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Gut Microbiota

Brain Axis

Edited by Alper Evrensel and Barış Önen Ünsalver

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and **Barış Önen Ünsalver**

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Meet the editors

Dr. Alper Evrensel is currently an assistant professor of psychiatry at Uskudar University, Turkey. He has been working at the NP Istanbul Brain Hospital for 10 years specializing in the areas of neuropsychiatry and neuropsychophilosophy. He has published over 50 papers in peer-reviewed journals, as well as four invited chapters in books from Springer Nature editions. His research and clinical interests focus on the gut–brain axis and fecal microbiota transplantation in neuropsychiatric disorders.

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Contents

Preface

The gut–brain axis has gained considerable attention from different branches of the scientific community in recent years. In this book, scientists from different disciplines present current scientific knowledge on the topic.

The brain's processes are not confined solely to neuronal activity. Besides the endocrine, metabolic, and other organ systems the brain is also affected both directly and indirectly by the functions of non-human cells. These co-residents living in the human body are called "microbiota."

Most of the bacterial communities that are colonized throughout the body are situated in the intestines and mainly in the colonic mucosa. These microorganisms result in localized and generalized inflammation in three ways: they enter the systemic circulation actively, they secrete metabolites, and through their cellular elements these metabolites spread into the lumen as a result of their cellular destruction.

This book focuses on the effects of microbiota on brain functions and microbiota-based treatments for neuropsychiatric disorders using references from the current scientific literature.

The first section is called "General Outlook on the Gut–Brain Axis" and in the first chapter the world of prokaryotes is examined widely. Prokaryotes have an ability called "quorum sensing." The author explains the mechanisms for the interactions, communication, cooperation, and competitive struggle among prokaryotes through their quorum-sensing ability. Prokaryotes have an important impact not only on the order and continuity of humans but also on all other living things on earth.

Probiotics may offer positive effects on brain functions. The second chapter presents a detailed explanation of the potential healing role of probiotics in the brain through their effects on the stress pathway and neuroinflammatory processes.

The third chapter focuses on the philosophy of nutrition, which is the starting point for understanding and solving dysbiosis. Regarding the current relationship of humans with food, attention is given to food and its function as a drug throughout history.

The second section is called "Role of Microbiota in Specific Neuropsychiatric Disorders" and the fourth chapter focuses on autistic disorder. Early microbiota dysbiosis may interact with neuronal development and differentiation, which may be related to autistic disorder development. The effects of dysbiosis on the gastrointestinal and neuronal functions of the infant are described in detail in this chapter.

The fifth chapter concentrates on the consequences of dysbiosis in the geriatric population. Fecal microbiota transplantation (FMT) is a treatment method for the restoration of the dys-

biotic intestinal mucosa. FMT and its promises for the geriatric population are explained widely by the author.

Probiotics constitute one of the microbiota-based treatments. In the final chapter, the possibility of reversing the cognitive impairment in Alzheimer's disease with probiotic augmentation is discussed.

Surprising pieces of evidence for various functions of the microbiota are being published in an ever-increasing way and this book is an effort to present and discuss these current scientific findings on the gut–brain axis from various perspectives. We hope that the reader benefits from the presented material.

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Section 1

General Outlook on the Gut-Brain Axis

Chapter 1

Prokaryotes Rule the World

Bishnu Adhikari, Young Min Kwon,
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Additional information is available at the end of the chapter

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Abstract

For millions of years, prokaryotic organisms have functioned as a vital selective force shaping eukaryotic evolution. It is now widely accepted that gut bacteria play a vital role in various physiological and metabolic activities of hosts, and thus, it is essential to maintain their homeostasis. Previous studies have shown an association of gut bacterial imbalance (dysbiosis) associated with several pathologies. However, very little is known about possible mechanisms involved between bacteria and hosts to maintain their homeostasis in the gut. Bacterial activities, such as cooperation (biofilm formation, horizontal gene transfer, quorum sensing, etc.), antagonism, and combination, and host responses of their immune system, gut barrier functions, and different dietary components have been identified as crucial factors for maintaining bacterial homeostasis in the gut. Our understanding of several possible mechanisms involved in gut bacterial homeostasis should be widened to modulate their composition or treat diseases. The objective of this chapter is to provide an overview of different factors involved in gut bacterial homeostasis with an emphasis on host intestinal barrier and immune system, dietary components, and quorum sensing. Also, brief information regarding roles of microbiota on gut-brain axis has also been included.

Keywords: prokaryotes, *quorum sensing*, gut microbial homeostasis, microbiome

1. Background

It is now well-established fact that almost any metazoan either invertebrates or vertebrates harbor gut microbiota [1]. Complex and diverse bacterial populations were reported from the alimentary tract of humans which were previously estimated to be around 10^{14} [2]. Moreover, the total microbiome present in a human was estimated to be 10 times higher than the total

number of their somatic and germ cells [2]. On the contrary, a recent study showed the variations in gut bacterial number from 10^7 (Stomach, Duodenum, and Jejunum) to 10^{14} (Colon) and estimated the almost equal number of total bacterial and human cells [3]. Approximately, 3.3 million nonredundant genes were reported to be present in the microbiome of the human gut, whereas only around 20,000 genes were present in a human genome suggesting substantial genetic diversities of microbial populations [4]. Besides, more than 99% of these genes represent 1000–1150 different bacterial species [5] which suggests the presence of diverse and complex microbiota in the gut of humans.

During these days, there has been enormous progress in sequencing technologies regarding both increasing the throughput and decreasing the cost and error rate. Significant efforts have been made in characterizing compositions and functions of microbiota along with this advancement in sequencing technologies and have reported complex and diverse groups of microbiota residing in various regions of hosts including skin, oral cavity, nasal cavity, urogenital tract, and gut [5, 6]. Such type of variations can occur not only among different regions but can also within different locations of the same area (e.g., lumen vs. mucosa of the gut), as shown in **Figure 1** [7]. Among various microbes residing inside and outside of both humans and animals, bacteria living in the gut have been widely studied and have been found to have an effect on health and diseases through complex interactions with their hosts. Various factors such as diets, antibiotics, a method of delivery and infant feeding, illness, stress, aging, lifestyles, and host genetics can affect gut microbiota [8, 9]. The proper balance

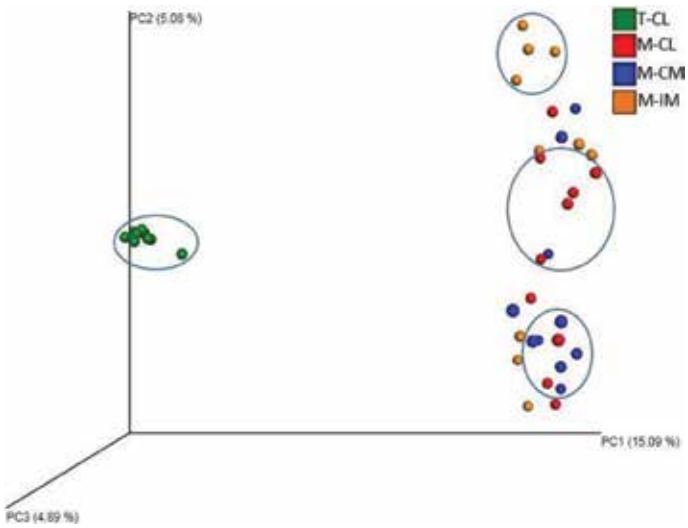

Figure 1. PCoA plot showing significant difference in bacterial community structure among different regions and locations of gastrointestinal tract of 3-week old chickens. MRS-recovered cells from cecal lumen (M-CL), cecal mucosa (M-CM) and ileal mucosa (M-IM), and total bacterial cells from cecal lumen (T-CL) (ANOSIM results; $R = 0.67$, $p = 0.001$). This figure is adapted from reference [7], figure 6(A).

of microbiota is needed to maintain microbial homeostasis inside gut, which potentially affect the health of individuals. Change in composition of gut microbiota by any factors as described earlier is called dysbiosis, which can cause several diseases and disorders including allergies, inflammatory bowel disease (IBD), diabetes, cancer, and autism as reviewed earlier [8]. Even though detail mechanisms that are responsible for maintaining gut microbial homeostasis need to be explored more in the future, host intestinal barrier and immune system, dietary components and Quorum sensing are some of the critical mechanisms identified and studied so far [10].

2. Intestinal barrier and host immune system for maintaining microbial homeostasis

Prokaryotes are prevalent in all environments [11, 12] having to live in mutualism with eukaryotes [13–16]. Adaptive diversification is a process intrinsically tied to species interactions [17]. The endosymbiotic theory states that several vital organelles of eukaryotes originated as symbioses between separate single-celled organisms [18, 19]. Hence, organelles such as mitochondria and plastids once free-living bacteria that were taken by the more important cell as an endosymbiont [20–22]. The microbiome of the gastrointestinal tract (GIT) contains over 50 genera and at least 1000 different species [23–29], and the cecum and colon of humans, harbor ~10^{13} cfu/g [29], covering to 40–55% of solid stool matter and weights [30–32]. The microbiome modulates the development of the innate and acquired immune system [33–35], gastrointestinal physiology [36–41] and digestibility of nutrients [42–46] of metazoans. Many factors including nutrient composition, stress, and antibiotics can alter the microbiome [47–51]. In fact, the western obesogenic diet is associated to induce and promote several metabolic disorders and cancer [52–58]. Microbiome and its host are working as one single organism. One of the fascinating aspects of this mutualism is the impact in the regulation of inflammatory responses [59–63]. Enterocytes not only participate in digestion and absorption of nutrients, but they also involve as antigen presenting cells and regulates gut permeability. The host's intestinal epithelial cells provide both physical and chemical barriers to pathogenic bacteria through the production of mucus, secretion of antimicrobial peptides from Paneth cells, IgA from plasma cells, forming intercellular tight junction complexes, and recognition of MAMP [63, 64]. Furthermore, specific products that are synthesized and secreted from symbionts can prevent colonization of pathogenic or opportunistic commensal bacteria. For instance, a single microbial molecule (PSA) synthesized by *Bacteroides fragilis* was found to protect from colitis induced by *Helicobacter hepaticus* through the suppression of pro-inflammatory interleukin-17 and enhancement of interleukin-10-producing $CD4^+$ T cells [65]. Likewise, commensal bacteria can activate innate and adaptive immune system to eliminate pathogens through the invasion of host's epithelial cells [64]. Furthermore, commensal bacteria can play a vital role in the promotion of lipopolysaccharides (LPS) detoxification through

the activation of epithelial intestinal alkaline phosphatase (IAP) expression and can also involve in gut-associated lymphoid tissue (GALT) development and secondary bile acids formation [63].

3. Effects of different dietary components on microbial homeostasis

Various nutrients present in diets are sources of microbial metabolism and affect significantly on structure, composition, and diversities of microbiota which have been reviewed previously [66, 67]. Dietary fibers are the most common source of fuel for fermentation by human microbes among different nutritional components [68]. Dietary fibers are complex carbohydrates of plant origin which cannot be digested by the host's enzymes and need specific enzymes of microbial origin for digestion [69]. Western diets are lower in dietary fibers in comparison with traditional diets, and these differences can have a significant impact on microbiota composition and diversity. Studies have reported changes in microbiota composition, reduced microbial diversity and lower production of short chain fatty acids (SCFA) in individuals having a Western diet in comparison with those having a traditional diet [70–72]. Those carbohydrates that can be metabolically utilized by gut microbes and can affect their composition, functions and metabolic activities have recently been termed as "microbiota-accessible carbohydrates" (MACs) [68]. A recent study reported the progressive loss of microbial diversity in mice fed with low dietary MACs, which could not be recovered with higher MACs after second, third, and fourth generation [73]. Similarly, supplementation of diet with a brown seaweed *Laminaria japonica* that are higher in MACs resulted desirable shift in intestinal microbiota composition of rats through decrease in obesity-associated bacterial genera (*Allobaculum*, *Turicibacter*, *Coprobacillus*, *Mollicute*, and *Oscilibacter*), and bacterial genera with pathogenic potentials (*Mollicute*, *Bacteroides*, *Clostridium*, *Escherichia*, and *Prevotella*) and increase in Lactic acid bacteria (*Subdoligranulum*, *Streptococcus*, *Lactobacillus*, *Enterococcus*, and *Bifidobacterium*) [74]. Besides, a diet deprived in MACs can cause a detrimental impact on gut homeostasis and stimulate the development of different inflammatory diseases including allergies, infections, and autoimmune diseases as reviewed earlier [75].

Short-chain fatty acids (SCFA) such as acetate, propionate, and butyrate that are produced through fermentation of MACs by enteric microbiota play an essential role in maintaining homeostasis of gut microbiota through various activities including induction of IgA, secretion of mucus, and promotion of intestinal barrier, besides immune tolerance to commensal bacteria through indirectly regulation of B and T cells [59].

4. Interactions between prokaryotes and eukaryotes

Complex interactions occur within microbes and with their hosts through various communicating mechanisms to keep their niches homeostasis. Those interactions can be either

mutualistic or antagonistic through horizontal gene transfer, biofilm formation, and *quorum sensing* or compete for nutrients and combat with other species including pathogens through the stimulation of bacteriocins, microcins, and colicins secretion [63].

5. Communication between prokaryotes and eukaryotes

Communication/signaling between Prokaryotes such as bacteria and their eukaryotic hosts is known as interkingdom communication. For the first time, the interaction between bacteria was described in two marine bioluminescent bacteria, *Vibrio fischeri* and *Vibrio harveyi* as an autoinduction [76, 77] which was later termed as *quorum sensing* (QS) [78]. *Quorum sensing* is a cell-to-cell communication process in bacteria which enables them to monitor changes in bacterial density and alter genes expression accordingly. QS is a complicated process which involves production, detection, and response to extracellular signaling molecules known as autoinducers (AIs). An increase in population density results increases in the concentration of AIs which helps bacteria to monitor changes in their cell numbers and response collectively by changing genes expression globally. Traditionally, QS was believed to occur only among bacteria. However, several recent studies reported the existence of interkingdom communication [79, 80].

6. Communication between Gram-positive and Gram-negative bacteria

It is now accepted the fact that both Gram-positive and Gram-negative bacteria use QS. But there exist differences regarding both AIs they detect and the mechanisms they respond to respective AIs. Secreted peptides serve as the signaling molecule in Gram-positive bacteria. Peptides are synthesized inside bacterial cells and are modified through processing and cyclization during the process of secretion fascinated with specialized transporters [81–85]. Once secreted peptides reach a threshold concretion, they are detected at the bacterial surface by the sensor protein which enables bacterial cells to modulate gene expression at a population level [86]. Some peptides produced by these bacteria bind membrane-bound histidine kinase receptor inducing phosphorylation responses with the consequent activation of gene expression in the QS regulon. [87]. In sum, QS in Gram-positive bacteria occur by using secreted peptides through a two-component system that consists of membrane-bound histidine kinase receptor and a cognate cytoplasmic response regulator that regulates transcription.

Gram-negative bacteria typically use acyl-homoserine lactones (AHLs) as an autoinducer in QS [88]. These bacteria can utilize other signaling molecules like AI-2 and CAI-1 whose production is mainly dependent on S-adenosylmethionine (SAM) as a substrate [89]. LuxI/LuxR regulatory system of *V. fischeri* is a typical example of QS in Gram-negative bacteria [90]. LuxI catalyzes synthesize of AHLs and LuxR which is a cytoplasmic receptor regulates

transcriptional factor after binding with AHLs. Thus, in Gram-negative bacteria QS regulatory system, AIs receptor is a cytoplasmic receptor whereas membrane-bound in case of Gram-positive bacteria. Similarly, the AIs in case of Gram-negative bacteria can diffuse in and out of the cell. In contrast, in Gram-positive bacteria, those molecules need to be transported.

7. Communication between bacteria and hosts

Communication between bacteria and hosts involves hormones produced by host and hormones, that is, autoinducers (AIs) produced by bacteria [91]. The hormones produced by hosts can be divided into three broad categories: protein or peptides, steroid, and amines. Among them, protein or peptides serve as prohormones. Other hormones such as epidermal growth factor (EGF), insulin, glucagon, and amine hormones such as catecholamines, adrenaline, noradrenaline (NA), dopamine are some of the essential hosts' hormones involved in interkingdom signaling [92].

The presence of specific bacterial receptors of these hormones produced by mammalian cells is a crucial factor for communication between them. QS is affected by different mammalian hormones and the ways of sensing by bacteria to modulate their activities. As described earlier [92], adrenaline and noradrenaline (A and NA) secreted by mammalian cells are detected by bacterial membrane-bound histidine kinases (QseC and QseE). Also, QseC and QseE sense bacterial AI-3 signaling and sources of sulfates (SO_4) and phosphates (PO_4), respectively. These signalings phosphorylate KdpE, QseB, and QseF that leads to activate the expression of T3SS, motility, and Shiga toxin. Dynorphin, which is a crucial neuropeptide involved in the stress signal [93], has been found to enter into bacterial cells and sensed by MvfR/PqsR receptor leading to increase in virulence of bacteria though *quorum sensing*, through direct or indirect sensing of dynorphin by MvfR/PqsR needs to be explored. Lipid hormones such as, estrone, estradiol, and estriol can enter into bacterial cells and effect on LuxR-type regulators that inhibit *quorum sensing*, albeit it is not clear whether LuxR-type regulators are the receptors of those hormones or not. Although receptors for natriuretic peptides are not known, they are found to promote virulence, biofilm formation, and lipopolysaccharides (LPS) modifications in bacteria.

Apart from those host's hormones and bacterial receptors as described above, there are several examples where bacteria sense host's hormones. Gastrin has been associated with an increase in the growth of *H. pylori*. Also, *H. pylori* infection has been found to associate with an increase in gastrin secretion suggesting the interkingdom communication [92]. Other examples include sensing of EGFs, opioid hormones.

Besides hormones, different nutrients such as ethanol-amine (EA) and sugars have also been reported to involve in QS. Also, bacteria can sense various components of the immune system such as cytokines, apolipoprotein B (ApoB), Nox2, and antimicrobial peptides, modulating the host immune responses [92]. The possibility of interkingdom communication between Nef protein of HIV-1 virus and the host through exosomes has been recently reviewed, which extends the existence of QS other than in bacteria [94]. Likewise, QS can occur in animals

and plants [92]. Furthermore, recent studies have demonstrated the possibilities of host microRNA-microbiota communication and emphasized needs of exploring more in the future regarding the involvement of microRNAs in QS [95, 96].

8. The microbiome-gut-brain axis

Prokaryotes in the GIT secrete or induce the secretion of several neuropeptides that participate in the communication between the enteric and the central nervous systems, involved in several aspects from brain development to inflammation and behavior [16, 97–100]. These interactions are today described by a relatively new field of study known as microbial endocrinology [101–109]. This is a two-way communication because just as prokaryotes can regulate brain activities, the central nervous system can also induce dramatic changes in the gut microbiome [110–112]. For instances, chronic ingestion of live *Lactobacillus plantarum* PS128 in germ free mice increased levels of serotonin and dopamine in the striatum suggesting the possibility of improving behaviors related to anxiety through daily intake of that particular strain of *L. plantarum* [113]. Besides, stress hormones such as adrenaline and corticosteroids can increase the virulence of enteropathogens [114–117]. Although different routes and mechanisms involved in the bidirectional communication between microbiota and brain are still being explored, some of those that have been previously described include the vagus nerve, signaling of gut hormones, bacteria derived metabolites such as SCFA, the immune system, and tryptophan metabolism [118, 119].

