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# Herbal Medicine

*Edited by Philip F. Builders*

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# Meet the editor

Philip Fafowora Builders obtained his Bachelor of Pharmacy degree from the University of Jos in 1991, and Master of Pharmacy and Doctor of Philosophy (Pharmaceutics) degrees from the University of Nigeria, Nsukka, Nigeria, in 1997 and 2008, respectively. He works as a research fellow in the Department of Pharmaceutical Technology and Raw Materials Development, Abuja, Nigeria, and also as an associate professor in the Department of Pharmaceutics and Pharmaceutical Microbiology, Faculty of Pharmaceutical Sciences, Kaduna State University, Nigeria. He has published several research and review articles as well as book chapters. His research interests include biopolymers for drug delivery, dosage form design of conventional and herbal medicines, nanoparticulate drug delivery systems, and stability and quality assessment of herbal medicines and conventional drugs.

# Contents

# Preface

Even in the light of increased sophistication and access to conventional healthcare the use of herbal medicine has continued to thrive in both poor and rich societies for many and probably different reasons. Hence, it is important for the various stakeholders in healthcare—governments, healthcare providers, farmers, biomedical scientists, and engineers—to have enough information to give due attention to herbal medicines in a deliberate effort to develop them alongside conventional medicine. Therefore, there is an urgent need for appropriate and sufficient information on herbal medicines, especially that which highlights important topics such as uses, efficacy, safety, herbal/drug interactions, research and development, regulation, analytical techniques, and quality control. *Herbal Medicine* collates and presents in a simple, unambiguous, and readable manner, wide and in-depth information that will be useful to all who have a stake in herbal medicine and healthcare in general.

To make this important book a reality I wish to thank the management of Intech who provided the platform on which such great knowledge and information can be disseminated. The resilient, patient, and experienced counsel of Ms. Kristina Kardum, the Author Service Manager, for this book project is highly appreciated and commended. The efforts of all the contributing authors, who painstakingly researched and presented the various topics that brought this book to fruition, are highly commended as well as many others who contributed to make this book possible. Thank you.

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Chapter 1

# Introductory Chapter: Introduction to Herbal Medicine

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## 1. Herbal medicine

Herbal medicine (HM) is the fulcrum of complementary and alternative medicine, which in recent times is increasingly gaining widespread popularity all over the world and gradually streaming toward integration into the mainstream healthcare systems [1]. The use of HM cuts across gender, social and racial classes in both developing and developed countries of the world [2–7]. Due to the increasing popularity of HM, stakes in the world markets (local and international) are also rapidly increasing and the annual sale is rapidly approaching US $62 billion [8]. An important driver in this upsurge in patronage and use includes low cost, the wide acceptance due to its status of being a natural product with the acclaim of low toxicity, efficacy in certain challenging diseases, flexibility in its accessibility, preparation and use.

HM includes preparations of biologically active natural products that consist largely of herbs or herbal materials, some recipes may contain materials such as fungal and bee products, as well as minerals (kaolin, bentonite), ash, shells, insects and animal parts, and are used for the maintenance of health and management of various diseases. HMs can elicit numerous benefits just as some can cause adverse effects. The pharmacologic and most of the toxic effects that are elicited by HMs have been linked to the activities of the secondary metabolites. In many instances, HMs have been appropriately used, misused and sometimes misunderstood. The benefits of HMs as a means of healthcare depends largely on the correct and adequate knowledge, and experiences while misuse as well as misunderstanding have been tracked to the knowledge gap on herbal medicines especially as it relates to their benefits and potential drawbacks by the primary healthcare professionals: doctors, pharmacists, nurses and the public. The attraction to herbal medicine will continue to increase across the globe for various reasons, hence the urgent need for appropriate and enough information on HM especially that which highlights on important topics such as benefits, efficacy, safety, toxicity, research and development, formulation, regulation, analytical techniques, quality control, economic

importance, and so on [9]. This book harnesses important information on various aspects of HM, thus, serving as a compendium to enlighten scientists, healthcare professionals and lay users appropriately.

With many people now using herbal medicine, safety issues are also becoming an important concern. Indeed, certain HM have been implicated in some important adverse events relating to cardio-, neuro- and nephro-toxicities as well cancers [10–12]. Toxicity due to HMs may occur and their seriousness may vary depending on the type of herb or herbal material, preparation and user: varying from minor to severe and sometimes fatal. Adulterations and concomitant use of herbal medicines with conventional medicines constitute another area of attention, thus, the need for a strict regulation and enlightenment and control.

## 2. Benefits of herbal medicine

Herbal medicines (HM) include herbs, herbal materials, herbal preparations and finished herbal products that contain as active ingredients parts of plants, or other plant materials, or combinations and are used especially for the prevention and treatment of diseases [13].

In contemporary times, HM remains a major component of the primary healthcare in many rural African and Asian communities. It also constitutes an integral part of the culture of many societies of the world. Many herbs and herbal recipes have a long traditional history of folk uses and claims of health benefits. Scientific research has shown that HMs contain complex chemical compounds that are responsible for the pharmacological activities, which corresponds to health benefits and/or toxicity they elicit [1]. HMs have been used as prophylaxes for the passive maintenance of health as well as for radical treatment of varieties of mild to serious diseases [14–17].

In contemporary times, HMs are prepared and used in different forms, which also affect their activity outcomes. The dosage form of herbal medicines varies widely depending on such factors as the type of disease to be treated, route of application, patient, culture and even philosophical backgrounds. In homes and traditional medicine clinics, HMs are prepared often from fresh or dried herbs which are commonly made into infusions, decoctions, poultices, powders to be poured into open wounds or incorporated into native beverages, puddings, and so on. Conventional commercial HMs products are commonly available as pills, capsules, tablets, powders/granules, creams, ointments, and so on. The presentation of HMs in pharmaceutical dosage forms is expected to enhance accurate dosing, esthetics as well as compliance by enticing usage.

Safety and efficacy is another important factor overriding the use and commercialization of HMs. The quality of herbal products is essentially dependent on the safety and efficacy of the herbal material in relation to the intrinsic chemical components, type of contaminants as well as the production processing. The chemical compounds that are contained in herbal materials have shown a wide range of benefits in the management of various diseases including challenging diseases/conditions such as HIV/AIDS, cancer, sickle cell disease, malaria and other infectious diseases as well as noninfectious diseases such as diabetes, obesity, infertility, and

so on. Despite the wide acceptance, benefits and sometimes the misconceptions: there is a compelling need for a decisive control of HMs to ensure that enough and correct information on herbal materials and herbal products are always available to especially healthcare providers and the general public particularly on subjects such as identification, quality, safety and efficacy of the HM.

## 3. Poly herbal

In contrast to the pharmaceutical drugs which often consist primarily of single chemical entity (pure compounds), HMs are typically made up of numerous compounds usually in the crude, unpurified state. Many finished herbal products are made from folk recipes often containing more than one herbal material as the active component [18]. The polynomial constitution of most HMs may be the reason for many of their benefits [14, 19].

The constituent polynomial ingredients of many HMs as indicated in many folk recipes are often important for the completeness of the product if desired effects are to be produced. The multicomponent ingredients may boost benefits by enhancing simultaneously certain important pharmacological activities such as absorption, distribution, metabolism and elimination of bioactive components. Also, some constituents may act on more than one receptor or physiological system: probably the reason why many HMs show a wide range of therapeutic benefits.

## 4. Efficacy

In general, HMs are used for cure, mitigation, treatment and prevention of diseases especially those endemic to the local environment of the herbs [14, 16, 20]. Numerous plants species with folk claims of health benefits/cure abound, however only few have scientific proof or corroboration of efficacy. All the activities of HMs benefits and toxicities are linked to the presence of especially the secondary metabolites. The increasing attention on HM has also stimulated increased research in this area resulting in more information as far as efficacy and folk claims are concerned. Many research efforts have corroborated claims resulting in the commercialization of many herbal products and their nomination as leads in the development of pharmaceutical drugs. Nevertheless, many native HMs still remain untested and their benefits unauthenticated. The limited knowledge on these products has made information on the therapeutic benefits and side effects very limited thus heightening the doubt of their health benefits. It is also common knowledge that many people use HM concurrently with pharmaceutical drugs and for many HM information on the likely outcome of this practice is not available because no study has been carried out. Hence, there is a need for information regarding the likely outcomes of the interactions of sundry HM and the commonly used conventional medicines. This information should be generated during the research and development stage of all commercialized HM and enforced by regulation. Such interactions should also be disclosed in package inserts of products.

## 5. Secondary metabolites

The pharmacological activities of HMs are responsible for their benefits and for most of their toxicities. These bioactivities are essentially due to the presence of certain complex chemical entities: the secondary metabolites [21, 22]. While some are responsible for the radical active actions, others act as buffers which modulate and modify the pharmacological actions produced by active components to make them less toxic or more active. This is probably responsible for the reason why several plant extracts or recipes may not be reproduced by the isolated purified chemical constituents of the herb or recipe [23]. The various complex compounds elicit a long range of different activities in man and, animal models and cell cultures. In many instances the degree of activities of the active secondary metabolites vary depending on such factors as the plant species, parts of the plant, geographic origin, time of collection, method of preparation, amount ingested, and so on.

Plant secondary metabolites (PSM) are a large group of compounds that are synthesized and concentrated optimally in certain plant species and organ. The primary functions of these compounds in the plants in which they occur includes defense against such adversaries as herbivores, bacteria, fungi and viruses. Many also show variable degrees of antioxidants and UV protectants effect against harmful elements [24], while some also play important roles during pollination (to attract pollinating and seed-dispersing factors or signaling agents. This wide group of chemicals contains reactive functional groups in their chemical structures that are capable of forming covalent bonds with other biocompounds such as proteins, peptides and sometimes DNA [23].

PSMs are primarily organic compounds and can simply be grouped into three major classes, terpenes: volatiles, cardiac glycosides, carotenoids and sterols; phenolics: phenolic acids, coumarins, lignans, stilbenes, flavonoids, tannins and lignin; nitrogen containing compounds: alkaloids and glucosinolates [25].

## 6. Health benefits of herbal medicines

Correspondingly to conventional medicines, the indications of folk HMs are diverse, being employed for the treatment of a wide range of diseases [26]. The indications spread from simple health conditions such as cold, pain, surface wounds to serious conditions such as psychosis, diabetes, malaria, sickle cell disease, tuberculosis, cancer, hypertension, infertility, and so on. In certain communities, HM is a major component of the primary healthcare. Indeed, up to 80% of the rural population in Africa use herbal-based traditional medicines for most of their healthcare. In Ghana, Mali, Nigeria and Zambia, the first line of treatment for 60% of children with high fever resulting from malaria and other diseases is HM, which are often administered at home. Rural South Africa also has a strong culture of traditional medicine that is based on HM. In China and India, HM accounts for about 50% of the total health product consumption. With the increasing attention to HM all over the world, the list of medicinal herbs and products is increasing so also is the consumption rate even in societies

where conventional healthcare is available and easy to access. Also, in the USA, about 40% of the adult population has used herbal medicine [27]. The sales output of HM in Canada [28], Australia [6] and Europe especially in Germany and France is rapidly increasing [29].

## 7. Reasons for the upsurge in the use of HM

In recent times, the popularity and use of HMs have cut across geographical, gender, economic and socio-cultural divisions. Indeed, HM is occupying a strategic position in the general healthcare of people worldwide. Some of the probable reasons adduced for this include:

### 7.1. Personal preferences for HM

The use of HM is an age long tradition which is enshrined in the culture of many societies. In past times, people have relied on it as their primary source of healthcare with much success. Despite modernization and the proliferation of conventional healthcare that hinges on the use pharmaceutical drugs. Some people especially in Africa and Asia still lay personal preferences on HM: this group of people will always prefer HM as their first line of therapy whenever possible irrespective of their economic, educational and social status.

### 7.2. Perception of safety

Generally, many lay users have the opinion that HMs are safe and carry no risk or side effects. Though HMs are natural products derived from plant materials, minerals and some animal matter, this belief is nevertheless erroneous as many HMs are not totally devoid of adverse effects. While, it is true that many HMs are comparatively more tolerable than pharmaceutical drugs especially in long time use for the management of chronic ailments [30, 31]. Studies have shown that in some countries such as South Africa and Ghana, herbalists far outnumber the conventional medical doctors, whereas in India, China, and Vietnam, the number of herbalists and the conventional doctors are comparable.

### 7.3. Easy accessibility

Especially in rural African and Asian communities where access to conventional medical services is either expensive or difficult the only reliable, easy and quick access to healthcare is the traditional medical practitioners (TMPs) whose therapy is always based on HM. Even in societies where pharmaceutical products are highly regulated, HM is easily obtained at low cost and without prescriptions.

### 7.4. Low cost

In many rural communities, the cost of HMs is often low when compared to those of the conventional medicines. The TMPs who provide the services are usually community members who often live in the neighborhood of their clients (patients), as against the long distances to be traversed to reach the conventional medical centers. Most HMs are extemporaneously

prepared or the herbal materials are given to the patient with an oral direction on how to prepare and use. The modalities of payment are usually more flexible as the TMPs, may accept part payments or payment in kind with items such as clothing, chickens, goats, and so on. This is nevertheless in variance to the exotic proprietary herbal products whose prices are often as high as those of the conventional medicines.

### 7.5. Efficacy of treatments

In recent times, there have been increased research activities to verify claims and determine safety and quality control standards for herbal materials and products. The safety and efficacy of some herbal products have been scientifically evaluated to corroborate claims. The scientific proof of safety and efficacy has contributed to the increasing confidence and popularity of many herbal products. There are also certain diseases where patients have indicated preferences for HM instead of on pharmaceutical drugs [32].

### 7.6. As the last resort

Sometimes HMs are used as the last resort in the management of certain diseases especially when the conventional drugs have failed to yield the desired results or are accompanied by serious side effects especially in chronic diseases [33].

## 8. Standardization and regulation

The therapeutic benefits of HM in relation to general healthcare will continue to expand and attract popularity even with increased sophistication of the conventional healthcare systems as associated with genetic engineering and medical biotechnology. In many societies where HM constitutes an integral part of the healthcare system, the scheme to integrate it into the primary healthcare system is still farfetched because of matters that pattern to issues of standardization, quality control and regulation.

The traditional method used for monitoring and assuring quality of HM consists mainly of organoleptic evaluations. These are critically simple and subjective thus not compatible with the modern concept of quality control. In many countries, mandatory regulation of HM now requires scientific-based evaluations that employ high-tech analytical techniques to monitor and control the quality of products [34, 35]. At present, no official techniques or standards are available for the universal evaluation of HM. Many manufacturers of herbal products are either adopting tests and parameters as well as limits used for pharmaceutical drugs or self-determined in-process parameters and limits for their quality control evaluations. Though, these are good shots towards an effective standardization and quality control. In most cases, nevertheless, the techniques are not officially validated according to ISO standards, which is critical for universal acceptance. Standardization of HM using official techniques though doable will be a herculean task because of the complex nature of HMs.

However, the regulation of HM in many countries is less rigorous when compared to those of pharmaceutical drugs. The issues of therapeutic efficacy, safety, or quality are often not strictly regulated. In many of these countries, they are promoted as natural and harmless [36].

## 9. Conclusion

Even in the light of increased sophistication of modern healthcare as enriched by science and technology, the use of herbal medicine will continue to thrive in both poor and rich societies for many and probably different reasons. It is important for stakeholders: governments, farmers, scientists, healthcare providers (physicians, pharmacists and nurses) and biotechnical engineers to give enough attention to herbal medicines and its challenges in a deliberate effort to create for it appropriate niche that will ensure that it develops alongside with conventional medicine. The application of science and technology especially in area of information resources, conservation and cultivation, production, analytical techniques and quality control, clinical trials and regulation should be promoted. These efforts will boost benefits, confidence and safety in the use of HMs and its possible induction into the mainstream healthcare. Though, there are several literatures on HM, this book nevertheless has stooped to collate in a simple, unambiguous and readable manner a wide and indebt information that will be useful to all who have a stake in HM: scientist, healthcare professionals, engineers and the general public.

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Chapter 2

# Plants Secondary Metabolites: The Key Drivers of the Pharmacological Actions of Medicinal Plants

Rehab A. Hussein and Amira A. El-Anssary

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**Abstract**

The vast and versatile pharmacological effects of medicinal plants are basically dependent on their phytochemical constituents. Generally, the phytochemical constituents of plants fall into two categories based on their role in basic metabolic processes, namely primary and secondary metabolites. Primary plant metabolites are involved in basic life functions; therefore, they are more or less similar in all living cells. On the other hand, secondary plant metabolites are products of subsidiary pathways as the shikimic acid pathway. In the course of studying, the medicinal effect of herbals is oriented towards the secondary plant metabolites. Secondary plant metabolites played an important role in alleviating several aliments in the traditional medicine and folk uses. In modern medicine, they provided lead compounds for the production of medications for treating various diseases from migraine up to cancer. Secondary plant metabolites are classified according to their chemical structures into various classes. In this chapter, we will be presenting various classes of secondary plant metabolites, their distribution in different plant families and their important medicinal uses.

**Keywords:** secondary plant metabolites, phenolics, alkaloids, saponins, terpenes

## 1. Introduction

Plant chemistry is the basis of the therapeutic uses of herbs. A good knowledge of the chemical composition of plants leads to a better understanding of its possible medicinal value. Modern chemistry has described the role of primary plant metabolites in basic life functions such as cell division and growth, respiration, storage and reproduction. They include the components of processes such as glycolysis, the Krebs or citric acid cycle, photosynthesis

and associated pathways. Primary metabolites include small molecules such as sugars, amino acids, tricarboxylic acids, or Krebs cycle intermediates, proteins, nucleic acids and polysaccharides. Eventually, the primary metabolites are similar in all living cells [1].

Secondary plant metabolites are numerous chemical compounds produced by the plant cell through metabolic pathways derived from the primary metabolic pathways. The concept of secondary metabolite was first defined by Albrecht Kossel, Nobel Prize winner for physiology or medicine in 1910 [2]. Thirty years later, Czapek described them as end-products [3]. According to him, these products are derived from nitrogen metabolism by what he called 'secondary modifications' such as deamination. In the middle of the twentieth century, advances of analytical techniques such as chromatography allowed the recovery of more and more of these molecules, and this was the basis for the establishment of the discipline of phytochemistry.

Secondary metabolites have shown to possess various biological effects, which provide the scientific base for the use of herbs in the traditional medicine in many ancient communities. They have been described as antibiotic, antifungal and antiviral and therefore are able to protect plants from pathogens. Besides, they constitute important UV absorbing compounds, thus preventing serious leaf damage from the light. It was noticed that some herbs as forage grasses such as clover or alfalfa can express estrogenic properties and interact with fertility of animals [4].

Secondary plant metabolites are classified according to their chemical structures into several classes. In this chapter, the nature of secondary plant metabolites will be discussed as a foundation for a review of the main categories of constituents considered to be of therapeutic importance. Each section includes an overview of a class of the secondary plant metabolites regarding structure, botanical distribution and generalizations about pharmacology, followed by examples of representative molecules. The classes of secondary plant metabolites include:

- Phenolics
- Alkaloids
- Saponins
- Terpenes
- Lipids
- Carbohydrates

## 2. Phenolics

Phenolics probably constitute the largest group of plant secondary metabolites. They share the presence of one or more phenol groups (**Figure 1**) as a common characteristic and range from simple structures with one aromatic ring to highly complex polymeric substances. They are widespread in plants where they contribute significantly to the color, taste and flavor of many herbs, foods and drinks. Some phenolics are valued pharmacologically for their

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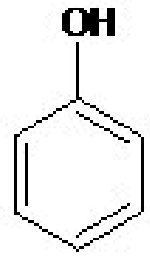


**Figure 1.** Phenol.

anti-inflammatory activities such as quercetin or antihepatotoxic properties such as silybin. Others exert phytoestrogenic activity as genistein and daidzein, while others are insecticidal as naringenin [5]. Many of the phenolic molecules are also effective antioxidants and free radical scavengers, especially flavonoids. Phenolics can be classified according to their structure or biosynthetic origin. According to their structures, phenolics can be classified into:

- Simple phenolics
- Tannins
- Coumarins
- Flavonoids
- Chromones and xanthones
- Stilbenes
- Lignans

### 2.1. Simple phenolics

Phenolic acids are ubiquitous among plants; although free phenols are rare, gallic acid is relatively widespread and is the parent compound of the gallotannins (**Figure 2**). Gallic acid is well known for its astringent properties but has demonstrated many other activities in vitro, including antibacterial, antiviral, antifungal, anti-inflammatory, antitumor, antianaphylactic, antimutagenic, choleretic and bronchodilatory actions. It also inhibits insulin degradation and promotes smooth muscle relaxation [6]. The phenolic compounds in this group vary according to their functional group, which may be hydroxyl, aldehydic, or carboxylic group; these include eugenol (a phenolic phenylpropane), vanillin (a phenolic aldehyde) and salicylic, ferulic and caffeic acids (phenolic acids). Hydroquinone is also among the most widely distributed of the simple phenols, occurring in a number of plants as the glycoside arbutin. Glycoside formation is common, and the widely distributed glycoside coniferin and other derivatives of phenolic cinnamic alcohols are precursors of lignin [7, 8].

The pharmacological properties of these widely found constituents are probably best demonstrated by the urinary tract antimicrobial arbutin [9] and the anti-inflammatory salicylates [10]. A property shared by all phenols is antimicrobial activity. In fact, phenol itself was the first antiseptic used in surgery [11].

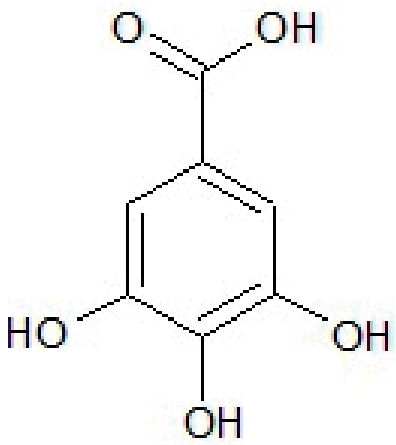


**Figure 2.** Gallic acid.

The pharmacological activities of many plants are attributed to simple phenolics among which the antimicrobial and diuretic activities of *Arctostaphylos uva-ursi* were attributed to its phenolic content [12]. *Capsicum* spp. showed circulatory stimulant, rubefacient and analgesic activities due to the presence of capsaicinoids, which are simple phenolic compounds [13]. Moreover, the cholagogue activity of *Cynara scolymus*, the anthelmintic activity of *Dryopteris filix-mas*, the anti-inflammatory analgesic activity of *Filipendula ulmaria* as well as the anticatarrhal and diuretic activities of *Solidago virgaurea* are all attributed to the action of simple phenolics [8]. **Figure 3** illustrates some examples of simple phenolics.

### 2.2. Tannins

Tannins are polyphenols which have the ability to precipitate protein. These compounds have been used for decades to convert raw animal hides into leather. In this process, tannin molecules crosslink the protein and make it more resistant to bacterial and fungal attack. Today, however, many substances considered to be tannins by virtue of their structure and biosynthetic origin have limited, if any, ability to make leather [14]. There are two major types of tannins: hydrolyzable tannins and condensed tannins. Hydrolyzable tannins are formed from several molecules of phenolic acids such as gallic and hexahydroxydiphenic acids, which are united by ester linkages to a central glucose molecule. Two principal types of hydrolysable tannins are gallotannins and ellagitannins, which are, respectively, composed of gallic acid and ellagic acid units. Ellagitannins found in plants of medicinal interest and for which structures have been elucidated include geraniin (isolated from *Geranium robertianum* (Herb Robert) and *Geranium maculatum* (American cranesbill) [15]) and tellimagrandins 1 and 2 [16] (isolated from *Quercus alba* (Oak bark), *Punica granatum* (pomegranate) and *Filipendula ulmaria* (Meadowsweet)) [7].

Condensed tannins, or proanthocyanidins, are compounds whose structures are based on oligomeric flavonoid precursors and vary in the type of linkages between flavonoid units; hydroxylation patterns; stereochemistry of carbons 2, 3 and 4 of the pyran ring and the

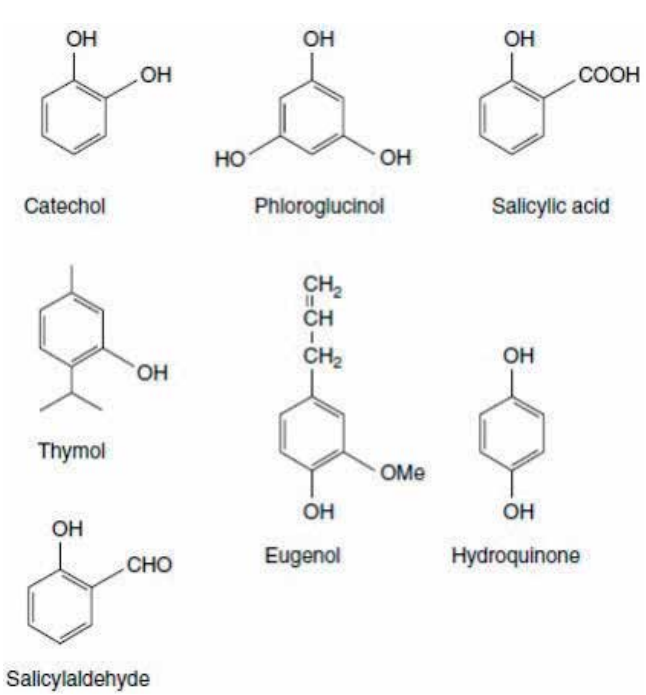


**Figure 3.** Examples of simple phenolics.

presence of additional substituents. Some drugs (e.g., *Camellia sinensis* (tea), *Hamamelis virginiana* leaves and bark) contain both hydrolyzable and condensed tannins [17].

Tannin-containing drugs act as antidiarrhoeals and have been employed as antidotes in poisoning by heavy metals and alkaloids. Epigallocatechin-3-gallate, the active principal in tea, has been shown to be antiangiogenic in mice. *Vaccinium oxycoccos* (cranberry) juice has long been used as urinary antiseptic [18], which was scientifically proven in a randomized, double-blind, placebo-controlled trial that has been carried out on 153 elderly women [19]. **Figure 4** illustrates some examples of hydrolysable tannins.

### 2.3. Coumarins

Coumarins are derivatives of benzo-$\alpha$-pyrone, the lactone of *O*-hydroxycinnamic acid, coumarin. Some 1000 natural coumarins have been isolated. Coumarin itself has been found in about 150 species belonging to over 30 different families. The richest sources of coumarin are sweet clover or melilot (*Melilotus* spp.), *Dipteryx odorata* (tonka bean) and *Galium odoratum* (sweet woodruff) [8]. Aesculetin, umbelliferone and scopoletin are common coumarins present in plants both in the free state and as glycosides. Plants rich in coumarins include *Atropa belladonna*, *Datura stramonium* (Solanaceae), *Daphne mezereum* (Thymeliaceae), *Ruta graveolens* (Umbelliferae) and certain *Aesculus hippocastanum* (Horse-chestnut) (Hippocastanaceae) and certain Rosaceae [7]. Anti-inflammatory, anticoagulant, anticancer and anti-Alzheimer's activities are the most important biological activities reported for coumarins [20]. Examples of coumarins are shown in **Figure 5**.

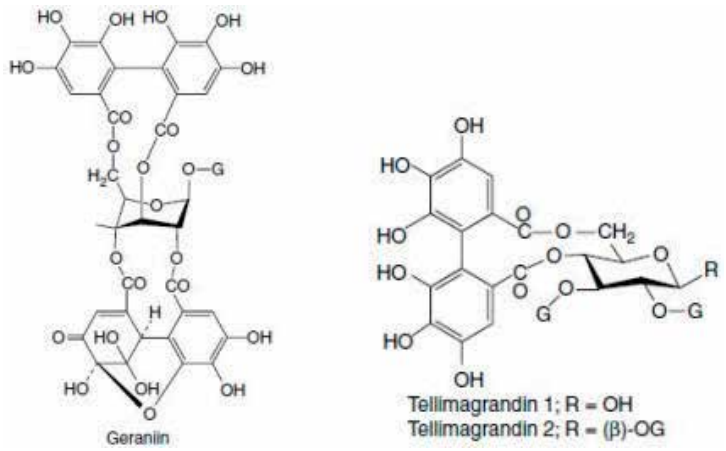


**Figure 4.** Examples of hydrolysable tannins.

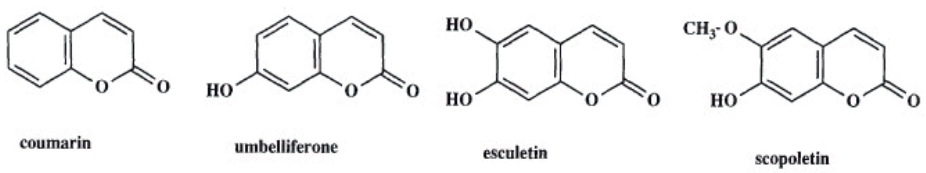


**Figure 5.** Examples of coumarins.

### 2.4. Flavonoids

Flavonoids are the largest group of naturally occurring phenols. More than 2000 of these compounds are now known, with nearly 500 occurring in the free state [7]. The structural skeleton of flavonoids includes a chroman ring bearing an aromatic ring in position 2, 3 or 4. Flavonoids may be divided into various classes according to the oxidation level of the central ring (ring C). The most common of these are anthocyanins, flavones and flavonols. The flavones and their close relations are often yellow (Latin *flavus*, yellow). They are widely distributed in nature but are more common in the higher plants and in young tissues, where they occur in the cell sap. They are abundant in the Polygonaceae, Rutaceae, Leguminosae, Umbelliferae and Compositae. Recent researches have demonstrated the medicinal action of drugs containing flavonoids such as *Glycyrrhiza glabra* (liquorice root), *Chamaemelum nobile* (Roman chamomile) and *Ginkgo biloba* (gingko). A number of flavonoid-containing herbs have now been included in the *British Pharmacopeia,* examples are *Betula pendula* (Birch Leaf), *Calendula officinalis* Flower, *Sambucus nigra* (ElderFlower), *Equisetum ramosissimum* (Horsetail), *Tilia cordata* (Lime Flower), *Leonurus cardiaca* (Motherwort) and *Passiflora edulis* (passion flower). The group is known for its anti-inflammatory and anti-allergic effects, for antithrombotic and vasoprotective properties, for inhibition of tumor promotion and as a protective for the gastric mucosa [21, 22]. Examples of flavonoids are shown in **Figure 6**.

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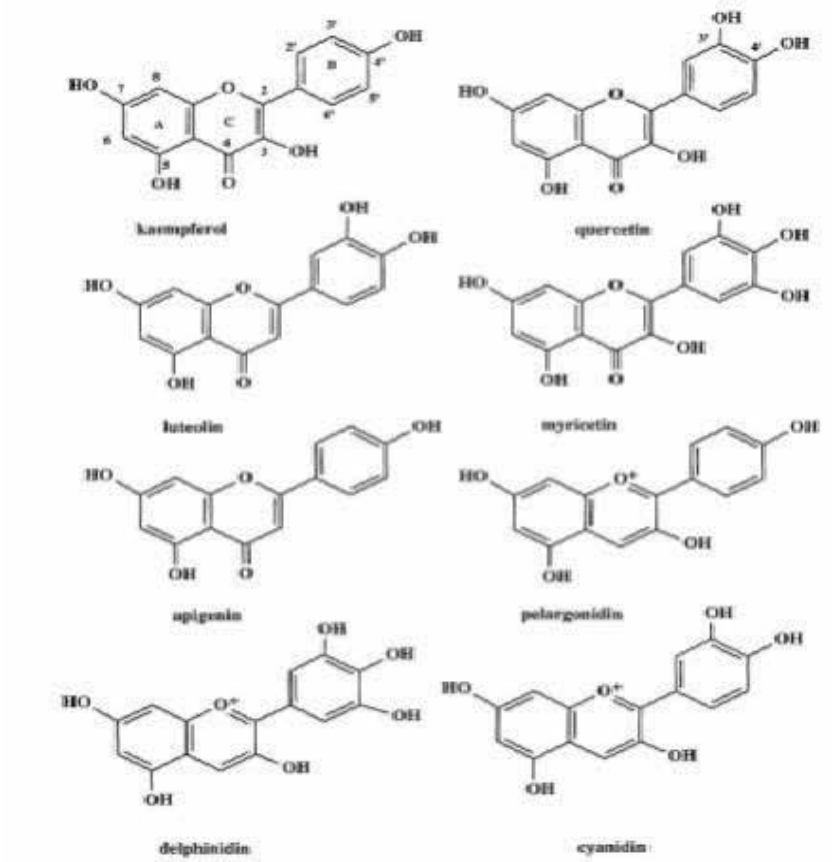


**Figure 6.** Examples of flavonoids.

### 2.5. Chromones and xanthones

These compounds are structural derivatives of benzo-γ-pyrone, and although not of great pharmaceutical importance, a few compounds are worthy of mention; eugenin is found in the clove plant and khellin from mustard seeds [7]. More complex are the furanochromones, the active constituents of the fruits of *Ammi visnaga*. Xanthones are found mainly in the Gentianaceae and Guttiferae, otherwise scattered sporadically throughout the plant kingdom as in the Moraceae and Polygalaceae. *Polygala nyikensis* is used by the highlanders of Malawi and bordering countries to treat various skin problems of fungal origin. The root of the plant was recently shown to exert its antifungal activity owing to the presence of xanthones [23].

### 2.6. Stilbenes

Stilbenes are a relatively small, but widely distributed, group of plant secondary metabolites found mostly as heartwood constituents in a heterogeneous assembly of plant species. They are especially important in the heartwood of trees of the genera *Pinus* (Pinaceae), *Eucalyptus*

(Myrtaceae) and *Madura* (Moraceae) [1]. The *para-hydroxylated* compound, resveratrol, is the most widespread stilbene in nature. Resveratrol possesses estrogen-like activity and occurs in *Picea*, *Pinus*, the Fabaceae, Myrtaceae and the Vitaceae [24].

### 2.7. Lignans

Lignans are dimeric compounds formed essentially by the union of two molecules of a phenylpropene derivative reported from the members of Asteraceae (e.g., *Achillea lingulata* [25]), Pinaceae (e.g., *Cedrus deodara* [26]) and Rutaceae (e.g., *Fagara heitzii*) [27]. Four major subtypes occur: dibenzylbutane derivatives, dibenzylbutryolactones (lignanolides or derivatives of butanolide), monoepoxy lignans or derivatives of tetrahydrofuran and bisepoxylignans or derivatives of 3,7-dioxabicyclo(3.3.0)-octane. Many of these compounds showed antimicrobial and antifungal activities [1], while others showed cytotoxic activities such as wikstromal, matairesinol and dibenzyl butyrolactol from *Cedrus deodara* [26].

## 3. Alkaloids

Alkaloids are organic compounds with at least one nitrogen atom in a heterocyclic ring. Their definition is problematic, as they do not represent a homogeneous group of compounds from any standpoint, whether chemical, biochemical, or physiological. Except for the fact that they are all nitrogen-containing compounds, no general definition fits all alkaloids. Alkaloids can be divided according to their basic chemical structure into different types. The following are basic types of alkaloids: acridones, aromatics, carbolines, ephedras, ergots, imidazoles, indoles, bisindoles, indolizidines, manzamines, oxindoles, quinolines, quinozolines, phenylisoquinolines, phenylethylamines, piperidines, purines, pyrrolidines, pyrrolizidines, pyrroloindoles, pyridines and simple tetrahydroisoquinolines [28].

Although plants containing alkaloids have been used by man for at least 3000 years as medicines, teas and potions, the compounds responsible for activity were not isolated and characterized until the nineteenth century [1]. Alkaloids are not common in lower plants. Lysergic acid derivatives and sulfur-containing alkaloids, e.g., the gliotoxins, are detected in fungi. Concerning the pteridophytes and gymnosperms alkaloids reported for their medicinal uses include the lycopodium, ephedra and *Taxus* alkaloids. Alkaloids are unevenly distributed among the angiosperms. The following are the orders reported to be rich in alkaloids: Centrospermae (Chenopodiaceae), Magnoliales (Lauraceae, Magnoliaceae), Ranunculales (Berberidaceae, Menispermaceae, Ranunculaceae), Papaverales (Papaveraceae, Fumariaceae), Rosales (Leguminosae, subfamily Papilionaceae), Rutales (Rutaceae), Gentiales (Apocynaceae, Loganiaceae, Rubiaceae), Tubiflorae (Boraginaceae, Convolvulaceae, Solanaceae) and Campanulales (Campanulaceae, sub-family Lobelioideae; Compositae, subfamily Senecioneae). However, there is no report for the presence of alkaloids in Salicales, Fagales, Cucurbitales and Oleales dicot orders till the present time [7].

Alkaloids demonstrate a diverse array of pharmacological actions including analgesia, local anesthesia, cardiac stimulation, respiratory stimulation and relaxation, vasoconstriction,

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muscle relaxation and toxicity, as well as antineoplastic, hypertensive and hypotensive properties. The activity of alkaloids against herbivores, toxicity in vertebrates, cytotoxic activity, the molecular targets of alkaloids, mutagenic or carcinogenic activity, antibacterial, antifungal, antiviral and allelopathic properties have been reported in literature. Many alkaloids are sufficiently toxic to animals to cause death if eaten. Several (e.g., nicotine and anabasine) are used as insecticides [1, 8].

Examples of some alkaloids:

### 3.1. Nicotine

Nicotine is found in the tobacco plant (*Nicotiana tabacum*) and other *Nicotiana* species; it has tranquilizing properties and is the addictive component of tobacco. It is also extremely toxic, causing respiratory paralysis at high doses (**Figure 7**). Nicotine is a ganglion cholinergic-receptor agonist with complex pharmacological actions, including effects mediated by binding to receptors in the autonomic ganglia, the adrenal medulla, the neuromuscular junction and the brain [29].

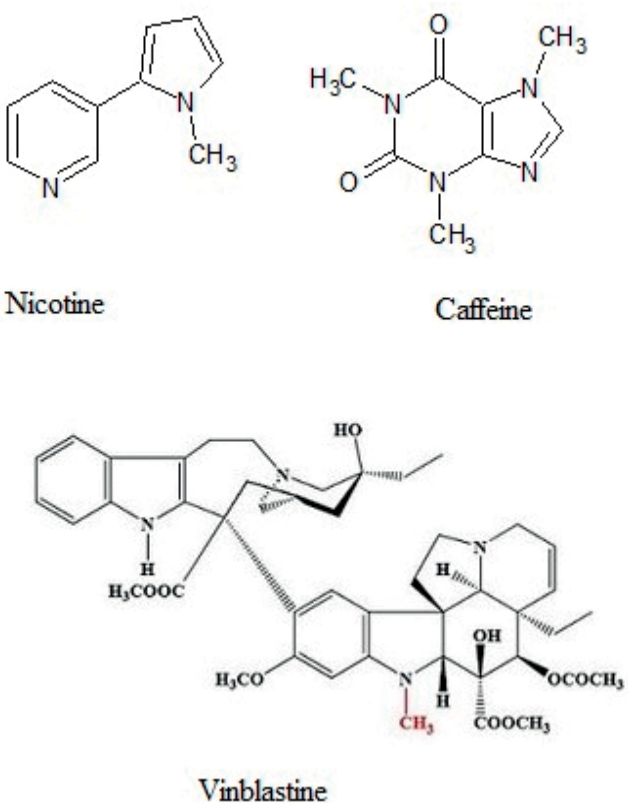



**Figure 7.** Examples of alkaloids.

### 3.2. Caffeine

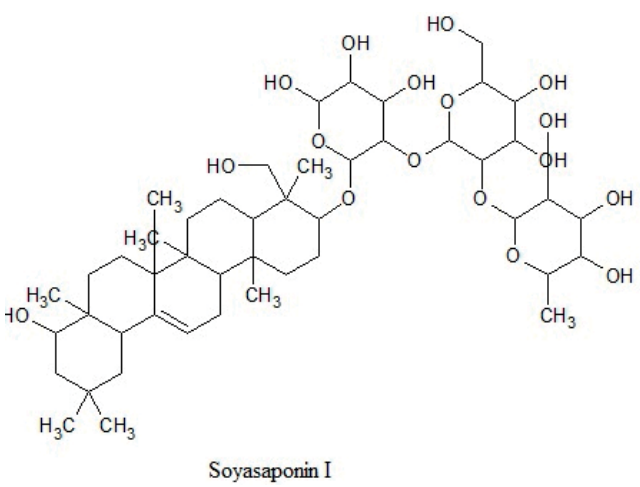
Caffeine occurs in a number of botanically unrelated species, including coffee (*Coffea* spp.), tea (*Camellia sinensis*), mate (*Ilex paraguariensis*), guarana (*Paullinia cupana*) and kola (*Cola acuminata*) (**Figure 7**). Caffeine is bound to chlorogenic acid in raw coffee beans. The roasting process liberates the caffeine and other compounds that contribute to the aroma of coffee. Caffeine is a diuretic and has stimulant effects on the respiratory, cardiovascular and central nervous systems [30].

### 3.3. Vinblastine

Vinblastine is isolated from *Catharanthus roseus* G. (**Figure 7**) and has been used to treat diabetes and high blood pressure and as disinfectant. Nevertheless, Vinblastine is so important for being cancer fighters. It is used along with the other vinca alkaloids vinorelbine, vincristine and vindesine, which are in clinical use in the United States and Europe [31].

## 4. Saponins

Saponins are compounds that possess a polycyclic aglycone moiety with either a steroid (steroidal saponins) or triterpenoid (triterpenoidal saponins) attached to a carbohydrate unit (a monosaccharide or oligosaccharide chain) (examples illustrated in **Figures 8** and **9**). These sugar units are composed variously of pentoses, hexoses, or uronic acids. This hydrophobic-hydrophilic asymmetry means that these compounds have the ability to lower surface tension and are soap-like. They form foam in aqueous solutions and cause hemolysis of blood erythrocytes in vitro. The aglycone portion of the saponin molecule is called the *genin* or *sapogenin*. Saponins are widespread among plants, having been reported from more than 500 plants from at least 90 different families; these substances have been isolated from all parts of




Soyasaponin I

**Figure 8.** Example of triterpenoidal saponin.

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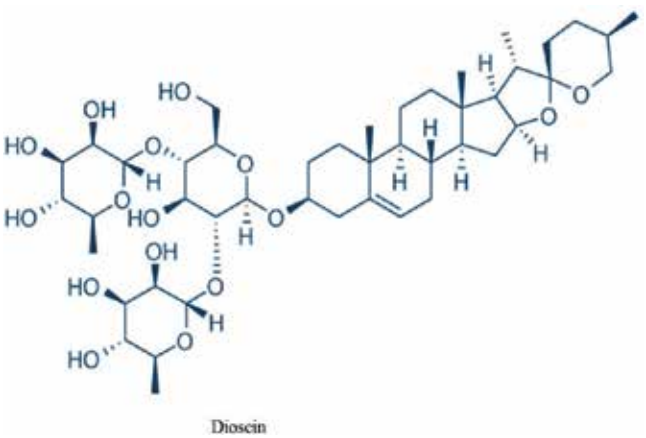


**Figure 9.** Example of steroidal saponin.

plants: leaves, stems, roots bulbs, flowers and fruits, although they tend to be concentrated in the roots of many species such as *Digitalis purpurea* (*foxglove*), *Dioscorea villosa* (*wild yam*), *Eleutherococcus senticosus* (*Siberian ginseng*), *Gentiana lutea* (*gentian*), *Glycyrrhiza* spp. (*licorice*) and *Panax ginseng* (*Korean ginseng*) [32].

Saponins have demonstrated numerous pharmacological properties. Some saponins have antitumor, piscicidal, molluscicidal, spermicidal, sedative, expectorant and analgesic properties. Glycyrrhizin from *glycyrrhizae radix* (from *Glycyrrhiza glabra*, Fabaceae) is useful as expectorant and antitussive agent. It is also used to treat chronic hepatitis and cirrhosis. Some saponins have anti-inflammatory properties as the saponins from *Bupleurum falcatum* (Apiaceae). *Phytolacca americana* roots are reputed to possess anti-inflammatory properties in Korean medicine. Similar properties have been demonstrated for a number of other saponins, for example aescin, from horse chestnut (*Aesculus hippocastanum*), has been shown to be 600 times more effective than rutin in reducing rat paw edema [33].

## 5. Terpenes

Terpenes are the largest and most diverse group of plant secondary compounds. The name "terpene" is derived from the word "turpentine," which in turn comes from the old French *ter(e)bintb*, meaning "resin." They are all derived chemically from 5-carbon isoprene units assembled in different ways [8]. Terpenes are classified according to the number of isoprene units in the molecule; a prefix in the name indicates the number of terpene units as follows.

### 5.1. Hemiterpenes

They consist of *a single isoprene* unit. Isoprene itself is considered the only hemiterpene, but oxygen-containing derivatives such as angelic acid isolated from *Angelica archangelica* and isovaleric acid from *Vaccinium myrtillus* are hemiterpenoids [1].

### 5.2. Monoterpenes

They consist of *two isoprene* units and have the molecular formula $C_{10}H_{16}$ (see **Figure 10**). They are important components of plant essential oils or volatile oils. Monoterpenes tend to occur in members of certain plant families, such as Lamiaceae, Pinaceae, Rutaceae and Apiaceae, from which many essential oils are commercially produced. Some of these compounds, such as geraniol, are almost ubiquitous and can be found in small amounts in the volatile secretions of most plants. Monoterpenes are further classified into unsaturated hydrocarbons (e.g., limonene), alcohols (e.g., linalool), alcohol esters (e.g., linalyl acetate), aldehydes (e.g., citronellal) and ketones (e.g., Carvone). Monoterpenes and other volatile terpenes have a number of widespread medicinal uses. Compounds such as camphor and menthol are used as counterirritants analgesics and anti-itching agents. Many monoterpenes have been used as anthelmintics. A series of monoterpene glycosides appear to have vasodilation effect on coronary vessels and the femoral vascular bed [16].

### 5.3. Sesquiterpenes

They consist of *three isoprene* units and have the molecular formula $C_{15}H_{24}$ (see **Figure 11**). Based on biogenetic origin, there are more than 200 different structural types of sesquiterpenes, and several thousand such compounds are known. These compounds can be conveniently classified into three main groups according to structure: acyclic (e.g., farnesol), monocyclic (e.g., bisabolol) and bicyclic (e.g., caryophyllene). A number of sesquiterpene lactones show antibacterial, antifungal and antiprotozoan activities. Sesquiterpenes from *Vernonia colorata* inhibit *Entamoeba histolytica* at concentrations comparable to metronidazole, an antiamoebic drug. Helenalin and a series of related compounds are responsible for the cardiotonic properties of *Arnica montana* flowers. *Atractylodis rhizoma*, from *Atractylodis macrocephala* (Asteraceae), is clinically used as diuretic, analgesic and anti-inflammatory. The activity is related to the presence of active compounds including eudesma-4(14)-7(1 l)-dien-8-one and atractylenolide I. Several related medicinal plants are also used for the same purposes due to the presence of sesquiterpenes [1, 34].

### 5.4. Diterpenes

They are composed of *four isoprene* units and have the molecular formula $C_{20}H_{32}$ (see **Figure 12**). Diterpenes are classified into acyclic and macrocyclic compounds. Moreover, macrocyclic

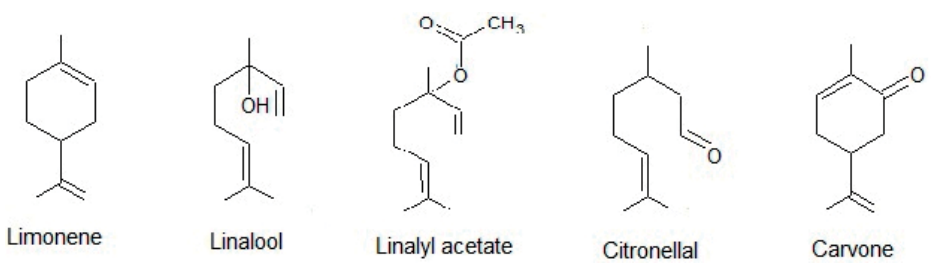


**Figure 10.** Examples of monoterpenes.

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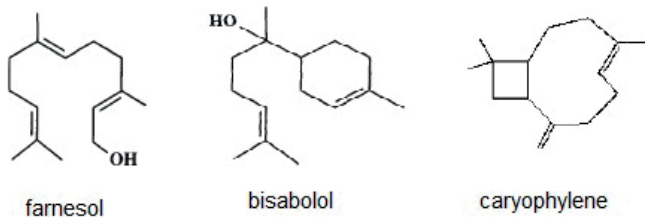



**Figure 11.** Examples of sesquiterpenes.

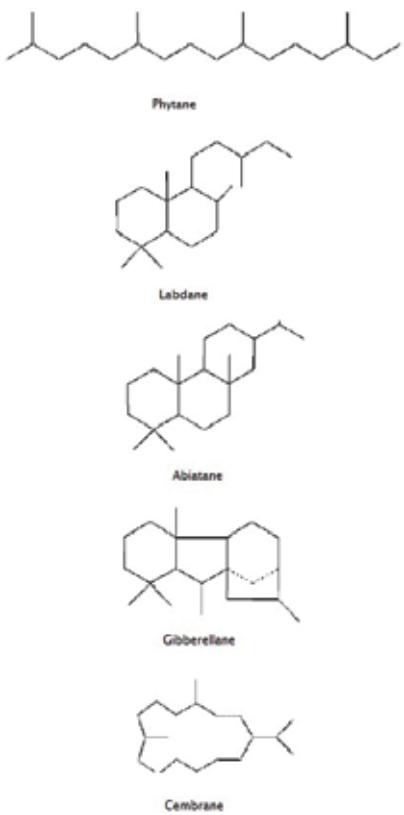



**Figure 12.** Examples of diterpenes.

diterpenes are classified according to the number of ring systems present. Diterpenes may be 6-membered ringed structures or they may have fused 5- and 7-membered ringed structures. In addition, many diterpenes have additional ring systems. These occur as side substitutions as esters or epoxides [8]. Diterpenoids constitute the active constituents of a number of medicinal plants. Vitamin K1, an antihemorrhagic compound, first discovered in plants in 1929, is a diterpene. Vitamin A, a diterpenoid, is referred to, together with the related compounds, as "carotenes." The bitter principles of *Jateorhiza palmata* (calumba root) belong to furanoditerpenes. *Teucrium chamaedrys* (wall germander) and *T. scorodonia* (wood sage) family

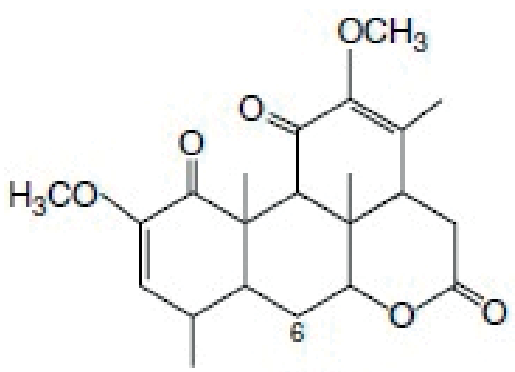
Labiatae, both produce diterpenes of the neoclerodane type. They are used in herbal medicine as diaphoretics and antirheumatics [35]. Like all groups of terpenes, diterpenes have demonstrated a range of pharmacological properties including: analgesic, antibacterial, antifungal, anti-inflammatory, antineoplastic and antiprotozoal activities [8]. Some diterpenes from *Kalmia latifolia* (Ericaceae) have antifeedant properties with respect to the gypsy moth. The gibberellins, first obtained from fungi of the genus *Gibberella* but also found in higher plants, are diterpenoid acids, which have a marked effect on growth of seedlings [7].

### 5.5. Sesterterpenes

Terpenes having 25 carbons and *five isoprene* units are rare relative to the other sizes (the *sester-* prefix means half to three, i.e. two and a half). An example of a sesterterpenoid is geranyl farnesol isolated from seed oils of *Camellia sasanqua* (sasanqua) and *Camellia japonica* (camellia), family Theaceae [36]. Geranyl farnesol showed cytotoxic activity in mouse leukemic M1 cells [37].

### 5.6. Triterpenes

They consist of *six isoprene* units and have the molecular formula $C_{30}H_{48}$ (see **Figure 13**). The linear triterpene squalene, the major constituent of shark liver oil, is derived from the reductive coupling of two molecules of farnesyl pyrophosphate. Triterpenes constitute a significant portion of the lipid substances of all plants; more than 4000 triterpenoids have been isolated. These compounds are precursors to steroids in both plants and animals. Both triterpenes and steroids occur free, as glycosides or in other combined forms. The structures of triterpenes and steroids may be subdivided into about 40 major types [1]. β-Boswellic acids (ursane-type triterpene) and α-boswellic acids (oleanane-type triterpene) that are isolated from the oleo-gum-resin of *Boswellia carterii* are known for their anti-inflammatory and anti-rheumatic activities [38].




Quassin

**Figure 13.** Example of triterpene.

One group of compounds showing a range of interesting biological activity is the quassinoids isolated from *Quassia amara*. These are degradation and rearrangement products of triterpenes. Quassia is used as a bitter tonic, as an insecticide and as an enema for the expulsion of thread worms.

Terpenes also include sesquarterpenes (*seven isoprene* units, $C_{35}H_{56}$), tetraterpenes (*eight isoprene* units, $C_{40}H_{64}$) as well as polyterpenes and norisoprenoids (long chains of *many isoprene* units.

## 6. Lipids

Lipids comprise a group of naturally occurring molecules that include fixed oils, waxes, essential oils, sterols, fat-soluble vitamins (such as vitamins A, D, E and K), phospholipids and others. Lipids serve various biological actions as major structural components of all biological membranes and as energy reservoirs and fuel for cellular activities in addition to being vitamins and hormones [39, 40]. Although lipids are considered primary plant metabolites, recent studies revealed pharmacological activities to members of this class of phytochemicals.

### 6.1. Fixed oils

Fixed oils constitute of high molecular aliphatic long-chain fatty acids, such as palmitic, stearic and oleic acids, esterified with glycerol. Fixed oils contain a relatively higher percentage of liquid glycerides (polyunsaturated) such as glycerin oleate, while fats are rich in solid glycerides such as glycerin stearate. [39]. Flax and linseed and its oil are obtained from *Linum usitatissimum*, family Linaceae. Polyunsaturated fatty acids in some fixed oils cause reduced excretion of lipid peroxidation products and hence are potent antioxidants and anti-inflammatory. They are used as prophylactic to decrease the risk of atherosclerosis and cardiovascular disease [41].

### 6.2. Waxes

Waxes are lipoidal matter constituting mainly from long aliphatic chains that may contain one or more functional groups. They may contain hydroxyl groups as in the case of primary and secondary long-chain alcohols that are frequently present in the form of esters. Others contain unsaturated bonds, aromatic systems, amide, ketonic, aldehydic or carboxylic functional groups. On the other hand, synthetic waxes constitute of long-chain hydrocarbons (alkanes or paraffins) that lack functional groups. They are similar to the fixed oils and fats since they are esters of fatty acids, but with the difference that the alcohol is not glycerin. The seeds of *Simmondsia chinensis* yield the liquid wax, jojoba wax, which consists of straight chain esters of fatty acids and alcohols [42]. Jojoba wax has anti-inflammatory, anti-aging and wound healing activities, and hence it can be utilized in several skin conditions. Jojoba wax has also been used in topical medications to enhance drug absorption. In addition, it is used in skin care products and in cosmetics such as sunscreens and moisturizers [43].

### 6.3. Essential oils

Essential oils are volatile aromatic complex mixtures of relatively low molecular weight compounds. Although they may contain up to 60 components, yet they are characterized by the presence of two or three major components at fairly high concentrations (20–70%) compared to other components present in trace amounts. For example, *Origanum compactum* essential oil contains carvacrol (30%) and thymol (27%) as major components. Linalol is the major component of *Coriandrum sativum* essential oil reaching up to 68%. Other examples are *Artemisia herba-alba* essential oil which contains $\alpha$- and $\beta$-thuyone (57%) and camphor (24%) as major constituent, *Cinnamomum camphora* essential oil with 1,8-cineole (50%) as major constituent and finally *Mentha piperita* essential oil with menthol (59%) and menthone (19%) being the major constituent. Generally, these major components determine the biological properties of the essential oils [44]. They have many and important medical uses such as antiseptic, antimicrobial, analgesic, sedative, anti-inflammatory, spasmolytic and locally anesthesic remedies. They are also used as fragrances in embalmment and in food preservation [45].

## 7. Carbohydrates

Carbohydrates are universally present in living beings on our planet. As the first product of photosynthesis, carbohydrates are the starting point for all phytochemicals and also, by extension, for all animal biochemicals. More carbohydrates occur in nature than any other type of natural compound. The most abundant single organic substance on Earth is cellulose, a polymer of glucose, which is the main structural material of plants. Although carbohydrates are primary metabolites, they are incorporated in plenty of secondary metabolites through glycosidation linkages. Polymers of simple sugars and uronic acids produce mucilages and gums [46].

Carbohydrates consist of carbon, hydrogen and oxygen with the last two elements usually present in the same proportions as in water. They are classified into four chemical groups: monosaccharides, disaccharides, oligosaccharides and polysaccharides. Monosaccharides contain from three to nine carbon atoms, although those with five and six carbon atoms (pentoses, $C_5H_{10}O_5$, and hexoses, $C_6H_{12}O_6$) are accumulated in plants in greatest quantity. Condensation of monosaccharides results in the other types according to the number of saccharide units involved. In addition to the important biological and structural function of carbohydrates in plants, some members show medicinal effects such as mucilage. Mucilage, viscous sticky material produced by almost all plants and some microorganisms, plays a protective role in thickening membranes in plants. It also serves in storage of water and food and in seed germination. Chemically it constitutes of a polar glycoprotein and an exopolysaccharide. Mucilage is used medicinally as demulcent. Cactus (and other succulents) and *Linum usitatissimum* (flax seeds) are the major sources of mucilage. The extract of the mucilaginous root of the marshmallow plant (*Althaea officinalis*); used traditionally to make marshmallows, were used as cough suppressant due to its demulcent effect. *Ulmus rubra* (the slippery elm) inner bark, is also used as a demulcent due to its mucilaginous content. Mucilage acts primarily as a local demulcent or emollient when it comes in direct contact with mucous membrane

surfaces or skin. Here, they produce a coating of "slime" that soothes and protects exposed or irritated surfaces of the gastrointestinal tract. They are used extensively in the management of inflammatory digestive disorders, especially when there is ulceration. Their relative indigestibility and hydrophilic properties have important influences on bowel behavior [47].

## 8. Conclusion

According to the abovementioned data, there are several classes of secondary plant metabolites that are responsible for the biological activities of herbal medicines. Eventually, secondary plant metabolites exert their action on molecular targets that differ from one case to the other. These targets may be enzymes, mediators, transcription factors or even nucleic acids. The use of herbal medicines should be based on comprehensive phytochemical studies for the determination of the chemical constituents of the herbs involved. Hence the knowledge of the resultant pharmacological and toxicological effects can be deduced, as well as the possible synergistic or antagonistic effects due to the use of multiple component herbal formulae. For this reason, the isolation and structural elucidation of secondary plant metabolites, though ancient, is still a huge and fast growing approach, and the techniques used for separation and analysis are advancing continuously.

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Chapter 3

# Ergastic Crystal Studies for Raw Drug Analysis

Thara K. Simon and Justin R. Nayagam

Additional information is available at the end of the chapter

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**Abstract**

Phytochemical constituents are distributed in various parts of plants and their localization is indicative of their therapeutic properties. Ergastic crystals such as calcium oxalate crystals are also found in almost all plant parts, which is an anti–nutrient as the dietary oxalates contributes to human ailments. Several of the medicinally useful plants contain these crystals and consumption of such plant materials in raw form can cause health problems in humans. Ergastic crystals can be an important diagnostic tool for the identification of raw drug as in *Costus pictus* a medicinal spiral ginger commonly called Insulin plant is devoid of cuboidal crystal but its related *Costus speciosus* leaves possess characteristic cuboidal shaped crystal in its leaf mesophyll. Gene manipulation technology may be promising in removing such deleterious genes or introduction of altered bio-chemicals to nullify such effects for the future generation.

**Keywords:** ergastic crystals, calcium oxalates, medicinal raw drugs

## 1. Introduction

Plants are the storehouses of multifunctional components with nourishing, healing, refreshing, curing and replenishing qualities. Such chemical constituents are distributed in various parts of plants and their localization is indicative of their therapeutic properties. Even though plants can be classified into medicinal and non-medicinal there is no such distinction in traditional systems such as Ayurveda, which denote that the whole earth with its living and non-living entities have curative properties. Among the vast combination of phytochemicals that are useful for the consumer world there are certain deleterious chemicals or its combinations. The undesirable component in phytochemicals requires to be eliminated either by chemical treatments or simply avoiding its usage. Several of the plant resources are being used as

raw materials for medicinal drugs. Therefore the knowledge of ergastic crystals in food and medicinal raw materials and in finished products is expected to bring out furnished products for longevity.

## 2. Classification of ergastic crystals in plants

Classifications of cytoplasmic constituents at various levels are available. Ergastic substances represent waste products, which are solid and secondary. Of these secondary products are alkaloids, glycosides, tannins, volatile oil, resins, gums and mucilage. Solid products include calcium oxalate, calcium carbonate, hesperidin, diosmin and silica. Non-living inclusions are classified as ergastic substances [1]. Their categorization into secretory products, excretory products and reserve materials indicate their functional association. The secretary products include nectar, enzymes and coloring matter. Proteins, fats and oils, and carbohydrates represent reserve materials. Excretory products represent alkaloids, tannins, resins, latex, volatile oils and mineral crystals. The common mineral crystals are calcium oxalate, calcium carbonate and silica. According to Esau ergastic substances are products of metabolism the examples being, carbohydrates proteins, fats, tannins and various types of crystals [2]. They are mainly non-protoplasmic components distributed in the vacuoles, in the cell wall and associated with the protoplasmic components. Fahn considers ergastic substances as organic and inorganic by products of metabolism [3]. Crystals of inorganic compounds such as gypsum and silica are less common. Crystals of organic substances such as carotene, berberine and saponin are relatively common.

## 3. Shapes and size of ergastic crystals

Ergastic crystals are reported from almost all plant parts such as rhizome, corm, tuber, adventitious roots, leaves, fruits and even in seeds. Calcium oxalate exists in varying crystal shapes and sizes in plants, with raphides being the predominant crystal form [4–8]. Various types of calcium oxalate crystals exist in the form of prisms, acicular, raphides, clusters, rosettes etc. The shape of crystals may be cuboidal, rhomboidal, octahedral or elongated. Elongated crystals when massive and solitary are known as styloids as found in Iridaceae. When they are compound and cluttered in spherical masses they are called as druses. Small prismatic crystals as well as minute crystals are known as crystal sand. Special crystal containing cells are called idioblasts, which are cells that differ distinctly from surrounding cells in both shape and structure. Raphides are usually found in very large cells which when mature do not contain living protoplast, but are filled with mucilage. Raphides at maturity are dead structures usually filled with mucilage and are reported to be capable of swelling. Parts of the cell wall of such raphide idioblasts remain thin and if the mucilage swells, the thin wall bursts and the raphides are ejected.

Idioblasts with raphides are found in many monocots and also in some dicots such as in the petals of *Impatiens balsamina.* Silicon salts are often deposited in cell walls as is common in the grasses but they can also be found within the cell. Cystoliths are internal outgrowths of cell

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wall that are encrusted with Calcium Carbonate or impregnated with minerals. They occur in ground parenchyma and epidermis. In epidermis, they may be formed in hairs, or in special enlarged cells, the lithocytes.

Silica is deposited mostly in cell walls, but sometimes it forms bodies in the lumen of the cells. Poaceae the grass family is a well-known example of the plant group having silica in both the walls and cell lumen [3].

## 4. Histochemical methods for observation of ergastic crystals

For the temporary mount preparation of free hand sections fresh or preserved materials can be used for light microscopic study that reveals large sized crystals. Russell classifies the light microscopic study for the calcium determination in two groups [9]. They are metal substitution technology and dye lake reactions. Calcium oxalate identification is done by various methods including light microscope, polarizing optics and scanning electron microscopic (SEM) studies. Yasue histochemical method is highly efficient as it can localize calcium oxalate even in plant trichomes [10, 11]. SEM studies reveals crystals of very small size. The application of X-ray diffraction technology and infrared spectra in determination of calcium oxalate reveals both monohydrate and dehydrate forms. The techniques for precipitation in the specimen by reaction procedure methods also contributed in histological identification and confirmation for the presence of ergastic crystals [9].

## 5. Economic importance of ergastic substances

Ergastic crystals and related substances have well defined economic importance that includes protective, defensive and remedial properties. Applying ergastic substances in taxonomic consideration can be of considerable importance for review of existing taxonomic delimitation for clearer circumscription and evolutionary history of the taxa [12]. Diversity relationship of five genuses in the family Polygonaceae based on ergastic evidences has been worked out by Conrad and Idu [13].

Inulin as a carbohydrate is considered indigestible, which necessitates extensive processing (i.e., roasting) prior to consumption, hence the above effect if unprocessed or form a large percentage of diet [14]. Tannins are usually non-bioavailable and like inulin show some degree of anti-nutritive properties as they can bind and precipitate proteins and carbohydrates [15].

Raphide crystals play a role in reducing metal toxicity. This suggestion has largely been based on the observation that such crystals can have many other divalents [16–18]. Quantity of oxalic acid content in plants is different in different parts i.e. in many cases rhizomes are observed to with higher content than in leaves or tender parts [19]. Oxaloacetic acid is component in functioning of guard cells in plants, which follow Hatch and Slack pathway Oxalates provide tolerance to aluminum toxicity. According to Rajendra and Shivay, oxalates have involvement in phytoremediation of soils rendered toxic by heavy metals like lead, cadmium and

zinc [20]. Oxalic acid is also reported to help in the accumulation of heavy metals, cadmium, nickel, zinc, etc. by hyper- accumulators that are being utilized in phytoremediation of soils affected by toxicity of these heavy metals [21–23].

Of the five types of calcium oxalate crystals, raphides are prominent ones in terms of size and quantity as it can occur intercellular and intracellular. Calcium oxalates gets incorporated in human body through plant-based food. These along with the endogenously synthesized content contribute to kidney problems. Studies reveal that calcium oxalates are present in algae, fungi and lichens in addition to their presence in higher plants. Out of all the three forms of calcium oxalate, the monohydrate form is the one widely reported to cause kidney problems [24].

Calcium oxalate, a potential causative agent of human kidney stones, can range from 3 to 80% of the dry weight of various plants [25, 26] and it can contribute up to 70 or 75% of the composition of kidney stones [27]. Deleterious influence of raphides includes promoting kidney stone formation, irritation to throat, mouth and skin [28–32]. Excess presence of raphides, in conjugation with cytotoxic compounds [5, 33], can render the food poisonous and is responsible for mentionable fatalities every year [34, 35].

Crystallized calcium oxalates that appear, as bundles of needles under light microscopes are usually raphides [28, 36]. It is believed that herbivory enhances raphide production in plant cells and the coexisting cysteine proteases together with other defensive chemicals promote protection against grazing animals. The needle like raphides cause bruising the alimentary tract lining of herbivores and also causes irritation due to presence of cysteine proteases [31]. The additive effect of irritants such as cysteine proteases and raphides has been proved in larvae and caterpillar [37].

## 6. Plant families and the types of ergastic crystals in plants

The distribution and characterization of ergastic crystals indicate that they are unique entities in the circumscription and delimitation of various taxa. A review of the calcium oxalate crystals in plants is presented in detail [30]. Calcium oxalate crystals are widely distributed and enlisted in 215 plant families [38]. Systematic significance of the formation, occurrence and distribution of crystals were studied in leaves of 22 species of *Combretum* [39]. Studies on anther anatomy of 167 species of Fabaceae plant family and wood anatomy of 139 species of Verbenaceae plant family reported several types of crystals [40, 41]. The wood anatomy of the plant family Lauraceae revealed the presence of significant prismatic crystals while the plant family Tiliaceae shows the presence of conglomerate crystals [42].

Christina reviewed the structure and systematics of calcium crystals in monocotyledons especially their occurrence of these crystal types, with respect to current systematics [43]. The three main types of calcium oxalate crystal that occur in monocotyledons are raphides, styloids and druses, although intermediates are sometimes recorded. It is inferred that the presence or absence of the different crystal types may represent ‘useful’ taxonomic characters. Further, styloids are characteristic of some families of Asparagales, notably Iridaceae, where

raphides are entirely absent. Raphides are predominant in Monocots mainly seen in leaf petiole of Araceae [42, 44] Styloids are seen in Agavaceae [45]. In *Dracaena sanderiana* (Liliaceae) two types of intracellular calcium oxalate deposits are reported: calcium oxalate monohydrate raphides and solitary calcium oxalate dihydrate crystals [46]. Archeological significance of raphides in Araceae is studied by [6].

In Gymnosperms, druses, prismatic crystals and solitary crystals are observed. Druses are seen in the leaf vascular tissue of *Ginkgo biloba* [47]. In Pinaceae, wood CaOx ray cells and cork of stem contain solitary and prismatic crystals. Calcium oxalate crystals are considered to enhance internal source of carbon dioxide in plants [48]. This is recorded in *Amaranthus hybridus (Amaranthaceae), Dianthus chinensis (Caryophyllaceae), Pelargonium peltatum (Gesneriaceae)* and *Portulacaria afra (Portulacaceae)*. Occurrence, type and location of calcium oxalate crystals have been investigated in *Achyranthes aspera (*Amaranthaceae), *Adhatoda zeylanica (*Acanthaceae), *Aerva lanata* (Amaranthaceae), *Asparagus racemosus* (Asparagaceae), *Atalantia monophylla* (Rutaceae). *Bridelia crenulata* (Euphorbiaceae) *Carica papaya* (Caricaceae) *Carissa spinarum* (Apocynaceae), *Plumeria rubra* (Apocynaceae) *Monochoria vaginalis* (Pontederiaceae) [49].

The types and distribution of calcium oxalate crystals in leaves and stems of some species of poisonous plants have been studied. Crystal sands and prismatic crystals were of rare occurrences. Prismatic crystals were observed in the leaf mesophyll cells of *Nerium oleander* and *Cynanchum acutum*. It was concluded that there is no absolute correlation between the presence and type of calcium oxalate crystals and toxic plant organs.

An extensive enumeration of calcium oxalate crystal reports has been done [28] in 215 plant families including genus *Sida* of Malvaceae. Further, the relation between herbivory and calcium concentration has been recorded in the leaves of *Sida* species. Cell mediated crystallization of calcium oxalate is reported by Webb [25]. The structures of cystoliths in selected taxa of the genus Ficus L. (Moraceae) in the Malaysia Peninsular have been investigated [50]. The characteristics of the cystoliths may not suitably be used as a taxonomic marker but it can be useful as additional character for group identification in *Ficu*s.

New and unusual forms of calcium oxalate raphide crystals in the plant kingdom [51] from the tubers of *Dioscorea polystachya*—six-sided needles with pointed ends and four-sided needles with beveled ends. The production of calcium oxalate crystals has a long evolutionary history and probably evolved independently in major clades of symbiotic fungi and several times in the plantae, as part of the overall process of bio-mineralization [29].

## 7. Genes that contributes in production of ergastic crystals

Even though the nature of control of crystal shape and composition phenomena is yet fully unknown the taxonomic value of crystal shape assumes that it is under genetic control. The scanty knowledge about the mechanisms regulating production and crystal formation is another reason to establish the genetic contribution. Leaves from a chemically mutagenized *Medicago truncatula* population were visually screened for alterations in calcium oxalate crystal

formation was performed by Nakata and Mc Conn and seven different classes of calcium oxalate defective mutants were identified. Genetic analysis suggested that crystal formation is a complex process involving more than seven loci [52]. Oxalate-producing plants, which include many crop plants, accumulate oxalate in the range of 3–80% (w/w) of their dry weight [25].

Of the several metabolic pathways proposed, cleavage of ascorbic acid appears to be the most appreciable [53]. According to this view, once produced the oxalate combines with calcium to generate variety of crystal shapes and sizes. Further studies are required to identify the pathway(s) of oxalate production and calcium oxalate crystal formation.

A genetic approach would circumvent such technical limitations (e.g. idioblast number) and is a proven complement of biochemical and cellular investigations. Although the specific genes that have been altered are not yet to be identified it is understood that the control of crystal morphology is complex and under strict genetic control. As suggested by studies in other systems, mutations affecting protein, lipid, or polysaccharide function could contribute to alterations in crystal size or shape. Roles in ion balance (e.g. calcium regulation), in tissue support, in plant defense, in light gathering and reflection, and in detoxification have all been proposed [30]. Calcium oxalate crystals rapidly increase in size and number as the concentration of calcium in the plant environment is increased [54].

Nutritional studies have shown that oxalate is an anti-nutrient that sequesters calcium in a state that renders it unavailable for nutritional absorption by humans. Even though increasing nutritional quality by biotechnological method is fast in progress attempts to reduce or nullify the amount or effect of potential anti-nutritional agents from the economically useful plants is important.

## 8. Ergastic crystals and medicinal raw drug identification

Correct taxonomic identification of plants is most important before proceeding to any analytical procedure and utilization. Comparative approach on morphological and anatomical features provides distinguishable features for species to species, which is well established in identification of some medicinally useful plants [19]. Morphological features of vegetative parts with qualitative value vary with respect to habitat change and growing regions when cultivars are considered. As flowers fruits and seeds are produced seasonally and when the economically important part is leaves rhizome, corm or tuber identification based on reliable anatomical characteristics may be useful for making differentiation. Ergastic crystals can serve as an important diagnostic tool for the identification of economically important species. Presence of characteristic cuboidal ergastic crystal in the leaves of several plant species including *Costus speciosus* has been well reported [1, 55]. Cuboidal crystals of calcium oxalate are present in the mesophyll cells of *Costus speciosus* and are not reported in mesophyll cell of *Costus pictus* leaves, it can become a consistent and easily identifiable characteristic between these two species. Calcium oxalate crystal is smaller in size towards the tip of the aerial shoot in *Costus pictus* but bigger towards the base of the aerial stem. The crystal size in underground rhizome was found comparatively bigger than those in aerial

shoot [19]. So the presence of ergastic crystals from various plant parts, its size and structure is an important taxonomic key for the making difference between medicinally important species *Costus pictus* and *Costus speciosus.*

## 9. Conclusion

Land resources are blessed with numerable plants, which are of multifarious use. The combined effect of plant introduction and cultivation has largely accelerated the interest of scientists and industrialists to focus on herbal medicine and other economic products. For the sake of consumption of various plants with diverse phyto combinations processing of various level is suggestive. Even though modern biotechnological methods for analyzing and ensuring standards for stabilizing ergastic crystal concentration in raw, prepared food and herbal medicine is not available; traditional methods such as heating, boiling, frying, baking, battering, mashing, fermentation and sun drying, likely work by neutralization of cysteine proteases or through release of raphides from idioblasts or both. Neutralization of calcium oxalate from the dietary compounds still remains a bigger health question than the neutralization of specific crystal form of raphides. A traditional approach of avoiding plant pericarp rich in calcium oxalate and multilayered skin with lignified walls has beneficial effects. Discovery of fungi and bacteria that can break down calcium oxalate and plant genes that regulate calcium oxalate formation and crystallization have offered hope to counteract calcium oxalate toxicity.

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Chapter 4

# Guidelines for the Development of Herbal-Based Sunscreen

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Additional information is available at the end of the chapter

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**Abstract**

Sun protection is a complex topic, which involves various classes of compounds. The photoprotective effectiveness of a sunscreen involves many biological activities, such as ultraviolet (UV) radiation filter properties and antioxidant, anti-inflammatory, and antimutagenic effects. Formulation strategy is also a key factor. Several studies have examined the role of natural molecules as photoprotective compounds, and a considerable number of commercially available sunscreens contain herbal extracts but not as sunfilters. Indeed, the process of evaluation of UV-filtering and photoprotective activity of herbal compounds presents certain specific difficulties and needs in vitro and in vivo studies. Nowadays, no natural compound or vegetal extract has been approved by any country as official UV filter for sunscreen. With these premises, the aim of this chapter is to define a set of tests, which can help to evaluate the efficacy of an herbal extract in the field of sun protection; in other words, we propose a rational approach to the discovery of natural UV-filtering extract and molecules. The following electronic databases have been used as a source of information: SciFinder, PubMed, Google Scholar, ISI-Web of Science, and Scopus.

**Keywords:** natural sunscreen, rational development, sustainable resources, SPF (sun protection factor), skin, cosmetic

## 1. Introduction

The use of herbal extract and natural molecules in the field of solar protection represents a new trend in the cosmetic industry; in fact, over the last few years, a significant increase of the usage of herbal extracts has been registered given the growing interest of the costumer for

"green" and "natural" ingredients in the finished product. A large number of studies appearing in scientific literature demonstrate the photoprotective activity of natural products due to UV-filtering activity, antioxidant activity, and DNA-protecting effects [1–3]. Despite these findings, studies regarding photoprotection activity have been developed with a wide range of different methods and different strategies of investigation, thus making difficult to understand both the actual and the claimed potential of the activity. The main cause of this situation is the lack of repeatability of the in vitro SPF tests available nowadays.

In the USA, sunscreen is classified as an OTC (over-the-counter) product. In the European Union (EU) countries, it is listed as cosmetics, and its production must follow the EC Regulation 1223/2009 of the European Parliament on Cosmetic Products. Regarding the SPF determination, the ISO 2444:2010 is nowadays regarded as the reference method; this method involves an in vivo procedure carried out on human volunteers. Due to ethical problems, the in vivo UVAPF determination by the ISO 24442:2011 has been recently substituted by the in vitro ISO 24443:2012 method.

The "gold standard" for the SPF determination nowadays is provided by the ISO 2444:2010 in vivo test. It is not applicable in the initial screening phase of the new filtering compounds due to ethical problems connected to the exposure of healthy subjects to the potentially harmful effects of UV radiation. As far as the UVA Protection Factor (UVAPF) determination is concerned, in 2012, a new in vitro method was established and integrated into the ISO 24443:2012. Also, for in vivo tests, no authority or legislator has released an official statement to support all this. In the sunscreen research field, more effective guidelines for the evaluation of naturally derived actives are required. Despite the numerous scientific reports, there is no officially approved natural commercial sunfilter. Moreover, a consistent number of commercially available solar products (sunscreen) contain herbal derivatives, but an official and a widely approved validation of this method is not available, and so it is indispensable to correct labeling of the final product's UV protection. Hence, the objective of this study is to collect any current data and exhaustive critical overview regarding the use of herbal extract and natural molecules in sunscreens. Finally, the intent of the present chapter is to provide solid types of research methodology approach in order to develop herbal or natural-based sunscreen, useful as a set of guidelines.

### 1.1. Ultraviolet radiation

Sunlight is composed of about 40% visible light (VIS), 50% infrared light (IR), and 10% ultraviolet light (UV). As far as the biological effects of solar radiation exposure are concerned, ultraviolet radiation is the most important part of the electronic spectrum. Ultraviolet (UV) radiation can be divided into UVC (200–280 nm), UVB (280–315 nm), and UVA (315–400 nm) [2].

UV radiation (sun) is essential to human health; it is necessary for the production of vitamin D3 in the skin. Vitamin D3 is necessary for the intestinal absorption of calcium and phosphorus, and deficiency may cause osteoporosis in adults and growth retardation and skeletal deformities in children. Solar radiation has other therapeutic effects on some skin diseases such as psoriasis and eczema, thus making the outdoors a healthy lifestyle choice [2, 4].

On the other hand, the negative effects of an excessive exposure to UV radiation are well known, and these are harmful to human health; the interaction of the radiation with the most

important constituents of human skin (DNA, RNA, proteins, lipids) represents the basis of the UV-mediated negative biological activities [2]. More in particular UVB radiation is responsible for the most known acute negative effect that comes after some hours of UV exposition: the UVB-induced erythema. This radiation also has a potential carcinogenic effect because it can cause direct damage to the DNA and RNA. An over exposition to deeply penetrating radiation, namely, UVA, is responsible for premature skin aging, excessive degradation, and inhibition of the synthesis of collagen fibers [5].

Protection from solar radiation thus represents a complex issue involving various biological activities and factors that influence the efficacy of a sunscreen product, as demonstrated by studies during the last decade. The most important biological activities in the field of sun protection can be summarized in six main categories:

- Filtering activity against UVB/UVA radiation
- Antioxidant and reactive oxygen species scavenging activity
- Antimutagenic activity
- Anticancer properties
- Booster effect
- Safety stability of the active compounds

In our opinion, the research effort should be focused on the discovery of multifunctional compounds or mixtures that present the abovementioned biological activities. Therefore, the reports of in vitro SPF values of herbal extracts and compounds are more valuable if they are accompanied by other types of useful biological activities that are of equal importance in the prevention of skin problems relating to UV exposure [2].

## 2. Biological activities connected with solar protection

### 2.1. Antioxidant and reactive oxygen species scavenging activity

Antioxidant effect represents one of the key mechanisms of photoprotective activity of herbal extracts. The UV skin damage depends also on the generation of reactive oxygen species (ROS). ROS are considered as oxidant agents and are responsible for the development of skin disorders like skin aging, lipid peroxidation, and cancer [6]. These species include hydroxyl radicals, peroxyl radicals, superoxide anion, and, mainly, their active precursors: ozone, hydrogen peroxide, and singlet oxygen. ROS react negatively with DNA, proteins, and unsaturated fatty acids that in turn induce carcinogenic processes and inflammatory response from cells. Phenolic/polyphenolic compounds and flavonoids usually represent the main source of natural antioxidant compounds, and several types of research highlight the usefulness of including natural antioxidant extracts in topical products [6–8].

Antioxidant compounds from herbs offer new possibilities and strategies for an effective prevention and treatment of UV-mediated damages and diseases, which are mainly due to the

generation of reactive oxygen species suppressing immune reactions. The benefits of natural antioxidants in topical products are nowadays generally accepted in light of the information available [9]. There are several effective in vitro tests for antioxidant activity. Each of them is based on different mechanisms and, thus, evaluates different kinds of oxidative protection. In order to obtain a sufficient evaluation on in vitro antioxidant, it is thus necessary to perform different types of tests to assess the studied compounds on different kinds of oxidative species.

Listed below are some examples of tests that should be carried out to define the whole spectrum of protection. The tests include:

- 1,1-Diphenyl-2-picrylhydrazyl (DPPH) assay
- Luminol photochemiluminescence (PCL) assay
- 2,2′-Azino-bis-3-ethyl-benzothiazoline-6-sulfonic (ABTS) acid assay
- Oxygen radical absorption capacity (ORAC)

### 2.2. Antimutagenic activity and anticancer properties

UV radiation is capable of damaging DNA and therefore participating in cancer pathogenesis through multiple mechanisms such as immunosuppression, oxidative stress, direct DNA damage, inflammatory response, and p53 tumor suppressor gene mutations. On the other hand, it should be taken into account that immunosuppression might be the desired effect in subjects affected by autoimmune diseases [10].

Several methods are available for a predictive in vitro antimutagenic or anticancer activity evaluation, and it is quite difficult to identify a list of preferred tests [11]. However, a good practice should include at least one of the validated methods in the screening of a new substance or mixture [11].

### 2.3. Anti-inflammatory activity

UV radiation induces the inflammatory response. UVB-induced cyclooxygenase-2 (COX-2) expression leads to an increase in the production of prostaglandin (PG) metabolites. COX-2 expression in the skin has been linked to the pathophysiology of inflammation and cancer. Exposure to UV radiation is also known to increase the expression of pro-inflammatory cytokines like tumor necrosis factor, interleukin (IL)-1, and interleukin IL-6. These anti-inflammatory properties including various herbal substances and medicines can be evaluated by a number of methods [12, 13].

### 2.4. Booster effect

This topic is yet quite complex because it is relatively new and not fully explored. There are already known compounds that can boost the SPF of UV filters [10, 14], but the mechanisms that are responsible for booster effects are heterogeneous and often unpredictable; some are linked to the nature of the UV filter(s) that the formulator wants to enhance. It is, in fact, difficult to uniquely define the general characteristics of an ingredient with booster effect, but it is possible to describe the two main aspects of this topic. The three main strategies available

to achieve "booster effect" are interaction with the UV filters at the physical-chemical level to improve efficiency (optimize the efficiency of the UV absorber mixture) [10], implement a correct formulation strategy, and improve the film-forming properties (use of emollients and film-forming agents). One of the reasons of the growing importance of the booster effect is the consolidated marketing trend of placing on the market sunscreen products with higher SPF values; as a consequence of this, the formulator has to find all the possible stratagems to use the smallest possible amount of UV filters in the product. Considering the evaluation of herbal materials as "booster ingredients," this activity is, in some cases, identifiable by the in vitro tests that will be described later. Ingredients that improve UV filter distribution and enhance spreadability are also valuable [15].

According to EU regulation [16], Annex VI reports the list of UV filters allowed in cosmetic products.

List of sunscreen ingredients approved in the USA as presented in the sunscreen drug products for over-the-counter human use monograph" (21 CFR 352.10) [17].

## 3. Guidelines for the determination of SPF in vitro

Currently, several in vitro tests for determination of SPF exist. They are all used for screenings performed in the research and developing phase. The first method proposed is the one by Diffey (1989); it is still the most accredited reference [14]. The fundamental characteristic of all the in vitro methods is that they are based on spectrophotometric measurement of the absorbance (calculated from transmittance) of a thin film of product applied on UV transparent substrates. Substrates should be as close as possible to the physical characteristics of the skin. The amount of product applied varies from 0.7 to 2.0 mg $cm^2$. There are different types of suitable substrates; they can range from plastic perforated surgical tape such as Transpore™ to standardized plastic plates such as polymethyl methacrylate (PMMA) plates [14]:

- Transpore™ tape: it is a surgical tape (provided by 3M Health Care Company, Maine, USA). It is used according to the Diffey-Robson's method; this tape has a perforated structure, and it allows the distribution of the sunscreen sample in a way similar to the irregular surface of the skin.
- Sand-blasted PMMA plates: this substrate is easy to use and can be supplied with a reproducible roughness. (i.e., Schonberg GmbH, Munich, Germany). The plates have an area of 2 $cm^2$ and standard roughness of 5 μm. The features of this substrate meet the recommendation of ISO 24443 for in vitro UVA protection assessment.

Our experience in the research of useful compounds in the solar protection field and an accurate bibliographic research indicate that it is possible to point out several factors and variables which are able to affect the accuracy and the repeatability of the in vitro SPF tests. The most important ones are:

- Different compositions of filters
- The formulation of the sunscreens

- The thickness and the homogeneity of the applied sunscreen
- The type of spectrophotometer
- Substrates used and their relative roughness

The main concern, about this type of evaluation, is the lack of data to support correlation to in vivo results [14].

At present, the in vivo method is still the official standard for UVB protection (ISO 2444:2010), and product developers should perform the in vivo test on the final product and the in vitro one during all the phases of the development bringing attention to the ethical issue and on the costs.

In order to provide practical indications, we suggest two methods that have proven, in our experience, to be among the most reliable:

### 3.1. Method A

This is based on the Diffey-Robson's method [14]. The support used is a Transpore™ surgical perforated tape, cut to have an area of 20 $cm^2$, in which an amount of 0.0400 ± 0.002 g (2 mg $cm^{-2}$) of the product is weighed and laid in small spots through all the area. The tape is then positioned on a scale where the spreading phase is carried out with a finger cot, performing a pattern of six movements in horizontal, vertical, and circular directions and checking the pressure applied in all the movements. As far as the spreading pressure is concern, an internal procedure must be developed by the performing laboratory in order to be repeatable (see the end of this paragraph). At least three tapes have to be prepared for each product, recording five measures each, collecting therefore 15 spectra [14].

### 3.2. Method B

This method has been recently proposed by us [14], adapting to UVB the ISO 24443:2012 standard for the in vitro UVA protection determination. The support used is a PMMA (polymethyl methacrylate) plastic plate with an area of 25 $cm^2$ and standardized 5 μm roughness, in which an amount of 0.0320 ± 0.0005 g (1.3 mg $cm^{-2}$) of the product is weighed and laid in small spots through all the area. The plate is then positioned on a scale where the spreading phase is carried out performing with pre-saturated finger cot a sequence of six movements in horizontal, vertical, and circular direction and checking the pressure applied throughout the spreading. Before the measurement, the sample lies for a minimum of 15 min in a dark place, allowing the evaporation of volatile components. Three plates have to be prepared for each product, recording five measures each, collecting therefore 15 spectra [14].

In both methods, the spectra were recorded with an appropriate spectrophotometer, wavelength ranging from 290 nm up to 400 nm, with increment step set at 1 nm. The tests carried out for the evaluation of new herbal compounds are usually performed including them, at a known concentration, in a stable formulation suitable for cosmetic use. The obtained SPF data are then compared to those of the same formulation without the studied compounds.

SPF in vitro is defined as follows:

$$In\ vitro\ SPF = \frac{\int_{\lambda=290nm}^{\lambda=400nm} E(\lambda)I(\lambda)d(\lambda)}{\int_{\lambda=290nm}^{\lambda=400nm} E(\lambda)I(\lambda)10^{-A(\lambda)}d(\lambda)} \quad (1)$$

$E(\lambda)$ is the erythema action spectrum (CIE-1987) at the wavelength $\lambda$. $I(\lambda)$ is the spectral irradiance received from the UV source at the wavelength $\lambda$. $A(\lambda)$ is the monochromatic absorbance of the test product layer at the wavelength $\lambda$. $d(\lambda)$ is the wavelength step (1 nm).

Both methods have to be conducted in highly standardized operating conditions with regard to the operator, the environmental conditions, the substrates used, and the instruments. We have worked with spreading pressures of 100 ± 15 g and 200 ± 15 g, and comparing different application pressures on the same substrate, no statistically significant difference subsists in terms of repeatability.

The two fundamental parameters in the in vitro SPF measurement process are in vivo correlation and reproducibility. In our experience, Method B with a spreading pressure of 200 ± 15 g is the most reliable method with respect to reproducibility and accuracy. Nevertheless, Method A can be still considered as a useful in vitro method during the early research phase, especially in laboratories with limited financial resources and limited equipment. In this case, the correlation is not influenced by the choice of operator's pressure (100 ± 15 g or 200 ± 15 g).

The problem of photostability of UV filters should also be considered at this stage. It is necessary, seeking potential human applications, to verify that a new compound or vegetal extract does not present any photostability problems. This evaluation can be performed using solar radiation simulators; this procedure is also indicated in the ISO 24443:2012.

It is very important to assume that, at present, it is possible for a single laboratory to optimize internal methods and protocols to achieve repeatable and predictive in vitro results, whereas it is extremely difficult to develop methods reproducible and equally reliable between different laboratories due to external variables (e.g., the environmental, operator, etc.) [14].

## 4. Natural compounds in solar radiation protection: current knowledge

In recent years, many plant species have been investigated for their potential uses in the field of solar radiation protection, but much remains to be accomplished. As stated above, this depends on both a large number of under-investigated species and the lack of an official standard in vitro SPF evaluation method, to speed up the screening procedure. Depending on this, and on the many different and incomplete approaches led by different research groups, it is also complex to have a general picture of the existing knowledge. In the aim to achieve a "state of the art," we conducted a detailed bibliographic research on the plants already investigated in biological activities useful for sunscreen products.

In our previous investigation [2], we identified 54 plants, 5 lichens, and 14 pure molecules which have been studied in order to obtain herbal sunscreen products. It is remarkable how

many plant extracts showed preliminary natural UV filter activity and, in the same manner, antioxidant properties and/or synergistic photoprotective effects.

**Table 1** summarizes a selection of the abovementioned plants, lichens, and pure molecules which have been mentioned at least in two different types of research.

| Plant name | Plant part(s) used | Plant extract | Type of compound(s) | Major constituent(s) | Main effect(s) |
|---|---|---|---|---|---|
| *Calendula officinalis* | Flower | Hydroalcoholic extract | Polyphenol, flavonoid | Rutin, narcissin | Prevent UV irradiation-induced oxidative stress |
| *Camellia sinensis* | n.r. | n.r. | Polyphenols | EC—(−)epicatechin, ECG—(−)-epicatechin-3-gallate, EGC—(−)-epigallocatechin, EGCG—(−)-epigallocatechin-3-gallate | Anticarcinogenic, anti-inflammatory, photostabilizing capacity |
| *Coffea* genus (10 species) | Green dry coffee beans | Chloroform extract | Lipid fraction | Linoleic acid, palmitic acid | UV absorber, emollient |
| *Culcitium reflexum* | Leaf | Ethanolic extract | Phenolic compounds, flavonols | Rutin, kaempferol, quercetin, and its glycosylated derivatives and cinnamic acid derivatives | Antioxidant, reduces UVB-induced skin erythema, free-radical-scavenging effect |
| *Fragaria x ananassa* | Fruits | n.r. | Anthocyanins and hydrolyzable tannins | Pelargonidin | Antioxidant, reduces UVB-induced skin erythema, anti-inflammatory, diminishing DNA damage on UVA-induced skin damage |
| *Glycine max* | Seeds | Soybean cake | Soy isoflavone | Genistein | Antioxidant, reduces skin photo damage and transepidermal water loss (TEWL) |
| *Moringa oleifera* | Seeds | Petroleum ether extract | Lipid fraction | n.r. | UV absorber |
| *Pinus pinaster* | Bark | Picnogenol | Phenolic compounds, polyphenols, procyanidin derivatives | Catechin, epicatechin, taxifolin, caffeic, ferulic, p-hydroxybenzoic, vanillic, gallic, and protocatechuic acid | Reduces UVB-induced skin erythema, free-radical-scavenging effect |
| *Pimenta pseudocaryophyllus* | Leaves | Ethanolic extract | Flavonoids and polyphenolic compounds | n. r. | Inhibits UV-B irradiation-induced inflammation and oxidative stress of the skin Antioxidant, decreases oxidative damages of the skin |

| Plant name | Plant part(s) used | Plant extract | Type of compound(s) | Major constituent(s) | Main effect(s) |
|---|---|---|---|---|---|
| *Pongamia glabra* | Seeds | n.r. | n.r. | Pongamol, karanjin | UV absorber |
| *Punica granatum* | Fruits, peel | methanol extract | Anthocyanidins, hydrolyzable tannins | Delphinidin, cyanidin, and pelargonidin | Decreases in the number of UVB-induced dimers in the human skin, synergic photoprotective activity in nanostrustured lipid carrier |
| *Silybum marianum* | Seeds | n.r. | Flavonolignans | Silymarin, Silybin, silydianin, silychristin, isosilybin | Inhibits UVB-induced damage, antioxidant |
| *Vaccinium myrtillus* L. | Fruits | n.r., water-soluble extract | Polyphenols, anthocyanins | n.r. | Reduction of UV A-stimulated ROS formation, attenuation of UVA-caused peroxidation of membrane lipids, and depletion of intracellular GSH |
| *Vitis vinifera* | Seeds | n.r. | Polyphenols | Flavan-3-ol derivatives, catechin, epicatechin, oligomeric proanthocyanidins | Free-radical-scavenging effect, prevents UVB- and UVC-induced lipid peroxidation, reducing the oxidative stress and apoptosis |

n.r.—not reported.

**Table 1.** Selection of plant extracts useful for sunscreen application.

Lichens are mentioned by several types of research [18–23] as natural sources of photoprotective compounds and phytocomplexes. Some examples of bioactive compounds obtained by lichens are epiphorelic acid I and II, salazinic acid, usnic acid, secalonic acid, and calycine. According to the studies regarding lichens, the main highlighted activities were antioxidant properties and broad-spectrum UV-absorbing capacity. Regarding pure molecules, quercetin and resveratrol have been widely investigated [7, 24–30] for their antioxidant, antiproliferative, and anti-inflammatory properties, including also UVA and UVB filter enhancer activity.

## 5. Strategies and solutions

UV light is recognized by the US National Institute of Environmental Health Sciences, as the main etiological agent of a large number of skin cancers, sunburns, and oxidative stress (US Tenth Report on Carcinogens). Despite controversial data about photo-irritation, photo-sensitization, and contact dermatitis, synthetic and mineral sunscreens are used to prevent UV-induced skin damage and are very common in several skin care formulations. More often than not, the etiology of a skin disease is multifactorial and includes DNA damages, inflammatory

processes, oxidative stress from ROS, lipid peroxidation, etc. All the abovementioned causes need a multi-target approach, which is impossible to obtain with a "magic-bullet" molecule and neither in a blend of UVA/UVB/UVC filters. All synergic photoprotective claims may be integrated with a proven formulation strategy (oleosomes and/or other encapsulation technologies, coatings or stabilizers, film thickness, etc.) in order to stabilize and/or boost the suncare herbal ingredients.

Moreover, in view of the increased demand of natural, herbal ingredients, sunscreens will be the next trend for photoprotective formulations. To this end, it is mandatory to develop natural sunscreen formulations based on a sound scientific investigation to sustain safe and effective products. In these regards, in our laboratory, we have very recently developed a rational approach considering the synergistic properties that a good candidate should possess: proven UVB/UVA absorption capability, antioxidant effects, protection against DNA and other free radical cellular structure-mediated damages, potential synergic protective mechanisms, and, finally, good toxicological profiles and proven formulation efficacy. As a matter of fact, several herbal/natural molecules may provide, in theory, these activities. Herbal extracts are naturally composed of mixtures of synergistic ingredients developed by plants through the evolution process (i.e., polyphenols), to allow the earlier marine organisms to colonize the terrestrial environment inferring resistance to high UV-induced oxidative stress. Taking this into account, as the synthetic strategy goes toward the design of multifunctional molecules inspired by the above natural mechanism [7], herbal sunscreen goes in the same direction but starts from the other side that already is available in the phytocomplex. The weak point of this latter approach is the investigation strategy, often incomplete, that makes literature data not useful. To further complicate the picture, it must be noted that different portions of the plant may be used (leaves, bark, roots, owers, seeds, or fruits), they can be dried either in air or using instruments, and they can be cut or ground into particles and then extracted with either water or organic solvents at different herbs to solvent ratio (i.e., 1:4, w/v). But also fresh herbs are used; in this case, the herb to solvent ratio is usually 1:1. The extraction process might be different in function of the characteristics (physical and chemical) of the ingredients. Thus, the same approach for different compounds cannot be devised. Also, steam distillation is used in the preparation and extraction of essential oils from botanical materials. New technologies, i.e., supercritical carbon dioxide extraction technology, membrane separation technology, enzymatic extraction methods, and so on, are emerging, further complicating the pattern of the relative observed activities.

Taking all this into account, only a few studies on herbal extracts really match the abovementioned strategy. An ideal approach (**Figure 1**) should involve three different steps, typical of drug development:

1. Extraction and characterization of the properties of the extracts (i.e., composition, UV absorption, mutagenicity, cytotoxicity).
2. In vitro evaluation of synergic physiological activity (i.e., lenitive, antiradical, antioxidant, etc.).
3. Formulation strategies, new vehicles development, stabilization, and SPF evaluation in vitro and on volunteers.


**Figure 1.** A rational process in suncare active ingredients discovery from herbal extracts.

In our opinion, step 3 represents the main lack of evidence in order to develop a natural sunscreen product. Despite an improving number of recent studies regarding the incorporation of antioxidants into sunscreen [25, 27, 28], none of the researches we reviewed include herbal products and more sophisticated formulations, as nanostructured lipid carrier, elastic niosomes, nanoparticles, microemulsion, etc. We recommend this way as an essential trend for "green" sunscreen research.

## 6. Natural extracts as a source of active compounds: from ancient to modern times

Scientific reports directed to the discovery of novel natural photoprotective ingredients often describe only the UV-filtering activity (step 1), which is a necessary but not sufficient condition to support the speculation of the effectiveness if inserted into a sunscreen tested on volunteers. The same issue can be referred to the in vitro bioactivity studies (step 2). The hardest challenge is to enhance the already approved findings as models, mentioned in step 3. An extract or natural compound needs to be fully characterized also for its effect in humans in the final product. Without this, it will remain restricted to a scientific investigation, which will be seen as useless to understand the potential of application in substitution of synthetic or mineral filters. Finally, in order to demonstrate real "green" claims, we recommend completing the product development with aquatic ecotoxicity assay. This step is becoming quite relevant [31, 32] and could be a significant benefit for a new sunscreen product.

Natural extracts have often been used as a source of inspiration in the development of new drugs rather than drugs themselves. Thus, while the discovery of synthetic ingredients is based on a rational systematic approach, which takes into account "step-by-step" modifications driven by chemical-physical parameter, the approach to the discovery of herbal ingredients, to be used as extracts, is "experience driven" and mainly based on traditional uses. A step-by-step procedure applied to natural extract would imply (I) the preparation of extracts and eventually phytochemicals from herbs, (II) the phytochemical study of extracts of herbal preparation or compound isolation, (III) the structure/composition elucidation, (IV) the in vitro biological activity evaluation, (V) the compound characterization and principal activity investigation, (VI) and the in vivo proof of the in vitro elucidated activities.

Furthermore, on the one hand, a central government agency of countries with high biodiversity should consider establishing research projects that involve ecological ethics, such as the managing, care, and preservation of the environment. However, on the other hand, the discovery of such ingredients could lead to improving agriculture or farming of these plants which may become an important job opportunity, especially in countries where the land is not favorable for the traditional farming. Finally, biotechnology in fields of plants is already a precious source of ingredients (i.e., secondary metabolites), which can be obtained from cell culture rather than traditional farming, thus saving biodiversity and land to be dedicated to plants for food. This has already been proven possible in the field of medicinal plants (i.e., *Artemisia annua*) [33].

Due to the growing interest in herbal remedies, there is also a significant amount of data available on herbal ingredients (i.e., public databases containing analysis, efficacy tests, extracts preparation) even in relation to their molecular targets [33].

It is already possible, based on existing proofs, to envisage a stage of discovery from herbal ingredients, which includes the preparation of extract (by the same standardized methods) eventual isolation, structure/composition elucidation, and in vitro bioactivity evaluation. In the case of sunscreens, the class of compounds behaving abilities of solar radiation absorption and antioxidant capacities are well known (i.e., polyphenols); what is not known is how much the mixture of other ingredients present in the extract may contribute to the sunscreen activity with complementary mechanisms (i.e., booster activity). This implies that the evaluation of activity in vivo must be conducted for each single extract. As recently reviewed by Si-Yuan Pan et al., the herbal preparation may contain "hundreds" of active compounds, and in addition, the concentrations of some of them might be exceedingly low and thus insufficient for conducting in vivo studies on isolated molecules. They report that from 1960 to 1982 and from over 100,000 crude tested extracts (deriving from more than 30.00 plants) only two compounds, Taxol and camptothecin, were developed into marketable therapeutics [33].

Based on the experience from random trials and observations in animals, ancient people acquired the knowledge of using herbs to treat illnesses. However, herbs used in traditional medicines constitute only a small portion of naturally occurring plants; thus, a large part of work still remains to be developed.

## 7. Conclusion

In this chapter, we presented a systematic approach based on our experiences and proposed it as a possible standard approach in this field. The steps mentioned in **Figure 1** have to be considered as an initial set of guidelines needed for the development of herbal-based sunscreen. The end result is a complete and rational methodology for the research and development of herbal sunscreen. The authors consider it to be essential to match the initial in vitro studies about UV filter activities with synergic biological activities (antioxidant, anti-inflammatory, inhibitory UV-induced damage effect, etc.) and formulation strategies (boosters, encapsulation, etc.). A solid response in each step may be considered a complete strategy. Finally, regarding natural products and traditional knowledge, an eco-friendly and sustainable approach can complete the investigation process and the management of the industrial supply chains.

We believe that our contribution will be useful to expedite the discovery of sunfilters from herbs. With a solid discovery approach, chances of success will greatly increase.

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## A. Annex VI: List of UV filters allowed in cosmetic products according to EU regulation [11]

List of sunscreen ingredients approved in the USA as presented in the "Sunscreen Drug Products for Over-the-Counter Human Use" monograph (21 CFR 352.10) [12].

| Chemical name | Name of common ingredient glossary | Maximum concentration in ready-for-use preparation |
|---|---|---|
| 4-Aminobenzoic acid | PABA | 5% |
| *N*,*N*,*N*-Trimethyl-4-(2-oxoborn-3-ylidenemethyl) anilinium methyl sulfate | Camphor benzalkonium methosulfate | 6% |
| Benzoic acid, 2-hydroxy-, 3,3,5-trimethylcyclohexyl ester/ homosalate | Homosalate | 10% |
| 2-Hydroxy-4-methoxybenzophenone/oxybenzone | Benzophenone-3 | 10% |
| 2-Phenylbenzimidazole-5-sulfonic acid and its potassium, sodium, and triethanolamine salts/ensulizole | Phenylbenzimidazole sulfonic acid | 8% (as acid) |
| 3,3′-(1,4-Phenylenedimethylene) bis(7, 7-dimethyl-2-oxobicyclo-[2.2.1]hept-1-yl-methanesulfonic acid) and its salts/ecamsule | Terephthalylidene dicamphor sulfonic acid | 10% (as acid) |
| 1-(4-tert-Butylphenyl)-3-(4-methoxyphenyl)propane-1,3-dione/ avobenzone | Butyl methoxydibenzoylmethane | 5% |
| alpha-(2-Oxoborn-3-ylidene)-toluene-4-sulphonic acid and its salts | Benzylidene camphor sulfonic acid | 6% (as acid) |
| 2-Cyano-3,3-diphenyl acrylic acid, 2-ethylhexyl ester/octocrylene | Octocrylene | 10% (as acid) |
| Polymer of N-{(2 and 4)-[(2-oxoborn-3-ylidene)methyl]benzyl} acrylamide | Polyacrylamidomethyl benzylidene camphor | 6% |
| 2-Ethylhexyl 4-methoxycinnamate/octinoxate | Ethylhexyl methoxycinnamate | 10% |
| Ethoxylated ethyl-4-aminobenzoate | PEG-25 PABA | 10% |
| Isopentyl-4-methoxycinnamate/amiloxate | Isoamyl p-methoxycinnamate | 10% |
| 2,4,6-Trianilino-(p-carbo-2′-ethylhexyl-1′-oxy)-1,3,5-triazine | Ethylhexyl triazine | 5% |
| Phenol,2-(2H-benzotriazol-2-yl)-4-methyl-6-(2-methyl-3-(1,3,3, 3-tetramethyl-1-(trimethylsilyl)oxy)-disiloxanyl)propyl) | Drometrizole trisiloxane | 15% |
| Benzoic acid, 4,4-((6-((4-(((1,1-dimethylethyl)amino)carbonyl) phenyl)amino)-1,3,5-triazine-2,4-diyl)diimino)bis-, bis (2-ethylhexyl) ester/iscotrizinol (USAN) | Diethylhexyl butamido triazine | 10% |
| 3-(4-Methylbenzylidene)-d1 camphor/enzacamene | 4-Methylbenzylidene` camphor | 4% |
| 3-Benzylidene camphor | 3-Benzylidene camphor | 2% |

| Chemical name | Name of common ingredient glossary | Maximum concentration in ready-for-use preparation |
|---|---|---|
| 2-Ethylhexyl salicylate/octisalate | Ethylhexyl salicylate | 5% |
| 2-Ethylhexyl 4-(dimethylamino)benzoate/padimate O (USAN: BAN) | Ethylhexyl dimethyl PABA | 8% |
| 2-Hydroxy-4-methoxybenzophenone-5-sulfonic acid and its sodium salt/sulisobenzone | Benzophenone-4, benzophenone-5 | 5% (as acid) |
| 2,2′-Methylene-bis(6-(2H-benzotriazol-2-yl)-4-(1,1,3,3-tetramethyl-butyl)phenol)/bisoctrizole | Methylene bis-benzotriazolyl tetramethylbutylphenol | 10% |
| Sodium salt of 2,2′-bis(1,4-phenylene)-1H–benzimidazole-4, 6-disulfonic acid)/bisdisulizole disodium (USAN) | Disodium phenyl dibenzimidazole tetrasulfonate | 10% (as acid) |
| 2,2′-(6-(4-Methoxyphenyl)-1,3,5-triazine-2,4-diyl)bis(5-((2-ethylhexyl)oxy)phenol)/bemotrizinol | Bis-ethylhexyloxyphenol methoxyphenyl triazine | 10% |
| Dimethicodiethylbenzalmalonate | Polysilicone-15 | 10% |
| Titanium dioxide | Titanium dioxide | 25% |
| Benzoic acid, 2-[4-(diethylamino)-2-hydroxybenzoyl]-, hexylester | Diethylamino hydroxybenzoyl hexyl benzoate | 10% in sunscreen products |

| Name of common ingredient glossary | Concentration allowed |
|---|---|
| Aminobenzoic acid (PABA) | Up to 15% |
| Avobenzone | Up to 3% |
| Cinoxate | Up to 3% |
| Dioxybenzone | Up to 3% |
| Homosalate | Up to 15% |
| Menthyl anthranilate | Up to 5% |
| Octocrylene | Up to 10% |
| Octyl methoxycinnamate | Up to 7.5% |
| Octyl salicylate | Up to 5% |
| Oxybenzone | Up to 6% |
| Padimate O | Up to 8% |
| Phenylbenzimidazole sulfonic acid | Up to 4% |
| Sulisobenzone | Up to 10% |
| Titanium dioxide | Up to 25% |
| Trolamine salicylate | Up to 12% |
| Zinc oxide | Up to 25% |
| Ensulizole | Up to 4% |
| Homosalate | Up to 15% |

| Name of common ingredient glossary | Concentration allowed |
|---|---|
| Meradimate | Up to 5% |
| Octinoxate | Up to 7.5% |
| Octisalate | Up to 5% |
| Octocrylene | Up to 10% |
| Oxybenzone | Up to 6% |
| Padimate O | Up to 8% |

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Chapter 5

# Toxicity and Safety Implications of Herbal Medicines Used in Africa

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Additional information is available at the end of the chapter

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**Abstract**

The use of herbal medicines has seen a great upsurge globally. In developing countries, many patronize them largely due to cultural acceptability, availability and cost. In developed countries, they are used because they are natural and therefore assumed to be safer than allopathic medicines. In recent times, however, there has been a growing concern about their safety. This has created a situation of ambivalence in discussions regarding their use. Some medicinal plants are intrinsically toxic by virtue of their constituents and can cause adverse reactions if inappropriately used. Other factors such as herb-drug interactions, lack of adherence to good manufacturing practice (GMP), poor regulatory measures and adulteration may also lead to adverse events in their use. Many *in vivo* tests on aqueous extracts largely support the safety of herbal medicines, whereas most *in vitro* tests on isolated single cells mostly with extracts other than aqueous ones show contrary results and thus continue the debate on herbal medicine safety. It is expected that toxicity studies concerning herbal medicine should reflect their traditional use to allow for rational discussions regarding their safety for their beneficial use. While various attempts continue to establish the safety of various herbal medicines in man, their cautious and responsible use is required.

**Keywords:** traditional medicine, herbal medicine, medicinal plants, toxicity, safety

## 1. Introduction

This chapter is primarily to appraise the pertinent determinants of the safety of medicinal plants or herbal medicines used in African traditional medicine and the implications of their toxicity. In view of the current global upsurge in their usage, it has become necessary to

review issues related to herbal medicines toxicity within appropriate contexts to allow for their beneficial use. In this regard, the safety implications of medicinal plants used in traditional medicine and or in diets are discussed and some literature on animal toxicity, acute and chronic toxicities, and cytotoxicity of some African medicinal plants are reviewed.

Plants have been used since time immemorial for diverse purposes in the life of mankind particularly as food, and medicines for nutrition and the treatment of diseases, respectively, in both humans and animals. They are used in all cultures of the world and have been relied upon for several millennia to support, promote and restore human health. They form a vital component of traditional medicine (TM) and their use for the maintenance of health and well-being is a common practice in all African societies. They are used as remedies for the prevention and treatment or management of a plethora of disease conditions including relatively new ones such as HIV/AIDS [1].

Traditional medicine used to be the only health-care system available to the whole of the African population prior to the introduction of allopathic or conventional medicine [2]. The practice received international recognition after the 1978 Alma Ata Conference Declaration, which aimed to achieve primary health care for all by the year 2000 through the use of traditional medicine [3]. TM, especially herbal medicine, still forms the backbone of rural health care in Africa, supporting an estimated 80–90% of the population.

## 2. Justification for the use of herbal medicines

There exist diverse reasons for the continuing use of herbal medicines for health care in Africa; these include cultural acceptability, easy accessibility and affordability, and in some instances, non-availability and prohibitive cost of allopathic medicines [4]. Some people also employ herbal medicines under other circumstances, for example, in health conditions that had failed to respond to orthodox treatment or which allopathic medicines are deemed not to treat adequately and less safely [5]. Other health conditions believed to have spiritual origins [2] and those thought to need holistic therapies are also managed with herbal medicines.

## 3. Evolution of herbal medicine in traditional medicine

The practice of herbal medicine is embedded in traditional medicine which origins may be implied in varied anecdotes. It is claimed that its beginnings in humans were instinctive, as seems to be the case in animals. As humans were afflicted by various illnesses over time, they learned to pursue remedies from various formulations from plant and animal parts, and mineral substances. Over time, the therapeutic properties of medicinal plants for the treatment of certain diseases have been validated through scientific experiments; thus, medicinal plants usage gradually abandoned the anecdotal framework and became founded on empirical and explicatory facts [6].

Other diverse claims have been made in relation to the origin of herbal medicines used in traditional medicine in Africa. Some claimed the medicines originated from the deities

or superior beings as a gift to man through the medium of dwarfs or spirit beings who 'abducted' some individuals and took them away from human habitation into the spirit world either in the forest or in the water bodies. Such persons returned to human habitation trained and equipped to fight the diseases that threaten the well-being of not only individual sufferers but also the entire family or community. Some other knowledge of medicines is claimed to have come by revelation through dreams, visions and extrasensory perception. The above postulates on the origin of herbal medicines formed the basis of a sophisticated traditional medical system in Africa, a time-tested system where information on medicinal plants use was methodically collected over several years, and which provides remedies for most diseases today in Africa. The African Traditional Medicine practitioners' own experience, added to the accumulated knowledge passed on, usually orally, through generations, allow them to offer effective remedies for treating ailments that afflict the community [5].

Lately, the knowledge and use of traditional medicine have also been acquired through apprenticeship by individuals understudying a recognized practitioner over defined periods of time. More recently, with increased access to information, some practitioners, especially those outside the indigenous cultures, acquire the knowledge about medicinal plants and their uses from Internet sources including online scientific journals and books including e-books. Another avenue of knowledge acquisition has been through formal education and training in exclusively scientific settings as at colleges or universities where degrees or diplomas are awarded on graduation.

## 4. Attitudes toward traditional medicine

Ever since the dawn of the scientific era, prejudice against traditional medicine has been noted [7]. This has resulted in a situation described as 'passionate ambivalence' toward TM, fuelled by the influence of Western religion and education, urbanization and globalization phenomena in Africa [2]. The result has been continued as negative pronouncements from some segments of western-educated African elites concerning the use of TM especially concerning the quality, efficacy and safety of African medicinal products, creating doubts about the benefits of the medicines. This is in spite of the fact that TM still plays an important role in health-care delivery in Africa and had rarely witnessed major reported cases of adverse effects even after hundreds of years of practice [2].

Besides, some persons with little or no knowledge of herbal medicines tend to focus on reported toxicities and criticize the practice often out of context. Moreover, mass media reports of adverse events tend to be sensationalized and give a negative impression about the outcomes from the use of herbal medicines, instead of identifying the causes of these events, which may relate to a variety of issues [8]. Several scientific studies conducted on the biochemical properties of medicinal plants used in traditional medicines to treat various illnesses have confirmed their efficacy and safety especially in animals. As seen in several publications, the efficacy [9] and sometimes the safety of some medicinal plants and herbal medicines have been validated through research [10–12].

## 5. Toxicity of chemicals

Toxicity refers to the relative ability of a substance to cause adverse effects in living organisms [13]. It may also be defined as the extent to which an exposed tissue is damaged by a chemical substance and covers the effect on a whole organism and sub-structural component of an organism such as the cell (cytotoxicity) or organ (organotoxicity). Toxicity may further be defined to cover the study of the adverse effects of chemicals on living organisms as well as their symptoms, mechanisms and treatments. Toxicity studies may be classified as acute, subacute/subchronic and chronic effects depending upon the quantity and duration of administration of the agents [14].

### 5.1. Acute toxicity

Acute toxicological studies investigate the toxic effects produced by a single large-dose exposure to a toxicant lasting no longer than 24 h. This may result in severe biological effects (harm or death) to the organism. The results of acute toxicity are not only important in the consideration of accidental poisoning with a chemical but also are used for the planning of chronic toxicological studies [15]. The development of tolerance is usually revealed by an acute exposure. The starting point for toxicological classification of chemicals uses the $LD_{50}$ value, which is the dose administered in acute toxicity testing that causes death in 50% of experimental animals [16].

### 5.2. *Chronic* toxicity

Chronic exposure refers to the administration of a toxin over an extended period of time, usually measured in months or years; this can cause irreversible toxicity. Periods between acute and chronic exposure could be referred to as subacute or subchronic. The results of chronic and acute toxicological studies help in the evaluation of any possible hazardous effect of a new drug or a drug which is in use with little or no documentation of its systemic toxicity.

## 6. Toxicity of medicinal plants

Generally, medicinal plants contain bioactive compounds which demonstrate both intra- and inter-species variation in type and content. Plants by virtue of their chemical constituents are potentially toxic; thus, some plants used in traditional medicine are intrinsically toxic. Some plants well known in traditional medicine to be toxic or poisonous include *Atropa belladonna*, *Datura* spp., *Digitalis* spp. [17].

Many plants used in traditional medicine or used as food have demonstrated some toxicity (mutagenic and carcinogenic) effects [18]. The issue of the possible toxic, genotoxic and/or mutagenic effects of plants used in traditional medicine has been highlighted in the review by Fennell et al. [19]. However, some of the toxic plants are useful to man as medicines and also as poisons for hunting and for use as pesticides, for example, Datura (tropane alkaloids), Digitalis (cardiac glycosides) and Pyrethrum (pyrethrin insecticides). Well-known medicinal plants have demonstrated toxicity in laboratory studies and field observations. For example, *Lantana camara* used in the management of malaria and other diseases has been reported to be hepatotoxic in several animal species which could be of concern regarding its chronic use in man [20].

Similarly, *Momordica charantia*, a known anti-diabetic and antimalarial plant but also used in Ghana as an abortifacient [21, 22], has reportedly caused deadly hypoglycemia in children [23].

## 7. Medicinal plant use in therapy

The basis for the medicinal use of the plants is the presence of mixtures of different biologically active plant constituents or phytochemicals (secondary metabolites) such as alkaloids, glycosides, terpenoids, and so on that may act individually, additively or in synergy to demonstrate an effect which may be useful or harmful to health. Some of these plants have been designated as poisonous plants because of their effects in impacting biological functions in other organisms which are harmful [24]. They are therefore damaging to either the survival or the normal function of the individual. The dose received may be due to either acute (short) or chronic (long-term) exposure. However, in TM, plants with toxic constituents are known and are avoided or used cautiously in herbal product formulations. Even if these are employed in medicinal products, they are employed below toxic levels and hence, if at all, hardly result in any fatality when administered by professional practitioners or experienced persons.

## 8. Safety of medicinal plants and herbal medicines used in traditional medicine

Generally, plants used in traditional medicines have been considered safe as a result of the long history of use in the treatment of diseases based on knowledge accumulated over several centuries. In many cultural settings, toxic fatalities have been rare due to systematic selection of medicinal plants for use. While thousands of people die each year from even supposedly 'safe' over-the-counter remedies, deaths or hospitalizations due to herbs are so rare that they are hard to find; not even the United States National Poison Control Centers have a category in their database for adverse reactions to herbs [17].

When used appropriately as dietary supplements, food supplements or medicines, traditional medicines are generally regarded as safe. However, there are instances where adverse events ascribed to herbal medicines used have been reported in both humans and animals. For example, Barbosa et al. [25] reported clinical and pathological neurological disorders in horses following a large intake of fresh *Bambusa vulgaris* leaves. Paradoxically, the aqueous decoction is a popular antimalarial medicine in Ghana [11, 21] and this has been used without any report of adverse reaction. Besides, the aqueous extract of the leaves did not cause cytotoxicity in normal human cells [11, 21]. In these situations, the dose of the constituents administered is of great importance; as stated by Paracelsus that, 'All substances are poisons; there is none, which is not a poison. The right dose differentiates a poison and a remedy' [26]. This is to say that the toxicity of any substance, including medicinal plants and even food, is largely dependent on the amount or dose used. A non-toxic substance can be toxic at a high dose, and a very toxic substance can be considered safe if the dose is low [27]. Over-dosage in the course of treatment is bound to pose safety problems. The dose-toxicity relationship was illustrated by the toxicity of *Bupleuri chinense* in which the toxic dose was about 21 times than the common clinical dose of 9 g/60 kg [28].

Apart from an overdose, adverse events may also arise from the misidentification of medicinal plants, errors in the use of herbal medicines both by health-care providers and by consumers, and misuse and use over long periods even at tolerable dose [8, 29].

Interactions between herbs (herbal medicines) and drugs (allopathic medicines) may increase or decrease the pharmacological or toxicological effects of either component. Thus, synergistic therapeutic effects may complicate the administration of medications for chronic diseases, for example, herbs traditionally used to treat diabetes could theoretically lead to hypoglycemia if taken concomitantly with conventional antihyperglycaemic drugs [30].

In the formal herbal industry, the toxicity problems of medicinal plants could be attributable to insufficient quality assurance and non-compliance with the standards of good manufacturing practice [8, 31], and also inadequate access to the information required for the effective use of herbal medicines and inappropriate approaches to their use. Furthermore, the problem could be complicated by adulteration of herbal remedies by the addition of synthetic drugs and other potentially toxic compounds such as other botanicals, pathogenic microorganisms, toxins, pesticides and fumigants agrochemical residues or heavy metals [8, 29, 32]. The majority of adverse events related to the use of herbal products are attributable to weak quality control systems leading either to poor product quality [8]. According to WHO [8], poor regulatory measures and largely uncontrolled distribution channels could partly account for such events. These give rise to poor quality products arising from such situations as adulteration of herbal products with other undeclared medicines and potent pharmaceutical substances, such as corticosteroids and non-steroidal anti-inflammatory agents [8].

Usually, it is difficult to identify genuine adverse reactions to herbal medicines and herbal products until the cause of such events has been established. When appropriately employed, herbal medicines are relatively safe. Long historical including experience passed on from generation to generation has demonstrated their safety and efficacy [33].

It is worth noting that toxicity results of many medicinal plants are very often misinterpreted and wrong conclusions drawn with regard to traditional practices. Many toxicity studies were conducted on medicinal plants extracted in organic solvents such as methanol, dichloromethane, and so on other than aqueous extracts as used in traditional medicine practice. This was the case as reported in the degree of hepatotoxicity damage caused by the alcohol extracted *B. chinense* which proved more serious than that caused by the water extract [28].

## 9. Challenges of contemporary herbal medicine practice in Africa

Traditional medicines are increasingly being used outside the confines of traditional cultures and far beyond geographical areas without proper knowledge of their use and the underlying principles [8]. They are therefore practiced in ways that deviate from the traditional norm of practice within the specific traditional setting. Such deviations include the method of extraction—where highly efficient and sophisticated technological tools are frequently used for extracting medicinal plants and then reformulating the extract into a final product. Such an approach is entirely different from the hitherto traditional approaches of macerating

the plant materials either dried or fresh often in boiling water to produce decoctions, which are then administered. This traditional approach therefore tends to make the herbal medicine safe since potentially toxic compounds are not extracted due to the inherent inefficiency in the aqueous extraction method (preparation of the decoction). Also, doses employed in contemporary practice often tend to be different from the traditional doses, which were systematically established over several years of practice and proven to be safe. Besides, herbal medicines are used for non-traditional indications in recent years. A typical example is the use of herbal medicines for relieving constipation but abused as an abortifacient by the youth due to its induced contractive effect on smooth muscles such as the endometrial muscles. The concomitant use of traditional medicines with other types of medicines is quite outside the traditional context and has become a matter of particular safety concern [8].

Another challenge posed to the practice is the lack of appropriate foundational knowledge in traditional medicine practice and the herbal medicines used to treat diseases. This is a common occurrence among many contemporary practitioners, especially those in urban and cosmopolitan areas. The work of such practitioners is based on information gathered from indirect sources such as the Internet or from reading books and therefore lacking in specific knowledge. These 'neo-herbalists' most often lack the expertise and basic principles necessary for the use of herbal medicines. Their practice may therefore not be entirely safe and can put patrons at risk of adverse reactions.

Besides, documented knowledge about medicinal plants and their uses within cultural settings rarely contains information on potential toxicity of the plants. This is because many ethnopharmacologists tend to focus more on the therapeutic property of the plants and hence do not inventory their toxicological information. This failure to document and contextualize potential toxicity of plants in the perspective of local healing traditions and healing practitioners' methods and approaches to treatment does not promote the safe use of medicinal plants outside the boundaries of the cultures where the medicinal plants are used.

## 10. Cytotoxicity of African medicinal plants

Cytotoxicity refers to the ability of a substance to interfere with cell attachment, alter its growth, proliferation and or cause death [34]. Accurate determination of cytotoxicity is necessary to identify compounds or effective parts that might pose health risks to humans. Surprisingly, most cytotoxic assays are geared toward screening only bioactive compounds that can kill rapidly dividing cancer cells. Cytotoxic substances may destroy living cells via either necrosis/lysis (i.e. accidental cell death) or apoptosis (i.e. programmed cell death) [35]. In cancer drug discovery, for example, potential cytotoxic agents induce apoptosis instead of necrosis with very low or no toxicity toward normal cells. Only few case studies have investigated normal cells to determine the cytotoxicity of especially African medicinal plants.

Toxicity studies on most medicinal plants using animal models have provided results that strengthen their use among humans; however, many such plants could be associated with some cytotoxicity (**Table 1**). As a consequence, researchers have supported the use of human cell lines for *in vitro* cytotoxicity assays in predicting human acute toxicity as alternatives

| Species | Normal cell type | Popular medicinal use | Plant part | References |
|---|---|---|---|---|
| Low cytotoxicity (>50 μg/ml) | | | | |
| *Afrostyrax lepidophyllus* | MRC-5 cells | Anthelmintic, vomiting, urinary infections | Stem bark | [41] |
| *Drypetes gossweileri* | MRC-5 cells | Anthelmintic, purgative, tonic, bronchitis, cough, pains, relieve urethral discharge, diarrhea | Stem bark | [41] |
| *Napoleona vogelii* | MRC-5 cells | Dermatosis, sexual asthenia, stomach aches, diarrhea | Stem bark | [41] |
| *Tectona grandis* | HUVECs | Bronchitis, hyperacidity, dysentery, verminosis, diabetes, leprosy, inflammation, skin diseases, pruritus, stomatitis, ulcers, hemorrhages, constipation, piles, leucoderma, headache, biliousness, anuria, urethral discharges, body swellings, menstrual disorders | Leaf | [11] |
| Moderate cytotoxicity (30–50 μg/ml) | | | | |
| *Cryptolepis sanguinolenta* | V79 cells | Fever, hepatitis, malaria, hypertension, urinary and upper respiratory tract infections, colic, stomach complaints, amoebic dysentery, diarrhea, wounds, measles, hernia, snakebites, rheumatism, insomnia, antiplasmodial activity, anticancer, antifungal, antibacterial, hypotensive, antipyretic, anti-inflammation, antihyperglycemia | Root | [42] |
| *Isolona hexaloba* (Rb) | MRC-5 cells | Pains, sexual weakness, headache, intestinal cramps, malaria, rheumatism | Root back | [41] |
| *Mammea africana* (Sb) | MRC-5 cells | Wounds, filariasis, mycosis, skin diseases | Stem back | [41] |
| *Phyllanthus fraternus* | HUVECs | Malaria, chronic pyrexia, chills, intermittent fever, painful joints, diarrhea, ulcer, dysmenorrhea and edema | Whole plant | [11] |
| *Psidium guajava* | MRC-5 cells | Antispasmodic, astringent, febrifuge, vulnerary, astringent, dysentery, diarrhea, constipation, diabetes, hepatitis, gonorrhea, diarrhea. | Leaf | [41] |
| High cytotoxicity (10–30 μg/ml) | | | | |
| *Terminalia ivorensis* | HUVECs | Wounds, hemorrhoids, infections, gonorrhea, kidney disease, aphrodisiac | Leaf | [11] |
| *Tetrapleura tetraptera* | MRC-5 cells | Enema, malaria, fungal infections, arthritis, filariasis, gastritis, epilepsy | Fruit | [41] |
| *Harungana madagascariensis* | MRC-5 cells | Anemia, venereal diseases, nephrosis, gastrointestinal disorders, malaria. | Stem bark | [41] |
| Very high cytotoxicity (<5 μg/ml) | | | | |
| *Enantia chlorantha* | MRC-5 cells | Intestinal worms, spasms malaria, sexual asthenia. | stem bark | [41] |
| *Piptadeniastrum africanum* | MRC-5 cells | Sexual asthenia, Constipation, intestinal cramps, pain. | stem bark | [41] |

| Species | Normal cell type | Popular medicinal use | Plant part | References |
|---|---|---|---|---|
| *Quassia africana* | MRC-5 cells | Malaria, blenorragia, hypertension, scabies, gastrointestinal affections, hernia, febrifuge, anti-rheumatic, anthelmintic, antalgic, tonic, stomach pains, gastric hemorrhoids, diarrhea, antiwounds | root bark | [41] |

**Table 1.** Cytotoxic activities of aqueous extracts of African medicinal plants.

to acute lethality studies in rodents [36]. The selectivity exhibited by cytotoxic plants also underscores the need to distinguish highly active but toxic extracts from those that are selectively active against certain pathogens, diseased conditions and even cancerous cells. This provides good leads for continuous research on promising extracts, the sources of interesting biologically active and therapeutically useful compounds with excellent activity and low toxicity [37]. Toxicity testing at the cellular level is therefore very useful and recommended for all bioactive medicinal plants. Clearly, information on cytotoxicity of plants commonly used in traditional medicine in Africa is essential for assessing the quality, efficacy and safety of their preparations. Such knowledge is also critical in developing new therapeutic products to ensure the safety of end users of herbal medicine.

In spite of the assumed safety of African medicinal plants, studies have shown that many plants used as food or traditional medicines are also potentially cytotoxic, mutagenic and carcinogenic [38–40]. A comprehensive survey by [37], for instance, recorded 400 plants of African origin with cytotoxic effects. These plant species, according to the study, are used to treat diseases of considerable economic burden to the African continent, of which malaria, leishmaniasis and sleeping sickness received much attention. The study, however, identified approximately 14 or 56% of the listed plant species as having significant cytotoxic activities ($IC_{50}$ < 30 μg/ml) against some normal cells such as human normal lung fibroblast (MRC-5), human kidney epithelial and human monocytes. While the list compiled by McGaw et al. [37] comprised many species with high efficacy against cancerous cells or pathogens, it indicated that at least 14% of these African medicinal plants may be harmful to humans.

Although the above observation calls for great care in plant use and close monitoring of their potential side effects, there are also clear reasons why cytotoxicity results could not always be wholly extrapolated into safety prediction in TM: except when organotypic cultures are used [37].

## 11. Drawbacks of using cytotoxicity to predict safety of herbal medicines in TM

There are some shortcomings to extrapolating cytotoxicity studies to the safety of herbal medicine used in traditional medicine. Among this is the fact that tissue responses due to *in vivo* toxicity cannot be addressed by toxic responses in cells [37]. According to McGraw et al. [37], a critical factor in toxicology is metabolism *in vivo*, as some substances lacking toxicity initially may produce toxic metabolites after being exposed to liver enzymes, while other

substances that are toxic in vitro may become detoxified. Other factors such as the capacity of the substance to penetrate the tissue, and clearance and excretion of the product cannot be accounted for using the cellular model. The time of exposure and the rate of change for these extracts are not the same in both *in vitro* and *in vivo* studies. Notwithstanding these limitations of cytotoxicity assay, it still needs to be an integral part of evaluating the safety of medicinal plants because they provide direct information at the cellular level which may be important in assessing the true toxicity of such plants.

Other limitations in cytotoxicity studies with regard to safety prediction for herbal medicines is the use of organic solvent such as methanol, dichloromethane, petroleum ether, ethyl acetate, and so on extracts as against water decoctions/extracts. In situations like this, it is not reasonable to compare the cytotoxicity results of the organic solvent extract with what pertains in TM. Such studies are common because the focus of most cytotoxicity studies has not been the safety assessment of the plants as used in TM but to determine the fractions which contain the potentially safe and efficacious compounds. In some cases, while efficacy study was conducted for both organic solvent and aqueous extracts, cytotoxicity was determined for only the organic solvents. This makes it difficult to relate the toxicity of the plant to safety in traditional use. In most cases, the organic extracts tend to be more efficacious than the aqueous extracts. This could imply that the organic extracts are more cytotoxic than the aqueous extracts since, generally, they (organic extracts) tend to extract more active compounds, which are both efficacious and cytotoxic.

## 12. Some herbal medicine products clinically evaluated for safety

There have been few reports of the clinical safety of herbal product used in TM. A coded herbal medicine made of *Saraca indica,* Foeniculum vulgare, Juniperus communis*, Mentha piperita* and Zingiber officinale used to treat dysmenorrhea was found to be safe from such toxic effects as hepatotoxicity, nephrotoxicity and other side effects such as menorrhagia, gastro-intestinal disturbance and palpitation in a random-controlled clinical trial [43]. Also an unnamed herbal product made of Capparis spinosa root, Cichorium intybus seed, whole plant of Solanum nigrum, *Terminalia arjuna* bark, Cassia occidentalis seed, aerial part of *Achillea millefolium* and whole plant of Tamarix gallica and used for the management of liver disorders evaluated clinically was well tolerated and did not produce any adverse event in participants [44]. Tetteh et al. [12] reported that a Ghanaian polyherbal medicine, Adutwumwaa malamix, used in the treatment of malaria did not show any hepatotoxic or hematotoxic effects nor any adverse complaint in the populations studied for its clinical effectiveness and safety. Turkson et al. also reported the safety of another Ghanaian herbal medicine for the treatment of malaria and indicated that kidney and liver function tests and full blood count were within normal range at the end of the study, an indication that the product is clinically safe [45]. The tea bag formulation of the root powder of C. sanguinolenta has effectively treated acute uncomplicated malaria on relatively short treatment regimens and did not show any toxicity in man [46]. This was against the fact that the aqueous extract of the root is genotoxic in the Chinese hamster lung fibroblast (V79) cell line [42, 47] and the ethanolic extract of the stem increased platelet counts in albino rats [48].

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## 13. Toxicity studies on some African medicinal plants

### 13.1. *Cryptolepis sanguinolenta* (Lindl.) Schltr

*C. sanguinolenta* (Apocynaceae) is a West African climbing shrub. The aqueous extract of the root has been used for centuries in African traditional medicine for the treatment of diseases including malaria, bacterial infections, hepatitis and rheumatism. It is also used as a spasmolytic and tonic [49]. In Ghana, several cryptolepis-based products are prescribed in herbal medicine clinics, sold in pharmacies, licensed chemical and herbal medicine shops for the treatment of malaria [21].

#### *13.1.1. Animal and cell toxicity*

Acute and sub-acute oral toxicity evaluation of the aqueous extract of the root suggested general safety at oral dosages below 500 mg/kg in Sprague Dawley rats. The extract did not exhibit either physiological or behavioral abnormality [50]. However, the ethanolic extract of the stem demonstrated localized systemic acute and sub-chronic toxicity by selectively stimulating the bone marrow leading to an increase in platelet counts in albino rats [48]. On the other hand, the aqueous extract of the root demonstrated genotoxicity against the Chinese hamster lung fibroblast (V79) cell line inducing mutagenicity at high concentrations and causing DNA damage [42, 47]. The ethanolic extract of the stem thus poses hematological challenges to white blood cells and platelets and showed localized systemic toxicity by selectively stimulating the bone marrow.

### 13.2. *Artemisia afra* (Jacq. Ex. Willd), 'African wormwood'

*A. afra* has been used for coughs, colic, fever, loss of appetite, earache, headache, malaria and intestinal worms [51]. Several studies have been conducted to substantiate the traditional use of this herb; it is also being investigated in diseases like diabetes, cancer and respiratory diseases among others [51].

In acute toxicity studies of aqueous extract of *A. afra* in mice administered doses (i.p., 1.5–5.5 g/kg) caused a regular dose-dependent increase in the death rate and also of general adverse behavior, but with single doses (2–24 g/kg) administered orally, the previous observed increases in the incidence of death rate and adverse general behavior that did not show were dose-independent. The route of administration, acute intraperitoneal and oral doses, showed $LD_{50}$ of 2.45 and 8.96 g/kg, respectively [51].

#### *13.2.1. Animal toxicity*

In the chronic studies, rats administered *A. afra* aqueous extract (0.1 or 1 g/kg/day) survived the 3 months of daily dosing with $LD_{50}$ greater than 1 g/kg. No significant changes were observed in the general behavior, hematological and biochemical parameters except for a transient decrease in aspartate aminotransaminase (AST) activity. No significant changes were observed in the organ weights and histopathological results showed no morphological alterations. High doses of the extract were also shown to be hepatoprotective. The aqueous extract of *A. afra* has been shown to be nontoxic in acute use and low chronic toxicity potential in rodent models [51].

### 13.3. *C. occidentalis* L

*C. occidentalis* is an annual shrub found in many African and Asian countries. Its leaves and roots are used in some traditional herbal medicines, but its pods or beans are avoided or used sparingly [52]. In Ghana, however, the roasted seeds are used as a beverage in the treatment of hypertension [53]. Many popular herbal tonics and medicines for liver disorders contain the leaves or roots of the plant. *C. occidentalis* has also been used in the treatment of scabies, snake and scorpion bites, diabetes, edema, fever, inflammation, rheumatism and ringworm. It is widely used for the treatment of bacterial and fungal infections and to boost the immune system.

#### *13.3.1. Animal toxicity*

The fresh or dried/roasted seeds have demonstrated toxicity in several animal studies [54]. Toxicity in animals is usually seen on the kidney, liver, skeletal muscle and the heart. Grazing animals such as cattle, sheep, horses and goats have shown toxicity upon the ingestion of large amount of the seed pods, the most poisonous even though all parts of the plants have shown some level of toxicity [55, 56].

Although the toxicity of the plant has been demonstrated in different animal species, the toxicity of the pod and bean is dose-dependent: low doses result in mild liver damage and myodegeneration while higher doses cause fatal hepatic degeneration followed by myodegeneration [56]. As the amount of *Cassia* in the animal's diet increases, muscle degeneration becomes a predominant characteristic of the poisoning and cause of the clinical signs. Roasting the seeds from the pod has, however, been shown to reduce the toxicity. Studies in rats [57] and chicken [58] fed a ration with *C. occidentalis* seeds at different concentrations showed histopathological and biochemical changes in muscles, liver and central nervous system. Barbosa-Ferreira et al. [57] in a study involved Wistar rats in four groups of 10 animals each, three of them fed rations containing 1, 2 and 4%, respectively, of *C. occidentalis* seeds, and the control fed normal commercial ration for a period of 2 weeks; rats in the experimental groups showed lethargy, weakness, among other adverse reactions. Histopathological study showed fiber degenerations in the skeletal and cardiac muscles. In the liver parenchyma, vacuolar degeneration was observed and, in the kidney, mild necrosis in the proximal convoluted tubules. All the adverse effects occurred in a dose-dependent manner [57].

Haraguchi et al. [58] studied the chronic effect of varying concentrations of *C. occidentalis* seeds in broiler chicks. All birds were killed on day 49 of age. Low doses of seeds showed no significant variation in biochemical parameters compared to the control group. Degenerative changes in striated skeletal muscles particularly pectoral as well as the liver and myocardium were observed in chicks treated with 0.3 and 0.5% of *Cassia* beans.

#### *13.3.2. Human toxicity*

Studies have shown that the ingestion of *C. occidentalis* can cause severe purging possibly due to the anthracene glycoside content [59]. Whereas this may produce great discomfort and pain in adults, in a child, this can be fatal; thus, while few pods might not have any ill effect

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in an adult or an older child when eaten, it could cause death in a young child [60]. Other *Cassia* species products such as senna extract (*C. acutifolia*) consumed as health drink resulted in severe hepatotoxicity in an adult [61]. *C. senna* leaves and pods have been used in orthodox medicine and still form part of traditional pharmacopeia [53].

The clinical spectrum of *C. occidentalis* poisoning in children resembles the toxicity observed in animals. Most cases in children occur when they eat the beans. As with animals, the clinical toxic features depend upon the amount of beans eaten. While the consumption of two to three pods by a young child may not have any deleterious impact, a large quantity can lead to serious morbidity and even death [62, 63].

Since some children eat very few beans and remain asymptomatic, people tend to consider the beans as non-toxic. With a larger 'dose', such as the beans in six to seven pods, they develop a non-fatal illness with vomiting, diarrhea, malaise, giddiness, drowsiness, change in voice and general weakness among other effects. However, recovery occurs after about 3–4 days of illness. The fatal hepatomyoencephalopathy syndrome may occur with relatively larger amount of beans—such as the cupped hand of a child [63].

### 13.4. *Calotropis procera* (Aiton)

The plant is widely distributed in Asia, tropical and subtropical Africa [64]. In ancient Egypt, it was recommended for the treatment of nodular leprosy [64]. In Indian traditional medicine, the decoction is used for the treatment of asthma, dysentery, rheumatism, fever, painful muscular spasm and as a purgative and expectorant [65], and as a proteolytic enzyme for the coagulation of cow milk in Ghana [66]. The extract from the plant has been reported to possess antibacterial, nematocidal and larvicidal [67] and anticancer [68] properties. The flower of the plant has been shown to possess potent antimicrobial and anti-inflammatory activities [69].

#### *13.4.1. Animal toxicity*

*C. procera* has been shown to adversely affect early and late pregnancy in rats [70]. Acute toxicity studies in mice, however, showed no significant change in the hematological parameters. Behavioral changes, symptoms of toxicity and mortality were absent during the 24-h duration of the experiment. In the 3-month chronic toxicity study with 100 mg/kg, body weight per day, a 50% mortality of the animals was recorded. No significant changes in the hematological parameters were observed. This study suggested a safe use of the plant in single high dose but a serious health hazard may ensue with prolong use.

### 13.5. *Senna alata* (L.) Roxb

*S. alata* grows in several regions of Africa and in other parts of the world [71]. The leaves and stem bark of *S. alata* are widely used to treat hepatitis, skin diseases, jaundice, gastroenteritis, intestinal helminthiasis, eczema, tryphoenteritis and ringworm. The leaves of the plant have been shown to possess antibacterial activity on both Gram positive and negative bacteria, for example, *Bacillus megaterium, Streptococcus haemolyticus, Staphylococcus aureus, Salmonella typhi, Pseudomonas aeruginosa and Klebsiella pneumoniae* [71].

*13.5.1. Animal toxicity*

In acute toxicity studies, mice treated with the dose of 20 g/kg body weight showed some behavioral changes 120 min after oral administration. These changes included slow response to external stimuli, reduction of mobility and aggression, slight excitability sketching and sluggishness all of which disappeared after 24 h. On the contrary, no adverse changes were noted in mice treated with less than 12 g/kg body weight. Weight gain recorded was increased in both sexes 8 days after oral administration of *S. alata*.

In the sub-acute toxicity, the hydro-ethanolic extract of *S. alata* at doses of 500 and 1000 mg/kg given *per os* every 48 h for 26 days did not result in death of the animals. Also, there was no sign of toxicity *during* the experimental period. However, there was a progressive increase in body weight at the stated doses of 500 and 1000 mg/kg of the rats for 26 days of administration of the extract of *S. alata* which may indicate the improvement of the nutritional state of the animal. The relative weights of the control and treated animal groups showed variation from one organ to another: the hearts and livers from the control group had relative weights quite similar to those of the treated groups. Same observations were noted in the relative weights of the liver, lung and kidney [72].

The histopathological study of the liver of groups of rats showed a normal architecture but they showed slight abnormalities such as steatosis and ballooning of hepatocytes when treated orally with the extract of *S. alata* for 26 days at doses of 1000 mg/kg body weight. However, no necrosis, infiltration, edema and conjunction, which are the signs of hepatotoxicity, were found. The effect of *S. alata* seems to have a protective effect on hepatocytes and improves liver architecture, giving justification for the wide usage of the hydro-ethanolic extract of *S. alata* [72].

### 13.6. *Zanthoxylum xanthoxyloides* (lam.) Waterm

*Z. xanthoxyloides* (Lam.) is widely distributed in several African countries. It is known for varied uses in traditional medicine: the root-bark extract is used in treating elephantiasis, toothache, sexual impotence, gonorrhea, malaria, dysmenorrhea and abdominal pain [73]. Workers in West Africa have reported the anti-sickling and antimicrobial activity of the extracts of the plant [74]. In Nigeria, *Z. xanthoxyloides* is used as a chewing stick; water extracts from the plant showed activities against bacteria significant to periodontal disease [75]. It is a very popular anthelmintic among the various tribes in Uganda [76]. It has also been found that the alcoholic extracts of the root bark possess considerable antibacterial activity [77]. Its methanolic extract of the root bark has anthelmintic activity [76], anti-sickling [74] and is anti-inflammatory [78].

*13.6.1. Animal toxicity*

In a study of the acute toxicity of the methanol extract of *Z. xanthoxyloides*, mice were given 10.0 and 2.0 g/kg of extract. Animals that received 10.0 g/kg all died within 6 h of administration of the extract. However, those on 2.0 g/kg survived beyond the 24 h of observation.

No animals showed immediate behavioral changes on administration of the extract. Yet, mice on both doses showed piloerection and were restless for 24 h following extract administration. They, however, did not vomit nor was there ptosis. Those animals placed on higher doses went into convulsions and died in hyperextension. Post-mortem examination revealed no gross abnormality of the brain, the organs of the chest and abdominal cavities. On the other hand, histopathological examination showed congestion and focal necrosis in the liver and renal tubules [76].

### 13.7. *Vernonia amygdalina* del

*V. amygdalina* is a shrub which is widely found in West Africa. The leaves are very popular vegetables used for soup. The roots and the leaves are used in ethnomedicine to treat fever, hiccups, kidney problems and stomach discomfort among other uses [79]. Both aqueous and alcoholic extracts of the stem, bark, roots and leaves are used extensively as purgative, antimalarial and in the treatment of eczema [80]. The use of the plant has been validated in humans to possess potent antimalarial and antihelminthic properties [81], antitumorigenic properties [82] and antiparasitic activity. It has been found to be used for self-medication by parasitized chimpanzees [83]. It has also been shown that the leaf extract has both hypoglycemic and hypolipidemic properties in experimental animals [84].

#### *13.7.1. Animal toxicity*

Acute toxicity studies produced an $LD_{50}$ of 500 mg/kg body weight in Wistar albino rats. Biochemical parameters such as total, conjugated and unconjugated bilirubin levels showed no significant increase. The levels of both alanine aminotransferase and alkaline phosphatase in the presence of *V. amygdalina* leaf extract increased slightly in a dose-dependent manner when compared with the control but none of the observed increases was statistically significant ($P > 0.05$) when compared to the control or when compared within doses. The processed extracts of the plant were able to reverse carbon tetrachloride-induced hepatotoxicity in rats [85].

### 13.8. Herbal mixtures containing *Alstonia congensis* Engler bark and *Xylopia aethiopica* fruits (Dunal) A. Rich

In Africa and other parts of the world, herbal medications are prepared mostly from a combination of two or more plant parts which contain many active constituents with multiple physiological activities and could be used in the treatment of various health conditions [72] and possibly to reduce toxicity. The herbal formulation prepared with *A. congensis* bark and *X. aethiopica* fruits in equal proportion is a popular local herbal product taken over a long time for the treatment of diabetes.

#### *13.8.1. Animal toxicity*

In the acute and sub-acute study of the mixture in Swiss albino mice and Wistar albino rats, respectively, no changes in the behavior and in the sensory nervous system responses were

observed. Gastro-intestinal effects were not observed in either male or female mice used in the experiments. The median acute toxicity value ($LD_{50}$) of the extract was above 20.0 g/kg body weight [86]. There was no significant change observed in the protein levels of the rats treated with lower doses of the extract (50 and 100 mg/kg) compared with control, while an observed significant decrease in the protein levels of the rats treated with a high dose (500 mg/kg) may be a sign of impaired renal function. Also, there was a significant increase ($p < 0.05$) in the plasma creatinine levels of all the treated groups [86]. There was no significant increase in AST and alanine aminotransferase (ALT) in the animals treated with lower doses of the extract compared with control but a significant increase in ALT was observed in the group treated with a high dose of the extract (500 mg/kg). This implies that the extract at the doses used had no effects on the heart tissue but at a high dose could have some deleterious effects on the liver tissue. The extract did neither improve nor produced any deleterious effects on the hematological parameters [86].

### 13.9. *Aspalathus linearis* (Burm. F.) Dahlg

The popular herbal tea, rooibos, also known as the 'long-life tea' in South Africa [86], is produced from the plant *A. linearis*. It is endemic to the South Africa [87]. Rooibos tea is known to have several health benefits, including antispasmodic, antioxidant, antiaging and antieczema activities [87].

Rooibos is exported to the East and Europe [88] and is currently sold in several countries including The Netherlands, Japan, the United Kingdom, Germany and the United States of America. The tea is mainly patronized due to its health-promoting properties when compared to black tea (*Camellia sinensis*) [89]. Rooibos is used as a beverage by the Khoi-descended people of the Cape; pregnant women take it for the iron content, and to relieve nausea and heartburns associated with pregnancy. It also serves as a milk substitute for infants and as colic relief in babies. Rooibos is well known for its antioxidant activity which also relates to its hepatoprotective properties [87] and immune-modulating effect in stimulating antibody production [90].

#### *13.9.1. Animal toxicity*

The safety assessment of rooibos has been addressed by some studies [87, 89]. Although some compounds in rooibos have been shown to contain mutagenic properties [91], it is, however, very unlikely that the mutagenic effect of rooibos would be relevant to tea drinkers when considering the quantities consumed [87]. In a study in rats, chronic consumption of aqueous extracts of unfermented and fermented rooibos over a period of 10 weeks did not cause any adverse effects in the liver and kidney [87].

### 13.10. *Musanga cecropioides* R. Br. Ex Tedlie

This plant is widely found in the tropical rainforest, particularly in West Africa. In Nigeria, the boiled leaves are used by the Igbo tribe as a powerful oxytocic to induce or augment labor while others use the decoction as a remedy for hypertension [92]. Parts of the plant have been

used by traditional healers in the treatment of an array of diseases including lumbago, rheumatism, leprosy, chest infections and trypanosomiasis [92].

*13.10.1. Animal toxicity*

Acute toxicity study of *M. cecropioides* aqueous stem bark extract showed no mortality in rats, at a limit dose of 3000 mg/kg body weight given orally. This is an indication that the extract has low acute toxicity when orally administered. Administration of the aqueous extract for 28 days in a chronic study did not affect most of the biochemical parameters except for creatinine which was significantly elevated. Hematological parameters were not significantly affected during the 28-day treatment. Liver enzymes, AST and ALT, were not affected in the treatment showing that the extract is non-toxic on the hepatocytes. The study concluded that the absence of clinical signs of acute toxicities in human when the extract was orally administered as an antihypertensive may reflect the oral route of administration, low dose administration as well as short duration of exposure when used as an antihypertensive agent [93].

## 14. Conclusion

There is an increasing use of medicinal plants and herbal medicines which contribute significantly to the health of humanity worldwide, especially in developing countries. The limited scientific knowledge among the general population has led to the general assumption that herbal medicines being natural are therefore safe. However, evidence is being adduced from toxicological studies that show plant products to be potentially toxic thus affecting their safe use.

The source of potential toxicity could be traced to a number of factors: the type of constituents some of which may be intrinsically toxic such as tropane alkaloids and cardiac glycosides though they had been used in traditional medicine. Also, it is noted that the route of administration and dose, of any chemical, are important regarding safety due to chemical or pharmacological interactions; this is undergirded by the need for a regulatory regime for quality.

Serious adverse effects of therapies involving aqueous traditional medicines are rare. However, efforts to investigate toxicity, organ toxicity and cytotoxicity, have involved the use of organic solvent plant extracts and routes of administration which constitute a drawback to the conclusions drawn from such studies.

Information on the traditional formulation and use of the herbal medicines should be satisfactory to avoid possible toxicity from the medicinal plants. Manufacturers of herbal medicines should consider standardization of the products while patrons of herbal medicines need to inform their health-care providers about any herbal products they use to ensure effective and safe care. This is to avoid interaction between herbal and allopathic medicines which could yield adverse reactions.

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Chapter 6

# Application of Herbal Medicine as Proliferation and Differentiation Effectors of Human Stem Cells

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Additional information is available at the end of the chapter

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**Abstract**

One of the main streams of traditional medicine is herbal medicine; a wide range of medicinal plants and their individual parts are used for therapy. Though not scientifically validated, this traditional medicine practice is much popular in countries such as India, China and Sri Lanka and in many other countries in South, Southeast and Eastern Asia due mainly to its healing capabilities. More recently, scientists initiated the chemical analyses of these medicinal plants, obtaining invaluable results. The latest addition to such investigations is studies on effects of herbal extracts on different types of stem cells. An extensive summary of such reported studies is presented in this chapter, mainly categorizing these into proliferation stimulatory effects on stem cells and inhibitory effects on cancer stem cells (CSCs), where both properties are beneficial in cell therapy procedures. At present, standardizing the products and limited knowledge on the mechanisms of action and pathways of these have critically limited the use of herbal extracts in therapeutics. However, we believe that in the near future scientists would be focusing on herbal remedies to replace the use of synthetic stimulants and cancer drugs to overcome the disadvantages of these, such as toxicity, side effects and exorbitant costs.

**Keywords:** herbal extracts, stem cell therapy, cellular stimulants, proliferation and differentiation, cancer stem cells

## 1. Introduction

Traditional medicine is a popular treatment method for a wide range of diseases in many countries due to its claims of therapeutic activity by patients. The knowledge handed over from generation to generation since ancient ages is the foundation of traditional medicine; hence, the methods of treatment vary depending on the country and the region of origin.

In addition, a single region may use different types of traditional medicine due to different ethnic backgrounds of its citizens migrated from different regions of the world.

As the World Health Organization (WHO) defines 'Traditional medicine is the sum total of the knowledge, skills, and practices based on the theories, beliefs, and experiences indigenous to different cultures, whether explicable or not, used in the maintenance of health as well as in the prevention, diagnosis, improvement or treatment of physical and mental illness [1]'.

Herbal medicine is one of the main streams of every traditional medicine practice regardless of the different types such as Indian traditional medicine (ITM), Sri Lankan traditional medicine (SLTM), traditional Chinese medicine (TCM), Arabic traditional medicine (ATM), African traditional medicine and South American traditional medicine. According to the WHO, medicinal ingredients of herbal medicine include herbs, herbal materials, herbal preparations and finished herbal products that contain active ingredients as parts of plants or other plant materials or combinations; also, 75% of the world's population use herbs for their basic healthcare needs [2]. Archaeological proof of history in the use of herbal medicine dates back to more than 5000 years [3], along with evidence from ancient literature such as *Arkaprakasa* (pharmacology and pharmacy) and *Kumaratantra* (paediatric diseases and management) claimed to be written by the great king Ravana of Sri Lanka where different herbal preparations were introduced for treatment and management of different types of diseases [4]. An in-depth account of the historical events on the use of herbals is reviewed by Petrovska [5]. The same disease could be treated in different countries, with different types of plant-based remedies mainly depending on their indigenous plant varieties and traditional knowledge handed down to generations through thousands of years [6, 7].

Even though history strongly supports the use of herbal medicine, over the last century, traditional knowledge and its effective uses were challenged by Western medical practitioners due to lack of scientific validation of these claims and evidence [2]. However in the recent decades, perspectives on herbal medicine had been evolving into positive thoughts with the isolation of many different effective drugs from plant materials. Existing synthetic drugs are highly expensive, and most of these are required to be replaced due to their instability *in vivo* [8]. Continuous synthetic drug doses may cause side effects and toxicity [9]; hence, these disadvantages accelerated the search for alternatives derived from natural products. With the technological advances in health and basic sciences, multi screening drug facilities to investigate specific therapeutic activities was made possible. Isolated chemicals and bioactive compounds from plant materials are the main source of modern pharmaceutical drugs, which are either naturally derived or synthetic analogues of existing natural compounds [10]. Among the many different approved drugs derived from herbal material, anticancer drugs [11], antidiabetic drugs [12] and skin care products [13] have maintained topmost status in this long list. In cancer therapy, 25% of the drugs used in the last 20 years are directly derived from plant material [11], and 49% of the antidiabetic drugs approved in the last 10 years were plant derived [12]. Both in developing and developed countries, obesity is becoming a socio-economic burden rendering global populations unhealthy, leading to many non-communicable diseases [14]. There are many weight-reducing supplements prepared by herbal extracts selling in an increased rate in the local markets, even without clinical approval, due to the popularity of the products among the users. Hence, researches are in the timely search of antiobesity herbal preparations [14] as these would flourish as multimillion dollar businesses in the global market.

In order to investigate the different activities of plant-derived extracts, the use of experimental platforms is important prior to clinical trials. Human stem cells are one such experimental platform to investigate therapeutic activities of herbal extracts *in vitro.* Stem cells with the ability to self-renew and differentiate into many cell lineages have been accepted and extensively used by scientists globally as a reliable tool in their research. Of the many different sources of stem cells, bone marrow stem cells have been used widely in research due to their well-explained characteristics, but the usage paradigm is shifting towards umbilical cord- and cord blood-derived stem cells due to the advantages such as minimum ethical issues, high availability and easy isolation methods of the latter [15]. Since stem cells possess multi-lineage differentiation ability, stimulated differentiation of stem cells could be used to investigate on therapeutics applicable to different types of diseases. For example, human mesenchymal stem cells (hMSCs) could be differentiated into osteocytes, adipocytes and chondrocytes; hence, herbal extracts could be used to investigate the suppression or the stimulation of adipogenic, osteogenic and chondrogenic differentiation properties of stem cells and therefore used to investigate the therapeutic possibilities of diseases related to the above cell lineages *in vitro*. Human haematopoietic stem cells are the progenitors of cells of blood tissue; hence, those can be differentiated into different blood cell types, and herbal extracts could be used in the above manner to search for therapeutic agents for blood cell-related disorders. Induced pluripotent stem cells (iPSCs), a group of adult somatic cells which are genetically engineered to function as embryonic-like stem cells, are also widely used as disease model stem cell lines in investigations of therapeutic candidates for different disease targets [16]. iPSC-derived cardiomyocytes from patients with cardiovascular diseases and iPSC-derived neurons from patients with neurodegenerative disorders are currently used in high-throughput drug screening [17]. Undifferentiated stem cells are transplanted in order to regenerate tissue *in vivo*; hence, stimulation factors are important to increase the regeneration speed. The issues of synthetic growth factors and stimulants, i.e. possible side effects, high costs and low availability, remain unchanged; therefore, natural stimulants are preferred. Hence, research is ongoing in search of natural stimulants for stem cells [8]. Furthermore, growth factors, cytokines and vesicles secreted by hMSCs are known as the secretome of hMSCs, and these bioactive factors isolated singly or as a mixture are investigated as potential therapeutic agents, which could reduce the complexities of therapy using cell transplantations [18].

Although it is reported that over 53,000 plant species are used in herbal medicine globally [2], only a few are being tested and reported with scientific proof of their biological activities. The need for merging of traditional herbal medicine knowledge and cutting-edge scientific techniques is essential to produce novel drugs for the benefit of patients. Investigation of mechanisms of actions and pathways, stimulated by herbal extracts, is critical as this would support the scientific validation of such products prior to their market launch. Therefore, this chapter aims to elaborate such research published in the recent decade, in which herbal preparations, extracts and plant-derived bioactive compounds were utilized to produce scientific proof of anti-disease activity, proliferation stimulant activity and differentiation stimulation or suppression of stem cells and their related plausible mechanisms of action. Also, the chapter would identify research gaps related to effects of herbal extracts on stem cells for use in clinical therapy. This chapter harps on the potential of commercializing herbal-based stem cell therapy, which will also be affordable to the developing world.

## 2. Effects of herbal extracts on human stem cells

### 2.1. Stimulatory effects of herbal extracts on human stem cells

Our literature search for the use of herbal preparations to stimulate stem cell proliferation and differentiation in clinical trials resulted in no publications or records, explaining that this area of research is at its infancy harping on the vital necessity of this line of research. However, many studies have been reported on the use of animal models with end results of *in vitro* studies, cross-linking the above-mentioned research areas, suggesting that the impending phases of research would hopefully culminate in clinical trials, leading to natural products being marketed as commercial stem cell-stimulating agents.

There are several reviews published summarizing the effects of different herbal extracts and their isolated bioactive compounds on human and other mammalian stem cells isolated from different sources. Our review published in 2016 elaborates on osteogenic, anti-adipogenic, neurogenic, endothelial/vascular genesis, angiogenesis and proliferative effects of herbal extracts on human mesenchymal stem cells mostly confirmed by RNA expression studies [8]. Dried root of Korean herb *Dipsacus asper* had been used in Korean traditional medicine for the treatment of bone fracture and the crude extract, and an isolated compound from the herb hedraganin-3-O-(2-O-acetyl)-$\alpha$-L-arabinopyranoside demonstrated the osteogenic differentiation ability on bone marrow-derived hMSCs via the upregulation of bone-specific proteins and alkaline phosphatase activity [19]. Aloe emodin, present in Aloe latex, showed anti-adipogenic activity on hMSCs by reducing expression levels of mRNAs (resistin, adiponectin, aP(2), lipoprotein lipase, PPAR$\gamma$ and tumour necrosis factor-$\alpha$) involved in adipogenic pathways [20]. Treatment of adipose-derived hMSCs with dried root extract of *Angelica sinensis*, an herb used in traditional Chinese medicine, resulted in significantly higher differentiation of neural-like cells than a commonly used neural inducer, butylated hydroxyanisole [21]. The neuroprotective ability of the same extract was proven by decreased induced neurotoxicity in cultured cortical neurons, increasing the extract's value as a potential candidate in treating neurodegenerative disorders [22]. A patent was obtained for endothelial differentiation of hMSCs treated with olive leaf extract with overexpression of gene vascular endothelial growth factor, PCAM, platelet-derived growth factor receptor and vascular endothelial growth factor receptor (VEGFR)-1 [23]. An updated list of herbals and mechanism of actions on MSCs, as well as a list of phytochemicals (resveratrol, genistein, naringin, icariin) isolated from plant extracts, were presented in a similar review published in 2017 [24]. As elaborated here, all four isolated compounds had proven their ability to differentiate MSCs into osteoblasts and osteocytes, possibly through the Wnt signalling pathway, upregulating gene expression of RUNX2 and Sirt-1 genes [25–27]. Combined therapy of adipose-derived hMSCs with icariin showed significantly improved survival rates of hMSCs as well as increased expression of endothelial markers and smooth muscle markers in rat models with diabetes mellitus-induced erectile dysfunction (DMED) inhibiting oxidative stress via the regulation of PI3K/Akt-STAT3 signal pathway [28]. A previous review published in 2014 demonstrated the well-established link between herbal preparations used in Ayurveda for a wide array of disorders with their proliferation and differentiation effects which were utilized in similar capacities on stem cell differentiation and proliferation, providing scientific proof of thousands of years old Ayurvedic predictions and practices [29]. *Rasayana*, the branch of Ayurveda

which explains rejuvenation and immunomodulation, has listed the use of approximately 200 herbs [28] which could be investigated for their regeneration capacities on stem cells. *Medhya Rasayana,* an intellectual/retention rejuvenation therapy method in Ayurveda that consists of four herbal plants, could be used individually or in combination [30]. Studies on stem cells treated with *Medhya Rasayana* extracts have shown the expression of nestin on stem cells, an early neural stem cell marker [29], confirming the ability of *Medhya* herbs to treat disorders related to the neural system by increasing the differentiation ability of stem cells.

A growing concern of ameliorating radiation-induced normal tissue injury is arising as it affects the well-being of cancer patients. Stem cell therapy is used to replace these cells and tissues, and many examples are elaborated in the review of Benderitter *et al*. [31]. Authors have reviewed a number of studies related to ameliorating radiation-induced myelopathy by transplanting neural stem cells to the spinal code [32], potential applications of transplanting salivary gland stem cells in patients with radiation-induced xerostomia [31], potential benefits of transplanting stem cells and biomaterial in animal models with osteoradionecrosis [33] and transplanting autologous fat drafts including adipose-derived stem cells to treat radiation-induced late skin complications [34]. As herbal extracts had proven their differentiation aiding capabilities in *in vitro* studies, they could act as stimulants to produce increased numbers of stem cells required for patient transplantations. The following figure illustrates the different sources of human mesenchymal stem cells (hMSCs) and their differentiation capabilities with advantages and disadvantages of herbal stimulants and synthetic stimulants (**Figure 1**) [8].

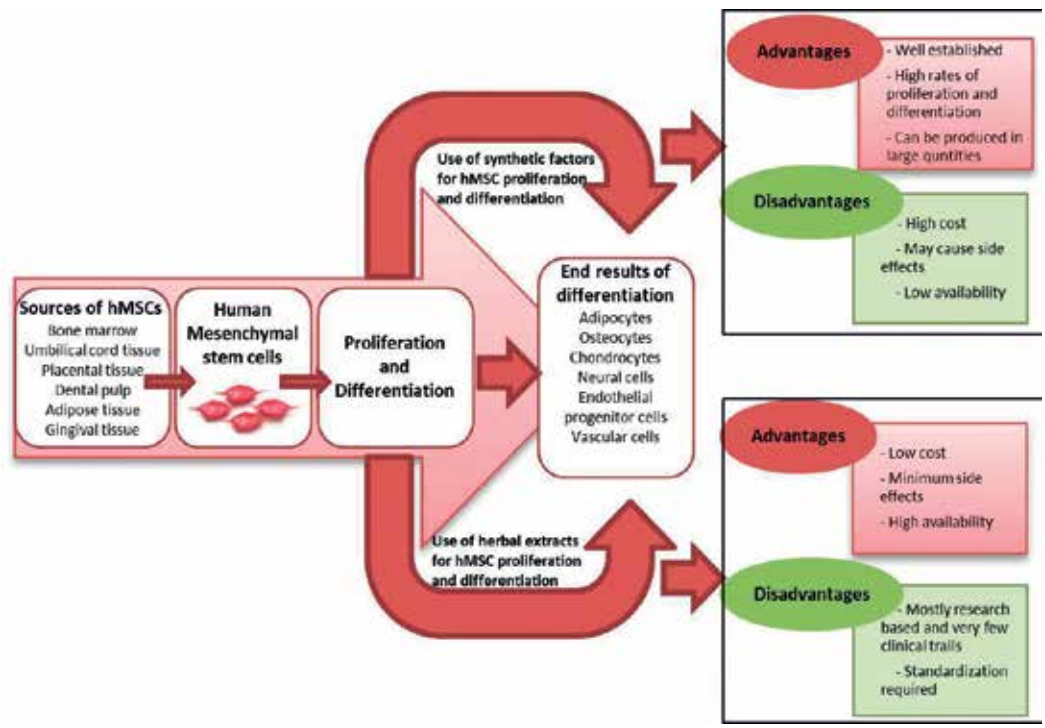


**Figure 1.** A glimpse of hMSC sources and their differentiation capabilities stimulated with herbal extracts or synthetic stimulants (Courtesy: Udalamaththa et al. [8]).

Although most of the reported research was on hMSCs, haematopoietic stem cells (HSCs) are also being investigated for their properties of proliferation and differentiation when treated with herbal extracts and their isolated compounds. Proliferation, differentiation and *in vitro* expansion of healthy hHSCs are important as many haematological malignancies disrupt the healthy hHSC populations. A review that summarizes a wide range of research publications on the use of Chinese herbal medicine (CHM) to promote recovery after HSC transplantation had elaborated the positive results of herbal extracts from plants such as Sheng Di Huang (*Rehmannia glutinosa*), Bai Zhu (*Atractylodes macrocephala*), Ren Shen (*Panax*), Dang Shen (*Codonopsis pilosula*), Mai Men Dong (*Ophiopogon japonicus*), Dang Gui (*Angelica sinensis*), Tai Zi Shen (*Pseudostellaria heterophylla*), Huang Qi (*Astragalus membranaceus*) and Ejiao (*Equus asinus*) [35]. A study on autologous and allogenic HSC transplanted in patients with chronic granulocytic leukaemia, acute non-lymphocytic leukaemia and lymphoma were treated with CHM concluded that treating with CHM reduces complications of transplantations and promotes recovery of haematopoietic functions [36]. More research on various other HSC transplantations against haematological malignancies such as severe aplastic anaemia patients [37], patients with myelodysplastic syndrome [38] and acute paediatric leukaemia [39] were cited herein [35], which had given positive results on patient survival rates, reduction of complications and increasing functional properties of haematopoietic cells. However, most of these studies were based on a low number of samples; hence, the need to perform such studies in large populations arises in order to validate and standardize the CHM procedures. *In vitro* studies and animal model studies had also been reported on HSC proliferation and differentiation to gather more scientific evidence to support small local clinical trials performed in isolation in individual countries. EMSA eritin, a polyherbal formulation had increased proliferation of HSC in irradiated BALB/c mice *in vivo* and triggered differentiation into the lymphopoiesis lineages [40]. Inducing of proliferation and attenuating of apoptosis were observed when an immune-mediated aplastic anaemia mouse model was treated with a modified Chinese herbal formula prepared with Radix astragali, Radix *Angelicae sinensis* and *Coptis chinensis Franch* [41].

Although stem cell therapy had boosted disease therapy into the next level of modern therapeutic medicine, a major limitation is their poor survival after transplantation into the host, which could be resolved by supplementing the microenvironment with vitamins and other antioxidants [29] and other preconditioning strategies such as exposure to hypoxic conditions, oxidative stress and heat shock treatments [42]. Scientists are studying natural plant extracts and their isolated compounds as alternatives to synthetic growth factors and other stimulants to precondition the microenvironment for the survival of stem cells *in vivo*, as there are many reports on the presence of a wide array of beneficial phytochemicals in plants. Pretreatment of adipose-derived hMSCs with *C. setidens* herbal extract had resulted in increased survival of hMSCs by inhibiting ROS-induced apoptosis, suggesting the suitability of the extract to prevent ROS-induced oxidative stress by regulating the oxidative stress-associated signalling pathway and suppressing the apoptosis-associated signal pathway [43]. Extract of *Origanum vulgare* had protected murine mesenchymal stem cells from oxidative stress when precon-

ditioned with high doses via significantly decreasing caspase-3 activity [44]. *Tinospora cordifolia* and *Withania somnifera*, two widely used herbs used in Ayurveda for rejuvenating and anti-ageing treatment, had shown increase in proliferation and inhibition of senescence in WJ-MSCs *in vitro* [45], suggesting that pretreatment with these herbals would aid in *in vivo* transplantation procedures.

### 2.2. Inhibitory effects of herbal extracts on cancer stem cells

Cancer stem cells (CSCs), the cells which are capable of self-renewal and produce the heterogeneous lineage of cancer cells [46], has become the most complicated issue in cancer therapy. A number of studies were reported which resulted in the reduction of cancer cells with the treatment of isolated phytochemicals such as epigallocatechin-3-gallate (EGCG), curcumin, resveratrol, lycopene, pomegranate extracts, luteolin, genistein, piperin, β-carotene and sulforaphane [45]. Specifically, sulforaphane, a phytochemical isolated from broccoli, had apoptosis-inducing effects on pancreatic CSCs [47] and could target breast CSCs effectively [48].

However, in this scenario, scientists are changing their approach in the search for natural products by trying to select herbal extracts and preparations known to be effective against cancers in traditional medicine. This approach would be advantageous for both ends of traditional medicine and modern therapeutics, as traditional medicine will have a chance of proving the remedies in a scientific platform and also the modern therapeutics would have the benefit of using time tested anticancer remedies rather than screening thousands of plant extracts for this purpose without any clues. A review on targeting CSCs using TCM remedies and their active compounds had elaborated several approaches of herbal remedies acting on CSCs. Reversion of drug resistance of CSCs, inducing cell death and inhibiting cell proliferation, inhibiting metastasis and targeting CSCs-related miRNAs are the explained methods of TCM remedies targeting CSCs [49]. Berberine liposomes, isolated from rhizome of *Coptis chinensis*, showed anticancer effects on human breast CSCs transplanted in nude mice by penetrating the cell membrane, accumulating in mitochondria of CSCs and resulting in reversion of drug resistance and apoptotic pathway inducing cell death and inhibiting cell proliferation [50]. Curcumin and epigallocatechin gallate (EGCG) had synergistically targeted breast CSCs by downregulating stemness genes and inducing differentiation of these into non-stem cells [51]. Prostate cancer metastasis had been reduced by a combination of quercetin, extracted from *Dysosma veitchii* and EGCG by reducing activity of LEF-1/TCF responsive receptor [52]. Honokiol, a lignan isolated from *Magnolia officinalis*, had inhibited renal cancer metastasis by regulating miR-141/ZEB2 signalling [53]. Triphala, a widely used formulation in Ayurveda, had shown anticancer properties on human colon cancer stem cells by p53-independent proliferation inhibition and apoptosis inducing [54]. Also, a Sri Lankan group of scientists had investigated on anticancer properties of gedunin, a major compound found in *Azadirachta indica*, which confirmed its apoptotic-inducing properties against human embryonal carcinoma cells—a cancer stem cell model [55].

### 2.3. Commercial herbal products with claims of stem cell rejuvenation

Many herbal products are commercialized with claims to be rejuvenating adult stem cells which are considered as stem cell supplements. The first stem cell enhancer was developed and patented by Dr. Sahelian of Stemtech HealthSciences, Inc. in 2005 [56] which included extracts of freshwater microalgae and marine macroalgae [57]. Stem Cell 100® is a patent pending product prepared from bioactive compounds of herbal plants *Astragalus membranaceus*, *Vaccinium*, Pine bark, *Camellia sinensis*, *Pterocarpus marsupium*, *Polygonum multiflorum*, *Schisandra*, Fo-Ti root and *Drynaria* rhizome mainly derived from TCM [58]. ProxyStem is another patent pending nutraceutical stem cell supplement with claims to be working on pro-inflammatory pathways, endothelial cell health, oxidative stress protection, mitochondrial function and artery support [59].

Another product, NutraStem Active, was awarded a patent for claims of its ability to promote adult stem cells with its four ingredients—blueberry extract, green tea extract, L-carnosine and vitamin D3 [60]. Stem-Kine, a clinically proven stem cell supplement, includes ellagic acid which protects stem cells from free radicals [61]; it is a polyphenol compound extracted from mainly a plant of the berry family [62].

## 3. Pros and cons of using herbal remedies to stimulate stem cells

Traditional herbal treatment provides a straightforward method to identify the link between plant/herbal remedies and their use in curing different diseases. Modern scientists now use the same strategy to identify herbal plants and their isolated compounds which could be used as stem cell stimulants for much needed stem cell therapeutic procedures. Studies were initiated in this line of research in developed countries as well as in the developing countries acquiring their own traditional herbal treatment knowledge. China seems to be much ahead in this hybrid system of research using Chinese traditional herbs/isolated compounds and cutting-edge screening technologies. Although there is a plethora of internationally published research by research groups from China, many clinical trials and small population studies seem to be concealed from the rest of the world as these reports are published in local journals in their native language [35]. China is not alone in this exercise. Other countries such as Iran and Pakistan too with rich traditional medicine cultures and also into stem cell research are posing the same issue, as the data they produce are not communicated to the international scientific community. This is an unfortunate situation which could be rectified to be more productive through collaborative research with the rest of the world.

In certain instances, developing countries offer their knowledge of traditional herbal medicine together with their rich local plant diversity to collaborate with developed countries to obtain cutting-edge technologies to achieve high potential results in their research. However, the strict local regulations and policies on shipping indigenous plant material or their compounds in developing countries, in order to protect their own plant species, had restricted this productive collaborative research frame work, as this process is lengthy which would lead to late initiation of laboratory investigations.

Another concern is that of the withdrawal of traditional herbal practitioners from providing information on their herbal remedies to the scientists for investigations; it is the latter who have the ability to scientifically prove that these remedies are actually therapeutically potent. Traditional practices are said to be handed down from generation to generation within families, and most of these practitioners treat patients *pro bono*, as a social service. Since these practitioners claim to have satisfactory results from providing such treatment, they have no reason to give away their herbal remedies, which had been a family secret for over hundreds of years. However, the modern graduates of traditional medicine are more into scientifically validating their treatment methods, as it is beneficial for their practice to have scientifically proven results to compete with Western medicine practitioners. Most traditional medicine practitioners vary the constituents of herbal preparations and the ratios used in their prescriptions even for the same disease depending on the patient's individual constitution, indicative of the practise of 'personalized/precision medicine'. 'Ayugenomics' irrevocably established that a genetic basis did indeed exist to the said individual constitutions [63]; differential DNA methylation signatures in the three distinct 'prakriti' phenotypes (based on distinctly descriptive physiological, psychological and anatomical features of different individuals) demonstrated the epigenetic basis of traditional human classification in Ayurveda with relevance to personalized medicine [64]. Yet, allopathic medicine strongly believes in standard preparations where only the dose is varied among individual patients. Hence, there arises the question whether modern standardized herbal preparations would be universally effective on every patient.

Nevertheless, herbal remedies that were scientifically investigated for their properties with elucidated mechanisms and pathways of action too may face further obstacles prior to their market launch. As mentioned in the review of Udalamaththa *et al*., a large-scale manufacturing process may reduce the crude properties of herbal remedies, solvents used to prepare extracts may produce adverse effects when used in therapy, complexity and variability of bioactive compounds may make clinical applications challenging [8]. As standardization of herbal products is a must prior to the market launch, similar and stringent regulations will be applied to herbal stem cell stimulants which are to be used in therapy.

Yet, despite all issues involved, pharmaceutical companies are competing for patents and commercializing herbal stimulants, supplements and many more drugs which could be used in stem cell therapy.

## 4. Conclusion

Herbal medicine has at all times been a trusted treatment method from ancient eras. The paucity of the use of herbal medicine or related treatment methods in allopathic medicine practices or other types of therapy using cutting-edge technology may pose the 'missing part of the puzzle' which scientists and clinicians have strived to solve. However, in recent years, both traditional medicine and novel technologies in synergy have resulted in beneficial outcomes advantageous to the patients. Examples presented in this chapter provide a glimpse of recent studies where herbal medicine and stem cells have been amalgamated in search of treatment against 'incurable diseases'. Although the use of medicinal plants in stem cell

research is in its infancy, with small population studies within local communities, with low numbers of related patents and many complexities in application in a clinical setting, the attraction of this area of research has never ebbed due to the promising results emerging from basic scientific research. Preliminary trials leading to the initiation of in-depth studies may well result in inexpensive, available, nontoxic drugs, stimulants and supplements useful in stem cell therapy.

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Chapter 7

# Herbal Medicine Use during Pregnancy: Benefits and Untoward Effects

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Additional information is available at the end of the chapter

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**Abstract**

The use of herbal medicine has been on an increase over time. The most commonly used herbs are ginger, cranberry, valerian, raspberry leaf, chamomile, peppermint, thyme, fenugreek, green tea, sage, anise, garlic and bitter kola. The use of herbal medicine during pregnancy is associated with educational status of women, income level of household and age of women. Herbal medicines were used during pregnancy to treat nausea and vomiting, reduce the risk of preeclampsia, shorten labour and treat common cold and urinary tract infection. Using herbal medicine occasionally causes trouble. Heartburn, pre-mature labour, miscarriage, increase in blood flow, abortion and allergic reactions are the common troubles of herbal medicine use during pregnancy. Using herbal medicine during the first trimester and the third trimester is unsafe for the foetus. Pregnant women should talk to health professionals before consuming any herbal medicines. The unfortunate consequences of using herbal medicine during pregnancy need further study for various herbs. Therefore, clinical trial research should be done to identify unfortunate consequences of herbal medicine use during pregnancy.

**Keywords:** benefits, herbal medicine, pregnancy, safety, untoward effect

## 1. Introduction

Herbal medicine has been used for disease prevention and treating ailments worldwide. It is known that between 65 and 85% of the world population used herbal medicine as their primary form of health care [1]. The prevalence of herbal medicine use during pregnancy ranges from 12 to 82.3% [2, 3]. Ginger, garlic, raspberry, cranberry, valerian, chamomile, peppermint and fenugreek are frequently used herbal medicines during pregnancy [2, 4–11]. Using herbal medicine during pregnancy has controversial issues. Even though, herbal medicine is easily available as

compared to other medicines, the safety issue during pregnancy is a concern. Using herbal medicine in first 3 months and late in third trimester is dangerous for the foetus. Before using any herbal medicine, it is better to consult the doctor and the pharmacist to ensure that the herbs are appropriate and safe to use during pregnancy [12]. In pregnancy, mothers are concerned about all medications that may affect their health, the health of the foetus, and the pregnancy outcomes. Availing evidence-based information about benefits and untoward effects of herbal medicine use during pregnancy is important for safer pregnancy and healthy foetus. The aim of this chapter is to provide the best available information on benefits and untoward effects of herbal medicine use during pregnancy. This chapter identified the prevalence of herbal medicine use during pregnancy across regions and countries. The chapter also identified the commonly used herbs and described the character of women who used herbs during pregnancy. The benefits and untoward effects of commonly used herbal medicine during pregnancy are reviewed based on scientific findings.

## 2. Herbal medicine use during pregnancy: benefits and untoward effects

Herbal medicine use during pregnancy is common across regions and countries. The prevalence of herbal medicine use during pregnancy is varied across regions and countries. Multinational study conducted in different countries showed that 28.9% of pregnant women used herbal medicine during pregnancy [2, 4]. A literature review from the Middle East revealed that up to 82.2% of the women used herbal medicine at some point during pregnancy. The study also identified that many women used herbal medicine during the first trimester [5]. An observational cohort study done in South West England found that 26.7% of the women used a complementary or alternative medicine at least once during pregnancy. The use of herbs rose from 6% in the first trimester to 12.4% in the second trimester and to 26.3% in third trimester [13]. In Australia, 36% of the women took at least one herbal medicine during pregnancy [14]. Studies done in Africa showed the prevalence of herbal medicine use during pregnancy was between 12 and 73.1% [3, 6–9, 15–19].

The most commonly consumed herbal medicines during pregnancy include; ginger [2, 4–11], cranberry [2, 4, 10–11], valerian [2, 4, 10], raspberry leaf [2, 4, 10–11, 13], chamomile [13–14], peppermint [5, 13], rosehip [13], thyme [5], fenugreek [5, 9], green tea, sage, and aniseed [5]. Eucalyptus, tenaadam (*Ruta chalepensis*), damakess (*Ocimum lamiifolium*), feto, omore are also other herbal medicines used during pregnancy [6–8]. Garlic [6–8, 15–18], palm kernel oil, bitter kola and dogonyaro (*Azadirachta indica*) are other herbs that are used during pregnancy [15–18].

Being students, having no education, having low income and having tertiary education level make women more likely to use herbal medicine during pregnancy [2, 4, 6–8, 15–18]. The other factors that make women more likely to consume herbal medicines are being primiparas [2, 4, 9], non-smoking [2, 9] and old age women [13–14].

Based on the available researches and literature reviews, the most commonly used herbal medicines during pregnancy are identified. The benefits and untoward effects of the herbs are also reviewed.

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### 2.1. Ginger (*Zingiber officinale*)

Common names of ginger is African ginger, black ginger, Cochin ginger, gingembre, ginger root, imber, and Jamaica ginger [20].

#### *2.1.1. Benefits of ginger*

Ginger is used as anti-nauseant and anti-emetic for nausea and for hyperemesis gravidarum. The recommended daily dose of ginger is up to 1g dried powder [21]. A single blind clinical trial showed ginger as an effective herbal medicine for decreasing nausea and vomiting during pregnancy. This study also suggested a daily total of 100 mg ginger in a capsule [22].

A randomized controlled clinical trial conducted on 120 women over 20 weeks of gestation with symptoms of morning sickness showed consumption of 1500 mg of dried ginger for 4 days improves nausea and vomiting. The study also revealed that newborns whose mothers consumed ginger during pregnancy had normal birth weights and normal APGAR score [23]. Consumption of ginger in amounts used in food preparation is likely to be safe. Taking 1–2 g dried ginger over the course of a day has been shown to relive symptoms of minor disorder of pregnancy [24–26]. Using higher doses of ginger is not safe for pregnant women. Thus, pregnant women should not use higher dose of ginger.

#### *2.1.2. Untoward effects of ginger*

A literature review reported that ginger is not a safe herb. It is a potential abortifacient with high doses (>1000 mg daily consumption). Higher doses of ginger can cause thinning of blood, stomach discomfort and heartburn [24–27].

### 2.2. Garlic (*Allium sativa*)

Garlic is a perennial herb cultivated in different countries. It is commonly used as a food ingredient and as a spice in different countries [28].

#### *2.2.1. Benefits of garlic*

Study conducted on antimicrobial and antifungal activity of garlic showed antibacterial and antifungal features of garlic make it nutritious to consume during pregnancy [29]. Garlic enhances a woman's immune system; this in turn helps women to have healthy pregnancy and healthy babies. Eating garlic during pregnancy is important to reduce the risk of preeclampsia and protein retention in urine [30]. A randomized controlled study was conducted where 100 primigravida were treated with either garlic tablets (800 mg/day) or placebo during the third trimester of pregnancy to determine the effect of garlic tablets supplementation on preeclampsia. With the exception of a garlic odour, the few side effects like nausea were reported because of garlic consumption during the third trimester of pregnancy. Pregnancy outcomes were comparable in both treated with garlic and the placebo group. The study did not report any incidence of major or minor malformations in newborn infants and there were no spontaneous abortions of the foetuses [31].

#### *2.2.2. Untoward effects of garlic*

Excessive use of garlic should be avoided in early pregnancy. Pregnant women with thyroid disorders should avoid its use. Pregnant women should also avoid using garlic prior to surgery including caesarean as it may interfere with blood clotting. Another untoward effect of using garlic during pregnancy is that it may aggravate heartburn [32].

### 2.3. Cranberry (*Vaccinium macrocarpon*)

There are different types of cranberries: American cranberry, Arandano Americano, Arandano Trepador, Cranberries, European cranberry, Grosse Moosbeere, kranbeere, large cranberry, Moosebeere, Mossberry [20].

#### *2.3.1. Benefits of cranberry*

Using cranberry during pregnancy is important to prevent urinary tract infection [33], stomach ulcer [34–35], periodontal diseases [36–38] and influenza [39]. A survey conducted on 400 Norwegian postpartum women reported that cranberry was one of the most commonly used herbs during pregnancy, mostly for urinary tract infection [40].

#### *2.3.2. Untoward effects of cranberry*

The untoward effects of cranberry use during pregnancy needs further investigations.

### 2.4. Valerian (*Valeriana officinalis*)

Valerian is native to Europe and Asia and has naturalized in Eastern North America. It has been extensively cultivated in Northern Europe [41].

#### *2.4.1. Benefits of valerian*

Valerian is used as a mild sedative to help patients fall asleep and relieve stress and anxiety. There is a lack of safety information on consumption of valerian during pregnancy. It is highly recommended that pregnant women talk to the doctor before taking valerian during pregnancy [24, 26, 42]. Study conducted on effect of valerian consumption during pregnancy on cortical volume and the levels of zinc and copper in brain tissue of mouse foetus showed valerian consumption in pregnancy had no significant effect on brain weight and cerebral cortex volume and copper level in foetal brain [43].

#### *2.4.2. Untoward effects of valerian*

Studies conducted on mouse foetus presented that consumption of valerian during pregnancy had significant decrease in the level of zinc in the brain [43]. This finding suggests that valerian use during pregnancy should be limited.

### 2.5. Bitter kola

Bitter kola is a plant that comes from Africa. Africans have been using bitter kola for pregnant women since ages. Nowadays, bitter kola popularity has spread worldwide [44].

#### *2.5.1. Benefits of bitter kola*

Drinking bitter kola is good for pregnancy. Bitter kola contains nutrients and vitamins good for pregnancy. For Africans, bitter kola is the best supplement for pregnant women. Health benefits of bitter kola include treating nausea and vomiting, making uterus healthier, strengthening pregnant women and normalizing blood circulation in pregnant women. Bitter kola contains very strong caffeine. One bean of bitter kola contains the same amount of caffeine as two glasses of coffee. Thus, pregnant women have to drink the recommended dose (one small cup of bitter kola in a day) [44].

#### *2.5.2. Untoward effects of bitter kola*

Using very high doses of bitter kola is not recommended. A very high dose of bitter kola is not good for the uterus of the woman [45].

### 2.6. Fenugreek (*Trigonella foenum-graecum*)

Fenugreek is an annual leguminous herb that belongs to the family fabaceae, which is found as a wild plant and cultivated in Northern India. It is a galactagogue [46].

#### *2.6.1. Benefits of fenugreek*

Consumption of fenugreek during pregnancy increases milk production in pregnant women. The exact mechanism of fenugreek consumption and increasing milk production is not well understood. However, it is believed that seeds of fenugreek contain the precursor of a hormone that increases milk production [45, 46].

#### *2.6.2. Untoward effect of fenugreek*

Large amounts of fenugreek may cause uterine contractions, miscarriage or premature labour. It could affect blood sugar levels, so pregnant women with insulin-dependent diabetes mellitus should avoid it. It can also cause heartburn [47].

### 2.7. Red raspberry leaf (*Rubus idaeus*)

Red raspberry leaf is known as garden raspberry leaf. The deciduous raspberry plant produces it [48].

#### *2.7.1. Benefits of red raspberry*

Red raspberry leaf has mineral rich nutritive and uterine tonic to promote an expedient labour with minimal bleeding. It can also be used as an astringent to diarrhoea. In a study

based on two clinical trials, there was positive association with red raspberry use and astringency in the case of diarrhoea. Daily recommended dose is 1.5–5 g [23–24]. Traditionally, red raspberry leaf has been used in late pregnancy to shorten the duration of labour and to reduce complications of pregnancy. Pregnant women should consult a doctor or a pharmacist for advice before using red raspberry leaf in pregnancy in a tea or infusion [49]. Red raspberry fruit is not believed to pose risk to the mother or to the baby during pregnancy. Some women take it as a labour aid during the last 2 months before delivery, whereas others take it throughout the pregnancy. In a randomized clinical trial, 192 women at 32 weeks of gestation received 1.2 g of raspberry leaf tablets twice daily. The study reported no adverse effects to mothers or infants. The active treatment with raspberry leaf shortened the second stage of labour and lowered the rate of forceps delivery. A retrospective observational study conducted on 108 pregnant women showed that 57 women who ingested raspberry leaves were less likely to have an artificial rupture of membranes or to require caesarean section, forceps or vacuum birth than 51 controls [50–51]. Women have used red raspberry leaves for painful periods in pregnancy, morning sickness, to prevent miscarriage, easing labour and delivery and enriching breast milk [52].

#### *2.7.2. Untoward effects of red raspberry*

The untoward effect of red raspberry needs further investigations.

### 2.8. Chamomile (*Matricaria recutita*)

There are two types of chamomile: German and Roman. The common German variety comes from the flower *Matricaria recutita*, and the less common Roman variety comes from the flower *Chamaemelum nobile*. German chamomile is used in teas and other supplements such as capsule and oils [53].

#### *2.8.1. Benefits of chamomile*

Chamomile is used as a mild sedative and to aid digestion [32]. It has been used for the treatment of morning sickness [54]. German chamomile is the type used most often as a medicinal herb, extracts of which have been reported to increase the tone of uterus muscle [53]. Chamomile does not contain caffeine, which makes it safer for pregnant women, but there is some controversy over the safety of certain herbs not fully described by the Food and Drug Administration. There is insufficient information to say for sure whether chamomile can cause harm during pregnancy. As with many other herbs, the full effect of chamomile, especially in association with other medicines and herbs, has not been studied conclusively [55].

#### *2.8.2. Untoward effect of chamomile*

Chamomile may cause increased blood flow, contractions, miscarriage or premature labour. It can also cause allergic reactions [47].

### 2.9. Clary sage (*Salvia officinale*)

Clary sage is a plant native to Italy, Syria and Southern France and grows in dry soil. The essential oil is distilled from the flowers and flowering tips [56].

#### *2.9.1. Benefits of clary sage*

It is recommended that clary sage only be used from 37 weeks onwards. It may be used to induce labour if the body is ready to go into labour. It may stimulate the release of oxytocin in pregnant women [56]. Using clary sage is highly recommended during labour to help contractions to intensify and become more effective in pulling up the horizontal uterine muscles to open the cervix and move the baby down into the pelvis and into the birth canal. The simplest and most common way to use clary sage during labour is to put a few drops on to dry cloth; the mother will inhale the aroma when she needs it to help herself become more calm and relaxed during contractions [56–57].

#### *2.9.2. Untoward effects of clary sage*

Large doses best avoided for concern of potential miscarriage and abortifacient effect [47].

### 2.10. Anise (*Pimpinella anisum*)

Anise is known as aniseed. There are two types of anise: anise (*Pimpinella anisum*) and star anise (*Illicium verum*) Chinese star anise [58].

#### *2.10.1. Benefits of anise*

Orally, anise is used for dyspepsia, flatulence, rhinorrhoea (runny nose) and as an expectorant, diuretic, and appetite stimulant. Anise is also used to increase lactation and facilitate birth. Topically, anise is used for lice, scabies and psoriasis treatment. Using anise during pregnancy is likely safe when used orally in amounts commonly found in food. There is insufficient reliable information available about safety of anise when taken orally in medicinal amounts during pregnancy [59]. Anise used in small amounts in herbal tea is safer in pregnancy because exposure is relatively low [58].

#### *2.10.2. Untoward effects of anise*

When used topically, anise in combination with other herbs can cause localized pruritis. In allergic patients, inhaled or ingested anise can cause rhino conjunctivitis, occupational asthma and anaphylaxis [59]. Essential oil and concentrated anise should be avoided in pregnancy for the concern that they might trigger early labour [58].

### 2.11. Green tea (*Camellia sinensis*)

Green tea is mostly consumed in Middle East.

### *2.11.1. Benefits of green tea*

Green tea is important to regulate blood sugar, cholesterol and blood pressure levels. It also speeds up the body's metabolic rate and provides a natural source of energy. It can help stabilize a pregnant mother's mood [60]. However, drinking too high a dose of green tea is not recommended. The recommended dose of caffeine per day is 300 mg [61].

### *2.11.2. Untoward effect of green tea*

Pregnant women who consumed green tea are at risk of spontaneous abortion as shown by the following two studies. A case control study conducted on 3149 pregnant women showed that serum paraxanthine (caffeine metabolite) was higher in women who had spontaneous abortions than in controls [62]. Another case control study conducted on 1498 pregnant women also showed that consumption of 375 mg or more caffeine per day during pregnancy might increase the risk of spontaneous abortion [63]. Pregnant women who consumed high caffeine during pregnancy have a chance to deliver low birth weight infants. This is supported by the following studies. A prospective study conducted on 2291 pregnant women reported that women who consumed more than 600 mg of caffeine per day are at greater risk for having low birth weight infants [64]. A prospective study conducted on 63 women also reported that pregnant women who consumed more than 300 mg/day of caffeine had low birth weight newborns [65]. Studies showed consumption of high doses of caffeine had increased risk of stillbirth. A prospective follow-up conducted on 18,478 singleton pregnancies showed that the consumption of eight or more cups of coffee in a day doubled the risk of having stillbirth compared with women who did not consume coffee [66].

Even though the above studies are conducted on coffee consumption, consumption of high doses of green tea can have adverse effects on mothers and their infants. Caffeine found in coffee and green tea is not very different. Consumption of too much caffeine (more than 300 mg per day or more than eight cups per day) can cause miscarriage as seen by the above research findings. Consumption of too much caffeine can also cause trouble of sleeping.

## 2.12. Thyme (*Thymus vulgaris*)

It is known as common thyme, French thyme, garden thyme, oil thyme, red thyme oil, rubbed thyme, Spanish thyme, thyme aetheroleum, thyme essential oil, thyme oil, thyme herbal, van ajwain, vanya yavani, white thyme oil [67].

### *2.12.1. Benefits of thyme*

A literature review conducted on herbal medicine use during pregnancy showed thyme is used to manage bloating and stomach aches. It is also used for treatment of common cold and urinary tract infection [2]. When used in amounts commonly found in food, thyme has a generally recognized safe status in the US. There is insufficient reliable information available about the safety of thyme when used in medicinal amounts during pregnancy [67]. Therefore, pregnant women should avoid using thyme in medicinal amount.

*2.12.2. Untoward effects of thyme*

Consumption of a large dose of thyme has an emmenagogue effect. Therefore, it is better to avoid it, especially in early pregnancy, because of concern of potential miscarriage [47].

**2.13. Coconut**

Countries within the Southeast Asian region are rich in coconut oil and other coconut by-products [67–69].

*2.13.1. Benefits of coconut*

Studies reported that coconut oil has been used to facilitate labour, delivery and prevent congenital malformation [70–72]. Coconut oil during pregnancy can be used as part of a healthy nutrient-dense whole food diet. Coconut oil supplies rich amounts of saturated fat with high amounts of lauric acid. The saturated fat content helps to build up adequate fat stores in pregnancy and in preparation for breast-feeding [73].

*2.13.2. Untoward effects of coconut*

The study conducted to investigate the effect of virgin coconut oil on mice showed that virgin coconut oil could affect infant growth and appearance via maternal intake. The study also suggests the use of virgin coconut oil as herbal medicine to be treated with caution [74].

**2.14. Echinacea (Echinacea spp)**

Echinacea species came from North America and were traditionally used by the Indians for a variety of diseases, including mouth sores, colds, injuries, tooth pain and insect bites [75].

*2.14.1. Benefits of Echinacea*

One clinical trial study shows positive association of echinacea consumption in reducing duration and recurrence of cold and urinary tract infection [76]. The recommended dose is 5–20 ml tincture.

*2.14.2. Untoward effects of Echinacea*

The untoward effect of using echinacea during pregnancy needs further study.

**2.15. Peppermint (*Mentha piperita*)**

Peppermint is one of the world's oldest medicinal herbs and is used in both Eastern and Western traditions. Ancient Greek, Roman and Egyptian cultures used the herbs in cooking and medicine. Peppermint is currently one of the most economically important aromatic and medicinal crops produced in the US [77].

*2.15.1. Benefits of peppermint*

Several clinical trials have shown that peppermint essential oil, a super concentrated form of herbs, can help relive irritable bowel syndrome [78]. Natural medicine's comprehensive database showed there are no reports in the scientific literature of peppermint being either safe or contra-indicated during pregnancy. Peppermint leaves and oil are believed to be safe during pregnancy when consumed in food amounts [79]. Study conducted on use of antiemetic herbs in pregnancy indicated that peppermint is used for treatment of pregnancy-induced nausea [80].

*2.15.2. Untoward effects of peppermint*

The untoward effect of peppermint consumption during pregnancy needs further investigation.

## 3. Conclusion

The use of herbal medicine during pregnancy is a common phenomenon. Different studies have shown that many women used one or more herbal medicines during pregnancy. Some women used herbal medicine in first trimester while others used it in second or third trimester or throughout pregnancy.

The common benefits of using herbal medicine during pregnancy include managing vomiting and nausea, reducing the risk of preeclampsia, managing urinary tract infection and common cold, and shortening of duration of labour.

The common untoward effects of using herbal medicine in pregnancy are heartburn, premature labour, miscarriage, increase blood flow, abortion and allergic reactions.

Different studies revealed that using herbal medicine during the first 12 weeks and the last 12 weeks of gestation is dangerous for the foetus. Pregnant women should consult doctors or pharmacists before using any herbal medicines.

The untoward effects of using herbal medicine during pregnancy need further investigation for many herbs. Thus, researches, especially a clinical trial study should be conducted to identify untoward effect of herbal medicine use during pregnancy.

## Terminologies

| | |
|---|---|
| Antiemetic | a drug that prevents or alleviates nausea and vomiting. |
| Astringent | a substance that contracts the tissues or canals of the body, thereby diminishing discharges, as of mucus or blood. |
| Emmenagogue | increases blood flow. |
| Abortifacient | cause a miscarriage "from Latin: abortus "miscarriage" and faciens 'making' is a substance that induce abortion. |

| | |
|---|---|
| Miscarriage | a term used for a pregnancy that ends on its own, within the first 20 weeks of gestation. |
| APGAR | referred to as an acronym for: appearance, pulse, grimace, activity and respiration. |
| Pruritis | itchy skin that makes one scratch. |
| Anaphylaxis | serious life threatening allergic reaction. |
| Galactagogue | milk-producing agent. |
| Tinctures | liquid extracts made from herbs that are taken orally (by mouth). |

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Chapter 8

# Plant-Derived Medicines with Potential Use in Wound Treatment

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Karin Stana Kleinschek and Uroš Maver

Additional information is available at the end of the chapter

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**Abstract**

The skin is among the largest and one of the most important organs in the human body. It represents the first line of defence of the body; provides protection from mechanical impacts of the environment, limits the influence of variations in the temperature, prevents entrance of chemicals and microorganisms and restricts radiation effect. Skin damage affects all skin functions; therefore, wounds can compromise patient's well-being, self-image, working capacity and independence. Due to all mentioned, a good wound management is necessary not only for the individual but also for the community. Herbal medicines have been used to accelerate wound healing since ancient times. Recently, scientists have been able to employ scientific methods to prove efficacy of many of these herbs and to get a better understanding of mechanisms of their actions. The popularity of herbal medicines may be explained by the perception that herbs cause minimal adverse effects. Preparations from traditional medicinal plants in wound management involve disinfection, debridement and the provision of suitable environment for natural healing process. In this chapter, the field of wound healing is briefly introduced. Further, the crucial information regarding plants, which are effectively used as wound healing agents in traditional medicine are gathered.

**Keywords:** wound physiology, wound healing, herbs, antimicrobial effect, anti-inflammatory effect, analgesic effect

## 1. Introduction

The human body consists of several organs, of which the skin is the largest. The human skin plays an important role in the bodies defensive processes, since it represents the first line of defence [1]. Two other important roles of the skin that also contribute to the defensive

mechanisms are regulation and sensation. All mentioned provide a crucial set of functions such as enable protection from mechanical impacts and pressure, restrict the influence of temperature changes, lower the potential impact of microorganisms, limit radiation effects and diminish the entrance of different chemicals. Other important skin functions include the regulation of body temperature (e.g. through sweat glands and hair), control over the peripheral circulation and fluid balance, and in the synthesis of vitamin D. Through its extensive nerve cell network, it enables detection and relaying of changes in the environment (e.g. heat/cold, touch and pain). Damage to these networks is called a neuropathy and impairs the sensation of the mentioned functions in the affected areas. The preservation of skin integrity is due to all mentioned functions crucial for maintaining a healthy body [2].

A wound is trauma-induced defect of the human skin, involving a multitude of endogenous biochemical events and cellular reactions of the immune system [3]. Wounds can compromise patient's well-being, self-image, working capacity and independence. Effective wound management is therefore necessary not only for the individual patient, but has an important impact also on the community [4].

## 2. Mechanism of wound healing

Wound healing is an extremely complex and dynamic process, which includes replacing of devitalized and missing cellular structures and tissue layers. It reflects in a set of biochemical events that integrate into an organized cascade of processes to repair the damaged tissue [5]. Immediately after injury, damaged vessels leak fluid, to which the body responds with haemostasis. Platelets start to aggregate in the wound bed and secrete multiple growth factors that contribute to an effective clot formation to hinder further loss of fluids from the defected area [6]. Simultaneously with the launch of haemostatic mechanisms, the inflammatory phase is induced as well [7]. It is characterized by local vasodilatation, platelet aggregation and phagocytosis, which together with the release of several cytokines, contribute to local inflammation of the wound site. Multiple chemokines, released by platelets, stimulate the immune and other cells (e.g. keratinocytes) to release growth factors and cytokines to regulate various signalling cascades that govern the inflammation and healing in general [8]. Macrophages and other immune cells are stimulated and they migrate towards the wound to dispose cell debris and fight invading bacteria during the wound healing. Angiogenesis occurs at this phase and new blood vessels transport essential nutrients to the wound bed [6]. The next phase in wound healing is the proliferative phase, which is characterized by granulation, wound contraction and epithelialisation. During granulation, fibroblasts form a bed of collagen, followed by the production of new capillaries [7]. During wound contraction, myofibroblasts decrease the size of the wound by gripping the wound edges and pulling them into the wound interior mechanisms that resemble that of smooth muscle cells. After completion of respective processes, unneeded cells undergo apoptosis (controlled cell death) [9]. Epithelialisation is initiated by keratinocytes proliferating and migrating across the wound site [8]. Fibroblasts are activated and differentiated into myofibroblasts that (either indirectly by production of cytokines or directly) regulate other cells to grow and form new epithelial tissue over the wound site. The final wound healing phase is the remodelling

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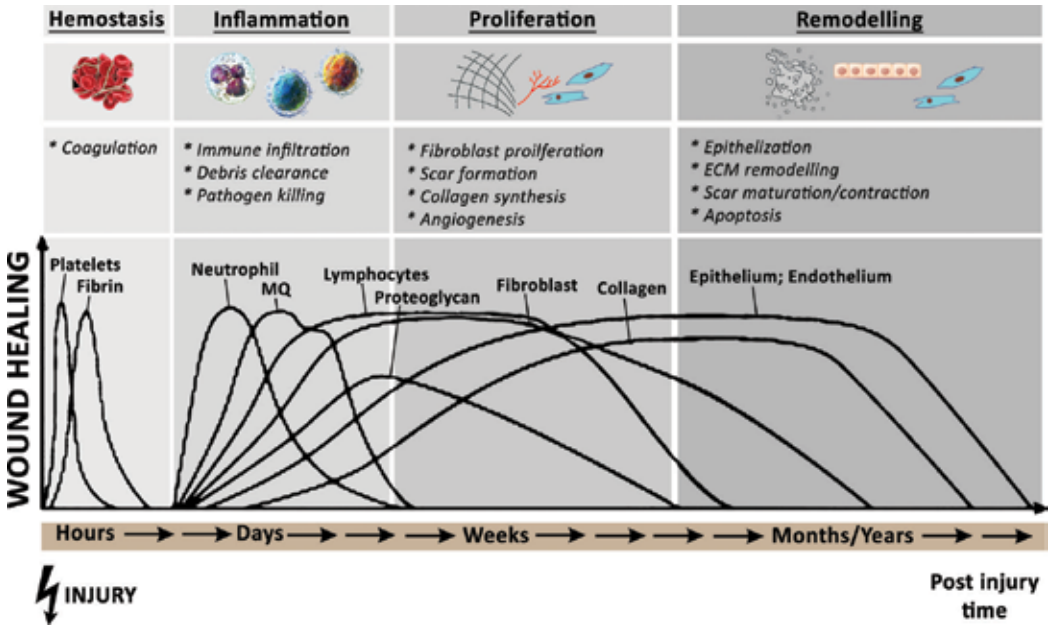


**Figure 1.** Schematic depiction of distinct phases during wound healing.

phase, which is governed by the rearrangement of the newly formed extracellular matrix (ECM) using increasing amounts of type I collagen. The fibres of collagen rearrange their structures with increasing interfibrillar binding and diameter [10]. The aim of wound treatment can be therefore described as a therapy to either shorten the time required for healing or to minimize the undesired consequences, for example extensive scarring [11]. A general overview of the wound healing is shown in **Figure 1**.

## 3. Wound healing management

The complex course of the wound healing with the various physiological events that occur simultaneously, as well as consecutively, is vulnerable to possible external interferences (e.g. infections) on one side, as well enables modulation, and hence improvement of the healing performance, through active treatment solutions (e.g. multifunctional wound dressings) [12, 13]. Among the most desired activities are the ones providing anti-inflammatory, antimicrobial, analgesic and antioxidant activities, regardless of the exact underlying mechanism of action [14].

Shortly after the injury, it is during the acute inflammatory response that different cytokines are formed. These are crucial for orchestration of the specific tissue growth, its repair, and hence regeneration [15]. Nevertheless, if this inflammation step persists, it can negatively affect the wound process, namely it leads to vicious cycle of ongoing inflammation, preventing the wound to reach the remodelling phase. If this happens, delays in wound closure occur, which are often accompanied with the increased sensation of pain in the wounded area and its surroundings that can additionally hinder the healing process [16]. Based on these findings

about the wound healing physiology, a lot of research has focused on the development of therapeutic approaches that would provide an anti-inflammatory and pain relieving activity to wound dressings [17].

An important complication related to wound treatment and healing is infection. Infections are known to significantly increase the treatment costs of wound care [18], which are also the reason that different strategies are being developed for their prevention [19]. Due to the impact of primary and secondary infections on the wound healing, which increase local inflammation, and hence lead to significant tissue destruction, prevention of their occurrence remains one of the main targets of wound dressing development [20]. An ideal medicine for the prevention of wound infection should therefore have antimicrobial activities, while also stimulating the body's natural immune system without damaging the surrounding healthy tissue [21].

Most wounds induce some level of pain sensation. Pain relates to patient's discomfort, release of stress hormones and often reduces the patients' overall quality of life. Hindered mobility and psychological issues connected with pain-induced stress lead to a less effective wound healing. According to McGuire et al. [22], chronic pain lowers the patients' capability of healing, thereby prolonging the overall recovery process [23]. Suitable and effective pain management can lead to an earlier release from the hospital, stress reduction and a general better reintegration into the community. All mentioned lead to facilitation of wound healing, while at the same time minimizing the risk for development of chronic pain, and finally in lowered treatment costs [24].

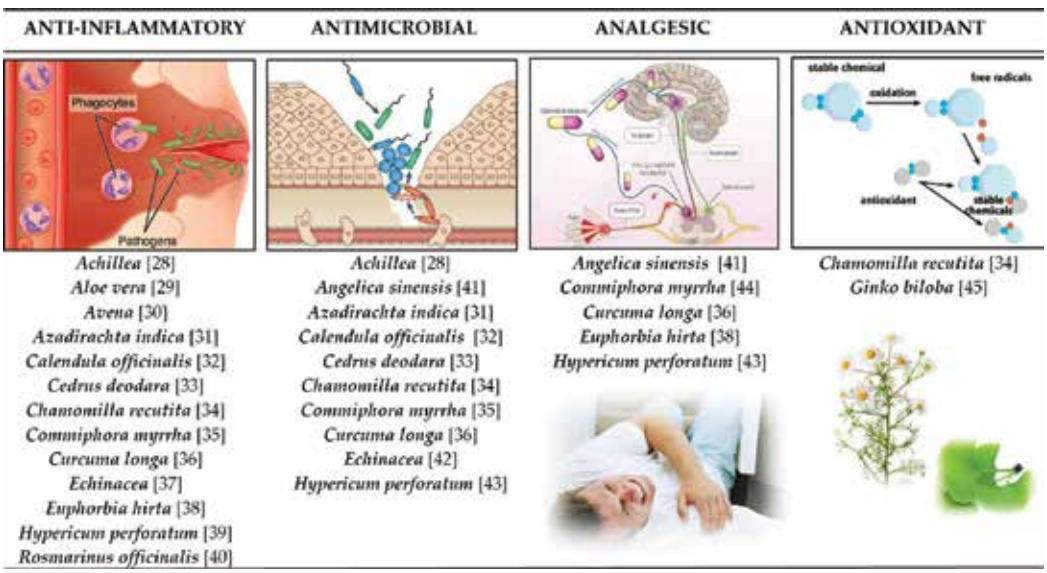


**Figure 2.** A diagram showing the most important beneficial properties that are desired in wound treatment (and some of the already known plants used in traditional medicine for this purpose). Anti-inflammatory: *Achillea* [28], *Aloe vera* [29], *Avena* [30], *Azadirachta indica* [31], *Calendula officinalis* [32], *Cedrus deodara* [33], *Chamomilla recutita* [34], *Commiphora myrrha* [35], *Curcuma longa* [36], *Echinacea* [37], *Euphorbia hirta* [38], *Hypericum perforatum* [39], *Rosmarinus officinalis* [40]. Antimicrobial: *Achillea* [28], *Angelica sinensis* [41], *Azadirachta indica* [31], *Calendula officinalis* [32], *Cedrus deodara* [33], *Chamomilla recutita* [34], *Commiphora myrrha* [35], *Curcuma longa* [36], *Echinacea* [42], *Hypericum perforatum* [43]. Analgesic: *Angelica sinensis* [41], *Commiphora myrrha* [44], *Curcuma longa* [36], *Euphorbia hirta* [38], *Hypericum perforatum* [43]. Antioxidant: *Chamomilla recutita* [34], *Ginkgo biloba* [45].

Part of the inflammation phase of wound healing causes also a coordinated influx of neutrophils to the wound site. One of the actions of neutrophils is also the activation of the so-called 'respiratory burst', which leads to productions of free radicals [25]. These produce oxidative stress that results in lipid peroxidation, DNA damage, and enzyme inactivation (e.g. free-radical scavenger enzymes and others), even those whose main activity is to limit the effects of reactive oxygen species (ROS). Considering the above mentioned, it is clear that antioxidants may be of therapeutic use in several diseases that are connected with potential pathologic actions of oxidants, including the wound healing [26].

Apart from the above-mentioned wound healing aiding activities, others are also reported in literature, e.g. the astringent activity, stimulated epithelisation and effective hydration of the wound site [27]. The most important properties of plant-derived medicines that are beneficial for the wound healing process are depicted in **Figure 2** together with some examples of plants that were already proven for the mentioned use.

## 4. Plants with potential use in wound healing

For thousands of years, we looked to nature for various types of medicinal treatments and plant-based systems continue to play an essential role in the primary health care of many less-developed, as well as developing countries [46]. Many plants and various preparations thereof have been used traditionally in relation to wound treatment, especially due to their immense potential to affect the wound healing process [65]. Plant-derived extracts and/or isolates induce healing and tissue regeneration through multiple connected mechanisms, which often have a synergistic effect on the overall healing efficiency [47]. Many plant-derived medicines (commonly called as phytomedicines) are affordable and cause minimal unwanted side effects [48]. Nevertheless, increasing awareness of their potential activities, especially considering the possible combinations of various plant-derived molecules, which could induce toxic effects as well, points out the need for a systematic approach towards their evaluation before efficient introduction to wound care (or other fields of medicine) [49]. In recent years, extensive research has been carried out in the area of wound healing and management through plant-derived medicinal products [38].

The following subchapters review the key details related to the potential use of medicinal plants in wound healing.

### 4.1. Groups of plant-derived molecules with beneficial effects on wound healing

When we describe the beneficial effects of plant-derived molecules on human health, mostly it is the secondary plant metabolites, producing pharmacological and/or toxicological effects, that we are discussing [48]. Secondary metabolites are produced within the plants and are regarded as by-products of biochemical reactions in the plant cells. As such, these molecules are not part of any crucial daily functioning of the plant, hence are not important for the plants main biosynthetic and metabolic routes that yield products with major significance for the plant growth and/or development [50]. Although this means that these molecules are not key to the plants basic functions, this does not mean that they do not importantly

contribute to the success of the plants overall survival in its ecosystem. For example, several of them play important roles in the living plants´ protection, attraction or signalling [51]. It seems that most plant species are capable of producing at least some of these compounds. But before we describe the most important groups of these secondary metabolites, let us first define the related term bioactive compounds. By definition, bioactive compounds in plants are compounds, produced by plants having pharmacological or toxicological effects in man and animals [52].

Bioactive compounds in plants can be classified considering different criteria. A presentation based on clinical function—their pharmacological or toxicological effects—is relevant for the clinician, pharmacist or toxicologist. The botanical approach on the other side considers the plant, from which they originate [53]. Finally, the biochemical approach seems to be the most commonly used. The latter is based on their classification according to the metabolic (biochemical) pathway, by which they are produced [54]. Using this approach, groups are more clearly understandable to most readers with at least basic knowledge in chemistry. The list of possible products is quite long, but since the focus of this chapter is on the ones with a beneficial effect on wound healing, we will focus on the groups, which could benefit the latter also in future clinical applications. The final subchapter summarizes some of the other groups, which might attract more researchers in the future.

### *4.1.1. Phenolic compounds*

Phenolic compounds present secondary metabolites that are known to contribute to several plant functions [55]. Apart from the important functions in relation to the plant host organism, phenolic metabolites (mostly called polyphenols in literature) are among the most important plant-derived molecules with a versatile range of potential beneficial biological properties on the human health [56]. Phenolic compounds were shown to possess beneficial effect on the human health, regardless of the type of intake/application [57]. For example, skin application can alleviate symptoms and inhibit the development of various skin disorders [58]. Because, in nature, there is an abundant source of various polyphenols with proven effect on the skin and due to the already proven low toxicity for many of them, these type of compounds have a great potential in wound healing, including treatment of various skin damage (e.g. wounds and burns) [55]. Polyphenols present an important source for future applications in wound care, ranging from reduction of minor skin problems (e.g., wrinkles, acne) [59] to more severe ones, such as cancer [60].

There are many available studies describing the potential of phenolic compounds to be used in treatment of various skin disorders, including reports about their beneficial influence on wound healing [61]. Phenolic compounds are among the most known plant secondary metabolites mostly due to their broad spectrum of biological properties [62]. The latter were shown to be related to their molecular structure, which consists of the main core, formed by at least one phenol ring, in which hydrogen is usually replaced by a more active moiety (e.g. hydroxyl, methyl or acetyl) [55]. The variability in their biological properties and activities is related to the type and degree of the substitutes on the phenol ring. Since many of the natural phenolic compounds contain more than one phenol ring, such compounds are often called polyphenols [62].

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At the moment, we know over 8000 different structures of plant phenolic compounds. Due to this huge number of compounds, it is important to use an effective classification system for their distinction. The most commonly used to distinguish phenolic compounds, groups them initially into flavonoid and non-flavonoid compounds. Both main groups are further divided as presented in **Figure 3**.

*4.1.1.1. Flavonoids*

Most likely the largest class of polyphenolic compounds found in nature are flavonoids [63]. Over 4000 structurally unique flavonoids were already identified from various plant sources [64]. Primarily, flavonoids were recognized as pigments responsible for many colors that occur in autumn, since they can provide various hues of yellow, orange and red in flowers, vegetables, nuts, seeds, fruits, etc., as well as the color of tea and red wine [65]. Several studies have shown that many plants contain therapeutic amounts of flavonoids [66]. These were (and still are) used in traditional medicine as anti-inflammatory, pain reducing, healing promoting, anti-allergic agents and others [67]. Most of the pharmacological effects found in flavonoids can be related to their (almost common) strong antioxidant activity [68]. They also act as free radical scavengers, can chelate metals, and are able to interact with enzymes, have an action on adenosine receptors and interfere with bio-membranes [69]. Among the main motivations for this review are several studies reporting different flavonoids with beneficial properties for wound-healing [47].

The core molecular structure of flavonoids consists of two aromatic rings connected by a three carbon bridge [70]. In plants, flavonoids often occur in association with sugar moieties

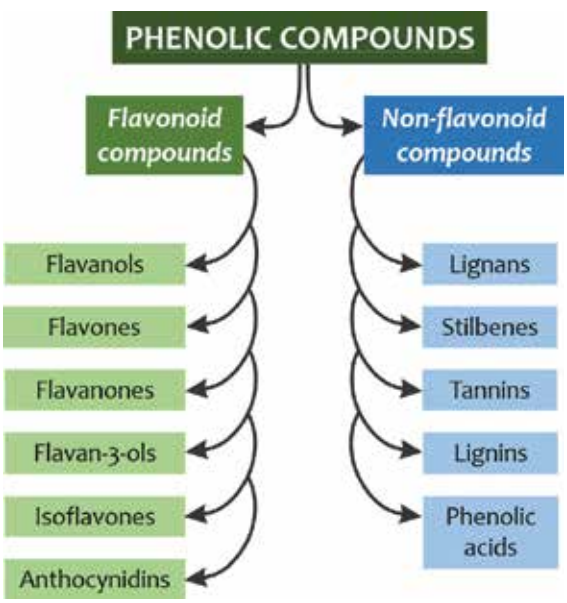


**Figure 3.** A diagram showing the classification of phenolic compounds.

as glycosides [70]. The main sources of flavonoids in the diet are fruits and vegetables. They occur also in certain grains, seeds, and spices, as well as in wine, tea, coffee, cocoa, and herbal essences [71]. All flavonoid compounds contain phenol-groups, which in general induces an antioxidant activity [72]. Other actions are diverse-several structures reduce inflammation or carcinogenicity [73].

#### *4.1.1.2. Non-flavonoid polyphenols*

Non-flavonoid metabolites also comprise several subgroups (**Figure 3**) [74]. Many of these compounds occur mainly as complicated biopolymers. In this, they are different from their flavonoid counterparts by lacking a defined primary carbon base, which results in unique chemical structures for respective polyphenols [75]. An important subgroup of non-flavonoid compounds from plants are phenolic acids, which can be further divided into hydroxycinnamic acids (e.g. caffeic acid, chlorogenic acid, o-, m- and p-coumaric acids, ferulic acids, and sinapic acids), and hydroxybenzoic acids (e.g. gallic acid, p-hydroxybenzoic acid, protocatechuic acid, vanillic and syringic acids) [55]. Both classes often occur in plants in the glycoside form. In plant tissues, phenolic acids can be bound to various compounds, e.g., flavonoids, fatty acids, sterols and cell wall polymers [76]. Another widely distributed group of phenolic compounds in plants are tannins, which may occur as hydrolysable tannins (formed in the pathway of the phenolic acids with sugar polymerization) and condensed tannins (a combination of flavonoids) [77]. Lignans are phenylpropanoid dimers, whereas the most commonly known ones include secoisolariciresinol, lariciresinol, pinoresinol and matairesinol [55]. The most known and researched stilbene is resveratrol, which is present in many edible plant species (e.g. grapes, peanuts, and berries) [78]. Resveratrol plays an important part in the plant defence against mechanical injury, pathogen infection, and UV radiation [78].

### *4.1.2. Essential oils*

By definition, essential oils are concentrated hydrophobic liquids that contain volatile aroma compounds derived from plants [79]. The term essential has not an analogous meaning as in the case of essential amino acids or essential fatty acids. In the latter cases, essential corresponds to a lack of mechanism for their respective synthesis in a specific organism, which also means that these have to be acquired by other means (e.g. diet) [80]. In general, essential oils are extracted by distillation (e.g. by steam). Other processes include expression, solvent extraction, absolute oil extraction, resin tapping and cold pressing [81]. Due to their (often) pleasant fragrance, they are commonly used as components in perfumes, cosmetics, soaps and other products, for flavouring food and drink, and for other similar applications [80]. There are several essential oils derived from plants with high potential to be used in wound treatment [82]. Some of the most important essential oils with proven beneficial effect on wound healing (either in traditional medicine or based on research studies), are described in more detail below.

#### *4.1.2.1. Lavender oil*

Lavender (*Lavandula*) oil, derived from lavender flowers, is one of the most commonly used essential oils in various therapies. Due to its antibacterial and antifungal properties, it has

been used to treat bites [82]. There are also reports describing its anti-depressant activity, as well as its effect on smooth muscles (acting as a muscle relaxant) [83]. Several researchers have performed many different studies in relation to the potential beneficial effect of lavender oil in various wound care applications [83]. One of these studies, conducted by Kane et al., reports about the significantly reduced pain intensity after aromatherapy using lavender oil during dressing changes in treatment of vascular wounds when compared with control therapies [84]. Another study showing a potential use of lavender oil in wound care is the study by Hartman and Coetzee [85]. They studied the effect of lavender and chamomile essential oils on wound healing in five patients with chronic wounds in a timespan of months. The wounds were graded using the US National Pressure Ulcer Advisory Panel (NPUAP) guidelines based on depth and visual characteristics [85]. The treatment protocol used in this study includes a treatment with a 6 wt.% solution of two drops of lavender oil and one drop of German chamomile, which were applied directly onto the wound, and subsequently covered with a gauze. Their result was that the wounds treated with the oils healed more quickly compared to the control wounds without the additional treatment using the essential oils, which were just covered by the gauze [85].

#### *4.1.2.2. Chamomile oil*

The wound healing aiding properties of chamomile (*Matricaria chamomilla* L.) oil, derived from chamomile flowers, were investigated also by Glowania et al. [86]. This double-blind study included 14 patients in which chamomile oil, when added to standard dressings, significantly improved the weeping and drying associated with dermabrasion wounds [86]. Another study that reports evaluation of potential positive effects on wound healing is a review of the bioactivity of chamomile, conducted by McKay et al. [87]. They found a moderate antimicrobial and a significant antiplatelet activity *in vitro*, as well as showed antimutagenic effects in animals [87].

#### *4.1.2.3. Tea tree oil*

The tea tree (*Melaleuca alternifolia*) oil is an essential oil derived from the leaves of the tea tree that are used as a complementary therapy in Australia. The latter is mostly related to its known antiseptic, antibacterial, antifungal and anti-inflammatory activities [82]. Several studies report about its potential use in wound healing applications. Halcon and Milkus, for example, tested the tea tree oil as an antimicrobial agent in the case of *Staphylococcus aureus* infections [88]. Although this study was based only on a small clinical trial combined with case studies, the authors nevertheless showed the potential of the tea tree oil treatment of osteomyelitis and in chronic wound healing [88]. Another study was performed by Hammer et al., who investigated the effect of tea tree oil on transient and commensal skin flora *in vitro* [89]. They compared the effectiveness of different concentrations to induce bactericidal action and found the tea tree oil to be effective against *Staphylococcus aureus* and most Gram-negative bacteria (reduction to 0.25%), but was less effective against coagulase-negative staphylococci and micrococci (8%) [89]. Two groups of researchers tested also commercially available products based on tea tree extracts (including the essential oil). Sherry et al. claimed that the antimicrobial preparation from extracts of tea tree oil and eucalyptus showed an activity against methicillin-resistant *Staphylococcus aureus* (MRSA) [90]. Faoagali et al. evaluated the activity

of another commercially available tea tree oil-based cream against different bacteria and confirmed its effectiveness against *Staphylococcus aureus* and *Escherichia coli* [91].

*4.1.2.4. Thyme oil*

Thyme (*Thymus vulgaris*) is an aromatic plant, commonly used in preparation of several dishes, whereas its essential oil has been widely reported to contribute to the healing of burns [82]. Thyme essential oil is derived from the steam distillation of the leaves, stems and flowers of the plant. One of such is the study by Dursun et al., who investigated the impact of thyme oil on the formation of nitric oxide, which is an important inflammatory mediator [92]. They studied the effect of thyme oil on burn wound in rats and showed that it not only decreased the amount of nitric oxide produced in response to the burn, but also facilitated wound healing [92]. Several other studies were conducted in regard of the potential antimicrobial activity of the thyme oil. For example, Bozin et al. showed an effective antibacterial and antifungal activity *in vitro* [93]. Their results are in agreement with another study that was performed by Shin and Kim, who determined a significant inhibitory action of thyme oil against both antibiotic-susceptible and resistant strains of *Streptococci, Staphylococcus aureus* and *Salmonella typhimurium* [94]. With the aim to evaluate the thyme oil's potential antifungal action, Giordani et al. combined it with amphotericin B and showed that it significantly potentiated the effectiveness of the latter [95]. Finally, Komarcevic discussed the available evidence showing that topically applied thyme oil increased collagen deposition, angiogenesis and keratinocyte migration, all together significantly contributing to the efficiency of wound healing [96].

*4.1.2.5. Ocimum oil (basil)*

Orafidiya et al. performed two studies regarding the potential use of ocimum oil derived from the leaves of *Ocimum basilicum* L. in wound healing applications [97]. First, they studied its potential effect on the healing of full-thickness excisional and incisional wounds in an animal model [97]. They found and improved wound healing performance in wounds treated with the essential oil in comparison with the control [97]. In the second study, Orafidiya et al. demonstrated a significant antiseptic effect of a 2% solution of ocimum oil against strains and isolates from boils, wounds and acne [98]. This group was not the only one testing the potential effect of basil extract. Another similar study was performed by Singh and Majumdar, who studied the potential anti-inflammatory action of ocimum oil. They found a significant inhibition of vascular permeability and leucocyte migration in animal studies [99]. Singh conducted another study, in which he determined that the anti-inflammatory activity of ocimum oil could be related to a blockading of the enzymes cyclooxygenase and lipoxygenase in the arachidonic acid metabolism [100].

*4.1.2.6. Other oils*

Other less well-known essential oils with a proven beneficial effect on wound healing include the bark oil of *Santiria trimera* (a member of the frankincense family) [101], oils from *Hypericum perforatum* (St. John's Wort) and *Calendula arvensis* [102], oils extracted from *Cinnamomum zeylanicum* (cinnamon) bark [103], and the extract from *Chromolaena odorata* (Siam weed) [104].

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An overview of the main chemical components of the above described essential oils is depicted in **Figure 4**.

*4.1.3. Other compounds with wound healing properties*

Research on plant-derived compounds with potential use in wound healing drugs is a developing area in modern biomedical sciences. Scientists who are trying to develop newer drugs from natural resources are looking towards different regions, where there is a strong evidence of plant in traditional medicine (India, Africa, etc.) [105]. Most of these herbal medicines are not isolated compounds, but rather extracts composed of several constituents, which synergistically aid the wound healing process [106]. Not many have been screened scientifically for the evaluation of their wound healing activity in different pharmacological models and patients, but the potential of most remains unexplored [107]. The most important groups of compounds were described above, whereas we briefly review some of the less commonly used compounds and groups.

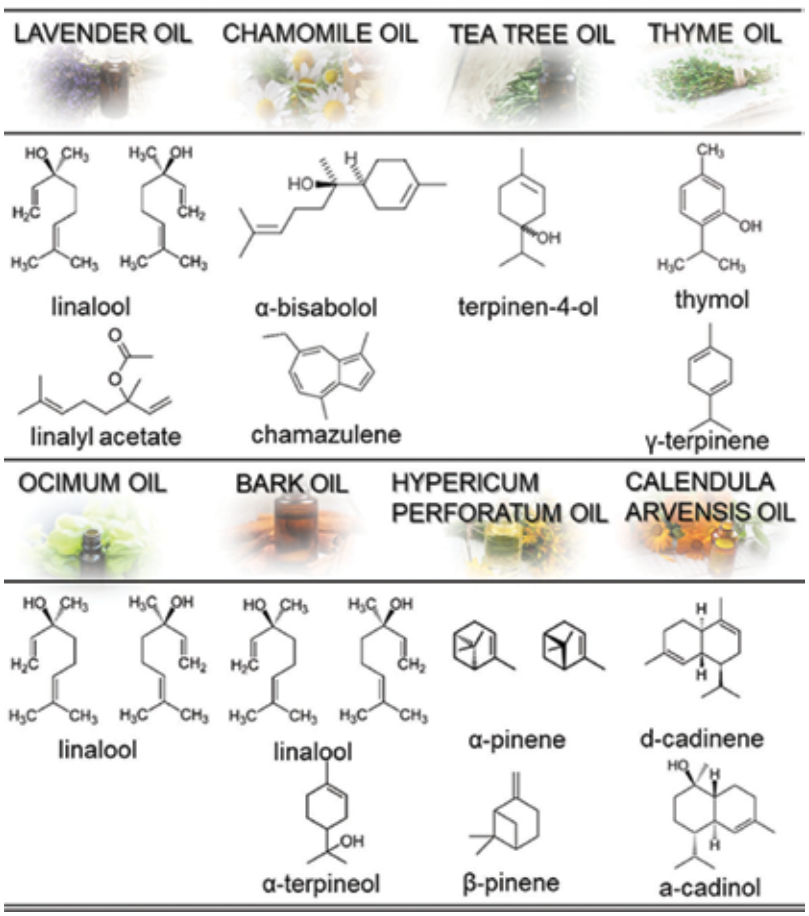


**Figure 4.** An overview of chemical structures of the above mentioned essential oils.

#### *4.1.3.1. Alkaloids*

Alkaloids are heterocyclic compounds that contain a nitrogen atom in at least one of the heterocycles [108]. They usually have various potent biological activities and are of bitter taste [109]. Some synthetic compounds of similar structure are also termed alkaloids. They are not that common in the plant kingdom, are represented by diverse chemical structures, and almost all show interesting properties for therapeutic use [110]. Alkaloids are produced also by other organisms including bacteria, fungi and animals [109]. Although alkaloids are not the first choice of chemicals to be used in relation to wound treatment, there are still some interesting plants that need further analysis due to their already proven potential for this purpose. Among the plants that produce alkaloids with potential beneficial effects on wound healing are the *Papaveraceae* (poppy family) and *Berberidaceae* (barberry family) families [111]. Both produce isoquinoline alkaloids that possess a range of biochemical effects relevant for medical use (e.g. inhibition of pain, growth inhibition of cancer cell growth, and growth of bacterial cells) [111]. Among other indirectly related beneficial properties are also the stimulation of bone marrow leucocytes, which modulate the inflammation phase of wound healing [112].

#### *4.1.3.2. Resins*

This group of plant-derived compounds presents a complex mixture of lipid-soluble chemicals [113]. These can be both non-volatile (e.g. diterpenoid and triterpenoid compounds) and volatile (mono- and sesquiterpenoids) [114]. Resins are most commonly found in nature as part of various wood-derived structures, although they are also present in herbaceous plants [115]. Among their common properties are a general stickiness, whereas their fluidity depends on the contents of volatile compounds [115]. When exposed to air they harden. Among their beneficial biological activities for wound healing are the antimicrobial activity, but their actions depend on the composition of the chemical mixture. Resins are generally safe, but contact allergy may occur [116].

The common structural precursor of terpenoids is the five-carbon building block isoprene [117]. Monoterpenoids are formed of two isoprene units, whereas sesquiterpenoids consist of three units. Both mentioned groups are commonly denoted as low-molecular-weight terpenoids, which are one of the most varied groups of plant products that include more than 25,000 compounds [118]. The phenylpropanoid group of terpenoids is less common and is based on a nine-carbon skeleton, whereas their synthesis pathway differs from the other terpenoids [119]. Compounds of all three mentioned groups have often strong odours and flavours, which is related to their properties (e.g. the lipophilicity and volatility) [120]. Since they exhibit various biological activities, they are found in several herbal remedies [121]. Of particular importance in relation to wound healing are their antibacterial and antiviral effects, whereas they possess also other activities like the antineoplastic activity, as well as stimulation gastrointestinal tract [118]. They are not toxic unless they are concentrated as volatile oils [122]. The plant family best known for these compounds is *Lamiaceae* (thyme family).

#### *4.1.3.3. Compounds with antimicrobial activity*

Looking at plant extract to find novel antimicrobial compounds is interesting for clinical microbiologists for two reasons, namely, it is very likely that these phytochemicals will be

sooner rather than later prescribed as antimicrobial drugs, and the public is becoming increasingly aware of problems with the over prescription and misuse of traditional antibiotics [123]. It is reported that, on average, two or three antibiotics derived from microorganisms are launched each year [124]. Phytochemicals with an antimicrobial activity can be divided into several categories, most of which were already described above. These include phenolics, terpenoids, essential oils and alkaloids [123]. Among the other ones, we will briefly review also the lectins and polypeptides, as well as polyacetylenes.

First antimicrobial peptides were reported back in 1942 [123]. Mostly, these compounds are positively charged and include disulphide bonds in their structure [125]. One of the known possible mechanism of actions involves the formation of ion channels in the microbial membrane [125], while the other is related to a competitive inhibition of adhesion of microbial proteins to host polysaccharide receptors [126]. Some of the most important subgroups of antimicrobial peptides include thionins, which are toxic to yeasts and Gram-negative and Gram-positive bacteria [125].

Polyacetylenes are another group of potential antimicrobial compounds with interesting properties. The compound 8S-heptadeca-2(Z),9(Z)-diene-4,6-diyne-1,8-diol was shown to be effective against *S. aureus* and *B. subtilis* but not to Gram-negative bacteria or yeasts [127]. In Brazil, acetylene compounds and flavonoids derived from single plant extracts traditionally are used for treatment of malaria fever and liver disorders [128].

## 5. Plants with beneficial effect on wound healing, approved by the Committee on Herbal Medicinal Products (HMPC)

Many plants and their extracts have great potential for the management and treatment of wounds. Natural agents induce healing and regeneration of the lost tissue by multiple mechanisms. The so-called phytomedicines are affordable and they cause minimal adverse effects. However, there is need for scientific standardization, validation and safety evaluation of plants of traditional medicine before these can be recommended for wound healing [49]. Therefore, an extensive research has been carried out in the area of wound healing and management through medicinal plants [38].

The following paragraphs outline some medicinal plants and their properties that exhibit wound healing activity.

***Achillea millefolium*** (Family: *Asteraceae*). Yarrow (a common name of the plant) has been known and used due to its healing effects by many cultures for hundreds of years [129]. Among its proven beneficial effects in wound healing are a good antibacterial activity against *Shigella dysenteriae* [130], moderate activities against *Streptococcus pneumoniae, Clostridium perfringens* and *Candida albicans*, and a weak antibacterial activity against *Mycobacterium smegmatis, Acinetobacter lwoffii* and *Candida krusei* [131]. Yarrow also has a proven anti-inflammatory effect [132].

***Aloe vera*** (Family: *Liliaceae)*. *Aloe vera* has been used for medicinal purposes in several cultures for millennia: Greece, Egypt, India, Mexico, Japan and China [133]. 3500 years ago, Egyptians used this herb in treating burns, infections and parasites [134]. Its gel has the ability to heal different kinds of wounds including ulcers and burns by forming a protective coating on the

affected areas and speeding up the healing process. Various constituents of *Aloe vera* stimulate wound healing and have anti-inflammatory activity [29].

***Angelica sinensis*** (Family: *Apiaceae*). Chinese angelica is widely used in Chinese traditional medicine. Its isolate has been found to stimulate wound healing and increase the strength of the healed wounds [135].

***Avena sativa*** (Family: *Poaceae*). The oats has been known for more than 4000 years as a food and the traditional medicinal usage has been documented since the twelfth century. For cutaneous use, mostly fruits of *Avena* are prepared as 'colloidal oatmeal' described in the USP 30 (1990) [136]. *In vitro* investigations are indicative of an anti-inflammatory activity of several oat fruit preparations. Pasta made with oat's flour mixed with beer yeast is used on infected ulcers and wounds, and to facilitate wound healing [137].

***Azadirachta indica*** (Family: *Meliaceae*). Neem has been used in India for over two millennia for many medicinal properties, particularly for skin diseases. Products made from neem trees possess anti-bacterial, anti-fungal, anti-viral and anti-inflammatory activities. Neem oil aids the building of collagen, promotes wound healing and maintains the skin elasticity. It also keeps the wound moist during the healing process. All mentioned mechanisms accelerate wound healing [138].

***Calendula officinalis*** (Family: *Asteraceae*). *In vitro* pharmacological studies confirmed its anti-viral, anti-genotoxic and anti-inflammatory properties [32]. Pot marigold was shown to possess also an antimicrobial activity against *Bacillus subtilis, Escherichia coli, Staphylococcus aureus, Pseudomonas aeruginosa, Candida albicans* [139], *Sarcina lutea, Klebsiella pneumoniae* and *Candida monosa* [140]. Different preparations of pot marigold are known (e.g. suspensions or tinctures) for topical use to reduce inflammation, as well as to control bleeding [141]. It was also shown to inprove the healing of poorly healing wounds [142].

***Cedrus deodara*** (Family: *Pinaceae*). Deodar possesses anti-inflammatory, anti-microbial, astringent and wound healing activities and is therefore particularly useful in treatment of infected wounds [33].

***Centella asiatica*** (Family: *Mackinlayaceae*). Extensive research has been conducted regarding its use in the treatment of leprosy and several other skin conditions, including the treatment of various wounds. For example, centella was used in the treatment of experimentally induced open wounds in rats. In this study, its aqueous extract increased collagen content and the overall thickness of the freshly formed epithelium [143]. Apart from the mentioned, the topical use of its aqueous extract increased proliferation of various cells, improved collagen synthesis at the wound site (all mentioned was proven by increased DNA and protein synthesis in the tested cells), through an increased collagen content in the granulation tissue, and in an improved tensile strength [144]. All mentioned confirms the potential of *Centella asiatica* to promote wound healing and to facilitate repair of the connective tissues [145].

***Chamomilla recutita*** (Family: *Asteraceae*). Chamomile has been used for centuries as an antimicrobial, antioxidant, anti-inflammatory agent, as a mild astringent and a healing medicine [34]. It helps in wound drying and it accelerates epithelization. Chamomile aids wound management also through increased granulation tissue weight, hydroxyproline content, rate of wound contraction and wound-breaking strength [146].

***Chromolaena odorata*** (Family: *Asteraceae*). The aqueous extract and the decoction from the leaves of this plant have been used throughout Vietnam for the treatment of soft tissue and burn wounds. It enhances haemostatic activity, inhibits wound contraction, stimulates granulation tissue and re-epithelization processes and can therefore be of much therapeutic value in the wound healing, minimizing post-burn scar contracture and deformities [147].

***Commiphora myrrha*** (Family: *Burseraceae*). Myrrh is among the oldest known traditional medicines used by humans, with a documented use even in the times of ancient Rome (found in texts written by Hippocrates). In addition, other cultures report its potential medical use. These include the Bible, as well as the Koran [148]. Various pharmacological activities of myrrh are reported (e.g. antibacterial and antifungal effects against several strains, as well as anti-inflammatory, local anaesthetic and analgesic activities). Presently, it is cutaneous used in the form of a tincture in the treatment of minor wounds, abrasions and skin inflammations [35].

***Curcuma longa*** (Family: *Zingiberaceae*). Turmeric possess anti-bacterial, anti-fungal, analgesic and anti-inflammatory activities [149]. Its anti-inflammatory properties, presence of vitamin A, as well as several proteins were shown to have a beneficial effect on the early formation of collagen fibres, which could be related to stimulation of fibroblastic activity [36]. As part of traditional medicines, fresh rhizome juice from turmeric is often used in treatment of fresh wounds, bruises and also leech bites.

***Echinacea*** (Family: *Asteraceae*). *Echinacea* species and various preparations thereof have one of the longest reported histories of use in the American people's medicine [150]. The most used species include *E. purpurea, E. angustifolia, E. palida, E. simulata* and *E. paradoxa* [151]. The documented use of *Echinacea purpurea* dates back to 1787 and includes its use for external application in treatment of wounds, burns and insect bites [152]. Its more specific activities are an antimicrobial activity against *Vesicular Stomatitis virus, Escherichia coli, Pseudomonas aeruginosa, Aspergillus niger, Candida albicans, Staphylococcus aureus, Pseudomonas aeruginosa* [153], *Encephalomyocarditis virus, Vesicular Stomatitis virus* [154], *Saccharomyces cerevisiae, Candida shehata, Candida kefyr, Candida albicans, Candida steatulytica and Candida tropicalis* [42]. Echinacea extracts exhibit also pain reducing effects, which are related to an inhibitory effect on cyclooxygenase-I, cyclooxygenase-II [155] and 5-lipoxygenase [37]. The mentioned activities contribute also to its anti-inflammatory activity. All described properties (e.g. antimicrobial, pain reducing effects, anti-inflammatory activity) present beneficial effects of *Echinacea* for wound healing [37].

***Euphorbia hirta*** (Family: *Euphorbiaceae*). The aqueous extract of the plant shows analgesic, anti-inflammatory activities and an inhibitory action on platelet aggregation. Ethanolic extract of the entire herb was found to possess significant wound healing activity [38].

***Ginkgo biloba*** (Family: *Ginkgoaceae*). Ginkgo leaf extracts have been therapeutically used for hundreds of years [156]. Its pharmacological activities include an increase in blood fluidity, anti-oxidative activity, membrane stabilization, improvement in cognition, and wound healing promotion. Various ginkgo preparations have been shown to improve granulation tissue breaking strength, as well as promote epithelization without influence on wound contraction [45].

***Helianthus annuus*** (Family: *Asteraceae*). In traditional medicine, the sunflower herb is used by Indian tribes for treating inflammation of the eyes, sores, tiger bites, and to treat bone

fractures [157]. The alcoholic extract of the whole plant of *Helianthus annuus* applied on the excised wounds of rats led to a significant reduction of the healing period which was indicated by earlier appearance and higher accumulation of mucopolysaccharides [158].

| GENUS<br>FAMILY | ***Achillea millefolium***<br>*Asteraceae* | ***Angelica sinensis***<br>*Apiaceae* | ***Aloe vera***<br>*Liliaceae* | ***Avena sativa***<br>*Poaceae* |
|---|---|---|---|---|
| |  |  |  |  |
| **BIOLOGICAL ACTIVITY** | Antibacterial activity.<br>Anti-inflammatory activity. | Stimulation of wound healing.<br>Increasing the strength of skin in healed wounds. | Formation of a protective coating on the affected areas.<br>Stimulation and speeding up of a wound healing process.<br>Anti-inflammatory activity. | Anti-inflammatory activity.<br>Facilitation of wound healing. |

| GENUS<br>FAMILY | ***Azardica indica***<br>*Meliaceae* | ***Calendula officinalis***<br>*Asteraceae* | ***Cedrus deodara***<br>*Pinaceae* | ***Centella asiatica***<br>*Mackinlayaceae* |
|---|---|---|---|---|
| |  |  |  |  |
| **BIOLOGICAL ACTIVITY** | Anti-bacterial activity.<br>Anti-fungal activity.<br>Anti-viral activity.<br>Anti-inflammatory activity.<br>Help in collagen forming.<br>Promotion of wound healing. | Anti-viral properties.<br>Anti-inflammatory activity.<br>Antimicrobial activity.<br>Facilitation of healing of poorly healing wound. | Anti-inflammatory activity.<br>Anti-microbial activity.<br>Astringent activity. | Increasing content of collagen and thickness of the epithelium.<br>Increasing cellular proliferation.<br>Promotion of collagen synthesis. |

| GENUS<br>FAMILY | ***Chamomilla recutita***<br>*Asteraceae* | ***Chromolaena odorata***<br>*Asteraceae* | ***Commiphora myrrha***<br>*Burseraceae* | ***Curcuma longa***<br>*Zingiberaceae* |
|---|---|---|---|---|
| |  |  |  |  |
| **BIOLOGICAL ACTIVITY** | Antimicrobial activity.<br>Antioxidant properties.<br>Anti-inflammatory activity.<br>Mild astringent properties.<br>Acceleration of epithelization. | Enhancement of hemostatic activity.<br>Inhibition of wound contraction.<br>Stimulation of granulation tissue synthesis and re-epithelization processes. | Antibacterial and antifungal effects.<br>Anti-inflammatory activity.<br>Local anesthetic and analgesic activity. | Antibacterial and antifungal effects.<br>Anti-inflammatory activity.<br>Analgesic activity.<br>Facilitation of collagen synthesis. |

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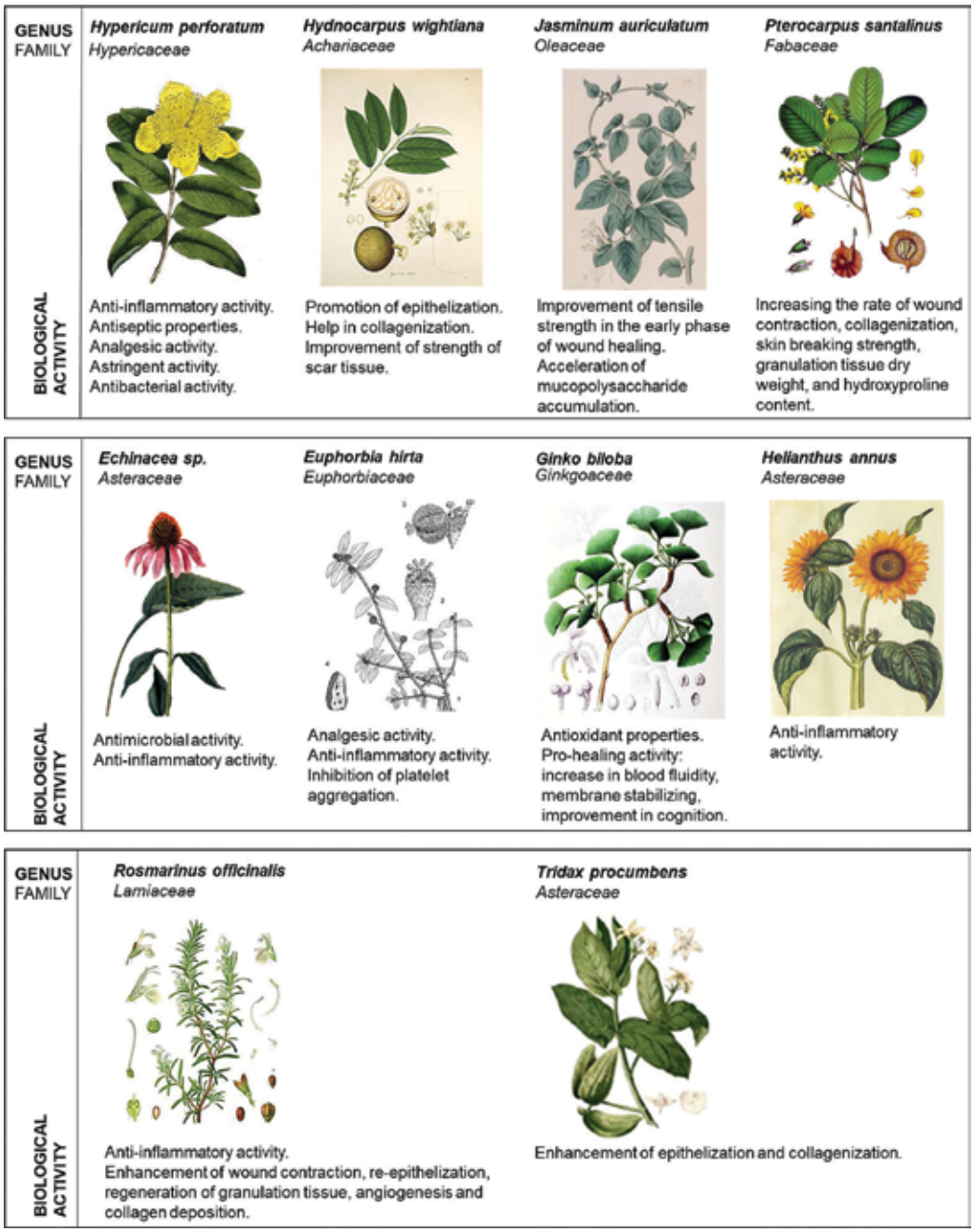


**Figure 5.** Overview of medical plants traditionally used in wound healing and their pharmacological activities (all plant images were obtained using the Google search engine with the enabled option for 'free use, share and modify').

***Hydnocarpus wightiana*** (Family: *Achariaceae*). The oil from chaulmoogra seeds has been widely used in Indian and Chinese traditional medicine [159]. The wound healing effect is substantiated by improved collagenation and strength of scar tissue, as well as by promoted epithelization [160].

***Hypericum perforatum*** (Family: *Hypericaceae*). Under its traditional names St. John's Wort, this plant has a long history of safe and effective use as part of various folk and herbal remedies. With proven anti-inflammatory [39], antiseptic [161], analgesic, astringent and antibacterial activities [43], it seems an ideal candidate for use in wound treatment. The latter has been confirmed also in different studies, which include its healing promoting action, when used externally on minor wounds [162], as well as through the positive effects of *Hypericum perforatum* tincture on epithelization, an increase in the wound contraction rate and an improved granulation tissue breaking strength [163].

***Jasminum auriculatum*** (Family: *Oleaceae*). The juice of the leaves of *Jasminum auriculatum* was found to promote wound healing through improved tensile strength in the early phase of healing [164] and due to acceleration of mucopolysaccharide accumulation [165].

***Pterocarpus santalinus*** (Family: *Fabaceae*). The wood of the red sanders possesses astringent and tonic properties. Ethanolic extract of the leaf and stem bark of *Pterocarpus santalinus* has demonstrated significant decrease in the period of epithelialisation, an increase: in the rate of wound contraction, the extent of collagenation, in the skin breaking strength, of the granulation tissue dry weight, and of the hydroxyproline content [38].

***Rosmarinus officinalis*** (Family: *Lamiaceae*). Rosemary is used for wound treatment. It reduces inflammation and enhances wound contraction, re-epithelization, and regeneration of granulation tissue, angiogenesis and collagen deposition [40].

***Tridax procumbens*** (Family: *Asteraceae*). The juice of *Tridax procumbens* promotes wound healing by accelerating epithelization and collagenization, resulting in the retardation of scar formation and granulation [166].

**Figure 5** presents a summary of plants with proven beneficial effect on wound healing.

## 6. Outlook and future development

There are many challenges in relation to the potential future use phytochemicals in wound treatment. These are not the same as in the case of use of phytochemicals for other indications, but are still related to the respective compound/extract solubility, biocompatibility with the respective cells of the targeted tissue (in this case the skin with all its components), as well as the lack of preclinical and clinical studies related to its safety and efficiency testing. Poor bioavailability, which is often a limiting factor in the use of phytochemical for other purpose, is mostly not relevant for the case of wound treatment, where were mostly a local activity is enough. Of course, a successful elucidation of molecular targets and mechanisms of phytochemicals is the target for future research. Extensive knowledge about the preclinical performance of extracts, isolated and specific compounds is a prerequisite for successful pre-formulation studies and development of effective materials and prototype products with a high possibility to reach the patient in the near future.

The chemo-preventive properties of many phytochemicals are well known and have been already proven beneficial in treating various disorders, including skin diseases. Different phytochemicals can contribute to the skin protective mechanisms by quenching free radicals and reducing inflammation through the inhibition of cellular and humoral immune responses. In the last decades, several strong research groups performed extensive research with the aim of identifying specific compounds from plant extracts and their molecular targets. This will provide a sound foundation for future clinical trials in the development of phytochemicals as potentially important therapeutic agents.

## 7. Conclusions

Various plants produce secondary metabolites and other products that have beneficial effects on wound healing, including the enhancement of the skins natural repair mechanisms. Due to the possibility to produce different plant preparations for topical use, these have a huge potential in future therapeutic approach in wound care. Recent developments of novel extraction technologies, newly found knowledge about traditional use of various plants, as well as our steadily improving knowledge about wound healing physiology importantly contribute to the popularization of studies of herbs and herbal materials from the physiological and therapeutic point of view. This in turn contributes also to a steadily increasing number of herbal products for wound treatment. Considering also the increasing number of clinical studies related to the safety and therapeutic efficacy of herbal products, many more herbs have a bright future either in curative or preventative uses in wound healing. Based on our present knowledge, future studies should aim at the isolation and identification of specific active substances from plant extracts, which could also disclose compounds with better therapeutic value. Finally, the combination of traditional and modern knowledge seems to be the best approach to produce novel effective therapeutic interventions for wound healing with a significantly improved treatment efficacy, lowered side effects and costs.

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## Conflict of interest

The authors declare no conflict of interest.

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Chapter 9

# Plant-Based Ethnopharmacological Remedies for Hypertension in Suriname

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Additional information is available at the end of the chapter

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**Abstract**

Hypertension is the most important modifiable risk factor for cardiovascular, cerebrovascular, and renal diseases which are together among the most frequent causes of morbidity and mortality in the world. Despite the availability of a wide range of effective medicines, many individuals suffering from hypertension use plant-derived preparations for treating their disease. The choice for these alternatives is often associated with the closer relationship of such approaches to specific social, cultural, and religious perceptions about health and disease. However, in most cases, the scientific evidence for clinical efficacy of such medications is scant. The Republic of Suriname is a middle-income country in South America with a relatively high prevalence of hypertension and other cardiovascular diseases. This country harbors descendants of all continents, all of whom have preserved their cultural customs including their ethnopharmacological traditions. As a result, many Surinamese are inclined to treat their diseases including hypertension as they have done for centuries, that is, with plant-based preparations. This chapter has compiled the plants used for treating hypertension in Suriname; extensively evaluates 15 commonly used plants for potential efficacy on the basis of available phytochemical, mechanistic, preclinical, and clinical literature data; and closes with conclusions about their potential usefulness against the disease.

**Keywords:** hypertension, medicinal plants, Suriname, preclinical studies, clinical studies, phytochemical composition, mechanism of action

## 1. Introduction

Blood pressure is the force exerted by the heart and the arteries to maintain the flow of blood through the body in order to supply all cells with oxygen and nutrients and remove waste products. This normally occurs at average systolic and diastolic pressures of 120 and 80 mm Hg, respectively [1]. High blood pressure or arterial hypertension (or hypertension for short) is

present when these values are persistently above 140 and 90 mm Hg, respectively [1]. This condition initially does not cause symptoms [1]. However, in the long-term, it is one of the most important predisposing factors for potentially fatal coronary artery disease, heart failure, stroke, peripheral vascular disease, vision loss, and chronic kidney disease [1].

Hypertension is classified as primary (or essential) hypertension and secondary hypertension [2]. Primary hypertension accounts for 90–95% of cases, typically begins in the fifth or sixth decade of life, and is associated with nonspecific lifestyle factors such as excess salt intake, obesity and a sedentary lifestyle, cigarette smoking, high alcohol intake, stress, and a family history suggesting the involvement of genetic factors in its etiology [3]. In the remaining 5–10% of cases categorized as secondary hypertension, the elevated blood pressure has an identifiable cause such as renal artery stenosis, chronic kidney disease, sleep apnoea, hyperthyroidism, pheochromocytoma, the use of oral contraceptives, or pregnancy [2].

In both situations, the elevated blood pressure is caused by an increase in the total peripheral resistance, that is, the total resistance to the flow of blood in the systemic circulation. The increased peripheral resistance is most often attributable to abnormalities in the sympathetic nervous system [4] and the renin-angiotensin-aldosterone system [5]. In the former case, the excessive release of adrenaline and noradrenaline leads to overstimulation of $\beta_1$- and $\alpha_1$-adrenoreceptors, contraction of arterial smooth muscles, constriction of the arterioles, and an increased peripheral resistance [4]. In the latter case, excess secretion of renin by juxtaglomerular cells following stimulation of $\beta_1$-adrenergic receptors on their surface, along with glomerular underperfusion, leads to the reabsorption of salt and water and the release of renin, enlarging vascular volume and further increasing peripheral resistance [5]. Impairments in the functioning of vasorelaxing factors such as nitric oxide due to endothelial dysfunction as well as that of vasoactive substances such as endothelin, bradykinin, and atrial natriuretic peptide may further contribute to and/or maintain the hypertension [6].

Lifestyle modifications such as dietary changes can lower blood pressure and decrease the risk of health complications. Examples of such alterations are diets low in sodium, high in potassium, rich in vegetables, fruits, and low-fat dairy products (the so-called Dietary Approaches to Stop Hypertension (DASH) diet, as well as vegetarian diets [7]. Lifestyle modifications other than dietary changes shown to reduce hypertension are increased physical exercise, weight loss, and stress reduction [8]. The potential effectiveness of these modifications is similar to, and may even exceed the effects of a single medication [9]. Notably, several randomized controlled trials have demonstrated that even a slight blood pressure decrease of 10 mm Hg reduces the risk of death due to cardiovascular disease by 25% and the risk of stroke-related mortality by 40% [10].

If lifestyle changes are not sufficient to reduce the elevated blood pressure, antihypertensive medications are prescribed. Still, lifestyle changes are recommended in conjunction with medication [6, 11]. Among the commonly used antihypertensives are thiazide-diuretics such as chlorthalidone and hydrochlorothiazide, calcium channel blockers such as nifedipine and amlodipine, β-blockers such as atenolol and metoprolol, angiotensin-converting enzyme (ACE) inhibitors such as captopril and enalapril, and angiotensin receptor blockers such as losartan and candesartan [6, 11]. These medications may be used either alone or at certain

combinations [6, 11]. β-blockers are widely used as a first-line treatment for hypertension, but their efficacy may be inferior to those of other antihypertensive drugs [12].

Currently, close to 1 billion adults or over 20% of the world population suffer from hypertension [13]. This leads to enormous medical, economic, and human costs. In the USA alone, the total economic burden of hypertension in terms of healthcare services, medications, and absent workforce was estimated at USD 47 billion to USD 73.4 billion between the years 2009 and 2011 [14]. And management of hypertension accounts for 30% of office visits for individuals of 45–64 years, and for more than 40% of visits in those aged 60–74 years and over 75 years [15].

Hypertension occurs slightly more often in males, individuals of low socioeconomic status, and those of older age [13, 16]. It is correspondingly common in high-, medium-, and low-income countries [13, 17], but prevalence rates vary widely throughout the world, with values as low as 3.4–6.8% in rural India and as high as 68.9–72.5% in Poland [17]. There are also large differences in prevalence rates within certain countries. For instance, African American adults in the USA have among the highest rates in the world at 44% but hypertension is less common in US whites and Mexican Americans [16, 18]. Still, deaths due to non-communicable diseases including those related to hypertension occur more frequently and at earlier stages in low- and middle-income countries when compared to industrialized countries [19]. By 2030, low-income countries are even expected to have eight times more deaths due to these ailments than high-income countries [19].

## 2. Background on Suriname

### 2.1. Geography, people, and economy

The Republic of Suriname is located on the north-east coast of South America and borders the Atlantic Ocean to the north, French Guiana to the east, Brazil to the south, and Guyana to the west (**Figure 1**). The country's land area of roughly 165,000 km$^2$ can be distinguished into a northern narrow low-land coastal area that harbors the capital city Paramaribo as well as other urbanized areas, a broad but sparsely inhabited savannah belt, and a southern forested area that comprises about three-quarters of its surface area and largely consists of dense, pristine, and highly biodiverse tropical rain forest. Roughly 80% of the population of about 570,000 lives in the urbanized northern coastal zone while the remaining 20% populates the rural and interior savannas and hinterlands [20].

Suriname is renowned for its ethnic, religious, and cultural diversity, harboring various Amerindian tribes, the original inhabitants of the country; descendants from runaway enslaved Africans brought in between the sixteenth and the nineteenth century (called Maroons); those from mixed Black and White origin (called Creoles); descendants from contract workers from China, India (called Hindustanis), and Java, Indonesia (called Javanese) who arrived between the second half of the nineteenth century and the first half of the twentieth century; descendants from a number of European countries; and more recently, immigrants from various


**Figure 1.** Map of Suriname depicting the administrative districts (from: https://goo.gl/images/gqdxwn). The insert (from: https://goo.gl/images/rWXrAL) indicates the location of Suriname in South America.

Latin American and Caribbean counties including Brazil, Guyana, French Guiana, Haiti, etc. [20]. The largest ethnic groups in the country are the Hindustanis, Maroons, Creoles, and Javanese, accounting for 27.4, 21.7, 17.0, and 15.7%, respectively, of the total population [20]. All ethnic groups have largely preserved their own specific identity [21], making Suriname one of the culturally most diverse countries in the world [22].

Suriname is situated on the Guiana Shield, a Precambrian geological formation estimated to be 1.7 billion years old and one of the regions with the largest expanse of undisturbed tropical rain forest in the world with a very high animal and plant biodiversity [23]. The high mineral density of Suriname's soil contributes to its ranking as the 17th richest country in the world in terms of natural resources and development potential [24]. Suriname's most important economic means of support are crude oil drilling, bauxite and gold mining, agriculture, fisheries, forestry, and ecotourism [24]. These activities contributed substantially to the gross domestic income in 2014 of USD 5.21 billion and the average *per capita* income in that year of USD 9325 [24]. This positions Suriname on the World Bank's list of upper-middle income economies [25].

### 2.2. Non-communicable diseases

At the same time, as observed in many low- and middle-income countries [19], more and more Surinamese are adapting a Western lifestyle. For instance, only about half of the country's overall population met the levels for physical activity recommended by the World Health Organization (WHO) [26]; almost three-quarters of school children aged 13–15 years had less than 1 hour of physical activity per day and 81% had a high calorie intake [27]; and

the average tobacco and alcohol consumption *per capita* in individuals of 15 years and older was unacceptably high [28].

As a result, in 2008, 25.1% of Surinamese was obese [28, 29]; 7.4% had prediabetes and 13.0% diabetes mellitus [30]; the overall estimated prevalence of the metabolic syndrome was 39.2% [31]; and more than 25% of adults had a raised blood pressure [29, 32]. These observations indicate that Suriname, similarly to many other economically developing countries [19], is facing increasing public health threats of lifestyle-related non-communicable diseases including cardiovascular disease.

Indeed, WHO assessments from 2014 attributed 68% of total deaths in Suriname to the four main non-communicable diseases (cardiovascular, neoplastic, diabetic, and chronic respiratory diseases) and estimated that the probability of dying between age 30 and 70 years from these conditions was 14% [29]. Notably, in all approximations and previsions, cardiovascular disease was the most important cause of morbidity and mortality in Suriname. For instance, in 2012, stroke (11%), ischemic heart disease (9.1%), diabetes mellitus (7.3%), and hypertensive heart disease (4.5%) were among the leading causes of mortality, together accounting for about 800 or almost one-third of the total number of deaths in that year [29]. Indeed, with 864 fatalities in 2013 (or more than one-quarter of the total number of 3260 deaths in that year), cardiovascular disease was by far the leading cause of mortality in Suriname, ahead of death due to malignant neoplasms, external causes, perinatal complications, diabetes mellitus, and acute respiratory infections [33].

### 2.3. Hypertension

The comprehensive, nation-wide Suriname Health Study on non-communicable diseases found an overall prevalence of hypertension of 26.2% [32]. This was in the range of values reported for many other developing countries [34] as well as the relatively large Surinamese diaspora in The Netherlands [35]. Mean values for systolic and diastolic blood pressure were higher in males than in females; increased with older age; and were highest in Creoles Hindustanis, and Javanese, and lowest in Maroons and Amerindians [32]. The prevalence of hypertension in demographic risk factor subgroups differed between ethnic groups, as did the associations of ethnic groups with hypertension [32], implying the need of tailor-made intervention programs to control hypertension in Suriname [32].

The findings from two other Surinamese studies suggest that an urban lifestyle may also contribute to the development of prehypertension and hypertension in Suriname, reporting higher prevalence rates in the urban areas of the country (39 and 41%, respectively [36]), and in an urban middle-income population (31 and 41%, respectively [37]). These studies found neither gender differences nor racial/ethnic differences in the prevalence of hypertension in their participants [36, 37], but prehypertension was more common in urban males than in urban females [36] and after adjusting for age, urban African-Surinamese had significantly higher odds of having hypertension than their Asian counterparts [36].

An apparent ethnic/racial predilection of hypertension was also observed in several Dutch epidemiological studies that included Surinamese migrants. These studies reported a higher incidence of prehypertension, hypertension, malignant hypertension, and related renal complications

in participants from Afro-Surinamese and Hindustani descent compared to white individuals [35, 38–40]. These differences were tentatively explained by ethnic disparities in the perception of hypertension (supporting one of the findings of the Suriname Heath Study [32]), as well in drug adherence, blood pressure control, and/or insurance status [38, 40–42].

### 2.4. Health care system

Suriname's healthcare system is coordinated by the Ministry of Health which is headed by the Minister of Health and the Director of Health (the Chief Medical Officer). The main responsibilities of the ministry are the planning, coordination, inspection, and monitoring and evaluation of, as well as policy development and setting standards to the country's health system [43].

In 2014, the Ministry spent 5.7% of the country's gross domestic product for health expenditures which corresponded to an average *per capita* sum of USD 589. The costs of those who cannot afford these expenses are covered by the Ministry of Social Affairs. Government employees and employees of government-related companies are mandatory insured at the State Health Foundation. Essential pharmaceuticals including those for treating hypertension are imported, stocked, and distributed by the National Pharmaceutical Import and Distribution Company and are in general readily available. These medicines are identified by the Board for Essential Pharmaceuticals that consists of various players in the field of pharmacy and pharmacology in Suriname.

Primary healthcare in Suriname's coastal area and hinterlands is provided by the government-subsidized Regional Health Service and Medical Mission, respectively, each operating about 40 clinics which also dispense medicines. In 2004, Suriname had 0.45 physicians per 1000 population. Secondary care and specialist care including that for patients suffering from complications of hypertension are provided by two private and two government-supported hospitals in Paramaribo and one public hospital in the western district of Nickerie.

The Academic Hospital Paramaribo also functions as training facility for both general practitioners and medical specialists, and has to its disposal a Thorax Center for specialized cardiology care and cardiothoracic surgery. Patients with kidney failure are treated by the government-supported Kidney Dialysis Center. Cases of hypertensive crisis and other medical emergencies can get help around-the-clock from the First-aid Stations of the Academic Hospital Paramaribo and the Sint Vincentius Hospital Suriname.

Patients who need specialized therapy that is not available in Suriname (particularly those suffering from certain malignancies) are sent abroad – in general to the Netherlands or Colombia – for treatment. All expenses are covered by the Ministry of Health that has reserved a special budget for these cases.

### 2.5. Use of traditional medicines against hypertension in Suriname

Despite the broad availability of affordable and accessible modern health care throughout the entire country, the use of traditional medicines is deeply rooted in all ethnic groups in Suriname [21, 44]. This is probably for an important part attributable to the fact that all ethnic

and cultural groups in the country have preserved much of their original cultural and ethnopharmacological practices as a means of strengthening the ethnic identity during the secluded lifestyle the former colonial authorities had forced them into [21, 22]. Furthermore, Suriname's large biodiversity provides ample and readily available raw material that can be processed into traditional medicines [23]. As a result, many disease conditions including hypertension are often treated with traditional plant-based medicines and may be used instead of, or in conjunction with prescription drugs.

The medicinal plants used throughout the country have extensively been discussed in the literature [45], and those used more commonly by Hindustanis, Maroons, and Javanese have also been reviewed [46–48]. Less comprehensive accounts of these plants have been presented as well [49–55]. Together, these publications have compiled 789 Surinamese medicinal plants, 65 of which (roughly 8%) are used for treating hypertension. The latter plants, plant parts, and methods of processing are given in **Table 1**. They belong to 38 different families, the most represented of which are the Fabaceae with 7 species, the Solanaceae with 5 species, the Malvaceae and the Piperaceae with 4 species each, and the Asteraceae and the Cucurbitaceae with 3 species each (**Table 1**). In 31 cases the leaves are used, in 9 cases the whole plant, in 6 cases the fruits, in 5 cases the bark, and in 1–3 cases other plant parts such as roots and flowers (**Table 1**).

| Family | Species (Vernacular names in English; Surinamese) | Part(s) used | Mode of preparation |
|---|---|---|---|
| Acanthaceae | *Justicia pectoralis* Jacq. (Freshcut; tonkawiwiri) | Leaves | Infusion |
| Acanthaceae | *Ruellia tuberosa* L. (Minnieroot; watrakanu) | Roots and leaves | Infusion |
| Amaranthaceae | *Alternanthera brasiliana* (L.) Kuntze (Brazilian joyweed; weti ede) | Whole plant | Infusion |
| Anacardiaceae | *Mangifera indica* L. (Mango; manya) | Leaves | Infusion |
| Anacardiaceae | *Spondias dulcis* L. (Ambarella; pomme cythère) | Fresh fruits; fresh peels | Pressed to obtain juice to drink; infusion |
| Annonaceae | *Annona muricata* L. (Soursop; zuurzak) | Fresh leaves | Infusion |
| Apiaceae | *Apium graveolens* L. (Celery; soepgroenten) | Fresh leaves | Infusion |
| Apocynaceae | *Catharanthus roseus* (L.) G.Don, 1837 (Rosy periwinkle; kotomisi) | Whole plant | Infusion |
| Apocynaceae | *Geissospermum laeve* (Vell.).Miers (Pao-pereira bark; bergi bita) | Fresh stem bark | Decoction |

| Family | Species (Vernacular names in English; Surinamese) | Part(s) used | Mode of preparation |
|---|---|---|---|
| Arecaceae | *Cosos nucifera* L. (Coconut tree; kronto) | Dried husk fibers | Infusion |
| Asteraceae | *Ayapana triplinervis* (Vahl) R.M. King & H. Rob (Water hemp; sekrepatuwiwiri) | Fresh or dried leaves | Infusion |
| Asteraceae | *Cyanthillium cinereum* (L.) H. Rob (Little ironweed; doifiwiwiri) | Whole plant | Infusion |
| Asteraceae | *Melampodium camphoratum* (L.F.) Baker (Sand bitters; kanfrubita) | Whole plant | Infusion |
| Bignoniaceae | *Mansoa alliacea* (Lam.) A.H. Genry (Garlic vine; konofrukutetey) | Leaves and hardwood | Infusion |
| Boraginaceae | *Cordia schomburgkii* DC. (Canalette; blaka uma) | Fresh leaves | Infusion |
| Boraginaceae | *Cordia tetrandra* Aubl. (Clammy cherry; tafrabon) | Dried leaves | Infusion |
| Caricaceae | *Carica papaya* L. (Papaya; papaya) | Fresh fruits | None; fresh fruit eaten |
| Cecropiaceae | *Cecropia peltata* L. (Trumpet tree; uma busipapaya) | Dried leaves | Infusion |
| Cecropiaceae | *Cecropia sciadophylla* Mart. (Congo pump; man busipapaya) | Dried leaves | Infusion |
| Combretaceae | *Terminalia catappa* L. (Tropical almond; zoete amandel) | Leaves | Infusion |
| Commelinaceae | *Tripogandra serrulata* (Vahl.) Handlos. (Pink trinity; redi gado dede) | Dried leaves | Infusion |
| Convolvulaceae | *Ipomoea aquatica* Forssk. (Water spinach; dagublad) | Young leaves and stem | Cooked and eaten as a vegetable |
| Cucurbitaceae | *Cucumis sativus* L. (Cucumber; komkommer) | Fresh fruits | Pressed to obtain juice to drink |
| Cucurbitaceae | *Cucurbita moschata* Duchesne (Squash; pompoen) | Dried flowers | Infusion |
| Cucurbitaceae | *Momordica charantia* L. (Bitter melon; sopropo) | Dried whole plant | Infusion |
| Dilleniaceae | *Davilla nitida* (Vahl.) Kubizki (Sandpaper tree; schuurpapier) | Stem | Pressed to obtain sap to drink |

| Family | Species (Vernacular names in English; Surinamese) | Part(s) used | Mode of preparation |
|---|---|---|---|
| Euphorbiaceae | *Acalypha hispida* Burm. f. (Red hot cat's tail; pus'pusitere) | Leaves | Infusion |
| Fabaceae | *Copaifera guyanensis* Desf. (Copaiba; hoepelhout) | Fresh stem bark | Infusion |
| Fabaceae | *Desmodium adscendens* (Sw.) DC. (Beggar lice; toriman) | Roots | Pressed to obtain sap to drink |
| Fabaceae | *Hymenaea courbaril* L. (West Indian locust; loksi) | Stem bark | Infusion |
| Fabaceae | *Machaerium lunatum* (L.f.) Ducke (Manatee bush; brantimaka) | Leaves | Infusion |
| Fabaceae | *Mimosa pudica* L. (Shy plant; Sing sing tap yu koto) | Whole plant | Infusion |
| Fabaceae | *Senna alata* (L.) Roxb. (Candle bush; slabriki) | Leaves | Infusion |
| Fabaceae | *Tamarindus indica* L. (Tamarind; tamarinde) | Leaves | Infusion |
| Lamiaceae | *Ocimum campechianum* Mill. (Amazonian basil; smeriwiwiri) | Whole plant | Macerated for herbal bath |
| Lauraceae | *Persea americana* Mill. (Avocado; advocaat) | Dried leaves | Infusion |
| Malvaceae | *Gossypium barbadense* L. (Sea island cotton; redi katun) | Leaves | Infusion |
| Malvaceae | *Hibiscus sabdariffa* L. (Roselle; syuru) | Leaves | Infusion |
| Malvaceae | *Waltheria indica* L. (Sleepy morning; malva) | Leaves | Infusion |
| Meliaceae | *Azadirachta indica* A. Juss. (Neem; nim) | Leaves | Infusion |
| Meliaceae | *Carapa guianensis* Aubl. (Crabwood; witte krapa) | Dried stem bark | Decoction |
| Meliaceae | *Carapa procera* D.C. (African crabwood; rode krapa) | Dried stem bark | Decoction |
| Musaceae | *Musa sp., Musa x paradisiaca* (Banana; banaan) | Leaves | Infusion |
| Oxalidaceae | *Averrhoa bilimbi* L. (Bilimbi; birambi) | Fresh fruits | Pressed to obtain juice to drink |

| Family | Species (Vernacular names in English; Surinamese) | Part(s) used | Mode of preparation |
|---|---|---|---|
| Passifloraceae | *Passiflora cocciea* Aubl. (Scarlet passion flower; sneki markusa) | Leaves and stem | Infusion |
| Phyllanthaceae | *Phyllanthus amarus* Schumach. & Thonn. (Stonebreaker; finibita) | Whole plant | Infusion |
| Phytolaccaceae | *Microtea debilis* Sw. (Weak jumby pepper; eiwitblad) | Fresh or dried whole plant or leaves | Infusion |
| Piperaceae | *Peperomia pellucida* (L.) Kunth. (Pepper elder; konsakawiwiri) | Fresh leaves or whole plant | Pressed to obtain sap to drink |
| Piperaceae | *Peperomia rotundifolia* (L.) Kunth. (Swan spice; tinsensiwiwiri) | Fresh leaves or whole plant | Pressed to obtain sap to drink |
| Piperaceae | *Piper betle* L. (Betel; pahnblad) | Leaves | Infusion |
| Piperaceae | *Piper marginatum* Jacq. (Marigold pepper; aneysiwiwiri) | Leaves | Infusion |
| Poaceae | *Eleusine indica* L. (Indian goosegrass; mangrasi) | Leaves | Infusion |
| Poaceae | *Zea mais* L. (Maize; karu) | Ripe ears | Decoction |
| Rhamnaceae | *Ziziphus jujuba* L. (Jujube; olijf) | Leaves | Infusion |
| Rubiaceae | *Sipanea pratensis* Aubl. (Water lagaga; wetibaka) | Leaves | Infusion |
| Sapindaceae | *Paullinia pinnata* L. (Bread and cheese; feyfifingawiwiri) | Leaves | Pressed to obtain sap to drink |
| Sapotaceae | *Chrysophyllum cainito* L. (Star apple; sterappel) | Dried leaves | Infusion |
| Scrophulariaceae | *Scoparia dulcis* L. (Licorice weed; sibiwiwiri) | Aerial parts | Infusion |
| Simarubaceae | *Quassia amara* L. (Bitter wood; kwasibita) | Hard wood | Infusion |
| Siparunaceae | *Siparuna guianensis* Aubl. (Ant bush; yarakopi) | Aerial parts | Macerated for herbal bath |
| Solanaceae | *Physalis angulata* L. (Angular winter cherry; batotobita) | Dried leaves | Infusion |

| Family | Species (Vernacular names in English; Surinamese) | Part(s) used | Mode of preparation |
|---|---|---|---|
| Solanaceae | *Solanum leucocarpon* Dual. (Bitayouli; uma parabita) | Leaves | Macerated for herbal bath |
| Solanaceae | *Solanum macrocarpum* L. (African eggplant; antruwa) | Fresh fruits | Cooked and eaten as a vegetable |
| Solanaceae | *Solanum stramoniifolium* Jacq. (Coconilla; makadroyfi) | Fresh fruits | None; fresh fruit eaten |
| Solanaceae | *Solanum subinerme* Jacq. (Juhuna; droyfimaka) | Leaves | Infusion |

**Table 1.** Plants used for treating hypertension in Suriname.

## 3. Scientific rationale for using Surinamese plants against hypertension

In this section, 15 plants that are commonly used against hypertension in Suriname, as well as preclinical and clinical indications for their blood pressure-lowering effect and their presumed bioactive constituent(s) and mechanism(s) of action are in detail addressed. The plants are most frequently mentioned as traditional treatments for hypertension in the above-mentioned publications [45–55]. The data are summarized in **Table 2**.

| Family | Plant species (Vernacular name in English; Surinamese) | Preclinical evidence | Clinical evidence | Presumed key active constituent(s) | Presumed mechanism of action |
|---|---|---|---|---|---|
| Acanthaceae | *Ruellia tuberosa* L. (Minnieroot; watrakanu) | No | No | Unknown | Decreased blood lipid levels |
| Anacardiaceae | *Mangifera indica* L. (Mango; manya) | Yes | No | Mangiferin | Vasodilation; stimulated diuresis |
| Annonaceae | *Annona muricata* L. (Soursop; zuurzak) | Yes | No | Alkaloids, essential oils | Vasodilation |
| Apiaceae | *Apium graveolens* L. (Celery; soepgroente) | Yes | Yes | 3-n-butylphthalide | Vasodilation, stimulated diuresis |
| Arecaceae | *Cocos nucifera* L. (Coconut; kronto) | Yes | Yes | Phenolics, flavonoids | Vasodilation; decreased blood lipid levels; stimulated diuresis |

| Family | Plant species (Vernacular name in English; Surinamese) | Preclinical evidence | Clinical evidence | Presumed key active constituent(s) | Presumed mechanism of action |
|---|---|---|---|---|---|
| Caricaceae | *Carica papaya* L. (Papaya; papaya) | Yes | No | Unknown | Vasodilation; stimulated diuresis |
| Cucurbitaceae | *Cucumis sativus* L. (Cucumber; komkommer) | Yes | Yes | Unknown | Stimulated diuresis |
| Fabaceae | *Desmodium adscendens* (Sw.) DC. (Beggar lice; toriman) | No | No | Unknown | Vasodilation |
| Fabaceae | *Hymenaea courbaril* L. (West Indian locust; loksi) | No | No | Unknown | Unknown |
| Fabaceae | *Tamarindus indica* L. (Tamarind; tamarinde) | Yes | No | Unknown | Sympatico-inhibition; decreased blood lipid levels |
| Lauraceae | *Persea americana* Mill. (Avocado; advocaat) | Yes | No | Unknown | Vasodilation; decreased blood lipid levels |
| Malvaceae | *Gossypium barbadense* L. (Sea island cotton; redi katun) | Yes | No | Unknown | Vasodilation |
| Malvaceae | *Hibiscus sabdariffa* L. (Roselle; syuru) | Yes | No | Polyphenolics, flavonoids | Vasodilation; stimulated diuresis; decreased blood lipid levels |
| Meliaceae | *Azadirachta indica* A. Juss. (Neem; nim) | Yes | No | Azadirachtin, nimbinin | Vasodilation |
| Oxalidaceae | *Averrhoa bilimbi* L. (Bilimbi; birambi) | Yes | No | Unknown | Vasodilation; decreased cardiac output; stimulated diuresis |

**Table 2.** Preclinical and clinical evidence for blood pressure-lowering activity of 15 commonly used plants in Suriname for treating hypertension, the presumed key active constituent(s) in these plants, and their presumed mechanism of action.

### 3.1. Acanthaceaea – *Ruellia tuberosa* L.

The minnie root *R. tuberosa* (**Figure 2**) is probably native to Central America but has spread to various other tropical regions in South America as well as South and South east Asia. Both the English vernacular name 'cracker plant' and the Surinamese vernacular name *watrakanu* ('water canon') are probably derived from the loud crack emitted when the ripe fruits in a pod with seven to eight seeds burst open on contact with water, hurdling the seeds away. The whole plant, the leaves, and/or the roots are used in various traditional medicinal systems including those in Suriname as an antidiabetic, antipyretic, analgesic, diuretic, antihypertensive, gastroprotective, anthelmintic, antigonorrheal, antioxidant, blood-purifying, and abortifacient agent [46, 48, 49, 55, 56]. Some of these activities were supported by the results from pharmacological studies [57, 58] and could be associated with certain alkaloids, triterpenoids, saponins, sterols, and flavonoids in the plant [59].

So far, no formal experimental evaluations on the presumed antihypertensive activity of *R. tuberosa* have been reported. However, crude extracts from the leaves of the closely related species *R. patula* and *R. brittoniana* as well as n-butanolic extracts and the aqueous layers of both plant extracts displayed cardiotonic effects in isolated rabbit hearts [60]. More importantly, a preparation from *R. patula* elicited a clear blood pressure-lowering effect in pentothal sodium-anesthetized rats [61]. This effect may be attributed, at least partially, to the blood lipid-lowering actions of *Ruellia* preparations [57, 58].

### 3.2. Anacardiaceae – *Mangifera indica* L.

The mango tree *M. indica* is indigenous to Bangladesh, India, and Pakistan where it is found in the wild. It has been domesticated in India around 2000 BC, and many cultivated varieties have been produced in other tropical countries including Suriname. Both sour, unripe, and sweet, ripe mangoes are widely used in cuisine, among others, in chutneys, curries, pickles, or side dishes, and to prepare juices, smoothies, nectars, jams, and as a flavoring in ice creams, sorbets, fruit bars, and pies.

**Figure 2.** Acanthaceaea – *Ruellia tuberosa* L. (from: https://goo.gl/images/vk862o).

Preparations from flowers, unripe fruits, stone, leaves, stembark, and roots of *M. indica* also have many traditional medicinal uses, among others, to treat certain parasitic infections, uterus disorders, gastrointestinal problems, and syphilis; strengthen the blood vessels; cure varicose veins; and lower an elevated blood pressure [46, 62–64]. Several of these properties have been attributed to a number of bioactive substances in leaves and stem bark of the plant including the polyphenolic compound mangiferin [65]. This compound also displayed notable blood pressure-lowering effects in *in vitro* models and laboratory animals [66].

The apparent antihypertensive effect of *M. indica* preparations and constituents may be attributed to at least two mechanisms, namely the induction of vasodilation and the stimulation of diuresis. Indications for the former possibility are provided by the inhibition of noradrenaline-induced contractions of mesenteric arteries isolated from spontaneously hypertensive rats by a *M. indica* stem bark extract (called 'Vimang' from 'vida del mango' meaning 'life of the mango') [62]. Support for the second possibility comes from the diuretic effect of 'Vimang' in laboratory rats [67].

### 3.3. Annonaceae – *Annona muricata* L.

The exact origin of the soursop or graviola *A. muricata* (**Figure 3**) is unknown, but it is believed to be native to the Caribbean and the tropical regions of the Americas. It is now widely cultivated for its fruit, the pulp of which contains substantial amounts of vitamin C, vitamin B1, and vitamin B2 and is used to make fruit juice drinks, smoothies, as well as candies, sorbets, and ice cream flavorings. Relatively recently, *A. muricata* fruit and graviola capsules have been promoted as an alternative treatment for cancer. However, there is no medical evidence for such an activity, even though preclinical studies have shown cytotoxic effects of *A. muricata* extracts against cultured cancer cells [68].

Importantly, *Annona* species including *A. muricata* are a rich source of annonaceous acetogenins such as annonacin and annonamine, potent neurotoxins that inhibit mitochondrial

**Figure 3.** Annonaceae – *Annona muricata* L. (from: https://goo.gl/images/K9WNHr).

complex I, thereby shutting down cellular respiration [69]. These compounds have been associated – although not conclusively – with the unusually high incidence of atypical parkinsonism in the Caribbean island of Guadeloupe where relatively large amounts of *A. muricata* fruits as well as infusions and decoctions from the leaves of the plant are consumed [70].

Nevertheless, all parts of *A. muricata* are extensively used – also in Suriname – as traditional medicines against a wide diversity of conditions, among others, insomnia; nervousness, anxiety, and depression; a hangover; epilepsy; parasitic and helminth infections; diabetes mellitus; cancer; and hypertension [45, 48, 49, 55, 71]. Pharmacological studies with preparations from leaves, bark, and roots of the plant have indeed shown sedative, anxiolytic, smooth muscle-relaxant, antispasmodic, and antihypertensive effects [71–73]. Some of these effects may be attributed to the presence in the plant of bioactive constituents such as alkaloids, flavonol triglycosides, phenolics, and essential oils [71].

Indications for an antihypertensive effect were provided by the decrease in blood pressure in normotensive Sprague-Dawley rats which were intravenously treated with an aqueous leaf extract of *A. muricata* [74]. Furthermore, the extract decreased the phenylephrine-induced contractions of isolated rat and guinea pig aortic rings [74, 75], and relaxed the contractions of isolated rat aortic rings caused by high $K^+$ while apparently blocking $Ca^{2+}$ channels [74]. These findings suggest that the hypotensive effects of the *A. muricata* leaf extract may involve vasodilation mediated through peripheral mechanisms involving antagonism of $Ca^{2+}$ [74]. This effect has been attributed to alkaloids such as coreximine, anomurine, and reticulin, and some essential oil components such as β-caryophyllene [74].

However, in light of the affinity of both crude extracts and isoquinoline alkaloids isolated from *Annona* species to 5-$HT_{1A}$ receptors *in vitro* [72], and the well-known decreasing effect of 5-$HT_{1A}$ receptor agonists on blood pressure and heart rate [76], it is also possible that the antihypertensive effect of these plants occurs through a central mechanism that causes peripheral vasodilation and stimulates the vagus nerve.

### 3.4. Apiaceae – *Apium graveolens* L.

The celery *A. graveolens* (**Figure 4**) originates from the Mediterranean region, but many cultivars are now grown throughout the world. This plant has been cultivated since ancient times, initially only for its medicinal qualities, but later also as a vegetable to counter the salt-sickness of winter diets based on salted meats without green vegetables. Today, *A. graveolens* stalks, leaves, and hypocotyl are eaten raw or as an ingredient in salads, cooked as a vegetable, or as a flavoring – either fresh or dried – in soups, stews, and pot roasts.

*A. graveolens* seeds – which are in fact very small fruits – yield a valuable volatile oil that is used in perfumes and, when ground and mixed with salt, to produce celery salt for enhancing the flavor of, for instance, Bloody Mary cocktails [77]. However, celery seeds contain relatively high levels of the phenylpropene apiole that can cause abortion – sometimes with fatal consequences [78] – as well as liver and kidney damage [79] and severe allergic reactions including potentially fatal anaphylactic shock [80].

**Figure 4.** Apiaceae – *Apium graveolens* L. (from: https://goo.gl/images/7RWqQ4).

Nevertheless, *A. graveolens* is extensively used in traditional medicinal systems – including those in Suriname-against numerous diseases ranging from respiratory ailments and liver diseases to menstrual problems and hypertension [45, 81, 82].

Support for an antihypertensive effect of preparations from *A. graveolens* came from the decreased blood pressure and heart rate in salt-induced hypertensive rats, normotensive rats, and normotensive rabbits following intraperitoneal administration of extracts from seeds, stalks, or roots of the plant [83–86]. The results from studies with isolated rat aortic rings suggested that these effects occurred through vasodilation [83] or the stimulation of muscarinic receptors [84]. However, extracts from celery leaves, stalks, and roots have also been reported to stimulate diuresis in several experimental models [87, 88], providing an alternative explanation for their blood pressure-lowering effects.

The antihypertensive effects of *A. graveolens* have been attributed to the presence in the plant of the benzofuran 3-n-butylphthalide [86, 89] that, along with sedanolide, is also primarily responsible for the aroma and taste of celery. Clinical studies indeed showed a reduction in blood pressure of patients who had been given celery juice [90, 91]. These and other clinical data first led to the approval in China of 3-n-butylphthalide for the treatment of cerebral ischemia, and the preparation of clinical studies to assess n-butylphthalide formulated as softgel capsules for its safety in patients with mild to moderate acute ischemic stroke [92].

### 3.5. Arecaceae – *Cocos nucifera* L.

The coconut tree *C. nucifera* is believed to originate from the South East Asian peninsular region. It has probably spread to many other parts of the world by sea-faring traders and through marine currents, and is now cultivated in many subtropical and tropical countries. Refrigerated coconut water or coconut juice is a much appreciated refreshing drink all over the world; the fleshy coconut 'meat' is used fresh or dried in confections and desserts; coconut milk is frequently added to curries and other spicy dishes; and coconut oil is used for frying and preparing margarine and in various cosmetics [93].

Almost all parts of *C. nucifera* have long been used in traditional medicine for treating many disease conditions, among others, diarrhea, fever and malaria, renal diseases, asthma, diabetes mellitus, hair loss, menstrual disorders, venereal diseases, as an oral contraceptive, and against hypertension [45, 94]. Pharmacological studies with extracts, fractions, and isolated compounds from parts of *C. nucifera* indeed showed a variety of activities ranging from antimicrobial and antiparasitic activities to vasodilatory and antihypertensive effects [95]. Some of these observations may be related to the presence in the plant of polyphenols, tannins, flavonoids, triterpenes, saponins, steroids, alkaloids, and/or fatty acids [94].

Evidence for an antihypertensive activity from *C. nucifera* came from the relaxation of isolated rat aortic rings by an ethanolic extract of *C. nucifera* endocarp and the reduced blood pressure in salt-induced hypertensive rats treated with this preparation [96]; the decreased blood pressure in a rat model of insulin resistance and acquired systolic hypertension following administration of tender coconut water [97]; and the decrease in heart rate of hypertensive Wistar rats which were given coconut water [98]. Notably, in a small clinical study, coconut water given for 2 weeks reportedly lowered the blood pressure in 71% of hypertensive individuals [99], while the fresh vascular sap from the immature, unopened inflorescence given once per day for 5 consecutive weeks led to a decrease in blood pressure as well as a reduction in total serum cholesterol in women with stage one hypertension [100].

The antihypertensive effects have been attributed to vasodilation following the direct activation of the nitric oxide/guanylate cyclase pathway as well as stimulation of muscarinic receptors and/or the cyclooxygenase pathway which would be caused by phenolic compounds and flavonoids [96]; inhibition of lipid peroxidation, upregulation of antioxidant status, and improved insulin sensitivity [97]; a decreased cardiac beating frequency [98]; and/or a (potassium-sparing) diuretic activity [99].

### 3.6. Caricaceae – *Carica papaya* L.

The papaya plant *C. papaya* probably has its origin in Mexico and the northern parts of South America and has subsequently become naturalized throughout other tropical and subtropical regions. Various cultivars are grown for their edible ripe fruits which are usually consumed raw. The juice from ripe papayas is a popular low-calorie beverage and is also added as a flavoring in candies, jellies, and ice cream; the unripe fruit is incorporated in various dishes; the young leaves and flower buds may be consumed as vegetables; and the ground black seeds are sometimes used as a substitute for black pepper.

The relatively high amount of the protease papain in unripe fruits has been taken advantage of for centuries by the indigenous peoples of the Americans and Caribbean to tenderize meat [101]. Based on this practice, papain is now included as a component in some powdered meat tenderizers [102]. A few other important contemporary uses of papain are its medical use against dyspepsia and other digestive disorders and disturbances of the gastrointestinal tract [103], and its addition to beer as a clarifying agent [104].

Preparations from papaya leaves are traditionally used for treating a wide variety of diseases ranging from dengue fever and malaria to diabetes mellitus, hypercholesterolemia, and

hypertension [51, 101, 105]. Some of these claims may be explained, at least partially, by the presence of carotenoids and polyphenols, benzyl isothiocyanates and benzyl glucosinolates, and/or the cyanogenic substance prunasin in papaya skin, pulp, and seeds [101].

Support for the alleged antihypertensive effect of *C. papaya* was provided by the decrease in blood pressure in renal and salt-induced hypertensive Wistar rats treated with a crude ethanol extract from the unripened fruit [106]. This preparation, as well as a pentane extract from papaya seeds and an aqueous extract from papaya leaves relaxed vascular muscle tone of isolated rabbit arterial strips [106], strips of dog carotid artery precontracted with phenylephrine [107], and rat aortic ring preparations [108]. The relaxing effect of the fruit preparation was counteracted by phentolamine, suggesting that *C. papaya* contains (an) antihypertensive substance(s) that mainly exhibits $\alpha$-adrenoceptor activity [108]. *C. papaya* preparations may also exert a blood pressure-lowering effect by stimulating diuresis, as suggested by the diuretic action of an aqueous root extract in laboratory rats, accomplishing similar effects on electrolyte excretion as hydrochlorothiazide [109].

### 3.7. Cucurbitaceae – *Cucumis sativus* L.

The cucumber plant *C. sativus* is originally from South Asia, most probably India, where it has been cultivated for more than 3000 years. Nowadays, hundreds of cultivars are grown throughout the world and traded on the global market. The mature fruit contains about 90% water and is relatively low in nutrients, and many enjoy its appetizing flavor and texture, making it a popular ingredient of fresh salads as well as pickles and relishes. Cucumber extracts are also widely used in facial tonics and moisturizers, presumably because their high water and antioxidant content would protect the skin from aging [93].

Preparations from *C. sativus* leaves, seeds, flowers, and fruits are also used in various traditional medicines for treating, among others, bacterial and parasitic infections, kidney and gall stones, as well as thrombosis and hypertension [45, 50, 52, 56, 110]. Preclinical evaluation of the plant parts showed various pharmacological activities including blood pressure-lowering effects [111, 112]. Some of these effects may be associated with the presence in the plant of bioactive compounds such as cucurbitacins, cucumegastigmanes I and II, cucumerin A and B, vitexin, and orientin [111, 112].

Importantly, a Chinese study found a significant reduction in blood pressure and a marked increase in coronary blood flow of patients receiving *C. sativus* vine compound tablets, as well as improved myocardial contraction in laboratory animals while no toxic effects were noted [113]. Furthermore, a relatively recent study conducted in Indonesia reported a reduction in mean blood pressure in elderly patients receiving 100 g of cucumber in juice form for 7 days [114].

The antihypertensive effects of these preparations may be associated with the stimulation of diuresis. Indeed, an ethanolic extract from the leaves of *C. sativus*, either alone or as part of a polyherbal formulation, had a moderately stimulatory effect on diuresis in laboratory rats when compared to furosemide [115]. Also, an ether extract from the seeds of *C. melo* increased diuresis in anesthetized dogs [116], and an aqueous extract from the leaves of *C. trigonus*

caused a comparable diuretic effect as hydrochlorothiazide in conscious albino rats [117]. In the former study, urinary chloride excretion was increased suggesting that the extract had decreased tubular reabsorption [116].

### 3.8. Fabaceae – *Desmodium adscendens* (Sw.) DC.

The glue sticks *D. adscendens* is commonly encountered in forests, grasslands, secondary/disturbed vegetation, old cultivated fields, and roadsidesin tropical areas. The leaves and stems have probably been used for thousands of years by native peoples for a variety of health issues, including liver ailments, respiratory diseases, backache, rheumatism, gonorrhea, ovarian inflammation, and epilepsy [118, 119].

Main compounds in *D. adscendens* are flavonoids, triterpenes, saponins, amines, and alkaloids [120]. Pharmacological studies with *D. adscendens* leaf extracts showed, among others, spasmolytic effects in isolated guineas pig trachea and ilei precontracted with histamine [121, 122].

In Suriname, *D. adscendens* is generally known as '*konkruman*' ('informer') or '*toriman*' ('story teller') because the sticky pods stay clinging to clothing, betraying the unapproved presence of the bearer 'in the field', that is, away from home. Indigenous folklore believes that preparations from the plant attract and hold fortune and prosperity while at the same capturing and removing bad luck and disease [45]. A tea prepared from the macerated roots is also used as an antihypertensive [46]. This effect may be attributable to the above-mentioned relaxing effect of certain constituents of the plant on smooth muscle cells [121, 122] – possibly including those in blood vessel walls – but there are no scientific indications to support this presumption.

### 3.9. Fabaceae – *Hymenaea courbaril* L.

The courbaril, West Indian locust, or jatoba *H. courbaril* (**Figure 5**) is a common tree in the Caribbean, Central America, and South America. The hardwood is very durable and is used for manufacturing furniture, flooring, window frames, staircases, as well as canoes. The seeds are situated in a hard pod and are surrounded by an edible dry pulp that has an unpleasant scent reminiscent of foot odor. For this reason, the tree is also known as 'stinking toe' and 'old man's toe'. However, the pulp has a high content of starches and proteins and a sweet taste. It is often eaten raw; may be dried and powdered for making snacks; and may also be mixed with water to prepare a drink called 'atole'.

The stembark of the tree produces an orange, soft, sticky resin called 'animé', French for 'animated', referring to the large numbers of insects that are entrapped in it [123]. Animé has a pleasant fragrance and is used for the production of incense, perfume, and varnish [123]. Interestingly, the indigenous peoples of the Amazon have used *H. courbaril* resin for centuries to preserve the colors on their pottery [45]. Preparations from this substance, along with those from several other parts of the plant, have traditionally also been used in various South American and African countries for treating a variety of conditions such as anemia, kidney problems, dysfunctions of the respiratory system, and abdominal ailments [45, 123, 124].

**Figure 5.** Fabaceae – *Hymenaea courbaril* L. (from: https://goo.gl/images/ePJjyr).

Many bioactive compounds have been identified in leaves, seeds, and trunk resin of *H. courbaril*, including flavonoids, terpenoids, phenolic acids, steroids, and coumarins [124, 125]. Some of these compounds have been related to the myorelaxant, anti-inflammatory, and antimicrobial effects including activity against dengue virus type-2 observed in pharmacological studies with *H. courbaril* preparations [124, 126, 127]. In Suriname, the stembark is used to prepare a tea that would treat a similar variety of ailments as well as hypertension [45]. Whether the latter activity may be associated with vasodilation following relaxation of the smooth muscles [126] including those in the blood vessel walls remains to be determined.

### 3.10. Fabaceae – *Tamarindus indica* L.

The tamarind *T. indica* is probably indigenous to tropical Africa where it grows in the wild. It has been cultivated for centuries on the Indian subcontinent, and has been introduced in South America including Suriname by Spanish and Portuguese colonists in the sixteenth century. The fruit is a pod with a hard, brown shell that contains up to 12 seeds surrounded by a sweet and sour pulp that is used in cooking, to flavor foods, in refreshing drinks, and as a key ingredient of Worcestershire sauce.

Preparations from *T. indica* leaves, seeds, fruits, and roots are extensively used in folk medicine, among others, for treating abdominal discomfort, microbial and parasitic infestations, as an aphrodisiac, and against hypertension [48, 128, 129]. These parts of the plant contain various phenolic compounds, terpenes, sugars, as well as mucilage and pectin [128, 129]. Some of these constituents have been associated with, among others, antioxidant, anti-hyperlipidemic, and cardioprotective effects of the plant in laboratory models [130].

Furthermore, an aqueous tamarind seed extract produced a decrease in blood pressure, heart rate, as well as serum LDL, cholesterol, and HDL levels in streptozotocin-induced diabetic and hypertensive rats [131]. As well, administration of the dried and pulverized fruit pulp led to a decrease in diastolic blood pressure as well as total cholesterol and LDL-cholesterol levels in human subjects [132]. The blood pressure-lowering effects of the *T. indica* preparations have

been suggested to occur through direct sympatho-inhibition [131], protection of the body against oxidative assault that could initiate the development of hypertension [131, 133], and/or lowering of blood lipid levels [133, 134].

### 3.11. Lauraceae – *Persea americana* Mill.

The avocado tree *P. americana* probably originates from Central America and the western parts of South America and was presumably domesticated as early as 5000 BC. Today, avocados are a successful cash crop with a high commercial value. Avocado is mostly eaten raw; (prolonged) cooking makes it inedible, causing a chemical reaction that confers a bitter taste to it. It is an ingredient of many servings and dishes and is often used in vegetarian cuisine as a substitute for meats because of its relatively high content of monounsaturated fats [135]. The rather expensive oil extracted from avocados is mostly used for salads or dips and in cosmetics and toiletries [136].

The stem bark, fruits, seeds, and leaves of *P. americana* are used in traditional medicine in Africa, the West Indies, as well as South and Central America including Suriname for treating, among others, menstrual problems, gastrointestinal ailments, bronchitis, diabetes mellitus, hypercholesterolemia, and hypertension [45, 46, 49, 52, 55, 137, 138]. Pharmacological evaluations with animal models provided some support for these ethnopharmacological claims [139]. These effects may partially be associated with the aliphatic acetogenins, terpenoid glycosides, furan ring-containing derivatives, flavonoids, and coumarins in various parts of the plant [140].

Evidence for an antihypertensive effect of *P. americana* leaf and seed preparations came from the relaxing effects they produced in isolated guinea pig atrial muscle strips, rat portal veins, and rat thoracic aortic rings precontracted with noradrenaline [141] and the blood pressure-lowering effects they produced in laboratory animals [141–143].

The mechanisms responsible for these effects may involve vasorelaxation by substances that inhibit $Ca^{2+}$ influx and stimulate the synthesis and release of endothelium-derived relaxing factors and vasoactive mediators [144], modulation of ACE activity [145], and/or lowering of total cholesterol, triglycerides, VLDL, and/or LDL [143, 145, 146]. However, a clinical study found no benefit with respect to body weight, BMI, and percentage body fat, and no difference in serum lipids, fibrinogen, blood flow, or blood pressure when avocados were substituted for mixed fats in an energy-restricted diet [147].

### 3.12. Malvaceae – *Gossypium barbadense* L.

The sea island cotton or Egyptian cotton *G. barbadense* (**Figure 6**) is believed to have emerged in Peru as a cross between *G. herbaceum* L. and *G. raimondii* Ulbrich or *G. gossypioides* (Ulbrich) Standley. It is now widely cultivated in the warmer parts of the world, and is an important industrial and export product of Egypt, the West Indies, Sudan, Peru, and the USA.

Cotton is the soft white fibrous substance that surrounds the seeds of the plant and helps in the dispersal of the seeds [148]. It consists of 88–96% $\alpha$-cellulose, 3–6% hemicellulose, and 1–2%

**Figure 6.** Malvaceae – *Gossypium barbadense* L. (from: https://goo.gl/images/NN46ra).

lignin [148]. Since about 2500 BC, the fibers are used for making sewing thread, yarn, cordage, and fishing nets, and more recently also for making coffee filters, paper, surgical dressings, and nitrocellulose-based explosives [148]. The seed oil can be incorporated in, among others, margarine and mayonnaise, but also in soaps, cosmetics, lubricants, and protective coatings [148]. The oil as well as other parts of *Gossypium* species contains the triterpenoid aldehyde gossypol that causes infertility in males [149]. Other constituents of *G. barbadense* are alkaloids, flavonoids, total phenols, cyanogenic glycosides, and saponins [148, 150].

*G. barbadense* preparations are widely used in traditional medicine. In many African countries as well as the Guianas including Suriname, preparations from leaves, roots, and seed oil are used for treating a multitude of diseases ranging from eye affections, otitis media, bronchitis, and menstrual problems to malaria, convulsions, gonorrhea, leprosy, and hypertension [45, 51, 52, 55, 151]. Pharmacological studies have supported some of these folk medicinal uses [151, 152].

The presumption of a blood pressure-lowering effect of *G. barbadense* was supported by the dose-dependent hypotensive effect of a fraction of a crude leaf extract in laboratory rats [153]. The results from parallel studies with several agonists and antagonists of acetylcholine receptors suggested that this occurred through an action on the central nervous system comparably to that of the centrally acting $\alpha_2$-adrenergic agonist clonidine [153]. On the other hand, an aqueous extract from *G. barbadense* leaves decreased the tension of isolated guinea pig aorta rings stimulated with phenylephrine (a selective $\alpha_1$-adrenergic receptor agonist) by 15–35% [75], suggesting that it may lower an elevated blood pressure by decreasing the peripheral vascular resistance.

### 3.13. Malvaceae – *Hibiscus sabdariffa* L.

The roselle *H. sabdariffa* (**Figure 7**) probably originates from Africa and is presumably domesticated in Sudan about 6000 years ago. It was initially cultivated for its seed and later for its leaves and bright red colored calyces which are particularly in the USA and Germany

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**Figure 7.** Malvaceae – *Hibiscus sabdariffa* L. (from: https://goo.gl/images/BRZcTZ).

processed to give food colorings. The seed oil can be used for cooking and the seeds are eaten roasted as a snack. However, *H. sabdariffa* seeds probably contain toxic substances and may be better used for manufacturing soaps and shrubs [154]. Young shoots, leaves, and calyces can be included in certain dishes, and fresh or dried calyces are used to prepare flavorful and slightly acidic herbal teas, refreshing beverages that may be carbonated, cocktails with rum, as well as jams.

Preparations from *H. sabdariffa* leaves, calyces, and roots are widely used in traditional medicines because of their presumed antimicrobial, antioxidant, anticancer, hepatoprotective, hypocholesterolemic, antidiabetic, diuretic, and antihypertensive properties [45, 155, 156]. Phytochemical and pharmacological studies supported some of these uses [155, 156].

The results from preclinical studies have associated the potential antihypertensive (and cardioprotective) properties of particularly tea made from roselle calyces with its abundant content of polyphenolic compounds such as chlorogenic acids [157], as well as flavonoid compounds such as kaempferol, quercetin, and anthocyanins [156, 158]. Chlorogenic acids (modestly) reduced an elevated blood pressure [157, 159]. Kaempferol may have a protective effect in heart diseases [160]. Quercetin caused the release of NO from vascular endothelium, increasing renal vasorelaxation and kidney filtration, stimulating diuresis and decreasing blood pressure [161]. And the anthocyanins may exert antioxidant effects which inhibit LDL oxidation, impeding atherosclerosis, an important cardiovascular risk factor [162]. Alternatively, anthocyanins may decrease blood pressure by inhibiting ACE activity [163]. These compounds, along with the flavonoids and the chlorogenic acids, have also been suggested to decrease hypertension by stimulating diuresis following modulation of aldosterone activity [164].

However, comprehensive reviews and a meta-analysis suggest that the evidence for the use of *H. sabdariffa* preparations against hypertension is insufficient and recommend more high-quality animal and human studies to demonstrate benefit from these substances in this condition [162, 165, 166].

### 3.14. Meliaceae – *Azadirachta indica* A. Juss.

The neem tree *A. indica* is originally from the Asian subcontinent and is now grown in various tropical and semi-tropical regions. The bitter-tasting shoots and flowers are incorporated into various dishes, while preparations from leaves, bark, and fruits are consumed during many Hindu ceremonies, festivals, and commemorations.

*A. indica* leaves and seeds contain potent antiparasitic, insecticidal, and antimicrobial compounds such as the limonoids azadirachtin and nimbinin [167]. For this reason, dried neem leaves are placed in cupboards and storage facilities for grains to prevent damage from insects and burned to keep away mosquitoes, while the seed oil is used as a key ingredient of non-synthetic ecofriendly pesticides in agriculture, acting as an antifeedant, repellent, and egg-laying deterrent for insects [168]. The seed cake that remains after oil extraction is used as a fertilizer, enriching the soil with organic matter, and at the same time reducing nitrogen loss by inhibiting nitrification and averting damage to crops by termites and nematodes [168]. Neem oil is also a valuable ingredient of a large variety of cosmetics such as soaps, shampoos, balms, creams as well as toothpastes and nail polishes [169].

Parts of *A. indica* have been used for centuries in traditional and alternative medicinal systems in India and Suriname against a wide variety of diseases ranging from microbial infections and malaria to diabetes mellitus and hypertension [45, 170]. Some of these applications are supported by the results from pharmacological studies and may be related to the actions of, among others, azadirachtin and nimbinin [167, 171].

Indications for a potential antihypertensive effect of *A. indica* preparations were provided by the inhibitory effect of *A. indica* yogurt on ACE activity *in vitro* [172], and the blood pressure-lowering effect of leaf extracts in (salt-induced) rat models [173, 174]. Studies with laboratory rabbits suggested that these effects might also be due to vasodilation mediated through a combination of $Ca^{2+}$ channel blockade, NO-inhibitory mechanisms, and cardiac depressant activity [175].

### 3.15. Oxalidaceae – *Averrhoa bilimbi* L.

The bilimbi *A. bilimbi* (**Figure 8**) presumably originates from Indonesia. It has been introduced in several Southeast Asian countries, and has spread to Australia as well as the Caribbean, Central America, and South America. The fruits can be eaten raw with salt and spice, pickled to obtain sweet and sour side dishes, incorporated in certain dishes as a souring agent, made into jams, or squashed to obtain a cooling beverage. However, *A. bilimbi* fruits (as well as leaves) contain high levels of oxalate [176] which may cause tubular necrosis and acute kidney failure when the concentrated juice is drunk on a daily basis [177].

Parts of *A. bilimbi* have been important sources of medicines since antiquity. Decoctions, infusions, powders, and pastes have been used in several traditional medicinal systems including those in Suriname for preventing and treating many diseases such as skin eruptions, cough, cold, syphilis, diarrhea, obesity, diabetes mellitus, microbial infections, and hypertension [46, 178]. Physicochemical and pharmacological studies supported some of these uses [179].

**Figure 8.** Oxalidaceae – *Averrhoa bilimbi* L. (from: https://goo.gl/images/THfTgV).

Indications for efficacy against hypertension of *A. bilimbi* came from the decreased contractility of isolated guinea pig atria precontracted with norepinephrine upon exposure to an aqueous extract from the leaves [180]. Such an extract also produced a substantial antihypertensive effect in an *in vivo* study with cats [181]. The mechanisms underlying these observations may be associated with a decrease in cardiac output following alterations in intracellular calcium metabolism and/or phenomena involving the muscarinic receptor [180]. It is also possible that the relatively high levels of oxalate in these preparations [176] promote diuresis. A third possible mechanism involves inhibition of ACE activity, as suggested by the *in vitro* ACE-inhibitory effect of an *A. bilimbi* leaf ethanol extract which was comparable to that of captopril [182].

## 4. Concluding remarks

This chapter has addressed the plants that are used in Suriname for treating hypertension. About 60 of the approximately 800 medicinal plants in Suriname are used against this condition ([45–55]; **Table 1**), indicating both the high need of antihypertensive medications and the high demand for traditional plant-derived for treating this condition in the country. As mentioned above, the prevalence of hypertension and other cardiovascular diseases is relatively high in Suriname [32, 36, 37], while most Surinamese have a long tradition of using ethnopharmacological preparations for treating their diseases [21, 44].

However, an extensive evaluation of 15 plants that are commonly used against hypertension in Suriname indicates that there is little scientific evidence for clinical efficacy against this condition. As shown in **Table 2**, 3 of the 15 plants (*A. graveolens*, *C. nucifera*, and *C. sativus*) had undergone preclinical as well as clinical evaluation against hypertension and turned out positive in at least some of the clinical studies. However, the clinical studies merely comprised a handful, although those with 3-n-butylphthalide in *A. graveolens* were sufficiently encouraging to prepare larger scale clinical evaluations [90–92].

Nine other plants (*M. indica*, *A. muricata*, *C. papaya*, *T. indica*, *P. americana*, *G. barbadense*, *H. sabdariffa*, *A. indica*, and *A. bilimbi*) have only been tested in preclinical models of hypertension (**Table 2**), relatively few of which involved animal studies. And three of the plants (*R. tuberosa*, *D. adscendens*, and *H. courbaril*) have never been assessed for potential antihypertensive effects, not even in preclinical models (**Table 2**). On the bright side, with the exception of *H. courbaril*, there were in all cases suggestions about the mechanisms that may be involved in the antihypertensive effects (**Table 2**). Then again, the chemical substances responsible for these effects were only provided for 6 plants (*M. indica*, *A. muricata*, *A. graveolens*, *C. nucifera*, *H. sabdariffa*, and *A. indica*; **Table 2**).

These data clearly indicate that the scientific evidence accumulated so far to support the use of plant-based traditional medicines in Suriname against hypertension is scant. This raises not only the possibility that patients treat their disease with substances that may be ineffective, but also that they may run the risk of unknown or unforeseen adverse effects. For these reasons, it is necessary to subject these plants to comprehensive phytochemical and pharmacological investigations, elaborate preclinical evaluations, and well-designed and well-executed clinical studies to definitely establish their roles in the treatment of hypertension. Obviously, these enterprises will require considerable efforts from both academia and industry, but may eventually payoff when considering the importance of ancient wisdom and folk medicine to drug discovery and development programs [183].

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Chapter 10

# Herbal Medicines in African Traditional Medicine

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Additional information is available at the end of the chapter

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**Abstract**

African traditional medicine is a form of holistic health care system organized into three levels of specialty, namely divination, spiritualism, and herbalism. The traditional healer provides health care services based on culture, religious background, knowledge, attitudes, and beliefs that are prevalent in his community. Illness is regarded as having both natural and supernatural causes and thus must be treated by both physical and spiritual means, using divination, incantations, animal sacrifice, exorcism, and herbs. Herbal medicine is the cornerstone of traditional medicine but may include minerals and animal parts. The adjustment is ok, but may be replaced with –' Herbal medicine was once termed primitive by western medicine but through scientific investigations there is a better understanding of its therapeutic activities such that many pharmaceuticals have been modeled on phytochemicals derived from it. Major obstacles to the use of African medicinal plants are their poor quality control and safety. Traditional medical practices are still shrouded with much secrecy, with few reports or documentations of adverse reactions. However, the future of African traditional medicine is bright if viewed in the context of service provision, increase of health care coverage, economic potential, and poverty reduction. Formal recognition and integration of traditional medicine into conventional medicine will hold much promise for the future.

**Keywords:** African, traditional, medicine, spirituality, divination, herbalism

## 1. Introduction

The development and use of traditional herbal medicine (THM) have a very long historical background that corresponds to the Stone Age. In the continent of Africa, the practice of traditional healing and magic is much older than some of the other traditional medical sciences [1] and seems to be much more prevalent compared to conventional medicine. African traditional medicine is a

form of holistic health care system that is organized into three levels of specialty, which include divination, spiritualism, and herbalism, though these may overlap in some situations [2, 3].

A traditional healer is one who provides medical care in the community that he lives, using herbs, minerals, animal parts, incantations, and other methods, based on the cultures and beliefs of his people. He must be seen to be competent, versatile, experienced, and trusted [4]. In other definitions, priestesses, high priests, witch doctors, diviners, midwives, seers or spiritualists, and herbalists are included. Traditional medical practitioner (TMP), however, seems to be a modern acceptable concept agreed on by the Scientific Technical and Research Commission (STRC) of the Organization of African Unity (OAU), which is now African Union (AU). In specific cultures, these people go by their local names, depending on their tribe, such as *Sangoma* or *inyanga* in South Africa, *akomfo, bokomowo* in Ghana, *niam-niam*, *shaman,* or *mugwenu* in Tanzania, *nga:nga* in Zambia, *shaman or laibon* in Kenya, and *babalawo*, *dibia,* or *boka*, etc. in Nigeria [5]. It is commonplace to see traditional healers dressed in certain peculiar attires, with head bands, feathers, and eyes painted with native chalk.

**Figure 1** below is a typically adorned traditional healer from South Africa.

Traditional medicine is viewed as a combination of knowledge and practice used in diagnosing, preventing, and eliminating disease. This may rely on past experience and observations handed down from generation to generation either verbally, frequently in the form of stories, or spiritually by ancestors or, in modern times, in writing [6]. It has also been said that before attaining knowledge in traditional African medicine, one is often required to be initiated into a secret society, as many characteristics of this form of medicine can only be passed down to initiates. The importance of traditional medicine, however, dwindled during the colonial period, whereby it was viewed as inferior to Western medicine. It was thus banned completely in some countries due to its association with witchcraft /voodoo, supernatural, and magical implications, in which case, it was also termed "*juju"* (Nigeria) or "native medicine," since it made use of charms and symbols which were used to cast or remove spells. Some forms of treatment may also involve ritual practices such as animal sacrifices to appease the gods, if the ailment was envisaged to be caused by afflictions from the gods, especially in the treatment of the mentally ill patients.

**Figure 1.** Spiritual healer or *Sangoma* from South Africa (Source—Ancient Origins).

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## 2. Concept of illness and disease

In African traditional setting, there was always an explanation as to why someone was suffering from a certain disease at a particular time. According to Ayodele [7], diseases mostly revolve around witchcraft/sorcery, gods or ancestors, natural, as well as inherited. Illness in the African society is different from the allopathic Western medicine point of view. Illness is believed to be of natural, cultural, or social origin [8]. Cultural or social illness is thought to be related to supernatural causes such as angered spirits, witchcraft, or alien/evil spirits, even for conditions now known to be well understood in modern medicine such as hypertension, sickle-cell anemia, cardiomyopathies, and diabetes. African traditional beliefs consider the human being as being made up of physical, spiritual, moral, and social aspects. The functioning of these three aspects in harmony signified good health, while if any aspect should be out of balance, it signified sickness. Thus, the treatment of an ill person involves not only aiding his/her physical being but may also involve the spiritual, moral, and social components of being as well. Many traditional medical practitioners are good psychotherapists, proficient in faith healing (spiritual healing), therapeutic occultism, circumcision of the male and female, tribal marks, treatment of snake bites, treatment of whitlow, removal of tuberculosis lymphadenitis in the neck, cutting the umbilical cord, piercing ear lobes, removal of the uvula, extracting a carious tooth, abdominal surgery, infections, midwifery, and so on. According to Kofi-Tsekpo [9], the term "African traditional medicine" is not synonymous with "alternative and complementary medicine." African traditional medicine is the African indigenous system of health care and therefore cannot be seen as an alternative.

## 3. Herbal medicine

Herbal medicine is a part and parcel of and sometimes synonymous with African traditional medicine. It is the oldest and still the most widely used system of medicine in the world today. It is used in all societies and is common to all cultures. Herbal medicines, also called botanical medicines, vegetable medicines, or phytomedicines, as defined by World Health Organization (WHO) refers to herbs, herbal materials, herbal preparations, and finished herbal products that contain whole plants, parts of plants, or other plant materials, including leaves, bark, berries, flowers, and roots, and/or their extracts as active ingredients intended for human therapeutic use or for other benefits in humans and sometimes animals [10, 11].

Herbal medicine is a special and prominent form of traditional medicine, in which the traditional healer, in this case known as the herbalist, specializes in the use of herbs to treat various ailments. Their role is so remarkable since it arises from a thorough knowledge of the medicinal properties of indigenous plants and the pharmaceutical steps necessary in turning such plants into drugs such as the selection, compounding, dosage, efficacy, and toxicity. The use of herbal medicines appears to be universal in different cultures. However, the plants used for the same ailments and the modes of treatment may vary from place to place. The plants used for medicinal purposes are generally referred to as medicinal plants, i.e., any plant in which one or more of its organs/parts contain substances that can be used for therapeutic purposes, or in a more modern concept, the constituents can be used as precursors for the synthesis

of drugs. For example, a number of plants have been used in traditional medicine for many years without scientific data to back up their efficacy. In this case, these plants, whole or parts, which have medicinal properties, are referred to as crude drugs of natural or biological origin. They may further be classified as "organized drugs," if such drugs are from plant parts with cellular structures such as leaf, bark, roots, etc., and "unorganized drugs," if they are obtained from acellular portions of plants such as gums, balsams, gels, oils, and exudates. Compared with modern allopathic medicine, herbal medicine is freely available and can easily be accessed by all [12, 13]. As a result, there is limited consultation with traditional healers because there is a fairly good knowledge of common curative herbs especially in the rural areas except in the case of treatment of chronic diseases [12]. Even where consultation is done, there is lack of coherence among traditional healers on the preparation procedures and correct dosage of herbal medicines [14]. However, according to WHO [15], at least 80% of people in Africa still rely on medicinal plants for their health care. In Nigeria, and indeed the entire West Africa, herbal medicine has continued to gain momentum, some of the advantages being low cost, affordability, availability, acceptability, and apparently low toxicity [16, 17].

A detail of plant parts used in herbal medicines is as follows:

1. Roots—i.e., the fleshy or woody roots of many African plant species are medicinal. Most of the active ingredients are usually sequestered in the root bark rather than the woody inner part.
2. Bulbs—A bulb is an underground structure made up of numerous leaves of fleshy scales, e.g., *Allium sativa* (garlic) and *Allium cepa* (onions).
3. Rhizomes—Woody or fleshy underground stem that grows horizontally and brings out their leaves above the ground, e.g., *Zingiber officinale* (ginger), which is used for respiratory problems; *Imperata cylindrica* (spear grass) for potency in men and *Curcuma longa* (turmeric), an antioxidant, anti-inflammatory, and anticancer drug.
4. Tubers—Swollen fleshy underground structures which form from stems/roots, e.g., potatoes and yams such as *Dioscorea dumetorum (ona-(igbo))* for diabetes and *Gloriosa superba* for cancer.
5. Bark—The outer protective layer of the tree stem or trunk. It contains highly concentrated phytochemicals with profound medicinal properties. A host of plants have barks of high medicinal value.
6. Leaves, stems, and flowers of many plants are also medicinal.
7. Fruits and seeds also contain highly active phytochemicals and essential oils.
8. Gums, exudates, and nectars, which are secreted by plants to deter insects and grazing animals and to seal off wounds, are very useful in the pharmaceutical industries.

Sale of herbs in form of dried or fresh plant parts is as lucrative as the prepared medicines. They are usually displayed in markets and sold with instructions on how to prepare them for maximum efficacy.

**Figure 2** is a photograph of an herbalist displaying his herbs for sale.

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**Figure 2.** Herbs on display (Source—Ancient Origins).

In many areas of Africa, the knowledge of plant species used and the methods of preparing and administering the medication, especially for serious ailments, still reside with traditional healers. Secrecy and competition still surround the use of these medications, with the healers often being reluctant to hand down their knowledge to anyone but trusted relatives and initiates [18].

### 3.1. Methods of preparation and dosage forms

Methods of preparation of herbal medicines may vary according to place and culture. The plant materials may be used fresh or dry. With experience, a particular method is chosen to increase efficiency and decrease toxicity. Generally, different methods of preparation include:

1. Extraction—This is prepared with solvent on a weight by volume basis. Sometimes, the solvent is evaporated to a soft mass.
2. Infusions are prepared by macerating the crude drug for a short period of time in cold or hot water. A preservative such as honey may be added to prevent spoilage.
3. Decoctions are made by boiling woody pieces for a specified period of time and filtered. Potash may be added to aid extraction and as preservative.

4. Tinctures are alcoholic infusions which if concentrated may be diluted before administration.
5. Ashing—The dried parts are incinerated to ash, then sieved and added as such to water or food.
6. Miscellaneous—Other types include liniments for external applications in liquid, semi-liquid, or oily forms containing the active substances; lotions which are liquid preparations intended for skin application. Poultices are prepared from macerated fresh part of plant containing the juice from the plant and applied to skin. Snuffs are powdered dried plant inhaled through the nostrils. Dried plants may be burnt, and their charcoal is used as such. Gruels are cereals/porridges made from grains, to which dried powdered plant or its ash is added to be taken orally. Mixtures are sometimes prepared with more than one plant to give synergistic or potentiating effects of the composite plants.

There are also different methods of administration. Apart from the common routes such as oral, rectal, topical, and nasal, other methods include smoking a crudely prepared cigar containing dried plant materials or by passive inhalation. Others are steaming and inhaling the volatile oils exuding from the boiling plant material. These can be used to relieve congestion, headaches, or pulmonary problems. Sitz baths are used for piles [19, 20].

### 3.2. Ethnobotanical surveys

Information on plants is obtained through ethnobotanical surveys, which involves the study of plants in relation to the culture of the people. Many plants are used in African traditional medicine, but little information is available on their active ingredients/constituents. Ethnobotanical surveys involve the interaction with the people and their environment and are therefore participatory approaches, in which local people are able to contribute their knowledge on the uses of plants within their environment. This may involve the identification, documentation, conservation, and utilization of medicinal plants. Much of the ethnomedicinal information is largely not validated. In Nigeria, a number of authors have published a lot of data on plants with their curative values [16, 20, 21]. These provide a vast array of information for scientific research and validation. Preliminary scientific knowledge is drawn from studies on *in vitro* and *in vivo* bioassays on crude extracts of various plants.

Using plants as medicine provides significant advantages for treating many chronic conditions. For example, information from folklore medicine in Nigeria has it that *Rauvolfia vomitoria* is used for treating hypertension and other nervous conditions while *Ocimum gratissimum* is used for treating diarrheal diseases. Others include *Citrus paradise* seeds for resistant urinary tract infections, pure honey for chronic wound treatment, *Carica papaya* seeds for intestinal parasites, *Garcinia kola* seeds for pain and inflammation, and *Aloe vera* for skin diseases. The same is also true for plants from other African countries [22]. Knowledge of most of these curative properties was accumulated over time from evidence-based observations. A few examples of some Nigerian plants and their uses are shown in **Table 1**.

**Table 1** shows some selected Nigerian medicinal plants and their uses.

The curative properties of herbal medicine are validated through scientific investigations, which seek to understand the active chemistry of the plants [23]. The therapeutic activity of a plant is due to its complex chemical nature with different parts of the plant providing

| Family | Specie | Local name | Part used | Medicinal uses |
|---|---|---|---|---|
| Acanthaceae | *Acanthus montanus* | | Stem, twig | Syphilis, cough, emetic, vaginal discharge |
| Amaranthaceae | *Amaranthus spinosus* | | Whole plant | Abdominal pain, ulcers, gonorrhea |
| Apocynaceae | *Alstonia boonei* | | Root, bark, leaves | Breast development, filarial worms |
| Bombacaceae | *Adansonia digitata* | | leaves, fruit, pulp, bark | Fever, antimicrobial, kidney, and bladder disease |
| Combretaceae | *Combretum grandiflorum* | Ikedike | leaves | Jaundice |
| Euphorbiaceae | *Bridelia ferruginea* | iri, kirni | leaves, stem, bark, root | insomnia, mouth wash, gonorrhea |
| Hypericaceae | *Harungana madagascariensis* | Otoro, alilibarrafi | Stem, bark, root bark | piles, trypanosomiasis |
| Fabaceae | *Afzelia africana* | Apa-igbo, akpalata | leaves, roots, bark, seeds | gonorrhea, hernia |
| Liliaceae | *Gloriosa superba* | mora, ewe aje, baurere | tubers, leaves | gonorrhea, headlice, antipyretic |

**Table 1.** Some selected Nigerian medicinal plants and their uses. Source: Abd El-Ghani [51].

certain therapeutic effects. Chemical components or phytochemicals found in plants that are responsible for the various therapeutic effects include alkaloids, glycosides, tannins, acids, coumarins, sterols, phenols, etc. Many modern pharmaceuticals have been modeled on or were originally derived from these chemicals, for example, aspirin is synthesized from salicylic acid derived from the bark of *Salix alba* and the meadowsweet plant, *Filipendula ulmaria*. Quinine from *Cinchona pubescens* bark and artemisinin from *Artemisia annua* plant are antimalarial drugs. Vincristine and vinblastine are anticancer drugs derived from Madagascar periwinkle (*Catharanthus roseus*), used for treating leukemia. Morphine and codeine, derived from the opium poppy (*Papaver somniferum)*, are used in the treatment of diarrhea and pain relief, while digitoxin is a cardiac glycoside derived from foxglove plant (*Digitalis purpurea*) [22, 24]. Medicinal plants are also important materials for the cosmetic industries.

The use of herbal drugs dwindled toward the end of the 19th century due to the advent of synthetic chemistry. However, there was a resurgence of interest in plant medicines in more recent years, as synthetic drugs became less effective due to high levels of resistance and also due to higher toxicity and cost. It is estimated that more than half of all synthetic drugs in use are derived from plants [25].

## 4. Clinical practice of African traditional/herbal medicine

In African traditional medicine, the curative, training, promotive, and rehabilitative services are referred to as clinical practices Clinical practice can also be viewed as the process of

evaluating conditions of ill-health of an individual and its management. These traditional health care services are provided through tradition and culture prescribed under a particular philosophy, in which the norms and taboos therein are strictly adhered to and form the basis for the acceptability of traditional health practitioners in the community they serve [26].

According to the World Health Organization (WHO), health is defined as "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity" [15, 27] and views health as one of the fundamental rights of every human being. The combination of physical, mental/emotional, and social well-being is commonly referred to as the health triangle.

The recognition of disease and illnesses in traditional Africa meant that every society needed to devise means of containing its problem. Worldwide, different societies have different herbal traditions that have evolved over a long period of time. Similar to modern day Western treatment patterns, African traditional societies also involved herbalism, surgery, dietary therapy, and psychotherapy, in addition to traditional exorcism, rituals, and sacrifice [28]. These medical technologies had evolved even before the coming of the "white man" (Arabs and Europeans). Successful treatments became formalized, sometimes with prescriptions of correct methods of preparation and dosage. In addition, the ingredients and the manner of preparation varied with the ailment but were also dependent on various factors such as geographical, sociological, and economic, but the significant point was that in many cases, patients were cured of their physical or psychological ailments [29]. In African traditional medicine, traditional health practitioners (THP) assess patients in order to diagnose, treat, and prevent disease using their expertise by the following methods:

### 4.1. Divination

Divination means consulting the spirit world. It is a method by which information concerning an individual or circumstance of illness is obtained through the use of randomly arranged symbols in order to gain healing knowledge. It is also viewed as a way to access information that is normally beyond the reach of the rational mind. It is a transpersonal technique in which diviners base their knowledge on communication with the spiritual forces, such as the ancestors, spirits, and deities [30]. It is, therefore, an integral part of an African traditional way of diagnosing diseases. The "spirit world" is consulted to identify the cause of the disease or to discover whether there was a violation of an established order from the side of the sick person. This is established through the use of cowry shells, throwing of bones, shells, money, seeds, dice, domino-like objects, or even dominos themselves, and other objects that have been appointed by the diviner and the spirit to represent certain polarities on strips of leather or flat pieces of wood. The divining bones that form the large majority of the objects include bones from various animals such as lions, hyenas, ant-eaters, baboons, crocodiles, wild pigs, goats, antelopes, etc. The bones represent all the forces that affect any human being anywhere, whatever their culture [31]. Because of the revealing powers of divination, it is usually the first step in African traditional treatment and medicine [32].

### 4.2. Interviews and medical reports

Oral interviews are sometimes used by some traditional healers to find out the history behind the sickness, where they have been for treatment and how long the person has been in that

condition. This approach enables them to know how to handle the matter at hand. In some cases, the healer might require other family members to speak on behalf of the sick person in cases where the patient is not able to express him/herself. In modern times, after the healing process, they also advise their clients or patients to go for medical diagnoses to confirm that they are healed, and the medical reports sometimes serve for record keeping for future reference and are a way of assuring other clients of their ability and credibility. Due to the holistic approach of the healing process, the healers do not separate the natural from the spiritual or the physical from the supernatural [33]. Thus, health issues are addressed from two major perspectives—spiritual and physical.

### 4.3. Spiritual perspective

Spiritual-based cases are handled in the following manner:

i. **Spiritual protection**: If the cause of the disease is perceived to be an attack from evil spirits, the person would be protected by the use of a talisman, charm, amulets, specially designed body marks, and a spiritual bath to drive the evil spirits away. These are rites aimed at driving off evil and dangerous powers, spirits, or elements to eliminate the evils or dangers that may have befallen a family or community [34].

ii. **Sacrifices**: Sacrifices are sometimes offered at the request of the spirits, gods, and ancestors. Sometimes, animals such as dogs and cats are slaughtered or buried alive at midnight to save the soul of the one at the point of death, with the belief that their spirits are strong enough to replace life [30]. There is also the view that because they are domestic animals and are very close to people, sometimes when they see that someone very close to them is about to die, they offer their lives for that person to live. This is true especially where the animal dies mysteriously; thus, it is believed that it had offered its life in place of the life of its owner. Rituals are sometimes performed in order to consecrate some herbs without which the medicine is meaningless. Divine and ancestral sanctions are considered necessary before and during the preparation and application of medicine [35].

iii. **Spiritual cleansing**: Spiritual cleansing may be required of the sick person to bathe at specific times for a prescribed number of days either with water or animal blood poured from head to toe. This practice is common among some communities in Ghana [34].

iv. **Appeasing the gods**: If a disease is perceived to be caused by an invocation of a curse or violation of taboos, the diviner appeases the ancestors, spirits, or the gods according to the severity of the case. The individual is often required to provide certain items for sacrifice and/or libation, such as spotless animals (dove, cat, dog, goat, and fowl), local gin, cola nut, eggs, and plain white, red, or black cloth. These items are usually specified by the gods. The used items may be thrown into the river, left to rot, or placed at strategic places, usually at cross roads at the outskirts of the community, depending on the nature and severity of the case [36].

v. **Exorcism**: This is a practice of expelling demons or evil spirits from people or places that are possessed or are in danger of being possessed by them. Many of the traditional communities believe that illness, especially mental illness, is mostly caused by evil spirits. Exorcism can only be performed by a religious leader or a priest who has the authorities

and powers to do so. Sometimes, an effigy made of clay or wax would be used to represent the demon and would ultimately be destroyed. Exorcism may be accompanied by dancing to the beating of drums, singing, and sometimes flogging the individual or touching him/her with strange objects such as animal tails and other objects to chase out the spirit. The possessed individual would be somewhat agitated but would only calm down as soon as the spirit is removed from the body. Exorcism is practiced, not only in Africa but also in ancient Babylonian, Greek, and other ancient cultures of the Middle East. This practice is also performed for those who are mentally challenged. In their view, until the possessed person is delivered from the power of that evil spirit, the person will not have his or her freedom. Hence, the practice of exorcism is considered necessary [37].

vi. **Libation**: Libation involves pouring of some liquid, mostly local gin on the ground or sometimes on objects followed by the chanting or reciting of words. It is usually regarded as a form of prayer. The liquid could also be water or in modern times, wine, whisky, schnapps, or gin. Some cultures also use palm wine, palm oil, and coconut water, while some others use corn flour mixed with water [38]. Libation pouring as is practiced in some communities has three main parts, namely invocation, supplication, and conclusion.

- **Invocation:** They first invoke the presence of the almighty God, mother earth, and the ancestors. According to the practitioners of libation pouring, offering the ancestors and spirits drink is a way of welcoming them
- **Supplication:** After invocation, requests are made to the invoked spirits, gods, or ancestors to intercede on their behalf for mercy and forgiveness of offenses such as taboo violations and to seek for spiritual consecration (cleansing) of either the community or individual(s). The content of the prayer is usually case specific [38].
- **Conclusion:** At the end of the libation pouring, they thank the invoked ancestors and spirits. They finally invoke curses on those who wish them evil or failure, meaning that in the process of prayer, it would be unwise to seek the welfare of one's enemy. Therefore, those who wish evil (i.e., enemies, witches, and people with evil powers) on them should fall and die [8]. In this process, the person pouring the libation would be pouring the drink or liquid on the ground as he is reciting the prayers, followed by responses to each prayer point by observers.

### 4.4. Physical perspectives

If the illness is of a physical nature, the following approaches are exploited:

a. **Prescription of herbs**: Herbs are prescribed to the sick person according to the nature of the illness. Each prescription has its own specific instructions on how to prepare the herb, the dose, dosing regimen, and timeframe

b. **Clay and herbs application:** Application of a mixture of white clay with herbs may be relevant in some of the healing processes. The mixture is applied to the entire body for a number of days, especially in the case of skin diseases. The view is that the human body is

made out of the dust or ground; therefore, if the body has any problem, you would have to go to where it came from to fix it. The use of clay with some special herbs is also sometimes used for preventive rituals to ward off the evil spirits responsible for illness.

c. **Counseling:** The sick person is sometimes counseled on the dos and don'ts of treatment, the foods to eat or avoid, to be generally of good behavior as established by society and culture, failure of which the good spirits would withdraw their blessings and protection and therefore, open doors for illness, death, drought, and other misfortunes. This is mostly done when it is an issue of a violation of a taboo [39].

The THPs use experience, added to the accumulated knowledge handed down by their ancestors in order to provide effective and affordable remedies for treating the main ailments (such as malaria, stomach infections, respiratory problems, rheumatism, mental problems, bone fracture, infertility, complications of childbirth, etc.) that afflict populations of the African region and in addition offer counseling/advice and solutions to prevent future reoccurrence.

## 5. Peculiarities in traditional herbal medicine practice from selected African countries

As there is an African way of understanding God, in the same way, there is an African way of understanding the visible world around us—the cattle, trees, people, and cities, as well as the unseen world, the supernatural world of spirits, powers, and diseases [40, 41]. People developed unique indigenous healing traditions adapted and defined by their culture, beliefs, and environment, which satisfied the health needs of their communities over centuries [15]. Different ethnic groups and cultures recognize different illnesses, symptoms, and causes and have developed different health-care systems and treatment strategies. In spite of these, profound similarities exist in the practice of traditional medicine in different African countries. The increasing widespread use of traditional medicine has prompted the WHO to promote the integration of traditional medicine and complementary and alternative medicine into the national health care systems of some countries and to encourage the development of national policy and regulations as essential indicators of the level of integration of such medicine within a national health care system. The peculiar practices of some countries are described below:

### 5.1. Ghana

In Ghana, herbal medicine is usually the first approach to treat any illness, especially in the rural areas. Lack of access to medical facilities, poor roads/infrastructure, and affordability of treatment are some of the main reasons for the prevalent use of traditional healers. Besides, ratio of medical doctors to the patients is about 1:20000, while for traditional healers, the ratio is 1:200. This plays a major role in health care decision making. Other influencing factors, such as financial situation, education, and advice from friends and family, contribute to choice of type of health care [42]. Traditional medicine has a long history in Ghana. This knowledge is typically in the hands of spiritual healers, but the vast majority of families have some knowledge of traditional medicine, which is often inherited and passed down through the generations via folklore.

Most people in Ghana fully accept modern science-based medicine, but traditional medicine is still held in high regard. They believe in the physical and spiritual aspects of healing. Herbal spiritualists collectively called "*bokomowo*" indulge in occult practices, divinations, and prayers and are common all over the country. Tribal vernacular names of traditional healers include "*gbedela*" (Ewe), "*kpeima"* (Dagomba), "*odunsini"* (Akan), and "*isofatse"* (Ga).

In some Ghanaian communities, especially in the Akan communities, traditional healers and practitioners are of the opinion that disobeying taboos is one of the ways that could lead to severe illness to the person(s) or community involved [43]. Taboos form an important part of African traditional religion. They are things, or a way of life, that are forbidden by a community or a group of people. One could also become sick through invocation of curses in the name of the river deity, *Antoa*, upon the unknown offender.

In today's Ghana, a traditional Medical Directorate has been established in the ministry of health to provide a comprehensive, recognizable, and standardized complementary system of health based on excellence in traditional and alternative medicine. Establishing centers for integrating scientific research into plant medicines and incorporating traditional medicine into university curricular are now the current status in Ghana [44]. Also, degree-awarding traditional medical schools now train and graduate traditional medical doctors.

### 5.2. Zambia

The first principle is diagnosis followed by complex treatment procedures using plants from the bush, followed by many rituals, the ultimate aim being to cure disease. Serious or chronic illnesses require "chizimba," which means sealing a disease or illness away forever. This involves killing a lizard and burning the heart with roots of certain trees and grinding with charcoal. Tiny cuts are made on the ailing area and left breast and the mixture rubbed into the cuts.

Plants may be used singly or in combination with other plants. The plant parts are harvested fresh, pulverized, and left to dry first, then soaked in water or other solvents like local gin. Some plant materials are burnt as charcoal and used as powder. Six major types of treatment common to the 72 or more ethnic groups in Zambia include drinking, eating, drinking as porridge, making small cut on skin and applying, bathing with herbs, dancing to exorcize spirits, and steaming with boiling herbs. The Zambian traditional healer is called *Nga:nga* [45].

### 5.3. Tanzania

In Tanzania, traditional medicine has been practiced separately from allopathic medicine since colonial period but is threatened by lack of documentation, coupled with the decline of biodiversity in certain localities due to the discovery of natural resources and excessive mining, climate change, urbanization, and modernization of agriculture. Traditional medicine in Tanzania is used by people of all ages in both urban and rural areas for both simple and chronic diseases. The traditional healers are of four different types: diviners, herbalists, traditional birth attendants, and bone setters. Erosion of indigenous medical knowledge occurred as most of the traditional health practitioners were aging and dying, and the expected youths who would inherit the practice were shying away from it and those in the rural areas dying of

AIDS. Another constraint to the development of traditional medicine in Tanzania was lack of data on seriously threatened or endangered medicinal plant species [46]. As it stands today, the traditional medical practice is under the Ministry of health. Efforts are being made to scale up traditional medical practice by creating awareness of the importance of traditional medicine and medicinal plants in health care and training of traditional health practitioners on good practice, conservation, and sustainable harvesting [47].

### 5.4. South Africa

Traditional medicine features in the lives of thousands of people in South Africa every day. In fact, it is estimated that 80% of the population uses traditional medicines that are collectively called muti. Muti is a word derived from medicinal plant and refers to traditionally sourced plant, mineral, and animal-based medicines.

In addition to herbs, traditional medicine may use animal parts and minerals. However, only plant muti is considered a sustainable source of medicines. South African traditional plant medicines are fascinating with so many colors, forms, and effects. It is an art to know these and to use them correctly to bring about health and harmony, which is the aim of all true traditional healers. The plant muti is commonly sold in specific sections of the open markets in South Africa, as shown in **Figure 3**.

**Figure 3.** *Muti* market in Johannesburg (Source—Ancient Origins).

**Figure 3** shows a muti market in Johannesburg.

The traditional healers known as the *Sangoma or Inyanga* are holders of healing power in the southern Bantu society. In a typical practice with a female traditional practitioner, the methods used depended on the nature of the complaint. For example, headaches are cured by snuffing or inhaling burning medicines, bitter tonics are used to increase appetite, sedative medicines for depression, vomiting medicines to clean the digestive system, and antibiotic or immune boosting medicines for weakness or infection. She often counseled patients before administering appropriate healing herbal medicines [48].

### 5.5. Kenya

As in many countries in Sub-Saharan Africa, Kenya is experiencing a health worker shortage, particularly in rural areas. Anecdotal evidence suggests that globally, traditional medical practitioners (THMPs) are the only point of contact for at least 80% of the rural poor [10]. In Kenya, very little quantitative evidence or literature exists on indigenous medicine and the health practices of alternative healers or the demand for traditional medical practitioners or on the role that they play in providing particular health services for the rural poor. As a result, TMPs currently do not have sufficient formal government recognition and are often sidelined in Human Resources in Health (HRH) planning activities; further, their activities remain unregulated. Community-derived data show that hospitals are preferred if affordable and within reach. There is also significant self-care and use of pharmacies, although THMPs are preferred for worms, respiratory problems, and other conditions that are not as life threatening as infant diarrhea and tuberculosis [49].

Traditional Medicine Practitioners in Kenya generally known as *"laibon"* far outnumber conventional or allopathic providers. Their practices are no different from other African countries. In many cases, they combine both modern and herbal medicines, especially if they are afflicted by chronic ailments such as HIV/AIDS, hypertension, cancer, and diabetes [50].

### 5.6. Nigeria

The various ethnic groups in Nigeria have different health care practitioners aside their western counterparts, whose mode of practice is not unlike in other tribes. The Yorubas call them "babalawos," the Igbos call them "dibia," while the Northerners or Hausas call them "boka" [5]. Traditional/herbal medicines have impacted the lives of people, especially in the rural areas where access to orthodox medicare is limited [51]. Apart from the lack of adequate access and the fear of expired or fake drugs, the prohibitive cost of western medicine makes traditional medicine attractive. Various training schools exist for both herbal medicine and homeopathy, and as such, most modern traditional health practitioners have great knowledge of pharmaceutical properties of herbs and the shared cultural views of diseases in the society and they combine their knowledge with modern skills and techniques in processing and preserving herbal medicines, as well as in the management of diseases. In oral interviews with two modern traditional medicine practitioners, Dr. Anselm Okonkwo of Saint Rita's Ethnomedical Research Center, Enugu, Nigeria, a Veterinary doctor, and Mr. Uche Omengoli of CGP Herba-Medical

Consultancy and Research, Enugu, Nigeria, a medical laboratory technologist, both revealed that their knowledge and 'gift' of medical practice were handed down by aged relatives who were also in the practice by both tutelage and supernatural means. Knowledge was however improved by further training, interaction, and discussion with colleagues, consultation of books on herbal medicine, and the Internet. They claimed that the practice was very lucrative, especially since some ailments that defied orthodox medicine such as epilepsy and madness could be completely treated by traditional medicine. The two men divulged that the old concept of secrecy and divination is gradually fading away and being taken over by improved skills, understanding, and use of modern equipment where necessary. Both however agreed to the "mystic" or esoteric power of plants, which they sometimes employ in their diagnosis and treatment. An Enugu, Nigeria-based nonprofit organization, the Association for Scientific, Identification, Conservation and Utilization of Medicinal Plants of Nigeria (ASICUMPON), of which the writer is a member, is committed to "highlighting the usefulness of medicinal plant resources and scientific assessment, preparation and application of these for the betterment of humanity and as Africa's contribution to modern medical knowledge," under the chairmanship of Reverend Father Raymond Arazu. Another prominent member of the association, Professor J.C. Okafor, who is a renowned silviculturist and plant taxonomist, is helping members to identify and classify plants. The group also shares and documents evidence-based therapeutic knowledge. Such groups and training schools exist all over Nigeria. ASICUMPON has published a checklist of medicinal plants of Nigeria and their curative values [19]. Other books have likewise produced useful information [16, 21]. The greatest problem still facing herbal medicine in Nigeria is lack of adequate standardization and safety regulations [52]. However, the interest and involvement of educated and scientific-minded people in herbal medicine practice have to a great extent demystified and increased the acceptability of these medicines by a greater percentage of would-be skeptical populace. A photograph of Dr. Anselm Okonkwo is shown here in **Figure 4**, who is a veterinary doctor and a typical educated and knowledgeable herbal practitioner with the writer after interviewing him.


**Figure 4.** The writer with Dr. Okonkwo of St Rita's Ethnomedical Research Center, Enugu, after the interview.

## 6. Adverse effects of herbal medicines

An adverse drug reaction is defined as "a harmful or troublesome reaction, due to intervention related to the use of a healing substance, which envisages risk from future administration and requires prevention or explicit treatment, or alteration of dose and method of administration, or withdrawal of the medical substance." Any substance with a healing effect can generate unwanted or adverse side reactions. As with synthetic drugs, the quality, efficacy, and safety of medicinal plants must also be assured. Despite the widespread use of herbal medicines globally and their reported benefits, they are not completely harmless. In as much as medicinal herbs have established therapeutic effects, they may also have the potential to induce adverse effects if used incorrectly or in overdose. The likelihood of adverse effects becomes more apparent due to indiscriminate, irresponsible, or nonregulated use and lack of proper standardization. These concerns have been the focus of many international forums on medicinal plants research and publications [53]. The rich flora of Africa contains numerous toxic plants, though with interesting medicinal uses. The toxic constituents (e.g., neurotoxins, cytotoxins, and metabolic toxins) from these plants can harm the major systems of the human body (cardiovascular system, digestive system, endocrine system, urinary system, immune system, muscular system, nervous system, reproductive system, respiratory system, etc.) [25].

In a survey in Lagos metropolis, Nigeria, among herbal medicine users, it was found that herbal medicine was popular among the respondents but they appeared to be ignorant of its potential toxicities [22]. Several herbal medicines have been reported to have toxic effects. Current mechanisms to track adverse effects of herbal medicines are inadequate [15, 54, 55]. Consumers generally consider herbal medicines as being natural and therefore safe and view them as alternatives to conventional medications. Only very few people who use herbal medicines informed their primary care physicians. It is therefore likely that many adverse drugs reactions go unrecorded with either patients failing to divulge information to health services, and no pharmacovigilance analyses are being carried out, or the observations are not being reported to appropriate quarters such as health regulatory bodies. Establishing a diagnosis of herbal toxicity can be difficult. Even when herbal-related toxicity is suspected, a definitive diagnosis is difficult to establish without proper analysis of the product or plant material. Very few adverse reactions have been reported for herbal medicines, especially when used concurrently with conventional or orthodox medicines [15]. The results of many literature reviews suggest that the reported adverse drug reactions of herbal remedies are often due to a lack of understanding of their preparation and appropriate use.

In a research of liver and kidney functions in medicinal plant users in South-East Nigeria, it was found that liver problems were the most prominent indices of toxicity as a result of chronic use [56]. **Figures 5** and **6** refer to the effect of consumption of herbal medicines and length of usage respectively, on serum enzymes, as an index of liver function. Toxic components in these herbs such as alkaloids, tannins, oxalates, etc., may likely be responsible for such observed toxicities.

Another important source of toxicity of herbal medicines worth mentioning is microbial contamination due to poor sanitary conditions during preparation [57]. Toxicity may also arise as a result of herb-drug interaction in situations where there is co-administration of herbal

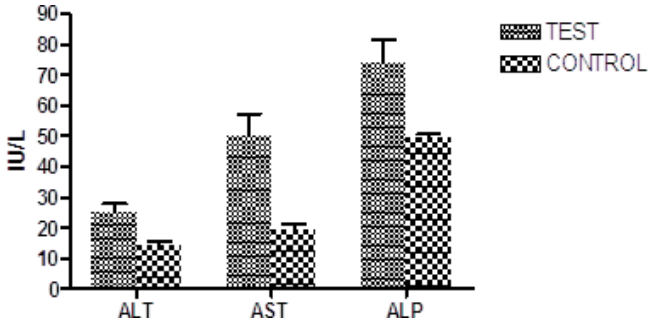


**Figure 5.** Serum enzyme levels in herbal medicine users (test group) and nonusers (control).

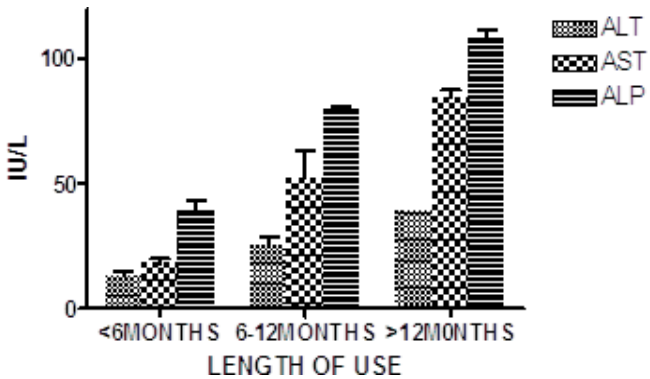


**Figure 6.** Effect of length of use of herbal medicine on serum enzyme levels.

medicines with some conventional drugs or supplements [11]. Incorrect identification and misuse of plants may also lead to toxicity.

It is therefore pertinent at this time to present correct, timely, and integrated communication of emerging data on risk as an essential part of pharmacovigilance, which could actually improve the health and safety of patients. This calls for improved collaboration between traditional practitioners and modern health care professionals, researchers, and drug regulatory authorities. The latency period between the use of a drug and the occurrence of an adverse reaction, if determined, can also help in its causality assessment in pharmacovigilance management [25]. Such information can be invaluable in the interpretation of drug safety signals, and facilitate decisions on further protective actions to be taken concerning future use.

## 7. Traditional African medicine and its relationship with modern medicine

Plants have been the primary source of most medicines in the world, and they still continue to provide mankind with new remedies. Natural products and their derivatives represent more than 50% of all drugs in clinical use, of which higher plants contribute more than 25%. These

are no doubt more important in developing countries but quite relevant in industrialized world in the sense that pharmaceutical industries have come to consider them as a source or lead in the chemical synthesis of modern pharmaceuticals [24, 58]. A number of African plants have found their way in modern medicine. These plants which had been used traditionally for ages have through improved scientific expertise been the sources of important drugs. Examples of such drugs and their sources include:

Ajmalicine for the treatment of circulatory disorders and reserpine for high blood pressure and mental illness both from *Rauvolfia serpentina*, L-Dopa for parkinsonism is obtained from *Mucuna* species, vinblastine and vincristine used for the treatment of leukemia from *Catharanthus roseus*, physostigmine from *Physostigma venenosum*, or "Calabar bean," used as a cholinesterase inhibitor, strychnine from the arrow poison obtained from the plant *Strychnos nux-vomica*, atropine and hyoscine from *Atropa belladonna* leaves. A host of other African plants with promising pharmaceutical potentials include *Garcinia kola*, *Aframomum melegueta*, *Xylopia aethiopica*, *Nauclea latifolia*, *Sutherlandia frutescens*, *Hypoxis hemerocallidea* (African wild potato), and *Chasmanthera dependens* as potential sources of antiinfective agents, including HIV, with proven activities [59], while *Cajanus cajan*, *Balanites aegyptiaca*, *Acanthospermum hispidum*, *Calotropis procera*, *Jatropha curcas*, among others, as potential sources of anticancer agents [60]. Biflavonoids such as kolaviron from *Garcinia kola* seeds, as well as other plants, have antihepatotoxic activity [61].

## 8. Advantages and disadvantages of traditional herbal medicine

Both Western or traditional medicine come with their own challenges. Currently, there are many western drugs on the market which have several side effects, in spite of their scientific claims. In like manner, African traditional herbal medicine or healing processes also have their own challenges. The following are reported as some of the advantages and disadvantages:

### 8.1. Advantages

African herbal medicine is "holistic" in the sense that it addresses issues of the soul, spirit, and body. It is cheap and easily accessible to most people, especially the rural population. It is also considered to be a lot safer than orthodox medicine, being natural in origin.

### 8.2. Disadvantages

Some of the disadvantages include improper diagnosis which could be misleading. The dosage is most often vague and the medicines are prepared under unhygienic conditions, as evidenced by microbial contamination of many herbal preparations sold in the markets [57]. The knowledge is still shrouded in secrecy and not easily disseminated. Some of the practices which involve rituals and divinations are beyond the scope of nontraditionalists such as Christians who find it incomprehensible, unacceptable, and difficult to access such services [8, 62].

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## 9. Conclusion

Long before the advent of Western medicine, Africans had developed their own effective way of dealing with diseases, whether they had spiritual or physical causes, with little or no side effect [63]. African traditional medicine, of which herbal medicine is the most prevalent form, continues to be a relevant form of primary health care despite the existence of conventional Western medicine. Improved plant identification, methods of preparation, and scientific investigations have increased the credibility and acceptability of herbal drugs. On the other hand, increased awareness and understanding have equally decreased the mysticism and "gimmicks" associated with the curative properties of herbs. As such, a host of herbal medicines have become generally regarded as safe and effective. This, however, has also created room for quackery, massive production, and sales of all sorts of substandard herbal medicines, as the business has been found to be lucrative.

African traditional herbal medicine may have a bright future which can be achieved through collaboration, partnership, and transparency in practice, especially with conventional health practitioners. Such collaboration can increase service and health care provision and increase economic potential and poverty alleviation. Research into traditional medicine will scale up local production of scientifically evaluated traditional medicines and improve access to medications for the rural population. This in turn would reduce the cost of imported medicines and increase the countries' revenue and employment opportunities in both industry and medical practice. With time, large scale cultivation and harvesting of medicinal plants will provide sufficient raw materials for research, local production, and industrial processing and packaging for export.

The scope of herbal medicines in Africa in the near future is very wide, but the issue of standardization is still paramount [64].

This therefore calls for ensuring that the raw materials should be of high quality, free from contaminations and properly authenticated, and samples deposited in University, National, and Regional herbaria. There is need for pharmacopeia to provide information on botanical description of plants, microscopic details, i.e., pharmacognosy, origin, distribution, ethnobotanical information, chemical constituents and structures, methods of quality control, pharmacological profile and clinical studies, including safety data, adverse effects, and special precautions [21, 62]. Such wealth of information will no doubt bring about uniformity in production quality. Rather than viewing African herbal medicine to be inferior, it may yet turn out to be the answer to the treatment of a host of both existing and emerging diseases such as malaria, HIV/AIDS, ebola, zika, etc., that may defy orthodox medicine.

### 9.1. Future perspectives

Future perspectives in this area include:

**a.** All countries in the African region must seek to recognize traditional medical practice by putting out regulations and policies that will be fully implemented to ensure that the

THPs are qualified and accredited but at the same time respecting their traditions and customs. They must also be issued with authentic licenses to be renewed frequently.

**b.** Incorporation of systems that will provide an enabling environment to promote capacity building, research, and development, as well as production of traditional herbal medicines of high standards.

**c.** Harnessing the importance of traditional herbal medicine and integrating the conventional medicine to combat priority diseases such as malaria, HIV/AIDS, diabetes, sickle cell anemia, hypertension and tuberculosis.

**d.** Raising the standards of African traditional herbal medicine to international standards through intercountry collaboration.

These if achieved would put African herbal medicine in an admirable position in the World health care system.

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Chapter 11

# Herbal Medicine

Nontokozo Z. Msomi and Mthokozisi B.C. Simelane

Additional information is available at the end of the chapter

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**Abstract**

Herbal medicine has gained cumulative popularity in today's medical practice. These treatments are the synthesis of therapeutic experiences of generations of traditional physicians for over hundreds of years. However, most of these applications are unorthodox, with over 80% of the world's population depending on some form of traditional medicine. The increase in the use of herbal products is due to their cultural acceptability, availability, affordability, efficacy and safety claims. This upsurge has led to the improvements in the quality and analysis of herbal products to be made with clinical research advancements in their safety and efficacy. The World Health Organization has recognized the importance of herbal medicine to the health of many people. Therefore, developing guidelines to evaluate herbal medicine by using modern control procedures and applying suitable standards. The current review aims to describe the present state and the projected future of herbal medicine.

**Keywords:** herbal medicine, safety and toxicity, regulations

## 1. Introduction

The practice of herbal medicine is the oldest form of healthcare which has been used for decades in developing and developed countries. Primitive people have depended on nature for food, shelter, clothing and medicine to cure ailments. These humans distinguished useful herbs with beneficial effects from those that were inactive or toxic [1]. According to literature approximately 50,000 plant species are stated to have medicinal properties [2]. Thus, the basis of modern medicinal drugs such as aspirin, morphine, digitoxin and quinine were synthesized through scientific validation of herbal medicine [3, 4]. Plant based drugs awareness advanced gradually and has been passed on, therefore setting a foundation for many traditional medicine systems around the globe [1].

Today herbal medicine is still the primary healthcare system for about 80% of the world's population, especially in the developing countries [1, 5, 6]. There has been also a sudden increase in the utilization of herbs as prescription drugs in developed countries such as France and Germany [3, 7]. However, there is a concern that not all herbal medicines are safe as reported [8]. Over the years the use of traditional medicine has provided us with valuable formulas on the selection, preparation and application of herbal remedies. The same vigorous method clinically and scientifically must be implemented to verify the effectiveness and safety of curative products, to be viable alternative to western medicine [4].

## 2. Herbal medicine

The World Health Organization (WHO) defines herbal medicine as a practice which includes herbs, herbal materials, herbal preparations and finished herbal products, that contain as active ingredients parts of plants, or other plant materials, or combinations [9]. These herbs are derived from plant parts such as leaves, stems, flowers, roots, and seeds [10].

Herbal drugs contain active ingredients, plant parts or plant materials in the processed or crude state with certain excipients, i.e., dilutions, solvents or preservatives [10, 11]. These active ingredients protect plants from damage and diseases and contribute to the plants aroma, flavor and color. Scientifically, they are known as phytochemicals which include several classes such as saponins, flavonoids, glycosides, tannins, alkaloids and terpenoids [12]. Phytochemicals have been scientifically validated over the years to provide health benefits for humans [13]. For example herbal remedies used as sedative and stomachic mixtures contain mainly aromatic plant species which have therapeutic essential oils, possessing antibacterial, stomach-soothing and antispasmodic properties. Plant species which have a high tannin content are used in mixtures for diarrhea and stomach ulcers; generally showing antimicrobials, astringents and anti-inflammatory activities [14, 15]. Bioactive and disease preventing phytochemicals present in medicinal plants are shown in **Table 1**.

| Class | Characteristic | Use | Pharmacological activity | Reference |
|---|---|---|---|---|
| Alkaloids | Organic nitrogenous bases, bitter taste, colorless/yellow, crystalline solids, liquids | Biosynthesis of pharmaceuticals | Anticancer, antimicrobial, amoebicidal, anti-inflammatory, | [16, 17] |
| Saponins | Soap-like forming property, bitter taste, | Detergent, wetting and emulsifying agent | Antifeedant, antifungal, antiobesity, antioxidant | [18] |
| Tannins | Water-soluble, leather hides, | Used for cationic dyes, production of ink, | Antimutagens, anticarcinogens, antimicrobial, | [12, 19] |
| Flavonoids | Free radical scavenger | Prevents microbial infection, | Anti-inflammatory, antimicrobial, antibacterial, antioxidant | [20] |

**Table 1.** Properties of some major constituents of medicinal plants.

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## 3. Historical perspective of herbal medicine

The use of plants as medicines dates 60,000 years ago according to ancient Babylon reports. In Egypt and China written material on herbal medicine dates approximately 5000 years back, in Asia Minor and Greece it dates 2500 years ago [21]. There are various herbal medicinal systems, the practices and philosophy of each are influenced by the region within which it first evolved [22]. In China, they have their own system known as the Traditional Chinese medicine which has been used throughout history [23]. The oldest known herbal book in the world *The Devine Farmer's Classic of Herbalism* was compiled in China about 2000 years ago, numerous herbal pharmacopeias and various monographs on specific herbs exist through the composed information on herbs [3]. Ayurveda, a healthcare system that has been used in India for over 5000 years, that was founded by ancient Hindu healers and saints. Its *materia medica* provides a comprehensive description of over 1500 herbs and 10,000 formulations. The Indian government has recognized Ayurveda to be a complete healthcare system in comparison to western medicine [24]. Kampo medicine, the Japanese herbal medicine dates back over 1500 years with approximately 148 formulations [25].

## 4. Common herbal medicines

### 4.1. *Echinacea purpurea*

*Echinacea* has an extensive history on the use as medicines, mainly for infections such as septic wounds and syphilis, also as an anti-toxin for snakebites [26]. The species *Echinacea purpurea* from this genus is a well-known medicinal plant used in treating snake bites, toothache, skin disorders, bowel pain, chronic arthritis, seizure and cancer, traditionally [27]. *E. purpurea* possesses secondary metabolites including caffeic acid derivatives, alkamides, glycoproteins and polysaccharides alleged to be biologically and pharmacologically active [26, 27]. Allergic reactions can occur and are usually mild, but individuals with a history of asthma, atopy, or allergic rhinitis may experience severe allergic reactions that include dyspnea and anaphylaxis [26, 28]. Other adverse effects include abdominal pain, urticarial, nausea, erythematous, rash and pruritus [26].

### 4.2. Garlic

Traditionally, garlic (*Allium sativum*) has been used to treat colds, chronic bronchitis, coughs, respiratory catarrh, bronchitic asthma and influenza [26]. Additionally it is used mainly to manage hypertension and hypercholesterolemia. It contains alliin, which upon chopping or crushing is activated by alliinase in the absence of acid or heat [8, 28]. Allicin produces both hydrophilic (cysteine) and lipophilic (sulfides, ajoene) sulfur compounds which are accountable for pharmacologic effects. Garlic is administered via oil-filled capsules, condensed dried powder, and enteric-coated tablets and capsules; it is also aged in aqueous alcohol [28]. Adverse effects of garlic extract include burning sensation in the gastrointestinal tract, diaphoresis, nausea, and light headedness. The extract may also cause contact dermatitis and excessive ingestion may cause morbid spontaneous spinal epidural hematoma [8, 28].

### 4.3. Ginkgo

Ginkgo (*Ginkgo biloba*) and its leaf extracts contain active compounds which have been found to improve circulation and cognition. The extracts are sold in both solid and liquid forms and appear to be relatively safe [28]. Medicinal use of ginkgo dates back 2800 BC, the seeds are used as an expectorant, antitussive and anti-asthmatic, and the leaves aid in asthma and cardiovascular disorders [26]. The most common side effects are dizziness, headache, restlessness, vomiting, nausea, diarrhea and dermal sensitivity. Cross-allergenicity with poison ivy has been reported. Ginkgo as an inhibitor of platelet-activating factor may alter bleeding times, therefore it may cause an upsurge of the anticoagulant effect of aspirin and warfarin [28].

### 4.4. Ginseng

Ginseng (*Eleutherococcus senticosus*) is the fourth most extensively used Chinese medicinal herb, treating a variety of conditions. It is used as a general tonic and is claimed to increase the body's resistance against stress and builds up general vitality besides treating diabetes, depression and hypertension [29]. Products are made from dehydrated roots, such as extracts, elixirs and tea, also tablets and capsules. Numerous active constituents, ginsenosides, respectively have specific pharmacologic effects that sometimes compete with each other, thus the whole root is used in preparations [28]. Excessive doses of ginseng have been reported to cause insomnia, agitation and elevation of blood pressure, mastalgia and vaginal bleeding have been detected at acclaimed doses [8].

### 4.5. Kava

Kava (*Piper methysticum*) is believed to be beneficial for health by soothing nervous illnesses, inducing sleep and relaxation, reducing weight and counteracting fatigue. It is often used to treat asthma, urinary infections, fever, headaches, syphilis, rheumatism and gonorrhea, it is also used as a stomachic and diuretic [26]. Kava is commonly known as an anxiolytic agent. Reported side effects include dizziness, gastrointestinal discomfort, headaches and localized numbness after oral ingestion. Long term use at high doses may cause scaly, dry skin and discoloration of nails and the skin, eye redness and photosensitivity. Diplopia and photophobia may also occur after excessive consumption. Interaction of central nervous system depressants and kava may lead to a comatose state [8, 28].

### 4.6. St John's wort

St John's wort (*Hypericum perforation*) is specified to possess astringent and sedative properties. It has been used for neuralgia, excitability, fibrositis, menopausal neurosis, sciatica, wounds, depression and anxiety. Modern interest is focused on its antidepressant use [26]. St John's wort possesses active compounds such as hyperforin, hypericin and melatonin. It is reported to have side effects which include fatigue, constipation, nausea, vomiting, dry mouth, headaches, dizziness and photosensitivity [8].

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### 4.7. Ma huang

Ma huang (*Ephedra sinica*) is a medicinal plant traditionally used to treat hay fever, bronchial asthma, colds, coughs, enuresis, myasthenia gravis, narcolepsy, rheumatism and chronic postural hypotension. It contains a number of alkaloids including ephedrine and pseudoephedrine [26]. Ma huang is not considered as a safe herb, with adverse effects including insomnia, dizziness, headaches, nervousness, stroke, seizures, hypertension, psychosis, irritability, myocardial infarction, premature ventricular contraction and death [28].

### 4.8. Valerian

Valerian (*Valeriana officinalis*) is a medicinal plant commonly used as a mild sedative and anxiolytic. Numerous constituents are found in the root of this plant, valerenic acid (C15 sesquiterpenoid) and valerena-4,7(11)-diene have been suggested to possess the active ingredients accountable for the sedative effect [30]. Valerian has been reported to cause excitability, headache, gastrointestinal complaints and ataxia. An oral overdose may result in abdominal cramps, onset of fatigue, light headedness, chest tightness, and tremors of feet and hands [28].

## 5. Why people use herbal medicine?

### 5.1. Accessibility and affordability

The documentation of medicinal plants of numerous cultures is extensive, these plants have been used in treating various diseases even without the knowledge of their constituents and accurate functions [31]. The high practice of herbal medicine is due to cultural acceptability, as plant remedies have been around for centuries [32]. In countries such as Zambia, Tanzania and Uganda the ratio of herbal medicine practitioners to the population was found to be 1:200–1:400. However, the ratio of western medicine practitioners is 1:20,000 or less [33]. A survey conducted in 1991 revealed that traditional practitioners in sub-Saharan Africa out number western practitioners by 100 to 1 [34]. Herbal medicine has remained affordable in comparison to high cost western medicine [35]. In over populated countries such as India, the rural population has almost no access to modern medicine, therefore, they are compelled to rely on herbal medicine for their basic healthcare needs [36].

### 5.2. An alternative approach to healthcare

Plants are perceived to be healthier than conventional biosynthetic drugs. Reports on conventional drugs adverse effects has been found to be much higher compared to herbal toxicity reports [4]. Other reasons for the use of herbal medicine include: (i) several claims on the efficacy and safety of plant medicines [11], (ii) improvements in the quality of herbal medicines with the development of scientific evaluation [21], (iii) to relieve symptoms related to chronic or

terminal illnesses [37], such as HIV/AIDS, malaria, diabetes and sickle-cell anemia [38]. A survey conducted in the USA showed that 78% of patients living with HIV/AIDS use some form of herbal medicine. In such cases, western medicine is perceived to have failed the public [4].

## 6. Challenges facing the use of herbal medicine

### 6.1. Safety and toxicological concerns of herbal medicine

The products of herbal medicine have a long history of being safe [39], however the misuse of these medicines may have side effects due to toxic constituents [29]. In some countries, toxicological assessment of herbal medicine and associated products are not employed before placing them in the market [8]. Herbal medicine of a single plant may contain hundreds of constituents and mixed products may contain numerous times that number. The time required to isolate every single active ingredient from every herb would be tremendous [22]. Moreover, these countries lack operative machinery to legalize manufacturing quality standards and practices. Thus making hazardous herbal products continually available to consumers [8]. A study related on the use of traditional eye medicine reported that it caused 26% of childhood blindness in Malawi and Nigeria, and 25% of corneal ulcer in Tanzania [4]. Pyrrolizidine alkaloids have been reported to be fatal, these are molecules within certain plants causing hepatotoxicity through a veno-occlusion illness [10]. Nausea and probably vomiting can occur with some herbs such as ephedra and echinacea. Herbs consumed as teas have been reported to cause diarrhea and hematologic, cardiac and gastrointestinal effects [40]. Herbal products from Asia have been reported to be problematic since it contains numerous contaminants. A study on the assessment of 260 Asian patent medications reported that 25% of these products contained high levels of heavy metals and 7% contained undeclared drugs, decisively and unlawfully added to produce desired effects [41].

### 6.2. Challenges of quality control

Quality control of herbal drugs and their formulations is of vital importance in order to justifying their acceptability in modern system of medicine. A major concern facing the herbal drug market is the unavailability of the source and quality of herbal materials and their formulations [42]. Other factors such as the temperature, use of fresh plants, light exposure, nutrients, water availability, period and time of harvest, method of harvesting, drying, packing, storage and transportation of raw herbal material, etc., can critically affect the beneficial value of medicinal plants and quality. Some plant elements are heat labile and the plants containing them need to be dried at low temperatures [11].

### 6.3. Lack of knowledge about herbal medicine within government regulations

Herbal remedies can be sold as supplements, for supporting, maintaining, stimulating and promoting health in many countries. These supplements require a label that defines the ingredients are intended to affect the functions within humans in line with Act 101 of 1965 and amendments (2002) [14]. The evidence on the efficacy, safety and quality of such herbal products is unknown, therefore, raising a concern on the safety of these herbal medicines [8].

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### 6.4. Need for scientific and clinical evaluation of herbal medicine

The concern surrounding safety of herbal medicinal products is increasing [8]. In order to allay these concerns and achieve public reliance on herbal medicine, manufacturers, researchers and regulatory authorities must follow inclusive clinical trials and vigorous scientific methodologies to ensure the quality and safety of herbal products [41]. The safety evaluation of any herbal drug considers two important factors; the nature and significance of the adversarial effect. Toxicity screening can disclose some of the risks related to the use of herbal medicine [43]. In 1991, WHO issued guidelines for the assessment of herbal medicine which include: (i) Quality assessment: crude plant material; plant preparation; finished product. (ii) Stability: shelf life. (iii) Safety assessment: documentation of safety based on experience or toxicology studies. (iv) Assessment of efficacy: documented evidence of traditional use or activity determination (animals, human) [6].The US Food and Drug Administration (FDA), the International Conference on Harmonization (ICH) and the United States Pharmacopeia (USPC, 1994–2001) follow these guidelines to validate herbal products [1].

## 7. National policies of herbal medicine

A national policy on herbal medicine may include the following: a defining role of herbal medicine in the health care system, provision for the necessary regulations and laws, contemplation of intellectual property concerns [22]. National policies vary from country to country regarding herbal medicine. Herbal medicines are classified as either prescription or non-prescription medicines. The Working Party on Natural and Nutritional Supplements was established by the Australian Parliament to evaluate the safety, efficacy, quality and labeling of herbal products (Therapeutic Good Act, 1990). The act states "that traditional claims for herbal remedies be allowed, providing general advertising requirements are complied with and providing such claims are justified by literature references" [11]. Herbal medicine in Canada must meet the terms of the National Health Products Regulations. In accordance to these regulations, a product license is required for all herbal products to be sold in Canada. The recommended use, potency, comprehensive information on the medicinal constituents, source and nonmedicinal constituents need to be provided in order for a license to be granted. The companies that manufacture, pack, label and import herbal medicine also need a site license [3].

The Dietary Supplement Health and Education Act (DSHEA) of 1994, states that any herb, natural and botanical concentrate, constituent and metabolite of extract, is categorized as a dietary supplement. These supplementations do not need any sanction from the FDA. Herbal medicine which is categorized as dietary supplements under DSHEA, are alleged to be safe and the FDA does not have the authority to require them to be approved for efficacy and safety before they enter the market. However, manufacturers of these herbal products are required to provide purity and identification standards, and confirm that claims made concerning their products are precise [39, 44].

In Chile the Unidad de Medicina Tradicional was established in 1992, with the aim of incorporating herbal medicine with established efficacy into health programs (Law No. 19.253,

October 1993). Directive No. 435/81 defines herbal drugs with therapeutic proposed claims and/or dosage recommendations as being medications, restricted from being sold in drugstores and pharmacies. Registration for marketing authorization is required for herbal products. These products are lawfully distinguished as follows: (1) drugs intended to alleviate, cure or prevent disease; (2) food products with therapeutic properties and for medicinal use, and (3) food products with nutritious purposes [11].

In Europe, the European Directive 2004/24/EC released in 2004 by the European Parliament and by the Council of Europe provides the guidelines for the use of herbal medicines. The guidelines state that for herbal medicine to be released in the market, it needs authorization from the national regulatory authorities of each country in Europe and the herbal products must have a standard level of efficacy and safety. The registration of herbal products from outside the European Union (EU) require substantial evidence of their medicinal use, at most a period of 15 years within EU and 15 years elsewhere [3]. In Germany, more than 300 monographs on medicinal plants have been regulatory evaluated, and in France more than 200 herbs have been recorded as acceptable ingredients of herbal medicine [4].

The widespread use of herbal medicine in Brazil is favored by two present public policies i.e. the National Policy on Integrative and Complementary Practices in the Public Health System (PNPIC) and the National Policy on Medicinal Plants and Herbal Medicines (PNPMF), through the Law 971/2006 and the Declaration 5813/2006, respectively. Currently, 382 herbal medicines are registered in Brazil, 357 of these are single medicines and the other 25 are composed of more than one medicinal plant [45].

## 8. The market for herbal medicine in the developed world

Herbal medicine has gained increasing popularity in the last two decades in industrialized countries. The congress of the United States of America (USA) established the Office of Alternative Medicine in the year 1989 within the National Institute of Health (NIH). This was formed to interest scientists in the field of medicinal plants [3]. According to the 2007 NIH survey, 4 out of 10 adults (38.8%) and 1 out of 9 children (11.8%) used some form of herbal medicine [37]. In USA, presently about 25% of prescription drugs contain at least one plant derived ingredient [21], the herbal market in this country has doubled from $4 billion since 1996 [6]. In 1989, the European Scientific Cooperative on Phytotherapy was formed with an aim to advance herbal medicine [3]. The herbal medicine market in European countries has been growing steadily from $6 billion in 1991 to over $20 billion currently, particularly in Germany, France and Italy [4, 6]. In Germany, herbal medicine is identified as one of the elements of naturopathy [46], approximately 600–700 plant derived medicines are accessible and prescribed by approximately 70% of German physicians [47]. In 2011, 20% of herbal drugs were sold as prescriptions and 80% over the counter in Germany [46]. In the year 2005, The National Centre for Complementary and Alternative Medicine at the National Institutes of Health in the USA spent about US$ 33 million on herbal medicine, the National Canadian Institutes disbursed approximately US$ 89 million for research in traditional therapies in 2004. These scientific evaluations have led to an upsurge in the investment of herbal medicine [3].

## 9. Future prospects of herbal medicine

In the past decade, about 121 pharmaceutical products have been formulated based on herbal medicine knowledge [42]. According to literature at least 25% of modern medicines are derived from plants, such as aspirin, picrotoxin and numerous others are synthetic analogues built on prototype compounds isolated from plants [48]. Because of the increase in the acceptance of plant derived drugs, the use of plants in medicine as a source of therapeutic agents will expand rapidly in the future [42]. This has extremely increased international trade of herbal medicine, attracting a number of pharmaceutical companies, including the multinationals [11]. The interest of WHO by documenting the use of medicinal plants used by ethnic groups, has increased scientific validation of the use of these plants. This will make people better informed concerning the effectiveness and safety of the treatment [21]. The regulation of herbs has assisted in improving herbal products, however additional changes need to be applied to advance and indorse high quality research [10].

## 10. Conclusion

The use of herbal medicine is not restricted to developing countries. Over the years, there has been an escalating interest in the use of herbal medicine worldwide. This has greatly expanded the demand for plant products, since herbal medicine has an advantage of being inexpensive with minimal side effects compared to synthetic medicines. The growth of the herbal drug market has attracted pharmaceutical companies which in turn have driven scientific validation and clinical studies on herbal medicines. Thus far, few programs have been established to study the safety and efficacy of herbal medicines as originally proposed by the WHO Guidelines for the assessment of herbal medicines. These guidelines have been helpful in establishing the role of herbal medicine in the health care industry. However, the data to provide a precise assessment on the safety, quality and efficacy of herbal medicine is inadequate generating concerns regarding the use of herbal products.

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Chapter 12

# Powerful Properties of Ozonated Extra Virgin Olive Oil

Elisabetta Carata, Bernardetta Anna Tenuzzo and Luciana Dini

Additional information is available at the end of the chapter

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**Abstract**

Extra virgin olive oil has been mainly produced and consumed in Mediterranean countries since ancient times; olive oil is one of the principal ingredients in the Mediterranean diet, and it constitutes the main source of nutritional fat. Aside from the high nutritional content of olive oil, it is also known for its cosmetic and therapeutic properties. In 1956, Thiers obtained satisfactory results in the treatment of scleroderma, stating that olive oil and its derivatives could be considered "a new group of therapeutic agents." Hincky reported the beneficial properties of olive oil in the treatment of dry, senescent and sensitive skins. This has opened a new perspective for the use of the olive fruit, thus contributing to the increase in research about new applications. One such application is ozonized olive oil, which combines the properties of ozone with those of olive oil, to obtain a peerless compound. The composition of olive oil makes it a suitable vehicle for cutaneous absorption, as it is able to stabilize ozone, which is a highly reactive molecule. The oxidant power of ozone has interesting effects on microorganism and on wound healing.

**Keywords:** extra virgin olive oil, ozone, herbal medicine, antimicrobial activity, wound healing

## 1. Introduction

Herbal medicine is commonly used to treat skin disorders, and the ethnobotanical remedies are developed in different regions, based on local plants. In particular, two different systems, Ayurvedic herbs, estabilished in India, and the traditional Chinese medicine, which uses the combination of different herbs, are known. In the occidental world, the use of herbal medicine is relative to purified extracts, often substituted for synthetic chemical drugs. In the last years, we assisted an intense return, in the occidental world, to herbal medicine, probably because we are living in the green revolution [1]. The use of vegetable raw materials in the preparation

of products for local application on the skin dates back to ancient times. The term phytocosmetics, from Greek *kosmesis*, which means adorn, and *phytos*, which means plant, is used to indicate the predominant and preferential use of botanical derivatives in cosmetic products. The vegetable field is an inexhaustible source of raw materials that, transformed by various processes, find many applications, both as functional substances and as excipients of the products. Contrary to some 50 years ago, when the cosmetic use of medicinal herbs was largely based on the mere observation of the traditional use, today, numerous scientific studies on the properties of plant-based drugs, as well as advanced knowledge on technical-scientific ones that allow to extract the active principles contained in the plants, are available. The herbal phytonutrient offers an enormous amount and heterogeneity of substances, which, by means of various extracellular processes, give rise to extracts with various functional applications. The active constituents of plants are in fact represented by a complex mixture of substances of different chemical nature (tannins, pectins, saponins, flavonoids, essences, fixed oils, etc.) whose concentration in the extract is essentially linked to the particular extraction process. The most widely used vegetable extracts are glycolic extracts, hydroalcoholic extracts, distilled water, dried extracts, oily extracts, essential oils, and vegetable oils. Vegetable oils are obtained by cold squeezing of plant drugs whose active ingredients are characterized by oily texture. The oil is predominantly made up of polyunsaturated fatty acids rich in triglycerides and also contains antioxidant substances, liposoluble vitamins, and the so-called insaponifiable fraction, a complex mixture of substances of extreme interest both from the dermatological and cosmetic field. Olive oil, coconut oil, wheat germ oil, borage oil, and almond oil are the main types of vegetable oils used in cosmetics. Compared to other types of oily ingredients, the advantage of using vegetable oils in cosmetics and cosmeceuticals lies primarily in their particular lipid composition, which is very close to the structure and function of that of the physiologic sebum present in the interstices and the surface of the corneal layer of the epidermis. The very high affinity to the skin sebum gives them an excellent ability to restore the physiological skin barrier by means of a protective, filmogenic, and emollient action. In this chapter, we describe the advantageous effects of ozonated olive oil in the treatment of skin disorders; in fact, olive oil is considered one of the most excellent foods for diet, but it has anti-inflammatory action, so it is used for skin disease. In the chapter, we report information about the safety and mechanism of action on microorganism and on wound healing.

### 1.1. Olive oil

Olive oil consists of glycerides, such as oleic, arachidic, palmitic, linoleic, and stearic acids, and of phenolic compounds. It is very important in the culinary use, but it has important applications in cosmetic and pharmaceutical fields. The olive tree *Olea europaea* is a common feature of the Mediterranean landscape, with the olive fruit and olive oil being the basic elements in the nutrition of civilizations around the Mediterranean basin for millennia. The principal reason is due to the tree's climatic requirements, which are found in limited areas of the earth's surface [2]. This longevous tree integrates and identifies economically, socially, and culturally with the inhabitants of this land and determines its rural landscape [3]. Even olive leaves have been used in popular medicine. The therapeutic and health properties of olive oil have been known for millennia so much that Hippocrates advised the juice of fresh

olives to cure mental illness and wraps to heal ulcers. During the Middle Ages and during the Renaissance, olive oil was used to cure gynecological infections and was considered useful in the treatment of heart disease, fever, and hypertension.

### *1.1.1. Beneficial effects of olive oil: health properties*

Virgin olive oil has been and still is the subject of numerous studies that have attributed great properties to it, both in the field of health and in cosmetology. Various epidemiological studies have shown that the incidence of inflammatory, cardiovascular, and tumor illnesses is generally lower in Mediterranean European countries (such as Greece, Italy, and Spain) than in other western and northern countries [4]. This can be attributed to the high consumption of olive oil in the Mediterranean diet, which contributes to the daily requirement of vitamin E, essential fatty acids, and specific antioxidants, particularly represented by phenolic compounds and tocopherols. In addition, antioxidants have a primary role in resistance to oxidation and hence in the stability of olive oil and have been shown to exert numerous beneficial effects on the human body. The antioxidants' protective effect is mainly due to their ability to inhibit the action of oxygen free radicals, indicated by the acronym ROSs [5]. ROSs are highly reactive species represented by atoms or molecules with one or more electrons being dissipated, capable of generating the so-called oxidative stress. When the organism is subject to an increase in oxidative stress, an increase of F2-isoprostanes (IsoPs) in plasma levels and of urinary excretion is observed. IsoPs are a type of novel compound, structurally similar to prostaglandins, biosynthesized *in vivo* from the free radical–catalyzed peroxidation of arachidonate independent of the cyclooxygenases (COX) [6]. Oxidative stress seems to be the main reason for many chronic and degenerative diseases and skin aging. More specifically, ROSs induce (i) DNA mutations and protein alterations that are the basis of carcinogenesis [7]; (ii) oxidation of low density lipoproteins (LDL) involved in the formation of atherosclerotic plaques [8]; (iii) the onset of chronic intestinal inflammatory diseases, such as Crohn's disease [9]; (iv) probable onset of neurodegenerative diseases, such as Parkinson's disease [10]; and (v) cellular aging, by lipid peroxidation of the membranes, which become more permeable and less effective. All this evidence allows us to understand the importance of antioxidants, even from exogenous sources such as diet. The beneficial effects, and in particular the antitumor activity, of olive oil on human health are attributed to the high content of phenolic substances with high antioxidant power [11]. Phenolic compounds, in synergy with $\alpha$-tocopherol and coenzyme Q, protect cells from oxidative damage by contrasting the toxic effects of ROS [12]. Through various epidemiological studies, the correlation between the consumption of virgin olive oil and the risk of onset of certain types of cancer has been demonstrated, such as breast [13], lung [14], colon [15], ovary [16], pancreas [17], and prostate cancer [18]. It has been shown that among the phenolic compounds, one of the most biologically active is hydroxytyrosol (3,4-DHPEA) that is able to inhibit the 5-lipoxygenase enzyme, by reducing the production of leukotriene B4 in the leukocytes, originating from the metabolism of the eicosanoids [19]. In addition, hydroxytyrosol is able to inhibit *in vitro* the oxidation of LDL [20] and *in vivo* [21] the aggregation of platelets [22]. Some experimental studies have also shown that the phenolic extract of virgin olive oil and two isolated compounds, the dialdehyde form of hydroxytyrosol (3,4-DHPEA-EDA) and thiol (p-HPEA-EDA), are able to inhibit uncontrolled cellular

proliferation by blocking the cell cycle at G0/G1 and to induce apoptosis in some lines of cancer cells, as demonstrated for HL60 cells of promyelocytic human leukemia [23, 24]. However, compounds with greater biological activity are those containing the ortho-diphenol residues; it has been shown that 3,4-DHPEA and 3,4-DHPEA-EDA are more effective than p-HPEA and p-HPEA-EDA in protecting DNA from damage caused by oxidation [25]. In an *in vitro* study, by examining different virgin olive oil extracts, a chemoprotective effect was demonstrated on HL60 cell lines in relation to their composition but not to the total content of phenolic substances [26]. ROS production is also closely related to inflammatory processes in which the cyclooxygenase enzymes (COX-1 and COX-2), belonging to the oxidoreductase class, catalyze the conversion of arachidonic acid into prostaglandins. The p-HPEA-EDA, also called oleocanthal, has the ability to inhibit the activity of such enzymes and has a pharmacological effect similar to that of ibuprofen, which belongs to the class of nonsteroidal anti-inflammatory drugs [27]. It has also been shown that the consumption of olive oil may improve blood pressure regulation and cholesterol content in the blood; these events, together with the inhibition of platelet aggregation and the reduction of LDL oxidation, are important to prevent the onset of atherosclerotic plaques and, in general, cardiovascular pathologies [28, 29]. Olive oil also contains many monounsaturated fatty acids, including oleic acid, which is a key component of cellular membranes and can progressively replace polyunsaturated fatty acids. Membranes rich in monounsaturated fatty acids are more fluid and less subject to lipid peroxidation [30]. Some studies have also shown that regular intake of this food may result in a reduction in the risk of developing diabetes [31]. The therapeutic properties of olive oil include a laxative effect and stimulation of biliary function [32]. Finally, some studies on animal models have shown that the intake of olive oil can help to counteract the damage caused by epidermal ultraviolet radiation [33].

### *1.1.2. Dermatological and cosmetic properties*

In recent years, in a number of fields, including cosmetics, there has been a renewed interest in materials of natural origin, particularly those of vegetable origin. Since ancient times, olive oil has been known not only for its high nutritional power but also for its cosmetic and therapeutic properties [34]. In 1971, Thiers was still pointing to its potential use in the cosmetic sector. To date, olive oil is certainly the most appreciated natural ingredient, alongside jojoba and avocado oils. The topical application of olive oil may be advised for its soothing action and its beneficial effects on eczema, surface wounds, and burns [35, 36]. In particular, the presence of phytosterols and triterpenoid compounds offers revitalizing and soothing properties for the skin. Vitamins E and A have an intense antioxidant action and have the ability to prevent irritation and aging of the skin, to help maintain its softness, smoothness, stability, and elasticity. As a result, in the cosmetic field, olive oil can be used to prevent signs of aging as a soothing emollient for dry skin and to strengthen hair [37]. Indeed, it is very often a component of lotions, lip balms, shampoos, bath oils, and massage oils. From a dermatologic point of view, olive oil has also proven to have antimicrobial activity, *in vitro*, against some positive and negative Gram and various types of fungi, including *Candida* spp. [38]. Some components of olive oil, especially certain aliphatic aldehydes, inhibit elastase activity; this enzyme is involved in the virulence process [39]. Olive oil is an important component of some

topical formulations used in the treatment of inflammatory and mycotic skin diseases [40]. The unsaponifiable fraction is rich in numerous active ingredients with sebum-regulating and moisturizing properties, as well as emollients; it can be a component of cosmetic products (in the form of creams, balms, gels, etc.) for the treatment of delicate, dry, and cracked skin. In fact, the unsaponifiable fraction is very useful in the case of particularly vulnerable skin, such as that of infants and children, or in the case of xerotic skin, such as that of the elderly. Skin hydration is above all important in the neonatal period and especially in premature infants: some clinical trials have been conducted to highlight the beneficial effects of emollient topical treatment [41, 42]. Furthermore, the unsaponifiable fraction exerts a good photoprotective effect on ultraviolet exposed skin: various studies have shown that the application of olive oil may reduce the incidence of skin epithelial tumors on UV-B–exposed mice compared to a control group [43, 44]. The unsaponifiable fraction can also be an additive in makeup products with the purpose of making them easier to apply, softer, and smoother. Butter contains high quantities of squalene (which is the most important constituent of sebum), waxes, and esters that guarantee high penetration of the skin. Butter is ideal for massages or as a vehicle for other active ingredients used in skin care. It acts also as an emollient and moisturizing agent, promoting skin elasticity and preventing the onset of wrinkles. Finally, it can be used as an additive in photoprotective products or in skin hygiene products due to its ability to neutralize aggressive detergent action.

An interesting and powerful way to use extra virgin olive oil is with ozone. The process of ozonization allows the properties of ozone gas to be combined with those of olive oil; the result is a peerless compound. Since ancient times, ozone has also been used in a large number of medical indications [45–49].

## 2. Ozone

Ozone is an oxygen derivative and is known primarily for its ecological role in the Earth's balance, absorbing most of the ultraviolet radiation from the sun and preventing it from reaching humans in a harmful way. It is an unstable gas that cannot be stored; in fact, it dissolves in very short time. Ozone is totally neutral to the human body, and in fact, it does not (i) modify pH, (ii) irritate skin or mucous membranes, (iii) damage hair or clothing, (iv) interact with drugs, and (v) cause allergic reactions. This molecule has been subjected to countless studies, and in particular, its strong oxidation capacity has been tested in order to underline its disinfectant and sanitizing properties principally applied as a disinfectant of drinking and waste water [45–47]. To this purpose, the dedicated design and construction of equipment for the production of gaseous ozone for air and water purification are increasing. But research into the properties of ozone has yielded promising results in biological applications, thus confirming the ozone activity in stimulating natural cell defenses and increasing their energy availability. Indeed, since ancient times, ozone has also been used in a large number of medical indications [48, 49]. Scientific studies have shown that ozone, while being highly unstable, can be trapped inside vegetable oils. These are composed of triglycerides in which saturated and unsaturated fatty acids are present, which have the ability to retain ozone, thus allowing

them to prolong their use. In addition, the greater the amount of unsaturated fats present, the greater the amount of ozone that will be retained [50]. Therefore, when extra virgin olive oil is ozonated, the produced product combines the beneficial properties of extra virgin olive oil with those of ozone. There are countless ozone-based products on the market, and in particular, in our laboratory, we have developed Bioxoil™, an ozonated extra virgin olive oil available in pharmacies. This product is exclusively made from olive cultivars from Puglia and Salento and the oil is ozonated by an innovative patented method (number: M2011A001045 titled: "Process for the ozonization of a vegetable oil") that confers quality and efficiency in various fields of application; in particular, Bioxoil™ is indicated for the treatment of acne, herpes, psoriasis, fungal infections, bed sores, and wounds in general, due to its healing and disinfectant properties (**Figure 1**).

Bioxoil™ is produced from extra virgin olive oils from two local *cultivars*, *Ogliarola* and *Cellina,* in Salento (Apulia, Italy). The ozone reacts with unsaturated compounds through the known Criegee mechanism. The quality of extra virgin oil is very important to obtain a higher grade of ozonization; for this reason, during the process, it is necessary to control different physical and chemical parameters. Of these parameters, the most important is the temperature, and in fact, during the reaction, the temperature increases provoking an alteration of antioxidant content. The oils' peroxide content and acidity value that indicate the level of hydrolytic modification and primary and secondary oxidation of oil are analyzed and reported in **Table 1**. Peroxide index (PI) and acidity index (AI) after ozonization of oils increase with respect to relative controls. In particular, *Cellina*'s oil sample has an acidity index of 0.2% and a peroxide index of 12 mmol $O_2$ $kg^{-1}$, while related ozonated oil has an AI of 1.8% and a PI of 533 mmol $O_2$ $kg^{-1}$. *Ogliarola*'s oil sample presents an acidity index of 0.3% and a peroxide index of 13 mmoli $O_2$ $kg^{-1}$, while respective ozonated oil has an AI of 1.3% and the PI increases to 677 mmoli $O_2$ $kg^{-1}$.

In our experiments, the ability of ozone to react with olive oil and in particular with the carbon-carbon double bonds present in unsaturated fatty acids was demonstrated by gas liquid


**Figure 1.** Bioxoil™ products. The Bioxoil products have different applications. Bioxoil with a red label is indicated for bed sores; the sky blue label is indicated as soothing medication; the green label is indicated for herpes labialis; the pink label is indicated for acne; and the orange tag is indicated for mycosis.

| Sample | Acidity index (AI), % (means ± SD) | Peroxide index (PI), mmol $O_2$ $kg^{-1}$, (means ± SD) |
|---|---|---|
| *Ogliarola olive oil* | 0.2 ± 0.03 | 12 ± 1.2 |
| *Ozonated Ogliarola olive oil* | 1.8 ± 0.02 | 533 ± 1.5 |
| *Cellina olive oil* | 0.3 ± 0.02 | 13 ± 1.5 |
| *Ozonated Cellina olive oil* | 1.3 ± 0.01 | 677 ± 1.6 |

**Table 1.** Physicochemical parameters of *Ogliarola* olive oil and *Cellina* olive oil after ozonization procedure.

| Composition of fatty acids (%) | *Cellina* | *Cellina* | *Ogliarola* | *Ogliarola* |
|---|---|---|---|---|
| | **Control** | **Ozonated oil** | **Control** | **Ozonated oil** |
| Palmitic acid | 12.45 | 11.91 | 11.89 | 11.30 |
| Linolenic acid | 5.57 | 2.19 | 4.96 | 2.06 |
| Cis-oleic acid | **70.27** | **39.82** | **67.00** | **41.25** |
| Trans-oleic acid | 8.22 | 6.68 | 7.88 | 7.2 |
| Stearic acid | 3.48 | 1.29 | 3.32 | 3.22 |
| Nonanal | 0 | 11.69 | 0 | 10.07 |
| Nonanoic acid | 0 | 1.36 | 0 | 1.98 |

**Table 2.** Composition of fatty acids in olive oil samples *Cellina* and *Ogliarola*.

chromatography (GLC). The composition of fatty acids of each olive oil and respective ozonated oil are analyzed by GLC. Data demonstrate that the amount of oleic acid decreases in both ozonized oil samples: in *Cellina*'s ozonated oil, we observed a 30% reduction, while in *Ogliarola*'s ozonized oil, the reduction was about 26% (**Table 2**). During the ozonization reaction, ozone etches mainly the double bond of acid oleic, the most abundant fatty acid in olive oil (about 80%). This explains the decrease in oleic acid and the contemporary appearance of new compounds, which are the reaction's products, among which are nonanal aldehyde and nonanoic acid, both compounds with nine carbon atoms (**Table 2**). In both cultivar ozonized oils, the composition of fatty acids changes, showing a gradual decrease in unsaturated fatty acids (C 18:1, C 18:2), with a gradual increase in ozone doses.

## 3. Biocompatibility of ozonated olive oil with skin

The skin is the largest organ of the body and is the major barrier between the inside and outside of our body. It is formed of two main layers: the epidermis, a thin outer portion, and the dermis, the connective tissue layer of skin. This portion is involved in the thermoregulation process, and the resident dermal fibroblasts secrete collagen, elastin, and substances that offer support and elasticity of the skin. The epidermis is subdivided into four layers: (i) the stratum

germinativum (SG) that provides the germinal cells necessary for the regeneration of epidermidis; (ii) the stratum spinosum (SS), in which the cells divided in the SG start to accumulate many desmosomes on their surface; (iii) the stratum granulosum (SGR), in which the keratinocytes accumulate dense basophilic keratohyalin granules that contain lipids, which help to form a waterproof barrier; and (iv) the stratum corneum (SC), the outermost layer, in which the cells are dead. The skin is constantly exposed to the environmental stress of pollutants or cigarette smoke, for example, so it is necessary for the wellness of the skin to preserve it from oxidative stress. To this purpose, there are a variety of antioxidants that include glutathione peroxidase, superoxide dismutase, catalases, and nonenzymatic low-molecular weight antioxidants such as vitamin E isoforms, vitamin C, glutathione (GSH), uric acid, and ubiquinol. Interestingly, the distribution of antioxidants in the SC follows a gradient with higher concentrations in deeper layers [51].

The biocompatibility of Bioxoil™ was investigated by MTT assay on fibroblast 3T3 and on keratinocytes HaCaT and compared with ozonated *dulcis* almond oils and nonozonated olive oil as controls. The MTT test values the cell metabolic activity and, in particular, measures the activity of oxidoreductase by reduction of the tetrazolium bromide dye in formazan. The *dulcis* almond oil was chosen because it is largely used in cosmetics, and as it is an oil, it is a possible vector of ozone. Data reported in **Figure 2** demonstrate the Bioxoil™ biocompatibility for both cell types. The viability of cells never significantly decreased in relation to the control and was the same as the nonozonated oil. Conversely, once ozonated, 10% of *dulcis* almond oil had a very significant negative effect on the viability of fibroblasts and keratinocytes but not when *dulcis* almond oil was nonozonated. Interestingly, the vitality test demonstrated that when these cells are exposed to a mixture of ozonated olive oil and 10% of ozonated *dulcis* almond oil (3:1), the adverse event induced by the ozonated almond oil alone was partially prevented (**Figure 2**).

### 3.1. Biological action of ozonides

By combining the beneficial properties of extra virgin olive oil with that of ozone, the ozonated extra virgin olive oil becomes very powerful for the topical treatment of acute and chronic skin lesions. The ozonides generated during the ozonization procedure possess many properties including a high germicidal activity on fungi, yeasts, viruses, and bacteria; activation of local microcirculation; stimulation of granulation and tissue growth; and revitalization of epithelial tissues.

#### *3.1.1. Germicidal activity*

The excessive consumption of antibiotics for the treatment of infectious diseases has fuelled the drug resistance phenomenon, *i.e.,* the microorganisms are resistant to antibiotics. Therefore, it is necessary to develop new molecules with antibiotic properties, preferably natural and nonsynthetic. In fact, this research is divided into the field of synthetic molecules produced by the chemical/pharmaceutical industry and the field of natural active compounds, in which plant extracts are studied also by the use of green chemistry. The plants are able to withstand fungal and bacterial infections and therefore their secondary metabolites can be applied in the field

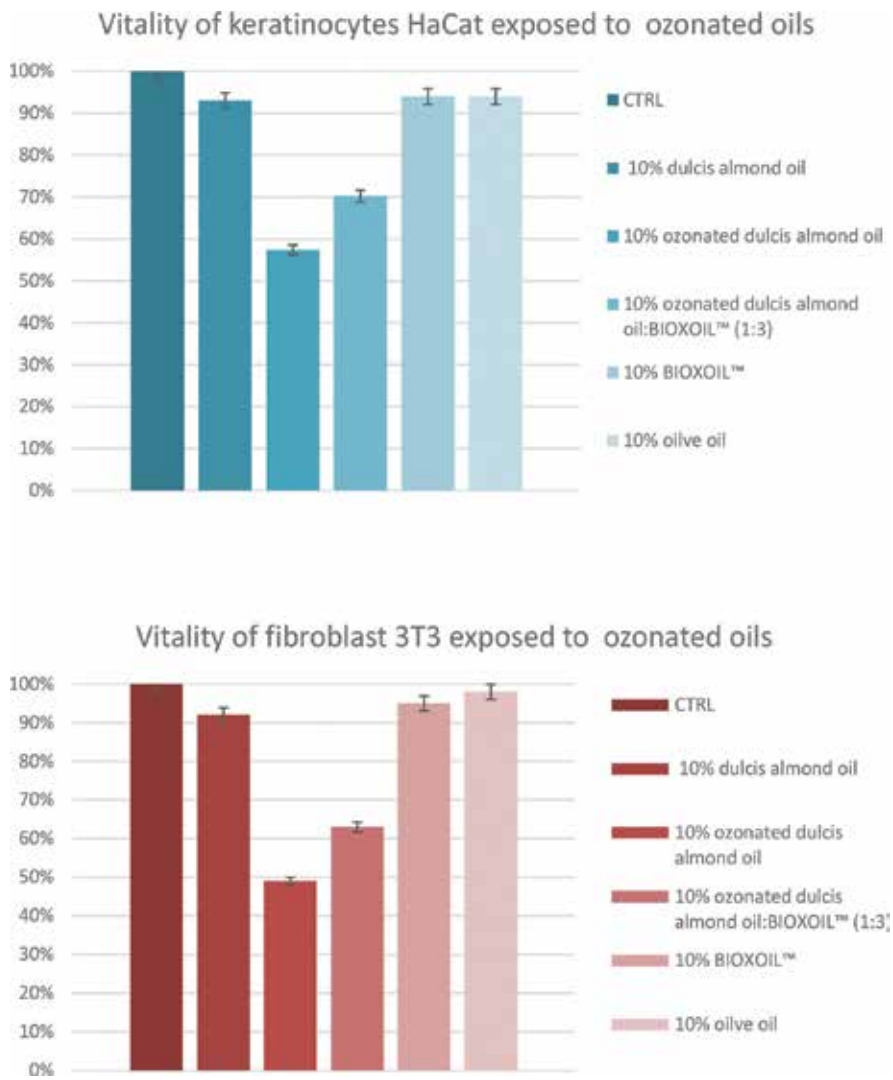


**Figure 2.** MTT assay on fibroblasts and keratinocytes.

of medicinal herbs. Maoz and Neeman in their research reported an antifungal action of olive oil due to the high content of oleic acid [52]. The ozonated oil increases this natural capacity, because ozone acts on microorganisms, thanks to its greater oxidizing power; in fact, it is able to break down the macromolecules that are the basis of the vital integrity of bacterial cells, fungus, protozoa, and viruses. The ozone in contact with the microorganism's lipoproteins forms $H_2O_2$ and the final products of lipid oxidation (LOP); $H_2O_2$ assures bacteriostatic and bactericidal activity, while final lipid oxidation products have induction activity and reactivate metabolic functions (**Figure 3**). Nagayoshi et al. [53] reported the capability of ozone to destroy Gram-positive and -negative microorganisms, and in particular, Gram-negative bacteria are more sensitive.

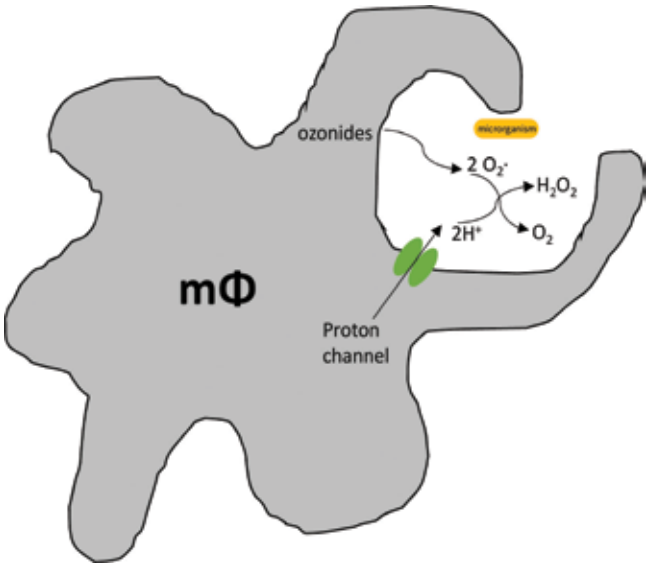


**Figure 3.** Molecular mechanism of antimicrobial activity of ozonides: the oxygen internalized from ozonides reacts with the proton/protons in order to form $H_2O_2$ that has a bacteriostatic and bactericidal activity.

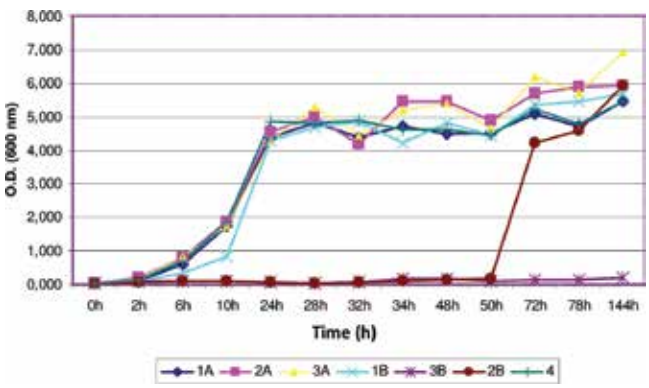


**Figure 4.** Growth curves of mycete *Epidermophyton floccosum* in liquid culture medium: 1A, 2A, and 3A are the positive controls with 12.5, 25, and 50 mg/ml of nonozonized olive oil, respectively; 1B, 2B, and 3B are ozonized olive oil samples with 12.5, 25, and 50 mg/ml of ozonized olive oil, respectively; 4 is the negative control.

For virus inactivation, a higher gas dosage than that required for bacteria is necessary. The ozone oxidates and subsequently inactivates the specific viral receptors used to bind the cell wall for virus invasion [54]. We tested the antibacterial activity of Bioxoil™ on mycete *Epidermophyton floccosum*, demonstrating its efficacy in the inhibition of mycete's growth in liquid and agar medium; the bacteriostatic effect is obtained in the presence of 5 μl/ml of ozonated olive oil, and the bactericidal effect is obtained in the presence of 15 μl/ml (**Figure 4**).

The antibacterial activity of Bioxoil™ was also tested on *Staphylococcus aureus* and *Staphylococcus epidermidis*, and its efficacy in inhibiting microbes growing both in liquid medium culture and

in agar medium was demonstrated. We defined the minimal inhibitory concentration (MIC) of 50 mg·ml$^{-1}$ for *S. aureus* and of 25 mg·ml$^{-1}$ for *S. epidermidis*. This study confirms that ozonated olive oil has antimicrobial properties, which can be exploited for cutaneous infections, by slow release of $O_3$, which displays effective disinfectant and stimulatory activities that lead to rapid healing.

*3.1.2. Biological activity*

The ozonides easily penetrate the cell membrane and, thanks to their biological properties, stimulate skin cells and improve the tropism of the skin by promoting wound healing and repair of ulcers of various kinds; from the experiments, it was found that topical application of products based on ozonides has determined a considerable increase of fibroblasts resulting in increased production of collagen, glycosoaminoglycans, and formation of elastic and reticular fibers. The healing of skin lesions includes complex movements like tissue hemorrhage, inflammation, re-epithelialization, granulation tissue, and finally remodeling. These events involve the coordination of many cell types and matrix proteins, which are important for the control of the various stages of tissue repair. Previous studies have shown that endogenous growth factors, such as fibroblast growth factor (FGF), growth factor derived from platelets (PDGF), the TGF-β factor, and vascular endothelial growth factor (VEGF) are important regulators in the healing of wounds [55]. They are released by macrophages, fibroblasts, and keratinocytes at the site of injury and participate in the regulation of re-epithelialization, formation of granulation tissue, collagen synthesis, and neovascularization [56–58]. The beneficial effects of ozone in the treatment of sores are due to the decrease of bacterial infection and the increasing oxygen tension in the wound. In the literature, it is reported that after exposure to ozone transcription factors are activated, such as NF-kB, and these are important regulators of the inflammatory response and tissue repair process [58]. In conclusion, the ozonated olive oil can accelerate acute cutaneous wound repair, by stimulation of dermal fibroblast, and the ozonized oil has shown to be effective against Gram-negative and -positive bacteria, mycetes, and viruses, so it can be used for the cure of infections.

## 4. Conclusions

The goal of pharmacological research has always been that of finding drugs that can cure diseases or soothe the pain that derives from them, and this research has evolved over the years in an extraordinary way both in the field of medical knowledge and scientific studies that are more and more powerful and sophisticated. Medicinal herbs, long popular in many parts of the world, are increasingly spreading in the western world and represent a large commercial market with an estimated annual growth of 25%, often replacing synthetic drugs. Among the medicinal herbs, particular interest is reserved to olive oil, called "yellow gold" by the Egyptians for its innumerable beneficial properties. Herbal trade today sees many products based on olive oil for both hygiene and personal care. In the field of oil-based products, particular interest is directed to products containing ozonated oil; these products are the result of the union of the beneficial properties of olive oil with those of ozone. Ozonated oil is the most practical, innovative, harmless, and noninvasive of the techniques of application developed in

the field of ozone therapy over the last 130 years. It has demonstrated interesting therapeutic results. The biological effects of ozone include antimicrobial activity (antibacterial, antiviral, and antifungal), antalgic action, and improved $O_2$ metabolism [59]. In this chapter, the possible applications of the Bioxoil™ products, already distributed in pharmacies and herbalist's shops, have been described; its production line includes five different products characterized by different concentrations of ozonides such as to allow the use for the most varied skin affections. Bioxoil with the highest content of ozonides is indicated for the treatment of bedsores at first and second stages, thanks to its anti-inflammatory and cicatrizing properties, Bioxoil with medium concentrations, but different from each other, is indicated for the treatment of herpes labialis, mycosis, and onychomycosis and for acne due to its antimicrobial action. Finally, Bioxoil with the lowest ozonide content is indicated to soothe contact or allergic irritations. The exceptional usability of the product and its completely natural origin offers a vast market.

## Abbreviations

| | |
|---|---|
| ROS | reactive oxygen species |
| IsoPs | F2-isoprostanes |
| COX | cyclooxygenase |
| LDL | low density lipoprotein |
| 3,4-DHPEA | hydroxytyrosol |
| 3,4-DHPEA-EDA | 3,4-dihydroxyphenylethanol-elenolic acid dialdehyde |
| p-HPEA-EDA | 2-(4-hydroxyphenyl)ethyl (4E)-4-formyl-3-(2-oxoethyl)hex-4-enoate |
| COX-1 | cyclooxygenase 1 |
| COX-2 | cyclooxygenase 2 |
| PI | peroxide index |
| AI | acidity index |
| SG | stratum germinativum |
| SS | stratum spinosum |
| SGR | stratum granulosum |
| SC | stratum corneum |
| GSH | glutathione |
| LOP | lipid oxidation |
| MIC | minimal inhibitory concentration |

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Chapter 13

# *Taraxacum* Genus: Potential Antibacterial and Antifungal Activity

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**Abstract**

Plants have been used in traditional medicine for centuries as antibacterial and antifungal agents. *Taraxacum* spp., commonly known as dandelion, is a well-known herbal remedy with a long history; however, limited scientific information is available to explain its traditional use. This review aims to provide current information and a general overview of the available literature concerning the antibacterial and antifungal properties of the *Taraxacum* genus to support its potential as a powerful herbal medicine. Though *Taraxacum* has demonstrated that it is capable of inhibiting the growth of a wide range of bacteria and fungi, the technical aspects of methodology lack standardization, and, therefore, the overall results of processing are difficult to compare between studies. Phytochemical composition and antimicrobial activity in *Taraxacum* are neither directly related, nor does the published data provide sufficient information for identifying the group of unique extraction conditions that are optimal against specific microorganisms. Antimicrobial research indicates that this plant is a promising species for treating several common infections in humans, animals, and plants.

**Keywords:** antimicrobial, antifungal, ethnopharmacology, extraction, *Taraxacum* species

## 1. Introduction

Plants have been used in traditional medicine for centuries due to the synthesis of several molecules that provide antibacterial and antifungal properties, the majority of which probably evolved as defenses against infection or predation [1]. The medicinal potential of many plants is still largely unexplored. Among the estimated 250,000–500,000 plant species, a relatively small percentage have been investigated phytochemically and the fraction submitted for

biological or pharmacological screening is even smaller [2]; approximately 20% of the plant species in the world have been investigated for these properties [3]. In this context, dandelion serves as an interesting species with which to unify decades-old information regarding its biological potential against diverse microorganisms. This review gathers the existing results to advance the search for products that could strengthen the domestication and mass production of this plant.

The *Taraxacum* spp. commonly called dandelion is an herbaceous perennial plant of the *Asteraceae* (Compositae) family. This common weed is found worldwide, though originally introduced from Eurasia, and can be found growing in parks, gardens, pastures, orchards, roadsides, vegetable gardens, and among agricultural and horticultural crops [4]. Primarily used as food, the role of *Taraxacum* in traditional medicine was mentioned during ancient times by the Greek physician Dioscorides in the first century and during the renaissance by monks in Cyprus [5]. This plant has been used to treat cystitis, liver and gastric ailments, hepatic and renal detoxification, diabetes, as an anti-inflammatory and anticarcinogenic agent, and, to a lesser extent, as an antimicrobial and antiviral agent, as described in several reviews [6, 7]. Ethnopharmacologically, its use as an antimicrobial agent has been known worldwide among varying cultures, though it has always been administered as a cataplasm (poultice) or infusion. The traditional antimicrobial uses of *Taraxacum* worldwide are displayed in **Table 1**.

Asia and Europe have an important historical background regarding the traditional uses of *Taraxacum*, primarily *T. officinale*, *T. mongolicum*, and *T. coreanum*. This traditional knowledge has been the principal reason for studying the potential uses and crop requirements of *Taraxacum*; studies in America remain scarce [18]. Due to the unscientific approach often present in oral traditions, uncertainty surrounds whether *Taraxacum* use effectively treats microbial infection or, instead, treats only the symptoms. Therefore, scientific research is extremely important in avoiding misinterpretation and myths regarding *Taraxacum* or any other plant.

The first antibacterial scientific study for *Taraxacum* was reported a mere 35 years ago [19]. More than a decade later, studies related to *Taraxacum* antimicrobial activity gained significant

| Species | Common use | Country | Part used | Consumption | References |
|---|---|---|---|---|---|
| *T. cyprium* | Catarrh and common cold, cough | Greece | Roots, leaves | — | [5] |
| *T. mongolicum* | Urinary tract infections | China | Leaf | Infusion | [8] |
| *T. officinale* | Malaria | Venezuela | Roots, leaves | Decoction | [9] |
| | Tuberculosis | Italy | — | — | [10] |
| | Cough | Italy | — | — | [11] |
| | Bacterial infection | Mexico | — | — | [12] |
| | Diuretic | Chikar | Roots | Tonico | [13] |
| *T. panalpinum* | Malaria | Portugal | Roots, leaves, juice | — | [14, 15] |
| *T. platycarpum* | Pleurodynia | Korea | Leaf, stem | Infusion<br>Brewing | [16, 17] |

**Table 1.** Ethnopharmacological information of *Taraxacum* genus used as an antimicrobial traditional medicine.

relevance as part of an Italian program between the University of Ferrara and the University of Naples for screening medicinal plants [20]. Nowadays, this plant is becoming a promising species in the treatment of several bacterial and fungal diseases due to the results of various antimicrobial-related studies. This chapter seeks to elucidate both the traditional uses and current state of *Taraxacum* in antimicrobial research to determine the potential that this genus has to become an industrial medicinal crop worldwide. Due to the high potential value that could be derived from the use of new technologies and industrial products developed from this type of plant species, the conservation and protection of the crop should be considered and sustainable global production strategies are developed in accordance with assessments of ecological, economic, and social factors.

## 2. Antimicrobial properties of the *Taraxacum* genus

Literature reviews providing information on the antimicrobial aspects of natural products, which had until now only been considered empirical, have been recently scientifically confirmed as a means of countering the increasing reports of pathogenic microorganisms resistant to synthetic antimicrobial agents. Some plant-derived compounds can control microbial growth, either separately or in association with conventional antimicrobials [21]. Currently, numerous studies seek to improve pathogen prevention by combining the application of medicinal herb extracts with an antibiotic or effective antipathogenic pesticide to reduce the active synthetic ingredient and resistant pathogenic strains.

### 2.1. *Taraxacum* species tested for antimicrobial properties

Among the *Taraxacum* genus, *T. officinale* is the most frequently reported species, with almost 80% of mentions in documents related to antimicrobial properties (see **Table 2**), followed by *T. mongolicum* and *T. coreanum*, though over 2500 *Taraxacum* species are currently identified [67]. Other, less studied species include *T. platycarpum*, *T. farinosum*, *T. ohwianum*, and *T. phaleratum*; however, the relevance of these species is confined to specific areas (mostly in Asia) in which they grow naturally since they are not deliberately cultivated for medicinal benefit. This indicates that the microbial properties of less than 1% of all *Taraxacum* species discovered have been studied, revealing the enormous research potential of this genus.

### 2.2. Bacterial and fungi strains tested

*Taraxacum* extracts have been tested on different bacterial and fungal strains affecting humans, animals, and plants to determine its antimicrobial profile, confirm its traditional usage, and expand its known uses. Antimicrobial agents are categorized based on the spectrum of action, namely "narrow" and "broad" spectrum, which indicates whether its use is specific for certain bacterial strains or active on a wider range. Bacterial infections can result in mild to life-threatening illnesses that require immediate antibiotic intervention. Alternatively, a superficial fungal infection is rarely life-threatening but can have debilitating effects and may spread to other people or become invasive or systemic, resulting in a life-threatening infection. The widespread, and sometimes inappropriate, use of chemical compounds can create antibiotic

| *Species* | Autentification/ Voucher | C: Collected P: Purchase | Zone | Season | Plant part* | Sample manipulation | Ratio | Solvent | Extraction time | Temp. | Agitation | Inhibition activity** | Ref. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *T. officinale* Wigg. | No/No | NI | NI | NI | Flower | NI | 1:10 | Acetic acid 10% | 1 h | RT | Homog. | + | [22] |
| *T. officinale* Wigg. | No/No | C | NI | Yes | Seeds | Grounded | 1:10 | Acetic acid 10% | 1 h | RT | NI | + | [23] |
| *T. officinale* Weber | Yes/No | C | Yes | Yes | NI | Dried | NI | Water, ethanol and ethyl acetate | 1 h | 80°C | Maceration | + | [24] |
| *T. officinale* | Yes/Yes | C | Yes | NI | NI | Air-dried | 1:14 | Acetone | 30 min | NI | NI | + | [25] |
| *Taraxacum* spp. | No/No | C | Yes | NI | NI | NI | 1:10 | Dichloromethane | 3 h | 20°C | Homog. | + | [26] |
| *T. officinale* | No/Yes | C | Yes | Yes | NI | NI | NI | Dichloromethane | 3 days | NI | Homog. | + | [27] |
| *T. coreanum* | No/No | NI | NI | NI | NI | NI | 1:3.3 | Ethanol 75% | 9 h | 60°C | Reflux | + | [28] |
| *T. mongolicum* | No/No | C | NI | NI | Aerial | Frezee-dried and grounded 20-mesh | 1:5 | Ethanol 75% | 2 days | NI | Soaked | + | [29] |
| *T. officinale* Weber | No/Yes | C | Yes | Yes | Root | Dried and grounded | NI | Ethanol 80% | NI | NI | Reflux | + | [20] |
| *T. officinale F. H. Wigg* | Yes/Yes | C | NI | NI | Aerial | Air-dried and crushed | 1:1 | Ethanol 90% | 2 days | RT | Intermitent shaking | + | [30] |
| *T. mongolicum H.* | | | | | NI | | 1:10 | Ethanol 95% | 3 h | 80°C | | + | [31] |
| *T. ohwianum* | No/No | NI | NI | NI | NI | Freeze-dried, air-dried (40°C, 24 h), grounded 24-mesh | 1:16 | Ethanol 95% | 24 h | RT (23°C) | Shaking | + | [32] |
| *T. officinale* | Yes/No | NI | NI | NI | Leaves | Air-dried | 1:5 | Ethylacetate | 24 h | RT | 150 rpm | + | [22] |
| *T. officinale F.H. Wigg.* | Yes/Yes | P | NI | NI | Root | Freeze-dried and blended | 1:10 | Hexane | Overnight | RT | 70 rpm | + | [33] |

| *Species* | **Autentification/ Voucher** | **C: Collected P: Purchase** | **Zone** | **Season** | **Plant part*** | **Sample manipulation** | **Ratio** | **Solvent** | **Extraction time** | **Temp.** | **Agitation** | **Inhibition activity**** | **Ref.** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *T. officinale* | No/No | NI | NI | NI | Leaves | Air-dried 1 month and grounded | 1:1.4 | Methanol 75% | NI | NI | NI | + | [34] |
| *T. officinale Weber* | No/No | C | Yes | NI | Aerial | Air-dried a 40°C (36–48 h) and grounded | 1:5 | Methanol 80% | 1 h | 100°C | Reflux | + | [35] |
| *T. officinale* Weber ex. F. H. Wigg | No/Yes | NI | NI | NI | Leaves | NI | 1:4 | Methanol | 5 days | RT | NI | + | [36] |
| *T. officinale* Weber | No/No | C | NI | NI | Aerial | Dry under shade and ground | 1:10 | Methanol | 3 weeks | 25°C | Homog. | + | [37] |
| *T. platycarpum* | No/No | NI | NI | NI | NI | Dried | NI | Methanol | 3 h | 80°C | NI | + | [38] |
| *T. platycarpum* | No/No | NI | NI | NI | NI | Dried | NI | Methanol | 3 h | 80°C | NI | + | [39] |
| *T. officinale* | | | | | NI | | NI | Methanol | 16 h | 50°C | | + | [40] |
| *T. officinale* | No/No | C | NI | NI | Leaves | Dried under shade and grounded | 1:2.5 | Methanol | 24 h | 37°C | 120 rpm | + | [41] |
| *T. mongolicum* Hand-Mazz | Yes/Yes | C | Yes | Yes | NI | Air-dried and grounded | NI | Water | 3 h | 100°C | By boiling | + | [36] |
| *T. officinale* | | | | | NI | | 1:05 | Water | NI | NI | Homog. | + | [42] |
| *T. officinale* | No/No | NI | NI | NI | NI | Dried at 25–30°C for 1 week., ground with a mortar | 1:20 | Water | 24 h | 35°C | Shaking | + | [43] |
| *T. officinale* F.H. (Webb) | No/No | C/P | NI | NI | Root | Cleaning prior freeze-dried, grounded | 1:10 | Water | 3 h | RT | 170 rpm | + | [44] |


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| *Species* | Autentification/ Voucher | C: Collected P: Purchase | Zone | Season | Plant part* | Sample manipulation | Ratio | Solvent | Extraction time | Temp. | Agitation | Inhibition activity** | Ref. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *T. officinale* | No/No | NI | NI | NI | NI | NI | 1:04 | Water | 45 min | 100°C | NI | + | [45] |
| *T. officinale* Weber ex Wigger | No/No | NI | NI | NI | leaves | Grounded | 1:01 | Water | 5 min | NI | NI | + | [46] |
| *T. mongolicum* | No/No | NI | NI | NI | NI | Grounded | NI | Water | 1 h | 100°C | By boiling | + | [47] |
| *T. officinale* | No/No | NI | NI | NI | NI | Dried at 60°C × 2 h and grounded 60-mesh | 1:10 | Water | NI | NI | NI | + | [48] |
| *T. officinale* H. | NI/NI | NI | NI | NI | NI | NI | | | | | | + | [49] |
| *T. officinale* F.H. Wigg | NI/NI | C | Yes | Yes | Honey | NI | NI | NI | NI | NI | NI | + | [50] |
| *T. farinosum* Hausskn. & Bornm | NI/NI | C | NI | Yes | Root | NI | NI | NI | NI | NI | NI | + | [51] |
| *T. officinale* | Yes/No | C | Yes | Yes | NI | Dried 40°C × 5 days and grounded | NI | NI | NI | NI | Reflux | + | [52] |
| *T. officinale* | NI/NI | NI | NI | NI | NI | NI | NI | NI | NI | NI | NI | +W | [53] |
| *T. officinale* | No/No | P | NI | NI | NI | NI | NI | Ethanol 35% | NI | NI | NI | +W | [54] |
| *T. platycarpum* | No/No | P | NI | NI | NI | Grounded 50-mesh | 1:10 | Ethanol | 24 h | RT | Homog. | +W | [55] |
| *Taraxacum* sp. | No/No | NI | NI | NI | Aerial | Grounded | 1:10 | Water | 4 h | 100°C | By boiling | +W | [56] |
| *T. officinale* F.H. Wigg. | No/No | C | Yes | Yes | Aerial | Frozen, cut and grounded | 1:01 | Ethanol 20% | 24 h | RT | NI | – | [57] |
| *T. officinale* | No/No | NI | NI | NI | Leaves | Dried | NI | Ethanol 40% | NI | NI | NI | – | [58] |

| *Species* | **Autentification/ Voucher** | **C: Collected P: Purchase** | **Zone** | **Season** | **Plant part*** | **Sample manipulation** | **Ratio** | **Solvent** | **Extraction time** | **Temp.** | **Agitation** | **Inhibition activity**** | **Ref.** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *T. officinale* | No/No | Extract (P) | NI | NI | NI | Diluted | NI | ethanol 45% | NI | NI | NI | – | [59] |
| *T. phaleratum* G. Hagl et Rech | Yes/Yes | C | Yes | NI | Aerial | Air-dried and grounded | NI | Ethanol 70% | NI | RT | NI | – | [60] |
| *T. officinale* Cass. | No/No | P | NI | NI | Root | Dried | 1:04 | Ethanol | 24 h | NI | | – | [61] |
| *T. officinale* | No/No | C | Yes | NI | flower | Chopped and frozen | NI | Methanol 90% | 30 min | 4°C | Homog. | – | [62] |
| *T. officinale* Weber | Yes/Yes | NI | NI | NI | NI | Dried and grounded | 1:40 | Methanol | Overnight | RT | NI | – | [63] |
| *T. mongolicum* Hand-Mazz | No/Yes | C | NI | NI | Whole | NI | 1:10 | Water | Overnight | NI | Homog. | – | [64] |
| *T. officinale* | No/No | P | NI | NI | Root | Grounded | 1:8.3 | Water | 30 min | 100°C | By boiling | – | [65] |
| *T. officinale* | No/No | C | Yes | Yes | Leafs, roots | NI | 1:03 | Water | | RT | Homog. | – | [66] |

*NI, No indicated.

**Table 2.** Physical parameters on *Taraxacum* extracts for testing antimicrobial activity.


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resistance. Due to this issue, the potential of *Taraxacum* as a useful, broad-spectrum antimicrobial and antifungal agent that can be "easily and worldwide grown," is highly valuable. A list of the strains against which *Taraxacum*'s antimicrobial activity has been tested is displayed in **Table 3**.

| **Bacterial strains** | **Fungi strains** |
|---|---|
| *Aeromonas hydrophila* (−) [22] | *Alternaria alternata* (+) [46, 68] |
| *Agrobacterium tumefaciens* (+) [24] | *Aspergillus carbonarius* (+) [35] |
| *Bacillus cereus* (+) [22, 33, 36, 44] (−) [66] | *A. niger* (+) [23, 35, 37, 68, 69] (−) [27, 66] |
| *B. pumilus* (−) [66] | *A. flavus* (+) [37] (−) [66] |
| *B. subtilis* (+) [20, 24, 25, 27, 29, 34, 38, 39, 41, 48, 69] (−) [37, 64, 66] | *A. fumigatus* (+) [37](−) [66] |
| *Campylobacter jejuni* (+) [54, 59] | *Bipolaris sorokiniana* (+) [23, 67] (−) [68] |
| *Chromobacterium violaceum* (+) [66] (−) [65] | *Botrytis cinerea* (+) [23, 35, 67] |
| *Clavibacter michiganense* (+) [69] | *Candida albicans* (+) [27, 34, 36, 52] (−) [55, 57, 66] |
| *Cupriavidus* sp. (−) [66] | *C. glabrata* (−) [55, 66] |
| *Enterobacter coccus* (−) [37] | *C. krusei* (−) [66] |
| *Enterococcus faecalis* (+) [53] (−) [37, 66] | *C. parapsilesis* (−) [55, 66] |
| *Erwinia carotovora* (+) [24] | *C. utils* (−) [55] |
| *Escherichia coli* (+) [22, 24, 25, 27, 29, 34, 36, 38, 39, 41, 43, 45, 47, 48, 58, 70] (−) [20, 32, 33, 37, 44, 57, 62, 64, 66] | *C. tropicalis* (+) [55] |
| | *Cladosporium herbarum* (+) [71] |
| *Helicobacter pylori* (+) [31, 54] | *Cochliobolus sativus* (+) [68] |
| *Klebsiella aerogenes* (−) [66] | *Colletotrichium gloesporoides* (−) [68] |
| *K. penumoniae* (+) [29, 36] (−) [20, 37, 45, 66] | *C. lagenarium* (+) [42] |
| *Listeria monocytogenes* (+) [38, 39] (−) [66] | *Cryptococcus neoformans* (+) [36] |
| *Micrococcus kristinae* (+) [25] | *Exophiala (Wangiella) dermatitidis* (−) [66] |
| *M. luteus* (+) [37, 41] | *Fusarium avenaceum* (+) [68] |
| *Mycobacterium aurum* (−) [63] | *F. graminearum* (−) [69] |
| *M. bovis* (−) [63] | *F. oxysporum* (+) [23, 56, 69] |
| *M. smegmatis* (−) [63] | *Microsporum canis* (+) [51] |
| *M. tuberculosis* (−) [60] | *Monilinia laxa* (+) [35] |
| *Propionihacterium acnes* (+) [49] | *Mucor piriformis* (+) [46] |
| *Proteus mirabilis* (+) [43] (−) [20] | *Penicillium sp.* (−) [66] |
| *P. vulgaris* (+) [25, 29] (−) [70] | *P. digitatum* (+) [35] |
| *Pseudomonas* sp. (−) [50] | *P. expansum* (+) [26, 46] (−) [35] |
| *P. aeruginosa* (+) [24, 27, 29, 36, 41, 49, 70] (−) [20, 37, 57, 64, 66] | *P. italicum* (+) [35] |

| Bacterial strains | Fungi strains |
|---|---|
| *P. fluorescens* (+) [24] | *Ph. betae* (+) [23, 68] |
| *P. syringae* (+) [69] | *Phytophthora infestans* (+) [69] |
| *Serratia/Rahnella sp.* (−) [66] | *Pityrosporum ovale* (+) [49] |
| *Salmonella typhimurium* (+) [36] (−) [33, 44] | *Pythium debaryanum* (+) [69] |
| *S. abony enterica* (+) [58] | *Rhizoctonia solani* (+) [37, 56] |
| *S. poona* (−) [66] | *Saccharomyces cereviseae* (+) [34] |
| *S. typhi* (+) [44, 51] (−) [20] | *Saprolegnia australis* (−) [61] |
| *Sarcina lutea* (+) [24] | *Scedosporium apiospermum* (−) [66] |
| *Serratia marcescens* (+) [25] (−) [66] | *Trichophyton longifusus* (+) [51] |
| *Shigella fiexeri* (−) [70] | *T. mentagrophytes* (+) [27] |
| *S. sonnei* (+) [36] | *Verticillium albo-atrum* (+) [23] (−) [68] |
| *Staphylococcus aureus* (+) [22, 24, 25, 28, 29, 32–34, 36, 38, 39, 41, 43–45, 48–52, 70] (−) [20, 27, 37, 57, 58, 62, 64, 66] | |
| *S. epidermidis* (+) [28] (−) [66] | |
| *Streptococcus haemolyticus* (+) [20] | |
| *S. agalactiae* (+) [47] | |
| *S. dysgalactiae* (+) [47] | |
| *Vibrio cholerae* (+) [37] | |
| *V. parahaemolyticus* (+) [38, 39] | |
| *Xanthomonas campestris* (+) [69] | |

(+) Extracts of *Taraxacum* active against the pathogen; (−) extracts of *Taraxacum* inactive against the pathogen.

**Table 3.** Bacterial and fungal strains on which *Taraxacum* extracts have been tested.

### *2.2.1. Human pathogens*

In the study of antibacterial properties of these plants, most attention has been focused on human pathogenic strains, including *S. aureus*, *E. faecalis*, *V. cholerae*, *B. subtilis*, *P. aeruginosa*, *K. pneumonia*, and *E. coli*. These are the pathogens commonly responsible for infections in gastrointestinal and massive organ systems such as the lungs and skin. *Taraxacum officinale* is the species generally studied to combat these pathogens, but it has demonstrated diverse results depending on the extraction characteristics or the bioassay performed. For instance, a methanolic extract of *T. officinale* at 0.2 mg/mL was as effective as an antibacterial agent against *M. luteus* and *V. cholera* with minimum inhibitory concentration (MIC) values of 1.0 and 12.5 mg/mL, respectively, but displayed no activity against *S. aureus*, *E. faecalis*, *E. bacter*, *V. cholerae*, *B. subtilis*, *P. aeruginosa*, *K. pneumonia*, *or E. coli* [37]. In the same study, the inhibition percentages achieved for mycelial growth of *A. niger*, *A. flavus*, *A. fumigatus*, and *R. solani* were 37, 71, 85, and 78%, respectively. Other works indicate that methanolic *T. officinale* leaf extracts ranging from 0.003 to 0.5 mg/mL were active against *S. aureus*, *P. aeruginosa*, *B. cereus*, *S. sonnei*,

*S. enterica* serovar *typhimurium*, *E. coli*, *K. pneumonia*, *C. albicans*, and *C. neoformans* with MIC values ranging from 0.04 to 5.0 mg/mL [36]. A similar extract at 10 mg/mL displayed moderate growth diameter inhibition for *S. typhi*, but was highly active for *S. aureus*, *B. cereus*, and *E. coli*, even when no activity was observed for *A. hydrophila* [22]. Ethanolic extracts of 2.0 mg/mL were active against *A. aureus*, *MRSA* clinical, and *B. cereus*, with MIC values between 0.38 and 0.5 mg/mL, but were not effective against *E. coli* or *S. typhi*. In the same work, a water extract at the same concentration showed no activity against any strain tested [33]. Moreover, 21 ethanolic extracts from various plants were tested against 20 *Salmonella* serovars. *Taraxacum* inhibited only 5% of these, and was therefore not considered for additional antimicrobial studies [72].

Recently, methanolic and chloroformic leaf extracts of *T. officinale* were found to be effective against *M. luteus*, *P. aeruginosa*, *B. subtilis*, *E. coli*, and *S. aureus* with MIC values of 0.3 mg/mL and no observable activity for water extracts [41]. In this study, the highest impact was noted with methanol and chloroform extracts against *S. aureus* and *E. coli*, respectively, and the lowest with both extracts against *P. aeruginosa*. Furthermore, an ethanolic extract was effective against *E. coli* and *S. aureus*, but no activity was observed for either extract against *K. pneumonia* and *P. aeruginosa* at 50, 100, and 200 mg/mL. Nevertheless, a water extract was effective only for *E. coli* at 100 and 200 mg/mL [45]. Water and ethanolic extracts at 1.0 mg/mL exhibit effective inhibition against *S. aureus* and fewer inhibitory effects were observed for *P. mirabilis*; against *S. aureus*, an ethanolic extract was active at 0.5 mg/mL, but a water extract was only active at 1.0 mg/mL; and inhibition was not achieved for either extracts at 0.1 mg/mL [73]. An ethanolic extract was slightly active against *B. subtilis* and *S. haemolyticus*, but was inactive against other Gram positive and Gram negative strains, resulting in no further studies with this extract [20]. Furthermore, only weak activity was achieved by methanolic extracts of this plant against *P. syringae* [74].

Both ethanolic and water extracts of *T. officinale* were active for *S. marcescens* and *M. kristinae*. The ethanolic extract alone was active on *P. vulgaris*, *E. coli*, *B. subtilis*, and *S. aureus* with MIC values ranging from 1.0 to 7.0 mg/mL for all strains tested [25]. Similar extracts had antimicrobial effects on four species that induce acne (*P. ovale*, *P. acnes*, *P. aeruginosa*, and *S. aureus*) in broth dilution tests with effects depending on the extract concentration, but no further information was available [49]. Moreover, a leaf extract (0.04 mg/well) was reported as a bactericidal agent against *S. aureus* and fungistatic against *C. albicans* [52]. Contrarily, extracts of 130 and 200 mg/mL from aerial parts were unable to prevent the growth of 34 microorganisms from genera *Bacillus*, *Enterobacter*, *Klebsiell*a, *Listeria*, *Pseudomonas*, *Salmonella*, *Staphylococcus*, *Aspergillus,* and *Candida*, among others; therefore, it was considered inactive at these concentrations in a disc diffusion assay [66]. A methanolic *T. officinale* flower extract was not active against *E. coli* or *S. aureus* at 1.0 mg/mL in a diffusion agar assay [62] and no activity was found on *S. aureus, E. coli*, *P. aeruginosa,* or *C. albicans* using a leaf ethanolic extract when 0.05 mL were placed in sterile discs [57]. Furthermore, an ethanolic extract of leaves displayed no activity against *S. aureus*, *E. coli,* or *S. abony* by the serial dilution method [58], with the same results for root and leaf extracts on *M. aurum* and *M. smegmatis* at 0.5 mg/mL [63].

Raw extracts of *T. officinale* have been widely tested, as well as solvent fractions. In a study in which the methanolic leaf extract was fractioned by different solvents, the methyl chloride,

ethyl acetate, and butanol fractions were active on *E. coli*, *S. aureus*, *B. subtilis*, *C. albicans*, and *S. cerevisiae* at 50 mg/mL, with inhibition percentages ranging from 13 to 76%. The water fraction showed moderate inhibition via the broth dilution method (10 and 14% for *E. coli* and *B. subtilis*, respectively) but no effect on the disc diffusion assay [34]. The only report in which a *Taraxacum* extract was compared to another natural antibacterial substance besides other plants extracts evaluated the use of *T. officinale* extract as an irrigation agent in endodontic treatments against *E. faecalis* in root canal infections. Leaf and root extracts at 0.7% were slightly active but propolis was more effective for this purpose [53]. In the case of commercial preparations, high activity has been reported for a commercial *T. officinale* ethanolic extract, showing antibacterial activity against *H. pylori* at 20 mg/mL with 26% inhibition but no observable activity for *C. jejuni* [54].

Considering other *Taraxacum* species, *T. platycarpum* anticandidal activity was determined against five different *Candida* sp. by agar diffusion assay. An ethanolic extract at 0.2 mg/mL weakly inhibited *C. tropicalis* but no other Candida strains [55]. A methanolic extract was active against *B. subtilis*, *S. aureus*, *L. monocytogenes*, *E. coli*, and *V. parahaemolyticus* at concentrations ranging from 0.5 to 2.0 mg/mL, with growth inhibition ranging from 5.1 to 100%, correlating to the concentration. In that study, chloroform, butanol, and ethyl acetate fractions were active in the disc diffusion assay for almost every strain tested, but an aqueous extract was inactive [38, 39].

An ethanolic extract of *T. mongolicum* at 0.2 mg/mL was not able to achieve growth inhibition in a microdilution assay for *B. subtilis*, *S. aureus*, *E. coli*, or *P. aeruginosa* [64]. In contrast, an ethanolic extract of this species was active for *E. coli*, *S. aureus*, and *P. aeruginosa* in the disc diffusion assay with MIC values between 0.05 and 0.1 mg/mL, which was three times higher than the values obtained for erythromycin. However, no activity was achieved for *S. fiexneri* or *P. vulgaris* [75]. Another report indicated that only the butanol fraction of an ethanolic extract of this plant was active on *H. pylori,* but water and methyl chloride fractions were inactive. Nevertheless, a different report indicated that a butanol fraction exerted higher inhibition (13%) than the aqueous fraction, possibly due to the flavonoid and luteolin content (28 and 1.1%, respectively) [31]. Against *S. aureus* and *S. epidermis,* an acetyl acetate fraction of an ethanolic *T. coreanum* extract was active at 0.5, 1.0, and 3.0 mg/disc, a chloroform fraction was active at 1.0 and 3.0 mg/disc, and a butanol fraction at 1.0 mg/mL, but displayed no activity against *MRSA* displayed [28]. An ethanolic *T. ohwianum* extract was active against *E. coli* at 240 and 320 mg/mL, but not against *S. aureus* [32]. These authors indicate that the pH and temperature of the bioassay were important parameters in the antimicrobial performance of the extract. An extract of the aerial parts of *T. phaleratum* was inactive at 0.2 mg/mL against *M. tuberculosis*, even when several solvent fractions were tested [60].

Limited studies have been conducted on humans establishing the antimicrobial potential of *Taraxacum* extracts. Chinese language studies have reported the effects of various formulas containing *T. mongolicum* for medical treatment. An herbal formula known as "fu zheng qu xie" was just as effective as the antibiotic gentamycin in 75 cases of gastric disease caused by *H. pylori*. Furthermore, an herbal formula called "jie du yang gan gao," which includes *T. mongolicum*, was significantly more effective than another botanical formulation in lowering elevated liver enzymes and curing patients with hepatitis B in a 96-person, double-blind trial [76].

### 2.2.2. Plant pathogens

Plant extracts have also been tested on bacteria and fungi that affect fruits and vegetables, causing rot diseases during postharvest handling, to find an alternative to chemical pesticides, which are harmful to the environment and human health. An aqueous *T. officinale* root extract (S) at different dilutions (S, S/2 to S/100) caused significant inhibition to mycelial growth in *A. alternata* (70% for S to 17% for S/100), *P. expansum* (67% for S to 5.3% for S/100), and *M. piriformis* (70% for S to 16% for S/100) [46]. In the case of *R. solani* and *C. sativus*, a *Taraxacum* acetyl acetate extract at a concentration of 100 mg/mL exhibited a weak effect on the growth of these plant pathogens and no inhibition of *F. oxysporum* [22]. A methanolic extract of *Taraxacum* at 0.2 mg/mL was not effective against *A. niger*, *A. flavus*, *A. fumigates*, or *R. solani* [37]. A methanolic extract of *Taraxacum* sp. displayed weak activity against *C. sativus*, *F. oxysporum*, and *R. solani* at 5 mg/disc and a water extract displayed no activity at all [56].

A *T. officinale* hydro-methanolic extract tested the inhibition of conidial germination and inhibition of germ tube elongation for several plant pathogens at several dilutions (0.25×, 0.5×, and 0.75×) using a microassay method on slides. Dilution at 0.75× showed inhibition of conidial germination values of 2, 3, 4, 9, 11, and 12% for *P. italicum*, *A. niger*, *A. carbonarius*, *B. cinerea, M. laxa*, and *P. digitatum,* respectively. For these same strains, excluding *A. carbonarius*, inhibition of germ tube elongation values were 56, 45, 38, 5 and 42%, respectively. For *P. expansum*, the plant extract did not show positive results for inhibition of conidial germination or inhibition of germ tube elongation. In artificially inoculated fruits, the extract applied to nectarines was not protective against brown rot development from *M. laxa*, while for apricots effects were similar to those of the negative control for *P. digitatum* [35]. Dichloromethane and diethyl ether *T. officinale* extracts were tested on *P. expansum* by applying either a solution or its vapor to paper discs. The dichloromethane extract was more active of the two models, though direct inoculation in apples offered no observable inhibition [26]. Water extracts of *T. officinale* and *T. platycarpum* were tested against *C. lagenarium* in cucumber, exhibiting inhibition rates of the anthracnose lesions of 1.9 and 13% in treated leaves, and 11 and 5.3% in untreated leaves, respectively. These results were not significant compared to other plant extracts [42]. *In vivo* evaluation of protective effects in plant tissue has not been as successful as the *in vitro* assays, which is typical in cases of inhibitory activity validation. To avoid these ineffective results, concentrations are increased to demonstrate the pathogen control effect.

### 2.2.3. Animal pathogens

Regarding animal pathogens, *Saprolegnia* infections can account for significant salmonid losses. Treatment is difficult and there are reservations regarding efficacy, prompting a search for suitable alternatives. A *T. officinale* root extract was not as effective as a fungistatic at 10, 100, 1000, or 10,000 mg/mL [61]. The effects of *Taraxacum* polysaccharides were studied on the preservation of white shrimp (*Penaeus vannamei*) during refrigerated storage (10 days at 4°C) by soaking the shrimps in aqueous extracts (1–3% w/v). Samples were periodically evaluated for total viable count, pH value, and total volatile basic nitrogen, which resulted in 2–3% of shrimp in fresh conditions (<30 mg/100 mg of total volatile basic nitrogen) and a total viable count that only increased slightly during storage. This indicated that the treatment effectively

retarded bacterial growth during refrigerated storage, prolonging shrimp shelf life for up to 10 days [76].

In the case of the meat industry, an herb mixture including *T. officinale* as a substitute for fodder antibiotics in pig feeding revealed positive growth of the animal and no change in meat quality, confirming the possibility of using herbs as an antibiotic substitute in pig feed [77, 78]. Aqueous and ethanolic extracts of *T. mongolicum* could also inhibit four pathogenic bacteria responsible for cow mastitis, a serious disease in the cow industry, at concentrations of 0.13, 0.25, and 0.5 g/mL. In this case, the ethanolic extracts displayed slightly better antibacterial activities than aqueous extracts. For *E. coli*, *S. aureus*, *S. agalactiae*, and *S. dysgalactiae*, inhibition zone diameters were slightly larger for aqueous than for ethanolic extracts but showed between medium and high sensitivity [79]. Dandelion extract can not only be used to control pathogens but also to supplement the diet of animals, which could result in increased meat, milk, whey, and other yields, contributing to the food industry. Alternatively, the extracts could be utilized in the agricultural industry as biofertilizers to promote plant growth and strengthen the plant against biotic and abiotic stress.

### 2.3. *Taraxacum* antimicrobial action mechanisms

Innate plant immunity involves various defense responses, including cell wall reinforcements, lytic enzyme biosynthesis, secondary metabolite production, and pathogenesis-related proteins. To protect themselves from non-beneficial microorganisms, plants accumulate secondary metabolites that form chemical barriers to microbial attacks (phytoanticipins) and produce antimicrobials (phytoalexins) [80]. Phenolics and terpenoids are considered the primary mechanisms for plant defenses because these reduce microbial attacks by disrupting the cell membranes in microorganisms, bind to adhesins and cell wall compounds, and inactivate enzymes, among other roles [81]. The action mechanisms of natural compounds are related to the disintegration of the cytoplasmic membrane and destabilization of the proton motive force, electron flow, active transport, coagulation of the cell content, inhibition of protein synthesis, inhibition of DNA synthesis, and the synthesis of metabolites used for DNA synthesis [82]. Some action mechanisms are specific to certain targets and some targets may also be affected by more than one mechanism [83]. A general scheme of the action's sites and antimicrobial potential mechanism is presented in **Figure 1** of Supporting Information.

Even though *Taraxacum* is a plant with extremely high pathogen resistance, the underlying molecular mechanisms of antimicrobial activity are poorly studied [68]. Until now, most of the research on *Taraxacum* has focused on elucidating the compounds present in the extract, and, to a lesser extent, on the mechanism involved in the antimicrobial activity itself. One study specifically illustrated the effect of four proteins from *T. officinale* flowers on fungi by light microscopy and distinguished two modes of antimicrobial action, depending on the fungus tested. *Taraxacum* proteins completely blocked conidia germination or induced thickening of multiple local hyphae and irreversible cytoplasm plasmolysis [68, 69]. Different extracts from this genus showed positive inhibitory activity in controlled studies and were characterized by protein synthesis inhibition (e.g. chloramphenicol, tetracycline, gentamicin, and kanamycin) and cell wall synthesis (e.g. amphotericin, cefixime, cephalothin, and penicillin). These

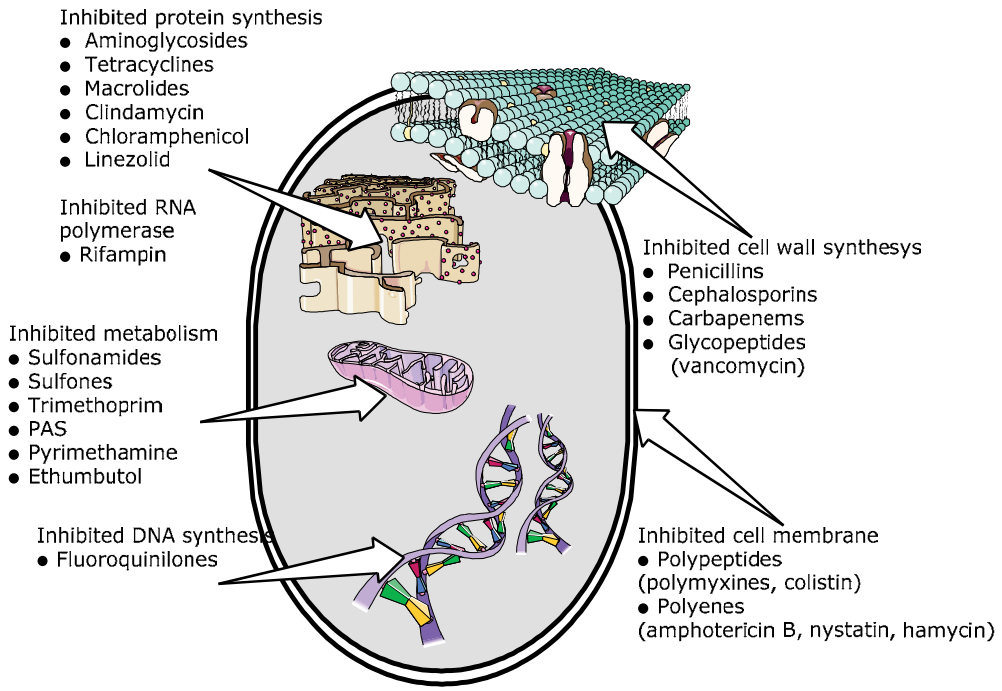


**Figure 1.** Main action mechanisms for antimicrobial agents (adapted from Mulvey and Simor [84]).

mechanisms need to be addressed to elucidate the *Taraxacum* active compound action mechanisms because a direct relation with the positive controls cannot be pursued.

Another response that has been studied is the modulation of microbe adherence to body tissues. Adhesion to epithelial cells has been represented as the first step in the subsequent bacterial invasion of host cells [59]. These authors reported the partial inhibition of intestinal adherence of *C. jejuni* HT-29 cells using a commercial ethanolic *Taraxacum* extract. Cytotoxic activity was less than 10%, but no antibacterial activity was observed. Moreover, *Taraxacum* has been tested with the aim of controlling bacterial diseases by inhibiting communication between bacteria. An ethanolic extract of *T. officinale* aerial parts disturbed bacterial communication systems (or quorum sensing) for *C. violaceum*, showing the moderately positive effect of the extract on the attenuation of microbial pathogenicity [30]. In contrast, an ethanolic and water extract of the rhizomes of the same plant showed no significant activity in the same assay [65].

### 2.4. *Taraxacum* compounds related to antimicrobial action

Several studies have named a wide range of compounds, including terpenes, flavonoids, and phenolic compounds, as responsible for the medicinal activity of different plants [85, 86]. For *Taraxacum*, only a few studies concerning its antimicrobial properties have considered

chemical identification of the obtained extracts and this identification is chiefly qualitative (e.g. using colorimetric methods indicating presence or absence). Authors report the presence of terpenoids, triterpenoids, steroids, coumarins, phenols, saponins, flavonoids, flavones, flavonols, chalcones, phlobatannins, and cardiac glycosides in antimicrobial extracts [22, 27, 34, 36, 37, 43–45, 87, 88] but neither compound isolation nor further identification were performed.

Taraxasterol acetate, lupeol acetate, tranexamic acid, and squalene, among others, were identified in the dichloromethane extract of *T. officinale* leaves, which show low activity against *E. coli*, *P. aeruginosa*, *B. subtilis*, *C. albicans*, and *T. mentagrophytes* in an agar well assay at 30 μg but no observed activity against *S. aureus* or *A. niger* [27]. Terpenoids and flavonoids were identified in the ethanolic extracts of the *T. farinosum* root, which displayed antibacterial activity against *S. aureus*, *S. typhi*, *M. canis*, and *T. longifusus* in an agar well diffusion and agar tube dilution, while the herb extract was active only against the latter two strains [51]. Fractions of a methanolic root extract indicated the significant presence of phenolic-based compounds and hydroxyl-fatty acids with liquid and mass spectrometry, and were active against *S. aureus*, *MRSA* clinical, and *B. cereus* at 2 mg/mL, with MIC values ranging from 0.05 to 0.19 mg/mL, and crude extracts indicating values of 0.25–0.5 mg/mL [33]. An oligosaccharide extract (DOs) from this species exhibited high antibacterial activity against *E. coli*, *B. subtilis*, and *S. aureus* at 100 mg/mL, indicating that these oligosaccharides could potentially be used as antibacterial agents [48].

Concerning specific compounds, isolated *Taraxacum* peptides displayed antimicrobial activity at 6 μg/μL, corresponding to 52–79% of kanamycin activity against *P. syringae*, *B. subtilis*, and *X. campestris* at the same concentration [69], which is a promising value that warrants further experiments. These authors indicated that though *A. niger* appeared sensitive to four proteins (ToAMP1, ToAMP2, ToAMP3, and ToAMP4) from *T. officinale* flowers, *F. graminearum* was not susceptible to any of these proteins. All proteins displayed inhibition activity against *B. cinerea*, *B. sorokiniana*, *A. niger*, *P. debaryanum*, *F. oxysporum*, and *P. infestans*, with IC50 values ranging between 1.2 and 5.8 μM. The ToAMPs were also active against *P. syringae*, *B. subtilis*, and *X. campestris*, similar to a kanamycin control. Additionally, ToAMP2 was active against *C. michiganensis* at up to 0.5 μg/μL. The disease development of *P. infestans* was inhibited by ToAMP2 at 1.3 μM (20–40%) to 5.2 μM (10–20%). In further studies, *B. sorokiniana*, *C. gloeosporioides*, and *V. albo-atrum* were insensitive to ToAMP4, another peptide isolated from the seed extract of *T. officinale*, at concentrations below 15 mM. The IC50 values for the agent-sensitive fungi *A. alternata*, *A. niger*, *F. avenaceum*, and *P. betae* ranged from 2.9 to 13.1 mM, with MIC values from 1.0 to 8.0 mM; no activity was observed for *P. syringae, B. subtilis*, *E. coli,* or *C. michiganensis* [68, 69]. Peptides supposedly have broad-spectrum activity, lack of microbial resistance, and high efficacy [69], but some action mechanisms in these molecules are still poorly defined [89]. Peptides related to albumin 2S from *Taraxacum* seeds are active against phytopathogenic fungi and bacteria. Antifungal assays displayed different activities for the 2S isoforms (ToA1, ToA2, and ToA3). The spore germination of *B. cinerea*, *A. niger*, and *P. debaryanum* were the most tolerant, and *H. sativum*, *P. betae*, and *V. albo-atrum* were the most sensitive at concentrations ranging from 0.063 mg/mL to 0.25 mg/mL. *H. sativum* and *P. betae* were inhibited by ToA1, ToA2, and ToA3, but *F. oxysporum* and *V. albo-atrum* were only inhibited by ToA2 and ToA3, respectively. In potato tubers, *P. infestans* was inhibited by ToA3 at 0.06 mg/mL at 96 and 120 h, but at 144 h ToA2 inhibited better at 0.13 mg/mL [23].

Interestingly, an antimicrobial filtrate isolated from the fungal strains of *P. betae* (PG23) from *T. mongolicum* was proven active against *E. coli*, *S. aureus*, *A. hydrophila*, *E. tarda*, and *P. multocida*, and proposed as a potential antimicrobial product for poultry and aquatic disease control [88].

## 3. Driving forces and tendencies in *Taraxacum* antimicrobial research

Between 2000 and 2010, approximately 40 new drugs originating from terrestrial plants, terrestrial microorganisms, marine organisms, and terrestrial vertebrates and invertebrates against different bacteria, fungi, and viruses were launched on the market [90]. This follows distinct research tendencies. Studies related to antimicrobial and antifungal properties generally aim, in developing and developed countries, to respond to the necessity of finding new drugs or products based on traditional medicine at a low cost, confirming already established activity originating from oral tradition. The driving force behind studying new antimicrobial alternatives is the necessity of finding new drugs or natural products that act against diseases due to the increased drug resistance in the latter. Furthermore, the toxicity of synthetic compounds currently utilized in farming and agricultural industries has created a market for natural compounds that are safer, cheaper, and more effective against pathogens.

Modern phytochemistry, scientific equipment, and technology have had a significant impact on natural product chemistry, including isolation, extraction, purification, and structure determination. However, this discipline still demands that research investigators establish the clinical significance of natural compounds and recognize them as drugs or industrial products (pesticides, bactericides, pharmaceutical products, etc.) [91]. Bioactive compounds in botanical drugs are purportedly superior to monosubstances because of synergistic effects. Similarly, multidrug therapy is highly important against resistant microbial strains due to the enhanced efficacy, reduced toxicity, decreased adverse side effects, increased bioavailability, lowered dosage, and reduced evolution of antimicrobial resistance [92].

Even when antibiotics have been effective in treating infectious diseases, resistance to the action mechanisms has led to the emergence of new and the re-emergence of old infectious diseases. Several plant extracts exhibit synergistic activity against microorganisms, with natural products (including flavonoids and essential oils) and synthetic drugs effectively combating bacterial, fungal, and mycobacterial infections. The mode of action of combinations differs significantly from the individual use of the same drugs; hence, isolating a single component may not highlight its importance, simplifying the task of the pharmacological industries [93].

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Chapter 14

# *Taraxacum* Genus: Extract Experimental Approaches

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Additional information is available at the end of the chapter

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**Abstract**

This chapter presents factors or considerations to be taken into account when selecting the procedure or method for obtaining extracts and bioactive compounds. The genus *Taraxacum* has proved to have several interesting properties and there are numerous techniques and bioassays used to test the antimicrobial properties of extracts. However, the extraction process is crucial to optimize the final biological outcomes. Extraction procedures that until now have been used are simple and inexpensive, however, we wanted to report a series of studies that group valuable results, which could be useful for future studies, enhancing the research carried out by authors from all over the world and also allowing the interrelated study of this genus.

**Keywords:** extract, antimicrobial activity, *Taraxacum* genus, phytochemical bioassay

## 1. Introduction

*Taraxacum* has been worldwide tested against several bacterial and fungal strains under various extract conditions and bioassays, and we compiled enough published information with the aim of comparing and/or relationship between the various existing methods and their result in the antimicrobial profile.

### 1.1. Antimicrobial bioassay methods used in *Taraxacum* genus

Several different methods have been used for testing antimicrobial activity, the application of which most often depends on the available instrumentation and the training of the investigators [1]. Screening for antibacterial and antifungal activity is often done by agar disc diffusion, agar well test diffusion, and agar dilution or microdilution broth. In agar disc diffusion, a paper disc soaked with the extract is laid on top of an inoculated agar plate and is generally

| Strains | Bioassay | Results expresion | Positive control | Active concentration | Main results | Reference |
|---|---|---|---|---|---|---|
| *Alternaria alternata* | Broth dilution assay | IC50, MIC, Morphological changes | None | 15 μM | 2.9 μM; 1.0 μM; + | [5] |
| *A. alternata* | Paper disc diffusion method | % Inhibition | None | S, S/2, S/10, S/100 | 16.7–76.2% | [6] |
| *A. carbonarius* (Bainier) Thom | Microassay method on slides | ICG, IGTE | Only in vivo assays (Imazalil, Fenhexamid) | 0.75X | 4%, 0% | [7] |
| *A. flavus* 0064 | Agar tube dilution | Inhibition growth | Terbinafine 12 mg/mL 100% | 15 mg/mL | 70.80% | [8] |
| *A. fumigatus* 66 | Agar tube dilution | Inhibition growth | Terbinafine 12 mg/mL 100% | 16 mg/mL | 84.80% | [8] |
| *A. hidrophila* (food poisoning patients) | Agar diffusion method | Inhibition zone | Cephalotin 30 μg/mL (20 mm) | 10 mg/mL | No activity | [9] |
| *A. niger* | Broth dilution assay | IC50, MIC, Morphological changes | None | 15 μM | 4.2 μM; 2.8 μM; + | [5] |
| *A. niger* 0198 | Agar tube dilution | Inhibition growth | Terbinafine 12 mg/mL 100% | 17 mg/mL | 37.40% | [8] |
| *A. niger* UPCC 3701 | Agar well diffusion | Inhibition zone, antimicotic index | Canesten (23 mm, 1.3) | 30 μg | No activity | [9] |
| *A. niger* van Thiegem | Microassay method on slides | ICG, IGTE | Only in vivo assays (Imazalil, Fenhexamid) | 0.75X | 3%, 45% | [7] |
| *A. niger* VKM F-33 | Broth dilution assay | IC50 (50% growth inhibition) | None | 6–10 μM | 1.2–5.6 μM | [10] |
| *A. niger* VKM F-33 | Microtiterd method | IC50 | None | 15.6–250 μg/mL | No activity | [11] |
| *A. flavus* QC 6658 | Disk diffusion method | Inhibition zone | Ciprofloxacin 5 μg/disc | 130–200 mg/mL | >200 mg/mL | [12] |
| *A. fumigatus* | Disk diffusion method | Inhibition zone | Ciprofloxacin 5 μg/disc | 130–200 mg/mL | >200 mg/mL | [12] |
| *A. niger* | Disk diffusion method | Inhibition zone | Ciprofloxacin 5 μg/disc | 130–200 mg/mL | >200 mg/mL | [12] |
| *B. cereus* | Agar diffusion method | Inhibition zone | Cephalotin 30 μg/mL (22 mm) | 10 mg/mL | 18 mm | [9] |
| *B. cereus* (spoiled rice) | Agar diffusion method | Inhibition zone | Cephalotin 30 μg/mL (20 mm) | 10 mg/mL | 18 mm | [9] |
| *B. cereus* ATCC 1778 | Broth dilution assay | MIC | Cloramphenicol (0.004 μM) | No information | 2.5 μM | [13] |
| *B. cereus* NCTC 7464 | Broth dilution assay | MIC | None | 2 mg/mL | 500 μg/mL | [14] |

| Strains | Bioassay | Results expresion | Positive control | Active concentration | Main results | Reference |
|---|---|---|---|---|---|---|
| *B. cereus* NCTC 7464 | Microtiterd method | MIC | None | 2 mg/mL | 250 μg/mL | [15] |
| *B. cinérea* | Microassay method on slides | ICG, IGTE | Only in vivo assays (Imazalil, Fenhexamid) | 0.75X | 9%, 38% | [7] |
| *B. cinerea* SGR-1 | Broth dilution assay | IC50 (50% growth inhibition) | None | 6–10 μM | 5.2–5.8 μM | [5] |
| *B. cinerea* SGR-1 | Microtiterd method | IC51 | None | 15.6–250 μg/mL | No activity | [11] |
| *B. sorokiniana* | Broth dilution assay | IC50, MIC, Morphological changes | None | 15 μM | >15 μM; >15 μM; | [10] |
| *B. sorokiniana* 6/10 | Broth dilution assay | IC50 (50% growth inhibition) | None | 6–10 μM | 5.2 μM | [5] |
| *B. sorokiniana* F-1446 | Microtiterd method | IC52 | None | 15.6–250 μg/mL | No activity | [10, 11] |
| *B. subtilis* | Agar diffusion method | Inhibition zone | Gentamicyn 1 mg/disc, Tetracyclin 2 mg/disc | 4–12 μg/disc | weak activity, not indicated | [16] |
| *B. subtilis* | Agar inoculation | MIC | None | No information | 7.0 mg/mL | [17] |
| *B. subtilis* | Disc diffusion method | Inhibition zone | None | No information | 12.04 mm | [18] |
| *B. subtilis* | Disc diffusion method | Inhibition zone | Tetracyclin 10 μg/disc (23.6 mm) | 10 mg/mL | 5.1–97.9% | [19] |
| *B. subtilis* | Broth dilution | MIC | Tetracyclin (MIC 5.0 μg/mL) | 10 μg/mL | 5.1–97.9% | [19] |
| *B. subtilis* | Agar well diffusion | Inhibition zone | None | 120 μg/mL | 10.0–14.0 mm | [20] |
| *B. subtilis* | Broth dilution assay | MIC | Tetracyclin 100 μg/mL (84%) | 50 mg/mL | 10–54% | [4] |
| *B. subtilis* | Disc diffusion method | Inhibition zone | Tetracyclin 100 μg/mL (22 mm) | 50 mg/mL | 11–19 mm | [4] |
| *B. subtilis* ATCC 1149 | Agar well diffusion | Inhibition zone, antimicotic index | Chloramphenicol (8 mm, 0.3) | 30 μg | 11 mm, 0.1 | [9] |
| *B. subtilis* ATCC 6633 | Agar diffusion method | Inhibition zone, MIC | Erythromicin 1.0 μM | 18 mg/mL | No activity | [8] |
| *B. subtilis* ATCC 6633 | Disc diffusion method | Inhibition zone | Control (8 mm) | 1000–2000 μg/mL | 0–12.5 mm | [21] |
| *B. subtilis* ATCC 6633 | Broth inhibition method | % Inhibition | None | 1000–2000 μg/mL | 5.1–97.9% | [21] |


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| Strains | Bioassay | Results expresion | Positive control | Active concentration | Main results | Reference |
|---|---|---|---|---|---|---|
| *B. subtilis* ATCC 6633 | Broth dilution assay | MIC | None | No information | No activity | [22] |
| *B. subtilis* KCTC 1021 | Disc diffusion method | Inhibition zone | Control (8 mm) | 500–2000 μg/mL | 8.5–12.5 mm | [23] |
| *B. subtilis* KCTC 1021 | Broth dilution | % Inhibition | None | 1000–2000 μg/mL | 5.1–97.9% | [23] |
| *B. subtilis* VKM 1053 | Agar diffusion method | Inhibition zone | | 6–10 μM | 0.8–1.2 μM | [5] |
| *B. cereus* NCTC 7464 | Disk diffusion method | Inhibition zone | Ciprofloxacin 5 μg/disc | 130–200 mg/mL | >200 mg/mL | [12] |
| *B. pumilus* (wildtype hand isolate) | Disk diffusion method | Inhibition zone | Ciprofloxacin 5 μg/disc | 130–200 mg/mL | >200 mg/mL | [12] |
| *B. subtilis* NCTC 10400 (NCIMB 8054) | Disk diffusion method | Inhibition zone | Ciprofloxacin 5 μg/disc | 130–200 mg/mL | >200 mg/mL | [12] |
| *C. albicans* | Disc diffusion method | Inhibition zone | No information | No information | No activity | [24] |
| *C. albicans* | Broth dilution assay | MIC | Tetracyclin 100 μg/mL (68%) | 50 mg/mL | 0–70% | [4] |
| *C. albicans* | Disc diffusion method | Inhibition zone | Tetracyclin 100 μg/mL (20 mm) | 50 mg/mL | 14–20 mm | [4] |
| *C. albicans* ATCC 10231 | Paper disc diffusion method | Inhibition zone | Chloramphenicol 30 mcg (27 mm) | 50 μL/disc | No activity | [25] |
| *C. albicans* ATCC 10231 | Agar diffusion method | Inhibition zone | Anfotericin (0.2 mm) | 200 μg/mL | >200 μg/mL | [26] |
| *C. albicans* ATCC 18804 | Broth dilution assay | MIC | Anfotericin B (0.0004 μM) | No information | 0.039 μM | [13] |
| *C. albicans* ATCC 90028 | Agar well diffusion | | Anfotericin B (100 μg/disc) | 40 μg | 3.0 mm | [27] |
| *C. albicans* UPCC 2168 | Agar well diffusion | Inhibition zone, antimicotic index | Canesten (18 mm, 0.3) | 30 μg | 12 mm, 0.2 | [9] |
| *C. glabrata* ATCC 2001 | Agar diffusion method | Inhibition zone | Anfotericin (0.4 mm) | 200 μg/mL | >200 μg/mL | [26] |
| *C. gloesporoides* | Broth dilution assay | IC50, MIC, Morphological changes | | 15 μM | >15 μM; >15 μM;- | [10] |
| *C. jejuni* | Broth dilution assay | Adhesion, cytotoxicity, Antibacterial | 3-sialyllactose (IC50 1.4 mg/mL) | 500 mg/mL | IC50 < 3 mg/mL, <10%, no activity | [28] |

| Strains | Bioassay | Results expresion | Positive control | Active concentration | Main results | Reference |
|---|---|---|---|---|---|---|
| *C. jejuni* NCTC 11168 (ATCC 700819) | Broth dilution assay | MIC, IC50, % Inhibition | Ampicillin (IC50 1.61 μg/mL) | 15 μM | No activity | [29] |
| *C. lagenarium* | Direct inoculation | Rates of Inhibition | Control untreated leaves | No information | 1.90 | [30} |
| *C. lagenarium* | Direct inoculation | Rates of Inhibition | Control untreated leaves | No information | 12.80 | [30] |
| *C. neoformans* ATCC 32608 | Broth dilution assay | MIC | Anfotericin B (0.0008 μM) | No information | 0.039 μM | [13] |
| *C. parapsilepsis* ATCC 22019 | Agar diffusion method | Inhibition zone | Anfotericin (0.4 mm) | 200 μg/mL | >200 μg/mL | [26] |
| *C. sativus* (S. Ito and Kurib.) | Paper disc diffusion method | Inhibition zone | Mancozeb, Thiram, Carboxin, Benomyl (1 mg/disc) | 5 mg/disc | weak activity, not indicated | [31] |
| *C. tropicalis* ATCC 750 | Agar diffusion method | Inhibition zone | Anfotericin (0.4 mm) | 200 μg/mL | 2.0 mm | [26] |
| *C. utilis* ATCC 22023 | Agar diffusion method | Inhibition zone | Anfotericin (0.4 mm) | 200 μg/mL | >200 μg/mL | [26] |
| *C. violaceum* ATCC 12472 | Quorum sensing | Inhibition zone | None | No information | 7 mm | [32] |
| *C. violaceum* ATCC 31532 | Quorum sensing | Inhibition zone | None | No information | No activity | [33] |
| *C. violaceum* NTCT 13274 | Quorum sensing | Inhibition zone | None | No information | No activity | [33] |
| *C. albicans* | Disk diffusion method | Inhibition zone | Ciprofloxacin (5 μg/disc) | 130–200 mg/mL | >200 mg/mL | [12] |
| *C. glabrata* ATCC 2001 | Disk diffusion method | Inhibition zone | Ciprofloxacin 5 μg/disc | 130–200 mg/mL | >200 mg/mL | [12] |
| *C. krusei* ATCC 6258 | Disk diffusion method | Inhibition zone | Ciprofloxacin 5 μg/disc | 130–200 mg/mL | >200 mg/mL | [12] |
| *C. parapsilosis* ATCC 22019 | Disk diffusion method | Inhibition zone | Ciprofloxacin 5 μg/disc | 130–200 mg/mL | >200 mg/mL | [12] |
| *C. michiganense* subesp. *Michiganense* Ac-1144 | Agar diffusion method | Inhibition zone | | 6–10 μM | 0.8–1.4 | [5] |
| *Cupriavidus* sp. | Disk diffusion method | Inhibition zone | Ciprofloxacin 5 μg/disc | 130–200 mg/mL | >200 mg/mL | [12] |
| *E. coccus* ATCC 13048 | Agar diffusion method | Inhibition zone, MIC | Erythromicin 1.0 μM | 19 mg/mL | No activity | [8] |
| *E. coli* | Disc diffusion, broth dilution | Inhibition zone, MIC | Erythromicin (MIC 27 μg/mL) | 10–500 μg/mL | 13.3 mm, MIC 50 μg/mL | [34] |
| *E. coli* | Agar inoculation | MIC | None | No information | 1.0 mg/mL | [17] |
| *E. coli* | Agar diffusion method | Inhibition zone | None | 0.1–1.0 mg/mL | >0.5 mg/mL (1–4 mm) | [35] |


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| Strains | Bioassay | Results expresion | Positive control | Active concentration | Main results | Reference |
|---|---|---|---|---|---|---|
| *E. coli* | Agar diffusion method | Inhibition zone | Cloramphenicol 10 mg/mL (30.5 mm) | 50–200 mg/mL | 5.25–23.5 mm | [36] |
| *E. coli* | Diet | CFU count | Control | No information | Inhibition | [8] |
| *E. coli* | Disc diffusion method | Inhibition zone | None | 1 g/mL | 10.2–18.5 mm | [37] |
| *E. coli* | Disc diffusion method | Inhibition zone | None | No information | 13.21 mm | [18] |
| *E. coli* | Disc diffusion method | Inhibition zone | Gentamycin 10 μg/disc (18.9 mm) | 10 mg/mL | 12.05–14.21 mm | [19] |
| *E. coli* | Broth dilution | MIC | Gentamycin (MIC 1.25 μg/mL) | 10 μg/mL | 250–500 μg/mL | [19] |
| *E. coli* | Disc diffusion method | Inhibition zone | No information | No information | 11–13 mm | [24] |
| *E. coli* | Agar well diffusion | Inhibition zone | None | 120 μg/mL | 2.0–3.0 mm | [20] |
| *E. coli* | Broth dilution assay | MIC | Tetracyclin 100 μg/mL (78%) | 50 mg/mL | 14–62% | [4] |
| *E. coli* | Disc diffusion method | Inhibition zone | Tetracyclin 100 μg/mL (18 mm) | 50 mg/mL | 12–15 mm | [4] |
| *E. coli* 7075 | Agar diffusion method | Inhibition zone | Gentamicyn 1 mg/disc, Tetracyclin 2 mg/disc | 4–12 μg/disc | No activity | [16] |
| *E. coli* 8739 | Agar diffusion method | Inhibition zone | None | 1 mg/mL | >1 mg/mL | [38] |
| *E. coli* ATCC 11229 | Disc diffusion method | Inhibition zone | Control (8 mm) | 500–2000 μg/mL | 11–13.5 mm | [21] |
| *E. coli* ATCC 11229 | Broth inhibition method | % Inhibition | None | 500–2000 μg/mL | 98.1–100% | [21] |
| *E. coli* ATCC 1229 | Broth dilution assay | MIC | None | No information | No activity | [22] |
| *E. coli* ATCC 15224 | Agar diffusion method | Inhibition zone, MIC | Erythromicin 1.0 μM | 20 mg/mL | No activity | [8] |
| *E. coli* ATCC 25322 | Agar well diffusion | Inhibition zone | Gentamycin | 240 mg/mL | 6.5 mm | [39] |
| *E. coli* ATCC 8677 | Paper disc diffusion method | Inhibition zone | Ticarcillin 75 mcg (27 mm) | 50 μL/disc | No activity | [26] |
| *E. coli* ATCC 8739 | Broth dilution assay | MIC | None | S, S/2 | Inhibition | [40] |
| *E. coli* DSM 1103 | Broth dilution assay | MIC | None | 2 mg/mL | No activity | [14] |
| *E. coli* DSM 1103 | Microtiterd method | MIC | None | 2 mg/mL | No activity | [15] |

| Strains | Bioassay | Results expresion | Positive control | Active concentration | Main results | Reference |
|---|---|---|---|---|---|---|
| *E. coli* KCTC 2441 | Disc diffusion method | Inhibition zone | Control (8 mm) | 500–2000 μg/mL | 9.0–12 mm | [23] |
| *E. coli* KCTC 2441 | Broth dilution | % Inhibition | None | 1500–2000 μg/mL | 13–98.4% | [23] |
| *E. coli* NCTC 25922 | Disk diffusion method | Inhibition zone | Ciprofloxacin 5 μg/disc | 130–200 mg/mL | >200 mg/mL | [12] |
| *E. coli* NCTC 9001 | Disk diffusion method | Inhibition zone | Ciprofloxacin 5 μg/disc | 130–200 mg/mL | >200 mg/mL | [12] |
| *E. coli* UPCC 1195 | Agar well diffusion | Inhibition zone, antimicotic index | Chloramphenicol (25 mm, 3.2) | 30 μg | 11 mm, 0.1 | [9] |
| *E. faecalis* | Irrigation in situ | | None | 7 mg/mL | weak activity, not indicated | [41] |
| *E. faecalis* ATCC 19433 | Agar diffusion method | Inhibition zone, MIC | Erythromicin 1.0 μM. Cefixime 1.0 μM | 21 mg/mL | No activity | [8] |
| *E. coli* 0157 NCTC 12900 | Disk diffusion method | Inhibition zone | Ciprofloxacin 5 μg/disc | 130–200 mg/mL | >200 mg/mL | [12] |
| *E. coli* DH5 | Disk diffusion method | Inhibition zone | Ciprofloxacin 5 μg/disc | 130–200 mg/mL | >200 mg/mL | [12] |
| *Enterobacter/Klebsiella* sp. | Disk diffusion method | Inhibition zone | Ciprofloxacin 5 μg/disc | 130–200 mg/mL | >200 mg/mL | [12] |
| *E. faecalis* NCTC 775 | Disk diffusion method | Inhibition zone | Ciprofloxacin 5 μg/disc | 130–200 mg/mL | >200 mg/mL | [12] |
| *Exophiala* (Wangiella) *dermatitidis* QC 7895 | Disk diffusion method | Inhibition zone | Ciprofloxacin 5 μg/disc | 130–200 mg/mL | >200 mg/mL | [12] |
| *F. avenaceum* | Broth dilution assay | IC50, MIC, Morphological changes | | 15 μM | 13.1 μM; 6.7 μM; + | [10] |
| *F. graminearum* VKM F-1668 | Broth dilution assay | IC50 (50% growth inhibition) | | 6–10 μM | >10 μM | [5] |
| *F. oxysporium* Schlecht | Paper disc diffusion method | Inhibition zone | Mancozeb, Thiram, Carboxin, Benomyl (1 mg/disc) | 6 μM | 5.7 μM | [31] |
| *F. oxysporium* TSKHA-4 | Broth dilution assay | IC50 (50% growth inhibiton) | Kanamycin | 6 μM | 5.7 μM | [5] |
| *F. oxysporium* TSKHA-4 | Microtiterd method | IC53 | None | 15.6–250 μg/mL | No activity | [11] |
| *H. pylori* | Paper disc diffusion method | Inhibition zone | Control (8 mm) | No information | 10 mm | [42] |
| H. pylori NCTC 11639 (ATCC 43629) | Broth dilution assay | MIC, IC50, % Inhibition | Gentamicin (IC50 0.081 μg/mL) | 500 mg/mL | 25% | [29] |


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| Strains | Bioassay | Results expresion | Positive control | Active concentration | Main results | Reference |
|---|---|---|---|---|---|---|
| *K. pneumoniae* | Agar diffusion method | Inhibition zone | Gentamicyn 1 mg/disc, Tetracyclin 2 mg/disc | 4–12 μg/disc | No activity | [16] |
| *K. pneumoniae* | Agar diffusion method | Inhibition zone | Cloramphenicol 10 mg/mL (26.5 mm) | 50–200 mg/mL | — | [36] |
| *K. pneumoniae* | Disc diffusion method | Inhibition zone | Gentamycin 10 μg/disc (18.9 mm) | 10 mg/mL | 13.24–17.72 mm | [19] |
| *K. pneumoniae* | Broth dilution | MIC | Gentamycin (MIC 5.0 μg/mL) | 10 μg/mL | 125–250 μg/mL | [19] |
| *K. pneumoniae* ATCC 13866 | Broth dilution assay | MIC | Cloramphenicol (0.001 μM) | No information | 0.625 μM | [13] |
| *K. pneumoniae* UC 5 | Agar diffusion method | Inhibition zone, MIC | Erythromicin 1.0 μM. Cefixime 1.0 μM | 22 mg/mL | No activity | [8] |
| *K. aerogenes* NCTC 9528 | Disk diffusion method | Inhibition zone | Ciprofloxacin 5 μg/disc | 130–200 mg/mL | >200 mg/mL | [12] |
| *K. pneumoniae* 700,603 | Disk diffusion method | Inhibition zone | Ciprofloxacin 5 μg/disc | 130–200 mg/mL | >200 mg/mL | [12] |
| *L. monocytogenes* KCCM 40307 | Disc diffusion method. Broth Inhibition method | Inhibition zone. % Inhibition | Control (8 mm). None | 500–2000 μg/mL | 0–12 mm. 5.1–97.9% | [21] |
| *L. monocytogenes* KCCM 40307 | Disc diffusion method. Broth Inhibition method | Inhibition zone. % Inhibition | Control (8 mm). None | 500–2000 μg/mL | 10.5–12 mm. 27.2–94% | [23] |
| *L. monocytogenes* NCTC 11994 | Disk diffusion method | Inhibition zone | Ciprofloxacin 5 μg/disc | 130–200 mg/mL | >200 mg/mL | [12] |
| *M. aureum* 4721 E | Broth dilution | MIC | Streptomycin (IC50 1.14 μg/mL) | 500 μg/mL | >500 μg/mL | [41] |
| *M. bovis* BCG | Broth dilution | MIC | Streptomycin (IC50 1.14 μg/mL) | 500 μg/mL | >500 μg/mL | [43] |
| *M. canis* | Agar well diffusion, agar tube dilution | No information | No information | No information | Inhibition | [44] |
| *M. kristinae* | Agar inoculation | MIC | None | No information | 5.0–7.0 mg/mL | [17] |
| *M. laxa* | Microassay method on slides | ICG, IGTE | Only in vivo assays (Imazalil, Fenhexamid) | 0.75X | 11%, 5% | [7] |
| *M. luteus* | Agar well diffusion | Inhibition zone | None | 120 μg/mL | 5.0–9.0 mm | [20] |

| Strains | Bioassay | Results expresion | Positive control | Active concentration | Main results | Reference |
|---|---|---|---|---|---|---|
| *M. luteus* ATCC 10240 | Agar diffusion method | MIC | Erythromicin 1.0 μM | 23 mg/mL | 1.0 μM | [8] |
| *M. piriformis* | Paper disc diffusion method | % Inhibition | None | S, S/2, S/10, S/100 | 5.3–66.7% | [6] |
| *M. smegmatis* MC2 155 | Broth dilution | MIC | Streptomycin (IC50 1.14 μg/mL) | 120 μg/mL | 5.3–66.7% | [43] |
| *M. tuberulosis* H37RA | Broth dilution method | MIC | Rifampim. Isoniazid. Kanamycin | No information | > 200 μg/mL | [44] |
| MRSA (clinical isolated) | Broth dilution assay. Microtiterd method | MIC | None | 2 mg/mL | 375 μg/mL. 500 μg/mL | [14] |
| MRSA AARM 3696 | Disc diffusion method | Inhibition zone | Gentamicin 0.2 mg/disc (20.1 mm) | 0.5–3.0 mg/disc | 6.8–16.5 mm | [45] |
| *P. acnes* | Broth dilution assay | No information | No information | No information | No information | [46] |
| *P. aeruginosa* | Broth dilution assay | No information | No information | No information | No information | [46] |
| *P. aeruginosa* | Disc diffusion, broth dilution | Inhibition zone, MIC | Erythromicin | 10–500 μg/mL | No activity | [34] |
| *P. aeruginosa* | Agar diffusion method | Inhibition zone | Gentamicyn 1 mg/disc, Tetracyclin 2 mg/disc | 4–12 μg/disc | No activity | [16] |
| *P. aeruginosa* | Agar diffusion method | Inhibition zone | Cloramphenicol 10 mg/mL (26.0 mm) | 50–200 mg/mL | — | [36] |
| *P. aeruginosa* | Disc diffusion method | Inhibition zone | Gentamycin 10 μg/disc (20.0 mm) | 10 mg/mL | 16.52–19.19 mm | [19] |
| *P. aeruginosa* | Broth dilution | MIC | Gentamycin (MIC 2.5 μg/mL) | 10 μg/mL | 125–250 μg/mL | [19] |
| *P. aeruginosa* | Agar well diffusion | Inhibition zone | None | 120 μg/mL | 8.0–13.0 mm | [20] |
| *P. aeruginosa* ATCC 15442 | Broth dilution assay | MIC | Cloramphenicol (0.015 μM) | No information | 2.5 μM | [13] |
| *P. aeruginosa* ATCC 7221 | Agar diffusion method | Inhibition zone, MIC | Erythromicin 1.0 μM. Cefixime 1.0 μM | 24 mg/mL | No activity | [8] |
| *P. aeruginosa* ATCC 9027 | Broth dilution assay | MIC | None | No information | No activity | [22] |
| *P. aeruginosa* ATCC 9721 | Paper disc diffusion method | Inhibition zone | Ticarcillin 75 mcg (20 mm) | 50 μL/disc | No activity | [25] |
| *P. aeruginosa* UPCC 1244 | Agar well diffusion | Inhibition zone, antimicotic index | Chloramphenicol (23 mm, 2.8) | 30 μg | 11 mm, 0.1 | [9] |


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| Strains | Bioassay | Results expresion | Positive control | Active concentration | Main results | Reference |
|---|---|---|---|---|---|---|
| *P. betae* | Broth dilution assay | IC50, MIC, Morphological changes | | 15 μM | 10.7 μM; 8.0 μM; + | [10] |
| *P. betae* F-2532 | Microtiterd method | IC54 | None | 15.6–250 μg/mL | No activity | [11] |
| *P. debaryanum* VKM F-1505 | Broth dilution assay | IC50 (50% growth inhibition) | None | 6–10 μM | 2.6 μM | [5] |
| *P. digitatum* (Perss) Sacc | Microassay method on slides | ICG, IGTE | Only in vivo assays (Imazalil, Fenhexamid) | 0.75X | 12%, 42% | [7] |
| *P. expansum* | Paper disc diffusion method | % Inhibition | None | S, S/2, S/10, S/100 | 15.7–69.7% | [6] |
| *P. expansum* Link. | Microassay method on slides | ICG, IGTE | Only in vivo assays (Imazalil, Fenhexamid) | 0.75X | No activity | [7] |
| *P. expansum* Link. ATCC 42710 | Paper disc diffusion method | Inhibition zone | Control (8 mm) | 0.1 g/mL | 12 mm | [47] |
| *P. infestans* | Microtiterd method | IC55 | None | 15.6–250 μg/mL | No activity | [11] |
| *P. infestans* OSV 12 | Direct inoculation (potato disc) | Disease development | None | 1.3–5.3 μM | 1.3–5.2 μM | [5] |
| *P. italicum* Wehmer | Microassay method on slides | ICG, IGTE | Only in vivo assays (Imazalil, Fenhexamid) | 0.75X | 2%, 56% | [7] |
| *P. mirabilis* | Agar diffusion method | Inhibition zone | Gentamicyn 1 mg/disc, Tetracyclin 2 mg/disc | 4–12 μg/disc | No activity | [16] |
| *P. mirabilis* | Agar diffusion method | Inhibition zone | None | 0.1–1.0 mg/mL | >0.5 mg/mL (4–10 mm) | [35] |
| *P. ovale* | Broth dilution assay | No information | No information | No information | No information | [46] |
| *P. syringeae* VKM B-1546 | Agar diffusion method | Inhibition zone | | 6–10 μM | 1.2–1.3 μM | [5] |
| *P. vulgaris* | Disc diffusion, broth dilution | Inhibition zone, MIC | Erythromicin (MIC 26 μg/mL) | 10–500 μg/mL | 10.1 mm, MIC 100 μg/mL | [34] |
| *P. vulgaris* | Agar inoculation | MIC | None | No information | 5.0 mg/mL | [17] |
| *P. vulgaris* | Disc diffusion method | Inhibition zone | Gentamycin 10 μg/disc (19.5 mm) | 10 mg/mL | 13.38–18.33 mm | [19] |

| Strains | Bioassay | Results expresion | Positive control | Active concentration | Main results | Reference |
|---|---|---|---|---|---|---|
| *P. vulgaris* | Broth dilution | MIC | Gentamycin (MIC 2.5 μg/mL) | 10 μg/mL | 250–500 μg/mL | [19] |
| *Penicillium* sp. QC 743275 | Disk diffusion method | Inhibition zone | Ciprofloxacin 5 μg/disc | 130–200 mg/mL | >200 mg/mL | [12] |
| *Pseudomona sp.* | Disc diffusion method | Inhibition zone | No information | No information | 11–21 mm | [24] |
| *P. aeruginosa* NCTC 1662 | Disk diffusion method | Inhibition zone | Ciprofloxacin 5 μg/disc | 130–200 mg/mL | >200 mg/mL | [12] |
| *P. aeruginosa* NCTC 27853 | Disk diffusion method | Inhibition zone | Ciprofloxacin 5 μg/disc | 130–200 mg/mL | >200 mg/mL | [12] |
| *Pseudomonas* sp. | Disk diffusion method | Inhibition zone | Ciprofloxacin 5 μg/disc | 130–200 mg/mL | >200 mg/mL | [12] |
| *R. solani* 18,619 | Agar tube dilution | Inhibition growth | Terbinafine 12 mg/mL 100% | 25 mg/mL | 77.47% | [8] |
| *R. solani* Kühn | Paper disc diffusion method | Inhibition zone | Mancozeb, Thiram, Carboxin, Benomyl (1 mg/disc) | 5 mg/disc | 4.75–17.63 mm | [31] |
| *S. aureus* NCTC 8178 | Microtiterd method | MIC | None | 2 mg/mL | 500 μg/mL | [15] |
| *S. abony enterica* NCTC 6017 | Broth dilution assay | MIC | None | S, S/2 | Inhibition | [40] |
| *S. agalactiae* | Disc diffusion method | Inhibition zone | None | 1 g/mL | 11.1–19.7 mm | [37] |
| *S. aureus* | Broth dilution assay | No information | No information | No information | No information | [46] |
| *S. aureus* | Disc diffusion, broth dilution | Inhibition zone, MIC | Erythromicin (MIC 33 μg/mL) | 10–500 μg/mL | 12.7 mm, MIC 50 μg/mL | [34] |
| *S. aureus* | Agar diffusion method | Inhibition zone | Gentamicyn 1 mg/disc, