic response. Together these provide a variety of sources to treat diseases related to PPARγ activity such as inflammation, diabetes, and heart disease.

Conflict of interest

The authors declare no conflict of interest.

Author details

Amy L. Stockert* and Sean Mild
Ohio Northern University, Ada, USA

*Address all correspondence to: a-stockert@onu.edu

References

[1] Mal S, Dwivedi AR, Kumar V, Kumar N, Kumar B, Kumar V. Role of peroxisome proliferator-activated receptor gamma (PPARγ) in different disease states: Recent updates. Current Medicinal Chemistry. 2021;**28**(16):3193-3215. DOI: 10.2174/0929867327666200716113136

[2] Hernandez-Quiles M, Broekema MF, Kalkhoven E. PPARgamma in Metabolism, Immunity, and Cancer: Unified and Diverse Mechanisms of Action. Frontiers in Endocrinology. 2021;**12**:624112. DOI: 10.3389/fendo.2021.624112

[3] Chandra M, Miriyala SA-O, Panchatcharam MA-O. PPARγ and Its Role in Cardiovascular Diseases. PPAR Research. 2017;**2017**:1-10. DOI: 10.1155/2017/6404638

[4] Wang L, Waltenberger B, Pferschy-Wenzig EM, Blunder M, Liu X, Malainer C, et al. Natural product agonists of peroxisome proliferator-activated receptor gamma (PPARγ): a review. Biochemical Pharmacology. 2014;**92**(1):73-89. DOI: 10.1016/j.bcp.2014.07.018

[5] Penumetcha M, Santanam N. Nutraceuticals as Ligands of PPARγ. PPAR Research. 2012;**2012**:858352. DOI: 10.1155/2012/858352

[6] Mueller M, Jungbauer A. Culinary plants, herbs and spices – A rich source of PPARγ ligands. Food Chemistry. 2009;**117**(4):660-667. DOI: 10.1016/j.foodchem.2009.04.063

[7] Argmann C, Dobrin R, Fau-Heikkinen S, Heikkinen S, Fau-Auburtin A, Auburtin A, Fau-Pouilly L, Pouilly L, Fau-Cock T-A, Cock TA, Fau-Koutnikova H, et al. Ppargamma2 is a key driver of longevity in the mouse. PLoS Genetics. 2009;**5**(12):e1000752. DOI: 10.1371/journal.pgen.1000752

[8] Lehmann JM, Moore LB, Smith-Oliver TA, Wilkison WO, Willson TM, Kliewer SA. An antidiabetic thiazolidinedione is a high affinity ligand for peroxisome proliferator-activated receptor γ (PPARγ). Journal of Biological Chemistry. 1995;**270**(22):12953-12956

[9] Kliewer SA, Umesono K, Noonan DJ, Heyman RA, Evans RM. Convergence of 9-cis retinoic acid and peroxisome proliferator signalling pathways through heterodimer formation of their receptors. Nature. 1992;**358**(6389):771-774

[10] Graves RA, Tontonoz P, Spiegelman BM. Analysis of a tissue-specific enhancer: ARF6 regulates adipogenic gene expression. Molecular and Cellular Biology. 1992;**12**(3):1202-1208

[11] Kletzien RF, Foellmi LA, Harris P, Wyse BM, Clarke SD. Adipocyte fatty acid-binding protein: Regulation of gene expression in vivo and in vitro by an insulin-sensitizing agent. Molecular Pharmacology. 1992;**42**(4):558-562

[12] Tontonoz P, Spiegelman BM. Fat and beyond: The diverse biology of PPARγ. Annual Review of Biochemistry. 2008;**77**(1):289-312. DOI: 10.1146/annurev.biochem.77.061307.091829

[13] Medina-Gomez G, Virtue S, Lelliott C, Boiani R, Campbell M, Christodoulides C, et al. The link between nutritional status and insulin sensitivity is dependent on the adipocyte-specific peroxisome proliferator–activated receptor-γ2

isoform. Diabetes. 2005;**54**(6):1706-1716. DOI: 10.2337/diabetes.54.6.1706

[14] Lehrke M, Lazar MA. The many faces of PPARγ. Cell. 2005;**123**(6):993-999. DOI: 10.1016/j.cell.2005.11.026

[15] Gong S, Han X, Li M, Cai X, Liu W, Luo Y, et al. Genetics and Clinical Characteristics of PPARγ Variant-Induced Diabetes in a Chinese Han Population. Frontiers in Endocrinology. 2021;**12**:677130. DOI: 10.3389/fendo.2021.677130

[16] Egawa D, Ogiso T, Nishikata K, Yamamoto K, Itoh T. Structural Insights into the Loss-of-Function R288H Mutant of Human PPARγ. Biological and Pharmaceutical Bulletin. 2021;**44**(9):1196-1201. DOI: 10.1248/bpb.b21-00253

[17] Sugii S, Olson P, Sears DD, Saberi M, Atkins AR, Barish GD, et al. PPARγ activation in adipocytes is sufficient for systemic insulin sensitization. Proceedings of the National Academy of Sciences. 2009;**106**(52):22504. DOI: 10.1073/pnas.0912487106

[18] Tontonoz P, Hu E, Spiegelman BM. Stimulation of adipogenesis in fibroblasts by PPARγ2, a lipid-activated transcription factor. Cell. 1994;**79**(7):1147-1156. DOI: 10.1016/0092-8674(94)90006-X

[19] Hollenberg AN, Susulic VS, Madura JP, Zhang B, Moller DE, Tontonoz P, et al. Functional antagonism between CCAAT/enhancer binding protein-α and peroxisome proliferator-activated receptor-γ on the leptin promoter. Journal of Biological Chemistry. 1997;**272**(8):5283-5290. DOI: 10.1074/jbc.272.8.5283

[20] Iwaki M, Matsuda M, Maeda N, Funahashi T, Matsuzawa Y, Makishima M, et al. Induction of adiponectin, a fat-derived antidiabetic and Antiatherogenic factor, by nuclear receptors. Diabetes. 2003;**52**(7):1655-1663. DOI: 10.2337/diabetes.52.7.1655

[21] Tomaru T, Steger DJ, Lefterova MI, Schupp M, Lazar MA. Adipocyte-specific expression of murine Resistin is mediated by synergism between peroxisome proliferator-activated receptor γ and CCAAT/enhancer-binding proteins. Journal of Biological Chemistry. 2009;**284**(10):6116-6125. DOI: 10.1074/jbc.M808407200

[22] Ahmadian M, Suh JM, Hah N, Liddle C, Atkins AR, Downes M, et al. PPARγ signaling and metabolism: The good, the bad and the future. Nature Medicine. 2013;**19**(5):557-566. DOI: 10.1038/nm.3159

[23] Chandra V, Huang P, Fau-Hamuro Y, Hamuro Y, Fau-Raghuram S, Raghuram S, Fau-Wang Y, Wang Y, Fau-Burris TP, Burris TP, Fau-Rastinejad F, et al. Structure of the intact PPAR-gamma-RXR- nuclear receptor complex on DNA. Nature. 2008;**456**:350-356. DOI: 10.1038/nature07413

[24] Yu C, Markan K, Fau-Temple KA, Temple KA, Fau-Deplewski D, Deplewski D, Fau-Brady MJ, Brady MJ, Fau-Cohen RN, Cohen RN. The nuclear receptor corepressors NCoR and SMRT decrease peroxisome proliferator-activated receptor gamma transcriptional activity and repress 3T3-L1 adipogenesis. Journal of Biological Chemistry. 2005;**280**(14):13600-14500

[25] Jiang X, Ye X, Guo W, Lu H, Gao Z. Inhibition of HDAC3 promotes ligand-independent PPARγ activation by protein acetylation. Journal of Molecular Endocrinology. 2014;**53**(2):191-200. DOI: 10.1530/jme-14-0066

[26] Kawai M, Rosen CJ. PPARγ: A circadian transcription factor in adipogenesis and osteogenesis. Nature Reviews Endocrinology. 2010;**6**(11):629-636. DOI: 10.1038/nrendo.2010.155

[27] Glass CK, Saijo K. Nuclear receptor transrepression pathways that regulate inflammation in macrophages and T cells. Nature Reviews Immunology. 2010;**10**(5):365-376. DOI: 10.1038/nri2748

[28] Stafylas PC, Sarafidis PA, Lasaridis AN. The controversial effects of thiazolidinediones on cardiovascular morbidity and mortality. International Journal of Cardiology. 2009;**131**(3):298-304. DOI: 10.1016/j.ijcard.2008.06.005

[29] Dussault I, Forman BM. Prostaglandins and fatty acids regulate transcriptional signaling via the peroxisome proliferator activated receptor nuclear receptors. Prostaglandins & Other Lipid Mediators. 2000;**62**(1):1-13. DOI: 10.1016/s0090-6980(00)00071-x

[30] Martens FMAC, Visseren FLJ, Lemay J, de Koning EJP, Rabelink TJ. Metabolic and additional vascular effects of Thiazolidinediones. Drugs. 2002;**62**(10):1463-1480. DOI: 10.2165/00003495-200262100-00004

[31] Gitlin N, Julie NL, Spurr CL, Lim KN, Juarbe HM. Two cases of severe clinical and histologic hepatotoxicity associated with Troglitazone. Annals of Internal Medicine. 1998;**129**(1):36-38. DOI: 10.7326/0003-4819-129-1-199807010-00008

[32] Neuschwander-Tetri BA, Isley WL, Oki JC, Ramrakhiani S, Quiason SG, Phillips NJ, et al. Troglitazone-induced hepatic failure leading to liver transplantation: A case report. Annals of Internal Medicine. 1998;**129**(1):38-41. DOI: 10.7326/0003-4819-129-1-199807010-00009

[33] Shibuya A, Watanabe M, Fujita Y, Saigenji K, Kuwao S, Takahashi H, et al. An autopsy case of Troglitazone-induced fulminant hepatitis. Diabetes Care. 1998;**21**(12):2140-2143. DOI: 10.2337/diacare.21.12.2140

[34] Kohlroser J, Mathai J, Reichheld J, Banner BF, Bonkovsky HL. Hepatotoxicity due to troglitazone: Report of two cases and review of adverse events reported to the United States Food and Drug Administration. The American Journal of Gastroenterology. 2000;**95**(1):272-276. DOI: 10.1016/S0002-9270(99)00766-2

[35] Forman LM, Simmons DA, Diamond RH. Hepatic failure in a patient taking rosiglitazone. Annals of Internal Medicine. 2000;**132**(2):118-121. DOI: 10.7326/0003-4819-132-2-200001180-00005

[36] Nissen SE, Wolski K. Rosiglitazone revisited: An updated meta-analysis of risk for myocardial infarction and cardiovascular mortality. Archives of Internal Medicine. 2010;**170**(14):1191-1201. DOI: 10.1001/archinternmed.2010.207

[37] Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. New England Journal of Medicine. 2007;**356**(24):2457-2471. DOI: 10.1056/NEJMoa072761

[38] Home PD, Pocock SJ, Beck-Nielsen H, Gomis R, Hanefeld M, Jones NP, et al. Rosiglitazone evaluated for cardiovascular outcomes — An interim analysis. New England Journal of Medicine. 2007;**357**(1):28-38. DOI: 10.1056/NEJMoa073394

[39] Jungbauer A, Medjakovic S. Anti-inflammatory properties of culinary herbs and spices that ameliorate the effects of metabolic syndrome. Maturitas. 2012;**71**(3):227-239. DOI: 10.1016/j.maturitas.2011.12.009

[40] Shin DW, Kim SN, Fau-Lee SM, Lee SM, Fau-Lee W, Lee W, Fau-Song MJ, Song MJ, Fau-Park SM, Park SM, Fau-Lee TR, et al. (−)-Catechin promotes adipocyte differentiation in human bone marrow mesenchymal stem cells through PPAR gamma transactivation. Biochemical Pharmacology. 2009;**77**(1):125-133. DOI: 10.1016/j.bcp.2008.09.033

[41] Sipahi H, Gostner JM, Becker K, Charehsaz M, Kirmizibekmez H, Schennach H, et al. Bioactivites of two common polyphenolic compounds: Verbascoside and catechin. Pharmaceutical Biology. 2016;**54**(4):712-729. DOI: 10.3109/13880209.2015.1072830

[42] Esser D, Geleijnse JM, Matualatupauw JC, Dower JI, Kromhout D, Hollman PCH, et al. Pure flavonoid epicatechin and whole genome gene expression profiles in circulating immune cells in adults with elevated blood pressure: A randomised double-blind, placebo-controlled, crossover trial. PloS. 2018;**13**:1-15. DOI: 10.1371/journal.pone.0194229

[43] Vazquez-Prieto MA, Bettaieb A, Fau-Haj FG, Haj FG, Fau-Fraga CG, Fraga CG, Fau-Oteiza PI, Oteiza PI. (−)-Epicatechin prevents TNFα-induced activation of signaling cascades involved in inflammation and insulin sensitivity in 3T3-L1 adipocytes. Archives of Biochemistry and Biophysics. 2012;**527**(2):113-118. DOI: 10.1016/j.abb.2012.02.019

[44] Li JE, Futawaka K, Yamamoto H, Kasahara M, Tagami T, Liu TH, et al. Cinnamaldehyde Contributes to Insulin Sensitivity by Activating PPARδ, PPARγ, and RXR. American Journal of Chinese Medicine. 2015;**43**(5):879-892. DOI: 10.1142/s0192415x15500512

[45] Do J, Kim N, Jeon SH, Gee MS, Ju YJ, Kim JA-O, et al. Trans-Cinnamaldehyde Alleviates Amyloid-Beta Pathogenesis via the SIRT1-PGC1α-PPARγ Pathway in 5XFAD Transgenic Mice. International Journal of Molecular Sciences. 2020; **21**(12):1-13. DOI: 10.3390/ijms21124492

[46] Comalada M, Camuesco D, Fau-Sierra S, Sierra S, Fau-Ballester I, Ballester I, Fau-Xaus J, Xaus J, Fau-Gálvez J, Gálvez J, Fau-Zarzuelo A, et al. In vivo quercitrin anti-inflammatory effect involves release of quercetin, which inhibits inflammation through down-regulation of the NF-kappaB pathway. European Journal of Immunology. 2005;**35**(2):584-592. DOI: 10.1002.eji.200425778

[47] Chuang CC, Martinez K, Fau-Xie G, Xie G, Fau-Kennedy A, Kennedy A, Fau-Bumrungpert A, Bumrungpert A, Fau-Overman A, Overman A, Fau-Jia W, et al. Quercetin is equally or more effective than resveratrol in attenuating tumor necrosis factor-{alpha}-mediated inflammation and insulin resistance in primary human adipocytes. American Journal of Clinical Nutrition. 2019;**92**(6):1511-1521. DOI: 10.3945/ajcn.2010.29807

Chapter 7

Food as a Dietary Source of Melatonin and Its Role in Human Health: Present and Future Perspectives

Purificación Ballester, Pilar Zafrilla, Raúl Arcusa, Alejandro Galindo, Begoña Cerdá and Javier Marhuenda

Abstract

Melatonin is a neurohormone produced and released by the pineal gland. Neurons placed in the eye surface send a signal when the person is exposed to darkness to the suprachiasmatic nuclei and that prompts melatonin release. This biomolecule is in charge of synchronizing body circadian rhythms such as sleep or hunger. Intense light exposure can avoid its release or healthy rhythm. Apart from that, the scientific literature has suggested that melatonin influences immune system, antioxidant capacity, or cell preservation. Moreover, melatonin can be supplied by dietary food such as grapes, dairy or fermented products. Interestingly, some foods contain a significant amount of melatonin and can be considered as good sources of that bioactive molecule. The information in this chapter will cover melatonin dietary sources, biological capacity, related metabolites, and proven benefits in the human body.

Keywords: melatonin, diet sources, foods, antioxidant, immune system, cell preservation

1. Introduction

The neurohormone melatonin (MEL) (N-acetyl-5-methoxytyramine) is produced in the pineal gland and can be also found as metabolite in plants. Moreover, the synthesis of MEL derives from the aminoacid tryptophan, leading to 5-hydroxytryptophan, serotonin, and finally, N-acetylserotonin. Moreover, MEL can also be produced by *O*-serotonin methylation followed by N-methoxytryptamine acetylation by the action of yeast [1, 2].

MEL content has been reported in seeds, for example, rice or corn and roots, leaves, or fruits of a significant range of plants. The occurrence of MEL has also been reported in olive oil, especially in extra virgin olive oil, and in sunflower oil [3]. Moreover, the content of MEL has also been reported in grapes and wines [4].

Scientific literature has revealed that MEL is formed after fermentation with wine yeast, mainly due to *Saccharomyces cerevisiae* [5].

MEL is a key modulator of human health, showing antioxidant, anticarcinogenic, or neuroprotective capacity between others [6]. The biological capacity of their main metabolites as N-1-acetyl-N-2-formyl-5-methoxyquinuramine (AFMK) and N-1-acetyl-5-methoxyquinuramine (AMK) is also significant. AFMK is considered a potent antioxidant compound, and AMK is also a potent antioxidant being able to inhibit the biosynthesis of prostaglandins related to diazepam receptors [7]. As other secondary metabolites, MEL can promote antioxidant enzymes and/or neutralize free radicals [1]. In vivo studies have also reported the antioxidant capacity of MEL, which decreases chronic oxidative stress related to aging [8] and reduces blood pressure in men with chronic hypertension [9]. MEL has been successfully used for sleep disorders restoring circadian rhythm and is especially effective in population with neurodegenerative illnesses.

The amphipathic property of MEL allows it to cross some physiological barriers, being present in the cytosol, mitochondria, and different biological membranes [10]. Therefore, MEL provides biological properties where it is needed.

2. Bioavailability, absorption, and adjuvant interactions of melatonin

Its amphiphilic character allows melatonin to penetrate all compartments of a cell because, helped by its small size, conferring a good solubility in both water and lipids. Melatonin and its derivatives have antioxidant ability and can start a radical scavenger cascade creating oxidation products (e.g., hydroxymelatonin) that help to eliminate oxygen reactive species [11]. Due to this, melatonin is effective and bioable in organisms [12]. Herbs that have been used in traditional Chinese medicine have up to several thousands of melatonin nanograms in their tissues [13], implying a decent source of the neurohormone. It was also measured in several parts, however, in seeds where the highest levels have been found, probably related with the needs of reproductive organs (e.g., defend from adversarial attacks), fluctuations of melatonin concentration are even in varieties of the same species [14]. While animals can only obtain melatonin from food, plants can synthesize it or absorb and accumulate it from the environment [15]. Eating foodstuffs rich in melatonin can increase melatonin serum concentration [16]. Organs that produce melatonin (e.g., pineal gland, retina [17], and gastrointestinal tract) can also process it from foodstuffs [18].

2.1 Bioavailability

Melatonin bioavailability from formulations and food ranges from 2.5% to 33% [19, 20] and with protein binding of 60% measured *in vitro* [21]. Oral administration of melatonin has been described as a proper absorption, extensively distributed, and potentially completely metabolized in humans [22]. Its receptors are widely distributed, and melatonin quickly penetrates the blood-brain barrier [23]. Considering that, it would be expected that melatonin from dietary sources would also likely be absorbed. Despite this may be accurate, melatonin uptake from herbal remedies or products and phytomelatonin (melatonin in plants) oral bioavailability have not been highly explored, except for St. John's wort. Thirteen participants were treated with a hydroethanolic extract of dried flowering tops or aerial parts of St. John's wort, and that significantly improved the nocturnal melatonin serum levels [24]. However, this study has the limitation of ignoring extract melatonin concentration or dose taken.

Regarding oral bioavailability in the experiments with chicks, we know that when feeding them with edible plants rich in melatonin, circulating melatonin levels increase, and it is proven that this melatonin is functional as it competed with melatonin binding sites in the brain.

In humans, serum melatonin levels have been assessed after beer intake. This study assessed 18 brands of beer, containing up to 170 pg/mL, males (n = 7) received 660 mL, and females (n = 3) 330 mL. Consumption resulted in an increase of 112 ng and 56 ng of melatonin, respectively, related to the volume taken, confirmed by serum analysis by ELISA prior and 45 min after the beverage [25]. Also in humans, serum melatonin raised from 10 to 12 pg/ml 60 min after a glass of 100 ml of red wine was drunk [26]. Melatonin bioavailability is also high in case of taking fruits, as a study with 12 volunteers consuming for breakfast a juice from either orange, pineapple, or bananas containing 302 ng, 150 ng, and 1.7 ng of melatonin, respectively, increasing melatonin in serum. Blood tests were carried out before juice and then hourly the next 3 hours. ELISA proved that serum melatonin concentration nadir was at hour 2 after breakfast. All values were significantly increased from time zero for pineapples (146 vs. 48 pg/mL, $p = 0.002$), oranges (151 vs. 40 pg/mL, $p = 0.005$), and bananas (140 vs. 32 pg/mL, $p = 0.008$) [27]. Further, an across ages study with three groups of participants (20 ± 10, 45 ± 10, and 75 ± 10 years old) reported after 5-day intake of 200 ml/day of grape juicehigher antioxidant capacity [28], as well as 6-sulfatoxymelatonin in urine [29].

2.2 Pharmacokinetics

Melatonin suffers great hepatic metabolism upon oral intake, with high hepatic first-pass effect [30, 31], which explains its low bioavailability [31]. Animal and human studies describe that melatonin metabolism mainly occurs through CYP1A2 and CYP2C19 hepatic enzymes [30, 32]. 6-Hydroxy-melatonin is conjugated with sulfate and forms the most abundant metabolite (80%): the 6-sulfatoxymelatonin (6-SM) [30, 33]. Then 6-SM metabolite can be measured in urine as an inactive metabolite [34]. Hence, further research is needed in human metabolites as some works have described the existence of active metabolites excreted [30].

2.3 Adjuvant interactions

The co-ingestion of melatonin-rich food with phenolic compounds (caffeic acid or quercetin) could increase its bioavailability [35]. When analyzing the relation of cherries with sleep cycle and urinary 6-hidroxymelatonin sulfate (MT6), it was observed that regardless of melatonin absence in some cherry varieties (Ambrunes had only 37.6 ± 1.4 ng of serotonin in 100 g fresh fruit [36]), an increase of urinary MT6s was detected [37, 38]. Thus, it was possible to infer that both MEL and serotonin present in cherries may have contributed to improvements in sleep parameters and MT6 excretion [37, 38].

3. Functions and effects described for melatonin

In this chapter, authors introduce MEL as a dietary source and its role in human health.

3.1 Antioxidant capacity

MEL promotes the synthesis of antioxidant enzymes as glutathione peroxidase or glutathione reductase [39, 40], improving the reducing capacity in the organism [41], neutralizes the nitrogenous toxins responsible for nitrosamine damage [42, 43], being able to chelate metals [44]. MEL and related metabolites have scavenging capacity [12] being able to neutralize up to 10 types of free radicals [18].

Limson et al. showed that MEL chelates zinc, lead, copper, iron, aluminum, and cadmium ion in a dose-dependent manner [44]. MEL is able to chelate Fe^{3+} and Fe^{2+}, preventing the formation of the hydroxyl radical. Moreover, MEL and its metabolites are also capable of chelating Cu^{2+}, preventing the first step in the Haber-Weiss reaction, and neutralizing the formation of hydroxyl radical.

Additionally, MEL modulates the activity of certain enzymes, limiting the emission of electrons from the mitochondrial respiratory chain, which reduces the formation of superoxide anion [45]. Due to the anti-inflammatory capacity of MEL and considering that inflammation promotes the generation of free radicals [17], oxidative processes with lower production of oxidant molecules can be regulated by the supplementation of MEL [46].

3.2 Cardiovascular protection

The benefits to cardiovascular health related to Mediterranean diet are widely reported and can be partially attributed to the high intake of MEL-rich foods [47].

Most of the studies reporting the effect of MEL on cardiovascular system are focused on ischemia-reperfusion and have been accomplished administrating high doses of MEL (between 1 and 50 μM). Moreover, other studies reported the cardioprotective capacity of MEL using similar concentrations than those found in foods. For example, related to the intake of as red wine [48], MEL at physiological concentration is able to significantly decrease the infarct size after ischemia-reperfusion accident. The mechanism responsible of these effects is related to the activation of the surviving activator factor enhancement (SAFE) pathway, which involves the stimulation of TNF-α and its receptor, leading to the activation of the transcription factor signal transducer and activator of transcription 3 (STAT3). That fact leads to down-regulation of reactive oxygen species (ROS) in the mitochondria and the electron chain transport [49].

Despite MEL being found in foods, more investigation is needed to determine if the consumption of MEL-rich foods is determinant to observe the cardiovascular benefits reported for the administration of MEL or if higher concentration are needed.

3.3 Neuroprotective capacity

The different neurodegenerative diseases are characterized by a rapid and progressive deterioration of the different structures that make up the central nervous system and the compromise of proper brain function. In addition, the degeneration of different parts of the neurons can increase the frequency of symptoms observed in the course of Alzheimer's disease, dementia, Parkinson's disease, amyotrophic lateral sclerosis, or Huntington's disease [50].

The effect that MEL has on the mitochondria is decisive in explaining its role as a neuroprotective agent. MEL is capable of reducing different metabolic pathways

that lead to neuronal death, such as chronic inflammation, increased oxidative stress, changes in the circadian rhythm, decreased autophagy, and increased mitochondrial damage. All these processes can lead to a lower adenosine triphosphate (ATP) production capacity and the consequent neuronal death. Various experimental models of the aforementioned diseases show the efficacy of MEL to slow down or even stop the progression of the disease, in addition to mitigating some of the related symptoms. In fact, it has been reported that the endogenous synthesis of MEL could be altered in diseases such as Alzheimer's and Parkinson's.

There is currently evidence that oxidative damage is decisive in favoring the development and progression of most neurodegenerative diseases. Similarly, the generation of free radicals is crucial in the development of the pathophysiology of these diseases, as well as all neurodegenerative diseases [51]. Thus, current evidence suggests the neuroprotective capacity of MEL in different neurodegenerative disorders, in addition to presenting little or no side effects, even at high doses and higher than those found in food [52].

3.4 Anticancer capacity

MEL can also play the role of anticancer molecule. In fact, MEL has scavenging capacity, which can prevent oxidative injury to nuclear DNA [53] leading to a possible way to prevent and treat some kinds of cancer as other bioactive compounds with similar scavenging ability. Interestingly, MEL can prevent cancer at its first stages, lessening the side effects because of its chronobiotic effects, reducing complications related with radio and chemotherapy used for the treatment of cancer [54].

MEL has reported to have a link with sirtuin 1 (Sirt1) and circadian rhythms as previously reported [53]. It was reported that the disturbance on the synthesis of MEL in the pineal gland decontrols the correct circadian rhythm, increasing the occurrence of cancer. Moreover, MEL is able to reduce the production of Sirt1 protein, reducing the proliferative potential of cancer cells. That fact was not observed in normal cells. Additionally, MEL has antiestrogenic capacity, which could reduce some kinds of cancers such as breast or prostate cancer, which are hormone-related cancers [55].

Furthermore, MEL can be effective in the decrease of brain-related endothelin-1 concentration in stroked patients. Endothelin-1 is considered a relevant compound for the advancement of angiogenesis, being related with regulation of cancer expansion [56]. Angiogenesis is a main cause of tumor growth, providing oxygen and nutrients to dividing cells for the continuation of cell division. Remarkably, the suppression of angiogenesis seems to be assisted by the reduction of endothelin-1 [57].

Therefore, the scientific literature has reported enough information to consider MEL as a promising molecule for the treatment and prevention of cancer particularly through its anti-gonadotropin and anti-estrogenic ability. Because of its low toxicity and the variety of health benefits reported for MEL, it can be concluded that MEL could be considered as a complementary treatment of different types of cancer [58].

3.5 Circadian rhythm

The endogenous production of MEL is restricted to the night, regardless of the activity or resting. In fact, MEL was described as the "chemical expression of darkness" [59], being reduced during the night blocks with light. Moreover, a usual consideration

used as indicator of the circadian rhythm is the "dim light MEL onset," which specifies the initiation of the endogenous production of MEL. Just then, the concentration of plasmatic MEL exceeds 10 pg/mL, compared with daytime levels (1 pg/mL).

After its spreading in the organism, MEL binds to MEL-membrane receptors (MT1 and MT2). The membrane receptors of MEL are situated in the brain (principally the MT2) but also in other peripheral tissues. The expected outcome varies depending on the target organ. For example, in pancreatic islet cells, the binding of MEL with its receptors leads to insulin release to glucose stimulation. Moreover, the MT1 activation in β-cells leads to the phosphorylation of the insulin receptor that controls its release [60]. Therefore, MEL can be determinant for circadian insulin stimulation and is synchronized with the activity-feeding/rest-fasting periods.

Related to this, MEL can act as a central regulator of the cycles of wakefulness, feeding, and rest, being decisive for the correct regulation of the circadian cycle in the different metabolic pathways. MEL links and regulates the sleep-wake cycle with energy metabolism. In fact, during the active phase of the day when low plasma levels of MEL are found, the use and storage of available energy by tissues and cells controlled by MEL can be observed. On the contrary, an increased sensitivity to insulin and glucose by the tissues can be seen, in addition to the synthesis of glycogen and glycolysis or the increase in lipogenesis. During the rest phase, by not eating food, the resulting fasting period means that energy has to be obtained from reserves and used to maintain the different physiological functions. This metabolic phase is characterized by increased insulin resistance, gluconeogenesis and glycogenolysis, lipolysis, and further leptin secretion [61].

4. Melatonin content in foods

The melatonin hormone exists in different types of food, although its content can be very different from one to another, being in nuts and some medicinal plants where it has been found the most [62].

In edible plants, the fruits seem to be the part that contains the least melatonin, while the roots and leaves contain the most [63]. It also depends on the environment where the plants grow, how they are cultivated, temperature, sun exposure, agricultural treatments, etc. [64].

In animals, melatonin has been found mainly in eggs and fish and to a lesser extent in meat. Melatonin has been found in human breast milk, and that of other animals, to vary with circadian rhythms, being lower during the day and higher at night [65, 66]. Regarding plants, melatonin has been found in cereals, although they are still being investigated in different species such as corn, black rice, barley, and oats, among others [67]. In fruits, melatonin has been found in grapes [68], cherries [69], and strawberries [68], other fruits seem to have relatively lower levels of melatonin.

We found melatonin in different vegetables, being undetectable in beets and potatoes [70], and instead we found higher concentrations in mushrooms, tomatoes, and peppers [68]. It has been found in seeds and legumes with relatively high levels; in addition, it has been seen that in the germination process it can increase melatonin levels. Highest levels of melatonin have been found in walnuts [62].

Melatonin has also been searched for in different medicinal plants and high values have been found, above 1000 ng/g [13], for example, it is the case of St. John's Wort, (*Hypericum perforatum*) [71].

4.1 Fermented food

Melatonin concentration can range from picograms to nanograms per mL of product in fermented beverages such as wine and beer. Although the content of melatonin can vary in different unfermented products, it has been proven that the alcoholic fermentation process is important for the melatonin formation process, since it is generated after the addition of yeasts, the role of *Saccharomyces cerevisiae* being fundamental [5, 72].

4.1.1 Wine

Melatonin concentration is modified with fermentation, presenting its highest value between the first and second days of fermentation [73, 74]. Different factors can affect the concentration of MEL in red wine, such as the agrochemicals used, wine-making practices, fermenting microorganisms, or even the composition of the grapes that has been used to produce wine [74–76].

The presence of melatonin in wines has been described by different authors. In Sangiovese red wines and Trebbiano white wine, Mercolini et al. found values of 0.4 and 0.5 ng/mL [77] and found 0.3 and 0.5 ng/mL in varieties of Albana grappa and grape juice [78]. Stege et al. found values of 0.24 ng/mL for Cabernet Sauvignon red wine, 0.16 ng/mL for Malbec red wine, and 0.32 ng/mL for Chardonnay white wine [79]. For Gropello and Merlot wine varieties, Vitalini et al. [80] found values of 4.1 and 8.1 ng/mL, respectively. Rodriguez-Naranjo et al. found values between 74 and 322 ng/mL for pressed wines (Tempranillo, Merlot, Sauvignon, Syrah, and Tintilla de Rota) and between 250 and 340 ng/mL for racked wines (Merlot, Sauvignon, Tempranillo, Syrah, and Tintilla de Rota [5]). For monovarietal red wines, Vitalini et al. found values between 0.14 and 0.62 ng/mL, for multivarietal red wines 0.05–0.31 ng/mL, for white wine 0.18 ng/mL, for dessert wines between 0 and 0.31 ng/mL, and for balsamic vinegar of Modena 0.11–0.13 ng/mL [81].

In a study in which tryptophan and certain metabolites, including melatonin, were analyzed simultaneously in various types of red wine, melatonin values ranged from 0.038 ± 0.001 g/L to 0.063 ± 0.004 g/L [81]. It should be noted that the presence of melatonin in the grape is not always reflected later in the wine, as shown in a study by Gómez et al [82], where the melatonin concentration of the grape was 120–160 ng/g; however, in the wine from these grapes there was no longer melatonin but a melatonin isomer that decreased its concentration with values from 18 to 24 ng/g.

It is important to note that the oral bioavailability of melatonin after ingesting a glass of wine is not known, which is not the case with polyphenols where it is known, perhaps due to the complex process that can influence the absorption of active metabolites [80]. However, it is known when it is consumed in supplement form since it is consumed in high doses and has been known for years [77, 83]. In addition, the presence of ethanol seems to improve the amount of melatonin, since it acts as a solvent, improving the permeability of the membranes [84].

In humans, Varoni et al. evaluated the serum levels of melatonin after administering a melatonin-enriched wine versus a placebo wine, and it was observed that the maximum concentrations were within 60 min, being 8.7 ± 2.2 pg/min for the melatonin group and 6.7 ± 0.6 pg/min for placebo wine, the results showed an area under the curve of 993 ± 162 vs. 745 ± 88 pg/min for the melatonin group versus placebo, respectively. No significant significant differences were observed between the concentration in saliva, the peak was reached at 45 minutes after melatonin intake, also without statistically significant differences, showing placebo levels after 120 min [80].

4.1.2 Beer

Beer is regularly consumed by a large number of people and is characterized by having a wide variety of bioactive nutraceutical and phytochemical compounds such as polyphenols and antioxidants [85]. In addition, they contain B complex vitamins, ascorbic acid, citric acid, etc. A study of 18 commercial brands of beer investigated the content of melatonin, with different degrees of alcohol, and showed that all the beers that participated in the study had melatonin, being directly proportional to the alcohol content. Thus, the higher the alcohol content, the higher the concentration of melatonin, with values ranging from 51.8 ± 2.2 pg/ml in nonalcoholic beer to 169.7 ± 8.7 pg/ml in normal beer [82]. This finding could be due to the fact that alcohol acts as a solvent for melatonin.

Furthermore, another study measured the concentration of melatonin in the different craft beer production processes, obtaining a final value of 333 pg/mL in a 5% vol. of alcohol after the second fermentation; these values are three times higher than that of commercial beers [86]. In terms of composition, in concentrated worth barley were found high levels of melatonin (339 ± 9 pg/mL) while low amounts were found in hops 33 ± 10 pg/mL [86]. The concentration of melatonin in beer can be attributed to the amount of melatonin in the barley, while in the case of wine, it seems to depend on the fermentation processes rather than the original amount in the grape.

5. Conclusions

Current literature highlights the high bioavailability of melatonin in human studies. The different MEL supplements are available for the treatment of sleep disorders or the effects derived from jet lag and are mainly used to reset the circadian clock. In addition, melatonin acts as a central synchronizer, capable of regulating a wide range of physiological functions, such as glucose and body lipid metabolism. Additionally, human clinical trials have shown that melatonin treatment can help improve or alleviate some of the most dangerous cardiovascular events. Similarly, melatonin has antioxidant capacity and is capable of neutralizing a wide variety of reactive oxygen and nitrogen molecules and indirectly modulates the activity of the endogenous enzymatic antioxidant system. Due to this cardioprotective capacity against oxidative stress, and taking into account the inhibition of different inflammatory and apoptotic pathways, melatonin is capable of exerting neuroprotective capacity. These findings reveal the great capacity and therapeutic potential of this molecule to combat different neurodegenerative pathologies.

Conflict of interest

The authors declare no conflict of interest.

Appendices and nomenclature

AFMK	N-1-acetyl-N-2-formyl-5-methoxyquinuramine
AMK	N-1-acetyl-5-methoxyquinuramine
ATP	adenosine triphosphate

CYP1A2	cytochrome P-450 1A2
CYP2C19	cytochrome P-450 2C19
ELISA	enzyme immunoassay adsorption assay
DNA	deoxyribonucleic acid
MEL	melatonin
MT1	melatonin receptor 1
MT2	melatonin receptor 2
MT6s	6-hydroxymelatonin sulfate
ROS	reactive oxygen species
SAFE	surviving activator factor enhancement
STAT3	signal transducer and activator of transcription 3
TNF-α	tumor necrosis tumoral alpha
6-SM	6-sulfatoxymelatonin

Author details

Purificación Ballester, Pilar Zafrilla, Raúl Arcusa, Alejandro Galindo*, Begoña Cerdá and Javier Marhuenda
Faculty of Health Sciences, Pharmacy Department, Catholic University of Murcia, Murcia, Spain

*Address all correspondence to: agalindo@ucam.edu

IntechOpen

References

[1] Hardeland R, Pandi-Perumal SR. Melatonin, a potent agent in antioxidative defense: Actions as a natural food constituent, gastrointestinal factor, drug and prodrug. Nutrition & Metabolism (London). 2005;**2**:22

[2] Sprenger J, Hardeland R, Fuhrberg B, et al. Melatonin and other 5-methoxylated indoles in yeast: Presence in high concentrations and dependence on tryptophan availability. Cytologia (Tokyo). 1999;**64**:209-213

[3] de la Puerta C, Carrascosa-Salmoral MP, García-Luna PP, et al. Melatonin is a phytochemical in olive oil. Food Chemistry. 2007;**104**:609-612

[4] Iriti M, Rossoni M, Borgo M, et al. Benzothiadiazole enhances resveratrol and anthocyanin biosynthesis in grapevine, meanwhile improving resistance to Botrytis cinerea. Journal of Agricultural and Food Chemistry. 2004;**52**:4406-4413

[5] Rodriguez-Naranjo MI, Gil-Izquierdo A, Troncoso AM, et al. Melatonin is synthesised by yeast during alcoholic fermentation in wines. Food Chemistry. 2011;**126**:1608-1613

[6] Fernández-Mar MI, Mateos R, García-Parrilla MC, et al. Bioactive compounds in wine: Resveratrol, hydroxytyrosol and melatonin: A review. Food Chemistry. 2012;**130**:797-813

[7] Schaefer M, Hardeland R. The melatonin metabolite N-acetyl-5-methoxykynuramine is a potent singlet oxygen scavenger. Journal of Pineal Research. 2009;**46**:49-52

[8] Nogués MR, Giralt M, Romeu M, et al. Melatonin reduces oxidative stress in erythrocytes and plasma of senescence-accelerated mice. Journal of Pineal Research. 2006;**41**:142-149

[9] Scheer FAJL, Van Montfrans GA, van Someren EJW, et al. Daily nighttime melatonin reduces blood pressure in male patients with essential hypertension. Hypertens (Dallas, Tex 1979). 2004;**43**:192-197

[10] Karbownik M, Lewinski A, Reiter RJ. Anticarcinogenic actions of melatonin which involve antioxidative processes: Comparison with other antioxidants. The International Journal of Biochemistry & Cell Biology. 2001;**33**:735-753

[11] Rosen J, Than NN, Koch D, et al. Interactions of melatonin and its metabolites with the ABTS cation radical: Extension of the radical scavenger cascade and formation of a novel class of oxidation products, C2-substituted 3-indolinones. Journal of Pineal Research. 2006;**41**:374-381

[12] Galano A, Tan DX, Reiter RJ. On the free radical scavenging activities of melatonin's metabolites, AFMK and AMK. Journal of Pineal Research. 2013;**54**:245-257

[13] Chen G, Huo Y, Tan D-X, et al. Melatonin in Chinese medicinal herbs. Life Sciences. 2003;**73**:19-26

[14] Tan D-X, Hardeland R, Manchester LC, et al. Functional roles of melatonin in plants, and perspectives in nutritional and agricultural science. Journal of Experimental Botany. 2012;**63**:577-597

[15] Tan D-X, Manchester LC, Helton P, et al. Phytoremediative capacity of plants enriched with melatonin. Plant Signaling & Behavior. 2007;**2**:514-516

[16] Iriti M, Varoni EM. The good health of Bacchus: Melatonin in grapes, the unveiled myth. LWT- Food Science and Technology. 2016;**65**:758-761

[17] Pandi-Perumal SR, Srinivasan V, Maestroni GJM, et al. Melatonin: Nature's most versatile biological signal? The FEBS Journal. 2006;**273**:2813-2838

[18] Reiter RJ, Mayo JC, Tan D-X, et al. Melatonin as an antioxidant: Under promises but over delivers. Journal of Pineal Research. 2016;**61**:253-278

[19] Harpsøe NG, Andersen LPH, Gögenur I, et al. Clinical pharmacokinetics of melatonin: A systematic review. European Journal of Clinical Pharmacology. 2015;**71**:901-909

[20] Andersen LPH, Werner MU, Rosenkilde MM, et al. Pharmacokinetics of high-dose intravenous melatonin in humans. Journal of Clinical Pharmacology. 2016;**56**:324-329

[21] Lalanne S, Fougerou-Leurent C, Anderson GM, et al. Melatonin: From pharmacokinetics to clinical use in autism spectrum disorder. International Journal of Molecular Sciences. 2021;**22**:1490

[22] Salehi B, Sharopov F, Fokou PVT, et al. Melatonin in medicinal and food plants: Occurrence, bioavailability, and health potential for humans. Cell. 2019;**8**:681

[23] Ng KY, Leong MK, Liang H, et al. Melatonin receptors: Distribution in mammalian brain and their respective putative functions. Brain Structure & Function. 2017;**222**:2921-2939

[24] World Health Organization. WHO Consultation on Selected Medicinal Plants. 2nd ed. Ravello-Salerno, Italy; 1999

[25] Maldonado MD, Moreno H, Calvo JR. Melatonin present in beer contributes to increase the levels of melatonin and antioxidant capacity of the human serum. Clinical Nutrition. 2009;**28**:188-191

[26] Iriti M, Varoni EM, Vitalini S. Melatonin in traditional Mediterranean diets. Journal of Pineal Research. 2010;**49**:101-105

[27] Sae-Teaw M, Johns J, Johns NP, et al. Serum melatonin levels and antioxidant capacities after consumption of pineapple, orange, or banana by healthy male volunteers. Journal of Pineal Research. 2013;**55**:58-64

[28] González-Flores D, Gamero E, Garrido M, et al. Urinary 6-sulfatoxymelatonin and total antioxidant capacity increase after the intake of a grape juice cv. Tempranillo stabilized with HHP. Food Functionals. 2012;**3**:34-39

[29] Schernhammer ES, Feskanich D, Niu C, et al. Dietary correlates of urinary 6-sulfatoxymelatonin concentrations in the Nurses' Health Study cohorts. The American Journal of Clinical Nutrition. 2009;**90**:975-985

[30] Andersen LPH, Gögenur I, Rosenberg J, et al. Pharmacokinetics of melatonin: The missing link in clinical efficacy? Clinical Pharmacokinetics. 2016;**55**:1027-1030

[31] Di W-L, Kadva A, Johnston A, et al. Variable bioavailability of oral melatonin. The New England Journal of Medicine. 1997;**336**:1028-1029

[32] Von Bahr C, Ursing C, Yasui N, et al. Fluvoxamine but not citalopram increases serum melatonin in healthy subjects–an indication that cytochrome P 450 CYP1A2 and CYP2C19 hydroxylate

melatonin. European Journal of Clinical Pharmacology. 2000;**56**:123-127

[33] European Medicines Agency. Assessment Report for Circadin. 2007. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/circadin [Accessed: August 03, 2018]

[34] Tordjman S, Chokron S, Delorme R, et al. Melatonin: Pharmacology, functions and therapeutic benefits. Current Neuropharmacology. 2017;**15**:434-443

[35] Jana S, Rastogi H. Effects of caffeic acid and quercetin on in vitro permeability, metabolism and in vivo pharmacokinetics of melatonin in rats: Potential for herb-drug interaction. European Journal of Drug Metabolism and Pharmacokinetics. 2017;**42**:781-791

[36] González-Flores D, Velardo B, Garrido M, et al. Ingestion of Japanese plums (Prunus salicina Lindl. cv. Crimson Globe) increases the urinary 6-sulfatoxymelatonin and total antioxidant capacity levels in young, middle-aged and elderly humans: Nutritional and functional characterization of their content. Journal of Food Nutritional Research. 2011;**50**:229-236

[37] Garrido M, Paredes SD, Cubero J, et al. Jerte Valley cherry-enriched diets improve nocturnal rest and increase 6-sulfatoxymelatonin and total antioxidant capacity in the urine of middle-aged and elderly humans. The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences. 2010;**65**:909-914

[38] Garrido M, González-Gómez D, Lozano M, et al. A Jerte valley cherry product provides beneficial effects on sleep quality. Influence on aging. The Journal of Nutrition, Health & Aging. 2013;**17**:553-560

[39] Fischer TW, Kleszczyński K, Hardkop LH, et al. Melatonin enhances antioxidative enzyme gene expression (CAT, GPx, SOD), prevents their UVR-induced depletion, and protects against the formation of DNA damage (8-hydroxy-2'-deoxyguanosine) in ex vivo human skin. Journal of Pineal Research. 2013;**54**:303-312

[40] Rodriguez C, Mayo JC, Sainz RM, et al. Regulation of antioxidant enzymes: A significant role for melatonin. Journal of Pineal Research. 2004;**36**:1-9

[41] Gitto E, Tan DX, Reiter RJ, et al. Individual and synergistic antioxidative actions of melatonin: Studies with vitamin E, vitamin C, glutathione and desferrioxamine (desferoxamine) in rat liver homogenates. The Journal of Pharmacy and Pharmacology. 2001;**53**:1393-1401

[42] Gilad E, Cuzzocrea S, Zingarelli B, et al. Melatonin is a scavenger of peroxynitrite. Life Sciences. 1997;**60**:PL169-74

[43] Noda Y, Mori A, Liburdy R, et al. Melatonin and its precursors scavenge nitric oxide. Journal of Pineal Research. 1999;**27**:159-163

[44] Limson J, Nyokong T, Daya S. The interaction of melatonin and its precursors with aluminium, cadmium, copper, iron, lead, and zinc: An adsorptive voltammetric study. Journal of Pineal Research. 1998;**24**:15-21

[45] Hardeland R. Antioxidative protection by melatonin: Multiplicity of mechanisms from radical detoxification to radical avoidance. Endocrine. 2005;**27**:119-130

[46] Mauriz JL, Collado PS, Veneroso C, et al. A review of the molecular aspects of melatonin's anti-inflammatory actions:

Recent insights and new perspectives. Journal of Pineal Research. 2013;**54**:1-14

[47] Meng X, Li Y, Li S, et al. Dietary sources and bioactivities of melatonin. Nutrients. 2017;**9**:367

[48] Lamont KT, Somers S, Lacerda L, et al. Is red wine a SAFE sip away from cardioprotection? Mechanisms involved in resveratrol-and melatonin-induced cardioprotection. Journal of Pineal Research. 2011;**50**:374-380

[49] Hadebe N, Cour M, Lecour S. The SAFE pathway for cardioprotection: Is this a promising target? Basic Research in Cardiology. 2018;**113**:9

[50] Spinedi E, Cardinali DP. Neuroendocrine-metabolic dysfunction and sleep disturbances in neurodegenerative disorders: Focus on Alzheimer's disease and melatonin. Neuroendocrinology. 2019;**108**:354-364

[51] Escames G, Lopez A, Antonio Garcia J, et al. The role of mitochondria in brain aging and the effects of melatonin. Current Neuropharmacology. 2010;**8**:182-193

[52] Weishaupt JH, Bartels C, Pölking E, et al. Reduced oxidative damage in ALS by high-dose enteral melatonin treatment. Journal of Pineal Research. 2006;**41**:313-323

[53] Jung-Hynes B, Schmit TL, Reagan-Shaw SR, et al. Melatonin, a novel Sirt1 inhibitor, imparts antiproliferative effects against prostate cancer in vitro in culture and in vivo in TRAMP model. Journal of Pineal Research. 2011;**50**:140-149

[54] Gil-Martín E, Egea J, Reiter RJ, et al. The emergence of melatonin in oncology: Focus on colorectal cancer. Medicinal Research Reviews. 2019;**39**:2239-2285

[55] Sánchez-Barceló E, Cos S, Mediavillla D, et al. Melatonin–estrogen interactions in breast cancer. Journal of Pineal Research. 2005;**38**:217-222

[56] Ahmed M, Rghigh A. Polymorphism in Endothelin-1 Gene: An Overview. Current Clinical Pharmacology. 2016;**11**:191-210

[57] Rosanò L, Spinella F, Bagnato A. Endothelin 1 in cancer: Biological implications and therapeutic opportunities. Nature Reviews. Cancer. 2013;**13**:637-651

[58] Kubatka P, Zubor P, Busselberg D, et al. Critical Reviews in Oncology / Hematology Melatonin and breast cancer: Evidences from preclinical and human studies. Critical Reviews in Oncology/Hematology. 2018;**122**:133-143

[59] Reiter RJ. Melatonin: The chemical expression of darkness. Molecular and Cellular Endocrinology. 1991;**79**:C153-C158

[60] Picinato MC, Hirata AE, Cipolla-Neto J, et al. Activation of insulin and IGF-1 signaling pathways by melatonin through MT1 receptor in isolated rat pancreatic islets. Journal of Pineal Research. 2008;**44**:88-94

[61] Cipolla-Neto J, Amaral FG, Afeche SC, et al. Melatonin, energy metabolism, and obesity: A review. Journal of Pineal Research. 2014;**56**:371-381

[62] Oladi E, Mohamadi M, Shamspur T, et al. Spectrofluorimetric determination of melatonin in kernels of four different Pistacia varieties after ultrasound-assisted solid-liquid extraction. Spectrochimica Acta. Part A, Molecular and Biomolecular Spectroscopy. 2014;**132**:326-329

[63] Reiter RJ, Tan DX, Burkhardt S, et al. Melatonin in plants. Nutrition Reviews. 2001;**59**:286-290

[64] Iriti M, Rossoni M, Faoro F. Melatonin content in grape: Myth or panacea? Journal of the Science of Food and Agriculture. 2006;**86**:1432-1438

[65] Tan D, Zanghi BM, Manchester LC, et al. Melatonin identified in meats and other food stuffs: Potentially nutritional impact. Journal of Pineal Research. 2014;**57**:213-218

[66] Milagres MP, Minim VPR, Minim LA, et al. Night milking adds value to cow's milk. Journal of the Science of Food and Agriculture. 2014;**94**:1688-1692

[67] Yılmaz C, Kocadağlı T, Gokmen V. Formation of melatonin and its isomer during bread dough fermentation and effect of baking. Journal of Agricultural and Food Chemistry. 2014;**62**:2900-2905

[68] Stürtz M, Cerezo AB, Cantos-Villar E, et al. Determination of the melatonin content of different varieties of tomatoes (*Lycopersicon esculentum*) and strawberries (*Fragaria ananassa*). Food Chemistry. 2011;**127**:1329-1334

[69] González-Gómez D, Lozano M, Fernández-León MF, et al. Detection and quantification of melatonin and serotonin in eight sweet cherry cultivars (*Prunus avium* L.). European Food Research and Technology. 2009;**229**:223-229

[70] Badria FA. Melatonin, serotonin, and tryptamine in some Egyptian food and medicinal plants. Journal of Medicinal Food. 2002;**5**:153-157

[71] Murch SJ, Simmons CB, Saxena PK. Melatonin ateşli ve diğer şifalı bitkilerde bulunur. Lancet. 1997;**350**:1598-1599

[72] Rodriguez-Naranjo MI, Torija MJ, Mas A, et al. Production of melatonin by Saccharomyces strains under growth and fermentation conditions. Journal of Pineal Research. 2012;**53**:219-224

[73] Waldhauser F, Waldhauser M, Lieberman HR, et al. Bioavailability of oral melatonin in humans. Neuroendocrinology. 1984;**39**:307-313

[74] Zhdanova IV, Wurtman RJ, Morabito C, et al. Effects of low oral doses of melatonin, given 2-4 hours before habitual bedtime, on sleep in normal young humans. Sleep. 1996;**19**:423-431

[75] Vitalini S, Gardana C, Simonetti P, et al. Melatonin, melatonin isomers and stilbenes in Italian traditional grape products and their antiradical capacity. Journal of Pineal Research. 2013;**54**:322-333

[76] Guardiola-Lemaitre B. Toxicology of melatonin. Journal of Biological Rhythms. 1997;**12**:697-706

[77] Mercolini L, Addolorata Saracino M, Bugamelli F, et al. HPLC-F analysis of melatonin and resveratrol isomers in wine using an SPE procedure. Journal of Separation Science. 2008;**31**:1007-1014

[78] Hornedo-Ortega R, Cerezo AB, Troncoso AM, et al. Melatonin and other tryptophan metabolites produced by yeasts: Implications in cardiovascular and neurodegenerative diseases. Frontiers in Microbiology. 2016;**6**:1565

[79] Stege PW, Sombra LL, Messina G, et al. Determination of melatonin in wine and plant extracts by capillary electrochromatography with immobilized carboxylic multi-walled carbon nanotubes as stationary phase. Electrophoresis. 2010;**31**:2242-2248

[80] Vitalini S, Gardana C, Zanzotto A, et al. From vineyard to glass: Agrochemicals enhance the melatonin and total polyphenol contents and antiradical activity of red wines. Journal of Pineal Research. 2011;**51**:278-285

[81] Vitalini S, Gardana C, Simonetti P, et al. Melatonin, melatonin isomers and stilbenes in I talian traditional grape products and their antiradical capacity. Journal of Pineal Research. 2013;**54**:322-333

[82] Gomez FJV, Raba J, Cerutti S, et al. Monitoring melatonin and its isomer in Vitis vinifera cv. Malbec by UHPLC-MS/MS from grape to bottle. Journal of Pineal Research. 2012;**52**:349-355

[83] Fracassetti D, Vigentini I, Lo Faro AFF, et al. Assessment of Tryptophan, Tryptophan Ethylester, and Melatonin Derivatives in Red Wine by SPE-HPLC-FL and SPE-HPLC-MS Methods. Foods (Basel, Switzerland). 2019;**8**:99-111

[84] Mercolini L, Mandrioli R, Raggi MA. Content of melatonin and other antioxidants in grape-related foodstuffs: Measurement using a MEPS-HPLC-F method. Journal of Pineal Research. 2012;**53**:21-28

[85] Meng J-F, Shi T-C, Song S, et al. Melatonin in grapes and grape-related foodstuffs: A review. Food Chemistry. 2017;**231**:185-191

[86] Varoni EM, Paroni R, Antognetti J, et al. Effect of red wine intake on serum and salivary melatonin levels: A Randomized, Placebo-Controlled Clinical Trial. Molecules. 2018;**23**:2472-2482

Chapter 8

Ginger in the Prevention of Cardiovascular Diseases

Begoña Cerdá, Javier Marhuenda, Raúl Arcusa, Débora Villaño, Purificación Ballester and Pilar Zafrilla

Abstract

Ginger, *Zingiber officinale*, is a member of the Zingiberaceae family, used in traditional medicine for treatment of a variety of conditions. Many pharmacological activities have been reported for this plant (anti-inflammatory, anti-tumorigenic, anti-apoptotic, anti-hyperglycemic, cancer-chemopreventive, and anti-lipidemic). Cardiovascular disease, which includes coronary artery disease, acute myocardial infarction, peripheral arterial disease, and stroke, is one of the leading causes of death worldwide. In recent years, several studies have described that ginger can control or improve some cardiovascular risk factors such as cholesterol levels, hypertension, or atherosclerosis. The aim of the present review is to summarize the effects of ginger bioactive compounds on cardiovascular diseases.

Keywords: cardiovascular disease, ginger, hypertension, obesity, gingerol, shogaol

1. Introduction

There is an urgent need to implement intervention measures and health policies to reduce mortality associated to cardiovascular disease (CVD), which will result in more adequate, healthy, and sustainable development per each country. CVD has caused 6.2 million deaths worldwide in people aged 30–70 years in 2019 [1].

Regarding cardiovascular health, there are certain modifiable risk factors that can be intervened upon to improve health. These factors include: hypertension, elevated fasting plasma glucose, elevated low-density lipoprotein (LDL) or cholesterol, and alterations in renal function. Environmental factors such as air and household pollution, smoking, low physical activity, and overweight and obesity are also included. In addition, in the case of women, the consumption of oral contraceptives and the presence of polycystic ovaries syndrome increase the risk of suffering CVD [2].

There are numerous studies linking diet and health, and this is most evident in the case of cardiovascular risk. Both dietary patterns, such as a diet rich in antioxidants, fiber (from vegetables, whole grains, fruits, nuts, pulses) fish, poor in processed foods (with high content in sugar or animal fats), together with the food intake containing specific bioactive substances or nutrients can modulate the risk factors [3, 4]. Therefore, changes in lifestyle and diet can prevent these diseases [5].

CVD is linked to the development of atherosclerosis and is directly related with an inflammatory response. This response is prompted by bad diet habits, sedentary lifestyle, obesity, and stress [6].

Herbal measurements are used to develop new drugs with higher potency and fewer adverse effects targeting the modulation of biological activities.

Ginger (*Zingiber officinale*) is among the medicinal plants with beneficial health effects that has been widely used in pharmaceutical products and food. Its crude extract is cardioprotective due to its antihypertensive, antiplatelet, and cardiotonic effects [7].

The term nutraceutical is used for any food or ingredient with a beneficial effect on health beyond the traditional nutritional effects; further, it has a positive impact on health, physical or cognitive state [8]. Numerous nutraceuticals are used for the prevention of CVDs, including ginger (see **Table 1**).

Apart from its cardioprotective effects, ginger has numerous properties such as antimicrobial, antioxidant, anti-inflammatory, anti-carcinogenic, and neurodegenerative diseases prevention. It prevents chemotherapy-induced emesis, nausea, and respiratory disorders [9, 10].

Ginger's flavor and aroma come from its volatile oils (~1–3% of the weight of fresh ginger) and nonvolatile pungent oleoresins. Further, the pharmacological properties are due to its oleoresin's composition, rich in zingerone (ZGR), gingerols (6/8/10-gingerols), and shogaols (6/8/10-shogaols and 6-hydroshogaol). The spiciness character of dried ginger rhizome comes from the gingerols, especially 6-gingerol. During drying, gingerols transform into ZGR, reducing pungency and providing a spicy-sweet aroma, and shogaols concentration increases [11].

Ginger inhibits lipid peroxidation through its antioxidant effect. 6-Gingerol increases Beclin1 expression to promote autophagy in human endothelial cells and inhibits *PI3K*/*AKT*/*mTOR* pathway signaling not affecting the cell cycle [12].

Ginger could prevent atherosclerosis, since consumption of a ginger extract has been observed to improve lipoprotein results in hamsters thanks to an increased activity of the liver enzyme CYP7A1 and decreased mRNA levels of intestinal cholesterol absorption proteins such as MTP, ACAT2, and NPC1L1 [13].

Nutraceuticals	**Properties**
PUFA n-3 (polyunsaturated fatty acid)	Arrhythmias, sudden death, hypertriglyceridemia, antiplatelet agents, anti-inflammatories
Q10 coenzyme	Antioxidant, antihypertensive
Vitamin D	Depression, atherosclerosis, valvular calcification
Resveratrol	Anti-inflammatories, antioxidant
Red yeast rice	Improves dyslipidemia
Phytosterols	Lowers cholesterol, LDL-C, antihypertensive
Flavonoids	Antiplatelet agents, anti-inflammatories antioxidant, antihypertensive
Dietary fiber	Dyslipidemia, metabolic syndrome decreases total cholesterol, LDL-C, triglycerides, blood glucose, and body weight
Ginger	Anti-inflammatories, antioxidant antiplatelet agent, antihypertensive
B complex	Reduces hyperhomocysteinemia

Table 1.
Nutraceuticals in the prevention of cardiovascular diseases [9].

6-Gingerol regulates lipogenesis, fatty acid oxidation, mitochondrial dysfunction, and oxidative stress of aging rats. Several authors observed that 8-gingerol due to its antioxidant properties could inhibit melanogenesis in murine melanoma cells. In addition, it increases the activity of the antioxidant enzyme superoxide dismutase (SOD) and decreases the levels of malondialdehyde (MDA), a marker of lipid peroxidation, in a concentration-dependent manner [14, 15].

Inflammation associated with CVD induces an increase in proinflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6). Several authors have observed that ginger significantly reduces TNF-α values, and 6-gingerol reduces the levels of inducible nitric oxide (NO) synthase enzyme and inflammatory factors [16].

Ginger can also be used in moderate obesity, a cardiovascular risk factor. Ginger increases lipolysis and thermogenesis and inhibits lipogenesis; therefore, it could be used to prevent obesity [17].

In summary, ginger consumption in the diet could improve cardiovascular health by lowering blood pressure, improving lipid profile, preventing obesity, improving glycemic control, and vascular health. The benefits of ginger on cardiovascular risk factors are mediated by transcription factors such as adenosine-monophosphate-activated protein kinase, peroxisome proliferator-activated receptors, peroxisome proliferator-activated protein kinase, and nuclear factor kappa B (NF-κB) [8, 18]. Having that in mind, the purpose of the present review chapter is to summarize the effects of bioactive compounds in ginger on CVD.

2. Cardiovascular risk factors

CVD is a group of disorders of the heart and blood vessels. It includes a large number of pathologies, among which it is worth highlighting: coronary heart disease, cerebrovascular diseases, peripheral arteriopathies, and rheumatic and congenital heart disease, among others. In most of them there is a common pathological process, atherosclerosis [19, 20]. This condition occurs when fat and cholesterol build up on the walls of blood vessels or in the arteries. This accumulation gives rise to atherosclerotic plaques. Over time, plaques can narrow blood vessels and cause problems throughout the body. If an artery becomes blocked, it can lead to a heart attack or stroke [21].

Cardiovascular risk factors are those that are associated with a greater probability of suffering from CVD. It is widely described that the most developed countries' lifestyles entail an increased risk of suffering from CVD. There are many studies that showed that a significant percentage of CVD and its mortality can be prevented by acting on cardiovascular risk factors [3].

Atherosclerosis is a multifactorial disease, in which several risk factors are involved [22]. The prevalence and potency of these risk factors vary. Cardiovascular risk factors improve CVD by reducing plaque formation.

Two types of risk factors can be differentiated: modifiable and non-modifiable. Pencina et al. established the importance of both and determined that the non-modifiable factors (sex, age, and race) account for between 63 and 80% of the risk factors, while the weight of the modifiable factors is much lower. But, control of modifiable risk factors leads to substantial reductions of cardiovascular events [23, 24].

2.1 Non-modifiable risk factors

Non-modifiable risk factors are sex, age, race, and genotype. They are those that are not likely to be modified, therefore nothing can be done about them. It has been proven that cardiovascular risk is higher in men than in women, increases after 35 years, and Hispanics, Latinos, and Southeast Asians have a higher cardiovascular risk [24].

2.2 Modifiable risk factors

Modifiable risk factors are hypertension, hypertension; obesity and diabetes; dyslipidemias; chronic stress; diet; tobacco; and sedentary lifestyle [25]. They are those that are likely to be modified, where actions can be directed attempting to prevent and/or improve atherosclerosis and therefore CVD.

2.2.1 Hypertension

Hypertension is the most important CVD risk factor. There is a direct relationship between increased blood pressure and the development of CVD. When properly treated, CVD mortality is reduced. Its pathophysiology is very complex and different mechanisms are involved, including the central nervous system, the immune system, and the neurohumoral system [26].

2.2.2 Obesity and diabetes

The prevalence of obesity in the world is increasing in a very worrying way across all ages [27]. The relationship between obesity and CVD is clear. It has been shown how it contributes to atherosclerosis through different mechanisms. On the other hand, it must be taken into account that obesity is a risk factor for other comorbidities such as diabetes, sleep apnea, dyslipidemia, hypertension, and even cancer [28, 29].

2.2.3 Dyslipidemias

Since lipids are involved in the formation of atherosclerotic plaque, especially LDL cholesterol and TG, increases of their plasmatic levels entail a risk of atherosclerosis and CVD. This is what happens in dyslipidemias. Reducing them is a fundamental therapeutic strategy to reduce CVD risk [30, 31].

2.2.4 Chronic stress

It is one of the most important cardiovascular risk factors. Chronic stress is a situation maintained over time in which the body generates a nonspecific and systemic response as a result of exposure to negative external factors. The relationship between chronic stress and the risk of CVD has been widely demonstrated [32].

2.2.5 Diet

It is clear that diet influences the maintenance of good cardiovascular health. And it is an essential tool to control other risk factors such as diabetes, obesity, dyslipidemia, and even hypertension. It has been proven that diets such as the Mediterranean

or DASH reduce cardiovascular risk. They are diets that improve markers of inflammation and oxidative stress and also contribute to improving the lipid and glycemic (improvement of insulin sensitivity) profiles, and endothelial function. In addition, they have proven antithrombotic properties. The consumption of fiber, omega-3 acids, vegetables and fruits, and whole grains seems to be decisive in reducing cardiovascular risk [33–36].

2.2.6 Smoking

Tobacco continues to be one of the most important cardiovascular risk factors. Since its consumption increases the formation of atherosclerotic plaque, through an enhanced inflammation, endothelial dysfunction, arterial stiffness, and lipid profile [37]. In addition, its consumption increases the heart rate; myocardial contractility; thrombus formation by increased platelet activation and adhesion and procoagulant profile [38].

2.2.7 Sedentary lifestyle

Regular and moderate physical activity, which modifies muscle tissue and adipose tissue, has been shown to have a positive impact on health. It reduces systemic inflammation and has an antiatherogenic effect. Therefore, lack of physical activity is a cardiovascular risk factor [39].

3. Bioactive compounds of ginger

Ginger, the rhizome of *Zingiber officinale* Roscoe that belongs to Zingiberaceae family, is commonly used as a spice or dietary supplement and has been widely used in traditional medicine throughout history [40]. Ginger has been identified as having a multitude of different bioactive compounds, including lipids, carbohydrates, terpenes, and phenolic compounds, and its pharmacological effects are largely due to phenolic compounds and terpenes [41, 42]. Ginger-derived terpenes (α-zingiberene, camphene, ar-curcumene, β-phellandrene, E-α farnesene, β-bisabolene, α-piene) [43] are known to have antioxidant, anti-inflammatory, antibacterial, antidiabetic, analgesic, gastroprotective, neuroprotective, and anti-carcinogenic properties [41]. Of the 400 types of compounds present in ginger, four phenolic compounds are mainly responsible for its pharmacological effects: gingerols, shogaols, paradols, and ZGR [44, 45]. There are also other types of compounds related to gingerol (8-gingerol, 10-gingerol, and 12-gingerol) and shogaol (1-dehydrogingerdione, 6-gingerdione, and 10-gingerdione) [42].

The main pungent and most abundant compound, 6-gingerol, which is present in fresh ginger, attenuates various chronic disorders. By dehydration and after long storage, this compound is converted into 6-shogaol, which is more stable and has greater pharmacological effects than its precursor 6-gingerol [46, 47]. 6-Shogaol is converted to 6-paradol by bacterial metabolism, and both possess similar anti-inflammatory and antioxidant properties [40, 47]. Antioxidant, antitumoral, antilipidermic, antibacterial, and anti-inflammatory actions are attributed to ZGR, and it is synthesized by reverse aldolization of gingerols when heating fresh ginger [47, 48]. **Figure 1** summarizes the metabolization pathways of 6-gingerol as a function of thermal processing.

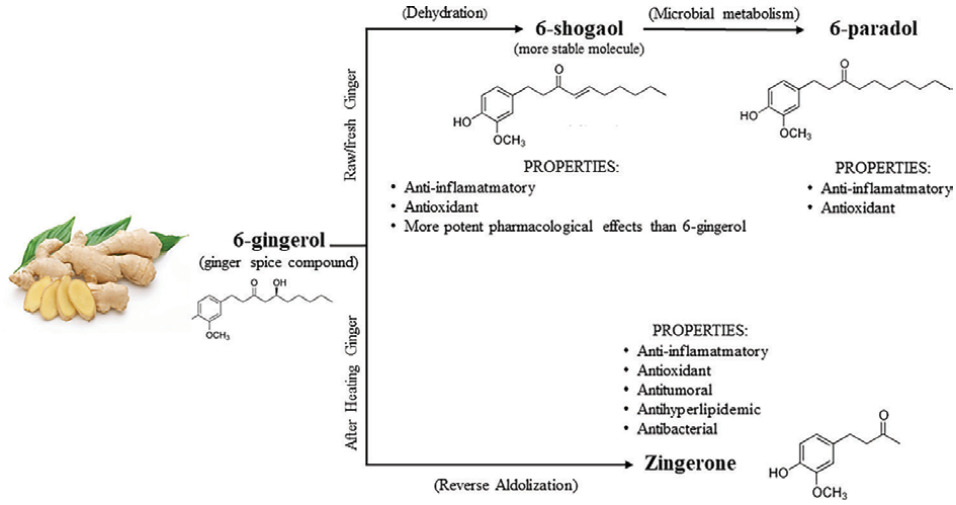

Figure 1.
Properties and metabolism of gingerols.

Zick et al. [49] observed that 6-shogaol and the 6-, 8-, and 10-gingerols have good bioavailability when consumed orally, being detected as sulfate and glucuronide conjugates. However, 6-gingerol has not been detected free in plasma after an oral dose of 2 g, despite it being the major compound in ginger extracts (2–64%) [50]. Pharmacokinetic studies showed that the half-life of the major compounds of ginger and its metabolites is approximately 1–3 hours. Based on bioavailability data, 6-, 8-, and 10-gingerol glucuronides and sulfates along with 6-shogaols could be good markers of ginger intake [50].

As for its therapeutic use, given its various anti-inflammatory, antimicrobial, anticancer, and antioxidant biological activities, ginger appears to be effective in the prevention and treatment of neurodegenerative, cardiovascular, obesity, diabetes mellitus, or respiratory disorders [45].

4. Effects of ginger in the prevention of cardiovascular disease

4.1 Antioxidant activity

Oxidative stress is increased under the condition in which there is a decrease in the body's antioxidant defenses; therefore, there is an imbalance between the production and elimination of reactive oxygen species (ROS). As a consequence of this imbalance, ROS accumulate, generating cellular damage in the different systems of the organism, since they produce lipid peroxidation [51, 52].

Ginger has great antioxidant activity; in fact, many of its therapeutic applications are due to this activity. That ginger has antioxidant activity is a fact that has been shown both in vitro and in vivo. Although studies on the effects to human are not as numerous, it is beginning to be verified that its intake is capable of increasing the concentration of antioxidant enzymes and decreasing oxidative stress markers in cancer patients [53]. Morvaridzadeh et al. carried out a systematic review and meta-analysis where they concluded that there is sufficient evidence to show that ginger intake

increases the levels of oxidative stress parameters [54]. There are many bioactive compounds in ginger that exhibit antioxidant activity, such as 6-gingerol, 8-gingerol, 10-gingerol, and 6-shogaol. Of all of them, the one with the highest antioxidant activity in vitro is 6-gingerol, followed by 6-shogaol [55].

The mechanism involved in its antioxidant activity has to do both with preventing the appearance of free radicals [56] and with being able to eliminate them [57]. 6-Gingerol has been shown to be capable of inhibiting xanthine oxidase, an enzyme that catalyzes the oxidation of hypoxanthine to xanthine and of xanthine to uric acid in the last stage of purine metabolic degradation, with the production of reactive oxygen species [58]. In addition, it has been proven that this compound is capable of increasing superoxide dismutase and catalase activity, two antioxidant enzymes [53].

It has been seen how the antioxidant activity depends on the time of harvest of ginger, if it is early, the antioxidant activity is higher, decreasing if the harvest is done later [59].

4.2 Anti-inflammatory activity

Another of the great biological activities attributed to ginger is its anti-inflammatory activity. Inflammation is one of the body's first responses to a risk situation [60]. When that inflammation is maintained over time, is then problematic. Today it is known that there are many diseases in which inflammation plays a determining role, in fact it is being studied how low-grade systemic inflammation is related to the development of different pathologies (autoimmune diseases, metabolic diseases, CVDs, cancer) [61, 62]. In chronic or low-grade inflammation, different proinflammatory factors are released, such as cytokines and prostaglandins [61].

Many researchers have shown that ginger reduces different proinflammatory markers such as: NF-κB, signal transducer activators of transcription (STAT), proteins of the Nod-like receptor family (NLRP), receptors toll-like (TLR), mitogen-activated protein kinase (MAPK), and mTOR (mTOR) pathways, in addition to inhibiting several proinflammatory cytokines [19, 58].

In the systematic review and meta-analysis carried out by Jalali et al, it is shown how ginger is capable of significantly reducing the levels of different proinflammatory parameters such as IL-6, TAC, CRP, TNF-α, MDA, and the serum prostaglandin E2 (PGE2) [63]. Song et al. have examined how ginger extract is capable of reducing proinflammatory markers produced by *Helicobacter pylori*. The expressions of interleukin (IL)-8, TNF-α, IL-6, inducible NOS (iNOS), and IFN-γ were reduced [64].

The most active compounds from the anti-inflammatory point of view of ginger are 6-shogaol, 6-gingerol, and 6-dehydroshogaol [45, 65, 66]. It has been described how 6-shogaol has an anti-inflammatory effect because it inhibits the production of PGE2 and proinflammatory cytokines (IL-1β and TNF-α) and decreases the expression of cyclooxygenase-2 (COX-2), p38 mitogen-activated protein kinase (MAPK), and nuclear NF-κB [45]. In other studies, 6-shogaol has been shown to inhibit LPS-induced iNOS and COX-2 expression in macrophages [67]. Furthermore, studies showed that 6-shogaol could protect against lipopolysaccharide (LPS)-induced toxicity in murine astrocytes [68].

4.3 Antiobesity activity

Worldwide, obesity has become the main pandemic of the twenty-first century [69, 70], as the rates of this pathology have increased considerably during the last

decades [71, 72]. According to the World Health Organization (WHO), obesity is characterized by an excessive accumulation of fatty tissue in the body, causing harmful effects on health [73]. Concerning problems associated with obesity are mainly its deleterious effect on other non-detectable diseases: CVDs, hypertension, nonalcoholic fatty liver disease, various types of cancer, and hyperlipidemia [74, 75]. In addition, it should be noted that patients with obesity show worse prognosis against COVID-19 infection and higher mortality rates [76, 77]. Additionally, it induces low-grade inflammation, oxidative stress, and contributes in the etiology of type 2 diabetes mellitus [78]. In recent years, natural compounds have aroused great interest in the prevention/treatment of obesity, and several studies have shown that ginger seems to be effective for this pathology [45].

It seems that gingerenone-A has a more potent inhibitory effect on adipogenesis and lipid accumulation than gingerols and 6-shogaol in 3T3-L1 preadipocyte cells, while it appears to activate the adenine monophosphate (AMP)-activated protein kinase (AMPK) pathway modulating fatty acid metabolism, thus attenuating obesity [79]. For its part, the daily dose of 2 g of ginger powder in obese women resulted in a decrease in body mass index (BMI) [80]. Daily dose of ginger powder also appears to increase fat oxidation in humans [81]. Several studies have shown that ginger can reduce body weight by increasing thermogenesis through catecholamines as well as lipolysis of white adipose tissue [78]. Therefore, it seems evident that both ginger and certain bioactive components are effective against obesity by enhancing lipolysis and inhibiting adipogenesis.

4.4 Antidiabetic activity

Diabetes is a serious metabolic disorder characterized by an abnormal increase in blood glucose. For this reason, several research studies have considered evaluating the possible effect of ginger and its main bioactive components in the reduction of blood glucose [82].

It has been shown that the administration of 6-gingerol stimulates the activity of glycogen synthase 1 and at the same time favors the translocation of the glucose transporter type 4 (GLUT-4) to the cell membrane, favoring insulin to allow glucose entry in skeletal muscles and subsequent storage as glycogen [83]. Ginger consumption seems to reduce our values of glycosylated hemoglobin (HbA1c), fasting plasma glucose, insulin, total cholesterol, and triglycerides in patients with type 2 diabetes mellitus [84].

4.5 Effect of ginger on lipid profile

The greatest cause of atherosclerosis is characterized by altered blood lipid values and consequently CVD. In addition, the factors previously mentioned, such as overweight/obesity and high blood glucose values, are factors that will have a greater effect on this pathology.

Impaired blood lipid values are the major cause of CVD. In a recent systematic review and meta-analysis of clinical trials in 2018, it was concluded that ginger has a favorable effect in reducing triglycerides and LDL cholesterol, without significant reductions in total cholesterol. However, doses lower than 2 g/day of dairy ginger powder seem to be more effective in lowering both triglycerides and total cholesterol [83]. Since it is a safe and inexpensive supplement, it could be used to improve the lipid profile of subjects and thus prevent CVD.

Clinical studies have been conducted to evaluate the effect of ginger supplementation on the lipid profile of different populations. Doses of up to 1.8 g/day have been shown to significantly reduce triglyceride, total and LDL cholesterol levels compared with placebo in obese patients treated with metformin (**Table 2**) [85].

Significant lowering effect of ginger compared with placebo has also been observed in [86, 87]. However, other studies failed to observe a positive effect, and ginger supplementation exerted no effect on blood lipid profiles and body composition [88] and no significant differences in cholesterol lipoproteins profile between ginger and placebo [89]. In some cases, the results are inconsistent, with significant differences in some markers as LDL/HDL ratio after ginger intake and no changes on mean levels of total cholesterol or triglycerides [90], or reductions in levels of serum triglycerides and LDL with no effects on total cholesterol or high-density lipoprotein (HDL) [91].

Levels of apolipoprotein B and apolipoprotein B/apolipoprotein A-I ratio reduced and apolipoprotein A1 increased after ginger supplementation (2 g/day) for 12 weeks [92]. The overexpression of ApoA1 could explain the increases observed in HDL levels in some trials.

Population	Intervention	Outcomes	Ref.
Obese Egyptian patients with new-onset T2DM (n = 80) 30–60 years	600 mg 3 times/day 8 weeks	↓ BMI, ↓ TC, ↓ LDL-C, ↓ TG ↑ HDL-C ginger vs. placebo	[86]
Hyperlipidemic non diabetic patients (n = 45 ginger, 40 placebo)	3 g/day 45 days	↓ TC, ↓ TG ginger vs. placebo	[87]
Obese men (n = 32) 18–30 years	1 g/day 10 weeks with/out resistance training	n.s. TC, TG, LDL-C, HDL-C ginger vs. placebo ↓ TC, ↓ fat mass training groups	[88]
Obese women with breast cancer (n = 40)	3 g/day, 6 weeks, with/out exercise training	↓ LDL, ↓ TC, ↓ TG, ↑ HDL ginger + exercise	[89]
T2DM patients (n = 64) 38–65 years	2 g/day 8 weeks	↓ LDL, ↓ TG	[90]
T2DM patients (n = 63) 20–60 years	1.6 g/day 12 weeks	↓ TC, ↓ TG	[85]
Obese women (n = 80) 18–45 years	2 g/day 12 weeks vs. placebo	↓ TG ginger vs. placebo Both groups: ↓ TC, ↓ TG, ↓ LDL/HDL ratio, ↓ TC/HDL ratio, ↑ HDL	[91]
T2DM (n = 50) 20–60 years	2 g/day 12 weeks	↓ ApoB, ↓ ApoB/Apo A1 ratio, ↑ Apo A1	[92]
T2DM (n = 88)	3 g/day 8 weeks	↓ TC	[93]
Hyperlipidemic patients (n = 100), 35–60 years	3 g/day 30 days	↓ TC	[94]
T2DM (n = 50)	2 g/day 10 weeks	↓ LDL/HDL ratio ginger vs. placebo	[83]
Menopausal women (n = 160) 50–60 years	1 g/day 16 weeks vs. 900 mg/day garlic with/out aerobic exercise	No effects in ginger groups ↓ TC, ↓ LDL with garlic	[95]

Table 2.
Summary of the effect of ginger supplementation on the lipid profile in different clinical trials and populations.

Discrepancies in the results could be due to the different characteristics of the populations studied, stage of the disease, pharmacological treatments, format of ginger administered.

Meta-analysis studies have concluded that ginger significantly increases HDL levels and reduces plasma levels of triglycerides and total cholesterol, with different extent depending on the clinical condition (hyperlipidemia and T2DM) [93, 94]. The analysis conducted by Pourmasoumi et al. [83] revealed a better effect of total cholesterol and triglycerides with doses < 2 g/day and a maximum of 50 days of supplementation.

Among the different mechanisms of action attributed to ginger components is the inhibition of intestinal lipase enzymes, thus avoiding fat hydrolysis and absorption and the increase in plasma levels of triglycerides. In case of cholesterol, its decrease in plasma concentrations has been related to an inhibition in cellular cholesterol synthesis and an increase of hepatic enzyme activity of cholesterol 7 α-hydrozylase CYP7A1a, implicated in the conversion of cholesterol into bile acids for its clearance by fecal excretion [95]. Ginger is implicated in the inhibition of expression of adipogenesis and lipogenesis genes as PPAR γ and carbohydrate-responsive element-binding protein (ChREBP) gene expression in the liver [66]. ChREBP reduced expression further decreases the expression of glucogenic and lipogenic enzymes (as fatty acid synthase, steatoryl-CoA-desaturase-1, acetyl-CoA carboxylase 1, among others [95].

4.6 Effect of ginger on blood pressure

It is well known that healthy diet and lifestyle can control blood pressure and endothelial dysfunction. Inflammation associated with cardiovascular events contributes to hypertension by affecting the renin-angiotensin system [96]. Elevated blood pressure (BP) has also been known to be a strong risk factor cardiovascular [97].

The compounds in ginger responsible for its antihypertensive effect are 6-shogaol and 9-gingerol. These compounds reduce cholesterol and LDL levels, inhibit atheroma plaque formation, and increase vessel elasticity. They also reduce the release of inflammatory mediators responsible for endothelial dysfunction by decreasing intercellular adhesion molecule 1 (ICAM-1) levels [98]. Several authors [99] show the antihypertensive effect of ginger in volunteers with mean ≤ 50 years, with ginger doses ≥ 3 g/day, and during an intervention period ≤ 8 weeks. This effect could be due to its antioxidant activity.

A systematic review with 345 participants from six clinical trials showed that ginger consumption has favorable effects on blood pressure. These authors observed that increasing ginger intake decreased the probability of ischemic heart disease and hypertension [100]. This result coincides with that observed in a clinical trial with 4628 participants in which the efficacy of ginger in coronary heart disease and as an antihypertensive was observed [101].

4.7 Antiplatelet aggregation activity of ginger

Platelet aggregation and activation play an important role in developing thrombosis and atherosclerosis. Numerous nutrients and bioactive compounds have a potential role in platelet function and may decrease cardiovascular risk. These include berries, caffeine, chocolate, garlic, ginger, the omega-3 polyunsaturated fatty acids (PUFA), onion, and tomato [102].

ZGR is a compound (phenolic alkanose) found in *Zingiber officinale*. It exhibits anti-apoptotic, anti-inflammatory, and protective properties against cardiovascular

events such as myocardial infarction. Several authors have observed its anticoagulant and antithrombotic properties. This compound inhibits platelet aggregation induced by adenosine diphosphate (ADP), and U46619 (not thrombin), Tx2 inhibitor, inhibits the catalytic activity of factor Xa (FXa) toward its substrate S-2222 in a non-competitive inhibition model, reduces P-selectin and PAC-1 expressions in platelets, and reduces activated partial thromboplastin time [103].

Several authors [104] observed that consumption of a 10 g dose of powdered ginger after 4 hours significantly reduced ADP- and adrenaline-induced platelet aggregation. McEwen analyzed the *in vitro* antiplatelet activity of ginger and showed that gingerol, its analogues (1 and 5), paradol and shogaol, exhibited antiplatelet activity with IC50 values between 5 and 7 μM [18]. To be noted, aspirin inhibitory effect shows IC50 values of 20 ± 11 μM, and paradol shows IC50 values of 4 ± 1 μM.

Ginger has a vascular protective effect mediated by different mechanisms such as reduction of inflammation and oxidative stress, increase of nitric oxide synthesis, which is a potent vasodilator, the promotion of autophagy, and inhibition of vascular smooth muscle cell [105].

Comparing different ginger compounds, several investigators have shown that 6-gingerol and 6-shogaol showed the most potent bioactivity against cholesterol (Chol), arachidonic acid (AA), thrombin, and PAF-induced platelet aggregation [106]. The 6-paradol, 10-dehydrogingerol, 10-gingerol showed the most significant inhibition of AA-induced aggregation [107].

Nurtjahja-Tjendraputra et al. observed that 8-paradol is the most effective anticoagulant, being a COX-1 inhibitor [108].

Thomson et al. fed rats with ginger aqueous extract and observed a decrease in triglyceride, thromboxane-B2 cholesterol and PGE2 levels, and in adenosine deaminase (ADA) activity of plaques, together with an increase in adenosine levels. In this way, it favors vasodilatation, reducing the complications of hypertension and preventing from unnecessary platelet aggregation [108].

5. Conclusions

Ginger contains diverse bioactive compounds and demonstrates multiple bioactive properties. It is a potent antioxidant, anti-inflammatory, regulator of lipid profile, inhibitor of VSMC proliferation, blocker of voltage-dependent Ca2+ channels, inhibitor of platelet aggregation, regulator of endothelial dysfunction and NO synthesis, enhancer of cholesterol efflux from macrophages, inhibitor of angiogenesis, and promoter of autophagy.

The biological activities, health benefits, and cardioprotective properties of ginger/ginger constituents along with related mechanisms of action gave new insights to show new avenues in the treatment of CVDs.

It is valuable to explore new anti-platelet aggregation drugs based on the skeleton of [*n*]-paradol or other principles reported from the *Zingiber* series.

Acronyms and abbreviations

ACAT2	acetyl-CoA acetyltransferase 2
ADA	adenosine deaminase
ADP	adenosine diphosphate

AMP	adenine monophosphate
AMPK	activated protein kinase
BMI	body mass index
ChREBP	carbohydrate-responsive element-binding protein
GLUT-4	glucose transporter type 4
COX-1	cyclooxygenase-1
COX-2	cyclooxygenase-2
CVD	cardiovascular diseases
DASH	dietary approaches to stop hypertension
FXa	coagulation factor Xa
Ginger	*Zingiber officinale*
HbA1c	glycosylated hemoglobin
HDL	high-density lipoprotein
HUVECs	human umbilical endothelial cells
ICAM-1	intercellular adhesion molecule 1
IL	interleukin
iNOS	inducible NOS
LDL	low-density lipoprotein
LPS	lipopolysaccharide
MAPK	mitogen-activated protein kinase
mRNA	messenger ribonucleic acid
mTOR	mammalian target of rapamycin
MTP	microsomal triglyceride transfer protein
NF-κB	factor kappa B
NLRP	nod-like receptor
NO	oxide nitric
NOS	oxide nitric synthase
NPCA1L1	Niemann-Pick disease, type C1, gene-like 1
PAC-1	is a mouse monoclonal antibody
PGE2	prostaglandin E2
PUFA	polyunsaturated fatty acids
ROS	reactive oxidative species
S-2222	substrate S-2222 in a non-competitive inhibition model
SOD	superoxide dismutase
STAT	signal transducer activators of transcription
TLR	receptors toll-like
TNF-α	tumor necrosis tumoral alpha
U46619	a stable thromboxane receptor (TP receptor) agonist)
VSMC	vascular smooth muscle cell
WHO	World Health Organization
ZGR	zingerone

Conflict of interest

The authors declare no conflict of interest.

DOI: http://dx.doi.org/10.5772/intechopen.103970

Author details

Begoña Cerdá, Javier Marhuenda, Raúl Arcusa*, Débora Villaño,
Purificación Ballester and Pilar Zafrilla
Faculty of Health Sciences, Pharmacy Department, Universidad Católica de San Antonio, Murcia, Spain

*Address all correspondence to: rarcusa@ucam.edu

References

[1] GBD 2017 Disease and Injury Incidence and Prevalence Collaborators*. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: A systematic analysis for the Global Burden of Disease Study 2017. Lancet (London, England). 2018;**392**:1789-1858

[2] GBD 2019 Risk Factors Collaborators. Global burden of 87 risk factors in 204 countries and territories, 1990-2019: A systematic analysis for the Global Burden of Disease Study 2019. Lancet (London, England). 2020;**396**:1223-1249

[3] Yusuf S, Hawken S, Ôunpuu S, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): Case-control study. Lancet. 2004;**364**:937-952

[4] Marhuenda J, Villaño D, Cerdá B, et al. Cardiovascular disease and nutrition. In: Mózsik G, Figler M, editors. Nutrition in Health and Disease. Rijeka: IntechOpen; 2019. DOI: 10.5772/intechopen.84370

[5] Rosengren A, Smyth A, Rangarajan S, et al. Socioeconomic status and risk of cardiovascular disease in 20 low-income, middle-income, and high-income countries: The Prospective Urban Rural Epidemiologic (PURE) study. The Lancet Global Health. 2019;**7**:e748-e760

[6] Arcusa R, Carrillo JÁ, Xandri-Martínez R, et al. Effects of a fruit and vegetable-based nutraceutical on biomarkers of inflammation and oxidative status in the plasma of a healthy population: A placebo-controlled, double-blind, and randomized clinical trial. Molecules. 2021;**26**. DOI: 10.3390/molecules26123604

[7] Fakhri S, Patra JK, Das SK, et al. Ginger and heart health: From mechanisms to therapeutics. Current Molecular Pharmacology. 2021;**14**:943-959

[8] Ma R-H, Ni Z-J, Zhu Y-Y, et al. A recent update on the multifaceted health benefits associated with ginger and its bioactive components. Food & Function. 2021;**12**:519-542

[9] Wei C-K, Tsai Y-H, Korinek M, et al. 6-Paradol and 6-shogaol, the pungent compounds of ginger, promote glucose utilization in adipocytes and myotubes, and 6-paradol reduces blood glucose in high-fat diet-fed mice. International Journal of Molecular Sciences. 2017;**18**:168

[10] Zhang M, Viennois E, Prasad M, et al. Edible ginger-derived nanoparticles: A novel therapeutic approach for the prevention and treatment of inflammatory bowel disease and colitis-associated cancer. Biomaterials. 2016;**101**:321-340

[11] Guarneri M, Mercado N, Suhar C. Integrative approaches for cardiovascular disease. Nutrition in Clinical Practice. 2009;**24**:701-708

[12] Wang S, Sun X, Jiang L, et al. 6-Gingerol induces autophagy to protect HUVECs survival from apoptosis. Chemico-Biological Interactions. 2016;**256**:249-256

[13] Lei L, Liu Y, Wang X, et al. Plasma cholesterol-lowering activity of gingerol- and shogaol-enriched extract is mediated by increasing sterol excretion. Journal of Agricultural and Food Chemistry. 2014;**62**:10515-10521

[14] Kiptiyah K, Widodo W, Ciptadi G, et al. 10-Gingerol as an inducer of apoptosis through HTR1A in cumulus

cells: In-vitro and in-silico studies. Journal of Taibah University Medical Sciences. 2017;**12**:397-406

[15] Li J, Wang S, Yao L, et al. 6-Gingerol ameliorates age-related hepatic steatosis: Association with regulating lipogenesis, fatty acid oxidation, oxidative stress and mitochondrial dysfunction. Toxicology and Applied Pharmacology. 2019;**362**:125-135

[16] Morvaridzadeh M, Fazelian S, Agah S, et al. Effect of ginger (*Zingiber officinale*) on inflammatory markers: A systematic review and meta-analysis of randomized controlled trials. Cytokine. 2020;**135**:155224

[17] Ebrahimzadeh Attari V, Malek Mahdavi A, Javadivala Z, et al. A systematic review of the anti-obesity and weight lowering effect of ginger (*Zingiber officinale* Roscoe) and its mechanisms of action. Phytotherapy Research. 2018;**32**:577-585

[18] McEwen BJ. The influence of herbal medicine on platelet function and coagulation: A narrative review. Seminars in Thrombosis and Hemostasis. 2015;**41**:300-314

[19] Steven S, Frenis K, Oelze M, et al. Vascular inflammation and oxidative stress: Major triggers for cardiovascular disease. Oxidative Medicine and Cellular Longevity. 2019;**2019**:7092151. DOI: 10.1155/2019/7092151

[20] Arnett DK et al. Writing committee members circulation. Circulation. 2019;**140**:596-646

[21] Zhu Y, Xian X, Wang Z, et al. biomolecules Research Progress on the relationship between atherosclerosis and inflammation. Biomolecules. 2018;**23**:80. DOI: 10.3390/biom8030080

[22] Schloss MJ, Swirski FK, Nahrendorf M. Modifiable cardiovascular risk, hematopoiesis, and innate immunity. Circulation Research. 2020;**126**:1242-1259. DOI: 10.1161/CIRCRESAHA.120.315936

[23] Pencina MJ, Navar AM, Wojdyla D, et al. Quantifying importance of major risk factors for coronary heart disease. Circulation. 2019;**139**:1603-1611

[24] Ghoshhajra BB, Hedgire SS, Koweek LMH, et al. ACR appropriateness Criteria® asymptomatic patient at risk for coronary artery disease: 2021 update. Journal of the American College of Radiology. 2021;**18**:S2-S12

[25] Atar D, Jukema JW, Molemans B, et al. New cardiovascular prevention guidelines: How to optimally manage dyslipidaemia and cardiovascular risk in 2021 in patients needing secondary prevention? Atherosclerosis. 2021;**319**:51-61

[26] Yusuf S, Joseph P, Rangarajan S, et al. Modifiable risk factors, cardiovascular disease and mortality in 155,722 individuals from 21 high-, middle-, and low-income countries HHS Public Access. Lancet. 2020;**395**:795-808

[27] Boccellino M, D'Angelo S. Anti-obesity effects of polyphenol intake: Current status and future possibilities. International Journal of Molecular Sciences. 2020;**21**:5642

[28] Csige I, Ujvárosy D, Szabó Z, et al. The impact of obesity on the cardiovascular system. Journal of Diabetes Research. 2018;**2018**:3407306. DOI: 10.1155/2018/3407306

[29] Fruh SM. Obesity: Risk factors, complications, and strategies for sustainable

long-term weight management. Journal of the American Association of Nurse Practitioners. 2017;**29**:S3-S14. DOI: 10.1002/2327-6924.12510

[30] Trautwein EA, McKay S. The role of specific components of a plant-based diet in management of dyslipidemia and the impact on cardiovascular risk. Nutrients 2020;**12**: 2671. DOI: 10.3390/nu12092671

[31] CPG ESCC for PG. 2019. ESC/EAS guidelines for the management of dyslipidaemias: Lipid modification to reduce cardiovascular risk. Atherosclerosis. 2019;**290**:140-205

[32] Yao B-C, Meng L-B, Hao M-L, et al. Chronic stress: A critical risk factor for atherosclerosis. The Journal of International Medical Research. 2019;**47**:1429-1440

[33] Ditano-Vázquez P, Torres-Peña JD, Galeano-Valle F, et al. The fluid aspect of the Mediterranean diet in the prevention and management of cardiovascular disease and diabetes: The role of polyphenol content in moderate consumption of wine and olive oil. Nutrients. 2019;**11**:2833. DOI: 10.3390/nu11112833

[34] Dobrosielski DA, Papandreou C, Patil SP, et al. Diet and exercise in the management of obstructive sleep apnoea and cardiovascular disease risk. The European Respiratory Review. 2017;**26**:160110. DOI: 10.1183/16000617.0110-2016

[35] Lechner K, Von Schacky C, Mckenzie AL, et al. Lifestyle factors and high-risk atherosclerosis: Pathways and mechanisms beyond traditional risk factors. European Journal of Preventive Cardiology. 2020;**27**:394-406

[36] Dekker Nitert M, Groen B, Li H, et al. Interactions between therapeutics for metabolic disease, cardiovascular risk factors, and gut microbiota. Frontiers in Cellular and Infection Microbiology. 2020;**10**:530160

[37] Kondo T, Nakano Y, Adachi S, et al. Effects of tobacco smoking on cardiovascular disease. Circulation Journal. 2019;**83**:1980-1985

[38] Digiacomo SI, Jazayeri M-A, Barua RS, et al. Environmental tobacco smoke and cardiovascular disease. International Journal of Environmental Research and Public Health. 2018;**16**:96. DOI: 10.3390/ijerph16010096

[39] Patterson R, Mcnamara E, Tainio M, et al. Sedentary behaviour and risk of all-cause, cardiovascular and cancer mortality, and incident type 2 diabetes: A systematic review and dose response meta-analysis. European Journal of Epidemiology. 2018;**33**:811-829. DOI: 10.1007/s10654-018-0380-1

[40] Mohd Yusof YA. Gingerol and its role in chronic diseases. Advances in Experimental Medicine and Biology. 2016;**929**:177-207

[41] Kiyama R. Nutritional implications of ginger: Chemistry, biological activities and signaling pathways. The Journal of Nutritional Biochemistry. 2020;**86**:108486

[42] Jafarzadeh A, Jafarzadeh S, Nemati M. Therapeutic potential of ginger against COVID-19: Is there enough evidence? Journal of Traditional Chinese Medical Sciences. 2021;**8**:267-279

[43] An K, Zhao D, Wang Z, et al. Comparison of different drying methods on Chinese ginger (*Zingiber officinale* Roscoe): Changes in volatiles, chemical profile, antioxidant properties, and microstructure. Food Chemistry. 2016;**197**:1292-1300

[44] Prasad S, Tyagi AK. Ginger and its constituents: Role in prevention and treatment of gastrointestinal cancer. Gastroenterology Research and Practice. 2015;**2015**:142979

[45] Mao Q-Q, Xu X-Y, Cao S-Y, et al. Bioactive compounds and bioactivities of ginger (*Zingiber officinale* Roscoe). Foods (Basel, Switzerland). 2019;**8**:185. DOI: 10.3390/foods8060185

[46] Kou X, Wang X, Ji R, et al. Occurrence, biological activity and metabolism of 6-shogaol. Food & Function. 2018;**9**:1310-1327

[47] Choi JG, Kim SY, Jeong M, et al. Pharmacotherapeutic potential of ginger and its compounds in age-related neurological disorders. Pharmacology & Therapeutics. 2018;**182**:56-69

[48] Jafarzadeh A, Nemati M. Therapeutic potentials of ginger for treatment of Multiple sclerosis: A review with emphasis on its immunomodulatory, anti-inflammatory and anti-oxidative properties. Journal of Neuroimmunology. 2018;**324**:54-75

[49] Zick SM, Djuric Z, Ruffin MT, et al. Pharmacokinetics of 6-gingerol, 8-gingerol, 10-gingerol, and 6-shogaol and conjugate metabolites in healthy human subjects. Cancer Epidemiology Biomarkers Prevention. 2008;**17**:1930-1936

[50] Yu Y, Zick S, Li X, et al. Examination of the pharmacokinetics of active ingredients of ginger in humans. The AAPS Journal. 2011;**13**:417-426

[51] Alsahli MA, Almatroodi SA, Almatroudi A, et al. 6-Gingerol, a major ingredient of ginger attenuates diethylnitrosamine-induced liver injury in rats through the modulation of oxidative stress and anti-inflammatory activity. Mediators Inflamm; 2021. DOI: 10.1155/2021/6661937

[52] Jelic MD, Mandic AD, Maricic SM, et al. Oxidative stress and its role in cancer. Journal of Cancer Research and Therapeutics. 2021;**17**:22

[53] Danwilai K, Konmun J, Sripanidkulchai B-O, et al. Cancer Management and Research Dovepress Antioxidant activity of ginger extract as a daily supplement in cancer patients receiving adjuvant chemotherapy: A pilot study. Cancer Management and Research. 2017:9-11

[54] Morvaridzadeh M, Sadeghi E, Agah S, et al. Effect of ginger (*Zingiber officinale*) supplementation on oxidative stress parameters: A systematic review and meta-analysis. Journal of Food Biochemistry. 2021;**45**:e13612

[55] Mohammed A, Ali A, Elamin M, et al. Total phenolic and flavonoid contents and antioxidant activity of ginger (*Zingiber officinale* Rosc.) rhizome, callus and callus treated with some elicitors. Journal, Genetic Engineering & Biotechnology. 2018;**16**:677-682

[56] Ali A, Gilani AH. Medicinal value of ginger with focus on its use in nausea and vomiting of pregnancy. International Journal of Food Properties. 2007;**10**:269-278

[57] Sueishi Y, Masamoto H, Kotake Y. Heat treatments of ginger root modify but not diminish its antioxidant activity as measured with multiple free radical scavenging (MULTIS) method. Journal of Clinical Biochemistry and Nutrition. 2019;**64**:143-147

[58] Rondanelli M, Fossari F, Vecchio V, et al. Clinical trials on pain lowering effect of ginger: A narrative review. Physiological Research. 2020;**34**:2843-2856. DOI: 10.1002/ptr.6730

[59] Li H, Rafie R, Xu Z, et al. Phytochemical profile and anti-oxidation

activity changes during ginger (Zingiber officinale) harvest: Baby ginger attenuates lipid accumulation and ameliorates glucose uptake in HepG2 cells. International Journal of Food Sciences and Nutrition. 2021;**10**:133-144. DOI: 10.1002/fsn3.2654

[60] León-Pedroza JI, González-Tapia LA, del Olmo-Gil E, et al. Low-grade systemic inflammation and the development of metabolic diseases: From the molecular evidence to the clinical practice. Cirugía y Cir (English Ed). 2015;**83**:543-551

[61] Duraisamy K, Janigro D, Riquelme MA, et al. The importance and control of low-grade inflammation due to damage of cellular barrier systems that may lead to systemic inflammation. Frontiers in Neurology. 2019;**1**:533

[62] Rea IM, Gibson DS, McGilligan V, et al. Age and age-related diseases: Role of inflammation triggers and cytokines. Front Immunol. 2018;**9**:586

[63] Jalali M, Mahmoodi M, Moosavian SP, et al. The effects of ginger supplementation on markers of inflammatory and oxidative stress: A systematic review and meta-analysis of clinical trials. Phyther Research. 2020;**34**:1723-1733

[64] Song M-Y, Lee D-Y, Park S-Y, et al. Steamed ginger extract exerts anti-inflammatory effects in helicobacter pylori-infected gastric epithelial cells through inhibition of NF-κB. Journal of Cancer Prevention. 2021;**26**:289

[65] Zadorozhna M, Mangieri D. Molecular sciences mechanisms of chemopreventive and therapeutic proprieties of ginger extracts in cancer. Epub ahead of print 2021. DOI: 10.3390/ijms22126599

[66] Unuofin JO, Masuku NP, Paimo OK, et al. Ginger from Farmyard to Town: Nutritional and pharmacological applications. Frontiers in Pharmacology. 2021;**12**:779352. DOI: 10.3389/fphar.2021.779352

[67] Chen C-Y, Kao C-L, Liu C-M. The cancer prevention, anti-inflammatory and anti-oxidation of bioactive phytochemicals targeting the TLR4 signaling pathway. International Journal of Molecular Sciences. 2018;**19**:2729 DOI: 10.3390/ijms19092729

[68] Han Q, Yuan Q, Meng X, et al. 6-Shogaol attenuates LPS-induced inflammation in BV2 microglia cells by activating PPAR-γ. Oncotarget. 2017;**8**:42001-42006

[69] Meldrum DR, Morris MA, Gambone JC. Obesity pandemic: Causes, consequences, and solutions-but do we have the will? Fertility and Sterility. 2017;**107**:833-839

[70] Huang H, Yan Z, Chen Y, et al. A social contagious model of the obesity epidemic. Scientific Reports. 2016;**6**:37961

[71] Williams EP, Mesidor M, Winters K, et al. Overweight and obesity: Prevalence, consequences, and causes of a growing public health problem. Current Obesity Reports. 2015;**4**:363-370

[72] Ng M, Fleming T, Robinson M, et al. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980-2013: A systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2014;**384**:766-781

[73] Serna A, Marhuenda J, Arcusa R, et al. Effectiveness of a polyphenolic extract (*Lippia citriodora* and *Hibiscus sabdariffa*) on appetite regulation in overweight and obese grade I population: An 8-week randomized, double-blind,

cross-over, placebo-controlled trial. European Journal of Nutrition. 2021:1-17

[74] Savino P. Obesidad y enfermedades no transmisibles relacionadas con la nutrición. Rev Colomb Cir. 2011;**26**:180-195

[75] Guh DP, Zhang W, Bansback N, et al. The incidence of co-morbidities related to obesity and overweight: A systematic review and meta-analysis. BMC Public Health. 2009;**9**:1-20

[76] Zhou Y, Chi J, Lv W, et al. Obesity and diabetes as high-risk factors for severe coronavirus disease 2019 (Covid-19). Diabetes/Metabolism Research and Reviews. 2021;**37**:e3377

[77] Yu W, Rohli KE, Yang S, et al. Impact of obesity on COVID-19 patients. Journal of Diabetes and its Complications. 2021;**35**:107817

[78] Tramontin NDS, Luciano TF, de Marques O, et al. Ginger and avocado as nutraceuticals for obesity and its comorbidities. Phytotherapy Research. 2020;**34**:1282-1290

[79] Suk S, Kwon GT, Lee E, et al. Gingerenone A, a polyphenol present in ginger, suppresses obesity and adipose tissue inflammation in high-fat diet-fed mice. Molecular Nutrition & Food Research. 2017;**61**:1700139

[80] Attari VE, Ostadrahimi A, Jafarabadi MA, et al. Changes of serum adipocytokines and body weight following *Zingiber officinale* supplementation in obese women: A RCT. European Journal of Nutrition. 2016;**55**:2129-2136

[81] Miyamoto M, Matsuzaki K, Katakura M, et al. Oral intake of encapsulated dried ginger root powder hardly affects human thermoregulatory function, but appears to facilitate fat utilization. International Journal of Biometeorology. 2015;**59**:1461-1474

[82] Bin SM, Mohsin M, Bin NA, et al. [6]-Gingerol, from *Zingiber officinale*, potentiates GLP-1 mediated glucose-stimulated insulin secretion pathway in pancreatic β-cells and increases RAB8/RAB10-regulated membrane presentation of GLUT4 transporters in skeletal muscle to improve hyperglycemi. BMC Complementary and Alternative Medicine. 2017;**17**:1-13

[83] Pourmasoumi M, Hadi A, Rafie N, et al. The effect of ginger supplementation on lipid profile: A systematic review and meta-analysis of clinical trials. Phytomedicine. 2018;**43**:28-36

[84] Arablou T, Aryaeian N, Valizadeh M, et al. The effect of ginger consumption on glycemic status, lipid profile and some inflammatory markers in patients with type 2 diabetes mellitus. International Journal of Food Sciences and Nutrition. 2014;**65**:515-520

[85] El Gayar MH, Aboromia MMM, Ibrahim NA, et al. Effects of ginger powder supplementation on glycemic status and lipid profile in newly diagnosed obese patients with type 2 diabetes mellitus. Obesity Medicine; 14. Epub ahead of print June 2019. DOI: 10.1016/j.obmed.2019.100094

[86] Alizadeh-Navaei R, Roozbeh F, Saravi M, et al. Investigation of the effect of ginger on the lipid levels: A double blind controlled clinical trial. Saudi Medical Journal. 2008;**29**:1280-1284

[87] Arablou T, Aryaeian N. The effect of ginger (*Zingiber officinale*) as an ancient medicinal plant on improving blood lipids. Journal of Herbal Medicine. 2018;**12**:11-15

[88] Atashak S, Peeri M, Jafari A, et al. Effects of ginger supplementation and resistance training on lipid profiles and body composition in obese men. Journal of Medical Plants Research. 2011;**5**:3827-3832

[89] Attari VE, Mahluji S, Jafarabadi MA, et al. Effects of supplementation with ginger (*Zingiber officinale* Roscoe) on Serum glucose, lipid profile and oxidative stress in obese women: A randomized, placebo-controlled clinical trial. Pharmaceutical Science. 2015;**21**:184-191

[90] Makhdoomi Arzati M, Mohammadzadeh Honarvar N, Saedisomeolia A, et al. The effects of ginger on fasting blood sugar, hemoglobin A1c, and lipid profiles in patients with type 2 diabetes. International Journal of Endocrinology and Metabolism. 2017;**15**:e57927. DOI: 10.5812/ijem.57927

[91] Mahluji S, Attari VE, Mobasseri M, et al. Effects of ginger (*Zingiber officinale*) on plasma glucose level, HbA1c and insulin sensitivity in type 2 diabetic patients. International Journal of Food Sciences and Nutrition. 2013;**64**:682-686

[92] Khandouzi N, Shidfar F, Rajab A, et al. The effects of ginger on fasting blood sugar, hemoglobin A1c, apolipoprotein B, apolipoprotein A-I and malondialdehyde in type 2 diabetic patients. Iranian Journal of Pharmaceutical Research (IJPR). 2015;**14**:131-140

[93] Jafarnejad S, Keshavarz SA, Mahbubi S, et al. Effect of ginger (*Zingiber officinale*) on blood glucose and lipid concentrations in diabetic and hyperlipidemic subjects: A meta-analysis of randomized controlled trials. Journal of Functional Foods. 2017;**29**:127-134

[94] Mazidi M, Gao HK, Rezaie P, et al. The effect of ginger supplementation on serum C-reactive protein, lipid profile and glycaemia: A systematic review and meta-analysis. Food and Nutrition Research; 2016;**60**: 2613. DOI: 10.3402/fnr.v60.32613

[95] Gao H, Guan T, Li C, et al. Treatment with ginger ameliorates fructose-induced fatty liver and hypertriglyceridemia in rats: Modulation of the hepatic carbohydrate response element-binding protein-mediated pathway. Evidence-Based Complementary and Alternative Medicine. 2012;**2012**:570948. DOI: 10.1155/2012/570948

[96] Mahn K, Borrás C, Knock GA, et al. Dietary soy isoflavone-induced increases in antioxidant and eNOS gene expression lead to improved endothelial function and reduced blood pressure in vivo. The FASEB Journal. 2005;**19**:1755-1757

[97] Kafeshani M, Entezari MH, Karimian J, et al. A comparative study of the effect of green tea and sour tea on blood pressure and lipid profile in healthy adult men. ARYA Atherosclerosis. 2017;**13**:109

[98] Azimi P, Ghiasvand R, Feizi A, et al. Effect of cinnamon, cardamom, saffron and ginger consumption on blood pressure and a marker of endothelial function in patients with type 2 diabetes mellitus: A randomized controlled clinical trial. Blood Pressure. 2016;**25**:133-140

[99] Hasani H, Arab A, Hadi A, et al. Does ginger supplementation lower blood pressure? A systematic review and meta-analysis of clinical trials. Phytheraphy Research. 2019;**33**:1639-1647

[100] Wang Y, Yu H, Zhang X, et al. Evaluation of daily ginger consumption for the prevention of chronic diseases in

adults: A cross-sectional study. Nutrition. 2017;**36**:79-84

[101] McEwen BJ. The influence of diet and nutrients on platelet function. Seminars in Thrombosis and Hemostasis. 2014;**40**:214-226

[102] Lee W, Ku S-K, Kim M-A, et al. Anti-factor Xa activities of zingerone with anti-platelet aggregation activity. Food and Chemical Toxicology. 2017;**105**:186-193

[103] Bordia A, Verma SK, Srivastava KC. Effect of ginger (*Zingiber officinale* Rosc.) and fenugreek (*Trigonella foenumgraecum* L.) on blood lipids, blood sugar and platelet aggregation in patients with coronary artery disease. Prostaglandins, Leukotrienes, and Essential Fatty Acids. 1997;**56**:379-384

[104] Vázquez-Fresno R, Rosana ARR, Sajed T, et al. Herbs and spices—Biomarkers of intake based on human intervention studies: A systematic review. Genes & Nutrition. 2019;**14**:18

[105] Liao Y-R, Leu Y-L, Chan Y-Y, et al. Anti-platelet aggregation and vasorelaxing effects of the constituents of the rhizomes of *Zingiber officinale*. Molecules. 2012;**17**:8928-8937

[106] Akinyemi AJ, Thomé GR, Morsch VM, et al. Dietary supplementation of ginger and turmeric rhizomes modulates platelets ectonucleotidase and adenosine deaminase activities in normotensive and hypertensive rats. Phytotherapy Research. 2016;**30**:1156-1163

[107] Nurtjahja-Tjendraputra E, Ammit AJ, Roufogalis BD, et al. Effective anti-platelet and COX-1 enzyme inhibitors from pungent constituents of ginger. Thrombosis Research. 2003;**111**:259-265

[108] Thomson M, Al-Qattan KK, Al-Sawan SM, et al. The use of ginger (*Zingiber officinale* Rosc.) as a potential anti-inflammatory and antithrombotic agent. Prostaglandins, Leukotrienes, and Essential Fatty Acids. 2002;**67**:475-478

Chapter 9

An Overview of Functional Food

Shakira Ghazanfar, Ghulam Muhammad Ali, Rameesha Abid, Arshad Farid, Nosheen Akhtar, Nahid Akhtar Batool, Sharjeel Khalid, Mohammad K. Okla, Saud S. Al-Amri, Yasmeen A. Alwasel and Yasir Hameed

Abstract

Functional foods are responsible for the improvement of human health and can significantly reduce the probability of disease in the host body. Functional foods are directly or indirectly part of different food ingredients and can induce functional activities in the host biological system. Functional foods are present in fruits, vegetables, dairy, bakery, cereals and meat products. Functional foods are not additional food supplements, drugs or antibiotics, they are the main component of a normal human and animal diet. Functional foods are cost-effective and easily available in the market. Daily consumption of functional foods can prevent the gastrointestinal diseases and also provide ease against different acute and chronic diseases. Adequate administration of probiotics in a human food can convert a normal food into functional food. This chapter will highlight the effective role of functional food in an individual's daily life.

Keywords: functional food, GI health, probiotic, microflora

1. Introduction

Functional foods are significant for human health as it is a major source of essential nutrients and can be used as a food supplement [1]. Different fruits, vegetables, grains, fishes, dairy, and meat products are naturally considered as the major source of functional food, moreover, all these foods can provide nourishment to the host body (**Figure 1**) [2]. Studies suggested that, tea and chocolate are also the part of functional food due to the presence of active compounds in them [3]. Balanced diet plays a considerable role throughout the consumer's life, it is necessary for the individual's mental and physical health as it can maintain human body functions actively [4]. Functional food can positively affect the body of an organism, it can fulfill basic requirements of the body and protect the host body against different malnutrition diseases and can remove various harmful particles from the body [5]. Studies suggested that, functional food can be recognized as a food product, that can contribute to enhance the body's metabolic rate without affecting the normal functions of the body and can stabilize the physical appearance of the body [6]. In this recent era, functional foods are responsible to provide energy to the individual's body so that the growth and development of the body can proceed smoothly [7]. Functional food has

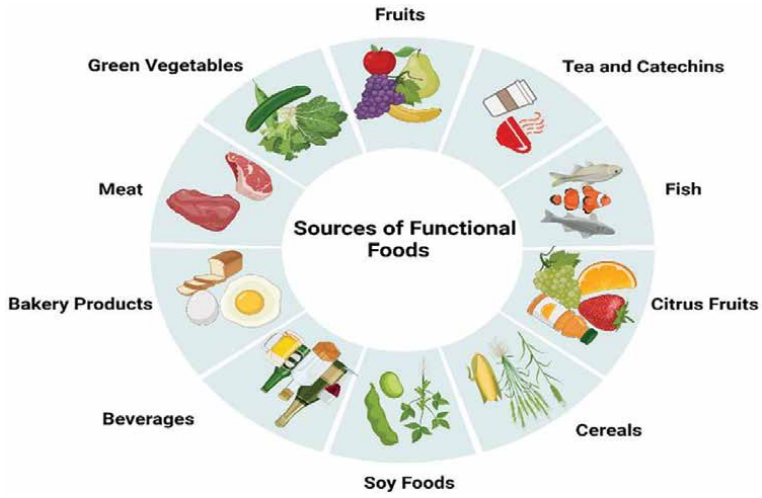

Figure 1.
Sources of functional foods.

the potential to mediate immune-modulatory response and subsequently decrease the risk of cardiovascular complications, osteoporosis, obesity and cancer which results to promote health promising effects in the individual's body [8]. Some of the examples of functional foods are vitamins, fortified food, fiber, minerals, peanuts, fruits and grain seed.

2. Why positive intake of functional food is necessary?

Functional foods are important to the human body as other basic needs. A balanced diet is responsible to keep the human body active and fit. According to the current investigations, individuals cannot consume a balanced diet due to their busy and careless attitudes. An appropriate balanced diet can significantly provide beneficial components to the human health [9]. Less consumption of functional food and individual's false lifestyle can induce health deteriorating effects and multiple diseases which include cardiovascular disease, high blood pressure, and type 2 diabetes (**Figure 2**). An unbalanced diet may also contribute to the poor psychological health and memory [10].

2.1 Fitness associated with functional food

Most developed aspects that promote the health of the individuals by consuming functional food may include a positive change in the physical and mental health. Several parameters can actively participate and ensure the normal health which include; gastrointestinal health, intellectual health, physiological health and somatic health. The risk of different diseases (e.g., cardiovascular disease, type 2 diabetes, metabolic disease and musculoskeletal disease) can also be reduced by consuming an adequate amount of functional food [11]. According to the United States study, functional foods are those types of foods that contain biologically active components which can maintain the normal gut microflora and detoxify the harmful chemicals from the host body [12]. Consumer demands must be taken into account when functional foods are designed, functional foods may be found in approximately all

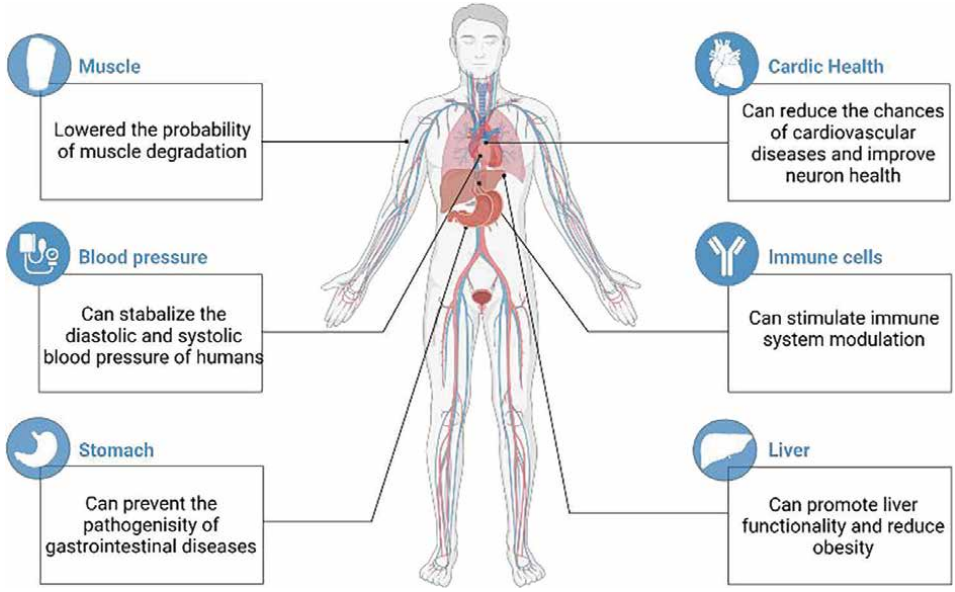

Figure 2.
Applications of functional foods.

food types. Almost every type of functional food is produced but their access towards customers is not consistent [13]. Functional food can be produced from dairy, sweet products, cold drinks, bakery, vitamins, minerals, plant source, animal source and many other due to its much importance in our monotonous life [14]. The producers classify it into two groups, i.e., conservative foodstuff and cheered nutrition.

3. Functional foods for the development of child health

Functional foods can also be considered as a nutritional additive which provide an ease to the parents for the growth and development of their children. The deficiency of nutritional additives can significantly affect the biological condition of the child and can lead to cause fluctuations in the normal blood pressure levels, cardiac rate and sugar levels [15]. Feeding mothers should have to maintain the nutritional needs of their bodies and should properly consume protein, carbohydrates, n-3, n-6 polyunsaturated fatty acids (PUFAs), amino acids and micronutrients (folic acid, iron, zinc, and iodine) so that, the health of the infant can also be ensured [16].

3.1 Effect of diet on children's growth and development

In the early stages of a child's development, more energy and nutrition are required as the child's metabolic rate is much low during this period. n-3 and n-6 PUFAs and trace minerals, such as iron, zinc, and iodine can affect the sensory functions of the child's body [17]. However, developmental probiotic-based functional food can play a key role in the growth and development of the child mental and physical health. Moreover, more consumption of oligosaccharides and insulin via functional food can significantly normalize the gastrointestinal health of the pediatrics in the early years of their development [18].

3.2 Nourishment impact on immunity

A balanced nutritious diet can positively affect the immune system of the host throughout their life span, nutritional components such as antioxidants, vitamins, trace elements copper zinc calcium and potassium functions boost growth and development and give strength to the immune system of immune-compromised patients [19].

4. Design of functional Food

4.1 Conservative foodstuff

Conservative foodstuffs are those foodstuffs that contain regular or whole-food components and provide functional constituents for example antioxidants, fatty acids, vitamins and minerals. A healthy diet contains more bioactive complexes and less dangerous constituents like pollutants, metabolites, insecticides, and fertilizers. Organic food helps to maintain a balanced lifestyle and reduces the risk of unindustrialized products. The purpose of these foods is to improve the nutritional quality [20].

4.2 Functional Foods - Phytochemicals and Health Promoting Potential

In this recent era, industrialized foods are more likely to be used as compared to traditional due to its easy making and availability. Dry and fresh seasonal fruits and vegetables, nuts, seeds, beans and sages are the predictable beneficial functional foods that contains bioactive substances that are beneficial and show positive effects on health [21].

4.3 Cheered nutrition

"Food protection" denotes that the accumulation of nutrients content is high as compared to the original food. Food protection is also called as the accumulation of nutrients to overcome the need for nutrients during food processing. Food fortification is usually done at the industrial level but also possible in homes [22].

The deficiency of micronutrients can be resolved with the consumption of adequate functional food which is useful for the improvement of human health. At global scale it is needed to improve micronutrient shortage, nutritional configurations, invention and advertising of potential foodstuff and functional food management domains [23].

5. Role of probiotics in functional food

Vitamins such as A, C and E act as antioxidants. These vitamins enhance oxidation progression due to their antioxidant activities. Approximately, about 2 billion people in the whole world are micronutrient deficient, moreover, their risks of death and development of different co-morbidities have subsequently increased. Food fortification by functional foods ensures the availability of nutrients and promote a healthy life. This technique is effective for the consumption of minerals, vitamins and other nutrients to fulfill the functional food need.

Functional food in addition to probiotics are living microbes that are administered into the body of the host and can stabilize the normal flora of the human gut.

However, new probiotics are in a developing phase for more progressive and concentrated investigations [24]. Functional food having probiotics as a major ingredient has the tendency to decrease the severity of gastrointestinal infections, it can also provide relief against lactose xenophobia and improve the gut functionality of the host and remarkably save the host from diarrheal associated diseases. Probiotics stimulate good bacterial growth. However, they are previously existing the gut and can transform metabolic accomplishments. They are also capable to increase the levels of short-chain fatty acids formed in the colon and also have the tendency to enhance mineral absorption, i.e., calcium and magnesium preservatives decrease the effectiveness of probiotics health risk [25]. The association of probiotics and prebiotics in a potential way is defined as symbiotic. The presence of glucose and sucrose in a functional food can significantly reduce the severity of pain in the host body. Caffeine can improve cognitive performance, alertness, memory, and other psychiatric performances. Cognitive performance and mental health maintenance in older individuals may be improved by consuming specifically vitamins B [26]. People often experience the association between sleep and normal foods with high carbohydrate food consumption. Tryptophan, an amino acid can reduce the sleepy condition of the individuals, while tyrosine and tryptophan can help in rehabilitation and are the part of functional food. Many ingredients, such as n-3 fatty acids, S-adenosylmethione (SAMe), and folic acid were considered as possible functional ingredients to improve depression [27].

In most cases, only animal or clinical research can be used to determine the viability of probiotics. According to the clinical research, per day consumption of probiotics via functional foods has typically been linked to promote human health. The beneficial effects of probiotics depend upon the nature of probiotic bacteria present in the functional food which ensures the development and survivability of itself in the functional food product [28]. However, several food additives such as aromatic compounds, salts, sugars, sweeteners and preservatives induce the probability of probiotic health risk [29]. The growth and survival of probiotics have been halted when chemicals and food additives interact with probiotics present in functional food. Oligosaccharide based functional foods can stimulate the growth of lactobacillus and bifdo-bacteria and induce health-promoting effects in the host body [30].

6. Improvement in functional food

Functional food production includes several distinct phases such as operational purchaser implementation, customers functional food demands, foodstuffs with vigor quality all these are recommended for the hands-on capability to encourage health outside the endowment of indispensable nutrients, that are important for the nutritional development of individuals living in less developed and remote areas [31]. FDA plays a significant role in improving health conditions by increasing the quality of functional food components, supported the formation of healthy food production and increased the buyer need and requirements such as omega-3 fatty acids, soy protein, plant sterols, and dietary fibers. In the recent past, a large number of functional food items for consumption breaks the stereotype of functional food quality. Unconscious cardiac health, invulnerable body functions, bone health are the focus of stabilized health conditions [32]. Deep ideas about the understanding of the materials for a successful product development is all needed for functional food production. Steps involved in the functional food development have been depicted in **Figure 3**. It is the time to improve the technique and those mechanisms which regulate health

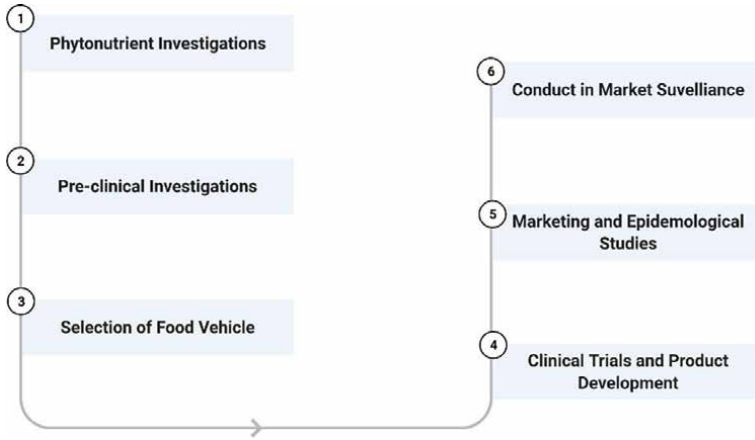

Figure 3.
Steps involved in the development of functional food product.

beneficial functional food [32]. Functional food can be used in a variety of ways. So many functional food products "are best for human's life which can treat common gastrointestinal and colon diseases and ultimately promote the health of slivery glands of children, improving their intellectual capacity and can provide favorable healthy environment. Despite this, functional foods are also helpful in biomarker formation for cognitive, interactive, and psychosomatic purposes which results to stimulate and support host body to treat general health disorders like obesity and high blood pressure [33].

7. Conclusion

In this recent era, the demand of functional food has remarkably increased due to its health-promoting effects. Busy daily routines and improper diet are the primary reason for the development of various health-related abnormalities. Enhanced administration of functional foods in terms of fruits, vegetables, meat and other nutritious products can significantly halt the pathogenicity of different diseases and their co-morbidities due to their antioxidant and anti-inflammatory effects.

Acknowledgement

This work was funded by the Researchers Supporting Project Number (RSP-2021/293), King Saud University, Riyadh, Saudi Arabia. The authors also acknowledge the National Agricultural Research Center (NARC, Islamabad, Pakistan), for providing special support for this book chapter.

Conflict of interest

The authors declare no conflict of interest.

Author details

Shakira Ghazanfar[1*], Ghulam Muhammad Ali[1], Rameesha Abid[1,2], Arshad Farid[3], Nosheen Akhtar[4], Nahid Akhtar Batool[1,5], Sharjeel Khalid[1], Mohammad K. Okla[6], Saud S. Al-Amri[6], Yasmeen A. Alwasel[6] and Yasir Hameed[7]

1 National Agricultural Research Centre, National Institute of Genomics and Agriculture Biotechnology (NIGAB), Islamabad, Pakistan

2 Department of Biotechnology, University of Sialkot, Sialkot, Pakistan

3 Gomal Centre of Biochemistry and Biotechnology, Gomal University, Khan, Pakistan

4 Department of Biological Sciences, National University of Medical Sciences, Rawalpindi, Pakistan

5 Department of Biotechnology, Mohi-u-din Islamic University Nerian Sharif, Pakistan

6 Botany and Microbiology Department, College of Science, King Saud University, Riyadh, Saudi Arabia

7 Department of Biochemistry and Biotechnology, The Islamia University of Bahawalpur, Bahawalpur, Pakistan

*Address all correspondence to: shakira_akmal@yahoo.com

IntechOpen

References

[1] Annunziata A, Vecchio R, Kraus A. Awareness and preference for functional foods: The perspective of older I talian consumers. International Journal of Consumer Studies. 2015;**39**(4):352-361

[2] Vigar V, Myers S, Oliver C, Arellano J, Robinson S, Leifert C. A systematic review of organic versus conventional food consumption: Is there a measurable benefit on human health? Nutrients. 2020;**12**(1):7

[3] Choudhary R, Tandon RV. Consumption of functional food and our health concerns. Pakistan Journal of Physiology. 2009;**5**(1)

[4] Plasek B, Lakner Z, Kasza G, Temesi Á. Consumer evaluation of the role of functional food products in disease prevention and the characteristics of target groups. Nutrients. 2020;**12**(1):69

[5] Topolska K, Florkiewicz A, Filipiak-Florkiewicz A. Functional food—Consumer motivations and expectations. International Journal of Environmental Research and Public Health. 2021;**18**(10):5327

[6] Bellisle F et al. Functional food science and behaviour and psychological functions. The British Journal of Nutrition. 1998;**80**(S1):S173-S193

[7] Sun-Waterhouse D. The development of fruit-based functional foods targeting the health and wellness market: A review. International Journal of Food Science and Technology. 2011;**46**(5):899-920

[8] Pandey K, Naik S, Vakil B, and others. Probiotics, prebiotics and synbiotics-a review. Journal of Food Science and Technology. 2015;**52**(12):7577-7587

[9] Aluko RE. Functional Foods and Nutraceuticals. Springer; 2012

[10] Sarkar D, Ankolekar C, Shetty K. Functional food components for preventing and combating type 2 diabetes. In: Emerging Trends in Dietary Components for Preventing and Combating Disease. ACS Publications; 2012. pp. 345-374

[11] Alongi M, Anese M. Re-thinking functional food development through a holistic approach. Journal of Functional Foods. 2021;**81**:104466

[12] Granato D, Branco GF, Cruz AG, Faria JDAF, Shah NP. Probiotic dairy products as functional foods. Comprehensive Reviews in Food Science and Food Safety. 2010;**9**(5):455-470

[13] Bigliardi B, Galati F. Innovation trends in the food industry: The case of functional foods. Trends in Food Science and Technology. 2013;**31**(2):118-129

[14] Asif M. The prevention and control the type-2 diabetes by changing lifestyle and dietary pattern. Journal of Education Health Promotion. 2014;**3**

[15] Kawicka A, Regulska-Ilow B. How nutritional status, diet and dietary supplements can affect autism. A review. Roczniki Państwowego Zakładu Higieny. 2013;**64**(1)

[16] Williamson CS. Nutrition in pregnancy. Nutrition Bulletin. 2006;**31**(1):28-59

[17] Schonfeldt HC, Hall N. 'Fish, chicken, lean meat and eggs can be eaten daily': A food-based dietary guideline for South Africa. South African Journal of Clinical Nutrition. 2013;**26**:S66-S76

[18] Tabrizi A, Khalili L, Homayouni-Rad A, Pourjafar H, Dehghan P, Ansari F. Prebiotics, as promising functional food to patients with psychological disorders: A review on mood disorders, sleep, and cognition. NeuroQuantology. 2019;**17**(6)

[19] Rashwan AK, Karim N, Shishir MRI, Bao T, Lu Y, Chen W. Jujube fruit: A potential nutritious fruit for the development of functional food products. Journal of Functional Foods. 2020;**75**:104205

[20] Wang K, Xu Z, Liao X. Bioactive compounds, health benefits and functional food products of sea buckthorn: A review. Critical Reviews in Food Science and Nutrition. 2021:1-22

[21] Adamidis T, Papageorgiou M, Zinoviadou KG. Food, nutrition, and health in Greece. In: Nutritional and Health Aspects of Food in the Balkans. Elsevier; 2021. pp. 107-124

[22] Bourn D, Prescott J. A comparison of the nutritional value, sensory qualities, and food safety of organically and conventionally produced foods. Critical Reviews in Food Science and Nutrition. 2002;**42**(1):1-34

[23] Hirschi KD. Nutrient biofortification of food crops. Annual Review of Nutrition. 2009;**29**:401-421

[24] Maqsood S, Adiamo O, Ahmad M, Mudgil P. Bioactive compounds from date fruit and seed as potential nutraceutical and functional food ingredients. Food Chemistry. 2020;**308**:125522

[25] Papamakarios G, Nalisnick E, Rezende DJ, Mohamed S, Lakshminarayanan B. Normalizing flows for probabilistic modeling and inference. Journal of Machine Learning Research. 2021;**22**(57):1-64

[26] Howe KL et al. Ensembl 2021. Nucleic Acids Research. 2021;**49**(D1): D884-D891

[27] Idowu AT, Igiehon OO, Adekoya AE, Idowu S. Dates palm fruits: A review of their nutritional components, bioactivities and functional food applications. AIMS Agriculture and Food. 2020;**5**(4):734-755

[28] Naghedi-Baghdar H et al. Effect of a functional food (vegetable soup) on blood rheology in patients with polycythemia. Avicenna Journal of Phytomedicine. 2018;**8**(5):389

[29] Reque PM, Brandelli A. Encapsulation of probiotics and nutraceuticals: Applications in functional food industry. Trends in Food Science and Technology. 2021;**114**:1-10

[30] Langa S, Van Den Bulck E, Peirotén A, Gaya P, Schols HA, Arqués JL. Application of lactobacilli and prebiotic oligosaccharides for the development of a synbiotic semi-hard cheese. Lwt. 2019;**114**:108361

[31] Jones PJ, Jew S. Functional food development: Concept to reality. Trends in Food Science and Technology. 2007;**18**(7):387-390

[32] Kumari A, Parida AK, Rangani J, Panda A. Antioxidant activities, metabolic profiling, proximate analysis, mineral nutrient composition of Salvadora persica fruit unravel a potential functional food and a natural source of pharmaceuticals. Frontiers in Pharmacology. 2017;**8**:61

[33] Khan RS, Grigor J, Winger R, Win A. Functional food product development-opportunities and challenges for food manufacturers. Trends in Food Science and Technology. 2013;**30**(1):27-37

Chapter 10

MIND Diet

Premagowri Balakrishnan

Abstract

Age-associated changes in the brain, injuries such as stroke or traumatic brain injury, mood disorders like depression, substance use disorder, or addiction, and diseases such as Alzheimer's disease will affect brain health. Some factors affecting brain health cannot be changed, but many lifestyle changes have the potential to make a difference. Dietary patterns have been associated with protective relations to cognitive decline and incident dementia in epidemiological studies. An amalgam of the Mediterranean-DASH diets, called the MIND diet, emphasizes the dietary components and servings linked to neuroprotection and dementia prevention. Analogous to the Mediterranean and DASH diets, the MIND diet score highlights natural plant-based foods and limited intakes of animal foods. The diet uniquely stipulates consumption of green leafy vegetables, other vegetables, berries, nuts, whole grains, olive oil, fish, beans, poultry, and wine, but does not specify high fruit consumption, dairy products, red meat, and fried foods. The MIND diet score was related to a slower rate of cognitive decline, equivalent to 7.5 years of younger age. It was evident that the MIND diet reduces a person's risk of developing Alzheimer's disease dementia and also the diet comprises a variety of nutrient sources in the right proportions.

Keywords: Alzheimer's disease, brain health, cognitive decline, Mediterranean-DASH diets, nutrient sources

1. Introduction

Cognitive decline is an alarming public health concern. Intellectual debility related to aging is a staid health issue, which increases the prevalence of neurodegenerative diseases as people are active longer and the proportion of aged persons globally remains increasing rapidly [1]. World Health Organization (WHO) reported that dementia affects an estimated 50 million people, and this prevalence is projected to rise over 130 million by 2050 [2]. Further epidemiological studies advocate an adverse interaction of aging and obesity with cognitive dysfunction [3, 4]. There are additional adverse implications for cognition health which are assessed as 30% prevalent among the overweight and obese adult population [5, 6]. The strong predictors of functional disability and dependence are dementia and cognitive impairment, which leads to major socioeconomic burden [7].

The usual part of the aging process is cognitive decline, but the rate of decline may differ depending on the variations in genetic and lifestyle-associated factors [8]. Elderly people develop these protein deposits, known as amyloid plaques and tangles. Plaques and tangles are a pathology found in the brain that builds up in

between nerve cells and typically interfere with thinking and problem-solving skills. Aging acquires a toll on the body and mind. For instance, the tissue of aging human brains sometimes develops abnormal clumps of proteins, which are the hallmark of Alzheimer's disease. Currently, the brain can be protected from these effects by a healthy diet.

A healthy diet has the potential in preserving the brain and maintaining cognitive health. The potential of modifiable lifestyle factors is important as there are no effective pharmacological agents identified for the improvement of cognition or delay of the progression of cognitive decline [9]. Diet is a key lifestyle risk factor. Personalized nutrients in foods have been contradictorily related to cognitive function, which includes some vitamins, carotenoids, long-chain n-3 polyunsaturated fatty acids (PUFAs) in kinds of seafood, whole grainy foods rich in polyphenols, nuts, olive oil, coffee, fruits, and vegetables [10–12].

2. An overview of MIND diet

As food is consumed as part of a dietary pattern, it is important to consider the interactions and associations of whole dietary approaches. Predominantly, three dietary patterns are put forward to have a beneficial impact on cognitive function. They are the Mediterranean diet (MedDiet), the Dietary Approaches to Stop Hypertension (DASH), and the MedDiet-DASH Intervention for Neurodegenerative Delay (MIND). At present, the MedDiet and DASH are advocated for their cardiovascular benefits [13] but also advisable to promote cognition in them and because of the association between the risk factors of vascular problems with dementia [14]. A relationship between adherence to MedDiet and cognitive function was proved by several epidemiological studies and clinical trials [15, 16], and the World Health Organization (WHO) has included this dietary pattern in their guidelines to reduce the risk of cognitive decline and dementia; on the other hand, it is conditionally considered the potency of the recommendation [2]. Even though it has been less comprehensively investigated in association with cognition and other cardiometabolic health outcomes, an amalgam of the MedDiet and DASH diet, the MIND diet, is also being promoted for brain health [17].

The potentially effective preventive strategies are dietary interventions because nutrition is a modifiable factor for intervention in cognitive disorders. The MIND diet aims to lessen dementia and the decline in brain health that is prevalent as people get older. The MIND diet is the combined aspects of two accepted diets, the Mediterranean diet, and the DASH diet. Many researchers consider the Mediterranean and DASH diets as one of the healthiest diets. Studies have proven that they can lower blood pressure and reduce the risk of heart disease, diabetes, and numerous other diseases also. The diet is tailored after the Mediterranean and DASH diets but with modifications based on the most persuasive findings in the area of diet for dementia.

The MIND diet combines the DASH and Mediterranean diets to create a diet aimed at reducing the risk of dementia and the decline in brain health that people often experience as they age. The MIND diet encourages the consumption of all kinds of vegetables, berries, nuts, olive oil, whole grains, fish, beans, poultry, and a moderate amount of wine. To improve cognition, currently, the MIND diet is found to be superior and beneficial when compared to various other plant-based diets including the Mediterranean, Dietary Approaches to Stop Hypertension, Pro-Vegetarian, and

Baltic Sea diets. MIND diet adherence is possibly related to an improved cognitive function in elderly people.

3. Potential mechanism of the MIND diet

Several studies proved that there is an impact on biological mechanisms of neurocognitive aging by antioxidant, vitamin, probiotic, plant protein, and unsaturated fatty acid content along with low glycemic index/load components in a regular diet [18]. Promotion of vascular health and neuroprotection by anti-inflammatory mechanisms and reducing oxidative stress, ameliorating glycemic control, and supporting a favorable microbiome possibly lead to enhanced cognitive function [19]. Specifically, the observations with the MedDiet and changes in cognitive function may be related to synergistic or individual associations of specific foods, such as olive oil and nuts, due to associations of these foodstuffs with the above-mentioned mechanisms [20–22].

The amalgamation of the Mediterranean and the DASH diet pattern is the MIND diet. Researchers substantiated through observational studies that Alzheimer's disease is prevented or potentially delayed by following these two dietary patterns. Morris et al. [23] in their observational studies found that the risk of developing Alzheimer's disease was reduced by 53% among people who followed the MIND diet strictly and by 35% reduction who followed moderately [24]. This combination of these two diets will reduce oxidative stress and inflammation in the body, which moderates brain cell damage. The recommended guidelines for the MIND diet focus more on plant-based foods that are marginally processed, limit animal-based foods that are high in saturated fats, and foods with added sugars. Portion control is also recommended but does not emphasize weight loss. The principles of the MIND diet include having 10 food groups and a limit to 5. The diet advises fundamentally to take 3 servings of whole grains, fruits, and vegetables, 1 to 2 servings of beans, poultry, and fish each week, and daily snacks can include nuts and berries every day. The diet highlights mostly choose olive oil as a healthy source of fat for cooking foods. There is no restriction on intake of meats and dairy products, the diet recommends to have sparingly as less than four times a week. As a substitute, the diet recommends protein-packed beans and legumes which are vital for brain health.

4. Role of MIND diet and protocol

The performance of the human brain is based on an interplay between the inherited genotype and external environmental factors, with diet. To maintain brain performance food and nutrition are essential which aid in the prevention and treatment of mental disorders. Various experimental models and epidemiological studies evidenced that the whole composition of the human diet with specific dietary components has an impact on brain function. The role of the MIND diet in 5 key areas of brain function linked to mental health and performance are displayed below (**Figure 1**).

5. Benefits of the MIND diet

To stick to and get benefited from the MIND diet, include at least three servings of whole grains, a green leafy vegetable with one other vegetable and fruits especially berries daily, snack most days on nuts, have beans every other day,

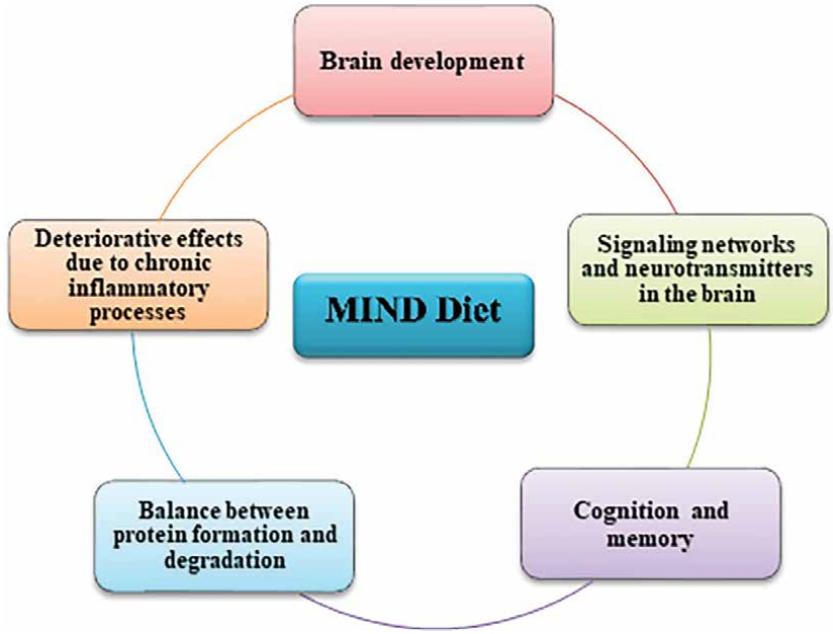

Figure 1.
Role of the MIND diet.

poultry at least twice a week and fish at least once a week. Intake of the designated unhealthy foods, ghee, butter, sweets and pastries, whole fat cheese, and fried or fast food should be restricted. Food groups recommended in the MIND diet are found to boost brain health as it is a rich source of fiber and packed with all necessary nutrients like vitamin E, folate, omega-3 fatty acids, carotenoids, and flavonoids. Research shows that the MIND diet can improve brain health and a lower

S. No	Included foods in the MIND diet	Recommendation
1	Green leafy vegetables	one serving daily
2	All other vegetables	2 or more servings per day
3	Berries	2 or more servings per week
4	Nuts	5 or more servings per week
5	Olive oil	2 tablespoons per day
6	Whole grains	3 or more servings per day
7	Fish/seafood	1 or more servings per week
8	Beans	4 or more servings per week
9	Poultry	2 or more servings per week
10	Wine	30 g per day, also can skip it

**One serving = 1 cup raw or ½ cup cooked.*
Source: Morris MC et al. [24], MIND diet associated with reduced incidence of Alzheimer's disease. Alzheimer's & Dementia; 2015.

Table 1.
The MIND Diet—Foods to be included.

S. No	Restricted foods in the MIND diet	Recommendation
1	Red Meat & Processed Meat	Not more than 3 servings per week
2	Butter & Stick Margarine	Less than 1 tsp per day
3	Regular Cheese	No more than 2 oz. per week
4	Pastries & Other Sweets	No more than 4 treats per week
5	Fried Foods & Fast Foods	No more than 1 meal per week

**One serving = 3 to 5 oz.*
Source: Morris MC et al. [24], MIND diet associated with reduced incidence of Alzheimer's disease. Alzheimer's & Dementia; 2015.

Table 2.
The MIND Diet—Foods to be restricted.

likelihood of developing conditions like Alzheimer's disease, dementia, and other forms of age-related cognitive decline. Studies indicate that including certain foods on regular basis and avoiding unhealthy ones will slow brain aging by 7.5 years (**Tables 1** and **2**).

6. Components of MIND diet and its role to health

6.1 Green leafy vegetables

Green leaves like kale, spinach, collards, and broccoli are the sources of brain-healthy nutrients like vitamin K, lutein, folate, and beta carotene. Research recommends that these plant-based foods will slow down cognitive decline. Due to the neuroprotective actions of phylloquinone, lutein, nitrate, folate, α-tocopherol, and kaempferol, the intake of green leafy vegetables 1 serving per day aids to lessen the decline in cognitive abilities with older age. Further, the daily serving of green leafy vegetables in a regular diet is an economic and simple mode to improve and maintain brain health [23]. The nutrients in green leafy vegetables will have independent mechanisms of action that synergistically protect the brain. Serum carotenoid levels were related to less severe periventricular white matter lesions, predominantly in elderly smokers. Lutein reduces phospholipid peroxidation in human erythrocytes, to attenuate oxidative stress, mitochondrial dysfunction, and neuroinflammation. Folate inhibits tau phosphorylation, APP, PS1, and Aβ protein levels which triggers Alzheimer's disease pathogenesis, to increase methylation potential and DNA methyltransferase activity.

6.2 All other vegetables

Scientific evidence has shown the association between vegetable intake and its polyphenols for the prevention or treatment of diseases. The compounds in vegetables act to improve neuronal plasticity through the protein CREB (Camp Response Element Binding) in the hippocampus, modulating pathways of signaling and transcription factors (ERK/Akt). In the same way, brain-derived neurotrophic factor (BDNF) is involved in the maintenance, survival, growth, and differentiation of neurons. All these effects are produced by an increase in cerebral blood flow, with an upsurge in the blood's nitric oxide levels and oxygenation [25]. Terpenoids,

carotenoids, phenolics, phytosterols, and glucosinolates are the most prominent bioactive compounds existing in vegetables found to be operational in preventing neurodegeneration.

6.3 Berries

Research indicates that flavonoids, the natural plant pigments in berries help to progress memory. Flavonoids in plants have potent antioxidant and anti-inflammatory properties. Stress and inflammation are the factors to contribute cognitive impairment and the regular consumption of flavonoids quantitatively will mitigate the harmful effects. Studies on the positive effects of flavonoids, particularly anthocyanidins, are limited to animal models or very small trials in the elderly but proved that greater consumption of foods with these compounds improved cognitive function. Studies show that regular intake of blueberries and strawberries, which are high in flavonoids, delayed cognitive decline in elderly people by up to 2.5 years [26].

6.4 Nuts

The outstanding sources of protein and healthy fats are the nuts which aid to improve memory as well as good for both the heart and brain. An omega-3 fatty acid called alpha-linolenic acid (ALA) is found to be high in walnuts. There is an association between intake of diets rich in ALA and omega-3 fatty acids to cardiovascular regulation as it lowers blood pressure and makes arteries cleaner. In 2015 a study was done by the University of California, Los Angeles (UCLA) related higher walnut consumption to improved cognitive test scores.

6.5 Vegetable oils

The beneficial effects of the MedDiet on cognitive functions have been attributed to its high MUFA content. Medium-chain triglycerides (MCTs) or medium-chain fatty acids in coconut oil improve cognition in Alzheimer's patients, also helps to improve insulin resistance, which is an excellent treatment for dementia patients and diabetics. Caprylic acid is the MCT derived from coconut or palm oil helps to improve cognitive function in Alzheimer's patients. Olive oil is a source of fatty acids and antioxidant-rich food. The best quality form of olive oil is extra-virgin olive oil (EVOO). Regular intake of EVOO is linked with lower mitochondrial oxidative stress, which counteracts age-related cognitive decline. The secoiridoid oleuropein, resp. oleuropein aglycone in olive oil is responsible for its neuroprotective effect. The results of in vitro and in vivo studies specify that the regular intake of EVOO is associated with enhanced cognitive functions, which proves that olive oil has a neuroprotective effect and positively prevents the development of dementia and Alzheimer's disease [27].

6.6 Whole grains

Whole grains are the richest source of protein, fiber, B vitamins, antioxidants, and trace minerals (iron, zinc, copper, and magnesium). A regular diet rich in whole grains reduces the risk of heart disease, type 2 diabetes, obesity, and some types of cancer. Naturally, whole grains are rich in amino acids, especially tryptophan, which

is vital for serotonin and melatonin production. Serotonin is the "feel-good hormone," which improves mood, relaxes the brain and body, whereas melatonin helps to establish and maintain stable sleep cycles. The dietary pattern with a higher intake of red meat, processed meat, peas, legumes, fried foods, and a lower intake of whole grains was related to higher inflammatory markers and accelerated cognitive decline in elderly people [28].

6.7 Seafood

Fatty fish like salmon, mackerel, herring, and sardines are abundant sources of omega-3 fatty acids, unsaturated fats that have been connected to lower blood levels of beta-amyloid, the protein responsible for the formation of clumps in the brains of people with Alzheimer's disease. Fish intake is recommended weekly twice and the best fish varieties to prefer for brain health are salmon, cod, canned light tuna, herring, and Pollack which are also low in mercury. Further, these varieties of fish also contain Vitamin B12, the essential nutrient to maintain nerves and blood vessels and involved in creating DNA. Omega-3 fatty acids are responsible for physiological functions that are interconnected to neurogenesis, neurotransmission, and neuroinflammation. Hence, they play dynamic roles in the development, functioning, and aging of the brain. The dietary deficiencies of omega-3 fatty acids in humans are linked with an increased risk of developing various psychiatric disorders, including depression, bipolar disorder, schizophrenia, dementia, attention-deficit/hyperactivity disorder, and autism [29]. Omega-3 fatty acids, docosahexaenoic acid (DHA), help to improve memory and brain health. The best sources of omega-3 fatty acid, DHA among the seafood, algae, and fatty fish are salmon, bluefin tuna, sardines, and herring.

6.8 Beans

Beans which also include other legumes, such as lentils, soybeans, black beans, chickpeas are another staple food staple good for brain health. High consumption of legumes like three or more servings per week has been related to enhance cognitive performance, with the utmost concentration of folate. Beans are rich in protein, carbohydrates, fiber, B-vitamins and omega fatty acids anti-oxidants, and minerals. Beans digest slowly as it takes 2 to 3 hours and while digesting they provide the brain with a consistent source of glucose. All the bean varieties with kidney and pinto beans are preferred for brain health as they comprise more omega-3 fatty acids. Beans have a remarkably high concentration of certain anti-inflammatory compounds which appears to be neuroprotective [30].

6.9 Poultry

Chicken is a rich source of lean protein and brain-healthy compounds like dietary choline and vitamins B6 and B12. Choline and the B vitamins play vital roles in healthy cognition and provide neuroprotective benefits. Studies evidenced that the intake of poultry enhances mental functions and developments used in working memory among healthy adults and short-term memory among healthy adults who experience stress in daily life [31]. The blend of vitamin B6, B12, and folate plays a key role in the reduction of cognitive decline and age-related memory loss, stroke, Alzheimer's disease, and depression [32].

6.10 Wine

One component of the Mediterranean diet is the intake of wine, which is associated with the promotion of human mental and heart health and the prevention of diseases. An optimum amount of wine for neuroprotection seems to be up to 30 g of alcohol per day. Moderate wine consumption is related to higher blood levels of omega-3 fatty acids that protect against heart disease, metabolize glucose, decrease cardiometabolic risk, increased levels of heme-oxygenase, prevention of blood clotting and also protect the brain from stroke. The risk of developing dementia and depression was advocated to be reduced by a moderate intake of wine [33]. A wide range of polyphenols present in red wine includes resveratrol, flavanols like quercetin, myricetin, phenolic acids, trihydroxystilbene, flavanols like epicatechin, catechin, procyanidins, and anthocyanins, which are responsible for the color of red wines. It was evidenced in humans from randomized clinical trials that resveratrol is able to improve cerebral blood flow, cerebral vasodilator responsiveness to hypercapnia, some cognitive tests, perceived performances, and the Aβ40 plasma and cerebrospinal fluid level [34].

7. Conclusion

Researches are evident that the DASH diet and the Mediterranean diet improve cognitive function and development [35, 36]. By the support of these studies, the two diets have been combined to construct a hybrid MIND diet which is specifically designed to improve brain health. The MIND diet lays emphasis on the regular intake of leafy green vegetables, other vegetables, berries, legumes, fish, nuts, and whole grains whereas it limits butter, cheese, and red meat consumption. Studies suggested that the MIND diet can slow down age-related cognitive decline and reduce the risk of Alzheimer's disease [37, 38]. The Dukan and Atkins diets radically cut carbohydrates and fat in favor of protein, while the Palaeolithic diet greatly restricts starch in favor of fat and protein. These nutrient imbalances have beneficial effects only in the short term, especially on weight loss, but there are serious doubts about their long-term results. Whereas in the MIND diet, all the nutrient groups are included and a variety of nutrient sources are recommended in the right proportions, as per international nutritional recommendations. The MIND diet is also found to be a good source of carbohydrates, protein fat, and all other nutrients. Adherence to the MIND diet will improve brain health, and slow down cognitive decline in individuals with Alzheimer's disease.

Acknowledgements

The infrastructural facilities provided and the support given by the management of PSG College of Arts & Science are duly acknowledged herewith.

Conflict of interest

The author does not have any conflict of interest whatsoever with regard to the content or opinions expressed above.

DOI: http://dx.doi.org/10.5772/intechopen.104463

Author details

Premagowri Balakrishnan
Clinical Nutrition and Dietetics, PSG College of Arts and Science, Coimbatore, India

*Address all correspondence to: premagowri@psgcas.ac.in

References

[1] United Nations, Department of Economic, and Social Affairs and Population Division. World Population Ageing 2020 Highlights: Living Arrangements of Older Persons. New York: United Nations; 2020

[2] World Health Organization [WHO]. Risk Reduction of Cognitive Decline and Dementia: WHO Guidelines. Geneva: World Health Organization Report; 2019

[3] Kanaya AM, Lindquist K, Harris TB, Launer L, Rosano C, Satterfield S. Total and regional adiposity and cognitive change in older adults: The health, aging and body composition (ABC) study. Archives of Neurology. 2009;**66**:329-335. DOI: 10.1001/archneurol.2008.570

[4] Hassing LB, Dahl AK, Pedersen NL, Johansson B. Overweight in midlife is related to lower cognitive function 30 years later: A prospective study with longitudinal assessments. Dementia and Geriatric Cognitive Disorders. 2010;**29**:543-552. DOI: 10.1159/000314874

[5] Ng M, Fleming T, Robinson M, Thomson B, Graetz N, Margono C. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980-2013: A systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2020;**384**:766-781. DOI: 10.1016/S0140-6736(14)60460-8

[6] Balasubramanian P, Kiss T, Tarantini S, Nyúl-Tóth Á, Ahire C, Yabluchanskiy A. Obesity-induced cognitive impairment in older adults: A microvascular perspective. American Journal of Physiology. Heart and Circulatory Physiology. 2020;**320**:H740-H761. DOI: 10.1152/ajpheart.00736.2020

[7] Petersen RC, Doody R, Kurz A, Mohs RC, Morris JC, Rabins PV. Current concepts in mild cognitive impairment. Archives of Neurology. 2001;**58**:1985-1992

[8] Wu Z, Phyo AZZ, Al-harbi T, Woods RL, Ryan J. Distinct cognitive trajectories in late life and associated predictors and outcomes: A systematic review. Journal of Alzheimer's Diseases. 2020;**4**:459-478. DOI: 10.3233/ADR-200232

[9] Petersen RC, Lopez O, Armstrong MJ, Getchius TSD, Ganguli M, Gloss D. Practice guideline update summary: Mild cognitive impairment report of the guideline development, dissemination, and implementation. Neurology. 2018;**90**:126-135

[10] Rutjes AWS, Denton DA, di Nisio M, Chong LY, Abraham RP, Al-Assaf AS. Vitamin and mineral supplementation for maintaining cognitive function in cognitively healthy people in mid and late life. Cochrane Database System Review. 2018;**12**:CD011906. DOI: 10.1002/14651858.CD011906.pub2

[11] Ammar A, Trabelsi K, Boukhris O, Bouaziz B, Müller P, Glenn MJ. Effects of polyphenol-rich interventions on cognition and brain health in healthy young and middle-aged adults: Systematic review and meta-analysis. Journal of Clinical Medicine. 2020;**9**:1598. DOI: 10.3390/jcm9051598

[12] Brainard JS, Jimoh OF, Deane KHO, Biswas P, Donaldson D, Maas K. Omega-3, Omega-6, and polyunsaturated fat for cognition: Systematic review and meta-analysis of randomized trials. Journal of American Medical Director Association. 2020;**21**:1439-1450

[13] Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ. ACC/AHA guideline on the primary prevention of cardiovascular disease: A report of the American college of cardiology/American heart association task force on clinical practice guidelines. Journal of the American College of Cardiology. 2019;**74**:e177-e232

[14] Gottesman RF, Albert MS, Alonso A, Coker LH, Coresh J, Davis SM. Associations between midlife vascular risk factors and 25-year incident dementia in the Atherosclerosis Risk in Communities (ARIC) cohort. JAMA Neurology American Medical Association. 2017;**74**:1246-1254. DOI: 10.1001/jamaneurol.2017.1658

[15] Loughrey DG, Lavecchia S, Brennan S, Lawlor BA, Kelly ME. The impact of the mediterranean diet on the cognitive functioning of healthy older adults: A systematic review and meta-analysis. Advanced Nutrition in American Society. 2017;**8**:571-586. DOI: 10.3945/an.117.015495

[16] Wu L, Sun D. Adherence to Mediterranean diet and risk of developing cognitive disorders: An updated systematic review and meta-analysis of prospective cohort studies. Scientific Reports. 2017;7:41317. DOI: 10.1038/srep41317

[17] Van den Brink AC, Brouwer-Brolsma EM, Berendsen AAM, van de Rest O. The Mediterranean, Dietary Approaches to Stop Hypertension (DASH), and Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diets are associated with less cognitive decline and a lower risk of Alzheimer's disease-a review. Advances in Nutrition. 2019;**10**:1040-1065. DOI: 10.1093/advances/nmz054

[18] Frisardi V, Panza F, Seripa D, Imbimbo BP, Vendemiale G, Pilotto A. Nutraceutical properties of mediterranean diet and cognitive decline: Possible underlying mechanisms. Journal of Alzheimer's Disease. 2010;**22**:715-740. DOI: 10.3233/JAD-2010-100942

[19] Caracciolo B, Xu W, Collins S, Fratiglioni L. Cognitive decline, dietary factors and gut-brain interactions. Mechanism of Ageing Development. 2014;**13**:59-69

[20] Creedon AC, Hung ES, Berry SE, Whelan K. Nuts and their effect on gut microbiota, gut function and symptoms in adults: A systematic review and meta-analysis of randomised controlled trials. Nutrients. 2020;**12**:2347. DOI: 10.3390/nu12082347

[21] Marcelino G, Hiane PA, Freitas K, Santana LF, Pott A. Effects of olive oil and its minor components on cardiovascular diseases, inflammation, and gut microbiota. Nutrients. 2019;**11**:1826. DOI: 10.3390/nu11081826

[22] Viguiliouk E, Kendall CWC, Mejia SB, Cozma AI, Ha V, Mirrahimi A. Effect of tree nuts on glycemic control in diabetes: A systematic review and meta-analysis of randomized controlled dietary trials. PLoS One. 2014;**9**:e103376

[23] Morris MC, Wang Y, Barnes LL, Bennett DA, Dawson-Hughes B, Booth SL. Nutrients and bioactives in green leafy vegetables and cognitive decline Prospective study. Neurology. 2018;**90**(3):e214-e222

[24] Morris MC, Tangney CC, Wang Y. MIND diet associated with reduced incidence of Alzheimer's disease. Alzheimer's & Dementia. 2015;**11**(9):1007-1014. DOI: 10.1016/j.jalz.2014.11.009

[25] Carrillo JÁ, Zafrilla MP, Marhuenda J. Cognitive function and consumption of fruit and vegetable polyphenols in a young population: Is there a relationship? Foods. 2019;**8**(10):507

[26] Elizabeth ED, Kang JH, Breteler MMB, Grodstein F. Dietary intakes of berries and flavonoids in relation to cognitive decline. Annals of Neurology. 2012. DOI: 10.1002/ana.23594

[27] Lee AY, Choi JM, Lee J, Lee MH, Lee S, Cho EJ. Effects of vegetable oils with different fatty acid compositions on cognition and memory ability in Aβ 25-35-induced Alzheimer's disease mouse model. Journal of Medicinal Food. 2016;**19**(10):912-921

[28] Ozawa M, Shipley M, Kivimaki M, Singh-Manoux A, Brunnera EJ. Dietary pattern, inflammation and cognitive decline: The Whitehall II prospective cohort study. Journal of Clinical Nutrition. 2017;**36**(2):506-512. DOI: 10.1016/j.clnu.2016.01.013

[29] Klaus W. Lange Omega-3 fatty acids and mental health. Global Health Journal. 2020;**4**(1):18-30

[30] Ganesan K, Xu B. Polyphenol-rich dry common beans (*Phaseolus vulgaris* L.) and their health benefits. International Journal of Molecular Science. 2017;**18**(11):2331

[31] Suttiwan P, Yuktanandana P, Ngamake S. Effectiveness of essence of chicken on cognitive function improvement: A Randomized Controlled Clinical Trial. Nutrients. 2018;**10**(7):845

[32] David O, Kennedy B. Vitamins and the brain: Mechanisms, dose and efficacy—A review. Nutrients. 2016;**8**(2):68

[33] Nooyens AC, Bueno-de-Mesquita HB, van Gelder BM, van Boxtel MP, Verschuren WM. Consumption of alcoholic beverages and cognitive decline at middle age: The Doetinchem Cohort Study. British Journal of Nutrition. 2014;**111**:715-723

[34] Cicero AFG, Ruscica M, Banach M. Resveratrol and cognitive decline: A clinician perspective. Archives of Medical Sciences. 2019;**15**(4):936-943. DOI: 10.5114/aoms.2019.85463

[35] Appel LJ, Moore TJ, Obarzanek E. A clinical trial of the effects of dietary patterns on blood pressure. New England Journal of Medicine. 1997;**336**(16):1117-1124. DOI: 10.1056/NEJM199704173361601

[36] Mario S, Jose L, Shakir C, et al. Effects of the Dietary Approach to Stop Hypertension (DASH) diet on cardiovascular risk factors: A systematic review and meta-analysis. British Journal of Nutrition. 2015;**113**(01):1-15. DOI: 10.1017/S0007114514003341

[37] Kheirouri S, Alizadeh M. MIND diet and cognitive performance in older adults: A systematic review. Critical Reviews in Food Science and Nutrition. 2021;**61**:1-19

[38] Dhana K, James BD, Agarwal P, Aggarwal Neelum T, Cherian Laurel J, Leurgans Sue E, et al. MIND Diet, common brain pathologies, and cognition in community-dwelling older adults. Journal of Alzheimer's Disease. 2021;**83**(2):683-692

Chapter 11

Mushroom; Chemistry, Bioactive Components, and Application

Ahmed M. Saad, Mahmoud Z. Sitohy, Belal A. Omar, Mohamed T. El-Saadony and Basel Sitohy

Abstract

Apposite energy is required for body activity. Energy is derived from the oxidation of various biomolecules like carbohydrates, lipids, and proteins. These bio-molecules in the proper amount are essential for the structural and functional activities of any living being. Certain vitamins and enzymes are also needed for the maintenance of biochemical processes. Our daily food is the major source of these biomolecules. From the last few decades, researchers have placed giant effort into searching for a food material that can provide nearly all the essential components required to maintain the energy need and consequently, balancing the body's homeostasis. Mushrooms have the potential to address the above-raised issues. Besides their pleasant flavor and culinary value, mushrooms are an important source of biomolecules that include large macromolecules (protein, carbohydrate, lipid, and nucleic acid) as well as small molecules (primary metabolites, secondary metabolites, and natural products). This chapter discusses the bioactive compounds in edible mushroom and their activities.

Keywords: mushroom, species, bioactive components, anticancer, antidiabetic

1. Introduction

Mushrooms are a group of fungi with a distinctive fruiting body that can be either epigeous or hypogenous and large enough to be seen with the naked eye and picked by hand [1]. They are either saprophytic, parasitic or mycorrhizal. Out of these three categories, the majority of them are saprophytic and they play an important role in the biodegradation and bioremediation of recalcitrant substances [2]. Notably, there are about 14,000 mushroom species that have been reported to date and a further 126,000 species more are yet to be discovered [3]. The majority of mushroom species are edible and over 400 species are poisonous [4]. Out of these more than 2000 edible species, 5–6 species are grown on a mass scale, 40 species are produced commercially and 80 species are cultivated experimentally (**Figure 1**). Edible mushrooms have very minimal calorie value as they contain less amounts fat and carbohydrate and are also cholesterol-free. In addition, edible mushrooms are rich in other vital nutrients like niacin, vitamin D, proteins, selenium, potassium, riboflavin. Mushrooms also contain a significant amount of fiber which helps in the appropriate digestion of food (**Table 1**) [1]. The active

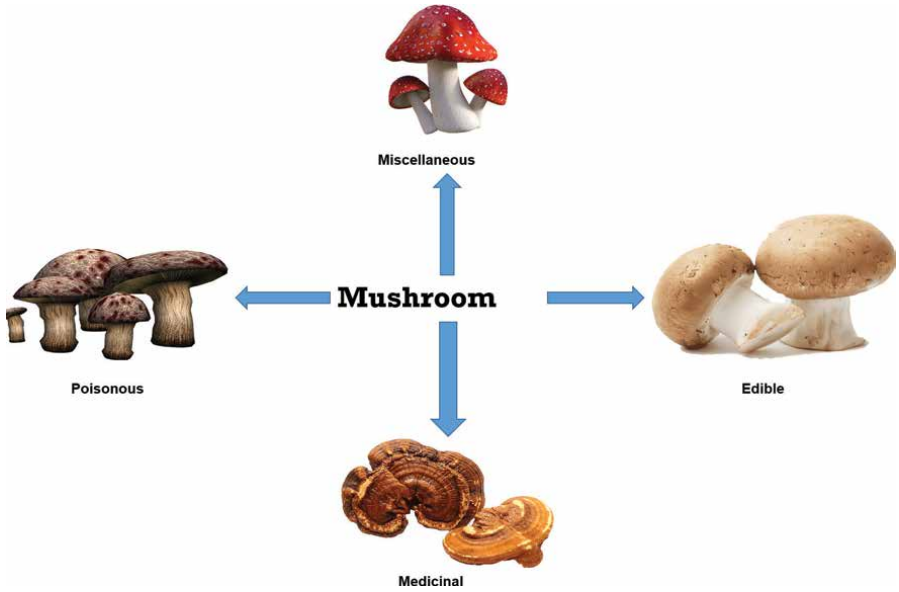

Figure 1.
Mushroom species based on their uses.

compounds in common mushrooms and the nutritional value of these mushrooms and their activities were showed in **Table 2** and **Figure 2**.

Oxidative stress (OS) is one of the major causes of any disease such as neurodegenerative (NDs), cardiovascular (CDs) and reproductive diseases (RDs), and diabetes [17]. Inflammation is the progressive result of the severe burden of OS. Any biomolecules with anti-oxidative and anti-inflammatory activity show a better response in the treatment of the above diseases [18]. The polyphenols, terpenoids, alkaloids, and other important biomolecules found in edible mushrooms prove their efficacy in therapeutics with minimal side effects [19]. Mushrooms and their biomolecules are known to have been used to cure diabetes by Indian and Chinese patents from ancient times [20]. The active components in these mushroom species; *Ganoderma lucidum, Lentinus edodes, Pleurotus ostreatus, Pleurotus sajor-caju, Grifola frondosa, Poriacocos*, have exhibited potent anti-diabetic activity [21]. For example, the polysaccharides derived from *Pleurotus ostreatus* exhibits potent antidiabetic activity in the streptozotocin-persuaded Diabetic Rat model [22]. β-glucans and several other biomolecules present in edible mushrooms show strong anti-diabetic activity [23]. Recently the edible oyster mushroom *Pleurotus fossulatus* aqueous extract improved liver and kidney function in the streptozotocin-induced diabetic rats, besides reducing blood glucose levels, total cholesterol (TC), triglyceride (TG), and high-density lipoprotein (HDL) [24].

Disorders related to the heart and blood vessels are grouped into cardiovascular diseases (CVDs) [25]. Mushrooms and their bioactive components can prevent CVDs [26]. Being functional foods, edible mushrooms contain a significant number of bioactive compounds that show strong potential in the treatment of CVDs [27]. The antioxidant and anti- inflammatory biomolecules present in mushrooms reduce the atherosclerosis risk which is directly related to CVDs [28]. Diseases related to the reproductive systems are very common now a day. Abnormalities in the endocrine system are mainly responsible for the progression of reproductive diseases (RDs).

Mushroom	Medicinal value	Protein (g/100 g)	Carbo (g/100 g)	Lipid (g/100 g)	Fibers (g/100 g)	References
Clitocybene	Anticancer	8.11–12.18	64.47–77.12	1.14–2.04	—	[5]
Cordyceps	Anti-asthma	21.9	24.2	8.2	—	[6]
Hericium	Antihypercholesterolic	22.3	57.0	3.5	7.8	[7]
Trametes	Antidiabetic	—	—	—	—	[8]
Lentinus	immunomodulator	26.3	65.1	2.3	—	[8]
Hypsizygus	Anticancer	19.6–21.0	65–68.5	4.0–5.6	—	[8]
Flammulina	Immunomodulator, anti-asthma,Antihypercholesterolic	3.9–17.8	86–70.8	1.8–2.9	—	[9]
Grifola	antidiabetic, anti- arthritic, anti-viral, anti- obesity anticancer, anti- osteoporosis,	21.1	58.8	3.1	10.1	[8, 9]
Agaricus	anticancer, immunomodulator, hepatoprotective, anti- viral, antimutagenicm antidiabetic, antihyperchlosterolic	56.3	37.5	2.7	—	[10]
Phellinus	Antidiabetic, hepatoprotective, Immunomodulator	6.11–10.9	75.04–83.82	0.96–15.86	—	[11]
Ganoderma	antiviral, antithrombotic, hepatoprotective, anti- osteoporosis, anticancer, hypoglycemic, anti- aging, antiallergenic, hypocholesterolemic, antimutagenic,	13.3	82.3	3.0	—	[12]
Pleurotus	hepatoprotective, antitumor, anticancer, antiviral, antioxidant, antibacterial, antidiabetic, anti- arthritic, anti-obesity	17–42	37–48	0.5–5	24–31	[13]
Tricholoma	Antihypercholesterolic	18.1–30.5	31.1–52.3	2–6.6	30.1	[14]
Sarcodona	Anti- aging	12	64.6	2.8	5.1	[15, 16]
Leucopaxillus	Anticancer	—	—	—	—	[15, 16]
Tremella	Anticancer, antidiabitic	40.6	94.8	0.2	1.4	[15, 16]

Table 1.
Nutritional values of edible mushrooms and their activities.

Mushroom	Common name	Bioactive compounds/ingredients	Health benefit
Tremella fuciformis	Snow Mushroom	propanediol, glycerin, arganiaspinosa (argan) kernel oil, seawater, sodium hyaluronate, sodium PCA, sodium lactate, 3-O-ethyl ascorbic acid, pentylene glycol, caprylyl glycol, N-prolylpalmitoyl tripeptide-56 acetate, hydroxyethylcellulose, polyglyceryl-4 caprate, diheptyl succinate, capryloylglycerin/sebacic acid copolymer, sodium carbomer, ethylhexylglycerin	Skin health
Agaricus blazei	Orivedavr	>27% beta-glucan	Anti-hyperglycemic,
	*Agaricusblazei*Murrill	>0.90% polyphenols	antihypercholestromic
	extract		
Ganoderma lucidum	Reishi Elixir Mix	Organic Reishi mushroom extract (1500 mg), 18 mg of vitamin c, tulsi, organic mint	Support the body's sleep
			cycles as well as
			support
			occasional stress
L. edodes	Shiitake Goldcapsules	15% Lentinan 60% Polysaccharides	For immune system,
			cardiovascular health,
			skin and muscle health
			support, anti-bacterial properties
Ganoderma lucidum	ReishiMax capsules	13% Polysaccharides (beta-1,3-glucans) and 6% triterpenes (ganoderic acids and others) nucleosides, fatty acids (oleic acid), and amino acids, Gelatin, Stearic acid	Antidiabetic
Cordyceps sinensis	*Cordyceps*extractcapsules	Amino acids, including L-tryptophan, ergosterol, polysaccharides (β-glucans)	Control blood glucose levels
Ganoderma lucidum	GANOHERB Reishi	Organic ganoderma spore powder and extract- balanced blood sugar level diabetes (non-GMO & gluten-free), 100% natural, 400 mg/capsules	Supports healthy glucose metabolism, blood purification, and healthy blood sugar levels
	mushroom		
	bitter melon		
Ganoderma lucidum	Pure red reishicapsules	>9.40% triterpenes	Boost immune system And antidiabetic attribute Levels of blood sugar balanced
	organic reishitablets	>16% beta-glucan	
		>1.80% polyphenols	
Pleurotus eryngii,	GlucoSANO-Diabetes,	Agaricusblazei, ErgoD2VR	
Agaricus blazei,	Health Formula	(enriched pleurotuseryngii),	
Hypsizygus		white beech, brown beech,	
tessellates,		cordycepsmilitaris, vitamin	
Cordyceps militaris		D2 (ergocalciferol),	
		vegetable capsules,	
		myceliated whole oats, rice	
		flour, silica	

Mushroom	Common name	Bioactive compounds/ingredients	Health benefit
Ganoderma lucidum	GanoUltraGanoSuper	Mycelium, primordia,	Anticancerous, anti-stress,
		fruitbodies, and	antidiabetic
		extracellular compounds	
		vegetarian capsule	
		(pullulan), 100% organic	
		white milo	
		(growing substrate)	
Lentinus edodes, Grifola	Agarikon.1	750 mg of high-quality soluble	Anticancer attributes
frondosa,		polysaccharides per table	
Ganoderma lucidum,			
Pleurotus ostreatus			
and *Agaricus blazei*			
Hericium erinaceus	Amyloban 3399	Fruiting body extract, AmycenoneVR, Standardized to contain *amyloban* including *hericenones* 1950 mg	Brain health
	super lion's mane		
	(tablets)		
Ganoderma lucidum	Ganoderma herbal,	Extract, polysaccharides	Boost immunity,
	antidiabetic capsules		antidiabetic
Ganoderma lucidum,	E & Rose Wellness'	Powdered extract, selenium, copper, B vitamins, vitamin D, as well as prebiotics, polysaccharides	Stress relief, liver & brain health, concentrations/ focus, brain & immune health, immune health, endurance, stamina & endurance, immune health, blood sugar & blood pressure control.
Cordyceps sinensis,	Magic Milk		
Grifola frondosa,			
Inonotus obliquus,			
Hericium erinaceus			

Table 2.
Bioactive components in common mushroom.

Several RDs like reproductive tract infections, prostate cancer, breast cancer, ovarian cancer, etc. are most common in different populations [29]. Mushrooms and their bioactive molecules show anti-tumor activity which can be immensely beneficial in the treatment of different RDs. RDs commonly lead to different types of cancer and several biomolecules present in edible mushrooms can prevent metastasis toward cancer [1, 26]. Neurodegenerative diseases (NDs) like Huntington's disease (HD), Alzheimer's disease (AD), and Parkinson's disease (PD), etc. have been effectively treated by edible mushrooms through their bioactive components [30]. Progression of the NDs is the main cause of death which can be significantly inhibited by the biomolecules present in edible mushrooms [31]. Polyphenols, alkaloids, and several other biomolecules in edible mushrooms prove their efficacy in the treatment of different neurodegenerative diseases [32]. Similarly, a different form of cancer can also be treated by the biomolecules found in edible mushrooms [23]. This review discusses the role of mushrooms and their biomolecules to be utilized for the treatment of some most common diseases like CVDs, RDs, NDs, diabetes, and the different forms of cancer.

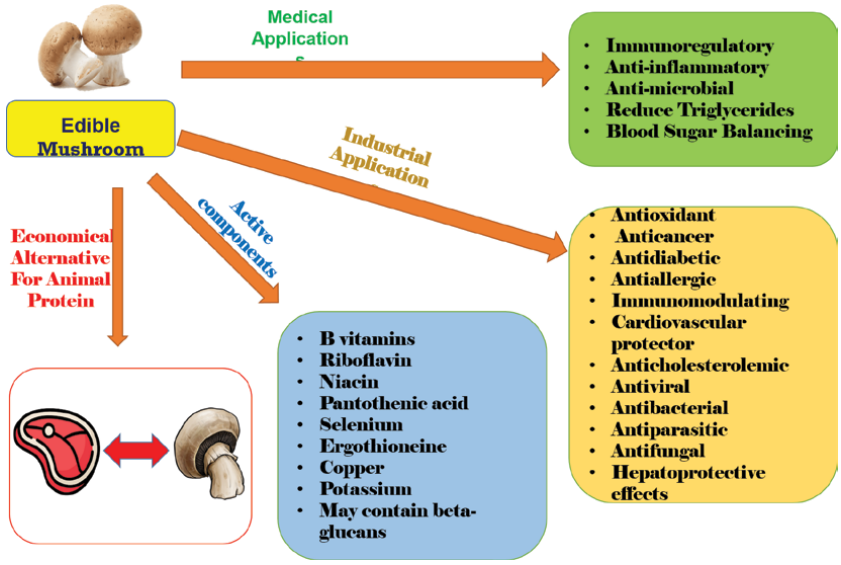

Figure 2.
Diverse application of elidable mushrooms.

2. Mushroom active compounds against cardiovascular diseases (CVDs)

Cardio Vascular Diseases (CVDs) are a category of heart and blood diseases, including coronary heart disease, cerebrovascular disease, rheumatic heart disease, and other diseases. CVDs are the leading cause of death worldwide. In the past few decades, researchers have shown the use of mushrooms and their bioactive compounds as therapeutic agents for CVDs. In 2010, Guillamon et al. reported the potentially positive effects of mushroom consumption on risk markers for CVDs and identified some potential bioactive compounds responsible for their therapeutic activity. Several studies have shown the influence of mushroom intake on some metabolic markers (total low-density lipoproteins (LDL), high-density lipoproteins (HDL): cholesterol, fasting triacylglycerol, homocysteine, blood pressure) which could potentially reduce the risk of cardiovascular disease. Relevant nutritional aspects of mushrooms include high fiber content, low-fat content, and low trans isomers of unsaturated fatty acids. Mushrooms also have low sodium concentrations and other significant components, such as eritadenine, phenolic compounds, sterols (such as ergosterol), chitosan, triterpenes, etc., which are considered to be potential agents for some previously healthy properties. The intake of mushrooms has a cholesterol-lowering or hypocholesterolemic effect which has been elucidated by different mechanisms, such as lowering of very-low-density lipoproteins (VLDL), improving lipid metabolism, inhibiting the activity of HMG-CoA reductase and therefore, prevents the development of atherosclerosis (**Figure 3**). Antioxidants and anti-inflammatory compounds found in mushrooms also reduce the risk of atherosclerosis [26]. *Ganoderma lucidum* play a curicral role in mitigating the toxicity of Adriamycin, where, Adriamycin treatment raised the number of marker enzymes found in serum including aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatine kinase (CK), and lactate dehydrogenase (LDH). In order to increase lipid peroxidation (LPO), adriamycin significantly decreased antioxidant

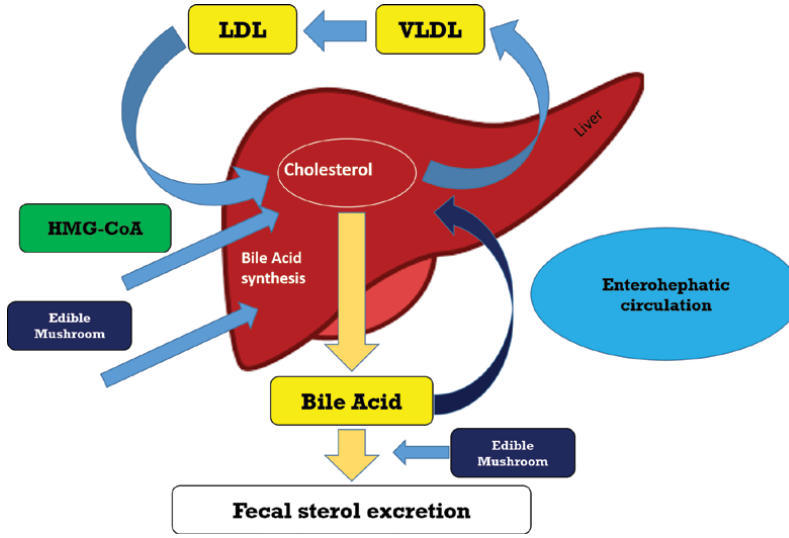

Figure 3.
Mushroom active compounds against cardiovascular diseases (CVDs).

enzymes in the cardiac tissues, including glutathione-S-transferase (GST), glutathione peroxidase (GPx), catalase (CAT), and superoxide dismutase (SOD). Adriamycin has also been shown to considerably lower glutathione (GSH) levels. This study has shown that *G. Lucidum* extracts have significant antioxidant properties and protect the heart from the free radical-mediated toxicity of adriamycin. *G. Lucidum* extract retrieves free radicals and also increases the levels of glutathione and antioxidant enzymes [33]. Important findings show that the edible mushrooms could be used as possible sources of novel hypocholesterolemia agents. Few studies have identified the levels of sterols, b-glucans, and HMGCoA-red as inhibitors in mushrooms. Ergosterol was the most plentiful sterol recorded in all the samples examined, apart from *G. lucidum*, which had identical levels of ergosterol and ergosta-7,22-dienol. *P. ostreatus, G. lucidum, A. aegerita,* and *L. edodes* mushrooms had high levels of b-glucan content, whereas *A. Blazeii, A. Bisporus*, and *L. procera* had low levels of β-glucan content. Because of the presence of lovastatin, a statin found in mycelia broths and its fruiting bodies, the oyster mushroom (*Pleurotus* spp.) reduces blood cholesterol levels. As a result, a mixture of bioactive supplements improves the nutritional ability of different mushrooms to lower serum cholesterol levels [31]. A study has assessed the effect of different mushroom-like *Lentinus edodes, Auricularia polytricha,* and *Flammulina velutipes* preparations on the levels of cholesterol in the rats which showed that the preparation of dried mushrooms significantly reduced plasma cholesterol levels. Lentinus edodes was more effective, while *Auricularia polytricha* (Jews-ear) and *Flammulina velutipes* were less effective than *L. edodes*, Kohshin. However, ergosterol supplements have caused a marked decrease in hepatic cholesterol levels [34]. A previous study, focusing on the hypolipidemic effects of polysaccharides, isolated from *Pholiota Nameko* (PNPS-1) was conducted on hyperlipidemic Wistar rats. The rats were treated with PNPS-1 at different doses which reduced very-low-density: lipoprotein/low-density lipoprotein cholesterol, triacylglycerol, phospholipids, and increased the atherogenic index and high-density lipoprotein cholesterol in the serum. PNPS-1 also improved pathological changes in the coronary arteries of hyperlipidemic rats.

These results suggest that PNPS-1 significantly reduces the development of hyperlipidemia and could be used as a potential therapeutic agent for CVD [35]. Antiatherogenic and antiatherosclerotic effects of different mushrooms belonging to the genera: *Armillaria, Agaricus, Boletus, Collybia, Cortinfrius, Coriolus, Flammulina, Hirneola, Lentinus, Ganoderrna, Lyophyllurn, Sarcodon, Pleurotus, Tricholoma,* and *Trenella* were detected in human intima aortic culture. The results showed that anti-atherosclerotic, anti-atherogenic, and hypolipidemic effects of certain species of mushrooms allow us to speculate that these edible fungi are beneficial dietary supplements that might be utilized in prophylactics and to a limited extent, in atherosclerotic medicines. Furthermore, the extraction and purification of the active substance from these mushrooms may result in the development of a strong antiatherosclerotic medicine [36]. Among the *Pleurotus* species, *P. ostreatus* was the best candidate for the prevention and treatment of atherosclerosis because it has been shown to contain a large number of antiatherosclerotic agents such as ergothionein, lovastatin, and chrysin [37].

3. Antidiabetic activity of mushroom biomolecules

Mushrooms are fungi that either grow above or below the ground. These are the macro fungi that can be easily seen with the naked eye. Mushrooms have been used since ancient times by the people of India and China or their medicinal properties. Nowadays many countries are consuming mushrooms for not only their unique flavor but also for their culinary effects. As many studies have revealed that mushrooms are rich sources of: proteins, carbohydrates, vitamins (B1, B2, B12, C, D, and E) and minerals like Mn, Mg, Se, Ca, Na, Cu, K, and Fe [38]. These nutritional factors in mushrooms have made it very efficient to fight diabetes. In vitro and in vivo studies have shown that the extract of mushrooms can reduce the expression of proinflammatory cytokines, induced by lipopolysaccharides which further improved the glucose uptake in skeletal muscle cell lines [39].

One of the most active biomolecules of mushrooms is β-glucans, a polysaccharide that can protect the pancreatic tissue from damage and restore the function of b-cells which helps to lower the blood glucose levels [40]. The low energy, lack of cholesterol and fats, less carbohydrates, and high minerals, proteins and vitamins made mushrooms an ideal food for diabetic patients. The consumption of mushrooms for a few days only can help to manage the low-density lipoproteins, total cholesterol, high-density lipoprotein, triglycerides levels in serum [10]. Besides bioactive molecules, mushrooms are very good in antioxidants activity and are also a good source of dietary fibers and water. Some of the most culinary properties containing mushrooms are *Agaricus bisporus, Agaricus subrufescens, Cordyceps millitaris, Cordyceps sinensis, Grifola frondosa, Ganoderma lucidum, Phellinus linteus, Pleurotus flabellatus, Pleurotus citrinopileatus, Pleurotus ostreatus, Poria cocos* [10, 41]. Extracts of Ganoderma lucidum contain: polysaccharides, triterpenoids, proteoglycans, and proteins which have been shown to reduce blood glucose levels. The proteoglycans of *G. lucidum* inhibit the tyrosine phosphatase 1B protein in diabetic patients. *G. lucidum* has proven to be very effective in controlling diabetes. Moreover, the triterpenoid from *G. lucidum* inhibits the aldose reductase and a-glucosidase enzymes which are responsible for the elevation of postprandial glucose levels [42]. Polysaccharides from *G. atrum* (PSG-1) increase insulin sensitivity and lower the serum lipid by increasing and decreasing the expression levels of Bcl-2 and Bax, respectively in pancreatic cells [43].

Heteropolysaccharides are one of the bioactive molecules of Pleurotus ostreatus that control diabetes by activating the Glycogen synthase kinase 3 (GSK3) by phosphorylation and facilitating the translocation of glucose transporter type 4 (GLUT4) in streptozotocininduced diabetic rats [44]. *Lentinula edodes* promote the growth of gut microbiota, which play a very important role to balance the energy in diabetic patients. Another mushroom, *Hirsutellas inensis* shows antidiabetic, antiobesogenic effects in high-fat-diet feed-mice by modification of the components of gut microbiota. The polysaccharides and fibers of mushrooms act as prebiotics that helps in the treatment of diabetic patients [45]. Recently, researchers have found the potential effects of mushrooms in diabetic nephropathy conditions. Polysaccharides from Auricularia auricula are very helpful in promoting the oxidation of glucose. This polysaccharide protects against diabetic nephropathy by the regulation of creatinine, inflammatory factors, blood urea nitrogen, and urine protein. Polysaccharides isolated from *Flammulina velutipes* provided protection against reactive oxygen species (ROS) and reduced the level of malondialdehyde (MDA) in the kidney. The studies have also revealed that the proteoglycans from Ganoderma lucidum can restore kidney function by providing antioxidant activity [46]. According to a study conducted by Chou, Kan, Chang, Peng, Wang, Yu, Cheng, Jhang, Liu and Chuu [47], low molecular weight polysaccharide of *Inonotus obiquus* (LIOP) significantly reduces the expression of NF-jB and Transforming growth factor-beta (TGF-b) in a dose-dependent manner [48]. They find that LIOP treatment can improve glucolipotoxicity induced renal fibrosis in diabetic nephropathy mice. *Hypsizigusm armoreus* have been used to examine its protective effect on the liver, kidney, and pancreas. The spent mushroom compost polysaccharide (SCP), its enzymatic lysates (ESCP), and acid-based hydrolyzed SCP (ASCP) were tested in streptozotocin-induced mice and found that it increased the: catalase, superoxide dismutase, and glutathione peroxidase activity whereas, it reduced the lipid peroxide and malonaldehyde levels [49]. a-glucosidase inhibiting polysaccharide (ePS-F4-1) with triterpenoids had been purified from Coriolus versicolor. Another bioactive molecule, MT-a-glucan (polysaccharide) from Grifola frondosa increases the expression of Interleukin-2 (IL-2) and prevents the injury of b-cells [50]. Submerged cultured mycelium of Agaricus brasiliensis and *G. lucidum* has shown a protective effect on red blood cells (RBCs) in Streptozotocin (STZ)-induced diabetic rats [51].

4. Anticancer activity

Reproductive system diseases are responsible for several types of cancers like: prostate cancer, breast cancer, ovarian cancer, cervical cancer, uterine cancer, colorectal cancer etc. The bioactive compounds present in the mushroom are playing an important role in the treatment of reproductive disease-associated cancers. There are several medicinal mushrooms like *Ganoderma lucidum*, *Trametes versicolor, Inonotus obliquus, Fomitopsis officinalis*, etc. which are frequently used in the treatment of cancer. Prostate cancer is the third leading cause of cancer deaths in men worldwide and the utmost common male malignancy in several western countries. The incidence rate of prostate cancer is highest in the United States, lower in European countries and lowest in Asia [52]. The common risk factor related to prostate cancer is age, obesity, family history, environmental factors and dietary factors [53]. Retinoblastoma (Rb) and p53 (tumor suppressor gene) play a vital role in the progression of prostate cancer [54]. The anomalous expression

in growth factors and receptors such as: transforming growth factor-a (TGF-a), epidermal growth factor (EGF), transforming growth factor-b (TGF-b), HER-2/neu, and c-erbB-3 oncogenes [41] also lead to the malignant prostate cancer. To combat these problems, natural compounds and fungal metabolites can be used as inhibitors for targeting cancerous cells in certain cancers [55–58]. Ganoderma lucidum belongs to the Ganoderma genus, oriental medicinally mushroom, which have been widely used in Asian countries for centuries to cure different diseases including cancer. Plenty of species of this genus have antiviral, antibacterial, antifungal, anticancer, and immune-stimulating activities [59]. These activities were due to the production of various bioactive compounds present in medicinally mushrooms such as proteins [60–62], terpenes, sterols, and polyphenols, etc. The dried powder of *G. lucidum* is used as dietary supplements and is also used as a chemotherapeutic agent for cancer therapy. It induced the apoptosis of prostate cancer (PC-3) cells by lowering the expression of NF-jB-mediated Bcl-2 and Bcl-xl expression while the upregulation of the Bax protein [63]. The extracts of *G. lucidum* suppress the proliferation of cells and induce the G1 cell cycle in prostate cancer and breast cancer cells line [64]. Trametes versicolor, is a medicinal mushroom, belongs to the class Agaricomycetes shows anti-proliferative effects upon hepatocellular carcinoma cells (HCC), prostate cancer (DU145) and human breast cancer (4 T1) [42]. Several studies suggested that in *T. versicolor* β-glucan-based polysaccharopeptide fraction (PSP) and polysaccharide fraction (PSK) are present which are used as immunotherapeutic anticancer agents [65]. PSP activates cells of the immune system by enhancing the secretion of histamine, chemokines and cytokines such as interleukins (IL-1b and IL-6), TNF-a and prostaglandin E which excites dendrite and T-cell infiltration into tumor and lowers the damaging undesirable effects of chemotherapy [66]. Breast cancer is becoming one of the most common leading causes of mortality among women. The molecular subtypes of breast cancer are identified by gene expression profiles and lead to the identification of biomarkers that may ease the prognosis and treatment of cancer [67]. The molecular and pathological marker for the treatment of breast cancer is based on the presence or absence of progesterone receptors (PR), estrogen receptor (ER), and human epidermal growth factor receptor 2 (HER2) [67]. To overcome this problem, the medicinally mushroom is widely utilized in modern integrative oncology and given to patients regularly. The clinical results suggested that *T. versicolor* inhibits the human triple-negative breast cancer cells (MDA-MB-231) in the in vitro culture and reduced their growth [68] and is used as a supplement in the treatment of breast cancer. The mushroom Inonotus obliquus, often known as Chaga mushroom, belongs to the Agaricomycetes class and is widely used as traditional medicine for cancer therapy in Korea, China, Japan, and Russia [69]. Scientists illustrated that the water extracts of Chaga mushroom have shown cytotoxic and antimitotic activity on HeLa cells. The polysaccharides from *I. obliquus* inhibit the migration of cancer cell lines and shows anti-metastatic activities in vitro. The polysaccharide suppressed the NF-jB, PI3K/AKT and MAPKs signaling pathways by blocking activity and the expression of matrix metalloproteinases 2 and 9 (MMP) [70]. The studies confirmed that the Chaga mushroom has Wnt/β-catenin-inhibitory properties due to the presence of one major compound namely inotodiol which suppressed the breast cancer proliferation via the Wnt-dependent signaling pathway in a diabetic rat model [71].

The bioactive compounds present in the *Ganoderma* species are a viable alternative to fight breast cancer. The aqueous extracts of *G. lucidum, G. sinense* and

G. tsugae were widely used against breast cancer cells. The data illustrated that the aqueous extract of these species has anti-proliferative activities against MCF-7 cells and MDA-MB-231 cells. However, the aqueous extract of *G. tsugae* was most effective against MCF-7 cells, although the activity of other Ganoderma species is similar to MDA-MB-231 cells. It also established that the extract did not show any cytotoxic activity against human noncancerous epithelial cells [72]. Several results showed that *G. lucidum* suppressed the proliferation of MDA-MB-231 cells in a dose and time-dependent manner [64]. The spore powder of *G. lucidum* also exhibited potent cytotoxic effects in the MDA-MB-468, triple-negative breast cancer cell lines, and SUM-102cell line and overexpressing the HER2 gene in MDA-MB435 [73]. *Fomitopsis officinalis* belongs to the family Polyporaceae and is generally known as 'Agarikon.' The fruiting bodies of mushrooms are used as a medicine in Western Europe, North America, and Asian countries for the treatment of gastric cancer, asthma, cough, and pneumonia [74]. Some auspicious evidence illustrated that using fungal extracts can help prevent breast and gastrointestinal cancers. Some studies confirmed antiviral, antibacterial, anticancer, and anti-inflammatory activity of crude extract of *F. officinalis* in different forms of cancers [75]. In *F. officinalis* extract, Lanostane-type triterpenoids, was reported which showed promising anticancer activity. Scientists showed that the ethanol extracts of *F. officinalis* are more effective in comparison with water extract against human breast cancer (MDAMB-231) cells, colon cancer (HCT-116), lung cancer (A549), mouse sarcoma 180 (S-180) and hepatoma (HepG2) cells [75].

Figure 4 shows the therapeutic activity of mushrooms and their biomolecules in the treatment of different forms of cancer. The immune system plays a very contributing role in the progression of tumors toward cancer. Mushroom shows its therapeutic activity by targeting the components of the immune system and also modulates the apoptotic processes. **Figure 4** suggests the therapeutic activity of mushrooms by modulating the different components of the immune system and also regulates the apoptotic processes in cancerous cells [76–78].

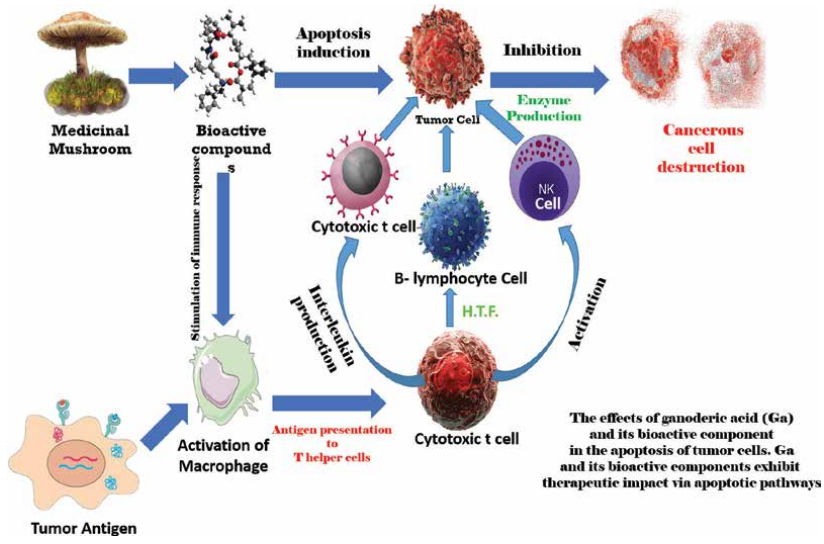

Figure 4.
Antitumor mechanism of bioactive compounds in medicinal mushroom.

5. Biomolecules of mushrooms in neurodegenerative diseases (NDs)

Bioactive molecules in mushrooms also prevent the progression of different NDs. Motor symptoms linked with Parkinson's disease (PD) are significantly prevented by a diet rich in mushroom supplements. In addition, the clinical symptoms of PD were also alleviated by mushroom supplements rich in phytochemicals, minerals, and vitamins [79]. Anti-inflammatory and antioxidative activity is exhibited by dietary mushrooms containing significant quantities of carotenoids, polysaccharides, minerals, polyphenols, and vitamins [80]. The two major factors that are responsible for the progression of PD are oxidative stress and neuroinflammation. Thus, the biomolecules present in edible mushrooms offer significant neuroprotection by their antioxidative and anti-inflammatory activity by preventing the progressive degeneration of dopaminergic neurons [79]. One of the major factors responsible for the generation of neuroinflammation in PD is the activation of microglial cells. *Ganoderma lucidum* extract (GLE) inhibited the activation of these microglial cells and ultimately preventing the progressive degeneration of dopaminergic neurons in PD. Tumor necrosis factoralpha (TNF-a) and interleukin-1b (IL-1b) are the examples of some important proinflammatory cytokines whose expression was downregulated by GLE in a dose-dependent manner and can be treated by natural antibiotics reported in [81]. Further progression of PD is prevented by inhibition of these proinflammatory cytokines by GLE. Thus, the treatment of PD, GLE should be utilized as an effective anti-inflammatory medication [82]. For the treatment of PD, niacin-rich food can be very beneficial and offers significant protective activity. Niacin-rich mushroom content offers potential therapeutic efficacy in the treatment of PD [83]. In the rotenone intoxicated model of PD, neuroprotective activity was shown by the Agaricus blazei extract (ABE). ABE also improves rotenone-induced non-motor and motor complications in PD. Therefore, for the treatment of PD, ABE might also be utilized as a nutritional supplement [84]. Some herbal plants like *Tinospora cordifolia*, *Withania somnifera*, *Mucuna pruriens* (Mp), and the essential oils also exhibit neuroprotective activity similar to mushrooms in toxin-induced PD mouse models [85–87]. In addition, bioactive components of Mp like Ursolic acid also exhibits potent antioxidative and anti-inflammatory property in toxin-induced PD model [88–90]. Chlorogenic acid also exhibits a similar AntiParkinsonian activity in the mouse model of PD [91]. Similar to PD, in Alzheimer's disease (AD), nutritional mushroom provides important biomolecules that help to improve the quality of AD patients. Neuroinflammation along with oxidative stress mainly contributes to the pathogenesis of AD. The redox status in the cell of AD is significantly impaired [1]. Mushrooms have all the essential components that restore the normal balance of the redox system in AD models and patients. Proper and accurate functioning of mitochondria is required to maintain energy homeostasis. The synthesis of vital energy equivalents is hampered by abnormal mitochondrial functioning. In the neuroprotective network, inflammasome is an example of a very vital component. In AD, mitochondrial functioning was improved by Coriolus and Hericium. Normal redox balance was also maintained by these two nutritional mushrooms. Thus, energy homeostasis in AD was maintained by the above-mentioned two mushrooms by their antioxidative and anti-inflammatory properties [92]. One of the best examples of both medicinal and edible mushrooms is the *Hericium erinaceus* (HE). Both in vitro and in vivo model systems show the neuroprotective activity of HE. The aqueous extract of HE rich in a mycelium polysaccharide shows potent anti-apoptotic activity in l-glutamic acid (l-Glu)-induced differentiated PC12 (DPC12) cell lines. The AD mouse model induces by

the combination of $AlCl_3$ with D-galactose. The aqueous extract of HE prevents the further progression of AD by its neuroprotective potential. Behavioral abnormalities were also improved by the aqueous extract of HE in the AD mouse model. In a dosedependent manner, HE is responsible for the enhancement of choline acetyltransferase (ChAT) and acetylcholine (Ach) in serum and hypothalamus. To avert the pathogenesis of AD, the hypothalamus and serum level of Ach and ChAT is very vital. HE could be an efficient neuroprotective agent in AD and for some other neurodegenerative diseases [22]. For the treatment of different diseases, Coriolus versicolor (CV) mushroom is also widely utilized as a nutritional supplement. The oxidative stress and neuroinflammation were considerably reduced by the CV in AD. CV also improve the quality of mitochondria and restores the normal redox balance [92]. Human wellness was effectively maintained by the bioactive molecules present in prebiotics such as legumes [93–95], spirulina [96], biological nanoparticles [93, 97], mushroom [30]. Similar to PD, some herbal plants like *Bacopa monnieri, Withania somnifera, Eclipta alba, Moringa oleifera* and cucumber also improves cognitive function as suggested by some researchers [98–103]. In addition, the neuroinflammatory pathways are also significantly modulated by a variety of medicinal mushrooms in AD [104]. In Huntington's disease (HD), the therapeutic efficacy was also shown by medicinal, non-edible, and edible mushrooms and their bioactive components. Cognitive dysfunction is the very basic clinical feature of HD. In the edible mushroom Polyozellus multiplex, Polyozellin is a very important biomolecule having significant therapeutic activity. In the HD model, glutamate-induced mouse hippocampal neuronal HT22 cell death was significantly ameliorated by Polyozellin by apoptosis and the MAPK pathway. In HT22 cells, biochemical anomalies like lipid peroxidation and reactive oxygen species (ROS) were reduced by Polyozellin. Therefore, Polyozellin might be utilized for the treatment of HD patients in near future [105]. In the animal model of multiple sclerosis (MS), the disease conditions were ameliorated by Piwep, a mushroom extract from Phellinus igniarius. The dietary mushrooms and their bioactive components also improve the disease pathology in MS as with other NDs [106]. NFjB and Nrf2 mediated neuroinflammatory pathways are mainly responsible for mitochondrial dysfunction and ultimately cause progressive neurodegeneration in all NDs. Thus, the biomolecules of mushrooms play a very potential role to reduce the pathogenesis associated with NDs. Further studies will need to characterize more biomolecules in mushrooms and test their efficacy in several NDs.

Author details

Ahmed M. Saad[1*], Mahmoud Z. Sitohy[1], Belal A. Omar[1], Mohamed T. El-Saadony[2] and Basel Sitohy[3,4]

1 Department of Biochemistry, Faculty of Agriculture, Zagazig University, Zagazig, Egypt

2 Department of Agricultural Microbiology, Faculty of Agriculture, Zagazig University, Zagazig, Egypt

3 Department of Radiation Sciences, Norrlands universitetssjukhus Umeå universitet, Umeå, Sweden

4 Department of Clinical Microbiology, Infection and Immunology, Umeå University, Umeå, Sweden

*Address all correspondence to: ahmedm4187@gmail.com

IntechOpen

References

[1] Valverde ME, Hernández-Pérez T, Paredes-López O. Edible mushrooms: Improving human health and promoting quality life. International Journal of Microbiology. 2015:1-14. DOI: 10.1155/2015/376387

[2] Singh M. Mushroom Biotechnology: The rise of the fallen. International Society for Optics and Photonics. 2019: 1-5. DOI: 10.1117/12.2511366

[3] Benjamin DR. Mushrooms: Poisons and panaceas. A Handbook for Naturalists, Mycologists, and Physicians. 1995:242-263

[4] Chang S-T. Development of the world mushroom industry and its roles in human health. Mushroom biology and biotechnology. 2007;**213**:1

[5] Pohleven J, Obermajer N, Sabotič J, Anžlovar S, Sepčić K, Kos J, et al. Purification, characterization and cloning of a ricin B-like lectin from mushroom Clitocybe nebularis with antiproliferative activity against human leukemic T cells. Biochimica et Biophysica Acta (BBA)-General Subjects. 2009;**1790**(3):173-181

[6] Heo J-C, Nam S-H, Nam D-Y, Kim J-G, Lee K-G, Yeo J-H, et al. Anti-asthmatic activities in mycelial extract and culture filtrate of Cordyceps sphecocephala J201. International Journal of Molecular Medicine. 2010;**26**(3):351-356

[7] Cheung P. The nutritional and health benefits of mushrooms. Nutrition Bulletin. 2010;**35**(4):292-299

[8] Gunawardena D, Bennett L, Shanmugam K, King K, Williams R, Zabaras D, et al. Anti-inflammatory effects of five commercially available mushroom species determined in lipopolysaccharide and interferon-γ activated murine macrophages. Food Chemistry. 2014;**148**:92-96

[9] Kalač P. A review of chemical composition and nutritional value of wild-growing and cultivated mushrooms. Journal of the Science of Food and Agriculture. 2013;**93**(2):209-218

[10] Jeong SC, Jeong YT, Yang BK, Islam R, Koyyalamudi SR, Pang G, et al. White button mushroom (Agaricus bisporus) lowers blood glucose and cholesterol levels in diabetic and hypercholesterolemic rats. Nutrition Research. 2010;**30**(1):49-56

[11] Kim HM, Kang JS, Kim JY, Park S-K, Kim HS, Lee YJ, et al. Evaluation of antidiabetic activity of polysaccharide isolated from Phellinus linteus in non-obese diabetic mouse. International Immunopharmacology. 2010;**10**(1):72-78

[12] Miyamoto I, Liu J, Shimizu K, Sato M, Kukita A, Kukita T, et al. Regulation of osteoclastogenesis by ganoderic acid DM isolated from Ganoderma lucidum. European Journal of Pharmacology. 2009;**602**(1):1-7

[13] Deepalakshmi K, Sankaran M. Pleurotus ostreatus: An oyster mushroom with nutritional and medicinal properties. Journal of Biochemical Technology. 2014;**5**(2):718-726

[14] Geng X, Tian G, Zhang W, Zhao Y, Zhao L, Wang H, et al. A Tricholoma matsutake peptide with angiotensin converting enzyme inhibitory and antioxidative activities and antihypertensive effects in spontaneously hypertensive rats. Scientific Reports. 2016;**6**(1):1-9

[15] Kobori M, Yoshida M, Ohnishi-Kameyama M, Takei T, Shinmoto H.

5α, 8α-Epidioxy-22E-ergosta-6, 9 (11), 22-trien-3β-ol from an edible mushroom suppresses growth of HL60 leukemia and HT29 colon adenocarcinoma cells. Biological and Pharmaceutical Bulletin. 2006;**29**(4):755-759

[16] Ren G, Zhao Y-p, Yang L, Fu C-X. Anti-proliferative effect of clitocine from the mushroom Leucopaxillus giganteus on human cervical cancer HeLa cells by inducing apoptosis. Cancer Letters. 2008;**262**(2):190-200

[17] Liguori I, Russo G, Curcio F, Bulli G, Aran L, Della-Morte D, et al. Oxidative stress, aging, and diseases. Clinical Interventions in Aging. 2018;**13**:757

[18] Oguntibeju OO. Type 2 diabetes mellitus, oxidative stress and inflammation: Examining the links. International Journal of Physiology, Pathophysiology and Pharmacology. 2019;**11**(3):45

[19] Dasgupta A, Acharya K. Mushrooms: An emerging resource for therapeutic terpenoids. 3. Biotech. 2019;**9**(10):1-14

[20] Lee K-H, Morris-Natschke SL, Yang X, Huang R, Zhou T, Wu S-F, et al. Recent progress of research on medicinal mushrooms, foods, and other herbal products used in traditional Chinese medicine. Journal of Traditional and Complementary Medicine. 2012;**2**(2):1-12

[21] Ganeshpurkar A, Rai G, Jain AP. Medicinal mushrooms: Towards a new horizon. Pharmacognosy Reviews. 2010;**4**(8):127

[22] Zhang Y, Hu T, Zhou H, Zhang Y, Jin G, Yang Y. Antidiabetic effect of polysaccharides from Pleurotus ostreatus in streptozotocin-induced diabetic rats. International Journal of Biological Macromolecules. 2016;**83**:126-132

[23] Chaturvedi VK, Agarwal S, Gupta KK, Ramteke PW, Singh M. Medicinal mushroom: Boon for therapeutic applications. 3 Biotech. 2018;**8**(8):1-20

[24] Dubey S, Yadav C, Bajpeyee A, Singh MP. Effect of Pleurotus fossulatus aqueous extract on biochemical properties of liver and kidney in streptozotocin-induced diabetic rat. Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy. 2020;**13**:3035

[25] Cao S-Y, Zhao C-N, Gan R-Y, Xu X-Y, Wei X-L, Corke H, et al. Effects and mechanisms of tea and its bioactive compounds for the prevention and treatment of cardiovascular diseases: An updated review. Antioxidants. 2019;**8**(6):166

[26] Guillamón E, García-Lafuente A, Lozano M, Rostagno MA, Villares A, Martínez JA. Edible mushrooms: Role in the prevention of cardiovascular diseases. Fitoterapia. 2010;**81**(7):715-723

[27] Elkhateeb WA, Daba GM, Sheir D, El-Dein AN, Fayad W, Elmahdy EM, et al. GC-MS analysis and in-vitro hypocholesterolemic, anti-rotavirus, anti-human colon carcinoma activities of the crude extract of a Japanese Ganoderma spp. Egyptian Pharmaceutical Journal. 2019;**18**(2):102-110

[28] Tan BL, Norhaizan ME, Liew W-P-P, Sulaiman Rahman H. Antioxidant and oxidative stress: A mutual interplay in age-related diseases. Frontiers in Pharmacology. 2018;**9**:1162

[29] Hunt PA, Sathyanarayana S, Fowler PA, Trasande L. Female reproductive disorders, diseases, and costs of exposure to endocrine disrupting chemicals in the European Union. The Journal of Clinical Endocrinology & Metabolism. 2016;**101**(4):1562-1570

[30] Phan C-W, Tan EY-Y, Sabaratnam V. Bioactive molecules in edible and medicinal mushrooms for human wellness. In: Mérillon J-M, Ramawat KG, editors. Bioactive Molecules in Food. Springer International Publishing AG; 2018. pp. 1-24. DOI: 10.1007/978-3-319-54528-8_83-1

[31] Gil-Ramirez A, Clavijo C, Palanisamy M, Soler-Rivas C, Ruiz-Rodriguez A, Marín FR, Reglero G, et al. Edible mushrooms as potential sources of new hypocholesterolemic compounds. Villenave d'Ornon Cedex, France: Institut National de la Recherche Agronomique (INRA); 2011

[32] Phan C-W, David P, Sabaratnam V. Edible and medicinal mushrooms: Emerging brain food for the mitigation of neurodegenerative diseases. Journal of Medicinal Food. 2017;**20**(1): 1-10

[33] Rajasekaran M, Kalaimagal C. Cardioprotective effect of a medicinal mushroom, Ganoderma lucidum against adriamycin induced toxicity. International Journal of Pharmacology. 2012;**8**(4):252-258

[34] Kaneda T, Tokuda S. Effect of various mushroom preparations on cholesterol levels in rats. The Journal of Nutrition. 1966;**90**(4):371-376

[35] Li H, Zhang M, Ma G. Hypolipidemic effect of the polysaccharide from Pholiota nameko. Nutrition. 2010;**26**(5): 556-562

[36] Ryong LH, Tertov VV, Vasil'ev AV, Tutel'yan VA, Orekhov AN. Antiatherogenic and antiatherosclerotic effects of mushroom extracts revealed in human aortic intima cell culture. Drug Development Research. 1989;**17**(2): 109-117

[37] Abidin MHZ, Abdullah N, Abidin NZ. Therapeutic properties of Pleurotus species (oyster mushrooms) for atherosclerosis: A review. International Journal of Food Properties. 2017;**20**(6):1251-1261

[38] Lee DH, Yang M, Giovannucci EL, Sun Q, Chavarro JE. Mushroom consumption, biomarkers, and risk of cardiovascular disease and type 2 diabetes: A prospective cohort study of US women and men. The American Journal of Clinical Nutrition. 2019;**110**(3):666-674

[39] Yang H, Hwang I, Kim S, Hong EJ, Jeung EB. Lentinus edodes promotes fat removal in hypercholesterolemic mice. Experimental and Therapeutic Medicine. 2013;**6**(6):1409-1413

[40] Xiao C, Wu Q, Tan J, Cai W, Yang X, Zhang J. Inhibitory effects on-glucosidase and hypoglycemic effects of the crude polysaccharides isolated from 11 edible fungi. Journal of Medicinal Plants Research. 2011;**5**(32):6963-6967

[41] Lu X, Chen H, Dong P, Fu L, Zhang X. Phytochemical characteristics and hypoglycaemic activity of fraction from mushroom Inonotus obliquus. Journal of the Science of Food and Agriculture. 2010;**90**(2):276-280

[42] Ma H-T, Hsieh J-F, Chen S-T. Anti-diabetic effects of Ganoderma lucidum. Phytochemistry. 2015;**114**:109-113

[43] Zhu K, Nie S, Li C, Lin S, Xing M, Li W, et al. A newly identified polysaccharide from Ganoderma atrum attenuates hyperglycemia and hyperlipidemia. International Journal of Biological Macromolecules. 2013;**57**:142-150

[44] Ma G, Yang W, Zhao L, Pei F, Fang D, Hu Q. A critical review on the

health promoting effects of mushrooms nutraceuticals. Food Science and Human Wellness. 2018;**7**(2):125-133

[45] Martel J, Ojcius DM, Chang C-J, Lin C-S, Lu C-C, Ko Y-F, et al. Anti-obesogenic and antidiabetic effects of plants and mushrooms. Nature Reviews Endocrinology. 2017;**13**(3):149-160

[46] Jiang X, Meng W, Li L, Meng Z, Wang D. Adjuvant therapy with mushroom polysaccharides for diabetic complications. Frontiers in Pharmacology. 2020;**11**:168

[47] Chou Y-J, Kan W-C, Chang C-M, Peng Y-J, Wang H-Y, Yu W-C, et al. Renal protective effects of low molecular weight of Inonotus obliquus polysaccharide (LIOP) on HFD/STZ-induced nephropathy in mice. International Journal of Molecular Sciences. 2016;**17**(9):1535

[48] Sitohy MZ, Ramadan MF. Granular properties of different starch phosphate monoesters. Starch-Stärke. 2001;**53**(1):27-34

[49] Liu M, Song X, Zhang J, Zhang C, Gao Z, Li S, et al. Protective effects on liver, kidney and pancreas of enzymatic- and acidic-hydrolysis of polysaccharides by spent mushroom compost (Hypsizigus marmoreus). Scientific Reports. 2017;**7**(1):1-12

[50] Inoue A, Kodama N, Nanba H. Effect of maitake (Grifola frondosa) D-fraction on the control of the T lymph node Th-1/Th-2 proportion. Biological and Pharmaceutical Bulletin. 2002;**25**(4):536-540

[51] Vitak T, Yurkiv B, Wasser S, Nevo E, Sybirna N. Effect of medicinal mushrooms on blood cells under conditions of diabetes mellitus. World Journal of Diabetes. 2017;**8**(5):187

[52] Rawla P. Epidemiology of prostate cancer. World Journal of Oncology. 2019;**10**(2):63

[53] Baillargeon J, Platz EA, Rose DP, Pollock BH, Ankerst DP, Haffner S, et al. Obesity, adipokines, and prostate cancer in a prospective population-based study. Cancer Epidemiology and Prevention Biomarkers. 2006;**15**(7):1331-1335

[54] Hickman ES, Moroni MC, Helin K. The role of p53 and pRB in apoptosis and cancer. Current Opinion in Genetics & Development. 2002;**12**(1):60-66

[55] Ali H, AbdelMageed M, Olsson L, Israelsson A, Lindmark G, Hammarström M-L, et al. Utility of G protein-coupled receptor 35 expression for predicting outcome in colon cancer. Tumor Biology. 2019;**41**(6):1010428319858885

[56] El-Sayed AS, Fathalla M, Yassin MA, Zein N, Morsy S, Sitohy M, et al. Conjugation of aspergillus flavipes taxol with porphyrin increases the anticancer activity of taxol and ameliorates its cytotoxic effects. Molecules. 2020;**25**(2):263

[57] Ohlsson L, Hammarström M-L, Lindmark G, Hammarström S, Sitohy B. Ectopic expression of the chemokine CXCL17 in colon cancer cells. British Journal of Cancer. 2016;**114**(6):697-703

[58] El-Sayed AS, Safan S, Mohamed NZ, Shaban L, Ali GS, Sitohy MZ. Induction of Taxol biosynthesis by aspergillus terreus, endophyte of Podocarpus gracilior Pilger, upon intimate interaction with the plant endogenous microbes. Process Biochemistry. 2018;**71**:31-40

[59] Abdelbacki AM, Taha SH, Sitohy MZ, Abou Dawood AI, Hamid MM, Rezk AA. Inhibition of tomato yellow leaf curl virus (TYLCV) using whey proteins. Virology Journal. 2010;**7**(1):1-6

[60] Osman A, El-Didamony G, Sitohy M, Khalifa M, Enan G. Soybean glycinin basic subunit inhibits methicillin resistant-vancomycin intermediate Staphylococcus aureus (MRSA-VISA) in vitro. International Journal of Applied Research in Natural Products. 2016;**9**(2):17-26

[61] Sitohy M, CHOBERT JM, Haertlé T. Study of factors influencing protein esterification using β-lactoglobulin as a model. Journal of Food Biochemistry. 2000;**24**(5):381-398

[62] Sitohy M, Mahgoub S, Osman A. Controlling psychrotrophic bacteria in raw buffalo milk preserved at 4 C with esterified legume proteins. LWT-Food Science and Technology. 2011;**44**(8):1697-1702

[63] Jiang J, Slivova V, Harvey K, Valachovicova T, Sliva D. Ganoderma lucidum suppresses growth of breast cancer cells through the inhibition of Akt/NF-κB signaling. Nutrition and Cancer. 2004;**49**(2):209-216

[64] Lu Q-Y, Jin Y-S, Zhang Q, Zhang Z, Heber D, Go VLW, et al. Ganoderma lucidum extracts inhibit growth and induce actin polymerization in bladder cancer cells in vitro. Cancer Letters. 2004;**216**(1):9-20

[65] Cui J, Chisti Y. Polysaccharopeptides of Coriolus versicolor: Physiological activity, uses, and production. Biotechnology Advances. 2003;**21**(2):109-122

[66] Chang Y, Zhang M, Jiang Y, Liu Y, Luo H, Hao C, et al. Preclinical and clinical studies of Coriolus versicolor polysaccharopeptide as an immunotherapeutic in China. Discovery Medicine. 2017;**23**(127):207-219

[67] Reis-Filho JS, Pusztai L. Gene expression profiling in breast cancer: Classification, prognostication, and prediction. The Lancet. 2011; **378**(9805):1812-1823

[68] Jiang J, Thyagarajan-Sahu A, Loganathan J, Eliaz I, Terry C, Sandusky GE, et al. BreastDefend™ prevents breast-to-lung cancer metastases in an orthotopic animal model of triple-negative human breast cancer. Oncology Reports. 2012;**28**(4):1139-1145

[69] Handa N, Yamada T, Tanaka R. An unusual lanostane-type triterpenoid, spiroinonotsuoxodiol, and other triterpenoids from Inonotus obliquus. Phytochemistry. 2010;**71**(14-15):1774-1779

[70] Lee KR, Lee JS, Kim YR, Song IG, Hong EK. Polysaccharide from Inonotus obliquus inhibits migration and invasion in B16-F10 cells by suppressing MMP-2 and MMP-9 via downregulation of NF-κB signaling pathway. Oncology Reports. 2014;**31**(5):2447-2453

[71] Zhang X, Bao C, Zhang J. Inotodiol suppresses proliferation of breast cancer in rat model of type 2 diabetes mellitus via downregulation of β-catenin signaling. Biomedicine & Pharmacotherapy. 2018;**99**:142-150

[72] Yue GG, Fung K-P, Tse GM, Leung P-C, Lau CB. Comparative studies of various Ganoderma species and their different parts with regard to their antitumor and immunomodulating activities in vitro. Journal of Alternative & Complementary Medicine. 2006;**12**(8):777-789

[73] Suárez-Arroyo IJ, Rios-Fuller TJ, Feliz-Mosquea YR, Lacourt-Ventura M, Leal-Alviarez DJ, Maldonado-Martinez G, et al. Ganoderma lucidum combined with the EGFR tyrosine kinase inhibitor, erlotinib synergize to reduce inflammatory breast cancer progression. Journal of Cancer. 2016;**7**(5):500

[74] Grienke U, Zöll M, Peintner U, Rollinger JM. European medicinal polypores—A modern view on traditional uses. Journal of Ethnopharmacology. 2014;**154**(3):564-583

[75] Wu H-T, Lu F-H, Su Y-C, Ou H-Y, Hung H-C, Wu J-S, et al. In vivo and in vitro anti-tumor effects of fungal extracts. Molecules. 2014;**19**(2):2546-2556

[76] Sitohy B, Chang S, Sciuto TE, Masse E, Shen M, Kang PM, et al. Early actions of anti-vascular endothelial growth factor/vascular endothelial growth factor receptor drugs on Angiogenic blood vessels. The American Journal of Pathology. 2017;**187**(10):2337-2347

[77] Sitohy B, El-Salhy M. Changes in the colonic enteric nervous system in rats with chemically induced colon dysplasia and carcinoma. Acta Oncologica. 2002;**41**(6):543-549

[78] Sitohy B, El-Salhy M. A comparison between double and triple therapies of octreotide, galanin and serotonin on a rat colon carcinoma. Histology and Histopathology. 2003;**1**:103-110

[79] Ciulla M, Marinelli L, Cacciatore I, Stefano AD. Role of dietary supplements in the management of Parkinson's disease. Biomolecules. 2019;**9**(7):271

[80] Kozarski M, Klaus A, Jakovljevic D, Todorovic N, Vunduk J, Petrović P, et al. Antioxidants of edible mushrooms. Molecules. 2015;**20**(10):19489-19525

[81] Abd El-Hack ME, El-Saadony MT, Elbestawy AR, Nahed A, Saad AM, Salem HM, et al. Necrotic enteritis in broiler chickens: Disease characteristics and prevention using organic antibiotic alternatives—A comprehensive review. Poultry Science. 2021;**101**(2):101590

[82] Zhang R, Xu S, Cai Y, Zhou M, Zuo X, Chan P. Ganoderma lucidum protects dopaminergic neuron degeneration through inhibition of microglial activation. Evidence-based Complementary and Alternative Medicine. 2011:1-9

[83] Aaseth J, Dusek P, Roos PM. Prevention of progression in Parkinson's disease. Biometals. 2018;**31**(5):737-747

[84] Venkateshgobi V, Rajasankar S, Johnson WMS, Prabu K, Ramkumar M. Neuroprotective effect of agaricus blazei extract against rotenone-induced motor and nonmotor symptoms in experimental model of parkinson's disease. International Journal of Nutrition, Pharmacology, Neurological Diseases. 2018;**8**(2):59

[85] Birla H, Rai SN, Singh SS, Zahra W, Rawat A, Tiwari N, et al. Tinospora cordifolia suppresses neuroinflammation in parkinsonian mouse model. Neuromolecular Medicine. 2019;**21**(1):42-53

[86] Rai SN, Birla H, Singh SS, Zahra W, Patil RR, Jadhav JP, et al. Mucuna pruriens protects against MPTP intoxicated neuroinflammation in Parkinson's disease through NF-κB/pAKT signaling pathways. Frontiers in Aging Neuroscience. 2017;**9**:421

[87] Abd El-Hack ME, El-Saadony MT, Saad AM, Salem HM, Ashry NM, Ghanima MMA, et al. Essential oils and their nanoemulsions as green alternatives to antibiotics in poultry nutrition: A comprehensive review. Poultry Science. 2021;**101**(2):101584

[88] Rai SN, Mishra D, Singh P, Vamanu E, Singh M. Therapeutic applications of mushrooms and their biomolecules along with a glimpse of in silico approach in

neurodegenerative diseases. Biomedicine & Pharmacotherapy. 2021;**137**:111377

[89] Rai SN, Zahra W, Singh SS, Birla H, Keswani C, Dilnashin H, et al. Anti-inflammatory activity of ursolic acid in MPTP-induced parkinsonian mouse model. Neurotoxicity Research. 2019;**36**(3):452-462

[90] Zahra W, Rai SN, Birla H, Singh SS, Rathore AS, Dilnashin H, et al. Neuroprotection of rotenone-induced parkinsonism by ursolic acid in PD mouse model. CNS & Neurological Disorders-Drug Targets (Formerly Current Drug Targets-CNS & Neurological Disorders). 2020;**19**(7):527-540

[91] Singh SS, Rai SN, Birla H, Zahra W, Rathore AS, Dilnashin H, et al. Neuroprotective effect of chlorogenic acid on mitochondrial dysfunction-mediated apoptotic death of DA neurons in a Parkinsonian mouse model. Oxidative Medicine and Cellular Longevity; 2020:1-14

[92] Trovato Salinaro A, Pennisi M, Di Paola R, Scuto M, Crupi R, Cambria MT, et al. Neuroinflammation and neurohormesis in the pathogenesis of Alzheimer's disease and Alzheimer-linked pathologies: Modulation by nutritional mushrooms. Immunity & Ageing. 2018;**15**(1):1-8

[93] Abd El-Hack ME, El-Saadony MT, Shafi ME, Alshahrani OA, Saghir SA, Al-Wajeeh AS, et al. Prebiotics can restrict Salmonella populations in poultry: A review. Animal Biotechnology; 2021:1-10. DOI: 10.1080/10495398.2021.1883637

[94] Saad AM, Elmassry RA, Wahdan KM, Ramadan FM. Chickpea (Cicer arietinum) steep liquor as a leavening agent: Effect on dough rheology and sensory properties of bread. Acta Periodica Technologica. 2015;**46**:91-102

[95] Saad AM, Sitohy MZ, Ahmed AI, Rabie NA, Amin SA, Aboelenin SM, et al. Biochemical and functional characterization of kidney bean protein alcalase-hydrolysates and their preservative action on stored chicken meat. Molecules. 2021;**26**(15):4690

[96] Abdel-Moneim A-ME, El-Saadony MT, Shehata AM, Saad AM, Aldhumri SA, Ouda SM, et al. Antioxidant and antimicrobial activities of Spirulina platensis extracts and biogenic selenium nanoparticles against selected pathogenic bacteria and fungi. Saudi Journal of Biological Sciences. 2022;**29**(2):1197-1209

[97] El-Saadony MT, Saad AM, Taha TF, Najjar AA, Zabermawi NM, Nader MM, et al. Selenium nanoparticles from lactobacillus paracasei HM1 capable of antagonizing animal pathogenic fungi as a new source from human breast milk. Saudi Journal of Biological Sciences. 2021;**28**(12):6782-6794

[98] Chaudhari KS, Tiwari NR, Tiwari RR, Sharma RS. Neurocognitive effect of nootropic drug Brahmi (Bacopa monnieri) in Alzheimer' disease. Annals of Neurosciences. 2017;**24**(2):111-122

[99] Mahaman YAR, Huang F, Wu M, Wang Y, Wei Z, Bao J, et al. Moringa oleifera alleviates homocysteine-induced Alzheimer's disease-like pathology and cognitive impairments. Journal of Alzheimer's Disease. 2018;**63**(3):1141-1159

[100] Mehla J, Gupta P, Pahuja M, Diwan D, Diksha D. Indian medicinal herbs and formulations for alzheimer's disease, from traditional knowledge to scientific assessment. Brain Sciences. 2020;**10**(12):964

[101] Sehgal N, Gupta A, Valli RK, Joshi SD, Mills JT, Hamel E, et al. Withania somnifera reverses Alzheimer's disease pathology by enhancing low-density lipoprotein receptor-related protein in liver. Proceedings of the National Academy of Sciences. 2012;**109**(9):3510-3515

[102] El-Saadony MT, Saad AM, Elakkad HA, El-Tahan AM, Alshahrani OA, Alshilawi MS, et al. Flavoring and extending the shelf life of cucumber juice with aroma compounds-rich herbal extracts at 4° C through controlling chemical and microbial fluctuations. Saudi Journal of Biological Sciences. 2022;**29**(1):346-354

[103] Saad AM, El-Saadony MT, Mohamed AS, Ahmed AI, Sitohy MZ. Impact of cucumber pomace fortification on the nutritional, sensorial and technological quality of soft wheat flour-based noodles. International Journal of Food Science & Technology. 2021;**56**(7):3255-3268

[104] Kushairi N, Tarmizi NAKA, Phan CW, Macreadie I, Sabaratnam V, Naidu M, et al. Modulation of neuroinflammatory pathways by medicinal mushrooms, with particular relevance to Alzheimer's disease. Trends in Food Science & Technology. 2020;**104**:153-162

[105] Yang E-J, Song K-S. Polyozellin, a key constituent of the edible mushroom Polyozellus multiplex, attenuates glutamate-induced mouse hippocampal neuronal HT22 cell death. Food & Function. 2015;**6**(12):3678-3686

[106] Li L, Wu G, Choi BY, Jang BG, Kim JH, Sung GH, et al. A mushroom extract Piwep from Phellinus igniarius ameliorates experimental autoimmune encephalomyelitis by inhibiting immune cell infiltration in the spinal cord. BioMed Research International; 2014:1-14

Chapter 12

Edible Mushrooms, a Sustainable Source of Nutrition, Biochemically Active Compounds and Its Effect on Human Health

Sakhawat Riaz, Arslan Ahmad, Rimsha Farooq, Munir Ahmed, Muhammad Shaheryar and Muneer Hussain

Abstract

Mushrooms are abundant in proteins, polysaccharides, micronutrients, unsaturated fatty acids, and natural compounds. Mushrooms have recently gained popularity as a source of biologically active substances with medical potentials, such as anticancer, antiviral, immune-boosting, hypocholesterolemic, and hepatoprotective agents. Some common edible and helpful mushrooms include Lentinus (shiitake), Flammulina (enokitake), Tremella (yiner), Hericium, Pleurotus (oyster), Grifola (maitake) and Auricularia (mu-er). Details on the nutritional content of mushrooms, functional components, and their influence on human health will be explored in this chapter. Mushrooms are used to cure a wide range of ailments. Mushrooms provide a lot of nutrients and are low in calories. They are also fat-free, low in sodium, cholesterol-free, and high in fiber, protein, and antioxidants. They lower the chance of acquiring significant health problems, including Alzheimer, heart disease, and diabetes. It also has antifungal activity. They are also high in selenium and other biochemically active compounds, which have the ability to lower the incidence of chronic illness.

Keywords: mushroom, nutrition, human health, bioactive substance, natural substance, chronic disease, antioxidant, antifungal, antiviral

1. Introduction

Mushrooms have long been regarded as a delicacy item, particularly for their distinct flavor, and have been regarded as a culinary marvel by humans. There are about 2000 types of mushrooms in the environment, but only about 25 are commonly acknowledged as edible and just a few are economically grown. Mushrooms are a delight with excellent nutritious significance, as well as a naturopathic food; they are of significant interest due to their overall acceptability worth, therapeutic characteristics, and financial relevance [1, 2]. Mushrooms are macrofungi that have

unique and apparent fruiting entities that may grow above and below ground [1]. Fungi miss the fundamental property of plants, namely the capacity to effectively consume power from the sun via chlorophyll. They depend on some other beings seeking food, and to get nourishment from the organic matter in which they exist. Mycelium is the fungus's live body, and it is made up of hyphae, which are small webs of threads (or filaments). Digestive products are absorbed by hyphae and can permeate the substrate. Interbreeding hyphae will join and begin to form spores under certain environments. Mushrooms are gigantic entities that produce spores. Since antiquity, many civilizations have utilized mushrooms as a foodstuff and medicinal. The industry has now clearly divided farmed and wild culinary mushrooms, which are utilized direct or indirect as food or ingredients, from medicinal mushrooms [2]. Beneficial mushrooms are commonly used as a meal in many nations. Edible mushrooms are precious constituents of the eating plan due to their appealing flavors, fragrance, and nutritive benefits. Their culinary and advertising value stems mostly from organoleptic qualities like texture and flavor, with edible mushroom species distinguishable based on their strong smell or aroma [3, 4]. Their nutritional benefit arises from their protein content, fiber, vitamin, and mineral composition, as well as their reduced fat content [5–8]. Mushroom peptides have the same amino acid composition as animal protein [9, 10], which is particularly important in light of the large intake of protein from animal dietary sources, particularly in industrialized nations. Furthermore, edible mushrooms encompass a wide variety of beneficial chemicals, eritadenine, and polyphenols, for example [7, 8, 11]. In this frame of reference, the International Life Sciences Institute (ILSI Europe) made available a widely accepted definition of functional food, stating that Food functional" has been shown to have a positive effect on the body, Aside from healthy dietary considerations, in a way that contributes to improved health and well-being and/or a reduced risk of developing the disease [12, 13]. Substantial research has indicated that several mushroom kinds are effective in the therapy of a wide range of diseases [14–16]. That is why edible mushrooms are categorized as a functional food. Mushrooms may be a novel source of antimicrobial chemicals, mostly secondary metabolites for example benzoic acid derivatives, asterpenes, anthraquinones, steroids, and quinolones, as well as oxalic acid, peptides, and proteins. The most researched genus, Lentinus edodesis, appears to exhibit microorganisms killing both gram-positive and gram-negative bacteria [17].

2. Mushroom cultivation

Vegetable Mushroom cultivation entails a number of various activities, each of which should be properly carried out. The substrate making, inoculation, incubation, and production needs are governed by the mushroom species to be grown. The initial step is to get pure mycelium mushroom strain. Mycelium can be derived via spores, which are part of a specific fungus, or through a variety of germplasm suppliers. Mycelium is cultivated on cereal grains such as wheat, rye, or millet to get inoculum and is referred to as "spawn" [18, 19]. The goal of the mycelium-coated grain is to colonize the selected bulk growth substrate fast. The sustainability of the "spawn," which must be produced in a clean environment in order to prevent contamination of the substrate, is critical to the success of mushroom cultivation. Several research has been conducted in order to enhance the quality and create new production procedures. P. Ostreatus spawn, for example, has indeed been produced in several ways: on grain, wheat, rice, and sorghum are a [20–22], and on grain strewn with grain are few

examples [23–25]. The growth in mushroom output has resulted from more specialized research conducted by a number of international institutes in various areas of mushroom growing. The adoption of DNA-based technologies has sped up breeding processes and will benefit mushroom breeding initiatives [26]. The discovery and identification of genetic markers have resulted in significant advancements in the development of breeding procedures [27]. The study of the biological component of mating-type DNA in strain creation cannot be overstated with excellent yield and tolerance to bacterial illnesses [28, 29], infectious infections [29, 30], and pathogenic organisms [31, 32]. To enhance mushroom cultivation production, it's critical to provide ideal conditions and, if feasible, provide automated monitoring of growth rooms, handling machines, hydroblending, and pre-wet equipment, or other current technology, as well as novel sterile procedures, to continue cultivating mushrooms on a non-composted substrate [33]. A computerized integrated environmental system is a major asset in mushroom cultivation. Environmental characteristics such as temperature, moisture, ventilation, elevation, and co2 and oxygen levels are monitored by the software. However, automatic ammonia concentration and moisture regulation in casing soil still seem to be uncommon. Dutch mushrooms were the first to use climate computer farming more than two decades ago, and they are now widely employed in the sector [34]. Climate control in industrial facilities enables monitoring and administration of numerous mushroom growth rooms with a little touch. A computerized environmental control method allows farmers to monitor and change the plant variables' ambient conditions electronically [35]. Placement, size, choices, and plucking of mushrooms are all part of the harvesting process. Compression investigations with cylindrical mushroom sample parts yielded the mechanical characteristics needed for automated harvesting analysis [36, 37], spawning generation is a barrier to mushroom growth because creating high-quality spawn demands a permanent facility, specific skills, and an autoclave, a sort of high-pressure cooker, expansion in low-resource locations is difficult, the facilities commonly seen in research labs and universities [38]. Producers in low-income countries must choose between producing their own spawn and purchasing it fully prepared. Producing spawn takes at least one year of competence as well as the capacity to maintain a sterile environment, which may be costly and energy-consuming. If growers are unable to produce viable spawn, most of the mushroom growth process will be halted. Because they lack the means to spawn high-yielding quality cultures, mushroom enterprises in low- and middle-income countries obtain seeds regularly from other developed countries like United State and Europe. Because locally produced cultures do not have high biological efficiency, the majority of commercial mushroom cultivation in Latin America is currently done with imported spawn. As a result, fruiting yields are less than half of those of foreign spawns [39]. Outdoor cultivation takes place periodically beneath the forest canopy, with mushroom beds built on a high platform made from bricks and bamboo poles. Hand or motorized cutters are used to cut the top leafy piece and a section of the sturdy stalk towards the roots to make straw bundles 45 cm long and 10 cm wide. After arranging the bundles side by side, the mushroom spawn is put in six to eight regions and coated with red gram dal powder. The spawn cycle needs at least 39 degrees Celsius and will take 6–7 days to complete. The mushrooms start to emerge after 12–13 days of spawning [40]. Internal gardening may be completed using a substrate/compost composed of cotton ginning mill refuse and paddy straw. Steam is brought into the cropping chamber in order to heat condition the compost. For 4–5 hours, the temperature is kept at 62 degrees Celsius. The plastic sheet will be used to cover the mattresses. During the spawn run,

the room temperature is kept at 32–34 degrees Celsius. Within up to five days, the compost colonizes, and the beds are watered once the plastic covering is removed. The pinhead appears on the fifth-sixth day of spawning. The initial flush of mushrooms is available for picking after another 4–5 days. The paddy straw mushroom should not be refrigerated and should be used shortly after collecting or for a few hours, it was maintained at cellar temperature [40].

3. Challenges in mushroom cultivation

The mushroom industry's development is hampered by a number of concerns and obstacles across the globe. The mushroom business is gradually establishing itself in many emerging regions, but progress is slow due to a lack of scientific study and dialog. Mushroom farming might possibly play a role in long-term agriculture and forestry [41]. Several difficulties and obstacles that might hinder effective mushroom cultivation among small-scale farmers have been highlighted, necessitating attention and ways to boost mushroom productivity and market access [42]. Personal efforts are necessary to face adversity such as a shortage of substrate, community commitments, and the creation of ideal mushroom homes, while government intervention is required for others (**Table 1**).

Challenge	Action required
Absence of up-to-date technologies	Based on local demands and agro-climatic circumstances, develop or acquire relevant technologies.
Inadequate funding and scientific investigation into mushrooms.	Invest more money
Deficiency of a suitable substrate	Look to expand the raw material and consider other options depending on what's easily obtainable.
Spawn of low quality	Construct a mushroom cultivation center, as well as spawn production facilities that are technologically advanced. Ensure a steady supply of high-quality spawn at a minimal expense.
Pest assault and poor agricultural management systems	Enhancing producers' experience and abilities in the areas of agricultural hygiene and integrated pest and diseases control.
Inadequate harvesting management	Enhancing skills and experience in the fields of selecting, assessing, and preservation, refrigerated storage, refrigerated transportation, adequate treatment, packaging design, and labeling at the appropriate stage.
Extreme environmental conditions	When the temperature is high, moisten the mushroom house's floor, roof, and walls often.
There aren't enough mushroom policies and rules in place.	Create and aggressively implement mushroom-related regulations and legislation. Increasing fresh investment in order to become more competitive. Establish special rules for mushroom commodities in terms of trade, marketing, and food safety.
Mushrooms fall short of market expectations.	Gather the mushroom in a reasonable timeframe to get a decent market price.

Table 1.
Challenges and action required in mushrooms cultivation [41, 42].

4. Global mushroom cultivation prospects

These Mushrooms have long been used in traditional medicine in China, Africa, the Middle East, and Japan particular. Edible mushrooms could only be found in nature and were hard to farm and sustain Wild forest collection is still popular across the world, especially in southern Asia [43, 44] and in developing nations [45]. Auricularia, Flammulina, and Lentinula are examples of mushrooms. Have been most probably initially farmed in China and other Emerging nations around the year 600–800 AD [46]. Pure mushroom cultures were first created from spores and tissue towards the turn of the twentieth century when they were first grown on a wide scale. The quantity of wild mushrooms is decreasing as a result of both degraded surroundings and natural resources, as well as more expensive labor, produced mushrooms provide more food items which decrease food insecurities, they also provide more affordable and healthier meals [47]. With the global population expanding and acreage per capita shrinking, fast industrial development, global warming, and a desire for excellent and functional foods, secondary agriculture and novel crops like mushrooms will be necessary. Mushroom farming might potentially play a significant role in sustainable agriculture and forestry. Agriculture, forestry, and food processing create massive amounts of a diverse range of organic waste. The mushroom industry has a major and extensive influence on livelihoods and reducing poverty. There have been hundreds of discovered fungus species that have made major contributions to human diet and medicine. Mushroom Young mushroom mycelium hypha total amount **Figure 1**: The basic mushroom life cycle 4 According to S. Gupta et al., there are now 110,000 species of fungus [48], 16,000 (15%) of which are mushrooms [48, 49]. There are around 3000 types of edible mushrooms from 231 genera [14, 49, 50], with only approximately 200 experimentally grown, In various countries, 100 are economically farmed, 60 are commercially cultivated, and more than ten are

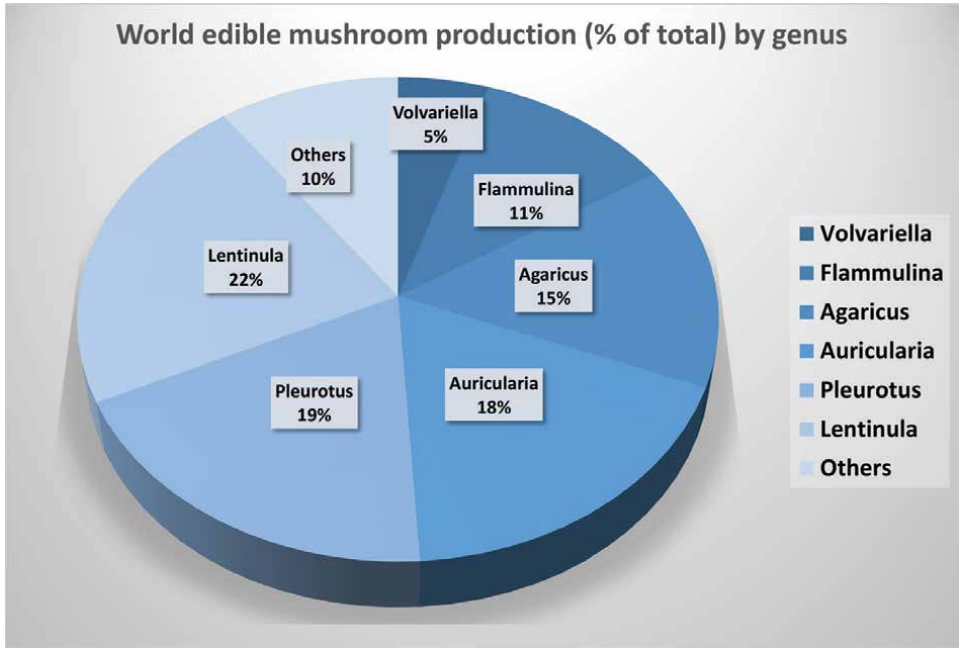

Figure 1.
Worldwide mushroom production.

produced industrially. Around 700 of the known 16,000 mushroom species are regarded harmless and have medicinal properties [49]. The inclusion of fresh varieties of mushroom farming for commercial purposes has resulted in a fast expansion of the worldwide mushroom business during the last two decades. Furthermore, mushroom cultivation and development have had a favorable influence in terms of economic growth worldwide, the influence of mushroom farming, mushroom derivatives, and mushroom foodstuffs on human well-being in the twenty-first decade may be termed as a "nongreen revolution."

5. Nutritional value

Mushrooms are frequently high in protein and necessary amino acids, but low in fat [7]. Furthermore, these fungi have a substantial quantity of carbs and fiber, as well as vitamins (such as thiamin, riboflavin, cobalamin, vitamin C and D) and minerals (Se, Cu, Mg, Na, K, P, Fe, Ca, and Mn) [7]. The edible mushrooms had moisture percentage (81.8–94.8%), which depends on the mushroom species and other parameters like harvesting, growing, preparing, and storing conditions (**Figure 2**) [5, 6].

Crude protein contents in edible mushrooms L. edodes had a dry weight (DW) of 15.2 g/100 g, while A had a DW of 80.93 g/100 g. [6, 8]. They are high in glutamate, arginine, and aspartic acid, but low in methionine and cysteine, according to the FAO/WHO [6]. The limiting amino acids in L. edodes, P. ostreatus, and P. eryngii are leucine and lysine. Surprisingly, two new amino acids have been discovered: GABA (aminobutyric acid) and ornithine have been shown to have important physiological functions [6]. As a result, the nutritional significance of mushrooms is expected to grow in the next years as a result of the world's rising protein need and a desire to avoid the risks connected with the usage of animal foods sources. Mushrooms that are edible have a low-fat content. Unsaturated fatty acids, notably palmitic acid (C16:0), oleic

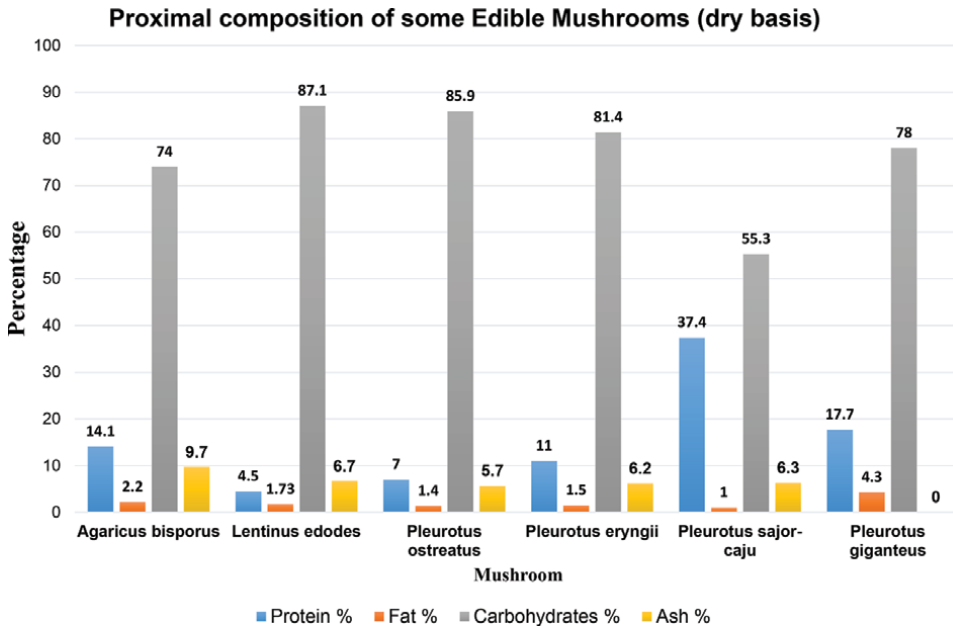

Figure 2.
Nutritional content of some edible mushroom.

acid (C18:1), and linoleic acid, prevail over saturated fatty acids in general (C18:2) [51–53]. While the other FA was only found in trace levels, with the exception of Lactarius deliciosus, which possesses a high concentration of stearic acid (C18:0) [51].

6. Phenolic compounds

Phenolic compounds are aromatic hydroxylated compounds that include one or even more aromatic rings and hydroxyl groups. Many mushrooms have anti-inflammatory characteristics due to the prevalence of phenolic substances examples include flavonoids, hydroxycinnamic acids, oxidized polyphenols, lignans, phenolic acids, Stilbenes, hydroxybenzoic acids, and tannins (**Table 2**).

[70, 71]. These chemicals have been observed to behave as peroxide decomposers, antioxidants, and metal inactivators [72]. One of the most significant classes of secondary metabolites identified in fungal fruiting bodies is phenolic chemicals, and they have been shown to have antioxidative and anti-inflammatory properties [73]. Imleria badia was the initial examined organisms, with phenolic chemicals discovered

Edible Mushroom	Bioactive Compounds	References
Agaricus campestris	Vitamin C, D, B12, folates, and polyphenols	[54]
Agaricus bisporus	Fibers, Oligopeptide	[55]
Agaricus brasiliensis	Polyphenols and flavonoids, Oligopeptide	[56]
Boletus bicolor, Leucopaxillus tricolor G. lucidum, Tricholoma giganteum Tricholoma matsutake, Tuber micheli, Hypsizygus marmoreus, Grifola frondosa	Oligopeptide	[57–60]
Catathelasma ventricosum	Heteropolysaccharide	[57]
Lactarius deterrimus	Polyphenols and flavonoids	[61]
Catathelasma ventricosum	Heteropolysaccharide	[62]
Lentinula edodes	Lentinan KS-2	[63]
Hericium erinaceus	Flavonoids	[64]
Lentinus lepideus	Lentinan KS-2, flavonoids	[65]
Pholiota nameko SW-02	Mycelia zinc polysaccharide	[66]
Pleurotus djamor	Mycelium zinc polysaccharides	[67]
Heterobasidion linzhiense, Ganoderma australe, Collybia peronata, Ganoderma lingzhi, Inonotus andersonii,Heterobasidion linzhiense,, Inocybe sp. Phellinus gilvus, Lactarius hatsudake, Phellinus conchatus, Phellinus gilvus, Betulina Lenzites, Panellus sp., Phlebia tremellosa, Trametes versicolor, Phellinus gilvus, Phellinus gilvus, Phellinus gilvus, Ph stiptica postia, Tricholoma caligatum, and Rigidoporus sp.	Polyphenol	[68]
Hericium erinaceus	Exo-polymer	[69]

Table 2.
Edible mushroom and some bioactive substance.

in the fruiting bodies, procatechuic, cinnamic, p-hydroxybenzoic, and p-coumaric acids, in particular. The phenolic content in total was 48.3 mg/kg dry weight. Additionally, the phenolic compounds of I. badia have unusually great antioxidant activity, reaching 99.2% in linoleic acid oxidation assays [74]. The cultivated species A. bisporus, on the other hand, includes gallic, caffeic, ferulic, p-coumaric, and protocatechuic phenolic acids [75].

7. The therapeutic effect of mushrooms

The hunt for medical compounds derived from fungus has piqued the public's curiosity. Higher basidiomycetes have been shown to contain bioactive compounds with anticancer, immunomodulatory, anti-inflammatory, hypoglycemic, antiatherogenic, antimutagenic, and other health-promoting properties [76]. Mushrooms may reduce the risk of disorders including Parkinson's, Alzheimer's, hypertension, stroke, and cancer, as well as work as an antimicrobial, immune system booster, and cholesterol-lowering agent [77]. Mushrooms include other metabolites (terpenoids, acids, sesquiterpenes, polyphenols, lactones, sterols, alkaloids, nucleotide analogs, metal chelating agents, and vitamins), as well as polysaccharides and glycoprotein, particularly –glucans. Additional proteins having bioactivity have also been found, including lectins, lignocellulose-degrading enzymes, protease inhibitors and proteases, hydrophobins, and ribosome-inactivating proteins, which can be used in biotechnological procedures to create new drugs [78]. Biologically active polysaccharides and protein complexes produced from mushrooms have anticancer effects both in animals and humans. Several of these mushroom polymers have been demonstrated to have immunotherapeutic effects by inhibiting and killing tumor cells in the past. Several mushroom polysaccharide components have been clinically studied and are widely and efficiently used to treat cancer and other illnesses in Asia. Certain mushrooms are estimated to generate a total of 126 therapeutic activities [79]. Anticancer polysaccharides generated from mushrooms are either acidic or neutral, have a powerful anticancer effect, and have a wide range of chemical structures. Antitumor activity has been identified in a broad variety of glycans, ranging from homopolymers to extremely complex heteropolymers. Mushroom polysaccharides have anticancer effect through stimulating the immune system of the host body; in other words, mushroom polysaccharides do not directly destroy cancer cells. Several substances help to reduce stress in the organism's systems and may result in a 50% reduction in tumor progression as well as a 50% improvement in tumor-bearing organism survival time [80, 81]. Glucans are the most often detected polysaccharides in mushrooms, accounting for about half of the fungal cell wall. Many edible mushrooms contain glucans, which are responsible for their anticancer, immunomodulatory, anticholesterolemic, anti-oxidant, and neuroprotective characteristics. They are also known as effective immune stimulators in humans, and their ability to treat a variety of disorders has been established. These biological reactions are induced when glucans bind to a membrane receptor.

Indole compounds are another class that has been shown to have radical scavenging and anti-inflammatory substance designated in mushrooms [82, 83]. These chemicals have a particularly powerful impact on animal immunological and neurological systems. Indole compounds identified in mushrooms comprise psychoactive compounds such as psilocybin and also non-hallucinogenic compounds

such as 5-hydroxy-L-tryptophan, L-tryptophan, serotonin, or tryptamine [82, 83]. Mushrooms have a great capacity to digest elements from the soil, making them a useful source of these compounds. Mushrooms collect bio elements with free radical scavenger and anti-inflammatory properties such as zinc, copper, iron, and selenium [84].

8. Mushroom and chronic diseases

The therapeutic qualities of mushrooms, as well as the existence of bioactive substances, are their most notable characteristics. Mushrooms' pharmacological qualities include immune boosting, homeostasis maintenance, biorhythm modulation, and, most critically, the treatment and prevention of a wide range of life-threatening diseases such as uncontrolled cell division, cerebral disorders, and cardiovascular disease Mushrooms offer, antifungal, antioxidant, immunomodulatory, anti-angiogenic, anticarcinogenic, antiviral, antibacterial, hepatoprotective, hypoglycemia, antidiabetic, anti-inflammatory and other therapeutic properties [85]. Some mushroom polysaccharides or complexes with protein to form polysaccharides-protein which can enhance the host's defense system, it enhances non-specific immune response, and anticancer action [86]. Mushrooms are high in natural antibiotics. The molecule responsible for the antimicrobial action has been identified as oxalic acid. Eating Tricholoma populinum resulted in the resolution of severe allergy symptoms in two patients, one with thromboangiitis obliterans and the other with urticarial [87].

8.1 Impact of mushroom on cardiovascular diseases

Cardiovascular disease is one of the leading causes of death in both the developed and the developing world [88]. Food has been found to notably modify etiological risk factors associated with blood pressure alterations, homocysteine metabolism, hemostasis, lipid and lipoprotein digestion, and oxidative damage [89]. Triacylglycerol, blood pressure, homocysteine, LDL, and HDL cholesterol are all well-established measurements and commonly recognized markers. Only LDL and blood pressure, however, are considered diet-related indicators [89]. The hypocholesterolemic characteristics of edible mushrooms have long been employed in medicine [90]. Consuming edible mushrooms, in general, reduces the risk of heart disease attributed to the prevalence of certain compounds and other bioactive molecules. **Figure 3** depicts the processes of cholesterol metabolism involved in the hypocholesterolemic action of edible mushrooms.

The FA content of edible mushrooms proves to help in lowering blood cholesterol [51, 91]. When the Fatty acid proximate analysis of many edible mushrooms was studied, significant amounts of PUFA were identified. The presence of Tran's isomers of unsaturated fatty acids has the greatest impact on raising the blood cholesterol to high-density lipoprotein ratio, which raises the risk of cardiovascular disease [91–93]. Mushrooms did not contain Tran's isomers of unsaturated fatty acids [51]. Dietary fiber ingestion may have an effect on plasma lipid levels and lower the risk of heart problems [94]. Soluble dietary fiber has been demonstrated to have effects on serum lipid, decreasing total cholesterol and LDL [95]. Their vicious qualities are connected to an increase in bile acid and Short-chain FA excretion inhibits acetate uptake into serum lipids [9, 96]. Auricularia auricula and Tremella fuciformis are two mushrooms

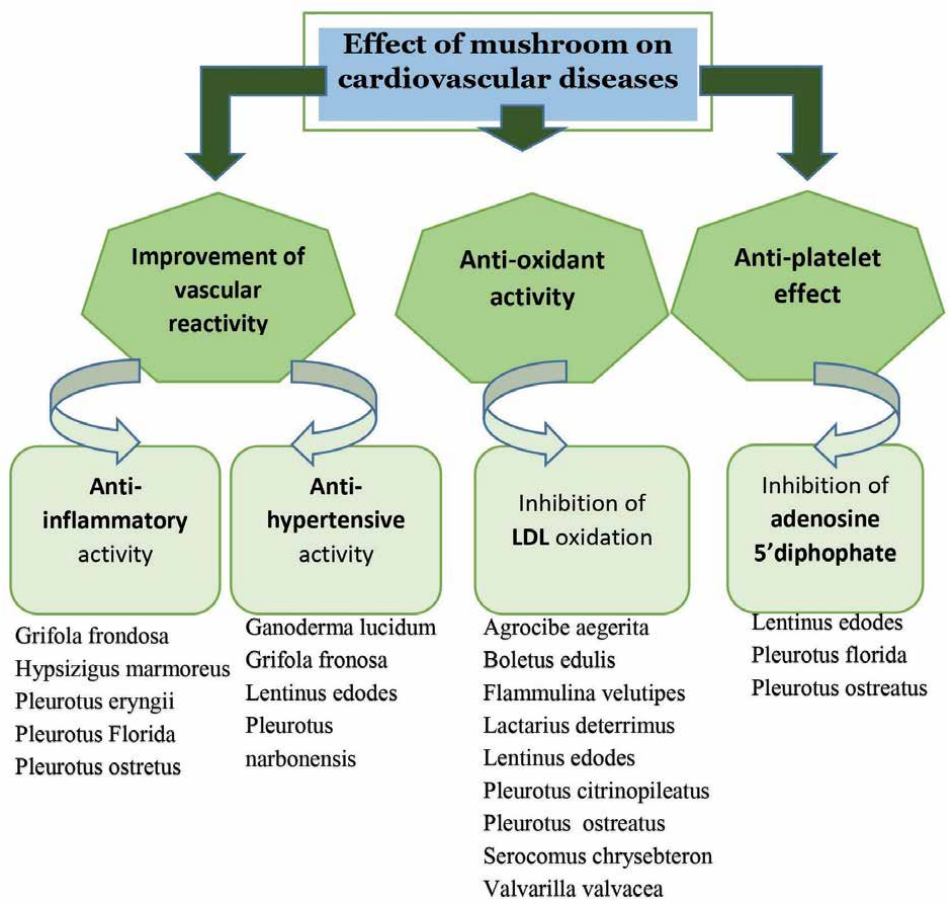

Figure 3.
Cholesterol metabolism and edible mushrooms.

with significant dietary fiber, that have been shown to reduce LDL levels and total cholesterol [97]. Mushrooms are especially interesting because they contain a high concentration of -glucan polysaccharides, which have hypocholesterolemic and anticoagulant properties (**Table 3**) [106, 107].

Some fungal species have been shown to have anti-inflammatory effects [108], and edible mushrooms have been used to obtain natural anti-inflammatory chemicals. P. florida's anti-inflammatory action has been indicated as a possible therapeutic application against cardiovascular illnesses [108]. Help to prevent cardiovascular disease, and there is evidence that proves that oxidative alteration of LDL (lipids or protein components) contributes to atherogenesis [109]. Mushrooms include a variety of antioxidant chemicals, including polysaccharides, nicotinic acid, triterpenes, ergosterol, and polyphenols [98]. Two extracts of P. citrinopileatus were shown to exhibit strong antioxidant activity, which may be related to antihyperlipidemic effects [110]. Oyster mushrooms decreased the frequency and size of lesions of atherosclerotic in coronary arteries [108]. High blood pressure. In terms of blood pressure effects, the mushroom's low salt concentration and high potassium content (182–395 mg/100 g) encourage its inclusion in the meal plan. In fact, from fruits and vegetable potassium has been shown to reduce blood pressure [6]. Several research

Edible mushroom	Hypocholesterolemia properties	References
Agaricus bisporus	↓Triglycerides in liver. ↓ Serum total cholesterol. ↓ Adipocytokine. ↓LDL. ↑Hepatic LDL receptor mRNA. ↓The fat deposition.	[98, 99]
Auricularia auricular Lentinus edodes	↓LDL. ↓cholesterol levels. ↓phospholipids of plasma. Modification of hepatic phospholipids metabolism.	[100]
Pleurotus citrinopiletus	↓Triglycerides in liver and blood. ↓Total lipids. ↑Bile acid excretion. ↓Total cholesterol. Inhibition of HMG-CoA reductase.	[101]
Pleurotus florida	↓Total lipids. ↓Total cholesterol. ↑Bile acid excretion. ↓Triglycerides in liver and blood. Inhibition of HMG-CoA reductase.	[102]
Pleurotus ostreatus	↓Plasma triglycerides, maintain normal Blood pressure ↓VLDL. ↓LDL. ↓Total cholesterol. Inhibition of HMG-CoA reductase.	[103, 104]
Tremella fuciformis	↓LDL. ↓ Plasma triglycerides. ↓Total cholesterol. ↓Hepatic total cholesterol.	[105]

Table 3.
Edible mushrooms with hypocholesterolemia properties.

has been conducted to study the antihypertensive activity of edible mushroom species such as Ganoderma lucidum, pleurotus narbonensis, G. frondosa, and L. edodes (**Figure 4**).

The potassium, vitamin C, and fiber found in mushrooms help to improve cardiovascular health. Potassium, like salt, aids in blood pressure regulation. Consuming shiitake can help reduce the risk of health problems and coronary heart disease since they are high in nutrients and low in salt. Mushrooms are especially interesting since they contain a lot of -glucan polysaccharides, which have anticoagulant and hypocholesterolemic properties [107]. Chitin (N-acetyl-D-glucosamine polymer) or Chitosan (D-glucosamine polymer) are two more fascinating fungal polysaccharides that have comparable properties to dietary fiber and lower triglyceride levels in the body [99]. Eritadenine, also known as lentinacin (or lentysine), is a purine alkaloid or an adenosine analog with hypocholesterolemic properties [109].

The angiotensin-converting enzyme (ACE) regulates the renin-angiotensin-aldosterone system's (RAAS) action and lowers blood pressure, which is inhibited by the majority of mushroom bio-components [110]. Polysaccharides and Triterpenoids, such as ganoderic alcohols, ganoderic aldehydes (ganoderals), and ganoderic acids are bioactive in Ganoderma (ganoderol). Ansor and colleagues recently reported that ACE

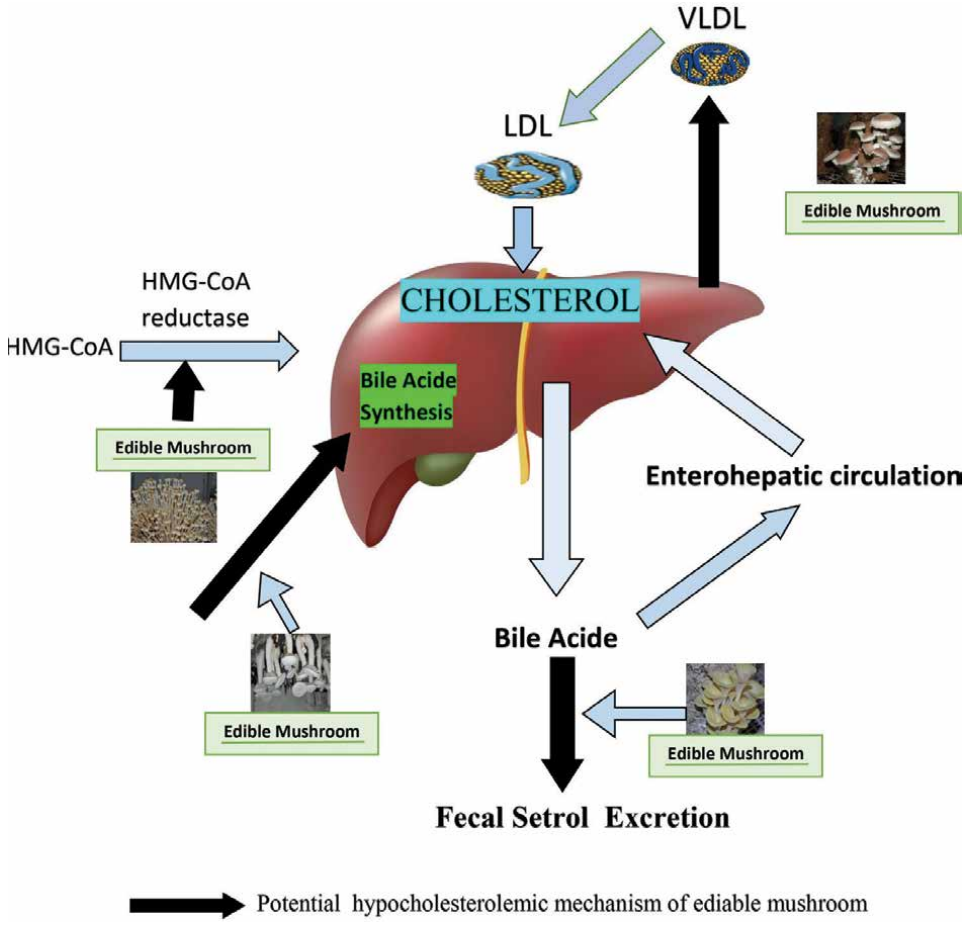

Figure 4.
Effect of edible mushrooms on cholesterol metabolism.

inhibitory peptides from Ganoderma lucidum can help to reduce blood pressure [111]. 3,3,5,5-tetramethyl 4-piperidone (TMP) from Marasmius androsaceus, l-pipecolic acid from Sarcodona spratus, d-mannitol from Pleurotus cornucopiae, Lentinan, chitin, and K+ from Lentinula edodes, are all anti-hypertensive mushroom bioactive elements [110].

8.2 Edible mushrooms and obesity

Since time immemorial, mushrooms have been widely utilized as meals, nutraceuticals, and medications [112]. Mushrooms have low energy properties in it, which is very crucial in weight loss. Mushrooms also contain a high vitamin-D and B-complex content, as well as high mineral content and a considerable amount of numerous trace elements, including selenium, which is a strong antioxidant [113]. Aside from their nutritional importance, mushrooms have unique qualities in terms of taste color, flavor, texture, and odor that are more fascinating for mankind's utilization. Many studies have advised that particular mushrooms be consumed on a regular basis, in food, or as an extracted substance. Some of these polysaccharides have antimicrobial and anti-inflammatory properties [114]. The beneficial benefits

of mushroom and polysaccharides on the gut microbiome, which has been related to diabetes and obesity, are currently being studied in a vibrant niche research field [115]. Because mushrooms have a high concentration of bioactive chemicals, they help to reduce obesity [63]. Numerous research has been carried out to study the polysaccharides produced from different mushrooms that have anti-obesity effects. Polysaccharides derived from Coriolus Versicolor stimulated splenocytes in mice via the MAPK-NF-B signaling pathway, resulting in an immunomodulatory result [116]. A polysaccharide from Tremella fuciformis decreased 3 T3-L1 adipocyte variation by reducing mRNA expression, indicating the carbohydrate's potential usefulness as an anti-obesity prebiotic [54]. G. lucidum consumption decreased adipogenic transcription factor expression, which enhances glucose and lipid transport and storage, and enables AMPK signaling pathways, demonstrating the polysaccharide's potential as an anti-obesity and antidiabetic drug [117]. Eating white mushroom (Agaricus bisporus) may have anti-diabetic and anti-obesity properties. Similarly, this research has been broadened to include more mushroom species that are extremely useful such as Lentinus edodes (shiitake) and Hericium erinaceus (Lion's mane) [118, 119].

8.3 Effect of mushroom on cancer

The cell cycle was arrested at the G0/G1 phase, according to flow cytometry data. Methanol extract inhibited cell proliferation and growth in breast cancer patients by upregulating p21, p19, p53, and p27genes and downregulating E2f transcription factor 1, PCNA, CDK4, CDK6, and Transcription factor DP-1 expression. Polysaccharides from Pleurotus ostreatus suppressed angiogenesis in MCF-7 cells by downregulating VEGF factor expression. Polysaccharides also increased the production of caspase-3, Bax, caspase-9, and phospho-JNK, as well as reducing mitochondrial membrane potential, resulting in cell death [120]. Supplementing rats with glucan produced from oyster mushrooms with breast cancer was associated with a decrease in tumor recurrence, tumor volume, and total tumor nodules [121].

Figure 5 shows a possible molecular signaling cascade implicated in Pleurotus species' anti-cancerous activity:

a. Pleurotus extract inhibits Cox-2-PGE2 pathway, which stimulates angiogenesis, and the VEGF (potent angiogenic factor) route, which is necessary for tumor development.

b. The bioactive chemicals found in N-cadherin decreased cell transformation. MMP-2 and MMP-9 (Zn-dependent endoproteases) are inhibited by mushroom extract, which is essential for EMT (Epithelial Mesenchymal Transition) in cancerous cells through tumor formation.

c. Mushroom extract inhibits anti-apoptotic protein (Bcl-2) while activating/upregulating pro-apoptotic components such as bid, bax, cytochrome c release, fas, and cellular damage occurs.

d. It prevents cells from progressing through the cell cycle and suppresses malignant cell growth via a p53-dependent and p53-independent route.

e. In several types of malignant cells, its bioactive chemical causes DNA fragmentation.

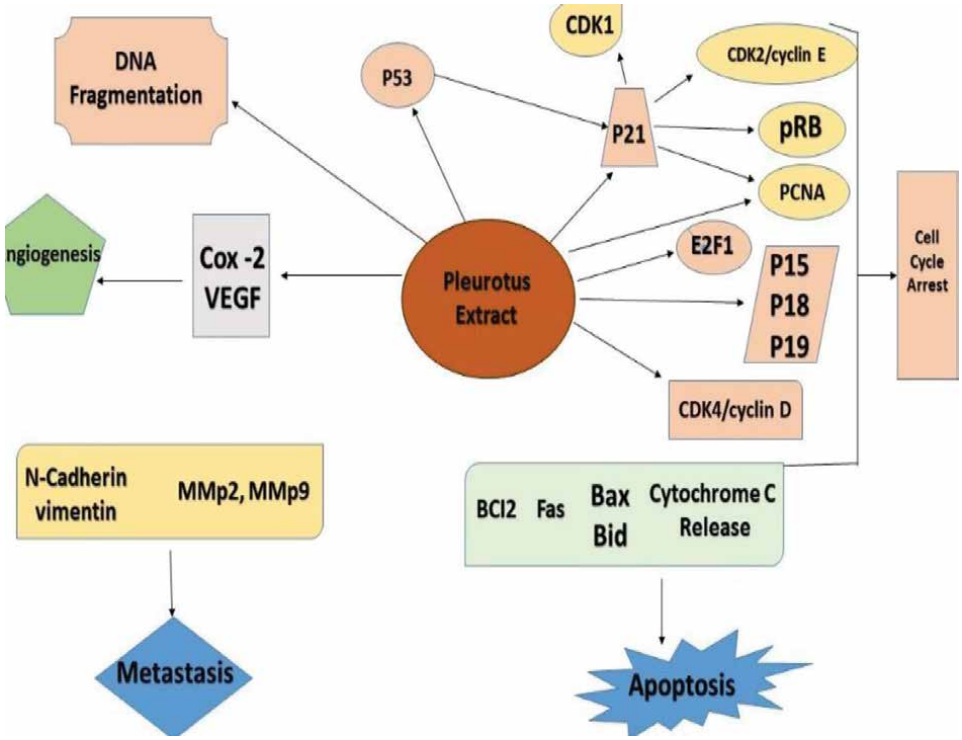

Figure 5.
Pleurotus extracts induced the activation and modulation of several signaling pathways in cancer cells, resulting in the prevention of cancer cell development, procreation, angiogenesis, and metastasis, as well as cell death.

After 72 hours of exposure, because of its potential to elicit humoral and cellular immune responses against cancer cells, HeLa cells were suppressed by 60% by Pleurotus sajor-caju extracellular polysaccharide which is a sulfated derivative and HPV16E7 vaccines derived from β-glucan produce from the same species can be used for cervical cancer therapy [122, 123]. The anti-proliferative impact of gold nanoparticles generated by photo-irradiation from Pleurotus Florida was dose-dependent against human chronic myelogenous leukemia cell lines K-562 [124]. Immunomodulation is a method that uses immune cell activation can aid in the targeting and destruction of tumor cells while also imbuing the encounter with long-term memory. The activities include lymphoid cell stimulation, cellular immune function enhancement phagocytosis stimulation [125, 126].

Colorectal cancer cell development is inhibited by methanolic extracts of Ganoderma dried fruiting bodies induce by cell growth in the G2–M cell cycle phase, which is caused by cell proliferation. Methanol extract promotes sp. 21 and p 27 while downregulating cyclin A and B kinase proteins [127]. Pleurotus ostreatus, an edible fungus, has antiapoptotic action due to the presence of β-glucan, a therapeutic carbohydrate with a low molecular weight. Lectin derived from the extract of the therapeutic fungus Clitocybene bularis has anti-proliferative action against human leukemic T cells. Most lectins have several carbohydrate-binding sites, which attach to a glycosylated cellular receptor of T cells, triggering the antileukemic signaling cascade [128]. The impact of triterpenes derived from Ganoderma lucidum mycelial extract on human leukemia cancer cell lines HT-29 exhibits cell cycle arrest in the G2–M phase [129]. Stomach cancer is caused by smoked meat, a high-salt diet, while

complex carbohydrate, fruits & vegetables, consumption of high dietary fiber, a low-fat diet, and dairy products lowers the incidence of gastric cancer [130]. Ganoderma lucidum is one of the most extensively used medicinal fungus species for combating stomach cancer [131].

8.4 Role of mushroom in diabetes

Hyperglycemia (abnormally high fasting and postprandial glucose levels in the blood) refers to a group of illnesses with various etiologies that are a serious public health concern globally. Mushrooms, which have historically been used as diabetic treatments, constitute an attractive topic for the development of novel forms of therapies for diabetes and its after-effects. Many mushrooms have been shown to manage blood glucose levels clinically and/or experimentally and to alter the course of diabetes problems without causing negative effects [41, 132]. Aside from improving hyperglycemia, β-glucan treatment in diabetes settings has been demonstrated to produce a systemic enhancement that may improve the body's resilience against the development of diabetic complications [133–135]. Mushroom-glucans are polysaccharides that do not include starch and have a core of glucose polymer chain with extra beta-(1–6) branch points. The length of the β-glucan main chains varies, as do the kinds and degree of complication of side-chain branching. High molecular weight glucans with more structural complexity are thought to outperform low molecular weight glucans in terms of efficacy. Mushrooms also include heteropolysaccharides D-glucans with xylose, mannose, galactose, and uronic acid chains, as well as glycoproteins D-glucanprotein complexes [136].

Mushrooms have a high fiber content of roughly 3 g. per cup, which can assist persons having type 1 diabetes control their blood glucose. Blood sugar levels, cholesterol, and insulin levels in patients with type 2 diabetes can all be improved. However, having diabetes is not a requirement for eating a high-fiber diet. According to usual eating standards, the female should eat 25 g of fiber per day while an adult man should take 38 g. In 100 g dried powder of Pleurotus florida, phytochemical screening revealed the presence of alkaloids 1.92 mg, flavonoids 2.78 mg, saponins 0.05 mg, phenols (61.85 mg catechol equivalent), tannins 0.52 mg, glycosides 0.12 mg, and terpenoids 0.08 mg, which show anti-diabetic characteristics by lowering blood glucose levels [128]. Mushrooms, particularly $\hat{a}$ - glucans and polysaccharides have the ability to improve the secretion of insulin by $\hat{a}$ -cells, improving pancreatic cellular functions, which reduces blood glucose levels. It has been demonstrated to increase insulin sensitivity in peripheral tissues [137]. In the pancreatic tissues of rats, lectins isolated from Agaricus campestris and Agaricus bisporus stimulated the release of the hormone insulin from islets of Langerhans [138].

8.5 Effect of mushroom on immune system

Immunomodulatory mushrooms are the most often employed medicinal mushrooms in today's Korea, China, Japan, and Asian nations. Some polysaccharides or polysaccharide-protein complexes from different types of edible mushrooms have been proven to enhance the non-specific immune system and perform anticancer action by activating the host's defensive system [86]. These medications cause effector cells such as T lymphocytes, macrophages, and NK cells to release antiproliferative cytokines such as IL-1b, IFN-g, TNF-a, and others, which induce tumor cell death and differentiation [139]. β -glucans contained in edible mushrooms have been shown to have an immune-boosting impact [140]. Specific β-glucans receptors are preferentially

expressed on the surface of neutrophils, dendritic, natural killer (NK) cells, and monocyte/macrophages, when β-glucans are consumed [141], The activation of the nuclear factor k-lightchain-enhancer of activated B cells (NF-kB), generation of cytokines, transcription of inflammatory-immune genes, reactive oxygen species (ROS) and nitric oxide (NO) occurs after the receptor recognition stage (ROS) [142, 143]. Other pattern recognition receptors (PRR) have been linked to -glucan recognition, and they may work in tandem with dectin-1/TLR or perhaps independently [144]. -Glucan receptors may be inhibited after damage, but -glucans from a fungal pathogen, which produce large quantities of the interleukin-1 receptor antagonist (IL-1RA), can activate a significant immunomodulatory response independent of these receptors [144].
One of the finest dietary sources of selenium is edible mushrooms [145]. Selenium is required for the immune system to operate properly. Selenoproteins are selenium-bound proteins that play a role in immune system cell differentiation, proliferation, and activation, regulating both the congenital and adaptive immunological responses. Selenium's immunoregulatory effect is further demonstrated by its impact on leukocyte activities such as migration, phagocytosis, adhesion, as well as cytokine release, which may be critical in chronic inflammation and autoimmune disorders. Furthermore, selenoproteins play important role in cellular antioxidative activities. Selenium is an important component in the fight against free radicals, thanks to its involvement in the architecture of Superoxide, or glutathione peroxidase, among other things.

Numerous mushroom species included ergosterol (vitamin D precursor) and ergocalciferol (vitamin D2), as well as other sterols. Ergosterol is abundant in the fruiting bodies of A. bisporus [146]. Vitamin D has a wide range of benefits for humans, according to current studies. Its scarcity has been linked to the onset of metabolic syndrome and hypertension, as well as intestinal inflammation, diabetes, and other health problems and certain types of malignancies, all of which are caused by chronic inflammation [147].

8.6 Mushrooms' effect on bone health

Mushrooms include a variety of bioactive chemical ingredients that aid in bone metabolism and reduce the risk of osteoporosis in humans. Mushrooms increase the osteogenicity of cultured bone cells and induce bone formation and mineralization [148]. Edible Mushrooms are a rich source of vitamin D. Vitamin D's main function is to keep bones healthy by stimulating calcium absorption from the gut and maintaining calcium homeostasis. Vitamin D insufficiency is a worldwide problem that also affects regions with enough sunshine [149]. Vitamin D deficiency may exacerbate bone loss by lowering calcium absorption and raising parathyroid hormone levels [150]. Rheumatoid arthritis is a degenerative joint condition that causes impairment. Inflammation in joints resulted in the loss of form and function as people become older, about 35–45 years old. Women are more impacted than males when it comes to chronic inflammation, joint pain, and autoimmune illness, which is characterized by chronic inflammation, joint pain, and autoimmune disease. A poly-branched (1,3/1,6)-D-glucans from P. Ostreatus has been shown to have anti-arthritic action [151, 152].

8.7 Neurodegenerative diseases and mushroom

Neurodegenerative diseases (NDs) are a type of neurological disorder that causes the brain or nervous system to deteriorate over time. Alzheimer's disease (AD) is the most common neurodegenerative disease and the most common cause of dementia.

The two major mechanisms that contribute to its advancement are oxidative stress and neuroinflammation [153]. Edible mushrooms have high levels of polyphenols, polysaccharides, vitamins, carotenoids, and minerals, all of which have antioxidant and anti-inflammatory properties [154]. Recent research has shown that mushrooms can help with some elements of neurodegenerative illness; nevertheless, human studies are inadequate to prove clinically significant consequences on brain health indicators. Although, it has been discovered that mushroom eating slows the onset of Alzheimer's disease and protects against -amyloid peptide toxicity in the brain and moderate intellectual disability [85]. Niacin-rich mushrooms have higher therapeutic effectiveness in the rehabilitation of Parkinson's disease [155]. Polyozellin, a bioactive substance found in edible mushrooms, might be used to test Huntington's disease sufferers [156]. Polysaccharides, hericenones and erinacines, Erinacine A, Psilocybin, Triterpenoids, nucleotides, sterols, steroids, Quercetin, −(1–3)-d-glucan, Ergothioneine, Selenium, vitamin D2, antioxidants, glutathione, and ergothioneine are examples of bioactive components present in edible mushrooms that have a protective effect against neurodegenerative disease [157].

9. Conclusion

Mushrooms, without a doubt, maybe called functional food. According to current dietary recommendations for disease prevention and treatment, edible mushrooms have adequate nutritional content, and their consumption can impact several identified risk indicators. Mushroom consumption obviously has a cholesterol-lowering or hypocholesterolemia impact through many methods such as reducing VLDL, enhancing lipid metabolism, blocking HMG-CoA reductase activity, and so delaying the chances of cardiovascular diseases. Several studies have shown that eating mushrooms on a daily basis considerably decreases chronic diseases like cancer, atherosclerosis, diabetes mellitus inflammation, obesity, and many other diseases. However, this technique should be accompanied by frequent physical exercise, nutritional and lifestyle adjustments. Regular mushroom eating may result in synergistic and better results. Mushrooms' antioxidant and anti-inflammatory components also help to lessen the burden of many ailments.

Acknowledgements

We thank the digital library GCUF for providing access to the publication.

Conflict of interest

There is no conflict of interest.

Author details

Sakhawat Riaz[1*], Arslan Ahmad[1], Rimsha Farooq[2], Munir Ahmed[2], Muhammad Shaheryar[1] and Muneer Hussain[3]

1 Department of Home Economics, Government College University Faisalabad, Pakistan

2 School of Food Science and Engineering, Yangzhou University, China

3 Department of Eastern Medicine, Government College University Faisalabad, Pakistan

*Address all correspondence to: sakhawt.sakhi@gmail.com

IntechOpen

References

[1] Miles PG, Chang ST. Mushroom Biology: Concise Basics and Current Developments. Singapore: World Scientific; 1997

[2] Food and Agriculture Organization of the United Nations, FAO. Available from: http://www.fao.org/corp/statistics/en

[3] De Pinho PG, Ribeiro B, Gonçalves RF, Baptista P, Valentão P, Seabra RM, et al. Journal of Agricultural and Food Chemistry. 2008;**56**:1704-1712

[4] Zawirska-wojtasiak R, Siwulski M, Mildner-Szkuddarz S, Wąsowicz E. Acta Scientiarum Polonorum. Technologia Alimentaria. 2009;**8**:47-61

[5] Bano Z, Rajarathnam S. Pleurotus mushroom. CRC Critical Reviews in Food Science and Nutrition. 1988;**27**:87-158

[6] Manzi P, Grambelli L, Marconi S, Vivanti V, Pizzoferrato L. Food Chemistry. 1999;**65**:477-482

[7] Mattilda P, Könkö K, Eurola M, Pihlava JM, Astola J, Vahteristo L, et al. Journal of Agricultural and Food Chemistry. 2001;**49**:2343-2348

[8] Barros L, Cruz T, Baptista P, Estevinho LM, Ferreira ICFR. Food and Chemical Toxicology. 2008;**46**:2742-2747

[9] Flegg PB, Maw G. Mushrooms and their possible contribution to the world. Mushroom Journal. 1997;**48**:395-403

[10] Gruen FH, Wong MW. Distribution of cellular amino acids, proteins and total nitrogen during fruit body development in Flammuling velutipes. Canadian Journal of Botany. 1982;**160**:1339-1341

[11] Barros L, Ferreira MJ, Queirós B, Ferreira ICFR, Baptista P. Food Chemistry. 2007;**103**:413-419

[12] Diplock AT, Aggett PJ, Ashwell M, Bornet F, Fern EB, Roberfroid MB. The British Journal of Nutrition. 1999;**81**:S1-S27

[13] Wasser SP, Weis AL. Medicinal properties of substances occurring in higher Basidiomycetes mushrooms: Current perspectives. Int J Med Mushrooms. 1999;**1**:31

[14] Wasser SP, Weis AL. Critical Reviews in Immunology. 1999;**19**:65-96

[15] Chang ST. Overview of mushroom cultivation and utilization as functional foods. In: Cheung PCK, editor. Mushrooms as Functional Foods. New Jersey: John Wiley & Sons Inc.; 2008. pp. 1-33

[16] Barros L, Baptista P, Correia DM, Morais JS, Ferreira ICFR. Journal of Agricultural and Food Chemistry. 2007;**55**:4781-4788

[17] Chang ST, Hayes WA. The Biology and Cultivation of Edible Mushrooms. New York: Academic; 1978. p. 137

[18] Chang ST, Miles PG. Edible Mushrooms and their Cultivation. Boca Raton: CRC Press Inc; 1989. p. 345

[19] Beetz A, Kustudia M. Mushroom Cultivation and Marketing. ATTRA; Jul 2004

[20] Nwanze PI, Ameh JB, Umoh VJ. The effect of the interaction of various oil types with different culture media on biomass production of Psathyrella atroumbonata pegler. African Journal of Biotechnology. 2005;**4**:1285-1289

[21] Elhami B, Ansari NA. Effect of substrate of spawn on medium growth of oyster mushroom species. Journal of Biological Sciences. 2008;**8**:474-477

[22] Muthukrishnan N, Venugopal MS, Janarthanan R. Recycling spent larval food of Corcyra cephalonica stainton for preparing spawn and sporophore of Pleurotus sajor caju (fr.) singer. World Journal of Microbiology and Biotechnology. 2000;**16**:26-270

[23] Sainos E, Díaz-Godínez G, Loera O, Montiel-Gonzaléz AM, Sánchez C. Growth of Pleurotus ostreatus on wheat straw and wheat-grain-based media: Biochemical aspects and preparation of mushroom inoculum. Applied Microbiology and Biotechnology. 2006;**72**:812-815

[24] Pathmashini L, Arulnandhy V, Wilson-Wijeratnam RS. Cultivation of oyster mushroom (Pleurotus ostreatus) on sawdust. Ceylon J Sci Bio Sci. 2008;**37**:177-182

[25] Stoop JM, Mooibroek H. Advances in genetic analysis and biotechnology of the cultivated button mushroom Agaricus bisporus. Applied Microbiology and Biotechnology. 1999;**52**:474-483

[26] Sonnenberg ASM. Genetics and breeding of Agaricus bisporus. Mushroom Sci. 2000;**15**:25-39

[27] Oliver JM, Delmas J. Vers la maîtrise des champignons comestibles. Biofutur. 1987;**1**:23-41

[28] Moquet F, Desmerger C, Mamoun M, Ramos-Guedes-Lafargue M, Olivier J-M. A quantitative trait locus of Agaricus bisporus resistance to pseudomonas tolaasii is closely linked to natural cap color. Fungal Genetics and Biology. 1999;**28**:34-42

[29] Sonnenberg ASM, Van Kempen IPJ, Van Griensven LJLD. Detection of Agaricus bisporus viral dsRNAs in pure cultures, spawn and spawn-run compost by RT-PCR. Mushroom Sci. 1995;**14**:587-594

[30] Dragt JW, Geels FP, Rutjens AJ, Van Griensven LJLD. Resistance in wild types of Agaricus bisporus to the mycoparasite Verticillium fungicola var. fungicola. Mushroom Sci. 1995;**14**:679-683

[31] Kerrigan RW. A brief history of marker assisted selection in Agaricus bisporus. Mushroom Sci. 2000;**15**:183

[32] Hawton P, Bartlett P, Nisbet LJ. Mycocell system. Mushroom Sci. 2000;**15**:897-908

[33] Lamber FHM. Computer control in mushroom growing: An updated inventory of applications. Mushroom Sci. 2000;**15**:15-21

[34] Walker S. Automated environments. Mushroom News. 1996;**44**:26-27

[35] Hiller S. Some properties of mushrooms. International Agrophysics. 1994;**8**:635-642

[36] Reed JN, Crook S, He W. Harvesting mushrooms by robot. Mushroom Sci. 1995;**15**:385-391

[37] Oei P. Mushroom Cultivation: With Special Emphasis on Appropriate Techniques for Developing Countries. Leiden: Tool Publications; 1996

[38] Martinez Carerra D. Current development of mushroom biotechnology in Latin America. Micologica Aplicada Inernational. 2002;**14**:61-74

[39] Gupta S, Summuna B, Gupta M, Annepu SK. Edible mushrooms:

Cultivation, bioactive molecules, and health benefits. Bioactive Molecules in Food, Reference Series in Phytochemistry. Springer; 2018:1-33. DOI: 10.1007/978-3-319-54528-8_86-1

[40] Arora D. Notes on economic mushrooms. Economic Botany. 2008;**62**:540-544

[41] Lo H-C, Wasser SP. Medicinal mushrooms for Glycemic control in diabetes mellitus: History, current status, future perspectives, and unsolved problems (review). International Journal of Medicinal Mushrooms. 2011;**13**:401-426

[42] Shivute FN. Cultivation of edible mushrooms in Namibia: Prospects and challenges of small scale farmers. African Journal of Agricultural Research. 2020;**16**(11):1582-1586

[43] Yang X, He J, Li C, Ma J, Yang XJ. Matsutake trade in Yunnan Province, China: An overview. Economic Botany. 2008;**62**:269-277

[44] Fanzo J, Cogill B, Mattei F. Metrics of sustainable diets and food systems. In: Technical Brief-Madrid Roundtable. Rome: Bioversity International and Daniel and Nina Carasso Foundation; 2012

[45] Chang ST, Wasser SP. The cultivation and environmental impact of mushrooms. Oxford Research Encyclopaedia of Environmental Science. 2017. DOI: 10.1093/acrefore/9780199389414.013.231

[46] Vinceti B, Termote C, Ickowitz A, Powell B, Kehlenbeck K, Hunter D. The contribution of forests and trees to sustainable diets. Sustainability. 2013;**5**:4797-4824

[47] Kirk PM, Cannon PF, David JC, Stalpers JA. Ainsworth & Brisby's Dictionary of the fungi. 10th ed. Wallingford: CAB International; 2008

[48] Wasser SP. Medicinal mushroom science: History, current status, future trends, and unsolved problems. Int J Med Mushrooms. 2010;**12**(1):1-16

[49] Wasser SP. Review of medicinal mushrooms advances: Good news from old allies. Herbal Gram. 2002;**56**: 28-33

[50] Chang ST, Wasser SP. The cultivation and environmental impact of mushrooms. Agriculture and Environment. 2017. DOI: 10.1093/acrefore/9780199389414.013.231

[51] Díez VA, Alvarez A. Food Chemistry. 2001;**75**:417-422

[52] Longvah T, Deosthale Y. Food Chemistry. 1998;**63**:331-334

[53] Alves M, Ferreira IFR, Dias J, Teixeira V, Martins A, Pintado M. A review on antimicrobial activity of mushroom (Basidiomycetes) extracts and isolated compounds. Planta Medica. 2012;**78**(16):1707-1718

[54] Jeong HJ, Yoon SJ, Pyun YR. Polysaccharides from edible mushroom Hinmogi (Tremella fuciformis) inhibit differentiation of 3T3-L1 adipocytes by reducing mRNA expression of PPARγ, C/EBPα, and leptin. Food Science and Biotechnology. 2008;**17**:267-273

[55] Fukushima M, Nakano M, Morii Y, Ohashi T, Fujiwara Y, Sonoyama K. Hepatic LDL receptor mRNA in rats is increased by dietary mushroom (Agaricus bisporus) fiber and sugar beet fiber. The Journal of Nutrition. 2000;**130**:2151-2156

[56] Tsubone H, Makimura Y, Hanafusa M, Yamamoto Y, Tsuru Y, Motoi M, et al. Agaricus brasiliensis KA21 improves circulatory functions in spontaneously hypertensive rats. Journal of Medicinal Food. 2014;**17**:295-301

[57] Geng X, Tian G, Zhang W, Zhao Y, Zhao L, Ryu M, et al. Isolation of an angiotensin I-converting enzyme inhibitory protein with antihypertensive effect in spontaneously hypertensive rats from the edible wild mushroom Leucopaxillus tricolor. Molecules. 2015;**20**:10141-10153

[58] Kang MG, Kim YH, Bolormaa Z, Kim MK, Seo GS, Lee JS. Characterization of an antihypertensive angiotensin I-converting enzyme inhibitory peptide from the edible mushroom Hypsizygus marmoreus. BioMed Research International. 2013;**2013**:283964

[59] Vitak TY, Wasser SP, Nevo E, Sybirna NO. The effect of the medicinal mushrooms Agaricus brasiliensis and Ganoderma lucidum (higher Basidiomycetes) on the erythron system in normal and streptozotocin-induced diabetic rats. Int. J. Med. Mushrooms. 2015;**17**:277-286

[60] Yurkiv B, Wasser SP, Nevo E, Sybirna NO. Antioxidant effects of medicinal mushrooms Agaricus brasiliensis and Ganoderma lucidum (higher Basidiomycetes): Evidence from animal studies. Int. J. Med. Mushrooms. 2015;**17**:943-955

[61] Grdović N, Dinić S, Arambašić J, Mihailović M, Uskoković A, Marković J, et al. The protective effect of a mix of Lactarius deterrimus and Castanea sativa extracts on streptozotocin-induced oxidative stress and pancreatic β-cell death. The British Journal of Nutrition. 2012;**108**:1163-1176

[62] Liu Y, Chen D, You Y, Zeng S, Hu Y, Duan X, et al. Structural characterization and antidiabetic activity of a glucopyranose-rich heteropolysaccharide from Catathelasma ventricosum. Carbohydrate Polymers. 2016;**149**:399-407

[63] Yamada T, Oinuma T, Niihashi M, Mitsumata M, Fujioka T, Hasegawa K, et al. Effects of Lentinus edodes mycelia on dietary-induced atherosclerotic involvement in rabbit aorta. Journal of Atherosclerosis and Thrombosis. 2002;**9**:149-156

[64] Hiwatashi K, Kosaka Y, Suzuki N, Hata K, Mukaiyama T, Sakamoto K, et al. Yamabushitake mushroom (Hericium erinaceus) improved lipid metabolism in mice fed a high-fat diet. Bioscience, Biotechnology, and Biochemistry. 2010;**74**:1447-1451

[65] Yoon KN, Alam N, Lee JS, Cho HJ, Kim HY, Shim MJ, et al. Antihyperlipidemic effect of dietary Lentinus edodes on plasma, feces and hepatic tissues in hypercholesterolemic rats. Mycobiology. 2011;**39**:96-102

[66] Zheng L, Zhai G, Zhang J, Wang L, Ma Z, Jia M, et al. Antihyperlipidemic and hepatoprotective activities of mycelia zinc polysaccharide from Pholiota nameko SW-02. International Journal of Biological Macromolecules. 2014;**70**:523-529

[67] Zhang J, Meng G, Zhang C, Lin L, Xu N, Liu M, et al. The antioxidative effects of acidic-, alkalic-, and enzymatic-extractable mycelium zinc polysaccharides by Pleurotus djamor on liver and kidney of streptozocin-induced diabetic mice. BMC Complementary and Alternative Medicine. 2015;**15**:440

[68] Bang TH, Suhara H, Doi K, Ishikawa H, Fukami K, Parajuli GP,

et al. Wild mushrooms in Nepal: Some potential candidates as antioxidant and ACE-inhibition sources. J. Evid. Based Complement. Altern. Med. 2014;**2014**:195305

[69] Yang BK, Park JB, Song CH. Hypolipidemic effect of an Exo-biopolymer produced from a submerged mycelial culture of Hericium erinaceus. Bioscience, Biotechnology, and Biochemistry. 2003;**67**:1292-1298

[70] Cote J, Caillet S, Doyon G. Bioactive compounds in cranberries and their biological properties. Critical Reviews in Food Science and Nutrition. 2010;**50**(7):666-679

[71] D'Archivio M, Filesi C, Vari R, et al. Bioavailability of the polyphenols: Status and controversies. International Journal of Molecular Sciences. 2010;**11**:1321-1342

[72] Dziezak JD. Antioxidants-the ultimate answer to oxidation. Food Technology. 1986;**40**(9):94

[73] Ferreira IC, Barros L, Abreu R. Antioxidants in wild mushrooms. Current Medicinal Chemistry. 2009;**16**(12):1543-1560

[74] Reis FS, Martins A, Barros L, Ferreira ICFR. Antioxidant properties and phenolic profile of the most widely appreciated cultivated mushrooms: A comparative study between in vivo and in vitro samples. Food and Chemical Toxicology. 2012;**50**:201-207

[75] Liu J, Jia L, Kan J, Jin CH. In vitro and in vivo antioxidant activity of ethanolic extract of white button mushroom (Agaricus bisporus). Food and Chemical Toxicology. 2013;**51**:310-316

[76] Valdez-Morales M, Barry K, Fahey GC Jr, et al. Effect of maize genotype, developmental stage, and cooking process on the nutraceutical potential of huitlacoche (Ustilago maydis). Food Chemistry. 2010;**119**(2):689-697

[77] Valverde ME, Hernández-Pérez T, Paredes-López O. Dible mushrooms: Improving human health and promoting quality life. International Journal of Microbiology. 2015;**2015**:1-14. DOI: 10.1155/2015/376387

[78] Erjavec J, Kos J, Ravnikar M, Dreo T, Sabotic J. Proteinš of higher fungi—From forest to application. Trends in Biotechnology. 2012;**30**(5):259-273

[79] Wasser SP. Current findings, future trends, and unsolved problems in studies of medicinal mushrooms. Applied Microbiology and Biotechnology. 2011;**89**(5):1323-1332

[80] Zhang M, Cui SW, Cheung PCK, Wang Q. Antitumor polysaccharides from mushrooms: A review on their isolation process, structural characteristics and antitumor activity. Trends in Food Science & Technology. 2007;**18**(1):4-19

[81] Wasser S. Medicinal mushrooms as a source of antitumor and immunomodulating polysaccharides. Applied Microbiology and Biotechnology. 2002;**60**(3):258-274

[82] Kała K, Krakowska A, Sułkowska-Ziaja K, Szewczyk A, Reczyński W, Opoka W, et al. Kinetics of extracted bioactive components from mushrooms in artificial digestive juices. International Journal of Food Properties. 2017;**20**:1796-1817

[83] Palacios I, Lozano M, Moro C, D'Arrigo M, Rostagno MA, Martinez JA, et al. Antioxidant properties of phenolic compounds occurring in edible mushroom. Food Chemistry. 2011;**128**:674-678

[84] Kalač P. Chemical composition and nutritional value of European species of wild growing mushrooms: A review. Food Chemistry. 2010a;**113**:9-16

[85] Xu T, Beelman RB. The bioactive compounds in medicinal mushrooms have potential protective effects against neurodegenerative diseases. Adv Food Technol Nutr Sci Open J. 2015;**1**(2):62-65. DOI: 10.17140/AFTNSOJ-1-110

[86] Reshetnikov SV, Wasser SP, Tan KK. Higher basidiomycetes as a source of antitumor and immunostimulating polysaccharides (review). Int J Med Mushrooms. 2001;**3**:361-394

[87] Kreisel H, Lindequist U, Horak M. Distribution, ecology and immunosuppressive properties of Tricholoma populinum (Basidiomycetes). Zentralblatt für Mikrobiologie. 1990;**145**:393-396

[88] Cannon CP. Clinical Cornerstone. 2007;**8**:11-28

[89] Mensink RP, Aro A, Den Hond E, German JB, Griffin BA, Ten Meer HU, et al. European Journal of Nutrition. 2003;**42**(Suppl 1):1/6-1/27

[90] Sun Q, Ma J, Campos H, Hankinson SE, Manson JE, Stampfer MJ, et al. Circulation. 2007;**115**:1858-1865

[91] Sun Q, Ma J, Campos H, Hankinson SE, Manson JE, Stampfer MJ, et al. Circulation. 2007;**115**:1858-1865

[92] Mauger JF, Lichtenstein AH, Ausman LM, Jalbert SM, Jauhiainen M, Ehnholm C. The American Journal of Clinical Nutrition. 2003;**78**:370-375

[93] Mensink RP, Zock PL, Kester AD, Katan MB. The American Journal of Clinical Nutrition. 2003;**77**:1146-1155

[94] Grundy SM, Denke MA. Journal of Lipid Research. 1990;**31**:1149-1172

[95] Erkkilä AT, Lichtenstein AH. The Journal of Cardiovascular Nursing. 2006;**21**:3-8

[96] Wolever T, Spadafora P, Cunnane S, Pencharz P. The American Journal of Clinical Nutrition. 1995;**61**:1241-1247

[97] Cheung PCK. Nutrition Research. 1996;**16**:1721-1725

[98] Elmastas M, Isildak O, Turkekul I, Temur N. J food Composition anal. 2008;**20**:337-345

[99] Neyrinck AM, Bindels LB, De Backer F, Pachikian D. International Immunopharmacology. 2009;**9**:767-773

[100] Rokujo T, Kikuchi H, Tensho A, Tsukitani Y, Takenawa T, Yoshida K, et al. Life Sciences. 1970;**9**:379-385

[101] Hu SH, Liang ZC, Chia YC, Lien JL, Chen KS, Lee MY, et al. Journal of Agricultural and Food Chemistry. 2006;**54**:2103-2110

[102] Bajaj M, Vadhera S, Brar AP, Soni GL. Indian Journal of Experimental Biology. 1997;**35**:1070-1075

[103] Khatun K, Mahtab H, Khanam PA, Sayeed MA, Khan KA. Mymensingh Medical Journal. 2007;**16**:94-99

[104] Hossain S, Hashimoto M, Choudhury EK, Alam N, Hussain S, Hasan M, et al. Clinical and Experimental Pharmacology & Physiology. 2003;**30**:470-475

[105] Cheng HH, Hou WC, Lu ML. Journal of Agricultural and Food Chemistry. 2002;**50**:7438-7443

[106] Alban S, Franz G. Biomacromolecules. 2001;**2**:354-361

[107] Zekovic DB, Kwiatkowski S, Vrvic MM, Jakovljevic D, Moran CA. Critical Reviews in Biotechnology. 2005;**25**:205-230

[108] Jose N, Janardhanan KK. Phytotherapy Research. 2004;**18**:43-46

[109] Chibata I, Okumura K, Takeyama S, Kotera K. Experientia. 1969;**25**:1237-1238

[110] Yahaya NFM, Rahman MA, Abdullah N. Therapeutic potential of mushrooms in preventing and ameliorating hypertension. Trends in Food Science and Technology. 2014;**39**:104-115

[111] Ansor NM, Abdullah N, Aminudin N. Anti-angiotensin converting enzyme (ACE) proteins from mycelia of *Ganoderma lucidum* (Curtis) P. Karst. BMC Complementary and Alternative Medicine. 2013;**13**:256

[112] Friedman M. Mushroom polysaccharides: Chemistry and antiobesity, antidiabetes, anticancer, and antibiotic properties in cells, rodents, and humans. Food. 2016;**5**:80

[113] Jayachandran M, Zhang T, Ganesan K, Xu B, Chung SSM. Isoquercetin ameliorates hyperglycemia and regulates key enzymes of glucose metabolism via insulin signaling pathway in streptozotocin-induced diabetic rats. European Journal of Pharmacology. 2018;**829**:112-120

[114] Wang K, Bao L, Xiong W, Ma K, Han J, Wang W, et al. Lanostane triterpenes from the tibetan medicinal mushroom Ganoderma leucocontextum and their inhibitory effects on HMG-CoA reductase and α-glucosidase. Journal of Natural Products. 2015;**78**:1977-1989

[115] Murphy EA, Velazquez KT, Herbert KM. Influence of high-fat diet on gut microbiota: A driving force for chronic disease risk. Current Opinion in Clinical Nutrition and Metabolic Care. 2015;**18**:515-520

[116] Mao GH, Ren Y, Feng WW, Li Q, Wu HY, Jin D, et al. Antitumor and immunomodulatory activity of a water-soluble polysaccharide from Grifola frondosa. Carbohydrate Polymers. 2015;**134**:406-412

[117] Delzenne NM, Bindels LB. Gut microbiota: Ganoderma lucidum, a new prebiotic agent to treat obesity? Nature Reviews. Gastroenterology & Hepatology. 2015;**12**:553-554

[118] Kim SP, Park SO, Lee SJ, Nam SH, Friedman M. A polysaccharide isolated from the liquid culture of Lentinus edodes (shiitake) mushroom mycelia containing black rice bran protects mice against a Salmonella lipopolysaccharide-induced endotoxemia. Journal of Agricultural and Food Chemistry. 2013;**61**:10987-10994

[119] Friedman M. Chemistry, nutrition, and health-promoting properties of Hericium erinaceus (Lion's mane) mushroom fruiting bodies and mycelia and their bioactive compounds. Journal of Agricultural and Food Chemistry. 2015;**63**:7108-7123

[120] Jin-Kai X, Yuan Q-G, Luo P, Sun X-L, Ma J-C. Pleurotus eous polysaccharides suppress angiogenesis and induce apoptosis via ROS-dependent JNK activation and mitochondrial mediated mechanisms in MCF-7 human breast cancer cells, Bangladesh. Journal de Pharmacologie. 2015;**10**:78-86

[121] Susanti I, Wibowo H, Siregar NC, Pawiroharsono S, Sujatna FD. Antitumor activity of beta glucan extract from oyster mushroom (Pleurotus ostreatus Jacq. P. Kum) on DMBA-induced breast

cancer in vivo. International Journal of PharmTech Research. 2018;**11**:190-197

[122] Randhawa K, Shri R. Pharmacological importance of Pleurotus sajor-caju (Fr.) singer. The Pharma Innovation Journal. 2017;**6**:321-327

[123] Roopngam PE. Increased response of human T-lymphocytes by dendritic cells pulsed with HPV16E7 and Pleurotus sajor-caju β-glucan (PBG), Iran. Journal of Immunology. 2018;**15**:246-255

[124] Bhata R, Sharanabasavaa VG, Deshpandeb R, Shettic U, Sanjeevd G, Venkataramana A. Photo-bio-synthesis of irregular shaped functionalized gold nanoparticles using edible mushroom Pleurotus florida and its anticancer evaluation. Journal of Photochemistry and Photobiology B: Biology. 2013;**125**:63-69

[125] Gao Y, Zhou S. The immunomodulating effects of Ganoderma lucidum (Curt.: Fr.) P. karst. (Ling Zhi, Reishi mushroom) (Aphyllophoromycetideae). International Journal of Medicinal Mushrooms. 2002;**4**(1):11

[126] Shukla S, Bajpai VK, Kim M. Plants as potential sources of natural immunomodulators. Reviews in Environmental Science and Biotechnology. 2014;**13**:17-33

[127] Hsua SC, Ouc CC, Li JW, Chuangg TC, Kuoi HP, Liuc JY, et al. Ganoderma tsugae extracts inhibit colorectal cancer cell growth via G2/M cell cycle arrest. Journal of Ethnopharmacology. 2008;**120**:394-401

[128] Pohleven J, Obermajer N, Sabotica J, Anzlovara S, Sepcic K, Kos J, et al. Purification, characterization and cloning of a ricin B-like lectin from mushroom *Clitocybe nebularis* with antiproliferative activity against human leukemic t cells. Biochimica et Biophysica Acta. 2009;**1790**(3):173-181

[129] Muller CI, Kumagai T, Kelly JO, Seeram NP, Heber D, Koeffler HP. *Ganoderma lucidum* causes apoptosis in leukemia, lymphoma and multiple myeloma cells. Leukemia Research. 2006;**30**:841-848. DOI: 10.1016/j.leukres.2005.12.004

[130] Wong JY, Abdulla MA, Raman J, Phan CW, Kuppusamy UR, Golbabapour S, et al. Gastroprotective effects of lion's mane mushroom *Hericium erinaceus* (bull.:Fr.) Pers. (Aphyllophoromycetideae) extract against ethanol-induced ulcer in rats. Evidence-Based Complementary and Alternative Medicine. 2013;**2013**:9. Article ID 492976. DOI: 10.1155/2013/492976

[131] Rony KA, Mathew J, Neenu PP, Janardhanan KK. Ganoderma lucidum (Fr.) P. karst occurring in South India attenuates gastric ulceration in rats. Indian Journal of Natural Products and Resources. 2011;**2**:19-27

[132] Jovanović JA, Mihailović M, Uskoković AS, Grdović N, Dinić S, Poznanović G, et al. Evaluation of the antioxidant and Antiglycation effects of Lactarius Deterrimus and Castanea Sativa extracts on Hepatorenal injury in Streptozotocin-induced diabetic rats. Frontiers in Pharmacology. 2017;**8**:793

[133] Mirjana M, Jelena A, Aleksandra U, Svetlana D, Nevena G, Jelena M, et al. B-glucan administration to diabetic rats Reestablishes redox balance and stimulates cellular pro-survival mechanisms. Journal of Functional Foods. 2013;**5**:267-278

[134] Mihailović M, Arambašić J, Uskoković A, Dinić S, Grdović N, Marković J, et al. B-glucan administration to diabetic rats alleviates oxidative stress

by lowering hyperglycaemia, decreasing non-enzymatic glycation and protein O-Glcnacylation. Journal of Functional Foods. 2013;**5**:1226-1234

[135] Uskoković A, Mihailović M, Dinić S, Jovanović JA, Grdović N, Marković J, et al. Administration of a β-glucan-enriched extract activates beneficial hepatic antioxidant and anti-inflammatory mechanisms in streptozotocin-induced diabetic rats. Journal of Functional Foods. 2013;**5**:1966-1974

[136] Chen Y, Xie M-Y, Nie S-P, Li C, Wang Y-X. Purification, composition analysis and antioxidant activity of a polysaccharide from the fruiting bodies of Ganoderma atrum. Food Chemistry. 2008;**107**(1):231-241. ISSN 0308-8146. DOI: 10.1016/j.foodchem.2007.08.021

[137] Kaur A, Dhingra GS, Shri R. Antidiabetic potential of mushrooms. Asian Journal of Pharmaceutics. 2015;**5**:111-125

[138] Ahmad N, Bansal R, Rastogi AK, Kidwai JR. Effect of PHA-B fraction of *Agaricus bisporus* lectin on insulin release and 45Ca^{2+} uptake by islets of langerhans in vitro. Acta Diabetologica Latina. 1984;**21**:63-70

[139] Reshetnikov SV, Wasser SP, Tan KK. Higher basidiomycetes as a source of antitumor and immunostimulating polysaccharides (review). International Journal of Medicinal Mushrooms. 2001;**3**:361-394

[140] Han B, Baruah K, Cox E, Vanrompay D, Bossier P. Structure-functional activity relationship of β-glucans from the perspective of immunomodulation: A Mini-review. Frontiers in Immunology. 2020;**11**:658

[141] Gantner BN, Simmons RM, Canavera SJ, Akira S, Underhill DM. Collaborative induction of inflammatory responses by dectin-1 and toll-like receptor 2. The Journal of Experimental Medicine. 2003;**197**:1107-1117

[142] Murphy EJ, Rezoagli E, Major I, Rowan NJ, Laffey JG. β-Glucan metabolic and immunomodulatory properties and potential for clinical application. Journal of Fungi. 2020;**6**:356

[143] De Marco Castro E, Calder PC, Roche HM. β-1,3/1,6-glucans and immunity: State of the art and future directions. Molecular Nutrition & Food Research. 2021;**65**:e1901071

[144] Smeekens SP, Gresnigt MS, Becker KL, Cheng SC, Netea SA, Jacobs L, et al. An anti-inflammatory property of Candida albicans β-glucan: Induction of high levels of interleukin-1 receptor antagonist via a Dectin-1/CR3 independent mechanism. Cytokine. 2015;**71**:215-222

[145] Dogan H, Coteli E, Karatas F. Determination of glutathione, selenium, and malondialdehyde in different edible mushroom species. Biological Trace Element Research. 2016;**174**:459-463

[146] Muszyńska B, Kała K, Rojowski J, Grzywacz A, Opoka W. Composition and biological properties of Agaricus bisporus fruiting bodies - a review. Polish Journal of Food and Nutrition Sciences. 2017;**67**:1-10

[147] Strange RC, Shipman KE, Ramachandran S. Metabolic syndrome: A review of the role of vitamin D in mediating susceptibility and outcome. World Journal of Diabetes. 2015;**6**:896-911

[148] Saif A, Lindequist U, Wende K. Stimulating effects of *Grifola frondosa* (Maitake) on human osteoblastic cell cultures. Journal of Natural Medicines.

2007;**61**:231-238. DOI: 10.1007/s11418-006-0132-5

[149] Holick MF, Chen TC. Vitamin D deficiency: A worldwide problem with health consequences. The American Journal of Clinical Nutrition. 2008;**87**(4):1080S-1086S

[150] Chailurkit LO, Kruavit A, Rajatanavin R. Vitamin D status and bone health in healthy Thai elderly women. Nutrition. 2011;**27**(2):160-164

[151] Bauerova K, Paulovicova E, Mihalova D, Svik K, Ponist S. Study of new ways of supplementary and combinatory therapy of rheumatoid arthritis with immunomodulators Glucomannan and Imunoglukan in adjuvant arthritis. Toxicology and Industrial Health. 2009;**25**:329-335. DOI: 10.1177/0748233709102945

[152] Rovensky J, Stancıkova M, Svk K, Bauerova K, Jurovicov J. The effects of b-glucan isolated from *Pleurotus ostreatus* on methotrexate treatment in rats with adjuvant arthritis. Rheumatology International. 2011;**31**:507-511. DOI: 10.1007/s00296-009-1258-z

[153] Uttara B, Singh AV, Zamboni P, R.T. Mahajan oxidative stress and neurodegenerative diseases: A review of upstream and downstream antioxidant therapeutic options. Current Neuropharmacology. 2009;**1**:65-74

[154] Kozarski M, Klaus A, Jakovljevic D, Todorovic N, Vunduk J, Petrović P, et al. Antioxidants of edible mushrooms. Molecules. 2015;**20**(10):19489-19525

[155] Aaseth J, Dusek P, P.M. Roos prevention of progression in Parkinson's disease. Biometals. 2018;**31**(5):737-747

[156] Yang EJ, Song KS. Polyozellin, a key constituent of the edible mushroom Polyozellus multiplex, attenuates glutamate-induced mouse hippocampal neuronal HT22 cell death. Food & Function. 2015;**6**(12):3678-3686

[157] Rai SN, Mishra D, Singh P, Vamanu E, Singh MP. Therapeutic applications of mushrooms and their biomolecules along with a glimpse of in silico approach in neurodegenerative diseases. Biomedicine & Pharmacotherapy. 2021;**137**:111377. DOI: 10.1016/j.biopha.2021.111377

Chapter 13

Medicinal Mushroom of Potential Pharmaceutical Toxic Importance: Contribution in Phytotherapy

Estella Tembe Fokunang, Mbong Grace Annih, Lem Edith Abongwa, Manju Evelyn Bih, Tchadji Mayoudom Vanessa, Dobgima John Fomnboh and Charles Fokunang

Abstract

Orthodox medical practice depends greatly on the use of high throughput (HTP) pure pharmaceutical new chemical entities, with a purity that can easily be evaluated and whose efficacy and toxicity can show a dose-dependent, clear structure-activity relationships (SAR). On the contrary, natural products contain mixtures of natural bioactive metabolites that have not undergone any chemical analyses and whose mechanism of action is not known. Medicinal mushrooms have been used throughout the history of mankind for the treatment of various diseases including cancer. Nowadays they have been intensively studied and generated research interest in an attempt to reveal the chemical nature and mechanisms of action of their bioactive molecules. Targeted treatment of diseases, non-harmful for healthy tissues, has become a major objective in recent times and metabolites of fungal origin provide a vast reservoir of potential new chemical entities. There are many examples of mushrooms common for use globally that demonstrate the complex nature of their pharmaceutical potential This review paper attempts to show that some aspects of fungotherapy of the disease have been well studied. We also give an insight into the role of mushroom metabolites for treatment of diseases types that are especially susceptible to the fungal treatments.

Keywords: medicinal mushrooms, fungotherapy, phytotherapy, nutraceutical, bioactive metabolites, cancer

1. Introduction

Medicinal mushrooms and fungi are known to contain more than 120 medicinal properties, which include antitumor, anti-hypercholesterolemic, antiviral, antibacterial immunomodulation, antioxidant, free radical scavenging, cardiovascular, anti-parasitic, antifungal, detoxification, hepatoprotective, and antidiabetic properties [1]. Most of the Basidiomycetes mushrooms contain bioactive metabolites in

fruiting bodies, cultured mycelium, and cultured broth, with special consideration to mushroom polysaccharides [2]. Studies on mushroom polysaccharides and different bioactive metabolites have been done for more than 700 species of higher hetero- and homobasidiomycetes [3]. Many bioactive metabolites from the medicinal mushrooms studied are known to enhance innate and cell-mediated immune responses, and exhibit antitumor activities in animals' models and clinical trials studies in humans [2, 4]. Even though the mechanism of antitumor properties of medicinal mushrooms is yet to be well understood, stimulation and modulation of major host immune responses by these mushroom bioactive are important [5]. Polysaccharides and low-molecular-weight secondary metabolites are very important due to their antitumor and immune-stimulating activities, based on Phase I, II, and III clinical trials. Mushroom compounds have been used extensively and successfully in low medium-income countries for the treatment of many categories of cancers and other pathologies [6]. More exploration has been directed and special emphasis orientated to investigate many important unsolved problems in the study of medicinal mushrooms [7].

1.1 Medicinal mushroom in phytotherapy

From an evolutionary point of view, nature produces vast biodiversity of bioactive molecules, which possess many therapeutic potentials, with respect to the treatment of diseases, such as cancers [1, 8]. Natural products have produced many secondary phytochemical compounds widely used in phytotherapy, whilst the application of such products in folk and traditional medicine has always been an important clue pointing to potential new chemical entities with therapeutic potential. Some examples of plant-based compounds of pharmaceutical importance for cancer treatment include camptothecin derived from the bark and stem of the tree *Camptotheca acuminata* used in Chinese traditional medicine [2], vinca alkaloids derived from *Madagascan periwinkle* [9] or taxanes derived from genus Taxus (yews), paclitaxel (Taxol), and docetaxel (Taxotere) widely used as chemotherapeutic agents [3, 10]. Generally, first-generation natural chemotherapeutic properties are orientated mostly against housekeeping processes (such as DNA replication or microtubule polymerization and stabilization), which are very active against fast proliferating cancer cells, but not cancer specific [11]. The natural products derived from mushrooms may produce potential adverse side effects on ingestion when used in herbal or conventional anticancer treatments, thus could provoke an eventual patient's death when consumed in overdose. Currently, the approaches used in the management and control of cancer pathologies are based on selected or targeted treatment applications with the intention to reduce to healthy uninfected tissues [11]. The discovery and development of potentially bioactive molecules from mushrooms for better selectivity in action to diseases, especially those to act on cancer cells or on tumorigenic processes, are faced with challenges. It is of importance to develop high through put (HTP) methods for the discovery and potential screening of the bioactive compounds of pharmaceutical importance [12].

1.2 Medicinal mushrooms in folk medicine

Mushrooms have been used in folk medicine as far back in ancient times [12]. Mushrooms species used varied in different cultures, in a way that more species have been identified and used in Asian countries than in the Western civilization [5, 13]. It is reported that the difference in usage is linked to the mycophilic and mycophobic nature of the different cultures [14]. In developed countries, the most common species and

possibly the only one that has been identified, at the time of the ancient Greeks, was *Fomitopsis officinalis*. Hippocrates was one of the pioneers to study the medicinal properties of fungi and elucidated their potential uses in the management of certain common diseases, however, it is not certain as to what species he studied. The contribution of Dioscorides, a physician around 55 AD, who was well known and recognized for his work entitled *De Materia Medica*, still stands as the most widely used herbal bioactive natural product during his era and for about 1500 years, he changed in a significant manner the nutraceutical concept of the Western world and played an important role in the use of mushroom as food and medicinal product, which was the onset of the science of nutraceuticals [15]. The work of Pliny and later Galen also studied and concluded that fungi were of medicinal and pharmaceutical importance. Their opinions, however, influenced the mycophobic nature of mushrooms in Western Society that continues, in the current day. However, *F. officinalis* was globally recognized among the medicinal plants that was used to treat various diseases. Other species used for medicinal applications were other bracket fungi; *Fomes fomentarius*, *Phellinus ignarius*, *Fomintopsis pinicola*, and others that were commonly used to stop the bleeding and as wound healing [7, 16]. In China, where mushrooms are known to be a part of the gastronomy and elixir of life, mushrooms have been considered to play an important role in medicine, nutraceutics for as far back as 7000 years. Many species of mushrooms are identified, including *Lentinula edodes*, *Hericium erinaceum*, *Flammulina velutipes*, *Auricularia polytricha*, and *Tremella fuciformis*, etc., and these are species that are very prized for eating [9, 17].

1.3 Mushrooms as a delicacy food in Cameroon

Mushroom is a delicacy for many around the world. In Cameroon, this crop (fungi) is harvested from the wild once a year during the month of April to May. This activity mobilizes many women and youths (girls and boys) who rely on it for income. Harvested mushrooms, mostly the Agaricus and the termitomyces species, are sold on the roadsides and more often by youths as it generates a substantial amount of money that is used to pay part of their school fees, buy school supplies, and even pay medical and telephone bills [18]. Many people in Cameroon solicit mushrooms because of their good taste, medicinal and nutritive value, cheap and available, especially during its peak season. During offseason, it is not the case. Mushrooms are practically absent in the market and very few traders (middlemen) are in possession of some bags of dry mushroom. A bucket (15 L) is often sold between 15,000 and 25,000 FCFA ($30–$50). A plate of mushrooms is very expensive in restaurants and hotels [19].

Cultivating mushrooms is a good business owing to its short production cycle and poor farmers or youths can easily start up a small farm if trained. This will put mushrooms on the table and in the market all year round generating a substantial amount of income to prospective growers. The government has not been very supportive of this activity and we still struggle to import mother spawns to produce base 2 cultured spawns that farmers use to grow mushrooms. In addition, many people are unaware of the different types of edible mushrooms, so there is inadequate sensitization. The absence of financial and technical support also contributes a great deal.

1.4 Usage of medicinal mushrooms

Most of the benefits of mushrooms studied and investigated through the scientific method are those that have been recognized to produce bioactive metabolites that

Mushroom	Immunomodulating compound
Lentinula edodes	Lentinan
Schizophyllum commune	Schizophyllan
Grifola frondosa	D-fraction
Coriolus versicolor	PSP (polysaccharide peptide) and PSK (also called Krestin)
Ganoderma lucidum	Polysaccharide (GLPS) fractions

Table 1.
Mushroom with immunomodulating bioactive compound [3, 19].

inhibit or can destroy cancer cells development [18]. Most species that produce these bioactive compounds do so by the process of immunomodulation, the modification, by suppressing or enhancing the immune system, and is used in the treatment of cancerous growth [3, 19]. These compounds as illustrated in **Table 1** include Lentinan, Schizophyllan, D-fraction to name but a few.

Just a few species containing these bioactive metabolites have been studied, and over 30 species of mushrooms studied have been shown to have anticancer properties in animals [20]. PC-SPES, which includes a GLPS fraction, has been demonstrated to control adenocarcinoma of the prostate cancer cell line by inhibition of the cell division and growth of their cells [21–24]. This is a very simple and logical explanation of the mechanism. Various species of mushrooms have been reported as nutritious and tasty food in many parts of the world and have been documented by many researchers [24–26]. The nutritious property of mushrooms is also another means by which they can be beneficial to the health of the person consuming mushrooms [27].

Many researchers have demonstrated the medicinal and nutraceutical properties of mushrooms' bioactive compounds, for the management of different illnesses [28]. Despite the bioactive activity demonstrated none of the phytoactive compounds have had approval by the Food and Drug Administration (FDA) of USA, and therefore still considered under the category of dietary supplements, as opposed to the drugs approved by FDA that are prescribed or used as over-the-counter drugs, failing to have undergone any clinical trials studies [29–31]. This category of supplements is marketed with the condition to carry the label of not being approved for use by the FDA [32].

2. Some example species of mushrooms that have been studied for medicinal properties

The examples of mushroom species indicated used in folk medicine do not have any demonstrated medicinal efficacy, and therefore the description of their usage is mostly non-evidence based [33].

2.1 *Coriolus versicolor*

This mushroom is under the species of bracket fungus that is widely referred to as Turkey tail. This common species is ubiquitous, but mostly in the temperate regions of the world [3, 34]. The fruiting body has many useful medicinal secondary metabolites, such as the immunoactive polysaccharopeptide (PSP) and polysaccharide-K (PSK) and especially the antitumor polysaccharide called coriolan [35]. The PSK and PSP are known to inhibit the growth of cancer cells and are administered by intravenous route or

Figure 1.
Coriolus versicolor *(Turkey Tail) [38].*

enterally in clinical studies of cancer volunteers. They have shown promising anticancer activities for the management of many forms of cancer, synergistically in combination with radiation therapy through improving the sensitivity of cancer cells to radiation. The survival of the treatment of PSK has shown the potential to increase the survival rate within 5 years by 21 and 52%, respectively [36]. In *Materia medica* within the traditional Chinese pharmacopeia, *C. versicolor*, is promising for the inhibition of phlegm, management of pulmonary disorder, energy booster for the treatment of chronic diseases [11, 37]. Medicinal mushrooms in Mexico used in traditional folk medicine, are applied for the treatment of ringworm [38]. *C. versicolor* is well illustrated in **Figure 1**.

2.2 Lentinula edodes

The shiitake belongs to the group of mushrooms mainly used for thousands of years, in Japan and China, for its food value and is very prized for its medicinal properties [39]. It is considered as the world's second most widely cultivated and consumed mushroom. In traditional medicine, shiitake has been widely studied, with many clinical studies reported [40]. It has the polysaccharide, lentinan, as well as other polysaccharides that have antitumor properties. Some studies have shown that the shiitake can inhibit bacteria resistant to bacteria [15]. For instance, studies show that clinical trials volunteers that were exposed to antibiotic-resistant strains of *Mycobacterium tuberculosis*, the causal agent of tuberculosis, showed recorded improved conditions when lentinan was administered to them and inhibited relapses of tuberculosis in the lungs [41]. The treatment for cancerous liver tumors in rats, liver protection increased the production of antibodies against hepatitis B, lowered cholesterol blood levels, lipids, and blood pressure [16, 42]. *Lentinula edodes* is illustrated in **Figure 2**.

2.3 *Tremella fuciformis*

These are particular species of jelly fungus that are commonly called the snow fungus. This species grows on hardwood trees, but it is not a wood decomposer as has been considered in the past. It is parasitic on hosts belonging to the order Xylariales, of the phylum Ascomycota [43]. Before understanding its true nature, the cultivation of this species was very challenging. This species belongs to the many Chinese traditional medicinal mushrooms important in the treatment of diseases, used mostly

Figure 2.
Lentinula edodes *(Shiitake) [42].*

as an immune tonic, stops asthma and coughing, reduces phlegm, supports the liver and exhaustion, cosmetics, anti-inflammatory, gastric ulcer, constipation, abnormal menstrual cycles, and many others [11, 44]. This species is common on hardwood in tropical and temperate areas, throughout the world.

From clinical trials studies, it has been shown to improve the level of blood cells as a result of losses from radio and chemotherapy treatment of cancer patients, to boost the immune system through the stimulation of white blood cell activity [45]. Ethnopharmacology studies indicate medicinal mushroom use in lowering cholesterol and the treatment of cardiovascular diseases, such as arteriosclerosis and abnormal clotting [46]. *Tremella fuciformis* has been illustrated in **Figure 3**.

2.4 *Ganoderma lucidum*

This mushroom variety commonly known as the Ling-Zhi in China and Reishi in Japan is considered one of the bracket fungi. However, contrary to most species, it is characterized by a long slender stalk attached to the side of the "cap" of the fruiting body [47]. This species is widely distributed in North and South America, Europe, and part of the African dense humid forest, where they grow on the hardwood. The species is very popular and widely used in Chinese and Japanese traditional pharmacopeia in the past 4000 years, for the treatment of multiple diseases of the liver, hypertension, gastric ulcer, arthritis, chronic hepatitis, insomnia, bronchitis, and asthma [9, 48].

A number of anti-cancer bioactive constituents have been isolated from *G. lucidum*, as illustrated in **Figure 4**. These compounds have shown immune-stimulating, anti-tumor activities [22]. *In vitro* studies have demonstrated that this species possess anti-allergic, bronchitis preventive effect, anti-inflammatory, antibacterial properties against a broad spectrum of bacteria isolate, lowers blood pressure, and has antioxidant properties [49]. Clinical studies have shown the beneficial potential in treating a variety of disorders.

2.5 *Auricularia auricula* and *Arabis polytricha*

Commonly referred to as Jew's Ear that according to folklore is linked to Judas Iscariot, the biblical story of his betrayal of Jesus Christ, who later committed suicide

Figure 3.
Tremella fuciformis *(Snow Fungus) [46].*

Figure 4.
Ganoderma lucidum *[22].*

by hanging on an elder tree. The ear-like shape of the mushroom is linked to the returned spirit of Judas, which serves as a reminder of his betrayal [27, 50]. This species is widely distributed in the temperate zones as opposed to *A. polytricha* that is located in the sub-tropical to tropical regions. The other species have a variety of common names, however, all of them contain the word "ear" in their name due to

Figure 5.
Morphology of Auricularia polytricha *(Pepieau) [42].*

the fact that they have ear-shaped basidiocarp, as shown in **Figure 5** [50]. In Hawaii, for example, the species is referred to as the "pepeiao," the Hawaiian name for the ear. Both species belong to the Basidiomycota known as the "jelly fungi" due to the consistency of their fruiting body [51].

Both species in China, have been used in folk medicine for the past thousands of years for the treatment of hemorrhoids and as a stomach tonic [52]. In Europe, *A. auricula* is traditionally used in a boiled liquid form for the treatment of inflammation of the throat and eye irritation. Studies have also shown more evidence of *A. auricula* wide use for the improvement of the immune system [53]. The potential uses in the lowering of blood cholesterol, as an anticoagulant and potential anti-diabetic activity has been demonstrated [54].

2.6 *Boletus edulis*

This species is widely considered as *King Bolete* and also as the *Cepe* in Italy. It is a mycorrhizal fungus associated with conifers and other hardwood trees [33, 54]. There are many known species of Boletus, but this variety of interest is the most valuable edible species and is recorded as the only species in the genus to have antitumor activities [55]. Boletus species has been widely used in Chinese traditional folk medicine for the treatment of lumbago, leg pains, numbness in limbs, and tendon complications [12, 56]. *Boletus edulis* is illustrated in **Figure 6**.

2.7 *Cordyceps sinensis*

This species is commonly called the Caterpillar Fungus and is probably the most extensively studied species. It is a parasitic species with the caterpillar as its primary host [19]. *C. sinensis* is also included in some food recipes in addition to its medicinal

Figure 6.
Boletus edulis *(Cepe or King Bolete) [37].*

use. It has activities similar to ginseng, antioxidant, anti-inflammatory, and very potent. The first documented use of *C. sinensis* was in 620 AD, during the Tang Dynasty, used for strengthening of the body after exhaustion or long term illness, impotence, backaches, and an antidote for opium poisoning [56]. Cordycepin is the active molecule in *C. sinensis*, as illustrated in **Figure 7**. Cordycepin or 3′-deoxy-adenosine, is a derivative of the nucleoside adenosine. It was initially extracted from the fungus *Cordyceps militaris* [9], but is now produced synthetically. It is also found in other *Cordyceps* species as well as *Ophiocordyceps sinensis* [27].

Based on the similarity of cordycepin to adenosine acting as an analog, some enzymes have affinity but cannot discriminate between the two bioactive compounds [57]. Cordycepin can participate in some biochemical reactions like, 3-dA for example, can provoke the premature termination of mRNA synthesis [34, 58], by acting as an adenosine analog [59]. Cordycepin has been shown to produce rapid, strong imipramine-like antidepressant effects in animal models of depression, and these effects, similar to those of imipramine, are dependent on the enhancement [60]. A photo of a mature *Cordyceps sinensis* in its natural habitat is illustrated in **Figure 8**. The AMPA receptor (AMPA-R) is a subtype of the ionotropic glutamate receptor coupled to ion channels that modulate cell excitability by gating the flow of calcium and sodium ions into the cell [61].

Many studies have been done on this fungus but with little confirmatory result [62]. In traditional Chinese medicine, Cordyceps has been used in the treatment of respiratory and pulmonary diseases, such as renal, liver, and cardiovascular diseases [3, 29]. It has been used in the treatment of immune disorders in association with cancer chemotherapy treatments and surgery [9]. It is also used as a remedy for impotence, fatigue and as a "rejuvenator" for the increase in energy [57]. Successful

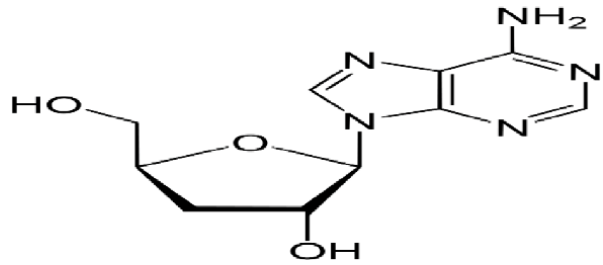

Figure 7.
Structure of cordycepin.

Figure 8.
A mature Cordyceps sinensis *in its natural habitat [39].*

treatment for impotence, acting as an aphrodisiac has also been reported in clinical trials testing. This fungus is considered to be a miracle mushroom [19].

2.8 *Fomitopsis officinalis*

This is a bracket fungus, commonly known as white agaric, agaric, puring agaric, and larch agaric [21, 46]. Apart from its medicinal properties, it is also known to be used as tinder and with the common names as tinder and touchwood [17]. This species is considered as the oldest traditional medicinal mushroom in Asia that has been used by both the Greeks and Romans. It was used in ancient times as an antidote for poisoning [36]. In the past century, it was recorded for use as a laxative, in preventing flatulence and to treat the intestine of worms and parasites [53]. It has contributed to Africa and the tropics for the successful treatment of malaria. Just prior to the mid-twentieth century, it was still used as a tonic for bronchial asthma and night sweats in tuberculosis patients [48, 55]. *Fomitopsis officinalis* is illustrated in **Figure 9**.

Fomitopsis officinalis species are among the most studied species for their medicinal properties. Although bioactivity studies for disease treatment have been done in most

Figure 9.
Fomitopsis officinalis *(White agaric) [30].*

cases this species is not highly recognized to be of pharmaceutical importance for the treatment of the diseases studied and therefore not approved by the FDA [21]. In addition, for its use as dietary supplement/nutraceuticals more research is needed before a strong consideration for use as a supplement, as some species have been reported to show toxicity if consumed more than the recommended established doses [34].

2.9 *Pleurotus ostreatus*

Pleurotus ostreatus, commonly called the oyster mushroom, oyster fungus, or hiratake, is a widely consumed edible mushroom [63]. It was first cultivated in Germany in subsistence farming to support food sources for the population during the World wars [63], and is currently widely cultivated on a commercial large-scale production worldwide for sustainable food production. It is closely related to the widely cultivated king oyster mushroom. This species of mushrooms is industrially used for mycoremediation purposes [9, 64]. The oyster mushroom is considered as one of the most widely sought-after wild mushrooms, even though they are highly cultivated on straw and other substrate media. It produces the bittersweet aroma of benzaldehyde, which is a characteristic of bitter almonds [15, 65]. The species of Pleurotus are shown in **Figure 10**.

The gastronomic effects are described by the addition of either the dried fruiting bodies of the oyster fungus *P. ostreatus*, or the ethanolic extract, to the diet of normal Wistar male rats and a strain with hereditary hyper-cholesterolemia. The addition of the dry oyster fungus to the diet is linked to a two-fold significant increase of the triacylglycerol (TAG) level in the plasma of both treatment groups of rats when

Figure 10.
(a) Pleurotus ostreatus *growing on a tree trunk. (b)* Pleurotus ostreatus *cultivated in Cameroon.*

compared with their respective controls [66–68]. On the contrary, the ethanolic extract alone did not significantly increase TAG levels. There was no significant change for total cholesterol and its high- and low-density lipoprotein fractions in the plasma, as well as the calculated atherogenic index.

3. Carnivorous fungi

They are fungi that are able to obtain most of their nutrients from trapping and eating microscopic animals [69]. They can develop a strong carnivorous feeding mechanism, and more than 200 species are well studied and documented. They belong to either the phyla Ascomycota, Mucoromycotina, or basidiomycota [70]. They are soil-dwelling mycorrhizal fungi and many species are capable of trapping the soil nematodes (nematophagous fungus), while others can invade amoeba or collembola [66].

This group of fungi species can grow on the epidermis, hair, skin, nails, or feathers of living or dead animals and thus known as dermatophytes instead of carnivores. Furthermore, fungi in orifices and the digestive tract of animals are neither carnivorous in nature, nor considered as internal pathogens [71]. The insects' pathogens that invade and colonize insects are called carnivorous if the fungal thallus is mainly in the insect as in the case of Cordyceps, or if it attaches to the insect-like in the case of the Laboulbeniales [72].

3.1 Common toxic mushrooms

Most common mushroom species, such as *Amanita phalloides*, produce bioactive compounds that are toxic in nature, antibiotic, antiviral, hallucinating, or have the bioluminescent potential [73]. Although only a small number of deadly species have

been reported, several other mushrooms have the potential to cause serious and unpleasant adverse effects. Mushroom toxicity can play a role in the protection of the function of the basidiocarp and the mycelium can possess considerable energy and protoplasmic material to develop a structure for spore distribution efficiency [42]. One major setback for the consumption of mushrooms is the production of toxins that makes the mushroom not suitable for consumption, by either causing side effects or symptoms like vomiting after the meal [74]. In addition, a report in 2008, on the ability of mushrooms to absorb heavy metals, radioactive substances, is an indication that some European mushrooms may have included toxicity from the 1986 Chernobyl disaster and many studies are still in progress [23].

3.2 Psychoactive mushrooms

Most mushrooms with psychoactive activities are known to play a vital role in traditional folk medicine worldwide. Psychoactive mushrooms have been used as a sacrament in rituals for mental and physical healing, and to facilitate visionary functions [24, 75]. One such ritual practice is the velada ceremony. A tradi-practitioner of mushroom use is called the *shaman* or *curandera* associated with a priest healer [76]. An example of a psychoactive mushroom *Psilocybe zapotecorum*, a hallucinating mushroom, is shown in **Figure 11**.

The Psilocybin mushrooms are also referred to as psychedelic mushrooms possessing psychedelic activity known as "magic mushrooms" or "shrooms." They are widely available in smart shops worldwide, or on the black market in countries that have outlawed their sale [11, 76]. Psilocybin mushrooms have been reported to facilitate a profound and life-changing effect often referred to as mystical experiences. Some scientific works have backed up these claims, as well as the long-lasting effects of the induced spiritual experiences [24, 77]. There are more than 100 psychoactive mushroom species of genus Psilocybe distributed worldwide. Psilocybin, a naturally occurring chemical in certain psychedelic mushrooms such as *Psilocybe cubensis*, has been studied for its ability in the treatment of psychological disorders, such as obsessive-compulsive disorder [77]. Small amounts have been shown to inhibit migraine headaches [78]. A double-blind study, done by the Johns Hopkins Hospital, showed psychedelic mushrooms promising potential to provide people an experience with substantial personal meaning and spiritual

Figure 11.
Psilocybe zapotecorum *(hallucinogenic mushroom) [23].*

Species	Compound/derivative	Targets/mechanisms of action	Cancer types affected	Experimental models	References
Fomitopsis pinicola	Methanol extract	Cytotoxicity	Hepatocarcinoma, cervical cancer	Cell lines	[24]
	Chloroform extract	ROS-mediated apoptosis	Colorectal cancer	Cell lines	[14]
		Metalloproteinase-mediated migration inhibition	Colorectal cancer	Cell lines	[35]
	Ergosterol	ROS-mediated apoptosis	Colorectal cancer	Cell lines	[14, 70]
	Ethanol extract	Tumor growth arrest	Sarcoma	Mouse xenograft tumors	[9]
Hericium erinaceus	Ethanol extract	Tumor growth arrest	Gastric, liver, colon cancer	Cell lines, mouse xenograft tumors	[70]
	Water extract	Metalloproteinasemediated migration inhibition, suppression of ERK and JNK kinase activation	Colon carcinoma	Mouse xenograft tumors	[11, 45]
		NK cells and macrophages stimulation, arrest of angiogenesis	Colon carcinoma	Mouse xenograft tumors	[72]
		Apoptosis via downregulation of antiapoptotic proteins	Leukemia	Cell lines	[21]
	Polysaccharides	Immunostimulation,	—	Mouse models	[45]
	Erinacine A (ditherpenoid)		Gastrointestinal	Cell lines, mouse xenograft tumors	[21]
		ROS-mediated cell cycle cancer, colorectal arrest cancer antiinvasive			
	Cerebroside E	Angiogenesis blocker		HUVEC cell line	[58]
	HEP3 protein	Immuno-stimulation via adenocarcinoma gut microbiota		Mouse xenograft tumors	[73]
	HEG-5 glycoprotein	Proapoptotic stimulation gastric cancer		Cell lines	[47]
	Ethanol extract	Gastric ulcer cytoprotective (carcinogenic condition)		Rat model	[52]

Species	Compound/derivative	Targets/mechanisms of action	Cancer types affected	Experimental models	References
	1-(5-chloro-2-hydroxyphenyl)-3-methyl-1-butanone,2,5-bis(methoxycarbonyl) terephthalic acid	Gastric ulcer *Helicobacter pylori* (carcinogenic growth inhibition condition)		*In vitro* bacterial growth models	[13]
Inonotus obliquus	Water extracts	Colon cancer, cytotoxic/cytostatic liver cancer		Cell lines	[40]

Table 2.
The metabolites found in medicinal mushrooms and their therapeutic potential against cancer.

significance. In the study, one-third of the volunteers reported that the ingestion of psychedelic mushrooms was the single most spiritually significant event of their lives [79].

3.3 Mushroom bioactive metabolites of therapeutic potential

Potential bioactive metabolites studied in medicinal mushrooms and their therapeutic potential against cancer are illustrated in **Table 2**. Secondary metabolites of higher fungi (mushrooms) are an underexplored resource compared to plant-derived secondary metabolites. An increasing interest in mushroom natural products has been noted in recent years [34, 80]. The divergent biosynthetic pathways from farnesyl pyrophosphate to sesquiterpenoids are also described. Selected triterpenoids with novel structures and promising biological activities, including lanostanes and ergostanes, ergosterol are reported from the genus Ganoderma, and the fungi *Antrodia cinnamomea* and *Poria cocos* [81].

4. Therapeutic potential of mushrooms

The major importance of mushrooms is attributed to their medicinal potential that has generated a lot of research interest on a global scale. The great pharmacological and physiological properties of mushrooms are linked to the immune enhancement, maintenance of homeostasis and regulation of biorhythm, management, and prevention of various diseases, quality of life improvement from life-threatening diseases, such as cancer and cardiovascular diseases [19, 27, 82]. Many activities of mushrooms have been reported, such as hypotensive and renal effects [ref], immunomodulatory and antitumor properties of polysaccharide-protein complex (PSPC) from mycelial cultures [9, 14] immunomodulatory and antitumor activities of lectins from edible mushrooms. Due to the great potential benefits of mushrooms to humans, many scientific publications are available to the extent that a database of scientific evidence is available about the specific health effects of mushrooms and their bioactive molecules. These potential benefits include the following:

4.1 Pharmacological properties of mushrooms

4.1.1 Antioxidant property of medicinal mushrooms

The reactive oxygen (ROS) and reactive nitrogen species (RNS) produced from the normal cellular metabolism are generally very reactive as studied for most organic compounds, [11, 33]. They could have either adverse or beneficial effects on living or biological systems [80]. ROS are free radicals made of atoms or molecular fragments with one or more unpaired electrons in their atomic or molecular orbitals [33, 83]. They are naturally produced in the body, especially in organelles like the mitochondria, as intermediates in a variety of normal biochemical and physiological processes, contributing a significant role in many normal cellular processes [30]. However, at high doses, ROS and RNS contribute to the oxidative damage of biological macromolecules, such as DNA, proteins, and lipids of the cell membranes. The damage to cells initiated by the free radicals, especially the damage to DNA, may lead to a significant development of many diseases, such as cancer and other metabolic disorders [22, 69].

Free-radical scavengers are chemicals with the potential to react with free radicals and then neutralize them, thus reducing the damages caused by those

reactive species [55]. Most living body cells produce antioxidant and repair systems that can protect the body against oxidative damage; however, these substances are not enough to prevent or repair the damage completely [30]. The body, therefore, requires the introduction of more antioxidant agents from the diet, which is fundamental for maintaining cell homeostasis and a stable a healthy organism [84]. Although synthetic antioxidants, such as butylhydroxytoluene (BHT), propyl gallate (PG) butylhydroxyanisole (BHA), and *tert*-butylhydroquinone (TBHQ), have been generally used as antioxidant additives in foods for many years, their safety has always been of great public health concern [38], the reason for increased interest in natural antioxidants research.

Many researchers have studied antioxidant activities on extracts and isolated secondary metabolites from edible mushrooms using different tests *in vitro* to evaluate the total antioxidant activity, lipid peroxide inhibitory property, reducing power capacity, the 1,1-diphenyl-2-picrylhydrazyl radical scavenging activity, hydroxyl radical scavenging properties, the ferric reducing antioxidant power, the nitric oxide (NO) scavenging activity, and the ABTS radical scavenging, and the superoxide radical, [13, 49]. A large number of results in the data mining, therefore, clearly indicates that several edible mushrooms have significant antioxidant properties due to their bioactive metabolites, such as polyphenols, polysaccharides, carotenoids, vitamins, and minerals nutrients [11, 19, 53].

4.1.2 Hypocholesterolemic effects

One of the common metabolic disorders such as cardiovascular disease is associated with atherosclerosis, low-density lipid (LDL) oxidation, and hypercholesterolemia, play a role in the regulation of the cholesterol level which is vital for the prevention and treatment of this disease [42, 83]. Edible mushrooms are important food for the management of atherosclerosis due to their high fiber content and low-fat content [16]. In addition, the incorporation of edible mushrooms in a natural hypocholesterolemic and anterosclerotic diet is commonly used in traditional medicine [85]. Studies on the cholesterol-lowering activities of mushrooms were studied in Japan in the early 1960s, and it was demonstrated that rats fed with high fat and high-cholesterol diet supplemented with 5% water of the fruiting bodies of *Lentinus. edodes* for 10 weeks, had a significant dose-dependent decrease in plasma cholesterol concentrations of the animals [31, 82]. The adenosine derivative lentinacin or lentysine, also known as eritadenine [2(R), 3(R)-dihydroxy-4-(9-adenyl)-butyric acid, was later isolated and identified to be one of the active hypocholesterolemic secondary metabolites in the shiitake mushroom [86]. Studies also showed that Eritadenine has been shown to reduce the serum cholesterol level in mice by the acceleration of the excretion of ingested cholesterol and its metabolic breakdown [9, 17, 86]. Eritadenine affects the metabolism of cholesterol, phospholipids, and fatty acids in rats [87]. The dietary supplementation of eritadenine is also considered to decrease phosphatidylcholine biosynthesis through the alteration of the phosphatidylethanolamine concentration [47, 88].

4.1.3 Mushrooms as hypoglycemic agents

Advanced research for traditional plant treatments for diabetes has shown that identified edible mushrooms are an ideal food for the dietetic prevention of hyperglycemia due to their high dietary fiber and protein and low-fat content [69, 89]. Studies have been conducted on the hypoglycemic activity of whole mushrooms and their

fruiting bodies and on mushroom bioactive molecules, including polysaccharides [24] and lectins [90] isolated from the fruiting bodies. In addition, the endo and exopolymers produced in submerged mycelial cultures have been reported to have a hypoglycemic effect [91]. The most common widely used animal models for the study of the hypoglycemic effects of mushrooms are rats and mice with insulin-dependent diabetes mellitus (IDDM), induced by streptozotocin (STZ), and genetically modified diabetic mice with non-insulin [13, 92].

4.1.4 Anticancer activity of mushroom steroids, phenols, and dietary fiber

Within the group of mushroom steroids, the glycosylated form of ergosterol peroxide obtained from the methanol extract of *Cordyceps sinensis* has been shown to be an inhibitor of the proliferation of cell lines, such as the WM-1341, HL-60, K562, Jurkat, and RPMI-8226 tumor cell lines [22, 93]. Anticancer sterol from *Sarcodon aspratus* shows inhibition of the growth of HT29 cancer cells, but not the WI38 normal human fibroblasts [48]. Studies on the anticancer mechanism have indicated that the sterol can induce expression of the cyclin-dependent kinase inhibitor 1A, thereby causing cell cycle arrest and apoptosis in HT29 cells [41, 78, 94]. Phenols can also show anticancer activity as a preventive agent with antioxidant activities that can trigger direct cytotoxicity on cancer cells. Quantitative and qualitative analysis of mushroom mycelia depends on various cultivation conditions, especially considering the substrate for cultivation. Synthetic culture media are known to suppress the generation of important secondary metabolites [50]. Consequently, there is the need for the selection of the most suitable cultivation media for obtaining the most active secondary metabolites of fungal mycelia [51]. **Table 3** illustrates mushroom antitumor polysaccharides and polysaccharide-protein complexes that have progressed to clinical trials studies.

4.1.5 Antiviral properties of mushrooms

Diseases caused by viruses are not treated by common antibiotics and therefore require target-specific drugs. Antiviral properties have been studied not only for whole extracts of mushrooms but also for isolated secondary metabolites derived compounds. These antiviral compounds may act directly through the inhibition of viral enzymes, synthesis of viral nucleic acids, or adsorption and uptake of viruses into the mammalian cells [87, 95]. The direct antiviral activities are effectively demonstrated by smaller molecules. Indirect antiviral activities are due to the immune-stimulating

Taxa origin of isolation	Trade name	Chemical structure	Reference
Grifola frondosa	Fruiting bodies and mycelium polysaccharopeptide (PSP)	D and MD fractions β-D-glucan	[7]
Lentinus edodes	Fruiting bodies polysaccharide krestin (PSK)	Lentinan β-D-glucan	[8]
Trametes versicolor	Mycelial mass PSP, PSK (krestin)	Polysaccharide protein complexes	Polysaccharide protein complexes
Schizophyllum commune	Cultured media broth	Schizophyllan β-D-glucan	[8]

Table 3.
Mushroom antitumor polysaccharide and polysaccharide-protein complexes that have passed clinical trials.

activity of polysaccharides or other complex compounds [33]. Small molecular bioactive compounds with antiviral properties, several triterpenes from *Ganoderma lucidum* such as ganoderiol F, ganodermanontriol, ganoderic acid B, all act as antiviral agents against human immunodeficiency virus IHIV) type 1 (HIV-1) [9, 51, 82]. *In vitro* antiviral activity for influenza viruses type A and B was shown for mycelial extracts of *Kuehneromyces mutabilis* [14], and two isolated phenolic compounds from *Inonotus hispidus* [64, 96] and also ergosterol peroxide identified in several mushrooms.

4.1.6 Mushrooms as antibacterial and antifungal agents

Mushrooms are capable of producing antibacterial and antifungal secondary bioactive compounds as an adaptive defense system to survive in their natural environment. Therefore, they are potential sources of natural antibiotics and many of the external bioactive compounds from extracellular secretions by the mycelium, that can inhibit bacteria [72] and viruses [3, 19]. Several metabolites compounds extracted from mushrooms have been demonstrated to have antifungal and antibacterial properties, especially against *Escherichia coli*, *Staphylococcus aureus*, and *Bacillus subtilis* [24, 49, 79]. The European-derived *Ganoderma* species, *Ganoderma pfeifferi* are known to inhibit the growth of methicillin-resistant *S. aureus* and other bacteria by a new compound sesquiterpenoid hydroquinones [19]. It has also been demonstrated that whole aqueous extracts of this mushroom can inhibit the growth of microorganisms linked to skin problems, such as *Staphylococcus epidermidis*, *Pityrosporum ovale*, and *Propionibacterium acnes* [33].

Infectious diseases caused by microorganisms, such as bacteria, viruses, fungi, or parasites, are among the most serious agents of global morbidity and mortality [23]. Currently, many pathogenic infections are often caused by multi-resistant microorganisms resulting in disease resistance and difficulty for drug therapy; with a well-known example like coronavirus (COVID-19), which is the latest pandemic killing millions of people worldwide. Consequently, the pharmacoeconomic of healthcare costs are on a rapid increase, and of public health concern in many countries [9, 24]. This pandemic situation has led to an increasing search for new chemical entities (lead compounds) of antimicrobial agents from different sources. Several researchers have studied the antimicrobial potential of natural or synthetic compounds of pharmaceutical importance [27]. Thus, natural sources of bioactive compounds mushrooms, are constantly on investigation for finding novel antimicrobial bioactive compounds [23, 38].

In the food industry, contaminants by bacteria and fungi may be a result of exposure to sources of contamination during post-harvest processing (harvesting, processing, and/or packaging process) [12, 64]. Food additives are now widely used in the food industries to enhance and increase the shelf life of food and to prevent the optimal proliferation conditions of microorganisms [14]. It is for this reason that natural antimicrobials, including those isolated from mushrooms, are increasingly popular as potential alternatives to synthetic preservatives, whose safety and impact on human health are still challenging [19, 78]. However, proof of the safety of many natural antimicrobials has been generally recognized in Europe, USA, and in Asia as opposed to sub-Saharan Africa where research is limited [34, 72].

4.1.7 Mushrooms as anti-inflammatory agents

Studies on the ethanolic extracts and a proteoglycan from *P. linteus* have shown potential anti-inflammatory activity some *in vitro* tests, such as in the

collagen-induced arthritis, the croton oil-induced ear edema test in mice, and antinociceptive effect in the writhing test [69, 71, 83]. Other bioactive compounds effectively elucidated in the writhing test include the ganoderic acids A, B, G, and H, isolated from *G. lucidum*. These compounds demonstrated a stronger anti-inflammatory activity in the animal model than acetylsalicylic acid [12, 45]. Methanolic extract of *Pleurotus pulmonarius* fruiting bodies at doses (500 and 1000 mg/kg) reduced carrageenan-induced and formalin-induced paw edema in mice. The activity was comparable to the reference diclofenac (10 mg/kg). The IC50 value for hydroxyl-radical scavenging was recorded as 476 mg/ml and for lipid peroxidation inhibition 960 mg/ml [11, 89]. The edible mushroom *Gaylussacia frondosa* is known to contain ergosterol, ergosta-4-6-8, 22-tetraen3-one, and 1-oleoyl-2-linoleoyl-3-palmitoylglycerol, which can potentially inhibit cyclooxygenases I and II activity [76].

4.1.8 Mushrooms as hepatoprotective agents

Early studies on bioactive compounds, ganoderic acids R and S and ganosporeric acid A from *Gonaderma lucidum* have shown *in vitro* antihepatotoxic activity in the galactosamine-induced cytotoxic test using primary cell-cultured rat hepatocytes [2, 44]. Further *in vivo* study of two fractions of total triterpenoids extract of *G. lucidum* (75% ethanol) demonstrated a protective activity in mice against hepatic necrosis induced by chloroform and D-galactosamine, respectively. The hepatoprotective properties were more associated with the scavenging promoting capacity of enzymes for hepatic free radicals in mice, and hence the increase in the antioxidant activity in mice [44, 45]. In addition to the widely investigated psychoactive mushrooms like *Amanita muscaria* or *Psilocybe* spp., some bioactive compounds mushroom extracts have shown special central nervous effects of pharmacological interest. Phenol-analogous compounds like (hericenons C, D, E, F, G, H) from *Holothuria erinaceus* are capable of inducing the synthesis of nerve growth factors, potential improved effect in Alzheimer's dementia [48]. Erinacin E from *Hericium coralloides* fermentation broth is a highly selective agonist at the kappa opioid receptor with (IC50 of 0.8 mM, receptor binding at the m opioid receptor with an I 50 of >200 mM). These metabolites could exhibit antinociceptive activity without little side effects observed with m receptor agonists like morphine [35]. Biochemical screening of selected basidiomycetes has shown inhibitory effects of *G. applanatum*, *H. annosum*, *P. betulinus*, *Fomitopsis pinicola*, and *Daedaleopsis confragosa* on neutral endopeptidase (enkephalinase) (IC50 values between 40 and 55 mg/ml) [93].

4.1.9 New approaches for cancer therapy with mushroom bioactive compounds (vaccinotherapy)

Vaccine preparations with preventive activities against liver and cervical cancer associated with hepatitis B and human papillomatosis infections have been developed in Belgium and USA [66]. Currently, there is no commercialized vaccine for the protection of existing tumors, metastases, or relapses [3, 19]. The addition of immunomodulating substances of natural and synthetic origin to vaccines has shown promising potential to sufficiently enhance their anticancer properties. Therefore,

there were high doses and schemes of *L. edodes* polysaccharide fraction administration in combination with a vaccine based on autological glycopeptides of Ehrlich's carcinoma, Sarcoma 37, LLC, L1210, and B16 cell lines [66]. Such preparations were prepared to improve the cytolytic activity of lymphocytes, the metabolic activity of peritoneal macrophages, and the cytolytic activation of blood plasma serum in the presence of complement in intact animals and in sarcoma-bearing animals [3, 47]. The recent identification of an immunomodulating protein Ling Zhi-8 has been reported from mycelia of *G. lucidum* with stimulatory activity on dendritic cells [67]. Industrial amplification of recombinant protein Ling Zhi-8 has been elucidated using a well-developed patented yeast system.

5. Mushroom toxicity

Since prehistoric times humans have heavily consumed mushrooms for nutritional and therapeutic use. Mushroom toxicity has also been known since man started the consumption of mushrooms, and has been the cause of death of many historical figures, including the Roman Emperor Claudius [3, 77]. Currently, several mushrooms are cultivated commercially, but foraging for mushrooms has gained popularity as a form of recreational activity in the community. Mushroom poisonings increasingly are common due to a lack of knowledge by foragers to identify and distinguish a poisonous mushroom species from edible species, and in some cases, problems occur as intentional ingestions [9, 31, 86]. Mushroom poisonings may an indication from a benign symptom of generalized gastrointestinal upset to very devastating outcomes that include liver failure, kidney failure, and neurologic disorders. Up to 14 described syndromes are documented, which manifest depending on the mushroom species, toxins, and quantity ingested [11, 94]. The mushroom poisoning symptoms are related to the toxin ingested, which include amatoxin, psilocybin, muscarine, coprine, allenic norleucine, gyromitrin, etc. [3, 7, 89]. Within the several mushroom species, there are about 100 species that are toxic in nature. Annual ingestion is recorded at a level of about 6000 ingestions yearly alone in the United States, and out of these, over 50% of the exposures are pediatric in nature, recorded in children under 6 years of age [88]. Most poisonings exhibit symptoms mainly of gastrointestinal upset, which is a common feature across several toxidromes, and this is most likely to occur with ingestions of small quantities of toxic mushrooms. Severe mushroom poisonings that take place, are primarily a consequence of misidentification by adults foraging for wild mushrooms who consume them as food [3, 14]. A summary table of Mushroom toxicity effects, symptoms, and examples of Mushrooms having the toxin has been illustrated in **Table 4**.

5.1 Pathophysiology of mushroom poisoning

The clinical presentation differs depending on the species of mushroom and toxin ingested. For **Acute gastroenteritis**: Most often secondary to one of a variety of "backyard mushrooms" such as *Chlorophyllum molybdites*. In most cases are developing symptoms of nausea, vomiting, gastrointestinal upset like abdominal cramping and possibly diarrhea associated with ingestion accounting for most of the reported poisonings [31, 90]. The symptoms of poisoning are manifested usually or typically within 1–3 hours of ingestion [3].

Class of toxins	Toxicity	Effects and examples of mushrooms having the toxin
Alpha-amanitin	Death	Main causes of fatal liver damage a day after ingestion. The principal toxin is the death cap (*Amanita phalloides*)
Phallotoxin	Non-lethal	Main cause of the severe gastrointestinal disorder. Common in most mushrooms eg *Gomphus automnalis*
Orellanine	Deadly	A redox cycler similar to pesticide paraquat. Main cause of kidney failure mostly 3 weeks after ingestion. Principal example is the genus Continarius
Monomethylhydrazine (MMH)	Deadly	Causes brain damage, seizures, gastrointestinal disorder, hemolysis. And metabolic poison. Principal toxin associated in genus Gyromitra. Antidote is administration of large doses of intravenous pyridoxine hydrochloride
Coprine	Not lethal	Causes adverse effects when consumed in combination with alcohol. Principal toxin in genus is coprinus
Ibotenic acid	Potentially lethal	Excitotoxin. Principal toxin in *Amanita muscarin*. *A pantherina*. *A gemmata*
Muscimol	Phytoactive	Causes central nervous depression and hallucination. Principal toxin in *Amanita muscaria*, *A pahtherina*, and *A gemmate*.
Psilocybin and psilocin	Phytoactive	Causes CNS activation and hallucinations. Principal side effects are from psilocybin mushrooms, many of which belong to the genus Psilocybin (often used as recreational drugs
Arabitol	Non-lethal	Causes diarrheal in some subjects.
Bolestatine	Non-lethal	Causes stomach upset, nausea and vomiting.
Ergotamine	Deadly	Affect the vascular system and can lead to loss of limb, cardiac arrest. Found in the genus Claviceps.

Table 4.
Of mushroom toxicity effects, symptoms, and examples of mushrooms having the toxin [12, 86, 95].

Hallucinations: The main cause is produced by the bioactive compounds from psilocybin and psilocin from the mushroom species such as *Psilocybe*, *Conocybe*, *Gymnopilus*, and *Panaeolus*. These chemically bioactive compounds act as agonists or partial agonists at 5-hydroxytryptamine (5-HT) subtype receptors [19, 40]. These species of mushrooms are cultivated for recreational purposes as substances of abuse, although they can grow naturally in warm, moist climates. The mushroom can be ingested as fresh mushroom caps or dried mushrooms preparations and can cause altered sensorium and euphoria occurring 30 minutes to 2 hours after ingestion that can last for about 4–12 hours, depending on the quantity ingested [24].

Cholinergic toxicity: This is caused by muscarine-containing mushroom in the genera *Clitocybe* and *Inocybe*. *Amanita muscari* contains small amounts of muscarine, but the concentrations are generally low to cause a cholinergic effect. Cholinergic effects, however, of diaphoresis, salivation, lacrimation, bronchospasm, abdominal cramping, bronchorrhea, and bradycardia generally may occur within 30 minutes of ingestion, and the duration is dose-dependent and usually short-lived as compared to other pesticide-related cholinergic poisoning [95].

Disulfiram-like reaction: Caused by coprine-containing species such as *Coprinus atramentarius*, known as inky cap mushrooms. The toxin's bioactive metabolites can result in the inhibition of aldehyde dehydrogenase causing headache, nausea,

vomiting, flushing, tachycardia, and in rare cases hypotension. The adverse effect is very obvious and only occurs in cases where alcohol is ingested a few hours to days after the consumption of coprine-containing mushrooms. Co-ingestion of alcohol and the toxin can lead to reduced toxic effects due to slower metabolism of coprine to its toxic secondary metabolites [8, 15].

5.2 Mushroom liver toxicity

Toxicity from different species can be caused by amatoxin observed in species like *Galerina*, *Lepiota* and particularly *Amanita* [41]. The toxins can disrupt RNA polymerase II, resulting in cellular level protein deficiency. The toxicity consists of three distinct phases. Gastrointestinal effects can be observed typically 6–12 hours after ingestion, followed by a quiescent phase of 24–36 hours after ingestion with a symptomatic improvement [8, 14, 69]. During the quiescent phase, there may be clinical signs of hepatotoxicity. After 48 hours of ingestion, hepatic damage increases, leading to liver failure and other related clinical complications. Lethal occurrence recorded in mushroom toxicity may occur within a week in severe cases or require liver transplantation.

5.3 Nephrotoxicity

Nephrotoxic agent orellanine is produced by the genus *Cortinarius* producing renal complications in which the symptoms may be delayed for 1–2 weeks after ingestion [75]. Nephrotoxicity can lead to the production of allenic norleucine usually observed in *Amanita smithiana*, but this can also be seen in other *Amanita* species. *Amanita smithiana* is well distributed in the United States [94], and their typical toxic symptoms include acute gastroenteritis leading to renal injury within 12–24 hours. Although some subjects with toxicity may require hemodialysis, in most patient's full recovery with appropriate supportive care is possible [8, 27]. Cases of seizures can be due to the presence of gyromitrin in *Gyromitra*, *Paxina*, and *Cyathipodia micropus* species, although can be less common in the latter two. Mushroom foragers in search for morel (*Morchella esculenta*) may accidentally ingest *Gyromitra* and toxicity could result from a metabolite, monomethylhydrazine, that may potentially lead to secondary product pyridoxine (B6) and up with GABA depletion. With GABA depletion, the occurrence of seizures may be intractable to anticonvulsant therapy and may require supplemental treatment including pyridoxine [78, 82].

Other manifestations due to the wide range of mushrooms that foragers could accidentally several other clinical manifestations have been documented and reported such as vertigo, somnolence, headaches, palpitations, dysrhythmias, rhabdomyolysis (*Tricholoma equestre*), methemoglobinemia, hemolysis (*Paxillus involutus*), erythromelalgia (acromelic acid), dermatitis (shiitake mushrooms), and cramping [4, 22, 55].

5.4 Toxicity evaluation, treatment, and management

Toxicity evaluation is usually guided by many regulatory and clinical presentations, and may include:

Systematic and regular observation without testing in asymptomatic low-risk subjects, Serum electrolytes, kidney function testing, urinalysis, Serum creatinine kinase (CK), Liver enzymes, coagulation analysis, and complete blood count study

[37, 44, 91]. In critical highly symptomatic subjects, target specific studies based on the symptoms of hepatic failure, altered mental status, hypoxia or respiratory distress can be performed [44]. Treatment of many possible symptoms mainly consists of supportive care. Depending on the period or time of ingestion, activated charcoal or chelating agents may be used for clinical intervention to provide some health benefit [82]. Acute gastrointestinal manifestation may benefit from rehydration and antiemetics in response to correction of any electrolyte imbalance [12, 20, 92]. For most patients showing adverse hallucinations, benzodiazepines administration may provide anxiolysis. Cholinergic toxicity may be managed from the administration of anticholinergic agents such as glycopyrrolate or atropine [76], with consideration of the administration of Atropine 0.5–1 mg IV adults or 0.01 mg/kg for cases of pediatric patients [29, 55].

In some specific cases, patients with refractory seizures due to gyromitra ingestion, administration of pyridoxine (B6) could be at 25 mg/kg IV can be given as treatment or as prophylactic for seizure control, or in some cases, benzodiazepines could be an alternative [21, 97] In case of patients ingesting amatoxin, consideration of the administration of N-acetylcysteine (NAC), silibinin, and penicillin can be used for treatment intervention. Clinical toxicologists and other health practitioners are advised to evaluate and manage patients in consultation with the local poison control (toxicovigilance center) or toxicology resource. Complications of ingestion depend on the toxin ingested and may range from dehydration in benign cases to renal failure, liver failure, and death in severe toxicities [89, 91]. Most mushroom poisonings result in mild to moderate gastrointestinal manifestations which include nausea, vomiting, and diarrhea. Other varieties of disorders that may lead to organ failure and even death her been reported and therefore it is important for foragers to know that there are many differing mushroom species with potential morphological similarities; very challenging in particular for those who are new in the mushroom collection as a new hobby. An understanding of local edible and toxic mushroom species is the key for amateur foragers, especially as the onset of just mild nausea will require evaluation as this could be an early manifestation of severe illness [3, 11].

5.5 Stages of amanita poisoning

Amatoxin poisoning and stages of pathology have four phases as described.

Phase 1: The latency or lag period that may occur within 10–12 hours after ingestion, with the toxins absorbed via the digestive system and subject to the assault of the kidneys and liver.

Phase 2: Gastrointestinal phase. This is the onset of symptoms like severe abdominal pains, nausea, vomiting, diarrhea, delirium, hallucinations, hypoglycemia, and life-threatening dehydration.

Phase 3: Manifestation of severe gastrointestinal complications, a brief remission of symptoms after 3–4 days. The onset of jaundice, renal failures, toxic hepatitis, liver enlargement, liver hemorrhage.

Phase 4: Manifestation of lethality. Death can occur within 6–8 days after ingestion as a result of liver and kidney failure, followed by cardiac dysfunction.

The main challenge for the treatment of mushroom poison is the fact that there is no known antidote. Therefore, an immediate evacuation of gastrointestinal tract fluids, hemodialysis, slurry of activated charcoal, supportive measures, and if all else

fails, administering a liver transplant can be timely [41, 50]. The use of thioctic acid in glucose delivered intravenously has been recommended by some experts. Bastien treatment like the use of vitamin C, nifuroxazide and dihydrostreptomycin, fluids, electrolytes, and penicillin are also applicable [89].

5.6 Chemical test for mushroom toxicity

The Meixner mushroom toxicity test can be used to determine whether a particular mushroom contains amatoxins. The stalk or cap is crushed to a piece of newsprint or other crude paper containing lignin. This crushed mass is allowed to dry and a small drop of concentrated hydrochloric acid is added. The presence of a blue color appearing in 5–10 minutes is an indication that amatoxins are present. This procedure involves an acid-catalyzed reaction of the lignin in the paper with the alpha amatoxin as the main structure as is well illustrated in **Figure 12** showing the structure of alpha amanita [5, 37, 40].

5.7 Orellanine poisoning and symptoms

Orellanine poisoning symptoms are similar to poisoning induced by amatoxins. However, muscular pain, excessive thirst, and painful urination may occur after 36 hours and could be delayed as long as 1–2 weeks after ingestion [86]. Orellanine invades and destroys the kidney tubules and in extremely severe cases, the treatment may require blood dialysis or kidney transplant. Lethalities in some cases have been

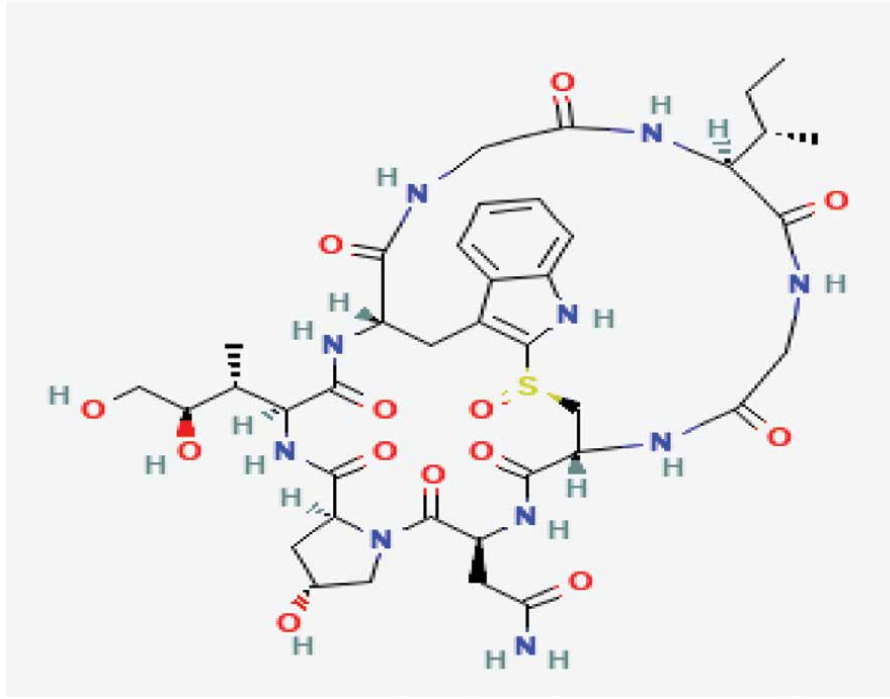

Figure 12.
Alpha amanitin (alpha-amanitin, 4-(2-mercapto-L-tryptophan)-(compound).

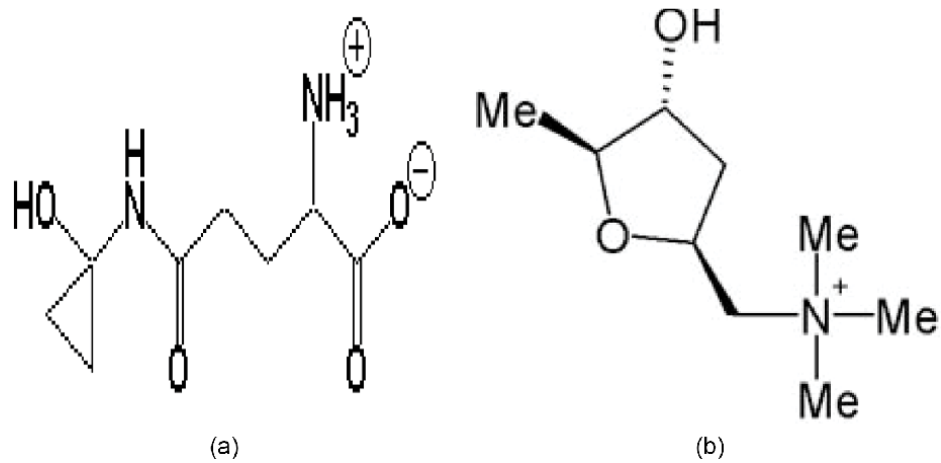

Figure 13
(a) A coprine (antabuse-like-disulfiram-like poisoning). *(b) Muscarine (me = methyl group –CH).*

reported, and therefore orellanine poisoning needs to be considered in cases when kidney failure occurs from an unknown cause. Toxic cyclopeptides from cortinarins may be present in some cases and could play a vital role in *Cortinarius* poisonings. There are about 800 recorded species of *Cortinarius* in North America, all of which are health risks for consumers. Mushrooms produced by members of the genus *Cortinarius* are characterized by the possession of a cobweb-like cortina that is the remnant of the partial veil covering the gills and potentially neurotoxic to the autonomic nervous system. Coprine structure of Antabuse-like disulfiram-like poisoning and muscarine are illustrated in **Figure 13a** and **b**.

5.8 Toxin found in certain species of *Coprinus*

Coprinus atramentarius also known as, *Coprinopsis atramentaria*, *Coprinus quadrifidus*, and the *Coprinopsis variegate* produce toxins that can bind to molybdenum and prevents normal acetaldehyde dehydrogenase activity, inhibiting ethanol metabolism [25]. Coprine poisoning is similar to acetaldehyde poisoning and symptoms begin 30 minutes to 1 hour after drinking alcohol when taken in 4–5 days after eating mushrooms or along with mushrooms. Symptoms include flushing of the neck and face, metallic taste in the mouth, tingling sensations in the limbs, numbness in the hands. Headache, throbbing of the neck veins, chest pains, nausea, vomiting, and sweating. Recovery from toxicity may be possible within several hours after ingestion [94].

5.9 Gastrointestinal irritants

Many varieties of undetermined toxins associated with wild mushrooms have been reported. On ingestion, the toxins may cause gastrointestinal disorders, such as nausea, vomiting, diarrhea, abdominal cramps that may occur after 30–90 minutes of ingestion. Symptoms generally may disappear spontaneously in 3–4 hours, and complete recovery can take place after 24 hours or more. Treatment strategy includes

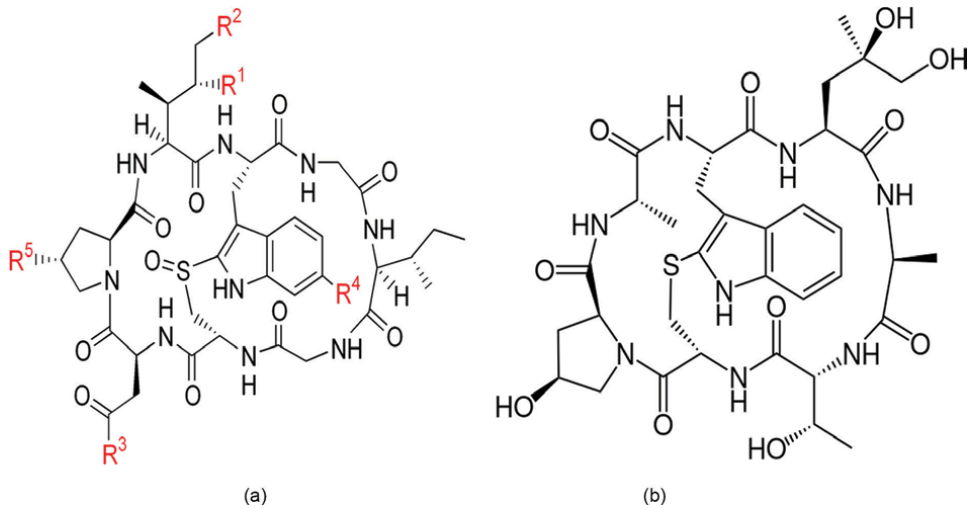

Figure 14.
Amatoxins and phallotoxins in toxic mushroom Amanita phalloides. (a) The backbone structure (black) is the same in all the amatoxins and five variable groups (red) determine the specific compound. (b) Phalliodin and Phallacidin constitute the main component structure of Phallotoxin.

emptying the stomach content, monitoring for possible dehydration, reduced blood pressure, and abnormal kidney function [17, 82].

6. Most common toxic mushrooms in Cameroon

In the forest of the Upper Nyong valley of Cameroon, some varieties of toxic mushrooms have been identified with other medicinal mushrooms. The intensive activities during the rain for mushroom harvesting come with accidental ingestion of toxic varieties, which can sometimes be fatal. Most cases of mushroom severe intoxication are linked to the dead cap mushrooms variety (*Amanita phalloides*), which is very toxic and quite common in the forests. Due to its high toxicity and common presence in our forests, *Amanita phalloides* is the most dangerous mushroom and the cause of the majority of fatal poisonings in Cameroon and the Centra African regions [14, 69]. Toxin compound amatoxins and phallotoxins are shown in **Figure 14**. A summary list of the most common toxic mushroom in Cameroon is illustrated in **Figure 15** as a guide to support mushroom foragers during field expeditions.

The list of most common toxic mushroom and edible species which they are often confused are indicated in **Figure 15**.

7. Conclusions

Mushroom is a very vital source of protein intake but some precautions should be taken for consumption and field identification of edible mushrooms. Those that cannot be identified or recognized properly should not be harvested and eaten. Cultivation of known species of mushrooms should be practiced so as to serve time

Figure 15.
The list of most common toxic mushroom and edible species which they are often confused. (a) Amanita phalloides. (b) Cortinarius orellanus. (c) Amanita verna. (d) Gyromitra esculenta. (e) Agaricus muscraris. (f) Amanita muscaria. (g) Omphalotus olearius. (h) Tricholoma pardinum. (i) Inocybe rimosa. (j) Lepiota brunneoincarnata. (k) Clitocybe dealbata. (l) Boletus satanas.

and avoid eating the poisonous ones and more advice must be taken by minors not to eat any mushrooms without showing it to parents or elderly person for proper recognition. Most mushrooms are consumed directly in different menus for healthy and medicinal purposes with contribution from their additive and synergistic effects of the bioactive compounds. The nutraceutical and therapeutic significance of mushrooms are well documented, although specific mechanisms of actions of the bioactive compounds and the many various health potentials to humans are still a subject of continuous research and intensive investigation, especially with the emergence of new technology and high throughput screening battery for new compounds, evaluation of pharmacological properties for documenting new findings of mushroom potential health benefits. The studies for the exploration of cultivated mushrooms

and isolation, chemical characterization of their secondary metabolites, and evaluation for pharmacological activities, with mechanistic based potential therapeutic evidence, is still a big challenge for researchers, and therefore mushrooms still remain an area of great research potential to generate more research interest in pharmaceutical and toxicity studies.

The complex pharmacologic and nutraceutical potential of mushrooms may be integrated not only through inhibition of certain cancer-specific processes or targeted activation of tumor-specific apoptosis, but also through indirect actions such as immunomodulation, hepatoprotection, and antioxidation. Another research dimension of mushrooms is in studying the mechanisms of action and targets of the natural products and their derivatives for different therapeutic endpoints for proof of concepts in phototherapeutics.

Acknowledgements

The work was supported by the Mobilization Research Grant of Ministry of Higher Education of the Republic of Cameroon. Support from the Small Grant projects of the Ministry of Agriculture and Rural Development (MINADER), of the Republic of Cameroon is highly appreciated.

Conflict of interest

The authors declare that there are no conflicts of interest between them for this manuscript.

Authors contribution

This work was carried out in collaboration among all authors. Author ETF, DJF FCN, MGA designed the study, TMV, LEA, and MEB conducted data mining and wrote the first draft of the manuscript. All authors read and approved the final manuscript.

Author details

Estella Tembe Fokunang[1], Mbong Grace Annih[2], Lem Edith Abongwa[3], Manju Evelyn Bih[4], Tchadji Mayoudom Vanessa[1], Dobgima John Fomnboh[5] and Charles Fokunang[1*]

1 Faculty of Medicine and Biomedical Sciences, Department of Pharmacotoxicology and Pharmacotoxicity, University of Yaoundé 1, Cameroon

2 Faculty of Science, Department of Plant Science, University of Dschang, Dschang, Cameroon

3 Faculty of Science, Department of Biological Sciences, University of Bamenda, Cameroon

4 Department of Plant Science, College of Technology, The University of Bamenda, Cameroon

5 Department of Nutrition, Food and Bioresource Technology, College of Technology, The University of Bamenda, Cameroon

*Address all correspondence to: charlesfokunang@yahoo.co.uk

IntechOpen

References

[1] Sushila R, Dharmender R, Rathee D, Kumar V, Rathee P. Mushrooms as therapeutic agents. Brazilian Journal of Pharmacognosy. 2012;**22**(2):459-474

[2] Wasser SP, Biomed J. Medicinal mushroom science: Current perspectives, advances, evidences, and challenges. Biomed J. 2014;**37**(6):345-356. DOI: 10.4103/2319-4170.138318

[3] Balandaykin ME, Zmitrovich IV. Review on Chaga medicinal mushroom, Inonotus obliquus (Higher Basidiomycetes): Realm of medicinal applications and approaches on estimating its resource potential. International Journal of Medicine Mushrooms. 2015;**17**(2):95-104

[4] White J, Weinstein SA, De Haro L, Bédry R, Schaper A, Rumack BH, et al. Mushroom poisoning: A proposed new clinical classification. Toxicon. 2019;**157**:53-65

[5] Money NP. Are mushrooms medicinal? Fungal Biology. 2016;**120**(4):449-453

[6] Berovic M. Cultivation of medicinal mushroom biomass by solid-state bioprocessing in bioreactors. Advanced Biochemical Enginerring and Biotechnology. 2019;**169**:3-25

[7] Liu X, Yu Z, Jia W, Wu Y, Wu D, Zhang H, et al. A review on linking the medicinal functions of mushroom prebiotics with gut microbiota. International Journal of Medical Mushrooms. 2020;**22**(10):943-951

[8] Wong JH, Ng TB, Chan HHL, Liu Q, Man GCW, Zhang CZ, et al. Mushroom extracts and compounds with suppressive action on breast cancer: Evidence from studies using cultured cancer cells, tumor-bearing animals, and clinical trials. Applied Microbiology and Biotechnology. 2020;**104**(11):4675-4703

[9] Friedman MJ. Chemistry, Nutrition, and Health-Promoting Properties of Hericium erinaceus (Lion's Mane) Mushroom fruiting bodies and mycelia and their bioactive compounds. Agricultural Food Chemistry. 2015;**63**(32):7108-7123

[10] Venturella G, Ferraro V, Cirlincione F, Gargano ML. Medicinal mushrooms: Bioactive compounds, use, and clinical trials. International Journal of Molecular Sciences. 2021;**22**(2):634

[11] Yasin H, Zahoor M, Yousaf Z, Aftab A, Saleh N, Riaz N, et al. Ethnopharmacological exploration of medicinal mushroom from Pakistan. Phytomedicine. 2019;**54**:43-55

[12] Chang ST, Wasser SP. Current and future research trends in agricultural and biomedical applications of medicinal mushrooms and mushroom products (Review). International Journal of Medical Mushrooms. 2018;**20**(12): 1121-1133

[13] Largeteau ML, Llarena-Hernández RC, Regnault-Roger C, Savoie JM. The medicinal Agaricus mushroom cultivated in Brazil: Biology, cultivation and non-medicinal valorisation. Applied Microbiology and Biotechnology. 2011;**92**(5):897-907

[14] Zhu T, Kim SH, Chen CY. A medicinal mushroom: *Phellinus linteus*. Current Medical Chemistry. 2008;**15**(13):1330-1335

[15] Wasser SP. Medicinal mushrooms in human clinical studies. Part I.

Anticancer, oncoimmunological, and immunomodulatory activities: A review. International Journal of Medical Mushrooms. 2017;**19**(4):279-317

[16] Muszyńska B, Kała K, Firlej A, Sułkowska-Ziaja K. *Cantharellus cibarius*—Culinary-medicinal mushroom content and biological activity. Acta Poloniae Pharmaceutica. 2016;**73**(3):589-598

[17] Li IC, Lee LY, Tzeng TT, Chen WP, Chen YP, Shiao YJ, et al. Neurohealth properties of *Hericium erinaceus* mycelia enriched with Erinacines. Behavioral Neurology. 2018;**2018**:5802634

[18] He X, Wang X, Fang J, Chang Y, Ning N, Guo H, et al. Structures, biological activities, and industrial applications of the polysaccharides from *Hericium erinaceus* (Lion's Mane) mushroom: A review. International Journal of Biological Macromolecules. 2017;**97**:228-237

[19] Zaidman BZ, Yassin M, Mahajna J, Wasser SP. Medicinal mushroom modulators of molecular targets as cancer therapeutics. Applied Microbiology and Biotechnology. 2005;**67**(4):453-468

[20] Yamanaka D, Liu Y, Motoi M, Ohno N. Royal sun medicinal mushroom, *Agaricus brasiliensis* Ka21 (higher Basidiomycetes), as a functional food in humans. International Journal of Medical Mushrooms. 2013;**15**(4):335-343

[21] Zhang BB, Guan YY, Hu PF, Chen L, Xu GR, Liu L, et al. Production of bioactive metabolites by submerged fermentation of the medicinal mushroom Antrodia cinnamomea: Recent advances and future development. Critical Reviews in Biotechnology. 2019;**39**(4):541-554

[22] Anjana Shree KG, Balamurugan TSB, Manivasagan V, Ramesh Babu NG. Phytochemical, antioxidant and antitumor activity of edible mushroom *Pleurotus ostreatus*. International Journal of Advanced Research and Biological Sciences. 2016;**3**(9):170-177

[23] 22.Alves MJ, Ferreira IC, Martins A, Pintado M. Antimicrobial activity of wild mushroom extracts against clinical isolates resistant to different antibiotics. Journal of Applied Microbiology. 2012;**113**:466-475. DOI: 10.1111/j.1365-2672.2012.05347.x

[24] Xin M, Ji X, De La Cruz LK, Thareja S, Wang B. Strategies to target the hedgehog signaling pathway for cancer therapy. Medical Research Review. 2018;**38**:870-913

[25] Namikawa T, Fukudome I, Ogawa M, Munekage E, Munekage M, Shiga M, et al. Clinical efficacy of protein-bound polysaccharide K in patients with gastric cancer undergoing chemotherapy with an oral fluoropyrimidine (S-1). European Journal of Surgical Oncology. 2015;**41**:795-800

[26] Fritz H, Kennedy DA, Ishii M, Fergusson D, Fernandes R, Cooley K, Seely D. Polysaccharide K and Coriolus versicolor Extracts for Lung Cancer: A Systematic Review. Integrative Cancer Therapies. 2015;**14**:201-211. https://doi.org/10.1177/1534735415572883.

[27] Jiang JH, Thyagarajan-Sahu A, Loganathan J, Eliaz I, Terry C, Sandusky GE, et al. BreastDefend (TM) prevents breast-to-lung cancer metastases in an orthotopic animal model of triple-negative human breast cancer. Oncology Reports. 2012;**28**:1139-1145

[28] Stamets P. Trametes versicolor (Turkey Tail Mushrooms) and the treatment of breast cancer. Global Advanced Health Medicine. 2012;**1**:20

[29] Standish LJ, Dowd F, Sweet E, Dale L, Weaver M, Osborne B, et al. Breast cancer integrative oncology care and its costs. Integrative Medicine (Encinitas). 2017;**16**:85-95

[30] Guggenheim AG, Wright KM, Zwickey HL. Immune modulation from five major mushrooms: Application to integrative oncology. Integrative Medicine (Encinitas). 2014;**13**:32-44

[31] Jiang J, Sliva D. Novel medicinal mushroom blend suppresses growth and invasiveness of human breast cancer cells. International Journal of Oncology. 2010;**37**:1529-1536

[32] Adams C. Uncloaking the Mysteries of Medicinal Mushrooms. Nutraceuticals World: http://www.nutraceuticalsworld.com/issues/2008/10/view_features/uncloaking-the-mysteries-of-medicinal-mushrooms/ [Accessed November 28, 2011]

[33] Hypericum Depression Trial Study Group. Effect of *Hypericum perforatum* (St John's Wort) in Major Depressive Disorder: A Randomized Controlled Trial. JAMA. 2002;**287**:1807-1814

[34] Linde K, Berner M, Egger M, Mulrow C. St. John's Wort for depression: Meta-analysis of randomised controlled trials. BJP. 2005;**186**:99-107

[35] Lu X, Guo J, Hsieh T. PC-SPES inhibits cell proliferation by modulating p21, cyclins D, E and band multiple cell cycle-related genes in prostate cancer cells. Cell Cycle. 2003;**2**:59-63

[36] Snitz BE, O'Meara ES, Carlson MC, Arnold AM, Ives DG, Rapp SR, et al. Ginkgo biloba for preventing cognitive decline in older adults: A Randomized Trial. JAMA. 2009;**302**:2663-2670

[37] Solomon PR, Adams F, Silver A, Zimmer J, DeVeaux R. Ginkgo for memory enhancement: A Randomized Controlled Trial. JAMA. 2002;**288**:835-840

[38] Zaidman B, Yassin M, Mahajna J, Wasser SP. Medicinal mushroom modulators of molecular targets as cancer therapeutics. Applied Microbiology and Biotechnology. 2005;**67**:453-468

[39] Reis FS, Pereira E, Barros L, Sousa MJ, Martins A, Ferreira ICF. Biomolecule profiles in inedible wild mushrooms with antioxidant value. Molecules. 2011;**16**:4328-4338

[40] Choi D, Park SS, Ding JL, Cha WS. Effects of Fomitopsis pinicola extracts on antioxidant and antitumor activities. Biotechnology and Bioprocess Engineering. 2007;**12**:51624

[41] Yoshikawa K, Inoue M, Matsumoto Y, Sakakibara C, Miyataka H, Matsumoto H, et al. Lanostane triterpenoids and triterpene glycosides from the fruit body of Fomitopsis pinicola and their inhibitory activity against COX-1 and COX-2. Journal of Natural Products. 2005;**68**:69-73

[42] Ren G, Liu XY, Zhu HK, Yang SZ, Fu CX. Evaluation of cytotoxic activities of some medicinal polypore fungi from China. Fitoterapia. 2006;**77**:408-410

[43] Shnyreva AV, Shnyreva AA, Espinoza C, Padron JM, Trigos A. Antiproliferative activity and cytotoxicity of some medicinal wood-destroying mushrooms from Russia. International Journal of Medical Mushrooms. 2018;**20**:1-11

[44] Wang Y, Cheng X, Wang P, Wang L, Fan J, Wang X, et al. Investigating migration inhibition and apoptotic effects of Fomitopsis pinicola chloroform extract on human colorectal cancer SW-480 cells. PLoS One. 2014;**9**:e101303

[45] Wu HT, Lu FH, Su YC, Ou HY, Hung HC, Wu JS, et al. In vivo and in vitro anti-tumor effects of fungal extracts. Molecules. 2014;**19**:2546-2556

[46] Colomer R, Sarrats A, Lupu R, Puig T. Natural polyphenols and their synthetic analogs as emerging anticancer agents. Current Drug Targets. 2017;**18**:147-159

[47] Thongbai B, Rapior S, Hyde KD, Wittstein K, Stadler M. *Hericium erinaceus*, an amazing medicinal mushroom. Mycological Progress. 2015;**14**:91

[48] Boddy L, Crockatt ME, Ainsworth AM. Ecology of *Hericium cirrhatum*, *H. coralloides* and *H. erinaceus* in the UK. Fungal Ecology. 2011;**4**:163-173

[49] He X, Wang X, Fang J, Chang Y, Ning N, Guo H, et al. Structures, biological activities, and industrial applications of the polysaccharides from Hericium erinaceus (Lion's Mane) mushroom: A review. International Journal of Biological Macromolecules. 2017;**97**:228-237

[50] Khan MA, Tania M, Liu R, Rahman MM. Hericium erinaceus: An edible mushroom with medicinal values. Journal of Complementary Integrative Medicine. 2013;**10**

[51] Friedman M. Chemistry, nutrition, and health-promoting properties of *Hericium erinaceus* (Lion's Mane) mushroom fruiting bodies and mycelia and their bioactive compounds. Journal of Agricultural and Food Chemistry. 2015;**63**:7108-7123

[52] Phan CW, David P, Naidu M, Wong KH, Sabaratnam V. Therapeutic potential of culinary-medicinal mushrooms for the management of neurodegenerative diseases: Diversity, metabolite, and mechanism. Critical Reviews in Biotechnology. 2015;**35**:355-368

[53] Li G, Yu K, Li F, Xu K, Li J, He S, et al. Anticancer potential of *Hericium erinaceus* extracts against human gastrointestinal cancers. Journal of Ethnopharmacology. 2014;**153**:52130

[54] Kim SP, Nam SH, Friedman M. *Hericium erinaceus* (Lion's Mane) mushroom extracts inhibit metastasis of cancer cells to the lung in CT-26 colon cancer-tansplanted mice. Journal of Agricultural and Food Chemistry. 2013;**61**:4898-4904

[55] Kim SP, Kang MY, Choi YH, Kim JH, Nam SH, Friedman M. Mechanism of *Hericium erinaceus* (Yamabushitake) mushroom-induced apoptosis of U937 human monocytic leukemia cells. Food Functionals. 2011;**2**:348-356

[56] Qin T, Ren Z, Huang Y, Song Y, Lin D, Li J, et al. Selenizing Hericium erinaceus polysaccharides induces dendritic cells maturation through MAPK and NF-kappaB signaling pathways. International Journal of Biological Macromolecules. 2017;**97**:287-298

[57] Sheng XT, Yan JM, Meng Y, Kang YY, Han Z, Tai GH, et al. Immunomodulatory effects of Hericium erinaceus derived polysaccharides are mediated by intestinal immunology. Food & Function. 2017;**8**:10207

[58] Lu CC, Huang WS, Lee KF, Lee KC, Hsieh MC, Huang CY, et al. Inhibitory effect of Erinacines A on the growth of DLD-1 colorectal cancer cells is induced by generation of reactive oxygen species and activation of p70S6K and p21. Journal of Functional Foods. 2016;**21**:474-484

[59] Srikram A, Supapvanich S. Proximate compositions and bioactive

compounds of edible wild and cultivated mushrooms from Northeast Thailand. Agricultural Natural Resources. 2016;**50**:432-436. DOI: 10.1016/j.anres.2016.08.001

[60] Díez VA, Alvarez A. Compositional and nutritional studies on two wild edible mushrooms from Northwest Spain. Food Chemistry. 2001;**75**:417-422. DOI: 10.1016/S0308-8146(01)00229-1

[61] Günç EP, Akata I, Kalyoncu F, Ergönül B. Fatty acid compositions of six wild edible mushroom species. Scientific World Journal. 2013;**2013**:163964. DOI: 10.1155/2013/163964

[62] Ren Z, Qin T, Qiu F, Song Y, Lin D, Ma Y, et al. Immunomodulatory effects of hydroxyethylated *Hericium erinaceus* polysaccharide on macrophages RAW264.7. International Journal of Biological Macromolecules. 2017;**105**:879-885

[63] Sarikurkcu C, Copur M, Yildiz D, Akata I. Metal concentration of wild edible mushrooms in Soguksu National Park in Turkey. Food Chemistry. 2011;**128**:731-734. DOI: 10.1016/j.foodchem.2011.03.097

[64] Surinrut P, Julshamn K, Rein NL. Protein, amino acids and some major and trace elements in Thai and Norwegian mushrooms. Plant Food for Human Nutrition. 1987;**37**:117-125. DOI: 10.1007/BF01092047

[65] Xu X, Yan H, Chen J, Zhang X. Bioactive proteins from mushrooms. Biotechnology Advances. 2011;**29**: 667-674. DOI: 10.1016/j.biotechadv.2011.05.003

[66] Falandysz J. Mercury accumulation of three *Lactarius* mushroom species. Food Chemistry. 2017;**214**:96-101. DOI: 10.1016/j.foodchem.2016.07.062

[67] Mironczuk-Chodakowska I, Socha K, Zujko ME, Terlikowska KM, Borawska MH, Witkowska AM. Copper, manganese, selenium and zinc in wild-growing edible mushrooms from the Eastern territory of "green lungs of Poland": Nutritional and toxicological implications. International Journal of Environmental Research and Public Health. 2019;**16**:3614. DOI: 10.3390/ijerph16193614

[68] Rashid MH, Rahman MM, Correll R, Naidu R. Arsenic and other elemental concentrations in mushrooms from Bangladesh: Health risks. International Journal of Environmental Research and Public Health. 2018;**15**:919. DOI: 10.3390/ijerph15050919

[69] Zhou R, Liu ZK, Zhang YN, Wong JH, Ng TB, Liu F. Research progress of bioactive proteins from the edible and medicinal mushrooms. Current Protein & Peptide Science. 2019;**20**:196-219. DOI: 10.2174/1389203719666180613090710

[70] Wang XM, Zhang J, Wu LH, Zhao YL, Li T, Li JQ, et al. A mini-review of chemical composition and nutritional value of edible wild-grown mushroom from China. Food Chemistry. 2014;**151**:279-285. DOI: 10.1016/j.foodchem.2013.11.062

[71] Fang Y-Z, Yang S, Wu G. Free radicals, antioxidants, and nutrition. Nutrition. 2002;**18**:872-879. DOI: 10.1016/S0899-9007(02)00916-4

[72] Kozarski M, Klaus A, Jakovljevic D, Todorovic N, Vunduk J, Petrović P, et al. Antioxidants of edible mushrooms. Molecules. 2015;**20**:19489-19525. DOI: 10.3390/molecules201019489

[73] Elkhateeb WA, Daba GM, Thomas PW, Wen T-C. Medicinal mushrooms as a new source of natural therapeutic bioactive compounds. Egypt

Pharmaceutical Journal. 2019;**18**:88-101. DOI: 10.4103/epj.epj_17_19

[74] Hsieh H-M, Ju Y-M. Medicinal components in *Termitomyces* mushrooms. Applied Microbiology and Biotechnology. 2018;**102**:4987-4994. DOI: 10.1007/s00253-018-8991-8

[75] Gebreyohannes G, Nyerere A, Bii C, Berhe SD. Determination of antimicrobial activity of extracts of indigenous wild mushrooms against pathogenic organisms. Evidence Based Complementary Alternative Medicine. 2019;**2019**:1-7

[76] Ramesh C, Pattar MG. Antimicrobial properties, antioxidant activity and bioactive compounds from six wild edible mushrooms of Western Ghats of Karnataka, India. Pharmacognition Research. 2010;**2**:107-112. DOI: 10.4103/0974-8490.62953

[77] Venturini M, Rivera C, Gonzalez C, Blanco D. Antimicrobial activity of extracts of edible wild and cultivated mushrooms against foodborne bacterial strains. Journal of Food Protection. 2008;**71**:1701-1706. DOI: 10.4315/0362-028X-71.8.1701

[78] Barros L, Venturini BA, Baptista P, Estevinho LM, Ferreira ICFR. Chemical composition and biological properties of Portuguese wild mushrooms: A comprehensive study. Journal of Agricultural and Food Chemistry. 2008;56:3856-3862; Diplock AT, Charleux JL, Crozier-Willi G, Kok FJ, Rice-Evans C, Roberfroid M, Stahl W, Viña-Ribes J. Functional food science and defence against reactive oxidative species. British Journal of Nutrition. 1998;80(Suppl. 1):S77-S112. doi: 10.1079/BJN19980106

[79] Valko M, Leibfritz D, Moncol J, Cronin MTD, Mazur M, Telser J. Free radicals and antioxidants in normal physiological functions and human disease. The International Journal of Biochemistry & Cell Biology. 2007;**39**:44-84. DOI: 10.1016/j.biocel.2006.07.001

[80] Kumari D, Reddy MS, Upadhyay RC. Nutritional composition and antioxidant activities of 18 different wild *Cantharellus* mushrooms of Northwestern Himalayas. Food Science and Technology International. 2011;**17**:557-567. DOI: 10.1177/1082013211427620

[81] Puttaraju NG, Venkateshaiah SU, Dharmesh SM, Urs SMN, Somasundaram R. Antioxidant activity of indigenous edible mushrooms. Journal of Agricultural and Food Chemistry. 2006;**54**:9764-9772. DOI: 10.1021/jf0615707

[82] Lehmann PF, Khazan U. Mushroom poisoning by Chlorophyllum molybdites in the Midwest United States. Cases and a review of the syndrome. Mycopathologia. 1992;**118**(1):3-13

[83] Bronstein AC, Spyker DA, Cantilena LR, Green JL, Rumack BH, Giffin SL. 2008 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 26th Annual Report. Clinical Toxicology (Philadelphia, PA.). 2009;**47**(10):911-1084

[84] Friedman M. Mushroom polysaccharides: Chemistry and antiobesity, antidiabetes, anticancer, and antibiotic properties in cells, rodents, and humans. Food. 2016;**5**:80. DOI: 10.3390/foods5040080

[85] Beuhler MC, Sasser HC, Watson WA. The outcome of North American pediatric unintentional mushroom ingestions with various decontamination treatments: An analysis of 14 years of TESS data. Toxicon. 2009;**53**(4):437-443

[86] Dinis-Oliveira RJ. Metabolism of psilocybin and psilocin: Clinical and forensic toxicological relevance. Drug Metabolism Reviews. 2017;**49**(1):84-91

[87] Diaz JH. Amatoxin-containing mushroom poisonings: Species, Toxidromes, treatments, and outcomes. Wilderness & Environmental Medicine. 2018 Mar;**29**(1):111-118

[88] Dinis-Oliveira RJ, Soares M, Rocha-Pereira C, Carvalho F. Human and experimental toxicology of orellanine. Human & Experimental Toxicology. 2016 Sep;**35**(9):1016-1029

[89] Mancini A, Assisi F, Balestreri S, Angelini P, Bozzi M, Cuzzola C, et al. A rare case of acute renal failure related to amanita proxima ingestion. G Ital Nefrol. 2015;**32**(4)

[90] Kirchmair M, Carrilho P, Pfab R, Haberl B, Felgueiras J, Carvalho F, et al. Amanita poisonings resulting in acute, reversible renal failure: New cases, new toxic Amanita mushrooms. Nephrology, Dialysis, Transplantation. 2012;**27**(4):1380-1386

[91] Lheureux P, Penaloza A, Gris M. Pyridoxine in clinical toxicology: A review. European Journal of Emergency Medicine. 2005;**12**(2):78-85

[92] Ivanova TS, Krupodorova TA, Barshteyn VY, Artamonova AB, Shlyakhovenko VA. Anticancer substances of mushroom origin. Experimental Oncology. 2014;**36**(2):58-66

[93] Sushila R, Dharmender R, Rathee D, Kumar V, Rathee P. Mushrooms as therapeutic agents. Brazilian Journal of Pharmacognosy. 2012;**22**(2):459-474

[94] Jo W-S, Hossain MA, Park S-C. Toxicological profiles of poisonous, edible, and medicinal mushrooms. Mycobiology. 2014;**42**(3):215-220

[95] Le Daré B, Ferron P-J, Gicquel T. Toxic effects of amanitins: Repurposing toxicities toward new therapeutics. Toxins. 2021;**13**:417

[96] Rajinder S, Spriha S. Mushroom poisoning: From toxicity to forensic analysis. Journal of Indian Society of Toxicology. 2016;**12**(1)

[97] Marmion VJ, Wiedemann TE. The death of Claudius. Journal of the Royal Society of Medicine. 2002;**95**(5):260-261

Chapter 14

Medicinal Mushroom Mycelia: Characteristics, Benefits, and Utility in Soybean Fermentation

Kohei Suruga, Tsuyoshi Tomita and Kazunari Kadokura

Abstract

The medicinal value of mushrooms is long known, but there is increasing awareness of their health benefits and interest in utilizing these in diet as food or nutritional supplement. In this chapter, we discuss the characteristics of 20 wild mushrooms and results from our work on their antioxidant activity, ability to promote nerve growth factor (NGF) synthesis and to convert the glycosylated forms of isoflavones to usable aglycon forms in soybeans fermented with their mycelia. Of the 20 mushroom types, we found that *Hericium ramosum* (*H. ramosum*) mycelia had higher antioxidant activity and showed greater capability for increasing the levels of aglycons, such as daidzein, glycitein, and genistein when used for fermentation of soybeans. In general, soybeans fermented with mushrooms increased the levels of aglycons compared to non-fermented ones. Taken together, all these results suggest that mushroom mycelia have a huge potential to be used as food and nutritional supplements for the health benefits they offer and present the prospects for utilizing them in soybean fermentation as natural resources for the large-scale production of aglycons.

Keywords: *H. ramosum* mycelia, antioxidant, NGF synthesis, soybean fermentation, isoflavone

1. Introduction

Mushrooms, their fruiting bodies and mycelia have served as food and food supplements around the world. They are relatively less toxic and are rich in bioactive compounds, such as polysaccharides, proteins, minerals, and other nutrients [1]. Beneficial activities associated with mushroom fruiting bodies and mycelia include antitumor [2], antimutagenic [3], antiviral [4], and antioxidant activities [5]. Some mushrooms alleviate the risk of diseases, such as Parkinson's and Alzheimer's disease, and hypertension [6].

Mushroom mycelia contain bioactive compounds as well as mushroom fruiting bodies, which have been investigated for their medicinal value. For example, oral administration of *Sparassis crispa* mycelia resulted in antitumor responses in

tumor-bearing ICR mice [7]. The ability of erinacines, the bioactive compounds of *H. erinaceum* mycelia, to promote nerve health has been documented [8]. However, published data on the bioactivity of mushroom mycelia are limited compared with those of mushroom fruiting bodies.

In this chapter, we first discuss the antioxidant activity of 20 different species of wild mushroom mycelia [9]. These mushrooms are considered edible in the Tohoku area in northern Japan. Second, we present our findings on the ability of the comb tooth cap medicinal mushroom, *H. ramosum* mycelia, to promote NGF synthesis [9]. Finally, we discuss our results from using these mushroom mycelia in soybean fermentation [10] and discuss the prospects of utilizing *H. ramosum* mycelia in soybean fermentation for large-scale production of aglycons.

2. Characteristics of wild mushroom mycelia

2.1 Collection of mushrooms and separation of mycelia

We investigated the characteristics of 20 species of mushrooms: #1, *A. brasiliensis* (Agaricaceae); #2, *Mycoleptodonoides aitchisonii* (Climacodontaceae); #3, *Ganoderma applanatum* and #4, *G. lusidum* (Ganodermataceae); #5, *H. erinaceum* and #6, *Hericium ramosum* (Hericiaceae); #7, *Inonotus obliquus* (Hymenochaetaceae); #8, *Lentinus edodes* (Pleurotaceae); #9, *Dendropolyporus umbellatus*; #10, *Grifola frondosa*; #11, *Laetiporus sulphureus*; #12, *Polyporellus badius* and #13, *Polyporus tuberaster* (Polyporaceae); #14, *Sparassis crispa* (Sparassidaceae); #15, *Pholiota aurivella* and #16, *Pholiota nameko* (Strophariaceae); #17, *Hypsizygus marmoreus*, #18, *Lepista nuda*; #19, *Lyophyllum shimeji* and #20, *Panellus serotinus* (Tricholomataceae).

Nineteen of these (#2–20) wild mushroom fruiting bodies were collected from the Akita and Iwate prefectures in the Tohoku area in northern Japan. *A. brasiliensis* (#1) mycelia were provided by Dr. Makoto Yoneyama, I.M.C. Institution (Yamanashi Prefecture, Japan). Pieces of mushroom fruiting bodies collected from natural sites were plated in a 90-mm Petri dish containing potato dextrose agar (PDA) medium and incubated at 25°C for 2 days until the mycelia germinated. Mycelia were allowed to germinate and then cultured for 14 days at 25°C, after which period, they were maintained at 3°C on PDA medium. Mushroom mycelia were grown in submerged culture following the methods of *A. brasiliensis* mycelia cultivation, as described previously [11]. The culture was incubated at 25°C for 14 days with gentle shaking and the mycelia were lyophilized by freeze-drying after cultivation.

2.2 Ethanol extract preparation from mushroom mycelia

Mushroom mycelia extraction with ethanol was performed following methods described in previous reports [12, 13] with a few modifications. Lyophilized mushroom mycelia (0.1 g) were extracted with 80% ethanol (10 mL) at 25°C for 24 h and the resulting solutions were concentrated and lyophilized to a powder.

2.3 Antioxidant activity of wild mushroom mycelia

Free radicals exert tissue damage through reactive oxygen species (ROS)-induced oxidative stress, which can be counterbalanced by antioxidants [14, 15].

ROS, such as superoxide anion radicals, hydroxyl radicals, and hydrogen peroxide (H_2O_2), induce aging and cell damage [16, 17], and have been implicated in several diseases [18]. Recent epidemiological data indicate the association between inactivation of ROS and the disease-prevention benefits resulting from consuming food containing antioxidants, such as fruits, vegetables, and certain cereals [19]. As a result, there is an increasing trend worldwide in the incorporation of antioxidant compounds and foods into regular diet. We measured the antioxidant activity of the 20 wild mushrooms listed above by DPPH radical scavenging activity assay.

2.3.1 Methods

Measurement of 2,2-diphenyl-1-picryhydrazyl (DPPH) radical scavenging activity of mushroom mycelia was performed as previously described [20]. Ethanol extracts of mushroom mycelia (0.3 mL) were mixed with 0.6 mL of 100 mM MES buffer (pH 6.0)/10% ethanol solution, and 0.3 mL of 400 μM DPPH in ethanol. The absorbance of the reaction mixture was quantified at 520 nm after the reaction was set to complete for 20 minutes at RT. The DPPH radical scavenging activity of mushroom mycelia was calculated from assay lines of Trolox (0, 5, 10, 15, 20, and 25 μM) and expressed as μmol Trolox/g dry powder.

2.3.2 DPPH free radical scavenging activity of mushroom mycelia

Eighty-percent ethanol extracts of mushroom mycelia were used for antioxidant activity measurements using DPPH radical scavenging activity (**Figure 1**). Among the 20 mushroom mycelia analyzed, *L. shimeji* (#19), *G. frondosa* (#10), *H. erinaceum* (#5), and *H. ramosum* (#6) showed more robust DPPH radical scavenging activities.

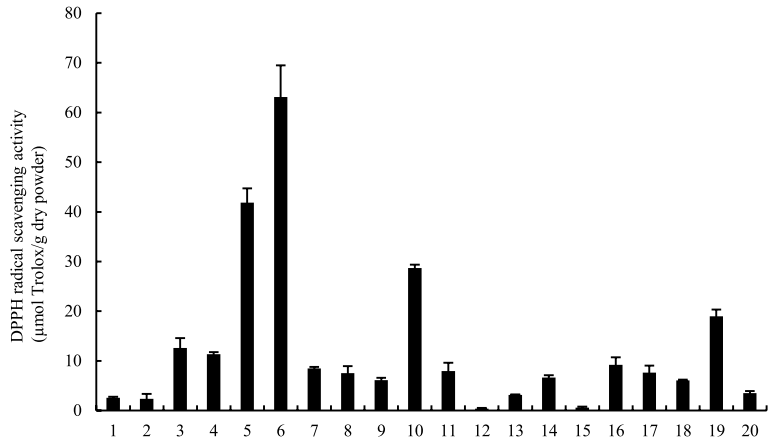

Figure 1.
DPPH radical scavenging activity of mycelial extracts from the 20 wild mushrooms [9]. 1, A. brasiliensis; 2, M. aitchisonii; 3, G. applanata; 4, G. lucidum; 5, H. erinaceum; 6, H. ramosum; 7, I. obliquus; 8, L. edodes; 9, D. umbellatus; 10, G. frondosa; 11, L. sulphureus; 12, P. badius; 13, P. tuberaster; 14, S. crispa; 15, P. aurivella; 16, P. nameko; 17, H. marmoreus; 18, L. nuda; 19, L. shimeji; and 20, P. serotinus. *The DPPH radical scavenging activity of mushroom mycelia was calculated and expressed as the Trolox equivalent. Data represent the mean ± SD (n = 5).*

Among the mycelia tested, *H. ramosum* showed maximum antioxidant activity, followed by *H. erinaceum*, *G. frondosa*, and *L. shimeji*.

2.4 Total phenolic content of the wild mushroom mycelia

Phenolic compounds are secondary metabolites of plants produced as defensive responses to threatening environments, including pathogen attack and UV radiation [21]. Generally, these polyphenols are classified as phenolic acids, flavonoids, lignans, and stilbenes [22]. These phenolic compounds possess antioxidant, antiglycemic, anticarcinogenic, and anti-inflammatory properties and can protect against bacterial and viral infections [23]. We analyzed the total phenolic content of the mushroom mycelia.

2.4.1 Methods

Folin & Ciocalteu method [24] with catechin as a standard was used for analysis. Ethanol extracts of mushroom mycelia (1 mL) were mixed with 0.5 mL of Folin & Ciocalteu solution and 5 mL of 0.4 M sodium carbonate solution. The absorbance of the reaction mixture was quantified at 660 nm after the reaction was set to complete for 30 minutes at 30°C. Methods are described in detail in Suruga et al. [9].

2.4.2 Measurement of total phenolic content

The phenolic contents of the samples were expressed as mg of catechin equivalent/g dry powder in **Figure 2**. *H. ramosum* (#6) showed the highest amount of phenol contents, followed by *H. erinaceum* (#5), *G. frondosa* (#10), *A. brasiliensis* (#1), *L. shimeji* (#19), *E. applanata* (#3), *G. lucidum* (#4), and *H. marmoreus* (#17).

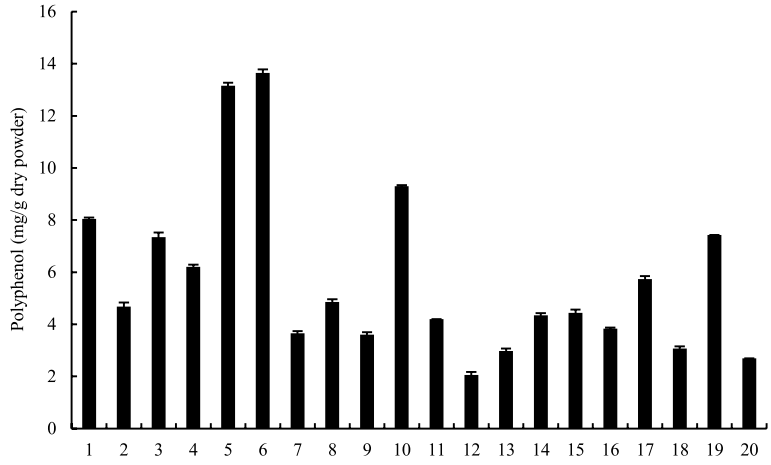

Figure 2.
Total phenolic content of wild mushrooms mycelia extracts [9]. 1, A. brasiliensis; 2, M. aitchisonii; 3, G. applanata; 4, G. lucidum; 5, H. erinaceum; 6, H. ramosum; 7, I. obliquus; 8, L. edodes; 9, D. umbellatus; 10, G. frondosa; 11, L. sulphureus; 12, P. badius; 13, P. tuberaster; 14, S. crispa; 15, P. aurivella; 16, P. nameko; 17, H. marmoreus; 18, L. nuda; 19, L. shimeji; and 20, P. serotinus. *Data represent the mean ± SD (n = 5).*

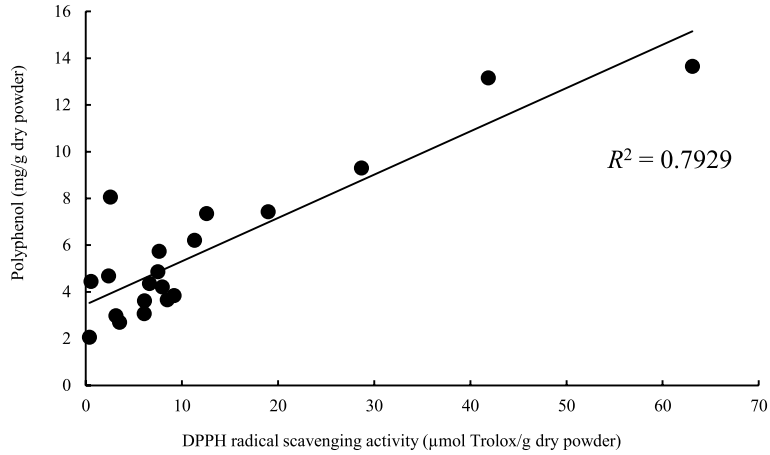

Figure 3.
Direct correlation between DPPH radical scavenging activity and phenolic content [9].

2.5 Phenolic compounds enable the DPPH radical scavenging capacity of mushroom mycelia

DPPH radical scavenging activity showed a significant correlation (R^2 = 0.7929) with the total phenolic content in the wild mushroom mycelia extracts (**Figure 3**). The Hericiaceae group, including *H. erinaceum* (#5) and *H. ramosum* (#6), which had a higher total phenolic content, showed stronger antioxidant potential. All these results suggest that the DPPH radical scavenging capacity of these extracts is driven by the phenolic compounds.

3. NGF synthesis of *H. ramosum* mycelia

Senile dementia, such as AD, is a severe problem, with no effective therapy [25]. Neurotrophic factors, including NGF, brain-derived neurotrophic factor (BDNF), neurotrophin 3, and glial-derived neurotrophic factor (GDNF), have been implicated in the prevention of neuronal death and promotion of neurite outgrowth [26]. Among them, NGF has been associated with AD [27], with decreased NGF levels in the basal forebrain of AD patients. Intracerebroventricular administration of NGF has been reported to eliminate degeneration and resultant cognitive deficits in rats after brain injury [28]. In rats, poor cognitive effects caused by neuronal degeneration have been shown to be eliminated by intracerebroventricular administration of NGF. However, since NGF cannot cross the blood-brain barrier, utilizing it for therapeutic application will be difficult. Several studies have investigated low-molecular-weight compounds, such as catecholamines [29], benzoquinones [30], hericenones [31], and erinacines [32], for their ability to promote NGF synthesis.

H. erinaceum is a common fungus found in the East Asian diet. Hericenones [33] have been isolated from the fruiting bodies of *H. erinaceum* and erinacines [34] have been identified in *H. erinaceum* mycelia. *H. erinaceum* may be valuable in the treatment and prevention of dementia [35, 36]. However, to our knowledge, no reports have shown the induction of NGF synthesis by *H. ramosum* mycelia. In this section, we show the results of our assessment on the ability of *H. erinaceum* and *H. ramosum* mycelia to induce NGF synthesis.

3.1 Methods

NGF synthesis was measured as described by Hazekawa et al. [37]. Male ddY mice (25–30 g weight) obtained from Kiwa Laboratory Animals Co., Ltd. (Wakayama, Japan), were housed under a 12-h light/dark cycle at room temperature and 55 ± 5% humidity. The lyophilized mycelia from *H. erinaceum* and *H. ramosum* were suspended in purified water and the samples were orally administrated to mice once a day for 14 days. NGF levels were analyzed in the cortex, striatum, and hippocampus 24 h after the last administration. Results are expressed as mean ± standard error of mean (SEM). The standard dose (300 mg/kg body weight) was determined based on Hazekawa et al. [37]. More detailed methodology can be found in Suruga et al. [9].

3.2 Stimulation of NGF synthesis by *H. ramosum* and *H. erinaceum* mycelia

The effects of 14-days of oral administration of 300 mg/kg *H. erinaceum* mycelia and *H. ramosum* mycelia on NGF levels in intact mouse brains are shown in **Figure 4**. *H. ramosum* mycelia were more potent than *H. erinaceum* mycelia in terms of NGF stimulation in the hippocampus of intact mice. Processing of *H. ramosum* mycelia over time significantly increased NGF levels in the hippocampus.

Different regions of the mouse brain responded differently to application of varying concentrations of *H. ramosum* mycelia on NGF synthesis [9]. The NGF levels in hippocampus increased with increased concentration of *H. ramosum* mycelia, while such dose-dependent response was not seen in cortex or striatum (**Figure 5**).

4. Soybean fermentation using mushroom mycelia

The legume soybean is highly proteinaceous (36% protein in dried beans), rich in major nutrients essential for human nutrition and can potentially be a good replacement for animal-derived proteins [38–41]. It can be used both in fermented and

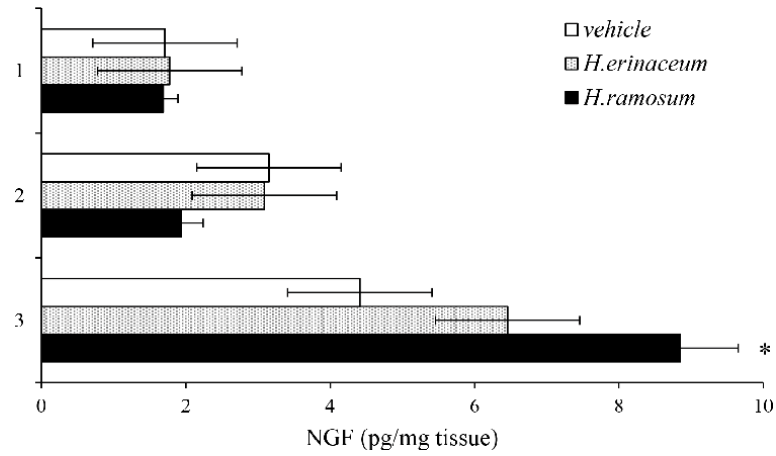

Figure 4.
Activation of NGF synthesis with wild H. erinaceum *and* H. ramosum *mycelia [9]. NGF levels in various parts of the brain were measured after 14 days of repeated oral administration of* H. erinaceum *and* H. ramosum mycelia *(300 mg/kg). 1, Cortex; 2, striatum; and 3, hippocampus. Data are expressed as the mean ± SEM. *p < 0.05, compared with vehicle (Student's test).*

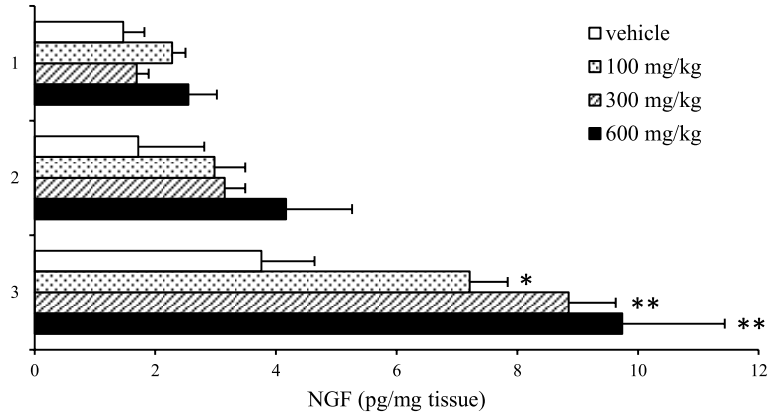

Figure 5.
Effect of varying concentrations of wild H. ramosum *mycelia on NGF synthesis in different parts of mouse brain [9]. 1, Cortex; 2, striatum; and 3, hippocampus. Data are expressed as the mean ± SEM. *p < 0.05 and **p < 0.01, compared with vehicle (Student's test).*

non-fermented forms [42]. While soybeans are rich in flavonoid groups such as genistein, daidzein, and glycitein isoflavones that have tremendous health benefits [43], they are not easily absorbed and incorporated in their natural glycosylated forms unless hydrolyzed by the microflora of the intestine through their beta-glucosidase production [44]. Isoflavones have health benefits against several diseases and hormone-related issues [45–48]. The easily absorbable form of flavones is the aglycon form, which is abundant in fermented sources of soybean, such as tempeh, miso, and natto [49].

Mushroom mycelia can be used as a source of beta glucosidase to convert isoflavone glycosides to their aglycon form. For example, *G. lusidum*, belonging to the basidiomycetes group, has been shown to increase serum concentration of the aglycon form of isoflavones in soybeans [50].

Studies from our laboratory investigated the health effects of fermentation using mushrooms, such as *G. lucidum*, *H. erinaceum*, and *H. ramosum* [10]. We measured DPPH scavenging activity, total phenolic content, antioxidant activity, alpha glucosidase inhibition, and isoflavone concentration, few major health parameters of paramount importance, in soybeans fermented with different mushroom types and compared them with non-fermented soybeans.

Soybean fermentation was carried out as described in Suruga et al. [10]. We found that *G. lucidum* was more effective in quickly fermenting soybeans compared to the other two mushroom types (**Figure 6**).

4.1 Antioxidant activity of fermented soybean

4.1.1 Methods

The DPPH radical scavenging activity and total phenolic content of fermented soybeans were analyzed using the methods described in Subsections 2.3.1 and 2.4.1. Oxygen radical absorbance capacity (ORAC) was determined using the OxiSelect™ ORAC Activity Assay Kit (Cell Biolabs Inc., San Diego, CA, USA) [51]. The assay was performed as described in Suruga et al. [10]. Briefly, fluorescence activity of the reaction mixture with antioxidant and fluorescein solution was measured after adding the free radical initiator. Increasing Trolox concentrations were used for the standard

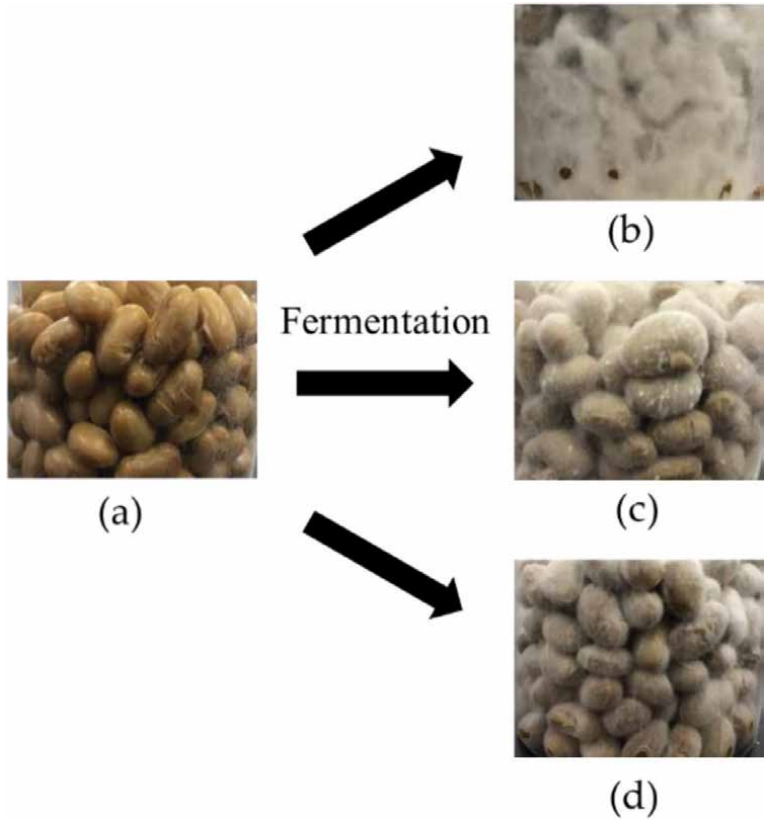

Figure 6.
G. lucidum *was faster in fermenting soybeans compared to other types (a) Control (non-fermented soybeans); (b)* G. lucidum*; (c)* H. erinaceum*; (d)* H. ramosum *[10].*

curve, and extracts were quantified and expressed as μmol Trolox equivalents/g of dry fermented soybean powder.

4.1.2 Total phenolic content and antioxidant activity of fermented soybean by mushroom mycelia

Total phenolic content was higher in all the fermented extracts compared to non-fermented control soybeans. Both DPPH radical scavenging activity and antioxidant activity were higher in fermented soybeans than in non-fermented ones (**Table 1**).

4.2 Alpha-glucosidase inhibitory activity of soybeans fermented with mushroom mycelia

4.2.1 Methods

Yeast alpha-glucosidase inhibitory activity was measured using methods reported before [52] with modifications as described in Suruga et al. [10]. Briefly, yeast alpha-glucosidase was incubated with fermented soybean extract solutions and then p-nitrophenyl α-D-glucopyranoside (pNP-glucoside) was added and absorbance was determined at 400 nm. For the mammalian reaction, alpha glucosidase from rat

	Control	*G. lucidum*	*H. erinaceum*	*H. ramosum*
Total phenolic content (mg/g dry powder)	1.547 ± 0.068	2.304 ± 0.035	2.074 ± 0.066	2.160 ± 0.014
DPPH radical scavenging activity (μmol Trolox/g dry powder)	1.847 ± 0.073	4.246 ± 0.010	2.246 ± 0.061	2.367 ± 0.173
ORAC (μmol Trolox/g dry powder)	49.763 ± 2.856	60.090 ± 1.506	66.147 ± 1.898	72.897 ± 2.113

Table 1.
Total phenolic content and antioxidant activity of soybeans fermented by mushroom mycelia [10].

intestinal acetone powder [53] was incubated with fermented soybean extract and the amount of glucose released was measured. We also used maltose as the substrate and calculated the % inhibition rate of alpha glucosidase [54].

4.2.2 Fermented soybean showed higher inhibition of alpha-glucosidase activity compared to non-fermented ones

Comparison of control (non-fermented soybeans) to soybeans fermented with mushroom mycelia showed that significant alpha-glucosidase inhibition could be achieved in the fermented soybeans using both pNP-glucoside and maltose (**Figure 7A** and **B**). Yeast alpha-glucosidase inhibition was the highest with *H. ramosum* compared to *G. lucidum* and *H. erinaceum*, while the mammalian alpha-glucosidase inhibition was significantly higher with *G. lucidum* fermentation (**Figure 7A-C**).

4.3 Comparison of isoflavone concentrations in soybeans fermented with mycelia versus non-fermented soybeans

4.3.1 Methods: high-performance liquid chromatography (HPLC) analysis

We followed the methods described in Kudou et al. [55] for measuring isoflavone concentrations in fermented and non-fermented soybeans. An LC-6A system (Shimadzu, Kyoto, Japan) equipped with a PEGASIL-ODS (4.6 mm i.d. × 250 mm) HPLC column (Senshu Scientific, Tokyo, Japan) was used for analysis. HPLC parameters used for the measurement of different isoflavones, such as genistein, daidzein, glycitein, daidzin, and glycitin, both in the glycosylated and in aglycone forms, are detailed in Suruga et al. [10].

4.3.2 Methods: liquid chromatography/mass spectrometry (LC/MS) analysis

An ACQUITY UPLC apparatus (Waters MS Technologies, Manchester, UK) equipped with a reversed-phase Acquity UPLC CHS C18 column with a particle size of 2.1 mm × 100 mm × 1.7 μm (Waters MS Technologies) was used for LC/MS analysis. Parameters of analysis are documented in detail in Suruga et al. [10].

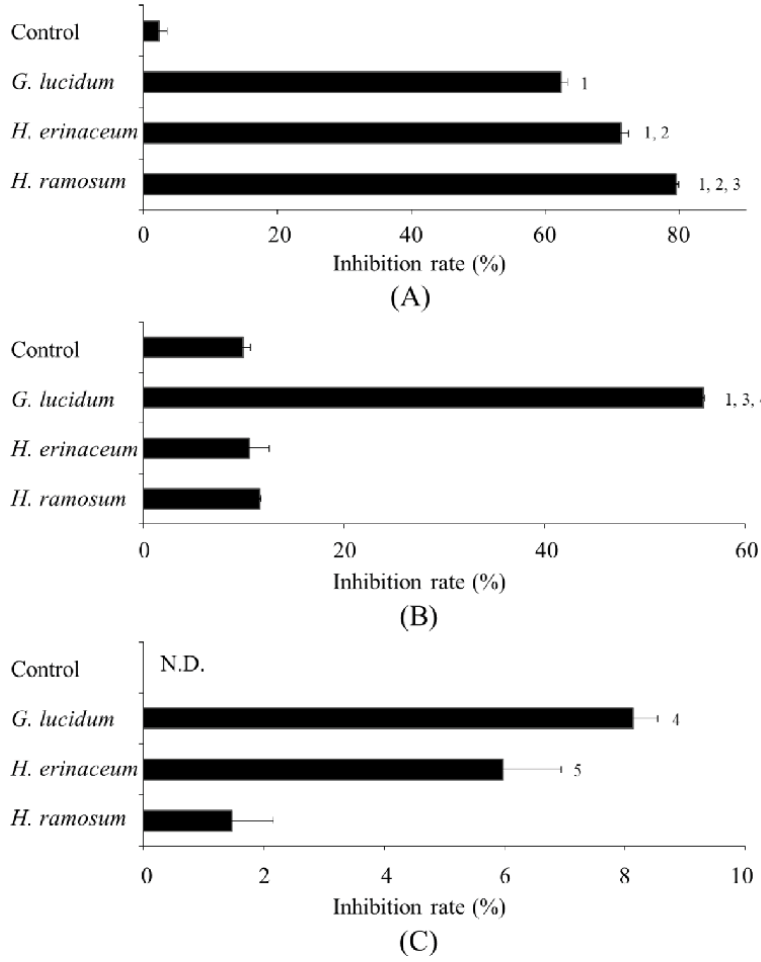

Figure 7.
Inhibition of alpha-glucosidase activity soybeans fermented by mushroom mycelia. (A) Yeast alpha-glucosidase inhibition using pNP-glucoside as substrate, (B) mammalian alpha-glucosidase inhibition using maltose as substrate, and (C) mammalian alpha-glucosidase inhibition using sucrose as substrate. Results are expressed as mean ± SD (n = 3). N.D.: not detectable. 1: p < 0.01 vs. control, 2: p < 0.01 vs. G. lucidum*, 3: p < 0.01 vs.* H. erinaceum*, 4: p < 0.01 vs.* H. ramosum*, and 5: p < 0.05 vs.* H. ramosum *[10].*

4.3.3 Fermentation with mushrooms decreased the concentrations of glycosylated forms of isoflavones and increased the concentrations of aglycon forms

LC/MS profile was shown in **Figure 8**. The concentration of glycosylated forms of isoflavones, such as daidzin, glycitin, and genistin was about 95.6% in non-fermented soybeans, while it was reduced to 52.5, 15.8, and 17.6% in soybeans fermented by the *G. lucidum*, *H. erinaceum*, and *H. ramosum* mycelia, respectively. The aglycone forms of these isoflavones, on the other hand, increased from 4.4% in the non-fermented controls to 47.5, 84.2, and 82.4% in soybeans fermented by *G. lucidum*, *H. erinaceum*, and *H. ramosum* mycelia, respectively. LC/MS profile shown in **Figure 8** corroborate these results. Based on the retention time and MS data, molecular formula and identity of compounds corresponding to 11 of the 12 peaks have been predicted: peak #1, daidzin; peak #2, glycitin; peak #3, 8-hydroxydaidzein; peak #4, genistin; peak #5,

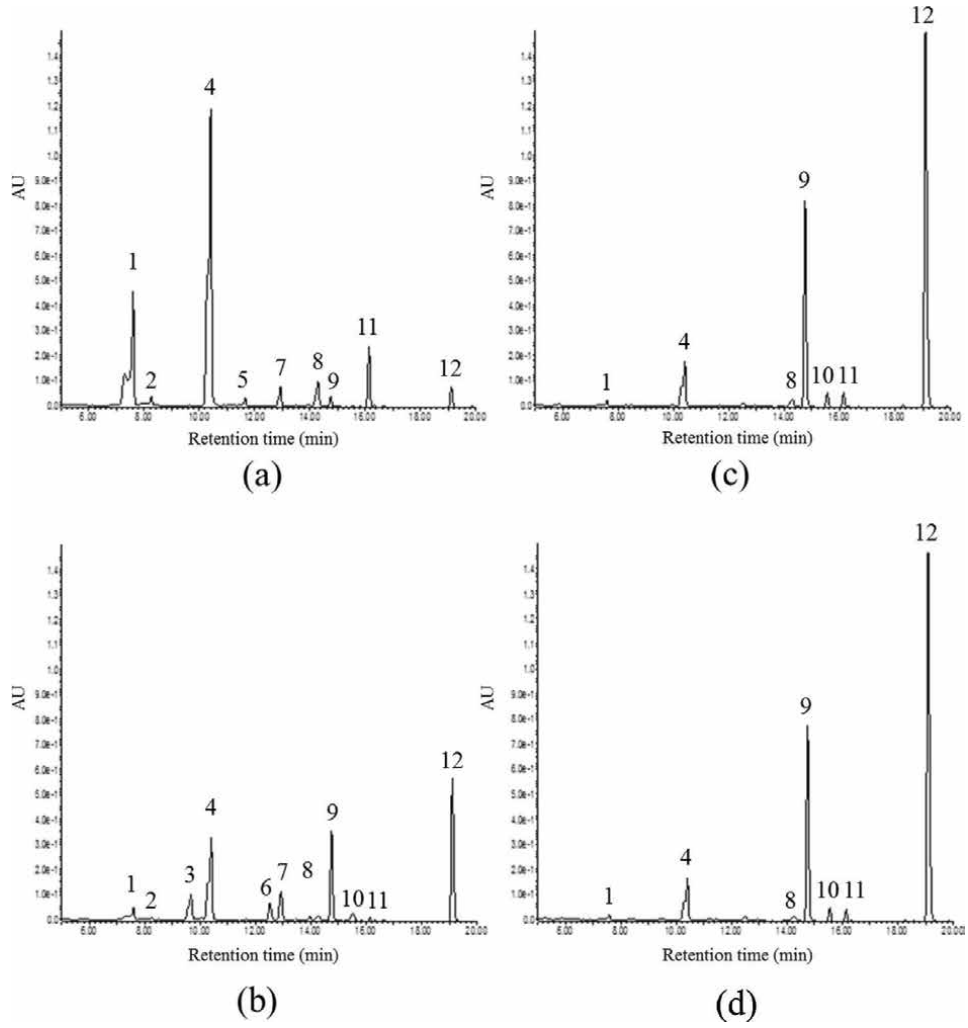

Figure 8.
LC/MS profile of soybean fermented using mushroom mycelia: a, control (non-fermented soybeans); b, G. lucidum*; c,* H. erinaceum*; and d,* H. ramosum *[10].*

6″-O-malonyldaidzin; peak #7, 6″-O-acetyldaidzin; peak #8, 6″-O-malonylgenistin; peak #9, daidzein; peak #10, glycitein; peak #11, 6″-O-acetylgenistin; and peak #12, genistein, respectively.

5. Discussion

5.1 Characteristics of *H. ramosum* mycelia and other mushroom mycelia

While the beneficial effects of mushrooms in human health and nutrition have long been known and their pharmacological use has been studied in several types of mushrooms, including *Pleurotus*, *Ganoderma*, *Cordyceps*, *Lentinus*, *Grifola*, and *Hericium* [56], there are plenty of rare species of mushrooms that have not been

investigated yet in terms of their biological functions, such as antioxidant activity, induction of NGF synthesis, etc. For example, there is only a single report that investigated the kappa opioid receptor binding activity of erinacine E on *H. ramosum*, indicating the rarity of this mushroom. Our analysis has provided a vast amount of data on the potential value of this mushroom. Given their vast health benefits and medicinal value, finding new mushrooms and analyzing their biological and pharmacological properties is of tremendous importance toward utilizing them in the development of new drugs and food supplements. We have investigated 20 mushroom types for their health benefits.

DPPH radical scavenging activity is a good indicator of antioxidant properties. Our study indicated that several mushrooms (*L. shimeji* #19, *G. frondosa* #10, *H. erinaceum* #5, and *H. ramosum* #6) were potent scavengers of DPPH (**Figure 1**). We also found a direct correlation (R^2 = 0.7929) between total phenolic content and DPPH radical scavenging activity (**Figure 3**). A direct relationship between total phenolic content and DPPH scavenging activity has been demonstrated in several studies. For example, a direct correlation (R^2 = 0.9788) between total phenolic content and total antioxidant activity has been shown in 11 kinds of fruits by Sun et al. [57]. A direct relationship (R^2 = 0.8181) between total phenolics volume and DPPH radical scavenging activity has also been reported in the fruiting bodies of 14 different kinds of commercially available mushrooms by Abdullah et al. [58]. A direct relationship was reported between the high antioxidant activity observed in rice fermented by *Monascus* mycelia and its high total phenolic compound levels [59]. Our results corroborate the findings from these reports.

From our analyses, we have found that *L. shimeji* (#19) and *G. frondosa* (#10) had potent DPPH radical-scavenging activities. Several studies have investigated the applications of these and other mushrooms in various diseases and for other purposes. Pyranose oxidase, a flavoprotein from *L. shimeji* (Honshimeji in Japanese), has been studied and its heterologous expression is reported to be under the control of the T7 promoter in *Escherichia coli* [60]. *L. connatum* fruiting bodies (Oshiroishimeji) have been shown to contain new ceramides [61]. The antitumor activities of (1 → 3)-ß-D-glucan and (1 → 6)-ß-D-glucan from *L. decastes* (Hatakeshimeji) hot water extract against Sarcoma 180 have also been described [62].

Several compounds responsible for DPPH and antioxidant activity have been isolated from mushrooms and studied in detail. However, little information has been published regarding the DPPH scavenging activity of active compounds from mycelia of *L. shimeji* and *G. frondosa*. DPPH active compounds ergothioneine, N-hydroxy-N′,N′-dimethylurea, connatin, and ß-hydroxyergothioneine have been isolated from *L. connatum* fruiting bodies [63]. Yeh et al. described the antioxidant compounds β-tocopherol and flavonoids in ethanol extracts of *G. frondosa* fruiting bodies, which are edible mushrooms in Japan [64]. Zhang et al. isolated three analogues of ergosterol from *G. frondosa* mycelia as compounds with antioxidant activity [65]. Reis et al. investigated the effects of five kinds of mushroom mycelia (*A. bisporus*-white, *A. bisporus*-brown, *P. ostreatus*, *P. eryngii*, and *L. edodes*) on antioxidant activity. The authors reported that the antioxidant compounds of these mushroom mycelia were gallic acid, protocatechuic acid, p-hydroxybenzoic acid, and p-coumaric acid [66]. Considering these observations, the potent DPPH scavenging activity of *L. shimeji*, *G. frondosa*, and other mushrooms could be attributed to the polyphenols ergothioneine, N-hydroxy-N′,N′-dimethylurea, connatin, ß-hydroxyergothioneine ergosterol, α-tocopherol, flavonoids, gallic acid, protocatechuic acid, p-hydroxybenzoic acid, and p-coumaric acid.

The present findings indicate that the DPPH radical scavenging activity of the Hericiaceae group, including *H. erinaceum* (#5) and *H. ramosum* (#6), was stronger

than those of other mushroom mycelia. The antioxidant activity of some phenolic compounds has been reported in the *H. erinaceum* and its mycelial extracts [67]. A strong antioxidant activity has also been shown in vitro in polysaccharides derived from an ethanol extract of *H. erinaceum* grown on tofu [68]. Thus, there has been minimal effect on *H. ramosum* mycelia which contain phenolic compounds and polysaccharides with strong antioxidant activity.

NGF plays a crucial role in nerve growth and neuronal cell function, and protection of neurons. NGF has been implicated in various diseases, including in Alzheimer's disease, the most common type of dementia that affects language, memory, processing of visual cues, judgment, and mood [69]. Reduced levels of NGF or increased accumulation of β-amyloid peptide and tau protein have been suggested as causes of AD [70]. Given its importance, there has been a demand for finding natural inducers of NGF synthesis. Natural compounds such as hericenones and erinacines isolated from *H. erinaceum* have been shown to induce NGF synthesis [33, 71]. We have shown that *H. ramosum* mycelia induced stronger NGF synthesis activity compared to *H. erinaceum* mycelia in the hippocampus of intact mice, and that processing of *H. ramosum* mycelia over time elevated the levels of NGF levels (**Figure 4**). We also found a dose-dependent response of NGF with increasing concentrations of *H. ramosum* mycelia in the hippocampi of intact mice (**Figure 5**). However, we have not determined the active compounds in the mycelia responsible for NGF synthesis. There are mounting evidence suggesting that erinacine species could be responsible, with the isolation of erinacine E from *H. ramosum* [72], and the observation that active substances other than hericenones stimulated NGF synthesis through c-Jun N-terminal kinase activation in *H. erinaceum* [73]. This evidence indicates that erinacine species could be involved in the induction of NGF synthesis in *H. ramosum* mycelia. There may be involvement from other unknown compounds as well, as our data comes from mycelia and not the fruiting bodies.

5.2 Soybean fermentation of mushroom mycelia

Mushrooms are effective in combating issues caused by obesity, diabetes, and other health issues [74]. The medicinal value of mushrooms has been known for thousands of years [75, 76] and they have been incorporated in nutrition supplements [74] and in the production of fermented foods, such as soybean-based foods, bread and cheese, and in alcoholic beverages [77]. However, detailed analysis of soybeans fermented by mushroom mycelia has not been conducted, insofar as their oxidative properties or alpha-glucosidase inhibitory activity are concerned. Our study analyzed all these properties and the LC/MS profiles of the bioactive products to glean more insights into the medicinal value of fermented soybeans.

We found that soybeans fermented with mushroom mycelia had stronger DPPH radical scavenging activity and ORAC than the non-fermented control ones. We also found that *H. ramosum* mycelia were more potent in DPPH radical scavenging and oxygen radical absorbance compared to all the other 19 mushroom groups we had tested (**Figure 1**) [9]. While this result was consistent in our subsequent study, we also found that DPPH radical scavenging activity and total phenolic content of *G. lucidum* mycelia-fermented soybeans was higher than soybeans fermented with *H. erinaceum* and *H. ramosum* mycelia [10].

The compound 8-hydroxydaidzein (peak #3 in **Figure 8b**) and one unidentified compound (peak #6) were identified by LC/MS analysis in soybeans fermented using *G. lucidum* mycelia. While we are investigating the identity of this unknown compound, we believe that this could possibly be 6-hydroxydaidzein or

3-hydroxydaidzein based on mass spectrometry analysis results. 6-Hydroxydaidzein has been isolated from soybean koji fermented with *Aspergillus oryzae* [78] and was found to be more potent in terms of antioxidative properties compared to daidzein [79], suggesting that phenolic compounds such as hydroxydaidzeins could influence the antioxidant effects of soybeans fermented with *G. lucidum* mycelia. Since oxidative stress is linked to several diseases [80], mushroom mycelia showing antioxidant activity is of much relevance toward producing antioxidant foods and nutritional supplements. We have shown high antioxidant activity in *G. lucidum* mycelia-fermented soybeans [10], as well as in fermented soy residue ("okara") with *Rhizopus oligosporus* [81–83].

Alpha-glucosidases are the primary enzymes responsible for hydrolyzing carbohydrates into glucose. Inhibition of alpha-glucosidase activity, therefore, is a strategy for controlling increase in blood glucose levels in diabetic conditions. We have shown that soybeans fermented with mushroom mycelia have significantly higher alpha-glucosidase activity than the non-fermented control groups. When pNP-glucoside was used as a substrate, the yeast alpha-glucosidase activity was inhibited in soybeans fermented with *H. erinaceum, H. ramosum*, and *G. lucidum* mycelia, with fermentation using the Hericiaceae members showing higher inhibition than with *G. lucidum* mycelia. Similar inhibition of alpha-glucosidase using pNP-glucoside has been achieved by the commercial soy isoflavone genistein by Lee et al. [84], suggesting that genistein might play a role. Despite pNP-glucoside's wide usage in testing anti-diabetic agents, maltose and sucrose are biologically more relevant as substrates than pNP-glucoside for mammalian systems. Therefore, we used these two substrates for testing inhibition of alpha-glucosidase activity in soybeans fermented using *H. erinaceum*, *H. ramosum*, and *G. lucidum* mycelia. We found that all three were able to inhibit alpha-glucosidase activity with varying degrees, with *G. lucidum* mycelia exhibiting higher inhibition with both maltose and sucrose as substrates compared to the other mushroom species. We suspect that in addition to genistein, hydroxydaidzein in soybeans fermented using *G. lucidum* mycelia could facilitate this inhibition. The precise identification of the active compounds in fermented soybeans using mushroom mycelia is yet to be completed, but fermented soybeans have potential use as nutritional supplements for treating diabetes.

The beta-glucosidase enzyme (EC 3.2.1.21) produced by microbes facilitates the breakdown of glycosylated isoflavones to their aglycon form, which is more easily absorbable [85]. Several microbes, including *Aspergillus niger* [86], *A. oryzae* [87], *Penicillium brasilianum* [88], and *Phanerochaete chrysosporium* [89], are being tapped for this fermentation purpose. We found that the levels of aglycons (daidzein, glycitein, and genistein), were higher in soybeans fermented with mycelia compared to non-fermented soybeans. While one previous report has shown the conversion of isoflavone glucosides to aglycons using *G. lucidum* mycelia to ferment soybeans [50], not many studies have investigated soybean fermentation using *H. erinaceum* and *H. ramosum* mycelia. We have shown that fermentation using these mycelia increased the amount of the aglycon form compared to non-fermented ones. The amount of aglycons was higher with *H. erinaceum* and *H. ramosum* mycelia compared to that when *G. lucidum* mycelia were used, possibly because the former produces more beta-glucosidase enzyme than the latter.

Our mass spectrometry analysis data revealed that the aglycon form of isoflavones obtained in soybeans fermented with *G. lucidum* mycelia contained 8-hydroxydaidzein and an unidentified compound, which we assumed to be 6-hydroxydaidzein or 3-hydroxydaidzein based on m/z data and molecular formula derived from LC/MS

analysis. 8-Hydroxydaidzein was first isolated from *Streptomyces* sp. fermentation broth [90] and has also been obtained from *A. oryzae* and recombinant *Pichia pastoris*, in addition to 6-hydroxydaidzein and 3-hydroxydaidzein [91]. This compound has been shown to have anti-proliferative, tyrosinase inhibition, aldose reductase inhibition, anti-inflammatory, and antioxidant activities [79, 92–95], indicating that soybeans fermented with *G. lucidum* mycelia might also have these properties. Since the mechanism of conversion of hydroxydaidzein to daidzin is known [96], and given its valuable properties, synthetic hydroxydaidzein is produced at the commercial level, but the process has its own limitations, such as the formation of undesirable by-products, lengthy reaction steps and low yield [97]. Large-scale production of hydroxydaidzein using natural resources such as *A. oryzae* are being investigated [96, 98]. Our results have added several suitable candidates for this purpose. In particular, soybeans fermented using *G. lucidum* mycelia have enormous potential to be used as food, nutritional supplement and as a source for commercial production of hydroxydaidzein.

Acknowledgements

We are grateful to the Chairman and CEO Masahito Hoashi, Kibun Foods Inc., for his support of this study.

Conflict of interest

The authors declare that there are no conflicts of interest.

Author details

Kohei Suruga*, Tsuyoshi Tomita and Kazunari Kadokura
Research and Development Division, Products Development Department, Kibun Foods Inc., Tokyo, Japan

*Address all correspondence to: kouhei_suruga@kibun.co.jp

References

[1] Wang Q, Wang F, Xu Z, Ding Z. Bioactive mushroom polysaccharides: A review on monosaccharide composition, biosynthesis and regulation. Molecules. 2017;**22**:955. DOI: 10.3390/molecules22060955

[2] Yang Y, He P, Li N. The antitumor potential of extract of the oak bracket medicinal mushroom *Inonotus baumii* in SMMC-7721 tumor cells. Evidence-based Complementary and Alternative Medicine. 2019;**2019**:1242784. DOI: 10.1155/2019/1242784

[3] Yang NC, Wu CC, Liu RH, Chai YC, Tseng CY. Comparing the functional components, SOD-like activities, antimutagenicity, and nutrient compositions of *Phellinus igniarius* and *Phellinus linteus* mushrooms. Journal of Food and Drug Analysis. 2016;**24**:343-349. DOI: 10.1016/j.jfda.2015.11.007

[4] Ellan K, Thayan R, Raman J, Hidari KIPJ, Ismail N, Sabaratnam V. Anti-viral activity of culinary and medicinal mushroom extracts against dengue virus serotype 2: An in-vitro study. BMC Complementary and Alternative Medicine. 2019;**19**:260. DOI: 10.1186/s12906-019-2629-y

[5] Fontes A, Alemany-Pagès M, Oliveira PJ, Ramalho-Santos J, Zischka H, Azul AM. Antioxidant versus pro-apoptotic effects of mushroom-enriched diets on mitochondria in liver disease. International Journal of Molecular Sciences. 2019;**20**:3987. DOI: 10.3390/ijms20163987

[6] Mori K, Obara Y, Hirota M, Azumi Y, Kinugasa S, Inatomi S, et al. Nerve growth factor-inducing activity of *Hericium erinaceus* in 1321N1 human astrocytoma cells. Biological & Pharmaceutical Bulletin. 2008;**31**:1727-1732. DOI: 10.1248/bpb.31.1727

[7] Kimura T, Yamamoto K, Nishikawa Y. Comparison of the antitumor effect of the fruit body and mycelia of Hanabiratake (*Sparassis crispa*). Mushroom Science and Biotechnology. 2013;**21**:129-132. DOI: 10.24465/msb.213_129

[8] Li IC, Lee LY, Tzeng TT, Chen WP, Chen YP, Shiao YJ, et al. Neurohealth properties of *Hericium erinaceus* mycelia enriched with erinacines. Behavioural Neurology. 2018;**2018**:5802634. DOI: 10.1155/20185802634

[9] Suruga K, Kadokura K, Sekino Y, Nakano T, Matsuo K, Irie K, et al. Effects of comb tooth cap medicinal mushroom, *Hericium ramosum* (Higher Basidiomycetes) mycelia on DPPH radical scavenging activity and nerve growth factor synthesis. International Journal of Medicinal Mushrooms. 2015;**17**:331-338. DOI: 10.1615/imtjmedmushrooms.v17.i4.20

[10] Suruga K, Tomita T, Kadokura K. Soybean fermentation with basidiomycetes (medicinal mushroom mycelia). Chemical and Biological Technologies in Agriculture. 2020;**7**:23. DOI: 10.1186/s40538-020-00189-1

[11] Yoneyama M, Meguro S, Kawachi S. Liquid culture of *Agaricus blazei* (in Japanese). Mokuzai Gakkaishi. 1997;**43**:349-355

[12] Mizuno M, Morimoto M, Minato K, Tsuchida H. Polysaccharides from *Agaricus blazei* stimulate lymphocyte T-cell subsets in mice. Bioscience, Biotechnology, and Biochemistry. 1998;**62**:434-437. DOI: 10.1271/bbb.62.434

[13] Nakamura T, Matsugo S, Uzuka Y, Matsuo S, Kawagishi H. Fractionation and anti-tumor activity of the mycelia of liquid-cultured *Phellinus linteus*. Bioscience, Biotechnology, and Biochemistry. 2004;**68**:868-872. DOI: 10.1271/bbb.68.868

[14] Osawa T, Ide A, Su JD, Namiki M. Inhibition of in vitro lipid peroxidation by ellagic acid. Journal of Agricultural and Food Chemistry. 1987;**35**:808-812. DOI: 10.1021/jf00077a042

[15] Marseglia L, Manti S, D'Angelo G, Nicotera A, Parisi E, Rosa GD, et al. Oxidative stress in obesity: A critical component in human diseases. International Journal of Molecular Sciences. 2015;**16**:378-400. DOI: 10.3390/ijms16010378

[16] Cutlar RG. Genetic stability and oxidative stress: Common mechanisms in aging and cancer. In: Emerit I, Chance B, editors. Free Radicals and Aging. Basel: Birkhäuser; 1992. pp. 31-46

[17] Zhang Y, Fischer KE, Soto V, Liu Y, Sosnowska D, Richardson A, et al. Obesity-induced oxidative stress, accelerated functional decline with age and increased mortality in mice. Archives of Biochemistry and Biophysics. 2015;**576**:39-48. DOI: 10.1016/j.abb.2014.12.018

[18] Halliwell B, Gutteridge JMC. Free Radicals in Biology and Medicine. 2nd ed. Oxford: Clarendon Press; 1989. pp. 20-30

[19] Peng X, Gao Q, Zhou J, Ma J, Zhao D, Hao L. Association between dietary antioxidant vitamins intake and homocysteine levels in middle-aged and older adults with hypertension: A cross-sectional study. BMJ Open. 2021;**11**:e045732. DOI: 10.1136/bmjopen-2020-045732

[20] Midoh N, Tanaka A, Nagayasu M, Furuta C, Suzuki K, Ichikawa T, et al. Antioxidative activities of oxindole-3-acetic acid derivatives from supersweet corn powder. Bioscience, Biotechnology, and Biochemistry. 2010;**74**:1794-1801. DOI: 10.1271/bbb.100124

[21] Shahidi F, Yao JD. Insoluble-bound phenolics in food. Molecules. 2016;**21**:1216. DOI: 10.3390/molecules21091216

[22] Eskin NA, Ho CT, Shahidi F. Browning reactions in foods. In: Eskin NAM, Shahidi F, editors. Biochemistry of Foods. 3rd ed. Cambridge, MA, USA: Academic Press; 2012. pp. 245-289

[23] Osakabe N, Yasuda A, Natsume M, Yoshikawa T. Rosmarinic acid inhibits epidermal inflammatory responses: Anticarcinogenic effect of *Perilla frutescens* extract in the murine two-stage skin model. Carcinogenesis. 2004;**25**:549-557. DOI: 10.1093/carcin/bgh034

[24] Singleton VL, Orthofer R, Lamuela-Raventos RM. Analysis of total phenols and other oxidation substrates and antioxidants by means of Folin-Ciocalteu reagent. Methods in Enzymology. 1999;**299**:152-178

[25] Collerton D. Cholinergic function and intellectual decline in Alzheimer's disease. Neuroscience. 1986;**19**:1-28. DOI: 10.1016/0306-4522(86)90002-3

[26] Obara Y, Nakahata N. The signaling pathway of neurotrophic factor biosynthesis. Drug News & Perspectives. 2002;**15**:290-298. DOI: 10.1358/dnp.2002.15.5.840042

[27] Allen SJ, Dawbarn D. Clinical relevance of the neurotrophins and their receptors. Clinical Science (London). 2006;**110**:175-191. DOI: 10.1042/CS20050161

[28] Kromer LF. Nerve growth factor treatment after brain injury prevents

neuronal death. Science. 1987;**235**: 214-216. DOI: 10.1126/science.3798108

[29] Furukawa Y, Furukawa S, Ikeda F, Satoyoshi E, Hayasghi K. Aliphatic side chain of catecholamine potentiates the stimulatory effect of the catechol part on the synthesis of nerve growth factor. FEBS Letters. 1986;**208**:258-262. DOI: 10.1016/0014-5793(86)81028-6

[30] Tekauchi R, Murase K, Furukawa Y, Furukawa S, Hayashi K. Stimulation of nerve growth factor synthesis/ secretion by 1,4-benzoquinone and its derivatives in cultured mouse astroglial cells. FEBS Letters. 1990;**261**:63-66. DOI: 10.1016/0014-5793(90)80637-x

[31] Obara Y, Nakahata N, Kita T, Takaya Y, Kobayashi H, Hosoi S, et al. Stimulation of neurotrophic factor secretion from 1321N1 human astrocytoma cells by novel diterpenoids, scabronines A and G. European Journal of Pharmacology. 1999;**370**:79-84. DOI: 10.1016/s0014-2999(99)00077-1

[32] Kawagishi H, Shimada A, Hosokawa S, Mori H, Sakamoto H, Ishiguro Y, et al. Erinacines E, F, and G, stimulators of nerve growth factor (NGF)-synthesis, from the mycelia of *Hericium erinaceum*. Tetrahedron Letters. 1996;**37**:7399-7402. DOI: 10.1016/0040-4036(96)01687-5

[33] Kawagishi H, Ando M, Shinba K, Sakamoto H, Yoshida S, Ojima F, et al. Chromans, hericenones F, G and H from the mushroom *Hericium erinaceum*. Phytochemistry. 1992;**32**:175-178. DOI: 10.1016/0031-9422(92)80127-Z

[34] Kawagishi H, Shimada A, Shirai R, Okamoto K, Ojima F, Sakamoto H, et al. Erinacines A, B and C, strong stimulators of nerve growth factor (NGF)-synthesis, from the mycelia of *Hericium erinaceum*. Tetrahedron Letters. 1994;**35**:1569-1572. DOI: 10.1016/S0040-4039(00)76760-8

[35] Kawagishi H, Ando M, Mizuno T. *Hericenone A and B as cytotoxic principles from the mushroom Hericium erinaceum*. Tetrahedron Letters. 1990;**31**:373-376. DOI: 10.1016/S0040-4039(00)94558-1

[36] Lee EW, Shizuki K, Hosokawa S, Suzuki M, Suganuma H, Inakuma T, et al. Two novel diterpenoids, erinacines H and I from the mycelia of *Hericium erinaceum*. Bioscience, Biotechnology, and Biochemistry. 2000;**64**:2402-2405. DOI: 10.1271/bbb.64.2402

[37] Hazekawa M, Kataoka A, Hayakawa K, Uchimasu T, Furuta R, Irie K, et al. Neuroprotective effect of repeated treatment with *Hericium erinaceum* in mice subjected to middle cerebral artery occlusion. Journal of Health Science. 2010;**56**:296-303. DOI: 10.1248/jhs.56.296

[38] Bahuguna A, Shukla S, Lee JS, Bajpai VK, Kim SY, Huh YS, et al. Garlic augments the functional and nutritional behavior of Doenjang, a traditional Korean fermented soybean paste. Scientific Reports. 2019;**9**:5436. DOI: 10.1038/s41598-019-41691-3

[39] Liu KS. Chemistry and nutritional value of soybean components. In: Soybeans, Chemistry, Technology, and Utilization. New York, USA: Chapman & Hall; 1997. pp. 25-113

[40] Derbyshire E, Wright DJ, Boulter D. Legumin and vicilin, storage proteins of legume seeds. Phytochemistry. 1976;**15**:3-24. DOI: 10.1016/S0031-9422(00)89046-9

[41] Sacks FM, Lichtenstein A, Van Horn L, Harris W, Kris-Etherton P, Winston M. Soy protein, isoflavones, and cardiovascular health: An American heart association science advisory for professionals from the nutrition committee. Circulation. 2006;**113**:1034-1044. DOI: 10.1161/ CIRCULATIONAHA.106.171052

[42] Kwon YS, Lee S, Lee SH, Kim HJ, Lee CH. Comparative evaluation of six traditional fermented soybean products in East Asia: A metabolomics approach. Metabolites. 2019;**9**:183. DOI: 10.3390/metabo9090183

[43] Křížová L, Dadáková K, Kašparovská J, Kašparovskŷ T. Isoflavones. Molecules. 2019;**24**:1076. DOI: 10.3390/molecules 24061076

[44] Friend DR, Change GW. A colon-specific drug-delivery system based on drug glycosides and the glycosidases of colonic bacteria. Journal of Medicinal Chemistry. 1984;**27**:261-266. DOI: 10.1021/jm00369a005

[45] Messina M, Kucuk O, Lampe JW. An overview of the health effects of isoflavones with an emphasis on prostate cancer risk and prostate-specific antigen levels. Journal of AOAC International. 2006;**89**:1121-1134

[46] Carroll KK. Review of clinical studies on cholesterol-lowering response to soy protein. Journal of the American Dietetic Association. 1991;**91**:820-827

[47] Ye YB, Tang XY, Verbruggen MA, Su YX. Soy isoflavones attenuate bone loss in early postmenopausal Chinese women: A single-blind randomized, placebo-controlled trial. European Journal of Nutrition. 2006;**45**:327-334. DOI: 10.1007/s00394-006-0602-2

[48] Lethaby A, Marjoribanks J, Kronenberg F, Roberts H, Eden J, Brown J. Phytoestrogens for vasomotor menopausal symptoms. Cochrane Database of Systematic Reviews. 2007;**17**:CD001395. DOI: 10.1002/14651858.CD001395.pub3

[49] Walker DE, Axelrod B. Evidence for a single catalytic site on the "β-D-glucosidase-β-D-glactosidase" of almond emulsin. Archives of Biochemistry and Biophysics. 1978;**187**:102-107. DOI: 10.1016/0003-9861(78)90011-5

[50] Miura T, Yuan L, Sun B, Fujii H, Yoshida M, Wakame K, et al. Isoflavone aglycone produced by culture of soybean extracts with basidiomycetes and its anti-angiogenic activity. Bioscience, Biotechnology, and Biochemistry. 2002;**66**:2626-2631. DOI: 10.1271/bbb.66.2626

[51] Ou B, Hampsch-Woodill M, Prior RL. Development and validation of an improved oxygen radical absorbance capacity assay using fluorescein as the fluorescent probe. Journal of Agricultural and Food Chemistry. 2001;**49**:4619-4626. DOI: 10.1021/jf10586o

[52] Matsui T, Yoshimoto C, Osajima K, Oki T, Osajima Y. In vitro survey of α-glucosidase inhibitory food components. Bioscience, Biotechnology, and Biochemistry. 1996;**60**:2019-2022. DOI: 10.1271/bbb.60.2019

[53] Ohta T, Sasaki S, Oohori T, Yoshikawa S, Kurihara H. Alpha-glucosidase inhibitory activity of a 70% methanol extract from ezoishige (*Pelvetia babingtonii* de Toni) and its effect on the elevation of blood glucose level in rats. Bioscience, Biotechnology, and Biochemistry. 2002;**66**:1552-1554. DOI: 10.1271/bbb.66.1552

[54] Sawada Y, Tsuno T, Ueki T, Yamamoto H, Furukawa Y, Oki T. Pradimicin Q, a new pradimicin aglycone, with α-glucosidase inhibitory activity. The Journal of Antibiotics. 1993;**46**:507-510. DOI: 10.7164/antibiotics.46.507

[55] Kudou S, Fleury Y, Welti D, Magnolato D, Uchida T, Kitamura K, et al. Malonyl isoflavone glycosides in soybean seeds (*Glycine max* MERRILL). Agricultural and Biological Chemistry.

1991;**55**:2227-2233. DOI: 10.1271/bbb1961.55.2227

[56] Lindequist U, Niedermeyer THJ, Jülish WD. The pharmacological potential of mushrooms. Evidence-based Complementary and Alternative Medicine. 2005;**2**:285-299. DOI: 10.1093/ecam/neh107

[57] Sun J, Chu YF, Wu X, Liu RH. Antioxidant and antiproliferative activities of common fruits. Journal of Agricultural and Food Chemistry. 2002;**50**:7449-7454. DOI: 10.1021/jf0207530

[58] Abdullash N, Ismail SM, Aminudin N, Shuib AS, Lau BF. Evaluation of selected culinary-medicinal mushrooms for antioxidant and ACE inhibitory activities. Evidence-based Complementary and Alternative Medicine. 2012;**2012**:464238. DOI: 10.1155/2012/464238

[59] Yang JH, Tseng YH, Lee YL, Mau JL. Antioxidant properties of methanolic extracts from monascal rice. LWT- Food Science and Technology. 2006;**39**:740-747. DOI: 10.1016/j.lwt.2005.06.002

[60] Salaheddin C, Takakura Y, Tsunashima M, Stranzinger B, Spadiut O, Yamabjai M, et al. Characterization of recombinant pyranose oxidase from the cultivated mycorrhizal basidiomycete *Lyophyllum shimeji* (hon-shimeji). Microbial Cell Factories. 2010;**9**:1-12. DOI: 10.1186/1475-2859-9-57

[61] Yaoita Y, Kohata R, Kakuda R, Machida K, Kikuchi M. Ceramide constituents from five mushrooms. Chemical & Pharmaceutical Bulletin. 2002;**50**:681-684. DOI: 10.1248/cpb.50.681

[62] Ukawa Y, Hisamitsu M, Ito H. Antitumor effects of (1→3)-β-D-glucan and (1→6)-β-D-glucan purified from newly cultivated mushroom, Hatakeshimeji (*Lyophyllum decastes* Sing). Journal of Bioscience and Bioengineering. 2000;**90**:98-104

[63] Barger G, Ewins AJ. CCLVII—The constitution of ergothioneine: A betaine related to histidine. Journal of the Chemical Society, Transactions. 1911;**99**:2336-2341

[64] Yeh JY, Hsieh LH, Wu KT, Tsai CF. Antioxidant properties and antioxidant compounds of various extracts from the edible basidomycete *Grifola frondosa* (Maitake). Molecules. 2011;**16**:3197-3211. DOI: 10.3390/molecules16043197

[65] Zhang Y, Mills GK, Nair MG. Cyclooxygenase inhibition and antioxidant compounds from the mycelia of the edible mushroom *Grifola frondosa*. Journal of Agricultural and Food Chemistry. 2002;**50**:7581-7585. DOI: 10.1021/jf0257648

[66] Reis FS, Martins A, Barros L, Ferreira ICFR. Antioxidant properties and phenolic profile of the most widely appreciated cultivated mushrooms: A comparative study between in vivo and in vitro samples. Food and Chemical Toxicology. 2012;**50**:1201-1207. DOI: 10.1016/jf2012.02.013

[67] Khan MA, Tania M, Liu R, Rahman MM. *Hericium erinaceus*: An edible mushroom with medicinal values. Journal of Complementary and Integrative Medicine. 2013;**10**:1-6. DOI: 10.1515/jcim-2013-0001

[68] Zhang Z, Lv G, Pan H, Pandey A, He W, Fan L. Antioxidant and hepatoprotective potential of endo-polysaccharides from *Hericium erinaceus* grown on tofu whey. International Journal of Biological Macromolecules. 2012;**51**:1140-1146. DOI: 10.1016/j.ijbiomac.2012.09.002

[69] Chételat G, Joie RL, Villain N, Perrotin A, Sayette VL, Eustache F, et al. Amyloid imaging in cognitively normal individuals, at-risk populations and preclinical Alzheimer's disease. NeuroImage: Clinical. 2013;**2**:356-365. DOI: 10.1016/j.nicl.2012.02.006

[70] Kawagishi H, Zhuang C. Compounds for dementia from *Hericium erinaceum*. Drugs of the Future. 2008;**33**:149-155. DOI: 10.1358/dof.2008.033.02.1173290

[71] Kawagishi H, Ando M, Sakamoto H, Yoshida S, Ojima F, Ishiguro Y, et al. Hericenones C, D and E, stimulators of nerve growth factor (NGF)-synthesis, from the mushroom *Hericium erinaceum*. Tetrahedron Letters. 1991;**32**:4561-4564. DOI: 10.1016/0040-4039(91)80039-9

[72] Saito T, Aoki F, Hirai H, Inagaki T, Matsunaga Y, Sakakibara T, et al. Erinacine E as a kappa opioid receptor agonist and its new analogs from a Basidiomycete, *Hericium ramosum*. The Journal of Antibiotics. 1998;**51**:983-990. DOI: 10.7164/antibiotics.51.983

[73] Kawagishi H, Shimada A, Shizuki K, Ojima F, Mori H, Okamoto K, et al. Erinacines D, a stimulator of NGF-synthesis, from the mycelia of *Hericium erinaceum*. Heterocyclic Communications. 1996;**2**:51-54

[74] Chaturvedi VK, Agarwal S, Gupta KK, Ramteke PW, Singh MP. Medicinal mushroom: Boon for therapeutic applications. 3 Biotech. 2018;**8**:334. DOI: 10.1007/s13205-018-1358-0

[75] El Enshasy HA, Hatti-Kaul R. Mushroom immunomodulators: Unique molecules with unlimited applications. Trends in Biotechnology. 2013;**31**:668-677. DOI: 10.1016/j.tibtech.2013.09.003

[76] Muszyńska B, Grzywacz-Kisielewska A, Kała K, Gdula-Argasińska J. Anti-inflammatory properties of edible mushrooms: A review. Food Chemistry. 2018;**243**:373-381. DOI: 10.1016/j.foodchem.2017.09.149

[77] Matsui T. Development of functional foods by mushroom fermentation (in Japanese). Mushroom Science and Biotechnology. 2017;**24**(4):169-175

[78] Esaki H, Kawakishi S, Morimitsu Y, Osawa T. New potent antioxidative o-dihydroxyisoflavones in fermented Japanese soybean products. Bioscience, Biotechnology, and Biochemistry. 1999;**63**:1637-1639. DOI: 10.1271/bbb.63.1637

[79] Esaki H, Watanebe R, Onozaki H, Kawakishi S, Osawa T. Formation mechanism for potent antioxidative o-dihydroxyisoflavones in soybean fermented with *Aspergillus saitoi*. Bioscience, Biotechnology, and Biochemistry. 1999;**63**:851-858. DOI: 10.1271/bbb.63.851

[80] Willcox JK, Ash SL, Catignani GL. Antioxidants and prevention of chronic disease. Critical Reviews in Food Science and Nutrition. 2004;**44**:275-295. DOI: 10.1080/10408690490468489

[81] Suruga K, Akiyama Y, Kadokura K, Sekino Y, Kawagoe M, Komatsu Y, et al. Synergistic effect on reactive oxygen scavenging activity of fermented okara and banana by XYZ system. Food Science and Technology Research. 2007;**13**:139-144. DOI: 10.3136/fstr.13.139

[82] Suruga K, Kato A, Kadokura K, Hiruma W, Sekino Y, Buffinton CAT, et al. "Okara" a new preparation of food material with antioxidant activity and dietary fiber from soybean. In: El-Shemy H, editor. Soybean and Nutrition. 1st ed. London, UK: IntechOpen; 2011. pp. 311-326. DOI: 10.5772/18821

[83] Noguchi S, Suruga K, Nakai K, Murashima A, Koshino-Kimura Y, Kobayashi A. An exploratory study of okara product on postprandial blood glucose and serum insulin responses. The Japanese Journal of Nutrition and Dietetics. 2018;**76**:156-162. DOI: 10.5264/eiyogakuzashi.76.156

[84] Lee DS, Lee SH. Genistein, a soy isoflavone, is a potent α-glucosidase inhibitor. FEBS Letters. 2001;**501**:84-86. DOI: 10.1016/s0014-5793(01)02631-x

[85] Doan DT, Luu DP, Nguyen TD, Thi BH, Thi HMP, Do HN, et al. Isolation of *Penicillium citrinum* from roots of *Clerodendron cyrtophyllum* and application in biosynthesis of aglycone isoflavones from soybean waste fermentation. Food. 2019;**8**:554. DOI: 10.3390/foods8110554

[86] Baraldo JA, Borges DG, Tardioli PW, Farinas CS. Characterization of β-glucosidase produced by *Aspergillus niger* under solid-state fermentation and partially purified using MANAE-agarose. Biotechnology Research International. 2014;**2014**:317092. DOI: 10.1155/2014/317092

[87] Langston J, Sheehy N, Xu F. Substrate specificity of *Aspergillus oryze* family 3 beta-glucosidase. Biochimica et Biophysica Acta, Proteins and Proteomics. 2006;**1764**:972-978. DOI: 10.1016/j.bbapap.2006.03.009

[88] Krogh KBRM, Harris PV, Olsen CL, Johansen KS, Hojer-Pedersen J, Borjesson J, et al. Characterization and kinetic analysis of a thermostable GH_3 beta-glucosidase from *Penicillium brasilianum*. Applied Microbiology and Biotechnology. 2010;**86**:143-154. DOI: 10.1007/s00253-009-2181-7

[89] Tsukada T, Igarashi K, Yoshida M, Samejima M. Molecular cloning and characterization of two intracellular β-glucosidase belonging to glycoside hydrolase family 1 from the basidiomycete *Phanerochaete chrysosporium*. Applied Microbiology and Biotechnology. 2006;**73**:807-814. DOI: 10.1007/s00253-006-0526-z

[90] Chang TS, Wang TY, Yang SY, Kao YH, Wu JY, Chiang CM. Potential industrial production of a well-soluble, alkaline-stable, and anti-inflammatory isoflavone glucoside from 8-hydroxydaidzein glucosylated by recombinant amylosucrase of *Deinococcus geothermalis*. Molecules. 2019;**24**:2236. DOI: 10.3390/molecules24122236

[91] Chiang CM, Ding HY, Tsai YT, Chang TS. Production of two novel methoxy-isoflavones from biotransformation of 8-hydroxydaidzein by recombinant *Escherichia coli* expressing O-methyltransferase SpOMT2884 from *Streptomyces peucetius*. International Journal of Molecular Sciences. 2015;**16**:27816-27823. DOI: 10.3390/ijms161126070

[92] Lo YL. A potential daidzein derivative enhances cytotoxicity of epirubicin on human colon adenocarcinoma Caco-2 cells. International Journal of Molecular Sciences. 2013;**14**:158-176. DOI: 10.3390/ijms14010158

[93] Tai SS, Lin CG, Wu MH, Chang TS. Evaluation of depigmenting activity by 8-hydroxydaidzein in mouse B16 melanoma cells and human volunteers. International Journal of Molecular Sciences. 2009;**10**:4257-4266. DOI: 10.3390/ijms10104257

[94] Fujita T, Funako T, Hayashi H. 8-Hydroxydaidzein, an aldose reductase inhibitor from okara fermented with *Aspergillus* sp. HK-388. Bioscience, Biotechnology, and Biochemistry. 2004;**68**:1588-1590. DOI: 10.1271/bbb.68.1588

[95] Wu PS, Ding HY, Yen JH, Chen SF, Lee KH, Wu MJ. Anti-inflammatory activity of 8-hydroxydaidzein in LPS-stimulated BV2 microglial cells via activation of Nrf2-antioxidant and attenuation of Akt/NF-κB-inflammatory signaling pathways, as well as inhibition of COX-2 activity. Journal of Agricultural and Food Chemistry. 2018;**66**:5790-5801. DOI: 10.1021/acs.jafc.8b00437

[96] Seo MH, Kim BN, Kim KR, Lee KW, Lee CH, Oh DK. Production of 8-hydroxydaidzein from soybean extract by *Aspergillus oryzae* KACC 40247. Bioscience, Biotechnology, and Biochemistry. 2013;**77**:1245-1250. DOI: 10.1271/bbb.120899

[97] Roh C, Seo SH, Choi KY, Cha M, Pandey BP, Kim JH, et al. Regioselective hydroxylation of isoflavones by *Streptomyces avermitilis* MA-4680. Journal of Bioscience and Bioengineering. 2009;**108**:41-46. DOI: 10.1016/j.jbiosc.2009.02.021

[98] Wu SC, Chang CW, Lin CW, Hsu YC. Production of 8-hydroxydaidzein polyphenol using biotransformation by *Aspergillus oryzae*. Food Science and Technology Research. 2015;**21**:557-562. DOI: 10.3136/fstr.21.557

Edited by Naofumi Shiomi and Anna Savitskaya

The market for functional foods is steadily expanding as more people worldwide realize the value of the daily consumption of healthy foods in maintaining good health. Recent studies have revealed new functional compounds in foods. Genetically modified foods will soon be commercially available. This book discusses the characteristics of functional foods and the health benefits of ingredients including ginger, herbs, probiotics, mushrooms, and dairy products. It also provides new ideas for the production of new functional foods and managing health through the daily diet.

Published in London, UK

IntechOpen

ISBN 978-1-80355-794-6
9 781803 557946