9. Concluding remarks

Colonization of microbiota before or after the birth of individuals is still a subject of debate [120], but it is widely accepted that methods of delivery affect the microbiota of infants. During the early life of individuals, they harbor less complex gut microbiota which changes along with their growth and becomes a conventional core microbiota at adult stage [121]. However, their composition, structure, and diversity are significantly affected by different factors such as diet, stress, medication, host-genetics, lifestyle, and so on. Dysbiosis of gut microbiota by any means can lead to severe outcomes, and thus, it is essential to maintain microbial homeostasis in the gut. A balance between pro- and inflammatory cytokines is needed to maintain gut microbial homeostasis [122]. Albeit detail mechanisms that are responsible for maintaining homeostasis between trillions of bacteria and human cells are still being explored, various microbial activities such as co-operation (biofilm formation, horizontal gene transfer, *quorum sensing* etc.), antagonism, and combination, host responses of their immune system, gut barrier functions, and different dietary components are some of the vital factors for maintaining homoeostasis in the gut. Microbes (bacteria/virus) can communicate with each other and also with hosts (mammalian or no mammalian) through the use of different hormones and signal molecules as described earlier. Such communications help microbes to alter their various activities including virulence and modulate host immune responses and thus, significantly

have an effect on health and diseases of hosts. Although multiple mechanisms involved in communication between microbes and host epithelial cells as well as their roles in health and diseases are still being explored, their various activities that have been identified and studied so far are so fascinating and seem that they are ruling the eukaryotes.

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Chapter 2

Influence of Probiotic Supplementation on Brain Function: Involvement of Gut Microbiome, Inflammation, and Stress Pathway

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Additional information is available at the end of the chapter

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Abstract

Probiotics were reported for several physical and psychological health benefits. Probiotics can positively alter the gut microbiome and nourish the commensal microbial load. Recent studies revealed that the cognitive functions (anxiety and depression) of human beings are meticulously associated with their genetic makeup, food habits, and gut microbiome. The gut microbiome may communicate with the brain through neural and humoral pathways, while involving several neurotransmitters and signaling molecules. The immune response, especially inflammatory system, plays a critical role in the microbiome and in mental health. Thus, many studies were conducted to explore the beneficial effect of probiotic, single and multistrain, formulations. Fruitful results were observed, but the underlying mechanism of probiotic-mediated improvement of mental health is not fully illustrated, even though some studies explained that the production of neurotransmitter-like metabolites by the probiotic strain could be the possible mediator of gut-brain axis. The present chapter summarizes the outcome of probiotic-based treatment for the improvement of stress and depression with respect to microbiome change, inflammation, and stress pathway.

Keywords: probiotics, stress, depression, anxiety, microbiome, inflammation

1. Introduction

According to FAO/WHO, probiotics are living bacteria that, which when administered in suitable amounts, confer a health benefit to the host. *Lactobacillus* (*Lactobacillus casei, L. paracasei,*

L. acidophilus, L. fermentum, L. rhamnosus, L. brevis, L. plantarum, L. johnsonii, and *L. delbrueckii* subsp. *bulgaricus*), *Bifidobacterium* (*Bifidobacterium bifidum, B. breve, B. longum, B. adolescentis, B. infantis, B. animalis* subsp. *animalis, B. animalis* subsp. *lactis*), *Enterococcus, Saccharomyces* (*Saccharomyces bayanus, S. boulardii*), *Streptococcus, Leuconostoc, Pediococcus,* and *Bacillus* are the common genera of probiotic strains [1]. Generally, probiotics are known for the improvement of digestion, nutrient absorption, immune modulatory property, maintaining the intestinal microbiota and supplement for metabolic disorders. But recent studies suggested that the supplementation of probiotic-containing traditional functional foods improved the mental health and cognitive function of the host [2, 3].

The brain is a vital organ involved in leading and coordinating the homeostasis of the body. The changes or defect in the brain functions are closely associated with the development of serious physiological and emotional impairment [4, 5]. The cognitive impairment is not only associated with a decline in brain function but also linked to the immune system and the changes in microbiome. The new finding and complexity of the network provide new perceptions into cognitive dysfunctions [6].

The microbes residing in the gastrointestinal tract of human have been referred as gut microbiota or gut microbiome. The commensal microbial population was closely associated with the host system, and they have a complex connective ecosystem, which influences the physical and functionality of the host. Bacteroides, Prevotella, and Ruminococcus families are three most abundant bacterial communities in the gastrointestinal tract. Recent studies demonstrated how the commensal microbes modify them according to the environment and the availability of nutrition [7].

Inflammation is one of the body processes of protecting against harmful stimuli or any antigens. Even though inflammation is a part of the immune system, the chronic inflammation may lead to the development of malignancy. The alteration in microbiome and release of endogenous microbial debris induce chronic inflammation. More significantly, the microbiome may play an imperative role in modulating behavior by linking the immune systems and neuroendocrine via cytokines and the nerve system [8].

The stress and immune-induced pathways, for example, kynurenine pathway (PK), are involved in several neurodegenerative diseases and psychiatric disorders. Manipulating the gut microbiome may diminish the effect of stress-induced neurological damages. Studies on the link between the gut microbiome and brain provide significant information about the role of the microbiome in brain function and development [9]. The metabolites of gut microbiome act as neurotransmitters, which regulate the brain function [10]. The role of the gut microbiome and probiotic supplementation on the improvement of memory has been reported [3]. The infection-mediated induction of cytokines altered the neuronal system and leads to the development of behavioral abnormalities [11].

Recently, probiotics were studied for their involvement in neurology, neurobehaviors, brain function, and cognition. Several preliminary studies revealed the importance of probiotics in neuroscience and cognition [12, 13]. The present chapter compiles the information about the probiotic-based improvement of brain health with respect to the cognitive function and discusses the microbiome changes upon probiotic supplementation.

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2. Gut microbiome, inflammation, and brain function

The microbial load in the human gastrointestinal tract is about 10^{14} cells; on the other hand, studies suggested that the ratio of microbial and human cells is 3:1. The diversity and richness of the microbial community are varied during the developmental stage of the host, and two-thirds of microbes are unique to every human being. This unique microbial community is responsible for the host individuality in terms of immunity, physical activity, and overall health status. The mislead in the symbiotic relationship between host and microbes cause some unwanted health conditions like diabetes, obesity, and inflammatory bowel diseases [14, 15].

The mutual communication between brain and gut is documented, and the information exchange has been carried out via several immunes, neuroendocrine pathways, and enteric nerve systems [16, 17]. About 500 million nerve endings, mostly enteric nerve system, and high concentrations of immune cells are present in the gastrointestinal tract (GI), so most of the bidirectional interaction between the gut and brain mainly occurs in the GI tract. The afferent neurons of the enteric nervous system communicate with the GI tract and brain through the vagus nerve [18].

Several biochemical and neuronal signaling pathways are established and involved in the GI tract and central nerve system (CNS), and the signaling network is known as gut-brain-axis. The malfunction of the gut-brain axis may cause pathophysiological events and is linked to inflammation, chronic abdominal pain, eating disorders, and stress [16, 17]. The vagus nerve system, cell wall components (pathogen-associated molecular patterns, e.g., lipopolysaccharide, peptidoglycan monomers, and lipoteichoic acids), fatty acids, metabolites, neurotransmitters and neuropeptides-like gamma-aminobutyric acid (GABA), serotonin, and brain-derived neurotrophic factors are the key players of the gut-brain axis [15].

The association of microbiome and immune system has been studied using germ-free mice. The supplementation of specific microbes, either pathogenic or commensal, to germ-free mice and the study of the changes in the behavior and immune system help to understand the role of particular microbes in host immune system and cognition. The results of studies using germ-free model revealed the importance of gut microbiome. The immune system of gut protects the system from pathogenic infection and supports the growth of commensal microbes [8]. The immune system of the antibiotic-treated mice was diminished during flu virus exposure compared to untreated mice, which revealed the importance of beneficial gut microbes, especially *Bifidobacterium* and *Lactobacillus* spp. [19].

A balanced communication between host immune system and gut microbiome is necessary to establish the homeostasis, which protects the system during adverse conditions. The weakening of gut-brain signaling is linked with the development of inflammation. If there is any alteration in the neuroendocrine system, for example, cortisol level, the barrier function of the gut is amended and the permeability increased, which in turn induces the release of cytokines by immune cells [16].

The lipopolysaccharide (LPS) injection is employed to induce a strong immune response, which increases the level of pro-inflammatory cytokines and glucocorticoids. The LPS challenging mimic as pathogenic infection and the elucidated immune response can weaken the development of the physiological system [20]. LPS can induce the release of pro-inflammatory cytokines, interferons, IL-1β, IL-2, IL-6, and TNF-α that can act on the brain, and initiates the

acute-phase responses like fever, reduced food intake, and boosted pain response [21, 22]. The responses, both physiological and behavioral, to pathogen-associated molecular pattern (like LPS, lipoteichoic acid, and flagellin) are comparable to the physiological and behavioral changes in neurological disorders like anxiety, depression, and autism. It is evidenced that gut-brain axis, microbiome, and immune system are related to each other [21–23].

3. Stress, microbiome, and immune system

Psychological disorders like anxiety and depression display consequences on the gastrointestinal function that links to the brain. The brain can communicate with the gut via the hypothalamic-pituitary-adrenal (HPA) axis, autonomic, and the enteric nervous system. Stress may be responsible for the dysregulation of gut-brain axis and cause gastrointestinal consequences [24]. The corticotrophin-releasing factor (CRF), a group of peptides of the central nervous system, is one of the regulators of immune, endocrine, and behavioral response to stress. The CRFs can alter the gut-brain interaction, which can alter the gastrointestinal motility, gastrointestinal secretion, intestinal permeability, intestinal microbiota, and visceral perception.

The pituitary gland releases the adrenocorticotropic hormone that stimulates the adrenal glands to produce cortisol, a stress hormone. All the processes were initiated by the release of CRF in the hypothalamus, which in turn activates the hypothalamic pituitary adrenal axis [25]. The crosstalk between gut-brain axis, the gut microbiome, and the immune system has a crucial role in the inflection of the stress response of the gut in terms of the development of gut disorders and diseases. The stress changes the microbial flora, which may have a reflective effect on the gut-brain axis and may alter the permeability, motility, and visceral sensitivity [26].

The microbiome of normal and depressed humans has been analyzed and the results revealed that there were no significant changes in the microbial group, but the amount of specific bacterial groups was altered (increase in Bacteroidetes species and decrease in Lachnospiraceae) among the depressed people. Especially, Oscillibacter (can produce GABA like neurotransmitter) and Alistipes were more abundant in depressed individuals. Alistipes was reported to be associated with stressed mice, chronic fatigue syndrome, and irritable bowel syndrome [27–30]. Jiang et al. reported that major depressive people have high amounts of Bacteroidetes, Actinobacteria, and Proteobacteria, while Firmicutes content was very low [31].

The stress brings the changes in inflammatory cytokines and neurotransmitter levels that could disturb the microbiota either directly or indirectly. The increase in norepinephrine alters the virulence of commensal bacteria like *Escherichia coli*. The sensitivity to pain can be altered in the gut microbiota, and stress-induced intestinal permeability has been suppressed by the probiotic supplementation [32]. For example, *E. coli* Nissle strain reduced the stress-mediated gastric lesions, and the effect was sensitive to capsaicin-mediated blockage of the sensory nerves. The probiotic effect of *E. coli* Nissle was restored by the addition of calcitonin gene-related peptide. The study proved the bidirectional talk between microbiota and the enteric nervous system [33]. The mast cells produced several vital mediators and acted as a receptor for CRF, thereby conveying the stress signal to the gut. The prolonged exposure to stress, chronic stress, may cause even permanent changes in the brain which affects the alertness of pain in the gut [32, 34].

Stress can induce the tryptophan metabolic pathways, also known as kynurenine pathway (KP). KP is known to be involved in several neurological regulations and neurodegenerative diseases [35, 36]. The connections between kynurenine pathway, stress, microbiota, and gut-brain axis are not fully elucidated. The involvement of KP in stress and neuropsychiatric disorder has been reported [37].

4. Impact of probiotic supplementation on brain function, immunity, and microbiome

4.1. *In vivo* studies

The mice (germ-free and specific pathogen-free) were supplemented with *B. infantis* or enteropathogenic *Escherichia coli* (EPEC) and then the acute restraint stress response was analyzed. The adrenocorticotropic hormone and corticosterone levels were high in germ-free mice, while brain-derived neurotrophic factor was low compared to specific pathogen-free mice. *B. infantis* intervention reduced the stress response in germ-free mice, whereas the EPEC enhanced the stress response. The authors suggested that the boost in HPA response in germ-free mice was associated with reformation of gut microbiota with the faces of specific pathogen-free mice. The development of postnatal hypothalamic-pituitary-adrenal (HPA) stress response is greatly associated with commensal microbes, which were exposed during the early stage of development [38].

The female Wister rats were supplemented with *L. farciminis*, with the ability to release nitric oxide, and proved to have anti-inflammatory property, (10^{11} CFU/day) for 15 days and were subjected to partial restraint stress study and hemoglobin measurement. The results proved that *L. farciminis* intervention suppressed the stress, reduced the colonial permeability, and colonocyte myosin light chain phosphorylation compared to control [39].

Trichuris muris mediated gastric inflammation was induced in the mice and were supplemented with *Lactobacillus rhamnosus* NCC4007 or *Bifidobacterium longum* NCC3001 for 10 days. The supplementation of *B. longum* NCC3001 normalized the behavior and expression of a brain-derived neurotrophic factor, whereas kynurenine and cytokines levels were not affected. The study suggested that chronic gastrointestinal inflammation mediated anxiety-like behavior can be normalized by *B. longum* NCC3001 via either inflammation-dependent or independent mechanisms [40]. The anxiolytic effect of *B. longum* NCC3001, in DSS-induced colitis mice, was associated with vagal integrity without the involvement of immune modulation and brain-derived neurotrophic factor. The histopathological status and myeloperoxidase activity were not affected by the probiotic intervention [41].

The male BALB/c mice supplemented with *L. rhamnosus* (10^9 CFU) for 28 days showed differential expression of $GABA_{B1b}$ mRNA in various regions of the brain and also exhibited the region-specific expression of $GABA_{A\alpha 2}$. The study also highlighted the involvement of vagus nerve system in the bidirectional communication between gut microbiome and brain. *L. rhamnosus* supplemented mice showed a reduction in anxiety and depression and stress-induced corticosterone levels [41].

The anxiolytic-like activity of probiotic preparation comprising of *L. helveticus* R0052 and *B. longum* R0175 (PP) has been reported in rats. The rats supplemented with PP for 14 days showed reduced anxiety-like behavior in conditioned defensive burying test [2].

The communication between gut-brain, inflammatory response, and function of probiotic were interconnected and also associated with diet and genetic makeup of individuals. *L. helveticus* ROO52 (10^9 CFU/d) was supplemented to wild-type and immune-deficient mice (IL-$10^{-/-}$) for 21 days, and the experimental animals were maintained with normal diet or high-fat Western-style diet (WSD) (33% of fat and 49% carbohydrates). The mice under the WSD increased body weight and showed altered cytokine expression, microbiome change, and anxiety-like behavior, irrespective of their genetic makeup. The intervention of *L. helveticus* ROO52 improved the anxiety-like behavior in wild-type mice with normal laboratory diet. The effect of *L. helveticus* ROO52 was negative in WSD mice. The microbiota analysis revealed that microbial clustering was associated with diet, immunity, and probiotic intervention. The study suggested that the diet and immune status of an individual greatly influence the functionality of an active probiotic supplement [42].

Due to the changes in brain function, inflammatory disease patients may have sickness behaviors. The supplementation of VSL#3 (a mixture of 1.7 billion cells of *Streptococcus salivarius* subsp., *thermophilis*, *B. longum*, *B. breve*, *B. infantis*, *L. casei*, *L. acidophilus*, *L. plantarum*, and L. *delbrueckii* subsp. *Bulgaricus*) for 10 days reduced the sickness behavior, which was associated with decrease in cerebral monocyte infiltration and microglial activation [43].

The rats were supplemented with 0.5–1.0% of *Lactobacillus* metabolites (LM) (containing lactate, organic and amino acids, enzymes, polypeptides, and microelements), and the animals were subjected to ratiometric Ca^{2+} imaging. The results suggested that the continuous supplementation of LM improved the release and absorption of Ca^{2+}, which in turn enhanced the psychological and cognitive functions and also stimulated the brain intracellular signaling [44].

L. rhamnosus (JB-1)™ was supplemented to C57BL/6 mice for 4 weeks and were exposed to chronic social defeat. The stress-mediated anxiety-like behavior was reduced and improved the social interaction in *L. rhamnosus* supplemented mice, without affecting the aggressor avoidance behavior. The intervention of *L. rhamnosus* weakened the dendritic cell activation while increasing the regulatory T cells. The social defeat exposure altered the fecal metabolites and gut microbiota. The study suggested that JB-1 can reduce the stress-induced behaviors, but failed to prevent dysbiosis [45].

4.2. Clinical trails

The mood and cognition of the healthy human volunteers were measured at baseline, during and after the intervention of *L. casei* strain Shirota (6.5×10^9 CFU) containing probiotic yogurt. The study results suggested that probiotic supplementation improved the stress, anxiety, and depression state of the subjects. Overall, probiotic yogurt enhanced the good mood [46].

The impact of probiotic supplementation on stress-induced gastrointestinal consequences was studied. The stressed people were treated with probiotic preparation, which contains 3×10^9 CFU of *L. acidophilus* Rosell-52 and *B. longum* Rosell-175, for 3 weeks. The probiotic supplementation significantly reduced the symptoms of stress-induced gastrointestinal problems

such as nausea and abdominal pain, while not affecting the social, emotional, mental, psychological, physical, and sleeping problems attributed to the stressful lifestyle [47].

The patients with chronic fatigue syndrome (CFS) were supplemented with *L. casei* strain Shirota (24 billion CFU/day) for 60 days. The Beck Anxiety and Beck Depression data were collected from the volunteers before and after the intervention. Anxiety was decreased and a load of Bifidobacteria and *Lactobacillus* spp. were increased after intervention compared to placebo control. The results suggested that single probiotic intervention could alter the gut microbiota and can improve the health status of CFS patients [48].

The intervention of probiotic preparation containing 3 billion CFU of *L. helveticus* R0052 and *B. longum* R0175 (PP) in human volunteers improved the psychological distress, measured by Hopkins Symptom Checklist, Hospital Anxiety and Depression Scale, and urinary free cortisol levels. There were no adverse effects recorded during the study period [2]. The supplementation of PP has not affected the learning and memory of human volunteers, and also not cause any addition [49].

The children with the autism spectrum disorder were supplemented with *L. acidophilus* strain Rosell-11 (5×10^9 CFU/g) for 2 months, and the urine D-arabinitol and the D-/L-arabinitol ratio at baseline and after the intervention period were measured. The level of D-arabinitol and the D-/L-arabinitol ratio was reduced after probiotic supplementation, and the results also suggested that probiotic intervention was an effective antifungal treatment. The study also reported that the supplementation of Rosell-11 significantly improved the concentration and response to the order among the autistic children [50].

The fermented milk with probiotics (FMP) consisting of 1.25×10^{10} CFU of *B. animalis* subsp. *Lactis* and 1.2×10^9 CFU of *Streptococcus thermophiles*, *L. bulgaricus*, and *Lactococcus lactis* subsp. *Lactis* was supplemented to healthy women volunteers twice daily for 4 weeks, and they were subjected to functional magnetic resonance imaging. The results suggested that FMP intake reduced the task-related responses and altered the midbrain connectivity. The FMP intervention influences the central processing of emotion and consciousness in healthy volunteers [51].

Acute psychological stress is linked to the onset of flu/cold. The supplementation of *L. helveticus* R0052, *B. longum* ssp. infantis R0033, and *B. bifidum* R0071 to healthy, but academically stressed, students for 6 weeks significantly reduced the flu/cold symptoms. Especially, those who were supplemented with *Bifidobacterium* spp. showed better protective effects than other groups [52].

The healthy volunteers were consumed the multispecies probiotic preparation containing *Lactococcus lactis*, *L. brevis* W63, *L. salivarius* W24, *L. acidophilus* W37, *L. casei* W56, *B. lactis* W52, and *B. bifidum* W23 for 4 weeks, and cognitive response to sad mood was measured. The results suggested that probiotic intervention reduced the negative thoughts, depression, and improved the ability to manage the sad situation compared to placebo group [53].

Kato-Kataoka et al. conducted a double-blind, placebo-controlled study on the impact of probiotic supplementation (*L. casei* strain Shirota) on the physical, psychological, and stress response of the students, those who prepared for the medical entrance qualification examination. An 8-week probiotic supplementation and measurement of salivary cortisol, serotonin, L-tryptophan, and psychophysical state at different points of intervention revealed that the consumption of probiotic drink reduced the consequences of stress and improved the general health [54].

The healthy petrochemical workers were randomized and supplemented with probiotic yogurt containing *L. acidophilus* LA5 and *B. lactis* BB12 or probiotic capsule containing *L. casei, L. acidophilus, L. rhamnosus, L. bulgaricus, B. breve, B. longum, Streptococcus thermophilus*, or conventional yogurt or placebo for 6 weeks, and the mental health of the participants was measured by using depression anxiety and stress scale scores and general health questionnaire. The study results suggested that the supplementation of probiotic yogurt and multispecies capsule improved the psychological state of petrochemical workers while conventional yogurt does not have any health promoting role [55]. The 8-week supplementation of *L. casei* strain Shirota (10^9 CFU/day) significantly reduced the stress-induced upsurge of cortisol level and improved the stress management among the academically stressed students [56].

5. Conclusion

Depression and stress are associated with several inflammatory consequences and dysregulation of gut microbiota. The brain function, microbiome, and immune system were interconnected. The childhood experiences like diet habit, stress, and immune activation can affect the development of specific microbiome and cognition in the later age of life. The supplementation of probiotic, especially multispecies formulation, can positively regulate the gut microbiota, brain function, and helps to maintain the typical immune state of the host (**Table 1**). The beneficial effects of probiotic are closely associated with diet, genetic makeup, and commensal microbiota of the host. The secretion of neurotransmitters-like molecules and promoting the growth of beneficial commensal microbes are the possible ways by which probiotics confer the mental health benefits. How the microbiome is influencing the cognition and brain function and its mechanisms are scope for further investigation.

S. No.	Model	Intervention	Duration	Effects	Refs.
In vivo studies					
1	Male BALB/c mice	*Lactobacillus rhamnosus* (10^9 CFU)	28 days	Modulation of the GABAergic system. Reduced the depression and anxiety	[12]
2	Germfree, specific pathogen-free, and gnotobiotic BALB/c mice	*B. infantis*	—	Normalized the inflated stress response	[38]
3	Female Wistar rats	*L. farciminis* (10^{11} CFU/day)	15 days	Reduced the partial restraint stress	[39]
4	Male AKR mice	*Bifidobacterium longum* NCC3001	10 days	Normalized the anxiety behavior	[40]
5	Dextran sodium sulfate treated mice	*B. longum* NCC3001	7 days	Normalized the anxiety behavior, but not myeloperoxidase activity	[41]
6	Wistar rats	*L. helveticus* R0052, and *B. longum* R0175	14 days	Reduced the anxiety-like behavior	[2]
7	Mice	*L. helveticus* R0052 (10^9 CFU/day)	21 days	Decreased anxiety-like behavior	[42]

S. No.	Model	Intervention	Duration	Effects	Refs.
8	Mice	VSL#3 (*Streptococcus salivarius* subsp., *thermophilis*, *B. breve, B. infantis, B. longum, L. acidophilus, L. plantarum, L. casei*, and *L. delbrueckii* subsp. *Bulgaricus*) (1.7 billion cells)	10 days	Reduced the inflammation-associated sickness behavior	[43]
9	Rats	*Lactobacillus* spp. fermented product (metabolites of *Lactobacillus*)	—	Improved the brain intracellular signaling	[44]
10	Male C57BL/6 mice	*L. rhamnosus* (1.67×10^9 CFU)	28 days	Protected from stress-induced behaviors	[45]
Clinical trials with human subjects					
11	Healthy human	Probiotic yogurt containing *L. casei* Shirota (6.5×10^9 CFU)	21 days	Improved the mood	[46]
12	Stressed human volunteers	*L.s acidophilus* Rosell-52, and *B. longum* Rosell-175 (3×10^9 CFU)	21 days	Reduced the stress-induced gastrointestinal problems	[47]
13	Chronic fatigue syndrome patients	*L. casei* strain Shirota	60 days	Reduced the symptoms of anxiety	[48]
14	Healthy human	*L. helveticus* R0052, and *B. longum* R0175	30 days	Reduced the psychological distress	[2]
15	Healthy human	*L. helveticus* R0052, and *B. longum* R0175	—	Reduced the cortisol level and improved the anxiety and depression. Not affecting the learning and memory	[49]
16	Autism spectrum disorder patients	*L. acidophilus* strain Rosell-11 (10×10^9 CFU/day)	60 days	Reduced the level of D-arabinitol, and D-/L-arabinitol ratio. Improved the responsiveness to the orders	[50]
17	Healthy women	*B. animalis* subsp. *Lactis* (1.25×10^{10} CFU), *Streptococcus thermophiles*, *L. bulgaricus* (1.2×10^9 CFU), and *Lactococcus lactis* subsp. *Lactis* (1.2×10^9 CFU) in fermented milk	28 days	Modulate the sensitivity of brain network in healthy women	[51]
18	Academically stressed students	*L. helveticus* R0052, *B. longum* ssp. *infantis* R0033, *B. bifidum* R0071.	42 days	Prevented the onset of stress-related cold/flu	[52]
19	Healthy volunteers	*B. bifidum* W23, *B. lactis* W52, *L. acidophilus* W37, *L. brevis* W63, *L. casei* W56, *L. salivarius* W24, and *L. lactis*	28 days	Reduced the negative thoughts	[53]
20	Healthy medical students	*L. casei* strain Shirota	56 days	Prevent the stress-related physical symptoms	[54]
21	Healthy petrochemical workers	*L. acidophilus LA5*, and *B. lactis BB12* (10^7 CFU); Multispecies probiotic capsule.	42 days	Improved the general health, and reduce the stress and depression	[55]
22	Healthy medical students	Fermented milk with *L. casei* strain Shirota (10^9 CFU)	56 days	Reduced the cortisol level, and reduced the symptoms of stress	[56]

Table 1. The influence of probiotic supplementation on brain function of the host system.

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Conflict of interest

The authors declare that there is no conflict of interests.

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Chapter 3

Philosophy of Nutrition: Past-Future Nutrition

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Additional information is available at the end of the chapter

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Abstract

"Back to the roots" is what we may call our experience in our researches concerning gut-brain axis. What Hippocrates, Plato, Ibn-Khaldun, Galen, and many other philosophers from antique ages suggested can be proven today with all our technological aids. The observation in the old of the link ages between nutrition and the well being of our souls, mind, and bodies was found to be true. In fact, what the ancient philosophers said about nutrition in connection with a healthy life is quite similar to what we hear in the recent years. This is a demonstration of how important it is to observe ourselves as humans. In the last researches, the connection between gut and brain and their formation of the personal mood showed the same results. Together with the mood, the spirit has also proven to be influenced by nutrition. Our industrial era put the focus right from the beginning more on feeding masses than on nurturing human kind. Leaving that aside, the doctors today concentrate more on diagnosis and their foreseen treatment than on observing and preventing dıseases. A healthy and conscious nutrition is the start of a healthy worth living lıfe. What philosophers and doctors found out hundreds of years ago should be applicable and excisable today.

Keywords: philosophy, nutrition

1. Past-future nutrition

Health is not only the absence of illness but also a complete state of physical, mental, and social well-being as defined by the Word Health Organization [1]. We can see the importance of environmental factors as well as the genetic factors in terms of people's view of health. To be a healthy individual, we should think physical health together with mental and spiritual health as a whole. We should not forget that the health of the location is connected with the environmental social circle [2].

When it comes to nutrition and philosophy, we can define that to search for wisdom. The philosopher is also the person who is trying to reach wisdom. Accordingly, philosophy has meant for the Greek "love of wisdom" or "quest for wisdom." Philosophy is also known as art of thought [3].

When examining the nutritional philosophy, it is necessary to examine the effect of the body, and why and what we eat. The first thing we need to examine is the nutrition itself. Nutrition is an action that must be done consciously to get the nutritional items needed by the body in sufficient quantities and at the right time to maintain health and improve quality of life. This action must be provided at every stage of the life cycle. Over the past three centuries, significant changes have occurred in people's habitats and eating habits. The modern agriculture and production practices that have developed from the Paleolithic period to the present day have laid the foundation of the intense energy-containing nutrition pattern of the century we are in and have caused human health to be adversely affected [4].

The ideas and interactions of human beings with regard to nutrition and their effects on humans have been conveyed throughout generations. Communication between healthy nutrition and mental health diseases has been described, and philosophers have expressed the influence of nutrition on people's mood and body.

We investigated the meaning of the term "Our bowels are leading us."

İn the ancient ages, philosophers and doctors were mostly the same persons. They observed the influence of nutrition on human behavior and emphasized that a healthy diet is a prerequisite for a healthy life. They were convinced that the way to get rid of diseases is mainly healthy nutrition. But the advent of medicine has turned from nutrition-health-related acceptance to drug-health-related acceptance, and medicine has put more weight on drug-oriented treatments.

While being able to be healthy by simply eating natural food, increasing technology and industry have laid ground for poor quality nutrition and have created new diseases. Medicine, however, has increased its awareness in recent years and has begun to find ways of preserving food without chemical add-ons. Nutrition for a healthy well-being is the most important of these.

In fact, what the ancient philosophers said about nutrition in connection with a healthy life is quite similar to what we hear in recent years. This is a demonstration of how important it is to observe ourselves as humans. The last researches, the connection between gut and brain and their formation of the personal mood showed the same results that had been found in ancient eras. Together with the mood, the spirit has also proven to be influenced by nutrition.

Fundamental researches have shown that a healthy long life is found by the importance of not only eating healthy but also eating less. We can put it as simple as the philosopher Ibn Khaldun said: "Hunger does not kill, an overfilled stomach does."

2. Philosophy of nutrition

2.1. Nutrition and philosophy in history

Physicians nowadays seem to have a good level of knowledge about the disease, but their approach to a healthy life is lacking. The development of technology of course accelerates

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the diagnosis of diseases. And the rapid diagnosis with the foreseen treatment of diseases causes the physicians to concentrate only on the diagnosis. As the diseases progressed in antique ages, some physicians have begun not only to heal but also to find ways to prevent illness. These first studies of the ancient world show amazing similarities to the recent studies, despite all the technological improvements we enjoy nowadays.

When we look at nutrition and health throughout history, we can find some common points of the most famous philosophers. It seems like a healthy life was more prevalent in antiquity. They were absolutely aware of the importance of nutrition in order to be healthy and get rid of diseases. Hippocrates [fifth century BC], the oldest Greek doctor, emphasized the importance of a diet after he observed the positive output on numerous patients. At that time, he actually linked many diseases to unhealthy eating habits and emphasized the importance of healthy food as a permanent therapy instead of an empirical drug treatment. İn addition, he also stated the importance of physical exercising on a regular basis [5].

Claudius Galenus, who is usually known as Galen, considered himself a student of the Hippocratic school. He extended his researches as a whole and explains the positive influence of a healthy diet in his book of six volumes, which contains the six "non-naturalia." The sense of the Greek term "d'iaita" was much broader than what nowadays has remained to be called "diet," so nutrition is only one of them. The other five aspects of a healthy life identified by Galen were environment; rest, including sleep; motion or exercise; evacuations including sexuality; and the state of mind or inner harmony [6, 7].

We can define nutrition philosophy as a part of the health philosophy. To look at the historical philosophy of nutrition and health, it is necessary to look from the antiquity to the twenty-first century.

With the development of the industrial and material era, the issue of a healthy nutrition has increased. What supposed to be the basis of a healthy life depreciated its value over the last century. We can find the roots of healthy nutrition again in the ancient civilization, especially the Greek era. The Greeks were the first who established physiocratic schools that teach that health is not separate from our social environment and our human behavior [5].

Regarding the connection of nutrition and health, we can refer to the social, physical, and environmental characteristics of the individual health of animals and plants. Nutritional knowledge, which is divergent in our narrow sense, is not only about eating and drinking and their biological aspects but also about the social and environmental concerns of animals and plants [6].

The new concepts are similar with what the ancient philosophers said. A new Meikirch model for individual care and public health was developed and published in 2014 [8]. According to this model, people's demands are based simply on physiological, psychosocial, and environmental matters. These physiological demands are oxygen, food, and water, and there are necessities such as birth, childbirth, and so on. Second, psychosocial demands are developing in the relations among people. Third, environmental factors are affecting the health, like clean water, air pollution, a safe working environment, etc. As of the healthy lifestyle described in the Meikirch model, environmental factors are important, as well as being aware of one's own health [8].

Unexpected guests once visited Heraclitus, found him in the kitchen, and were embarrassed to encounter this unbalanced situation for this distinguished man. However, it is reported that Heraclitus said: "Come in, there are Gods even here!" If nutrition is actually a human health issue, he was the first to identify the unity of nature [6].

Plato is one of the most important philosophers of Greece, with regard to health and speech. He was born in Athens, 428–348 BC. Plato also emphasizes the importance of proper nutrition and exercise to be healthy just like other philosophers, but according to Plato, olive oil is "useful"; however, it should not take an important place in the diet. He stated that olive oil is good for the outer parts of the human body but, at the same time, not too good to eat and digest. Fruits and dairy seem to have an important place in his diet; however, Plato's favorite foods were wheat and barley flour [9].

It is interesting that in ancient times olive oil cultivation plays an important role, but Plato does not recommend high amounts of olive oil. It is an important food value that encourages grain consumption.

The Pisagor School is clearly seen in the absence of the meat; vegetables and fruits are preferred, and consumption of meat was claimed to be related to obesity and disease. Plato's belief in the reincarnation of the souls might explain it. Plato said that the excess of nutrition causes excess diseases [9].

It is striking that philosophy associates obesity with disease and, at the same time, a short life expectancy. Dietary excess is considered to be an important contributor to human diseases. As a result, the diet should be kept in the hands of doctors or gymnastics instructors. In fact, the meaning of this concept is that dietetics should be seen as a separate field of medicine, not just an art.

The diet model depicted in Plato's works has distinct similarities with the Mediterranean diet. Over the last few decades, this diet has gained considerable popularity due to its beneficial effects on health. Many studies have shown that the Mediterranean diet is associated with lower incidence of stroke, coronary heart disease, and some types of cancer (although at the time, the basic elements of this diet model are based on ancient civilizations evolving around the Mediterranean). In fact, in the "Mediterranean diet," the main components are olive and olive oil, wheat, grape, and usually vegetables in all forms of salads [9, 10].

Avicenna is seen as the foundation stone of medicine. Avicenna's nutritional and health-related expressions suggest that eating habits have a health effect. While the habit was to eat twice a day full meals, he recommended to eat little by little and only small amounts. It has been argued that people interact with the environment; hereditary changes are based on diseases of the digestive system. To his relatives, he suggested eating mixed food from plants and animals to get rid of stomach and intestinal complaints [11].

Erzurumi İbrahim Hakkı, who lived in the eighteenth century and was a Turkish and Islamic thinker, has examined six titles in his "Marifet," "little food, little sleep, little talk."

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He emphasized that eating more food gives you the weight you do not need. He said that hunger can be a medicine and that the body's health would only be provided with few meals, not to say starvation. He stated that it gives you a good feeling to feel hungry and to have a better taste when you eat again. According to him, food is actually consumed by one's life, and a full stomach reduces the life span [12].

İbrahim Hakkı said that there are three things that cause problems in your life: too much food, too much sleep, and too much talk. If your stomach is full, your soul dies. If you eat less, your body turns into your soul.

You can provide the health of your body by eating less, and you can provide the health of your soul by sleeping less. If your stomach is completely full, it is like you are losing your spirit, and as long as you feel that full stomach, your true spirit will not come back. To stay a little hungry helps you to sleep less [12].

In Ibn Khaldun's first book, *Mukaddime*, the relationship between food stress and food abundance and physical condition, the mental and moral structures of man have been examined. Ibn Khaldun's view of health and ethics, which will be taken into consideration from the point of view of nutrition and health, is very thought-provoking. It has been observed that geographical regions have different soil fertility compared to climate changes and that the people living there influence the body structure and spirit of the feeding style [13, 14].

Ibn Khaldun observes that the bodies and morals of the nomadic people of the desert, lacking all kinds of negativity and deprivation, are more beautiful and esthetically pleasing than the bodies and morals of the people in fertile regions within abundance. In Ibn Khaldun's observation, the skin colors of people with little food are pure, clean, and beautiful, and people are pure in morality; he states that even the looks and clothes are perfect, and the characters are far from extremes. However, their minds quickly acquire knowledge and truth, and their understanding is excellent [13, 14].

According to Ibn Khaldun's observations, consuming too much food causes some bad nausea and stinking yellow bile, black bile, and sputum in proportion to the irregularity of the moisture of these foods. Therefore, the colors become distorted, and the shapes become ugly by taking excessive weight. Not being confined to the image¸ he finds the excessive consumption of nutrients as an idea of blinded minds. Ibn Khaldun's observations are that hunger makes the shapes and forms of desert animals beautiful. He maintains this determination for people. Therefore, people who experience a certain time of hunger also get beautiful shapes and minds. The people of the fertile crops, where the animals are rich and the fruits are abundant, are often characterized by weak minds and ideas. There is a difference in the mental states of people who live in the desert eating mainly dates, North African people who eat barley, olive-fed Andalusians. and people who live in the richest of varieties. In the years of famine, deaths from people in before-mentioned regions are rare. Those who live in abundance and prosperity often wrinkle their bowels when they are forced to eat less, contrary to their habits, because they are often accustomed to additives

and fat. The intestine, a weak organ, is ill-founded. Such a disease will kill quickly. In relation to nutrition and health, Ibn Khaldun has interesting findings. According to him, hunger does not kill those killed during hunger; it actually kills the satiety they are used to [13, 14].

If you are accustomed to this nutrition with limited additive and low fat, the alteration of the food will not dry up the bowels. While those living in abundance and eating all kinds of food and additives were seen dead at times of hunger. Ibn Khaldun says that hunger should be gradually brought into customary in people's lives. He says that many of the full eaters will be susceptible to diseases and it will be those people who suddenly go hungry [14].

2.2. History of nutrition philosophy

There is a point where philosophers of antiquity, daily philosophers, and those whom we considered to be the cornerstone of medicine are concerned about nutrition and human mood, illnesses, and the whole of life. The importance of nutrition for a healthy living is emphasized, and the importance of environmental factors is pointed out as well. The outcome of these observations was influenced by body and soul foods.

They were the first to hold nutrition for mental and physical health responsibly, with the same consensus that excess nutrients would cause obesity and illness. In the old era, the desire to find the secrets of staying healthy was the primary focus, while during the last years, the focus was put on medical treatments.

In recent years, it has been understood that studies on protection from diseases are important for the Mediterranean diet—barley, olive oil, and olive nutrition.

In recent years, gut-brain axis has been discovered. Observing the philosophers, the effect of food on the mood of people is scientifically proven today.

In the next steps, what food should we eat to protect ourselves from chronic diseases? These are observations of philosophers and medical men coming to this day from the antic ages that must be looked at:

People are influenced by their environment, and the food they eat will affect the resulting mood balance. It is not possible that one cannot think of a person as unimpressed by the nutrients and environmental conditions. In the last years, with the increasing technology, it is impossible to ignore the harm that technological devices give to people. Besides the loss of naturalism every year and besides the development of technological developments, the Internet and social media are inevitable.

The development of technology in the twenty-first century affects the mental and physical health of our children, especially in the school age, due to the rapid and convenient use of Internet/computer. We can think about media dependency, television, mobile phone, computer, and Internet dependencies. Among them, technology dependency is increasing day by day in terms of public health. Technology addiction is causing problems in the physical, psychological, social, and cognitive developments of children and youth [15–17]. As a result

of the studies carried out in our country, interlinked Internet addiction and obesity are facing a serious public health problem [18].

In the last years, it has become more difficult to be healthy. New health problems are added to the old ones that we cannot move away from our life, like technology to the deterioration of the nature of nutrition and the environmental factors that negatively affect human health. In order to remain healthy, all we can do is pay attention to the negativity of the twentieth and twenty-first centuries and to act accordingly.

2.3. Brain and gut reliability

Hippocrates said "All diseases start in the intestine," paying attention to the Hippocrates gut. The same question that has begun with Avicenna, Ibn Khaldun, and Hippocrates has been pushing us for centuries: do our guts rule us?

The role of intestinal microbiota in health and disease is increasingly recognized. The microbiota-intestinal-brain axis is a two-way path between the brain and the gastrointestinal tract. It is well known that intestinal microbiota affects the physiological, behavioral, and cognitive functions of the brain. Gut microbiota may include brain axis, intestinal microbiota and metabolic products thereof, enteric nervous system, sympathetic and parasympathetic branches within the autonomic nervous system, neural-immune system, neuroendocrine system, and central nervous system. In addition, there may be communication pathways between the intestinal microbiota and the brain, including the neural network of the intestine and brain, neuroendocrine-hypothalamic-pituitary-adrenal axis, intestinal immune system, some neurotransmitters synthesized by intestinal bacteria, and barrier pathways including neural regulators and intestines. Mucosal barrier and blood bar brain barrier. Irregularities in intestinal microbiota compositions have been described in a variety of neuropsychiatric disorders such as autism, schizophrenia, and depression. Furthermore, preclinical studies suggest that this may be the driving force behind behavioral abnormalities observed in these conditions. Understanding how the bacterial compartment plays a role in regulating brain functions may lead to new strategies for the development of microbiota-based therapies for these neurological diseases [19–22]. The bacterial colonists in our intestines communicate with the CNS and regulate brain neurochemistry and behavior in a number of different ways that are slowly resolving. These mechanisms include the production of bacterial metabolites, such as cytokines, and immunologic agents and signal directly to the brain via the vagus nerve.

2.4. Gut-brain axis mechanisms

2.4.1. Immune responses

The signals sent to the brain via immunoreactive cytokines are the vagus nerve or blood-brain barrier through the brain. Gram-bacteria stimulate the production of proinflammatory cytokines, IL-6 and IL-1 beta. These receptors appear on the monocyte macrophage microglia as a result of binding of the lipopolysaccharides of the cell wall of the gram-bacteria to the toll-like receptors (irritable bowel and intestinal gut permeability impairment). Stimulation in the

systemic circulation is the answer to the inflammatory response. This inflammation response is mediated via the brainstem vagus [23, 24].

2.4.2. The vagus nerve

It plays a vital role in facilitating two-way communication between the intestine and the brain.

Microbiota activates this. Cutting the vagus nerve facilitates anxiolytic behaviors in mice. Probiotics show antidepressant and anxiolytic effect via vagus [25, 26].

2.4.3. Short-chain fatty acids

Glycoside hydrolases and polysaccharıde lyase enzymes in the probiotic bacterium convert the fibers into short-chain fatty acids. It is well known that intestinal bacteria are the main source of short-chain fatty acids (SCFA) such as butyric acid, propionic acid, and acetic acid. These molecules, while not belonging to classical neuroactive substances, can act more finely on neuronal function. The best of them are probably butyrate. These SCFAs are histone deacetylase inhibitors. It is linked to free fatty acid receptors in the cell. SCFA can directly affect brain physiology and behavior [22, 27, 28].

Evidence shows that butyric acid and propionic acid can regulate neurotransmission. SCFA can directly affect brain physiology and behavior. Metabolic benefits of soluble fiber on body weight and glucose control is not fully understood. Studies have shown that intestinal gluconeogenesis (IGN) has beneficial effects on glucose and energy homeostases. Propionate and butyrate activated the intestinal microbiota to activate IGN through complementary mechanisms of soluble fiber fermentation. While butyrate activates IGN gene expression through a cAMP-dependent mechanism, propionate itself is an IGN substrate that activates IGN gene expression via an intestinal-brain neural cycle involving the fatty acid receptor FFAR3 [29, 30].

Short-chain fatty acids (SCFA), such as propionic (PPA) and butyric acid (BA), which are bacterial fermentation products, have an increased prevalence in host health but may also be neurodevelopmental environmental contributors [31]. Changes in the microbial composition of the intestine have a role in health and disease, including brain function and behavior.

2.4.4. Enteroendocrine cells

Enteroendocrine cells (EECs) are special cells that can produce intestines, peptides/signaling molecules (i.e. 5-HT, cholecystokinin [CCK], glucagon-like peptide [GLP]-1, and peptide YY [PYY] affecting their own cognate receptors on the vagus nerve to prevent gastric emptying, to induce satiety, and to reduce the size of the food [32].

SCFAs have been shown to affect the secretion of saturated peptides from EETs. Microbial metabolites increase CCK, PYY, and GLP-1 secretions by binding to FFAR1 and FFAR3 receptors of the same origin, also expressed on EECs [33].

2.4.5. Triptofan

The gut-brain axis is a two-way communication system between the central nervous system and the gastrointestinal tract. Serotonin, also serves as a key neurotransmitter at both

terminals of the network. Accumulated evidence suggests that the gut microbiota regulates the normal functioning of this axis. In particular, the metabolism of tryptophan in this arrangement is open and can play an important role in microbial effect on the serotonergic system. Behavior affected by the conflict between the intestinal microbiota is an important behavior based on serotonergic neurotransmission. Developing serotonergic systems may be vulnerable to different microbial colonization models determined prior to the occurrence of adult-like intestinal microbiota. On the other side of life, intestinal microbiota may determine the diversity and stability of decreased serotonin-related health problems in the elderly. These underlying mechanisms require more details but may be related to the ability to control the metabolism of tryptophan host along the pathway of the intestinal microbiota, thus reducing the fraction available for the synthesis of serotonin and increase the production of neuroactive metabolites. These pathways, enzymes, and immune stress-responsive systems will enhance the brain-gut axis. Additionally, in the gastrointestinal tract that may be affected by local changes in serotonin concentration, the signal processes are neural signals through the gut following scaffold to affect the CNS neurotransmission. Therapeutic targeting of intestinal microbiota could be a therapeutic strategy that can be applied to serotonin-related disorders of the gastrointestinal tract [34].

3. Gut-brain axis and philosophy

In the twenty-first century, the nutritional philosophy agenda is under the title of "intestines and probiotics" and focuses on the effects of probiotics on the immune response, enteroendocrine system, efferent pathways of the vagal nerves, tight intestinal connections, tryptophan, catecholamines, and short-chain fatty acids. When talking about probiotics as fuel, prebiotics are emerging. Glycoside hydrolases and polysaccharide lyases found in probiotics degrade barley fibers and convert them into acetic acid, propionic acid, butyric acid, and short-chain fatty acids. By inhibiting 1-histone deacetylase, these products inhibit tumor growth and metastasis. It also affects a number of physiological functions by binding to intracellular receptors. Efferent vagal nerve activation affects physiology and behavior. Maintaining glial homeostasis controls inflammation in the brain. Propionic acid affects glucose metabolism and body weight by activating fatty acid receptors in portal vein nucleic terminals. Butyric acid and propionic acid have the ability to change nerve conduction. Both of these increase tyrosine hydroxylase activity in the synthesis of dopamine and noradrenaline. These short-chain fatty acids reduce the activity of the dopamine beta hydroxylase enzyme, which controls the noradrenaline conversion of dopamine. In addition, propionic acid, which increases tryptophan hydroxylase activity, also has the ability to alter serotoninergic neurotransmission [22, 27–31].

The benefit of barley in ancient times has been proven by new studies. It is obvious that the food does not only give energy to us but also to our souls. Our new mental home is our hearings, our senses, our thoughts, our decisions, and sometimes the origin of certain neuroses.

3.1. Past traces in nutrition

Nutrition is also an important regulator of the physiological health. It is dependent on adult stem lines that differentiate into self-renewing, specialized cell types in the hemostasis, and

regeneration of the tissues. When the stem cells respond to the signals from the food, they affect the tissue biology by changing the function and activation of adult stem cells; high-fat diets and ketogenic diets affect stem cell function and microenvironment.

Calorie restriction has been shown to increase stem cell function in the intestine and skeletal muscle and has positive effects on adult stem cells and hematopoietic stem cells. Similarly, fasting provides protection against intestinal, hematopoietic, and neuronal stem cells from injury. While high-fat diets induce root-like properties, high-fat diets disrupt hematopoiesis and neurogenesis.

Caloric restriction and fasting are generally beneficial for adult stem cell function, whereas high-fat diets destroy stem cell function or create opportunities for tumor formation. Diets and nutrition must work to understand how adult stem cells respond to diet-induced signals and physiology.

Diet has a profound effect on tissue regeneration in various organisms and has beneficial effects on low-caloric conditions such as intermittent fasting, loss of organ health, and age-related tissue function [35, 36].

The new work defends the antic order of the day. Restriction of intake of nutrients and reduction of fat intake have been expressed by Plato, Hippocrates, Avicenna, Ibn Khaldun, and other philosophers. It is this nutritional way of being healthy in the communities that have fewer meals, less food, and healthy appearance of their skin and their bodies being athletic. Quite surprising words spoken hundreds of years ago are confirmed in recent studies.

Barley flour, an important nutrient in ancient times, has a beneficial metabolic effect in suppressing appetite and increasing insulin sensitivity. These effects of barley are the results of intestinal microbial metabolism SCFA production and their effect and stimulation of the secretion of intestinal hormones. SCFA and possibly other metabolites induced by changes in intestinal microbiology may contribute to metabolic disorders such as obesity and type 2 diabetes mellitus [37].

Flavonoids found in fresh green barley leaves revealed in studies have strong antioxidant activity of saponarin. There are many reports about the antioxidant activity of flavonoids found in natural plants. Therefore, it should be beneficial to health with supplements containing saponarin green barley leaves [38].

Fresh green barley leaves have a strong anti-stress property in mice as evidenced by the inhibition of the decline in voluntary wheel-running activity and hippocampal brain-derived neurotrophic factor (BDNF) messenger RNA(mRNA) reaction to restraint stress. These findings support that the young green leaves with barley supplementation may be beneficial in the prevention of stress-related psychiatric disorders such as depression [39].

Whole barley and barley products during daily nutrition may help alleviate oxidative stress-related disease states, cardiovascular diseases, and colon cancer, among others. However, there are many additional factors such as bioavailability, which can affect the antiproliferative effect in vivo [40].

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In ancient times, an important nutrient is olive oil, which is also linked to the high phenolic compound content that protects olive oil against different diseases. Olive oil phenolic compounds prevent cardiovascular disease, cancer, neurodegenerative disease, and osteoporosis. Antioxidant, antiproliferative, proapoptotic, and anti-inflammatory activities of olive oil phenolic compounds have protective effects against heart disease and cancer. Neuroprotective and neuromodulatory effects that inhibit the development of amyloid plaques also apply to neurodegenerative disease. Finally, it is known to protect against osteoporosis that promotes bone regeneration. Olive oil taken with diet may be proposed as an important source of phenolic compounds that prevent chronic disease and ultimately improve quality of life [41].

Taking virgin olive oil phenolic compounds (PC) alone or in combination with thyme PC mixture for 3 weeks decreases calorie-LDL in hypercholesterolemic people. This cardioprotective effect, together with the increase in the populations of bifidobacteria, can be mediated by an increase in PC microbial metabolites of antioxidant activities such as protocatalytic acid and hydroxytyrosol. The specific growth stimulation of bifidobacteria in the human gut initially demonstrates a potential prebiotic activity of an olive oil enriched in extra virgin olive oil and thyme PC [42].

3.2. Importance of nutrition philosophy education

Nutrition philosophy education is necessary so that individuals can get rid of their bad nutrition habits. Under the heading of nutrition philosophy, people who have been mentioned for centuries are able to gain the nutritional habit that will bring their spirit and body health to the best level and this nutrition is a way of life.

The acquisition of healthy eating habits by individuals will ensure that the community is fed better and that a general quality of life is achieved. The social cultural habits that society is in should be considered when giving the training of this nutrition philosophy. The subject to be focused on nutrition philosophy education is to describe that collection of nutrition habits. Why is it important to educate people about nutrition philosophy and what is the effect on the body and soul health of the foods we eat? İt is important to ensure that awareness occurs during meals. It is necessary to teach the delightful individual nutrition model which is both enjoyable and nourishing the body and feeding all the senses. It has been taught in person to choose the right food choice for emotional and physical well-being in balance, reaching awareness [43].

4. Conclusion

Many times since ancient times, it has been mentioned by philosophers that an important part of feeding the body is feeding the soul. In antiquity we often find barley and olives in the speeches on nutrition and health. In ancient times the gut-brain axis relation was known. In their observations, philosophers observed and told that the soul was influenced by nutrition.

Philosophers have stated that people who eat less recover faster and their tissues renew itself. Ibn Khaldun has observed with his own eyes that people who nurture themselves wıth a large variety of food do not only look physically unhealthy, but also theır minds and souls seem to be blurred.

In general, nutrition seems simple, but it is an art at first and nutrition is a philosophy. In the last years, the progress of medicine and the development of technology resulted in diagnosis and treatment instead of looking at people's faces and recognizing the whole picture. The deterioration of nature with technology makes it difficult to reach a certaın quality of natural food. The decline in the quality of our food disrupts people's physical and mental health.

Doctors are so busy nowadays with people's diseases that they cannot find the time to make profound researches concerning the reasons. Chronical diseases, depressions, and cancer and heart diseases are getting more frequent every year.

İn recent years, researches found clear links between the state of people's well-being beforehand and occurring diseases like chronical illness and cancer. İt is amazing how many similarities are between the written documents of the old philosophers and the researches today. A special focus is on barley, where we found out that it prevents chronical dıseases and how healthy it is to consume it in general. What they found out with their pure eyesight can be proven today with all our technological development. This demonstrates how important it is to observe people's alimentation.

The philosophy of alimentation might give us a clear start to see the patient as a whole again. İt can not only be drugs and medicine to treat the diseases. We have to find its beginning.

Every food can be the medicine already or vıce versa the beginning of an unhealthy state of mind. We shall consider to change our thinking from "feeding ourselves" to nurture our bodıes, minds, and souls.

Selective nutrition is more important than a variety of all kinds of food. We shall never forget that there is a clear lınk between our intestines and our brains: the gut-brain axis.

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Section 2

Role of Microbiota in Specific Neuropsychiatric Disorders

Chapter 4

Autism in Children Connected with Gastrointestinal Symptoms

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Additional information is available at the end of the chapter

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Abstract

Autism in children has increased significantly over the last few years. Eating disorders and ailments of the gastrointestinal system are a common affliction among these children. The hypothesis linking the autism spectrum disorder (ASD) and the digestive system with its bacterial microflora based on the concept of the gut-brain axis become very interesting and credible. This axis is a two-way communication between the central nervous system (CNS) and gut innervation. Mechanisms of this dependency include effects of neurological, immunological, and hormonal mediators. Among patients with ASD, mucosal permeability is frequently diagnosed, which may be caused by chronic inflammation. Such inflammation can damage cells of the intestinal membrane. Children with ASD also have a different composition of intestinal and gastric flora compared to healthy ones. Different types of environmental and situational stressors may contribute to the occurrence of gastrointestinal disorders such as irritable bowel syndrome, enteritis, as well as increase intestinal permeability and change their bacterial flora. The chapter presents eating disorders and nutritional deficiencies in children with ASD and shows how nutrition during pregnancy can affect ASD symptoms and how to reduce the severity of ASD symptoms through carefully selected nutritional interventions and supplementation.

Keywords: autism, eating, gut-brain axis, nutrition, gastrointestinal symptoms

1. Introduction

One of the most common symptoms of autism spectrum disorder (ASD) affecting children is problems related with nutrition and eating habits (46–89%) compared to healthy children (25%) [1]. Children with ASD usually prefer consuming products of one type and one color,

with a specific texture and smell, or having the same or similar packaging. They also refuse to try new foods and have specific nutritional behaviors, for example, they eat in a ritualistic way [2, 3]. Children with ASD have also problems with their digestive system, such as constipation, diarrhea, bloating, esophagitis, and reflux [4]. Due to the fact that gastrointestinal disorders may affect the incidence and severity of other symptoms in children with ASD, adequate nutrition should play an important role in treatment of mental symptoms. This can improve their life comfort and overall health.

In order to explain the etiology of autism, many hypotheses have been created that combine the occurrence of this disorder with genetic determinants, environmental influences, autoimmunity, viral infections, and drugs. One theory links the ASD symptoms with the gastrointestinal disorders and the composition of the intestinal flora [5]. It is based on the concept of the gut-brain axis, that is, the interaction between the gastrointestinal tract and the nervous system. This axis is a two-way communication between the central nervous system (CNS) and the gastrointestinal tract controlled with autonomic nervous system (with sympathetic and parasympathetic nerves). Mechanisms of this association include the action of neurological, immunological, and hormonal mediators [5, 6]. The increased permeability of the intestinal membrane, which commonly occurs in autistic children, can lead to excessive penetration of the blood exogenous peptides incompletely hydrolysed due to impaired digestion of casein and glutamine in the intestinal lumen. These peptides are transported to the brain, where they pass through the blood-brain barrier and as neuro- and immunoactive substances interfere with the neurological mechanisms of brain development [3, 7]. The biological activity of these compounds comes from their structural similarity to the endogenous opioid peptides [8]. The intestinal microflora can also affect the functioning of the CNS through the ability to synthesize identical or similar neuroactive molecules such as, inter alia, acetylcholine, catecholamine, histamine, or melatonin. On the other hand, the composition of intestinal bacterial flora may also depend on the level of stress or intensity of emotions; thus the digestive and nervous systems interact with each other [7].

2. Eating disorders and gastrointestinal complaints

Parents of children with ASD most frequently observe the selectivity of food and a very narrow range of consumer products [3, 9]. Eating disorders in children with ASD can be divided into the three following categories: (1) refusing to eat, (2) limited range of food consumed, and (3) frequent consumption of one product [10]. It was shown that children with ASD choose food based on its texture (69%), occurrence (55%), taste (45%), smell (36%), and temperature (22%). There was also a reluctance to try new food products in 69% of respondents [11].

Children with ASD aged 2–12 years are characterized by poorer skills of independent eating, more frequent occurrence of avoidance, and neophobia of food in comparison to the healthy peers [3]. These children also prefer energy-rich products such as hotdogs, peanut butter, cakes, fries, and pasta, while they eat a few vegetables and fresh fruit [12, 13]. It was also found that obesity in children with ASD can occur more likely than in healthy children [3].

The prevalence of eating disorders such as selectivity and refusal to eat reaches almost 90% in children with ASD [1, 2, 14]. A UK study found that 59% of children who had ASDs were eating less than 20 different foods [9].

The most common gastrointestinal complaints are constipation, diarrhea, abdominal pain, and reflux. It has been also found that they may suffer gastric acid hypochlorhydria, intestinal motility disorders, decreased activity of disaccharidases, and primarily lactase in intestinal juice [4, 8]. It has been also observed that 70% of children with ASD suffer from gastrointestinal disorders, where in healthy children this frequency was only 28% [5, 15]. In accordance with the other studies, gastrointestinal complaints are five times more frequent in children with ASD; abdominal pain occurs twice as often; and constipation and diarrhea are four times more often than in healthy controls [16]. However, the higher incidence of gastrointestinal complaints in children with ASD is not clearly stated, as not all studies show such dependence [3, 15]. It is often also suggested that gastrointestinal symptoms may be related to the medication being taken and the side effects they may cause [3].

Studies in which intestinal biopsy was performed among children with ASD suffering from food disorders showed a deficiency of disaccharidases and hexose transporters. This may indicate that the digestive system carries incorrect digestion of carbohydrates and their transport through enterocytes. Decreased digestion and absorption of these compounds may result in the accumulation of sugars in the intestinal lumen, and this can lead to the occurrence of osmotic diarrhea and bloating [5].

People suffering from ASD frequently have increased intestinal mucosal permeability, which may be due to their chronic inflammation. One of the studies carried out among children with ASD showed a significant increase in CD3 + and CD8 + lymphocytes in the intestinal epithelium and increased expression of proinflammatory cytokines in their mucosa. Elevated levels of cytokines were associated with the occurrence of behavioral and communication disorders [5].

Children with ASD can be characterized with a different composition of the bacterial flora of the stomach and intestines. Studies have shown in children with ASD a reduced amount of *Bifidobacteria* and more frequent occurrence of *Bacteroides vulgatus* and *Desulfovibrio* than in healthy ones [5, 7]. Higher amounts of *Clostridia* were found in their stool, which may be associated with a more frequent occurrence of problems from the digestive system [5].

3. Nutritional deficiencies

Due to the selectivity of food and a little varied diet, the intake of vitamins and minerals in children with ASD may be insufficient and lead to malnutrition. This applies in particular to vitamins A, D, K, and B12 as well as calcium and zinc [3, 9, 10, 17]. Research in which nutritional diaries were used, covering 3 days in the group of children aged 8–11 years, showed that insufficient intake of vitamin D, calcium, and vitamin A occurred more frequently in children with ASD than in the group of healthy ones. There was also an increase in protein

intake in children with ASD, higher than the recommended norm by 111%. Children with ASD were also characterized by a higher intake of vitamin B6 and vitamin E [3].

It was found that in people with ASD, the intake of vitamin E and B6 is higher than in healthy people, while the intake of iron, calcium, and vitamin D is significantly lower. It was also found that children characterized by food selectivity are more exposed to calcium, zinc, and vitamin D deficiency. Examining the amount of nutrients consumed in children with ASD with a narrow range of eaten products, they confirmed an increased risk of deficiency not only of vitamin D, calcium, and zinc but also vitamin B12 compared to healthy ones [17, 18]. Based on a study in which a 3-day nutritional interview was used, it was shown that in the group of children with ASD aged 4–8 years, the intake of calories and protein is too low and the intake of carbohydrates higher than recommended. Insufficient intake of vitamin D was diagnosed in 87% of children under the age of 4, in 89% of children between 4 and 8 years of age, and in 79% of children between 9 and 11 years of age [19]. Studies indicate a higher incidence of folic acid; vitamins B6, A, C; zinc; and calcium deficiency in children with ASD than in healthy ones [20]. Other studies show that the intake of protein in the children with ASD exceeded the norm by more than 171%, and the supply of animal protein was exceeded by 200%. The excessive consumption of sodium, phosphorus, magnesium, and vitamins A, C, and B and insufficient supply in the diet of vitamin D, calcium, iron, potassium, fiber, and cholesterol were also indicated [8]. However, the majority of people with ASD are characterized by excessive intake of vitamin C and low carotenoid intake [19, 21]. In another group of children with ASD examined for nutritional deficiencies, insufficient calcium intake and excessive supply of vitamin B6 and E were found. Too little intake of iron, calcium, vitamin D, and fiber was found in both children with ASD and in the group of children developing properly [9].

4. Nutrition and nutritional behavior during pregnancy

The diet of a pregnant woman affects the growth and development of the fetus, including the maturation of his brain. It can therefore be assumed that there is a probability of dependence between maternal nutrition and an increased risk of ASD in a child. It has been shown that the risk of ASD is about 40% lower among those children whose mothers took folic acid before conception 6 weeks and 6 weeks after conception. Women who had healthy children consumed 123.9 ± 46.4 μg more folic acid than mothers of children with ASD. Schmidt et al. found lower intake of folic acid in the first month of pregnancy in women who had children with ASD than mothers of healthy children. The relationship between the increase in folate intake and the decrease in the risk of ASD was demonstrated [22]. There was also a higher intake of polyunsaturated fatty acids (PUFA), before and during pregnancy, among women whose children developed normally than mothers of children with ASD. According to the study, women whose intake of omega-3 acids in the study group was the lowest had a 53% higher risk of giving birth to a child who had ASD than women with a middle range of consumption of these acids [23]. In other studies, there was no evidence of a decrease in the risk of ASD with an increase in the intake of omega-3 acids above the norm, but it has been proven that the risk increases with a very low intake of these acids [24]. It may also be important for pregnant

mothers to eat fish, which is a rich source of unsaturated fatty acids and vitamin D. However, no study has linked the amount of fish consumed by pregnant women to the occurrence of ASD in their children. It was suggested that a small intake of vitamin D, by a pregnant woman, may be a risk of ASD in a child, but this relationship was not confirmed by any study [22].

Obesity of the mother and eating a diet full of fat during pregnancy can also increase the risk of ASD in the child. The increase in the prevalence of ASD was associated with a higher rate of obesity [25]. The offspring of obese women are more exposed to the appearance of behavioral disorders such as depression, anxiety, ADHD, and ASD. It is related to the influence on the fetal development of factors related to maternal obesity, among others, hyperlipidemia, hyperglycemia, and insulin resistance [25]. Compared to children of women with normal body mass, in obese children (II and III classes) ASD was diagnosed more frequently [26]. A relationship between the occurrence of ASD and excessive weight gain in women during pregnancy has been demonstrated. There was also an increased risk of developing ASD in children whose mothers were obese prior to pregnancy [26]. One of the theories explaining the association of obesity in children with ASD is the occurrence of higher levels of leptin. This causes placental dysfunctions, which may disrupt the normal, neurological development of the child [25]. People with autism have more leptin in plasma than healthy subjects [11]. Obesity is considered to be an inflammatory disease; it causes an increase in inflammatory cytokines in the body that reach many organs, including the brain. Therefore, excessive body weight and maternal diabetes can activate the inflammatory response in the placenta [25]. Diet high in fat in pregnant women stimulates inflammatory cytokines, including interleukin (IL-4, IL-5) and monocyte chemoattractant protein-1 (MCP-1). These cytokines have been associated with the occurrence of ASD. In addition, these compounds transmitted by obese or mothers with diabetes to the fetus can initiate physiological and behavioral responses observed in children with ASD whose mothers during pregnancy have developed infections [25].

5. Nutritional interventions

A gluten-free diet relies on elimination from diet products containing wheat, oats, barley, and rye (as well as flour, bread, pasta, cakes, and other products made from these cereals). The casein-free diet (dairy free diet) relies on avoidance of the consumption of milk including breast milk, dairy products, yogurts, cheese, butter, cream, ice cream, and others [27]. Gluten-free and casein-free (GFCF) diets are one of the first nutritional interventions offered to patients with ASD. Many parents have reported improvements in maintaining eye contact and talking to children with ASD who have been on this diet [28]. In the study describing the study conducted on a group of 149 children diagnosed with ASD, it was found that after the introduction of the GFCF diet and its use for 3 months, a significant improvement in 81% of children was observed. However, the authors questioned the significance of the results of this study, because the conclusions on the health status of children and its improvement were drawn by their parents, aware of the conducted nutritional intervention [28]. A blind experiment was carried out among children with ASD regarding the use of the GFCF diet. In both control and research groups, there were 10 children with ASD. In one group, an intervention

was introduced relying on elimination of gluten- and casein-containing products from the diet, while the other group continued their previous diet. Observations were made before the beginning of a nutritional intervention and after 1 year from the beginning of its implementation. The tests that were used were based on, inter alia, nonverbal techniques. There was a statistically significant improvement in the ability to learn in a group of children using a diet with the elimination of gluten and casein [14, 20]. In another paper, in one of their presented examples, the GFCF diet began to bear effects after only 2.5 months of its use. An improvement in social communication and in emotional reactivity was recorded [29]. Antibodies of IgG, IgM, and IgA against gliadin, casein, basic myelin protein, maize, eggs, and soy in 50 children with ASD were measured. Analysis of blood samples showed that a large number of children produced antibodies against casein and gliadin. In addition, it was found that these proteins bind to lymphocytes and CD26 enzymes, which can cause inflammation and activate the immune system response [30]. Behavioral changes in ASD patients may result from abnormal activation of the opioid system due to excess receptor antagonists in the brain. It was found that gluten and casein are the source of compounds characterized with the activity of opioid peptides [31]. Fifteen children with ASD who did not show any food intolerance took part in another study. They were divided into two groups and blinded. For 12 weeks, one group was given a diet with the elimination of gluten and casein and the other a diet enriched with these substances. After this time, each group went on an alternative diet for the next 12 weeks. The carers or parents of the examined children were not aware of the kind of food their child was receiving. There was no difference in the behavior and development of the child in any group [15]. The influence of a diet containing gluten and casein on the behavior and complaints from the digestive system in children with ASD, which until then used diet with the elimination of these substances, was investigated. The study was randomized, double blind, and controlled; the experimental group consisted of 38 people and the control group of 36 people. According to the authors' hypothesis, the introduction of autistic gluten and casein into children's nutrition was to cause deterioration of their behavior and gastrointestinal complaints. Nutrition interventions were carried out for a week. There were no differences in the health status between the test and control groups. It was suggested that the result of the study could be affected with the short intervention time [32]. Many studies on the GFCF diet focus on the safety of the intervention [31]. In various studies, no differences were observed in the nutrition of children with ASD using the GFCF diet compared to children on the standard diet. However, a significant reduction in the concentration of amino acids was observed, including tryptophan in children using GFCF diets. In addition, patients using a gluten-free diet were found to consume larger amounts of proteins and fats but smaller amounts of carbohydrates, fiber, calcium, and iron [31]. Therefore, it warns against the risk of insufficient supply of micro- and macroelements while using the GFCF diet [29, 32]. The casein-free diet can cause calcium deficiencies. In addition, slower bone development in children using such nutritional intervention was also reported in comparison with children without any dietary restrictions. It was shown that patients with ASD on a non-denaturing diet had lower bone density than the control group. Lower vitamin D intake is also seen in such patients [11, 29, 32].

Another nutritional intervention in children with ASD is a ketogenic diet, which is characterized by an increased fat content, adequate to the amount of protein needed and insufficient for metabolism the amount of carbohydrates, which leads to the body's use of lipids as the

main source of energy. In the original ketogenic diet, the ratio of calories from fat to calories from carbohydrates and proteins was 4:1 (the proportions were 80% of lipids, 15% of proteins, and 5% of carbohydrates). With a standard diet, fatty acids are catabolized to acetyl-coenzyme A (CoA) in the oxidation beta reaction and then oxidized to CO_2 and H_2O in the Krebs cycle. However, when the amount of fatty acids is too high and exceeds the ability of the Krebs cycle to metabolize CoA (e.g., low carbohydrate or protein diets), in the acetyl-coenzyme A, the liver is converted to ketone bodies (acetoacetate and D-beta-hydroxybutyrate). Ketone bodies produce a similar amount of energy as proteins and carbohydrates; they can also cross the blood-brain barrier, so they can be used by brain cells as a source of energy [33]. Ketogenic diet is an alternative or supportive therapy for patients with drug-resistant epilepsy. It was found that in patients using these diets, it was easier to control epileptic seizures as well as their frequency. The ketogenic diet is also used in other diseases such as Alzheimer's disease, Parkinson's disease, migraine, and depression [33, 34]. The ketogenic diet is also used as an option to suppress symptoms accompanying ASD [35]. The study evaluated the effectiveness of the ketogenic diet in a group of 30 children with ASD. Children were evaluated before and after dietary intervention using the Childhood Autism Rating Scale (CARS) scale. It was found that a significant improvement occurred in two patients, the average in eight patients, and a slight improvement in eight patients. Nutritional intervention, in addition to the introduction of a ketogenic diet, also consists of supplementation of vitamins and minerals dosed depending on the age of the subjects. According to the authors, the research on the effectiveness of autistic treatment by ketogenic diet should be extended and continued. The studies showed that in patients who were characterized with a higher CARS score, the improvement in the results of ketogenic diet treatment was lower than in patients with moderate or light ASD [35]. Because the characteristic composition of the ketogenic diet is quite distasteful, often patients decide to interrupt this diet intervention and return to the previous method of nutrition. This diet may additionally lead to nutritional deficiencies [35]. It also has numerous side effects including weight loss, growth inhibition, fatigue, drowsiness, changes in appetite, constipation, diarrhea, nausea, and vomiting [33]. In one of the studies in which the impact of the ketogenic diet on the symptoms of ASD was analyzed, constipation or diarrhea appeared in 12% of children with ASD [35]. Due to the limited number of research results on humans and on animal models stating the reduction in the frequency of behavioral disorders, after using the ketogenic diet, it cannot be unambiguously determined its effectiveness in children with ASD.

6. Supplementation

Vitamins and minerals play an important role for human health, because they have numerous functions in the body, including enzyme cofactors for many reactions. In particular, attention is paid to the insufficient supply of vitamins and minerals in the diet, as one of the causes leading to many health problems in children, for example, anemia, hypothyroidism, or rickets. Recently, researchers have focused on the relationship between metabolic disorders and developmental disorders, including lack of concentration, learning disabilities, and intellectual development [21]. Children with ASD due to diets, often restrictive, may be exposed to nutrient deficiencies. Dietary supplements are one of the most frequently recommended

nutritional interventions for children with ASD, recommended by 49% of physicians [21]. Other studies suggest that 66% of people with ASD are taking supplements—most frequently probiotics, omega-3, vitamin B6, and melatonin [36].

Probiotics are defined as living, nonpathological microorganisms, which have a beneficial effect on the human body, when of course administered in the right dose. They consist mainly of lactic acid producing bacteria, *Lactococci* and *Bifidobacterium* or yeast, that is, *Saccharomyces boulardii* [36]. Probiotics have a beneficial effect especially in gastrointestinal problems such as infectious diarrhea, inflammatory bowel disease, or hypersensitivity syndrome of the large intestine. Their activity in shaping the host's immune system has also been proved [36]. They can also be effective in the treatment of inflammatory diseases of the gastrointestinal tract and affect the function and permeability of the intestinal epithelium. An important role is also played in restoration of the intestinal microbial balance [37]. It was found that probiotics can be effective in the treatment of children with ASD due to their health-promoting effects on the gastrointestinal tract and the entire body [36]. It has been pointed out that the use of probiotics may help in restoring the proper intestinal microflora and thus eliminate diarrhea and constipation, which are a common problem in people with autism [38]. It was also pointed out that this supplement may play a role in maintaining the continuity of the gut mucosa, activating the immune system and preventing inflammation [39]. A relationship was found between the severity of ASD and gastrointestinal disorders. It can therefore be considered that probiotics contributing to the improvement of this system may also positively affect the behavior of children with ASD. Almost 20% of physicians are encouraged to take probiotics in children with ASD, and 60% of physicians recommend continuing to use probiotics, if parents have decided to apply such supplementation [36]. It is also important to mention that although the US Food and Drug Administration (FDA) considered probiotics to be safe for health, so far no research has been conducted that would address the long-term effects of their supplementation.

In the studies carried out so far, 50% of children and adults with ASD have shown positive effects of vitamin B6 supplementation [40]. According to studies, children with ASD who do not take any supplements are characterized with a higher level of vitamin B6 in plasma than the control group subjects. There are more studies that confirm this phenomenon [40]. One of the explanations is the lower activity of vitamin B6 in people with ASD. It was also found that pyridoxal kinase—an enzyme responsible for the conversion of pyridoxal to the active form of vitamin B6 (PLP, pyridoxal phosphate), in this group of people—is also characterized with a slowed effect [39, 41]. This activity can be lowered by up to 40% compared to people developing properly. PLP is an essential component for the synthesis of mitochondrial components, among others, heme and coenzyme Q10. It has also been shown that this compound protects neurons from excessive oxidative stress by increasing the production of ATP and the use of excess glutamate [42]. People with ASD may notice an improvement in health during supplementation with a high dosage of vitamin B6, which will lead to increased energy production, decreased excitotoxicity, and reduction of oxidative stress. Some of the parents, when using such dietary intervention, observe in children with ASD improvement in the areas of attention, communication, learning, or maintaining eye contact [39, 40]. Often when supplementing vitamin B6, it is also recommended to take magnesium for the purpose of preventing its deficiency and reduction of the level of hyperactivity. In addition, this element

blocks excessive irritation of excitotoxic receptors in the brain by means of calcium channel modeling [42]. Supplementation of these two nutrients led to improved behavior in children with ASD [36, 39]. In one of the studies in which the double-blind method was used, it was found that in children supplementing magnesium and vitamin B6, behavioral improvement was noted, while in groups in which only magnesium or vitamin B6 was administered, this improvement was not observed [43]. One of the 9-year-old boys with ASD, who was prescribed supplements with B6, magnesium, and additionally vitamin B12, decreased sleep problems and improved behavior [43]. At present, it is not known what the possible side effects of taking vitamin B6 may be. Older studies show that long-term supplementation of this nutrient may increase the risk of developing peripheral neuropathy [44].

Omega 3 acids belong to the group of polyunsaturated fatty acids (PUFA). They include alpha-linolenic acid (ALA), docosahexaenoic acid (DHA), and eicosapentaenoic acid (EPA). A lot of research confirms that EPA and DHA are important for both the structure and functioning of the brain. Supplementation of these acids is recommended for the treatment of disorders of the nervous system, such as schizophrenia or ADHD [43, 44]. The anti-inflammatory effect of PUFA has also been proven, which may also include a reduction in the number of proinflammatory factors in the body such as Il-6, Il-10, and TNF alpha. The rich sources of EPA and DHA are fish products and seafood while ALA plant products [45]. There are many studies on the role of deficiency of omega 3 in children with ASD. Lower levels of omega 3 were observed in children with ASD compared to the healthy ones. According to the research, the difference in the level of these acids in the research and control group reaches about 10% and nearly 29% of children with ASD supplementing omega 3 [44, 45]. For 6 weeks, 1.5 grams of fish oil was given to 13 children with ASD aged 5–17 years. An improvement in the occurrence of hyperactivity in these children was sought [43, 44]. Similar results were obtained in studies where the supplementation was used for 12 weeks in patients with ASD aged 3–8 years [45]. Thirty children with ASD for 3 months were supplemented with omega 3, omega 6, and vitamin E. An improvement was noted in 20 children, which was confirmed by the Childhood Autism Rating Scale [46]. Omega 3 fatty acid supplements are generally considered safe but their consumption in larger quantities may increase the risk of bleeding and mercury poisoning, which may be contaminated with fish products, which are a good source of fatty acids.

Vitamin D is a fat-soluble vitamin; it occurs in three forms: D1 (calciferol), D2 (ergocalciferol), and D3 (cholecalciferol). The main source of Vitamin D is skin synthesis and food products (marine fish, fish oils, and to a lesser extent meat and dairy products, in which it occurs as a cholecalciferol). For a long time, vitamin D was only known for its positive effect on the skeletal system and mineral metabolism. For several years, numerous studies have been conducted and provided information on other functions of vitamin D, previously unknown to anti-inflammatory effect, protection of mitochondria against oxidation, elevation of glutathione levels, and influence on at least five proteins that regulate DNA repair, increase in seizure threshold, or increase regulatory T lymphocytes. One of the most frequently studied areas in relation to the effects of this vitamin is brain development and mental disorders. It has also been proven that vitamin D can have a positive effect on the treatment of certain autoimmune diseases, for example, multiple sclerosis, because the receptors of this vitamin have been found in lymphocytes and dendritic cells. The research into the possible impact of vitamin D deficiency on the incidence and course of autism

has also been intensively developed. Low levels of cholecalciferol in the body and ASD have many similarities with regard to their etiopathogenesis. ASD findings indicate that this disease is more common in urban areas, in a climate with less sunlight, and in areas with higher environmental pollution, which also coincides with the etiology of vitamin D deficiency [47]. A hypothesis was proposed in which the deficiency of vitamin D, both in mothers during pregnancy and in children, is considered as an environmental risk factor for ASD. As a justification, the role of this vitamin in the maintenance of homeostasis of the brain, embryogenesis, and development of the nervous system or modulation of the immune system is given. It was also noticed that the children of women who used antiepileptic drugs with negative effects on the metabolism of vitamin D in the body were more likely to have a deficiency of cholecalciferol and ASD [48]. Vitamin D may also play a role in reducing DNA damage, acting as an intermediary in its repair, and genetic mutations resulting from DNA damage are also involved in the pathogenesis of ASD. T-cell dysfunction in patients with ASD, which is also influenced by vitamin D, is also revealed. Another theory of ASD etiogenesis is insufficient supply of adequate amount of vitamin D during the first 12–24 months of life [49]. It has been shown that children with ASD have a lower level of calcidiol and calcitriol in the body than the control group, consisting of healthy children [50]. The level of vitamin D was compared in the group of 50 children with ASD with a control group including 30 healthy children. Children with ASD had a lower level of vitamin D than the control group, and as many as 48% of them had deficits in vitamin D, although it was found that the amount of time spent in the sun was similar in both groups [49]. One of the studies attempted to reduce the symptoms of ASD in children by supplementing vitamin D. Sixty-seven subjects were given 5000 IU of vitamin D per day. Improvements in behavior such as reduced irritability, drowsiness, social withdrawal, and hyperactivity were observed [51]. One of clinical cases included a 32-month-old child diagnosed with ASD, characterized with severe symptoms including impaired communication; reluctance to social interactions; lack of reaction to other people, to commands from their parents, when their name are called, and to physical contact; avoidance of the eye; and delayed language and communication development. The child also had tantrums. The tomographic examination did not show any changes in the brain, and serum and urine tests did not reveal any metabolic deviations. Diagnostics in the direction of autism was carried out using scales, for example, Autism Behavior Checklist and Childhood Autism Rating Scale. The patient also had low levels of vitamin D at 12.5 ng/ml. It was decided to subject the child to supplementation with vitamin D, intramuscularly at 150,000 IU once a month and orally 400 IU per day. After 2 months, parents noticed a significant improvement in the child's behavior. The child began to respond to his name, let his parents cuddle, and play with toys. Laboratory tests showed an increase in the concentration of vitamin D to 81.2 ng/ml. The results and assessment made with the aforementioned scales have also improved. This example may suggest that vitamin D plays a large role in improving the basic symptoms of ASD; however, the observations made in this clinical case cannot be transferred to all patients with ASD. It is worth emphasizing, however, that research in this direction should be broadened and continued [52].

7. Conclusion

One of the most common problems in ASD is eating disorders and gastrointestinal complaints. Nutritional problems occur 2–3 times more frequently in children with ASD than

in healthy children [1]. The most common symptoms from the digestive system are constipation, diarrhea, bloating, and reflux. Almost 70% of autistic children suffer from it [2, 53]. Given these reports, the hypothesis combining the symptoms of autism with the functioning of the digestive system and its bacterial microflora based on the concept of the gut-brain axis becomes very interesting and credible [54–57]. Different types of environmental and situational stressors may contribute to the occurrence of gastrointestinal disorders such as irritable bowel syndrome, enteritis, as well as increase intestinal permeability and change their bacterial flora [58–66]. Differences were found in intestinal microbiome in children with ASD compared to healthy ones based on the analysis of metabolic products and composition of fecal flora [59, 67]. Gut microbiota-mediated metabolites, such as short-chain fatty acids (SCFAs) and free amino acid (FAA) concentrations, are significantly higher in children with ASD than healthy ones [68, 69]. The SCFAs are mainly produced by *Clostridia*, *Bacteroidetes*, and *Desulfovibrio*, and they can cause symptoms similar to ASD [70]. Fecal samples from children with ASD compared to healthy ones have higher levels of the *Clostridium histolyticum* that can produce neurotoxins [71]. Children with ASD have less differentiation and lower levels of *Bifidobacterium*, *Coprococcus*, *Firmicutes*, *Prevotella*, and *Veillonellaceae* and higher levels of *Bacteroidetes*, *Caloramator Clostridium*, *Desulfovibrio*, *Lactobacillus*, and *Sarcina* [59, 72].

One of the most interesting and surprising results in our own research is that children with ASD were characterized by greater intake of offal and red meat than healthy children. As many as 32% of children with ASD eat red meat several times a week. On the other hand, offal is consumed 1–3 times a month by 25% of examined children with ASD [73]. Offal and red meat are a rich source of iron. Perhaps this mineral ingredient can cause frequent consumption of the abovementioned products by children with ASD. Iron plays an important role in the development of cognitive, motor, and behavioral functions. It is also an important mineral component which, as a component of some enzymes, is involved in synthesizing neurotransmitters. Iron deficiency in children with ASD is very common. It has been shown that 24.1% of examined children with ASD have reduced iron levels and 15.5% suffer from anemia due to deficiency. The reason for such frequent iron deficiencies and hence the low level of ferritin present in autism is unknown until now. One of the hypotheses concerns the symptoms of the digestive system and the possible absorption disorders, which makes the iron from food less absorbed. It was found that this hypothesis is erroneous because in their studies, supplementation of this element in children with ASD caused an increase in the level of ferritin and iron, which excludes the problem of absorption deficits [74].

Due to the large interest in this topic, many papers have been made to assess the nutrient intake of children with ASD. The results of these studies often differ from each other, which probably results from the preferences of nutrition of children with ASD. On the basis of numerous studies, it can be concluded that in people with ASD, an inadequate intake of nutrients is more common. These deficiencies may not only lead to an increase in ASD symptoms but may also initiate the development of diet-related diseases. Many pediatricians recommend their patients with ASD to check the level of calcium, iron, and vitamins in the blood and prescribe multivitamin preparations or probiotics [21, 36, 41, 55, 64].

Several studies have reported that the most common diet products chosen by children with ASD are fast food products, that is, French fries, hotdogs, hamburgers, as well as candies, sweets, and products containing preservatives [12, 13]. In the conducted research, 27% of

parents answered that the child does not prefer to consume any type of products, and 25% that the child most eats sweets. It is interesting that fast food products, sweets, and other products characterized by the content of artificial food additives are eaten much more often in the group of healthy children than people suffering from autism. Artificial food additives such as preservatives, dyes, flavor enhancers, and sweets can cause hyperactivity in some children as well as impede concentration or learning opportunities. These symptoms are characteristic of such disorders as autism or ADHD. Studies have been carried out in which a change in diet in people with ASD led to an improvement in the functioning of the gastrointestinal tract and to the improvement of the psychological and neurological symptoms of this disorder [55, 58, 63]. This indicates an important role of bacterial microflora, which is based on the concept of the gut-brain axis of etiopathogenesis and ASD therapy in children. The relationship between the digestive and nervous systems is closely related; therefore diet therapy should be an important element in the treatment of autism.

Conflict of interest

I confirm there are no conflicts of interest. The funding organization played no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the report for publication.

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Chapter 5

Fecal Microbiota Transplants as a Treatment Option for Parkinson's Disease

Inez A. Flameling and Ger T. Rijkers

Additional information is available at the end of the chapter

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Abstract

Parkinson's disease (PD) is a progressive neurodegenerative disease with an unknown cause, high prevalence, and no effective therapy. Alterations in gut microbiota composition and function have been found in PD, which could influence the gut-brain axis. Several mechanisms have been proposed and are investigated to explain the link between gut microbiota and PD. In model systems and in individual case reports, modulation of gut microbiota has been associated with improvement of PD. A safe and effective way of gut microbiota manipulation is fecal microbiota transplant (FMT). FMT is used successfully for treatment of recurrent gastrointestinal infections as well as other indications. We advocate randomized clinical trials with FMT as a treatment option for PD.

Keywords: Parkinson's disease, gut microbiota, fecal microbiota transplantation, clinical trial

1. Introduction

Parkinson's disease (PD) is a neurodegenerative disease which is accompanied by gastrointestinal dysfunction in 80% of patients [1]. PD has a high prevalence, affecting almost 2% of people over the age of 80 [2] and is currently incurable, although a variety of therapies are available to treat the symptoms [3]. In the last decade, the hypothesis has gained support that PD starts in the gut and spreads through the sympathetic and parasympathetic nervous systems to the substantia nigra and the central nervous system [4, 5]. More recently, it has been recognized that these brain-gut axis interactions in PD may be essentially influenced by gut microbiota.

In this opinion paper we want to encourage the design and initiation of clinical trial using fecal microbiota transplantation (FMT) as a therapeutic intervention for PD. We first elaborate on the evidence for the role of gut microbiota in PD, followed by a short discussion of FMT, and conclude with arguments to support the setup of clinical studies.

2. Alterations in gut microbiota composition in PD patients

A causal link between *Helicobacter pylori* infections and PD has been suggested for a long time [6, 7]. Even before the discovery of *H. pylori*, the connection between PD and gastric ulcers has already been reported [8, 9], and it was found that duodenal and gastric ulcers often preceded the onset of PD by many (10–20) years. Since then, numerous studies have reported that the incidence of small intestinal bacterial overgrowth is higher in PD patients than in healthy controls [10–13] that PD patients have higher *H. pylori* antibody levels [14] and that *H. pylori* infections are more prevalent in PD patients than in control groups [15, 16].

Several recent studies show that PD is also preceded or accompanied by changes in the abundance of other bacterial groups. It thus has been found that PD patients harbor lower concentrations of *Prevotella* bacteria [17–21], and the number of Prevotella bacteria is negatively correlated with the severity of PD symptoms [20]. Increased numbers of Enterobacteria are found in PD patients [17, 22], and the relative abundance of Enterobacteriaceae is positively associated with the severity of postural instability and gait difficulty [20]. In another study, significantly altered abundances of the Bifidobacteriaceae, Christensenellaceae, (Tissierellaceae), Lachnospiraceae, Lactobacillaceae, Pasteurellaceae, and Verrucomicrobiaceae families were found in PD patients [23]. In PD patients, *Lactobacillus* numbers were found to be higher and *Clostridium coccoides* plus *Bacteroides fragilis* numbers were lower compared to healthy controls, all contributing to a distinct composition of gut microbiota in PD [23]. Concentrations of hydrogen-producing bacteria were also higher in PD patients [24]. It has been suggested that cyanobacteria can be a source of neurotoxins that are related to PD [25, 26]. Molecular analysis of the gut microbiome has shown that 48 operational taxonomic units (OTU's) of the gastrointestinal microbiota have differential abundancy in PD patients versus healthy controls. Some of these OTUs were significantly related to motor symptoms and depression in PD patients. Functional analysis of gut microbiota also shows differences between PD patients and controls. Increased urinary indoxyl sulfate, a marker of intestinal dysbiosis, is found in PD patients [27].

Besides gut microbiota, microbiota at other ecological niches may also differ. The oral microbiota of PD patients and control subjects had differences in beta diversity and abundances of individual bacterial taxa [28].

3. Mechanistic link between gut microbiota and PD

Various studies suggest that gut microbiota do not just correlate with PD but that PD may actually start within the gut, with gut microbiota as a causative agent. The fact that

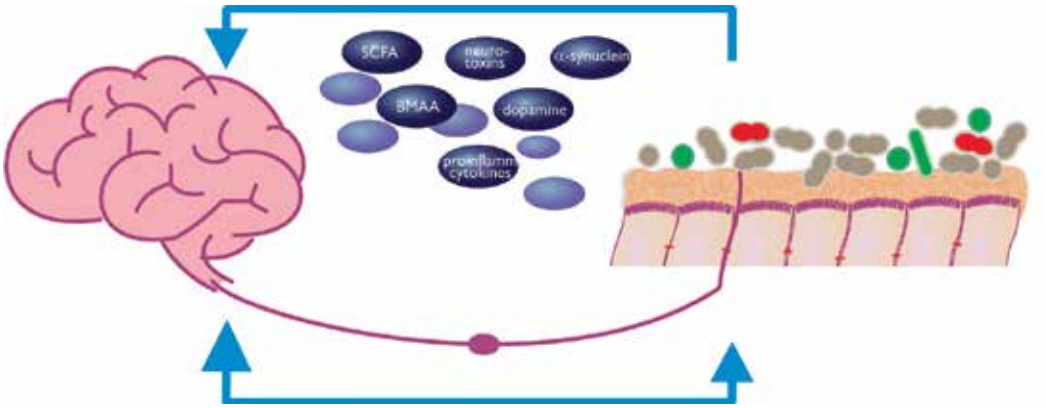

Figure 1. Potential mechanisms of interaction between gut microbiota and the brain in Parkinson's disease.

gastrointestinal dysfunction often precedes motor symptoms by 10–15 years already strongly suggests a role for gut microbiota. In addition, epidemiological studies in Sweden show that gotomy drastically reduces the risk of developing PD [29, 30], suggesting the nervus vagus as vagotomy a route via which PD may travel from the gut to the CNS (see also **Figure 1**). Sampson and co-workers found that fecal microbiota transplants from human PD patients in a mouse model of PD enhances physical impairments, compared to microbiota transplants of healthy donors [31]; a finding which may indicate that alterations in the human microbiome represent a risk factor for PD.

Various mechanisms and mediators have been proposed for the relation between gut microbiota and development of PD (**Figure 1**). PD may be initiated by toxins produced by the gut microbiota or because of a failure to produce key essential neuronal dopamine specific nutrients or enzymes, which are required by dopamine-producing cells [32]. For example, decreased numbers of *Prevotella* are linked to decreased production of important micronutrients like short chain fatty acids, thiamine and folate [19], whereas gut microbes like *Bacillus* spp. are known to produce dopamine [33]. Cyanobacteria are believed to produce the excitotoxin β-N-methyl amino-L-alanine (BMAA) which has been found to be increased in the brain of PD patients [26].

Since PD is assumed to be characterized by synucleinopathy, another potential mechanism may be that alpha-synuclein produced by gut microbiota spreads upwards from the gut along vagal nerve fibers [34, 35].

It has also been suggested that gut dysbiosis leads to chronic low-grade inflammation in the gut, which may ultimately trigger blood-brain barrier leakage, immune cell activation and inflammation, and ultimately neuroinflammation in the CNS [36]. Increased intestinal permeability has been described in PD, resulting in penetration of ***E. coli*** in the intestinal mucosa as well as oxidative stress and increased enteric α-synuclein levels [37].

A more general explanation which has been suggested is that the composition of the gut microbiota changes over the human lifespan, which may play a role in age-related diseases [38].

4. Therapeutic interventions in the microbiome as a treatment option for PD

The effect of interventions in the microbiome on PD has been demonstrated in mouse models. Administration of the antibiotic minocycline prevents nigrostriatal dopaminergic neurodegeneration in a mouse model of PD [39]. Sampson et al. have reported that antibiotic treatment of gut microbiota ameliorates physical impairment, whereas microbial recolonization, or the oral administration of specific microbial metabolites, promotes pathophysiology in a mouse model of PD [31].

In addition, a number of recent clinical studies in human patients show that various treatments of either gastrointestinal dysfunction or gut microbiota composition have a beneficial effect on PD. For example, maintenance laxative usage was associated with apparent stemming of the temporal increase in rigidity in PD [40]. PD patients who were treated for *Helicobacter pylori* infections experienced prolonged (2–3 years) improvement of motor symptoms compared to a control group [41–43]. Furthermore, *H. pylori*-positive PD patients have significantly poorer clinical scores as compared to *H. pylori*-negative PD patients [16]. Twelve weeks after treatment of the *H. pylori* infection, improvements in levodopa onset time and effect duration were observed, as well as better scores in motor performance and quality of life measures [16]. A single non peer-reviewed case study described a PD patient that became symptom-free after receiving a fecal microbiota transplant [44].

Other (non-PD related) effects of gut microbiota composition on the nervous system have also been reported. For example, a case report of three MS patients records dramatic improvement of neurological functions after fecal microbiota transplantation [45]. Significant improvement of myoclonus dystonia symptoms was observed in a female patient after receiving fecal microbiota transplantation [46]. Microbiota management via probiotic supplementation significantly reduced overall cognitive reactivity to sad mood in healthy participants of a placebo controlled, randomized clinical trial [47]. Finally, it has been demonstrated that gut microbiota from depressed patients could induce depression-like behavior in microbiota-depleted rats [48].

5. Fecal microbiota transplantation

Given the evidence described above, modification of the gut microbiota could be a valid and attractive treatment option for PD. The most powerful way to modify the gut microbiota is via a fecal microbiota transplantation (FMT). FMT is a relatively new treatment option for gut dysbiosis-related diseases; mainly *Clostridium difficile* infections, for which it is highly successful with cure rates of over 90% [49, 50]. FMT involves transfer of stool (containing both microbes and the bioactive molecules they produce) from a healthy donor to a patient (see [50] for a review). More recently, the therapy is also offered via orally administered capsules containing a screened sample of donor microbiota in freeze-dried form, which makes the treatment even safer and less invasive.

As of December 2017, nine stool banks have been installed worldwide [51]; the most recent ones being in Madrid and Hong Kong. One of them, OpenBiome, founded by Harvard and MIT microbiologists, also offers treatment via capsules (www.openbiome.org). For the time being, the stool banks only offer treatments to patients suffering from recurrent *C. difficile* infections. However, they also cooperate in studies on other diseases. FMT is considered the most cost-effective treatment option in the treatment of recurrent *C. difficile* infections [52].

FMT is a safe treatment, provided it is performed in a clinical setting and with the use of screened donor feces. Several clinical studies report mild side effects or no side effects at all [49, 53–57]. Even in high-risk groups, FMT was found to be safe: no adverse effects were found in cancer patients [58] as well as in solid organ transplant recipients [59]. A review by Baxter and Colville [60] on the adverse events associated with FMT concludes that "The vast majority of adverse events of FMT appear to be mild, self-limiting and gastrointestinal in nature." As for every new treatment, potential long-term negative effects are unknown.

It is important to note that outside clinical settings, there are risks associated with FMT. There is a growing "do it yourself" movement around FMT, where many people are experimenting with FMT as a last resort option for incurable diseases like PD. The Internet is teeming with discussion fora on which people exchange the best DIY techniques, which may involve kitchen blenders and various pumping devices. In a recent review of information regarding FMT on social media, it is concluded that "there is a vast amount of information available about FMT through social media that has the potential for causing harm" [61]. Donor screening does not take place if and when people perform the treatment themselves. This may lead to patients being put at risk to infections or perforations as a result of unprofessional treatment. For example, it has been reported that a child developed aspiration pneumonia as a result of the entrance of fecal matter in the bronchial system after the parents performed FMT without medical supervision [62]. Another case study describes a patient who developed a cytomegalovirus infection, after performing home FMT using unscreened donor feces [63]. These examples underline the importance of FMT to be provided in a clinical setting under controlled conditions.

6. Arguments in favor of an RCT

Given the above considerations, there are strong arguments for initiating a clinical study on the effect of FMT on PD patients.

a. FMT could potentially provide a treatment option for a disease that affects millions of people worldwide, is currently incurable, and is expected to become more prevalent as a result of an aging population. Given the idea that age-related diseases may be related to aging of the gut microbiota [38], using material from young donors may be especially beneficial.

b. FMT is considered safe, even in high-risk groups.

c. FMT is inexpensive

d. Safe, screened donor feces material can easily be obtained via one of the existing stool banks. A control group can be treated with autologous feces. Alternatively, OpenBiome offers the possibility to assist in designing a setup and provide orally administered capsules.

e. The best way to stem the DIY movement and prevent dangerous situations as a result of people experimenting with FMT, is to offer a safe and controlled alternative in a hospital setting or to develop safe protocols for home-administered fecal transplantations in a health care setting [49, 56].

So far, only one clinical trial has been initiated (ClinicalTrials.gov Identifier: NCT03026231) [64]. However, we argue that more clinical trials are warranted. The argument that the mechanism via which microbiota affect PD is still poorly understood [65–67] should not block further application of FMT. Aspirin, for example, has been effectively applied for centuries before the mechanism was finally elucidated in the 1970s. Likewise, levodopa has been used for the treatment of PD for decades before its mechanism was unraveled. It may take years before the pathways via which gut microbiota affect the brain are unraveled, and meanwhile a potentially promising treatment option remains unexplored. Given the relative ease and safety of the treatment and the fact that it is already applied on a routine basis to *C. difficile* patients, including these in high-risk groups like cancer patients or organ transplant recipients, we advocate more clinical studies. Moreover, a clinical study on FMT in PD could lead to a better understanding of the relation between microbiota and the nervous system.

Finally, several authors have already pointed out that FMT is a very promising treatment option for PD. As stated by Mulak and Bonaz: "The close relationship between gut dysbiosis, intestinal permeability and neurological dysfunction suggests that the gut microbiota modification may provide a promising therapeutic option in PD" [68]. Fang also stated that "Microbiota-based interventions that play a regulatory role in the gut microflora exhibit therapeutic potential" (for PD) [69]. Finally, Scheperjans in 2016 comments in an opinion article: "If this endeavor is successful, we may end up with completely new therapeutic approaches that could hopefully turn the ship around toward effective disease modification or even prevention" [70].

It took a long time before FMT was generally accepted as a treatment option for *C. difficile* infections because physicians were skeptical about this "19th century technique" or wary of any adverse effects [71]. It is unknown how many people died (or are still dying) unnecessarily from otherwise untreatable *C. difficile* infections or had their colons removed, while it was already known that FMT could cure them. The prognosis has finally changed for the betterment for these patients. In 2010, a study on the effect of FMT on recurrent *C. difficile* infection in Amsterdam was prematurely terminated because the data and safety monitoring board of the hospital considered it unethical to withhold the treatment from the control group [55]. FMT thus is on the way to becoming a standard treatment for recurrent *C. difficile* infections in most developed countries.

Given the fact that FMT is a very promising treatment for PD, is safe, not invasive (especially using orally administered capsules) and inexpensive, and people are exposing themselves

to risks by performing the treatment themselves without medical supervision, it could be argued that not starting a trial on the effect of FMT on PD would be similarly unethical. The roadmap is clear, and it now just needs to be taken.

Conflict of interest

The authors have no conflict of interest to declare.

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Chapter 6

Probiotics for Preventing Cognitive Impairment in Alzheimer's Disease

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Additional information is available at the end of the chapter

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Abstract

Alzheimer's disease (AD) is a progressive and irreversible neurodegenerative disease that results in gradual cognitive impairment and eventually leads to dementia. However, despite AD being one of the most prevalent neurodegenerative diseases in aging societies, no clinically successful therapeutic strategies for its treatment or prevention have been reported to date. Studies have indicated that gut microbial alterations are linked to AD. Probiotics are living microorganisms that are known to confer health benefits to the host when ingested in adequate amounts. Certain strains of probiotics appear to influence the central nervous system (CNS) and behavior via the microbiota-gut-brain axis. Increasing evidence from preclinical and clinical studies has demonstrated that probiotics possess preventive as well as therapeutic potential for AD. It is speculated that probiotics could ameliorate the progression of AD by modulating the inflammatory process, counteracting oxidative stress, and other possible mechanisms, although further studies are needed to understand the details. In this chapter, we will highlight the current understandings of the effects as well as the possible mechanisms of action of probiotics for preventing cognitive impairment in AD.

Keywords: Alzheimer's disease, probiotics, microbiota, gut-brain axis

1. Introduction

Alzheimer's disease (AD) is the most common form of neurodegenerative disease and the leading cause of dementia in the elderly, accounting for an estimated 60–80% of dementia cases worldwide [1]. It is a highly incapacitating disorder, progressing from gradual deterioration of memory and cognitive functions to a complete incapacity, which consequently leads

to death of patients within 3–9 years after diagnosis [2]. Aging is recognized as the major risk factor of all AD cases, and the aging of world population will lead to a steep increase in the prevalence of AD [1]. Despite much effort has been made in AD research in the past few decades, the pathophysiology of AD remains unclear, and to date, there is no effective therapeutic treatment for the disease. Hence, new therapeutic solutions that can effectively combat the disease are of utmost importance.

Recent studies have shown that the gut microbiota is involved in the neurodegenerative disorders and diverse cognitive functions through regulating the gut-brain axis [3, 4]. The concept of microbiota-gut-brain axis is emerging and its dysregulation has now been linked to the progression of AD [5]. In light of this, it is suggested that modulation of the gut microbiota through the use of probiotics might possibly prevent or ameliorate AD symptoms.

In this chapter, we discuss the roles of the gut microbiota in the development of AD, highlighting the specific contribution of probiotics intervention to the amelioration of AD progression. We examine recent scientific literature addressing the beneficial effects of probiotics for the prevention and treatment of AD and point out the possible mechanisms of action of probiotics for preventing cognitive impairments in AD.

2. Clinical features and pathogenesis of Alzheimer's disease

AD is a chronic progressive neurodegenerative disorder characterized by three clinical phases in which the patients exhibit different symptoms over time [6]. The first stage (early stage; mild AD) includes memory loss, language difficulties, and executive dysfunction. The second stage (middle stage; moderate AD) comprises psychiatric symptoms and behavioral disturbances such as depression, hallucinations, delusions, and agitation. The third stage (late stage; severe AD) comprises severe impairment of almost all cognitive functions and difficulties to perform activities of daily living. The symptoms of AD worsen gradually, and the disease may begin to develop decades before the manifestation of the earliest clinical symptoms [7].

Despite the massive worldwide research efforts that have been made in the past few decades, the exact cause and pathogenesis of AD are not fully understood. It is widely believed that the pathogenesis of AD is primarily driven by the abnormal deposition of extracellular β-amyloid peptide (Aβ) plaques in various areas of brain, although such hypothesis may not be the sole explanation [8, 9]. Aβ is a peptide consists of 37–43 amino acids, in which $A\beta_{42}$ is a more prevalent isoform and is considered to be the most neurotoxic in nature [10]. Aβ is derived from the sequential proteolytic enzymatic cleavage of amyloid precursor protein (APP) by two membrane-bound proteases, β- and γ-secretase [11, 12]. In the amyloid cascade hypothesis of AD, the disease is characterized as a series of abnormalities in the process and secretion of the amyloid precursor protein (APP), where an imbalance between production and clearance of Aβ is the triggering event that leads to the accumulation of Aβ in the brain parenchyma [13]. As a consequence, Aβ spontaneously aggregates into soluble oligomers that are eventually deposited in diffuse senile plaques [14]. The Aβ deposition and diffused senile plaques

formation eventually lead to local microglia activation and production of pro-inflammatory cytokines [15, 16]. In turn, these cytokines stimulate reactive astrocytes to produce further amounts of $A\beta_{42}$ oligomers, thus activating more amyloid plaque formation [17]. In addition, Aβ oligomer aggregations induce oxidative damage, which, in turn, seem to provoke inflammation and facilitate tau hyperphosphorylation, resulting in adverse effects on neuronal synapses and mitochondria [18].

Neurofibrillary tangles (NFTs), which are filamentous inclusions that accumulate in selective neurons of AD brains, are another major pathological hallmark of AD. The major component of NFTs is the microtubule-associated protein tau [19, 20]. The tau protein is a highly soluble protein that promotes microtubule assembly and stabilization for axonal transport and neuronal growth under normal conditions [21]. In AD, the tau protein exhibits altered solubility properties, becomes abnormally hyperphosphorylated, and forms filamentous structures [22]. Hyperphosphorylation of tau is known to induce a lower grade of interaction of tau proteins with microtubules that leads to greater self-aggregation of tau proteins and consequently induces malfunction of axonal transport [23], mis-stabilization of actin [24], synaptic impairment [25], and defects in mitochondrial integrity [26].

Nevertheless, NFTs seem not to be the main toxic entities leading to AD. Recent studies show that the intermediate tau oligomer is likely to be the key attribute of disease onset [27, 28]. Appearing prior to NFTs formation, hyperphosphorylated tau self-assembles into oligomeric forms and insoluble materials as paired-helical filaments (PHFs), triggering neurotoxic actions that affect the normal interaction patterns of the neuronal cytoskeleton and neuronal damage [28, 29]. As a result of neuronal death, tau oligomers are released into the extracellular environment, contributing to microglia activation with overproduction of pro-inflammatory cytokines that trigger deleterious signal cascades leading to progressive neuronal degeneration in AD brains [30]. Although the exact cause on why AD onset takes decades before symptoms occur remains unclear, AD progression is likely related to a reduced ability to eliminate misfolded, oligomerized, and aggregated tau proteins that increase with advancing age. Therefore, tau protein could be another important therapeutic target in AD pathology.

3. Gut microbiota and Alzheimer's disease

3.1. Microbiota-gut-brain axis

The gut-brain axis has long been recognized as a bidirectional communication between the brain and the gut in which the brain communicates with the gastrointestinal tract by modulating permeability, motility, secretion, and immunity, and concurrently, the gut can affect brain function and behavior [31]. The complex and multifaceted network of gut-brain axis consists of the gastrointestinal tract, central nervous system (CNS), autonomic nervous system (ANS), enteric nervous system (ENS), neuroendocrine system, and immune system which drive various afferent and efferent pathways such as vagus nerve and hypothalamic-pituitary adrenal (HPA) pathway for regulation of immune and metabolic homeostasis [31]. Recently, it is

becoming increasingly evident that gut microbiota play a pivotal role in regulating the gut-brain axis, thereafter the term microbiota-gut-brain axis was introduced [32–34].

Gut microbiota is proposed as a key regulator of centrally mediated events including metabolic homeostasis, immune function, and neurological diseases [33]. Gut microbiota is a complex community composed of trillions of microorganisms, mainly bacteria, but also bacteriophage particles, viruses, fungi, and archaea [35]. A majority of the microbiota belongs to the two bacterial phyla, Bacteroidetes and Firmicutes, while Proteobacteria, Actinobacteria, Fusobacteria, and Verrucomicrobia phyla are present in lower proportions [36]. Notably, it is increasingly evident that alterations in the gut microbiota composition may cause imbalanced gut homeostasis and detrimental effects on CNS [37]. For instance, a variety of gastrointestinal and metabolic diseases including inflammatory bowel disease (IBD), obesity, diabetes, and insulin resistance are common comorbidities in many neurological disorders [38]. More recently, metagenomics studies have revealed that gut dysbiosis is present in a variety of neurological diseases including AD. Consequently, it is inevitably important to maintain a well-balanced and healthy microbiota community in the regulation of gut-brain axis.

3.2. Gut microbiota alterations and Alzheimer's disease

Accumulating evidence suggests that gut microbiota alterations can influence the progression of neurological disease and may be a major factor in the development of AD [39, 40]. For instance, a recent preclinical study revealed a remarkable shift in the gut microbiota of APP transgenic mice as compared to healthy, wild-type mice, wherein a significant reduction in bacteria belonging to the phyla Firmicutes, Verrucomicrobia, Proteobacteria, and Actinobacteria with respect to an increase of Bacteroidetes and Tenericutes was observed in the intestine of conventionally raised transgenic APPPS1 AD mice [41]. It was strongly advocated that a distinct microbial constitution in AD mice may contribute to amyloid deposition wherein a remarkable increase in cerebral Aβ pathology was observed in APP transgenic germ-free mice colonized with microbiota from conventional APP transgenic mice, while control mice colonized with microbiota from wild-type mice was less effective in increasing cerebral Aβ levels [41]. In addition, a clinical study characterizing the gut microbiota composition of AD subjects reveals decreased microbial diversity and changes in bacterial abundance compared with controls; these changes include decreased levels of Firmicutes and *Bifidobacterium* and increased levels of Bacteroidetes [42]. Nonetheless, the exact causes and effects of gut dysbiosis on AD remain elusive.

It is plausible that microbiota alterations can lead to colonization of intrinsic pathogens and increase gut permeability that could perturb the gut-brain axis. For instance, recent study has demonstrated that enterobacteria infection exacerbated progression of AD by promoting immune hemocyte recruitment to the brain; thereby provoking tumor necrosis factor-c-Jun NH2-terminal kinase (TNF-JNK)-mediated neurodegeneration in a drosophila AD model [43]. Additionally, the intestinal opportunistic bacteria including *Bacillus subtilis*, *Escherichia coli*, *Klebsiella pneumonia*, *Mycobacterium* spp., *Salmonella* spp., *Staphylococcus aureus*, and *Streptococcus* spp. have been found to excrete immunogenic compounds of amyloids, lipopolysaccharides (LPS),

and other microbial exudates into their circumjacent environment [44]. For instance, LPS and the *E. coli* K99 pili protein were highly detected in the brain parenchyma and blood vessels of AD patients [45]. Additionally, LPS was found to colocalize with Aβ in amyloid plaques, suggesting that bacterial components can translocate from the gut, assessing the brain and further triggering Aβ deposition in AD [45]. It has also been hypothesized that bacterial-derived amyloids may reach the systemic circulation and accumulate in the brain, thereby triggering a series of downstream events that leads to impairment of phagocytosis and contributes to $A\beta_{42}$ deposition, resulting in dysfunction of specific brain regions, such as the cerebellum and the hippocampus [46, 47].

Another clinical study involving 83 elderly subjects (40 cognitive-impaired amyloid-positive patients, 33 cognitive-impaired amyloid-negative patients, and 10 cognitively healthy amyloid-negative controls) have demonstrated that an increased abundance of a pro-inflammatory gut microbiota taxon, *Escherichia/Shigella*, and a reduced abundance of an anti-inflammatory taxon, *Enterococcus rectale*, are possibly associated with a peripheral inflammatory state in patients with cognitive impairment and brain amyloidosis [48]. The results obtained from the study indicated the role of amyloid and related bacterial accumulation in the pathogenesis of cognitive damage [48]. A remarkable recent study using APP transgenic mice model has also demonstrated that AD pathology shifted gut microbiota composition during aging toward an inflammation-related bacterial profile and suggested that these changes could contribute to disease progression and severity [49]. Taken together, these findings highlight an intricate association between gut microbiota alterations and amyloid formation, increased systemic inflammatory responses and cognitive impairment in AD, suggesting modulation of gut microbiota with probiotics could be a promising therapy to alleviate its underlying symptoms.

4. Probiotics modulation of Alzheimer's disease

The connections between gut microbiota and AD have led to a great interest in modulation of the microbiota-gut-brain axis through probiotics. Probiotics are defined as live microorganisms that, when consumed in sufficient amounts, confer health benefits to the host [50]. The probiotics species that are most commonly studied usually belong to the genera *Lactobacillus* or *Bifidobacterium*, whereby some of the members are the natural inhabitants of the gut microbiota and generally regarded as safe. In recent years, the possibilities of probiotics exerting a positive cognitive effect in human health have emerged. A growing body of animal studies supports the idea that certain probiotics can counteract gut dysbiosis and may positively impact the pathogenesis of AD. Nonetheless, clinical data are less compelling than the animal model data.

4.1. Animal studies

Studies in rodents indicate that cognition and memory storage, particularly the hippocampal long-term potentiation, begin to decline in aging animals and these brain functions are dramatically disrupted in animal models of AD [51]. Many lines of evidence have shown that

probiotics modulation of the gut microbiota could improve age-related cognitive functions in animal models. For instance, treatment with VSL#3, a probiotics mixture containing eight different Gram-positive bacterial species, showed a significant alteration in gut microbiota, with increases in Actinobacteria and Bacteroidetes, both of which were reduced in vehicle-treated animals with a positive impact on long-term potentiation, inflammation, and neural plasticity [52]. Moreover, it was demonstrated that long-term dietary supplementation of multispecies live *Lactobacillus* and *Bifidobacterium* mixture (Lab4) to aging rats changes the brain metabolites (γ-aminobutyric acid (GABA) and glutamate) that are involved in neural signaling in the frontal cortex and hippocampus and improves task-specific memory [53]. Collectively, these findings represent proof of principle that probiotic modulation of gut microbiota can have a positive impact on cognitive functions and suggest a possible role of memory-enhancing probiotic strains in preventing cognitive impairment in AD.

A recent study has provided direct evidence for amelioration of cognitive dysfunction by probiotics treatment with the strain of *Bifidobacterium breve* strain A1 using Aβ-induced AD mice model (**Figure 1**). Administration of *B. breve* A1 to AD mice attenuated the impairment of alternation behavior in a Y maze test and reversed the reduced latency time in a passive avoidance test, indicating that *B. breve* A1 prevented cognitive dysfunction [54]. In addition to the promising effect on cognitive function, *B. breve* A1 also suppressed the immune response and neuronal inflammation induced by Aβ. Moreover, SLAB51 probiotic formulation, which consists of a mixture of lactic acid bacteria and bifidobacteria, was shown to reduce brain damage and Aβ aggregations and prevents the onset and delay progression of AD in mice in the early stage of AD [55]. Another report using $A\beta_{1\text{-}42}$-intra-hippocampal injected rats have also demonstrated that the administration of probiotics, which consisted of *L. acidophilus*, *L. fermentum*, *B. lactis*, and *B. longum*, could improve the common pathological features of AD including spatial memory and learning deficits and oxidative stress [56]. Taken together, these animal studies show that probiotics may play an important role in the bidirectional communication between the gut and the brain, and support the notion that probiotics modulation could ameliorate the development of AD; however, it clearly requires translation in humans.

4.2. Human studies

The health benefits of probiotics on numerous aspects of host health and homeostasis have been extensively studied in clinical trials. However, a detailed analysis of probiotics modulation in patients with AD is lacking and the effects of probiotics on the onset, symptoms, and pathogenesis of AD remain uncover. To date, there is only one clinical study of probiotics in subjects with AD has been carried out. The randomized, double-blind, and controlled clinical trial involved 60 patients with AD who were randomly assigned into two groups: the probiotics group (n = 30), received 200 ml/day of milk enriched with *L. acidophilus*, *L. casei*, *B. bifidum*, and *L. fermentum* (2×10^9 CFU/g each) for 12 weeks, and the control group (n = 30) received plain milk at the same amount [57]. All participants were introduced to the mini-mental state examination (MMSE) cognitive test for evaluation of learning and memory. After 12 weeks intervention, probiotic administration has significant improvement in the MMSE

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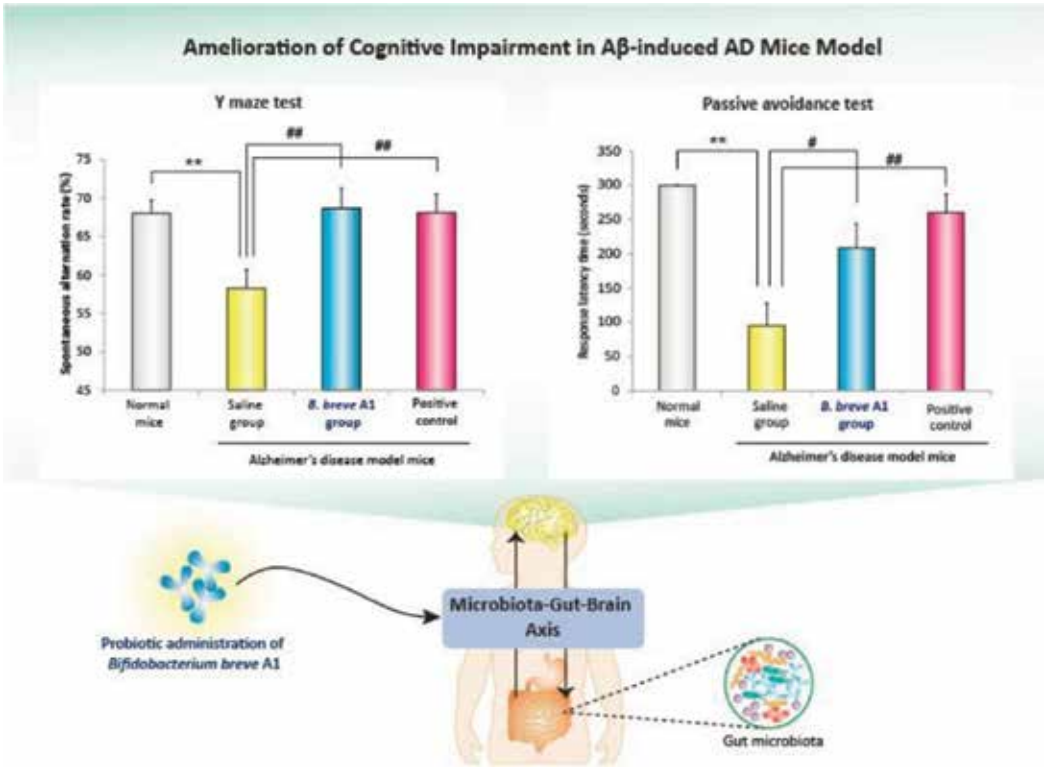

Figure 1. Probiotics intervention could potentially modulate cognitive decline in Alzheimer's disease (AD) via the microbiota-gut-brain axis. A prominent strain of probiotic, *Bifidobacterium breve* A1 ameliorated cognitive impairment in Aβ-induced AD mice model wherein administration of *B. breve* A1 to AD mice attenuated the impairment of alternation behavior in a Y maze test and reversed the reduced latency time in a passive avoidance test.

score of the subjects with AD in which the score (out of 30) was significantly increased in the probiotic group (from 8.67 ± 1.44 to 10.57 ± 1.64, +27.90 ± 8.07%) as compared to control group (from 8.47 ± 1.10 to 8.00 ± 1.08, −5.03 ± 3.00%). The probiotic treatment also has favorable effects on the levels of malondialdehyde (MDA) and high-sensitivity C-reactive protein (hs-CRP), improved insulin resistance, pancreatic beta cell secretion, and metabolic status with respect to controls; albeit the changes in other biomarkers of oxidative stress and inflammation, fasting plasma glucose (FPG) and other lipid profiles are negligible [57]. Based on the MMSE scores, the patients included in this study were having severe AD. It is generally recognized that the physiological effect of probiotics on human health is preventive but not therapeutic, thus, it is surprised to find a prominent effect of this probiotics mixture on patients with severe AD. Further investigations on the effects of probiotics on mild cognitive impairment (MCI) and moderate AD are undoubtedly needed. Collectively, the results from both animal and clinical studies offer hope for the future development of a novel probiotics-based approach to ameliorate symptoms of AD and provide a useful framework to explore the microbiota-brain axis.

5. Possible mechanisms of action of probiotics in preventing Alzheimer's disease

5.1. Modulation of immune reactions

Although many lines of evidence have shown the potential effects of probiotics in treating AD, the mechanisms of action are still speculated and unclear. One mechanism is the modulation of immune reactions. Accumulating evidence suggests that neuroinflammation has a causal role in the pathogenesis of AD wherein neuroinflammation is not a passive system activated by senile plaques and NFTs, but instead contributes as much as the plaques and tangles in AD [58]. This is substantiated by the presence of microglia cells in both AD patients and animal models of AD [59], and it is accompanied by increased levels of pro-inflammatory cytokines, such as TNF-α or interleukin (IL)-6 as found in the serum and brain tissue of AD patients [60]. In AD, aggregated Aβ as well as hyperphosphorylated tau proteins interfere with neuronal function and trigger the inflammatory activity of microglia [61]. Microglia activation leads to further accumulation of Aβ, neuronal debris, and, most probably, the sustained production of pro-inflammatory cytokines and reactive oxygen species (ROS), giving rise to a chronic, nonresolving inflammatory process [62]. Inevitably, modulation of neuroinflammation provides compelling targets for interventions in AD.

Probiotics intervention has been reported to improve the age-associated modifications of immunological features. It was demonstrated that probiotic treatments can ameliorate the immune reactions by modulating cytokine production, improving distribution and function of natural killer cells, macrophages, granulocytes, and T cells, and enhancing mucosal and systemic antibody responses [63–66]. In view of the immunomodulatory properties of probiotics, one might speculate that the probiotic bacteria may ameliorate symptoms of AD by modulating the inflammatory reactions driven by Aβ deposition and other risk factors, including inflammaging, obesity, and traumatic brain injury.

Studies have shown that probiotics could directly mitigate neuroinflammation as observed in the reductions of circulating pro-inflammatory cytokines and microglia activation. For example, chronic inflammation was suppressed after probiotic treatment with *L. pentosus var. plantarum* C29 in a D-galactose-induced accelerated aging mouse model for which the activation of transcription factor nuclear factor-kappa B (NF-κB), the pro-inflammatory cytokine TNF-α, and M1 macrophages were inhibited [67]. Moreover, administration of *B. breve* A1 ameliorated Aβ toxicity and prevented cognitive decline in AD model mice through its modulating effect on the excessive immune response and neuronal inflammation caused by Aβ injection [54]. Overall, these studies provide a mechanistic insight into the role of probiotics in modulation of inflammatory responses and amelioration of AD pathology.

5.2. Suppression of oxidative stress

In addition to the established pathology of senile plaques and NFTs, oxidative stress has emerged as an important factor contributing to the development of AD. Oxidative stress

represents the mechanism through which Aβ neurotoxic peptides and tau proteins mediate the pathological processes and cause synaptic impairment, neuroinflammation, neuronal apoptosis, and neurotransmitter dyshomeostasis in AD [68] that ultimately correlates with the typical behavioral symptoms of AD [69]. Oxidative stress is characterized as an imbalance between the production of ROS and the activities of antioxidant defense system that resulting in oxidative damage, as observed in AD patients [70]. Mounting evidence suggests that oxidative damage contributed to the onset and progression of AD wherein low antioxidant enzyme levels, high oxygen consumption, the presence of excitotoxic amino acids, and high iron content promote the production of ROS and reactive nitrogen species (RNS) in the brain [71, 72]. In addition, aberrant accumulation of Aβ can also enhance the generation of ROS through an N-methyl-D-aspartate (NMDA) receptor-dependent mechanism [73], and that oxidative stress may augment the production and deposition of Aβ as well as facilitate tau hyperphosphorylation and oligomerization, forming a viscous cycle that promotes the onset and progression of AD [74]. Therefore, it is tempting to postulate that probiotics with strong antioxidant potential may prevent and treat AD by counteracting oxidative stress and the molecular events implicated in the pathogenesis of AD.

A remarkable recent study supports the protective role of probiotics in the brain oxidative status of AD mice model and demonstrates the molecular mechanisms involved [75]. For instance, SLAB51 probiotics formulation significantly reduced oxidative damages in AD mice brain through a mechanism that involves the activation of SIRT1-related pathways [75]. SIRT1 is a deacetylase with a strong neuroprotective and antioxidant potential that regulates the expression of several antioxidant genes [76, 77]. Reduction of SIRT1 functionality and expression levels have been reported to contribute to the accumulation of Aβ and tau in the cerebral cortex of AD patients [78]. It was demonstrated that SLAB51 intervention restored the levels of SIRT1 by deactivating its nuclear receptor RARβ in AD mice [75], which, in turn, may stimulate the nonamyloidogenic pathway of APP processing and diminish Aβ production and accumulation [79]. Moreover, several studies have also reported that probiotic bacteria counteracted oxidative damage and improved cognitive impairment in AD rodent models through its antioxidant properties [56, 80]. Collectively, these findings represent the fundamental concept that probiotic ameliorates the symptomatology of AD through its antioxidative mechanism.

5.3. Modulation of CNS function mediated by bacteria-derived metabolites

Another possible mechanism of action by which probiotics can ameliorate AD is through the production of metabolites such as short-chain fatty acids (SCFAs). SCFAs, mainly acetate, butyrate, lactate, and propionate, are the main metabolites of the fermentation of dietary fibers by the gut microbiota [81]. A study using germ-free mice has revealed a substantial contribution of the gut microbiota, particularly the microbiota-derived SCFAs, to the regulation of microglia maturation and functions [82]. In addition, SCFAs have also been shown to play a role in regulation of several signaling pathways such as inhibition of NF-κB, inhibition of histone deacetylation (HDAc), and activation of G protein-coupled receptors (GPCRs), and are well known to have potent anti-inflammatory effects [83–85]. For instance, butyrate has a

direct stimulation effect on vagal afferents that have been shown in clinical trials to improve cognitive function of AD patients [86, 87]. Butyrate has also been shown to inhibit HDAc and improve memory function in a late-stage AD mouse model [88]. In addition, a study using PC12 cells demonstrated the potential neuroprotective roles of the enteric bacterial metabolites, butyrate and propionate, against AD whereby the expression of Aβ A4 protein precursor was significantly downregulated by these SCFAs [89]. Meanwhile, acetate supplementation was shown to be capable of attenuating neuroglia activation and pro-inflammatory cytokine expression in rat models of neuroinflammation [90].

Recent scientific studies indicate that probiotics modulation of gut microbiota ameliorated the inflammatory status of AD through the production of SCFAs. For example, in the study of the probiotic *B. breve* A1, the cognitive decline of Aβ-induced AD mice was also partially ameliorated by its metabolite acetate, implying that the production of SCFAs by the gut microbiota could be involved in the preventive mechanisms of Aβ-induced neuroinflammation and cognitive impairment [54]. In fact, several SCFAs produced by gut microbiota have been shown to be capable of potently inhibiting the formation of toxic soluble Aβ aggregates, *in vitro* [91]. A growing body of evidence has shown that circulating levels of SCFAs could affect CNS function [92, 93], suggesting a functional role of SCFAs in the modulation of amyloidosis, neuroinflammation, and other AD-related conditions in the brain. Moreover, in the 3xTg-AD mice model (which rapidly develops amyloid plaques and NTFs) treated with the probiotics SLAB51, the levels of the bacterial metabolites (i.e., propionate and acetate) are elevated [55]. Together with the positive interference of inflammatory cytokines, reduction of Aβ aggregates, and improvement of cognitive function by SLAB51 treatments, these data contribute to define the link between bacterial-derived metabolites and AD. Nonetheless, there is still no clear mechanistic study investigating the underlying mechanisms of SCFAs in the treatment of neurodegenerative diseases.

In addition, SCFAs were reported to be able to modulate neurotransmitter synthesis and have effect on the neurotrophic genes including brain-derived neurotrophic factor (BDNF) and nerve growth factor [92, 94]. Interestingly, a reduction in BDNF signaling was observed in both the brain and the serum of patients with AD [92], and such decline was reversed by probiotics intervention as demonstrated in rodent model [52, 95, 96]. These findings suggest that probiotic modulation may enhance the production of small ubiquitous microbiota-derived molecules like SCFAs that could act as important molecular signals between the microbiota and host, thereby improving the molecular events associated with cognitive impairment.

5.4. Amelioration of AD pathogenesis via alteration of gut microbiota composition

Another mechanism to consider is the alteration of gut microbiota composition by probiotics. Emerging evidence suggests that targeting the gut commensals through probiotics intervention could mitigate age-associated inflammation and cognitive impairment [52, 97]. It has also been reported that perturbations of gut microbiota community induced by antibiotic treatment could ameliorate Aβ deposition and inflammatory responses in an aged APP transgenic mice model of

AD [98]. Furthermore, many intervention studies in elderly subjects have also demonstrated that probiotics can augment the growth of the gut commensal, *Bifidobacterium*, while concomitantly decreasing the growth of opportunistically pathogenic enterobacteria [99].

While little is currently known regarding the role of the microbiota-gut-brain axis in AD, several scientific efforts have pointed out that probiotics can modify the gut microbiota for amelioration of AD-related pathological conditions. For instance, administration of the probiotic mixture SLAB51 induced larger shifts in the microbial communities of the 3xTg-AD mice, along with an increase in the proportions of *Bifidobacterium* spp. and a reduction in *Campylobacterales* population [55], suggesting a possible role of these bacteria in the regulation of inflammation in AD. This is substantiated by the reduced plasma concentration of pro-inflammatory cytokines in AD mice treated with SLAB51 [55]. In fact, certain strains of *Bifidobacterium* were reported to possess anti-inflammatory properties and could negatively modulate mRNA levels of pro-inflammatory cytokines produced from LPS-stimulated macrophages [100]. In contrary, *Campylobacter jejuni* and *Campylobacter coli* have been found to stimulate pro-inflammatory responses in human peripheral blood mononuclear cells [101] and chicken models [102]. Moreover, a high prevalence of *Campylobacterales* infections has been observed in patients with AD, and the parameters on cognitive function were ameliorated after *Helicobacter pylori* eradication [103]. These findings suggest that the alteration of gut microbial composition by probiotics could positively modulate the AD-related pathological conditions. Nevertheless, translational study in human subjects is undoubtedly required in order to determine whether probiotics modulation of the gut microbiota could display efficacy in mitigating the pathogenesis of AD in humans. Nonetheless, these promising findings suggest that targeting the microbiota by probiotics intervention could be a useful preventive measure for AD.

6. Conclusions and perspectives

Altogether, the results of the research summarized in this chapter suggest the potential of probiotics in preventing cognitive impairment in AD. In particular, probiotics intervention could effectively ameliorate cognitive impairment and symptomatology of AD and can be considered as an important advance in the field of AD. It is evident that the gut microbiota composition is altered in AD and the modulation of gut dysbiosis through probiotics could counteract various benchmarks of AD. Probiotics or its bioactive metabolites can improve gut microbiota homeostasis and influence the pathological factors involved in the progression of AD such as inflammatory reaction, oxidative stress, Aβ deposition, and cognitive functions (**Figure 2**). Despite still being a speculation, accumulated information from animal and human research provides fundamental proofs for the modulating effect of probiotics in AD and underlies the possible mechanisms of action involved. Further studies are definitely needed to fully elucidate the scope of probiotics for this debilitating disease, as well as to clarify the underlying mechanisms of probiotics for preventing cognitive impairment in AD.

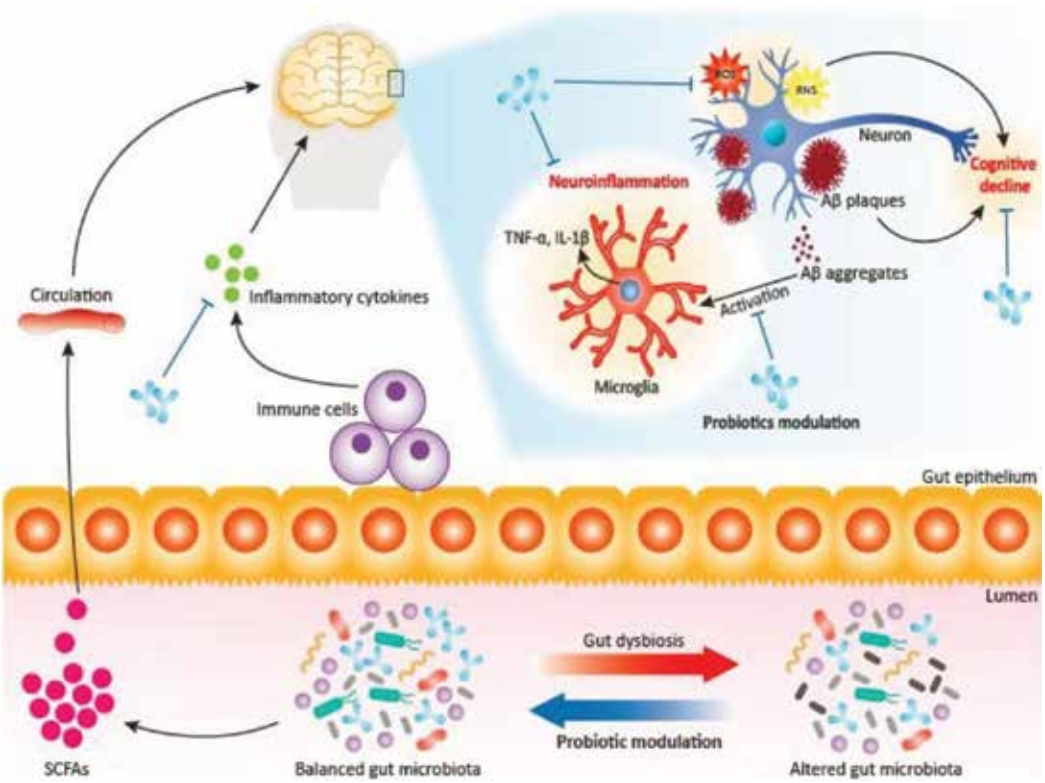

Figure 2. Schematic overview of the possible mechanisms of action of probiotics modulation for preventing cognitive impairment in Alzheimer's disease (AD). Probiotics or its bioactive metabolites such as SCFAs can improve gut microbiota homeostasis and positively influence the pathological factors involved in the progression of AD such as inflammatory reaction and oxidative stress, thereby ameliorating cognitive decline in AD.

Abbreviations

AD	Alzheimer's disease
Aβ	β-amyloid peptides
NFTs	neurofibrillary tangles

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Edited by Alper Evrensel and Barış Önen Ünsalver

The gut–brain axis has gained considerable attention from different branches of the scientific community in recent years. In this book, scientists from different disciplines present current scientific knowledge on the topic.

The interaction between the prokaryote and eukaryote cells stimulates the evolutionary processes, and results in various systemic illnesses such as neuropsychiatric disorders and may help the continuity of health.

Nature has provided us with healthy food that builds our pharmacy. This natural pharmacy store may help the body's healing processes through its effects on gut microbiota and the immune system.

This book aims to provide the reader with detailed analyses of the current scientific knowledge on the gut–brain axis and its relation with health and disease. We hope that the reader benefits from the presented material.

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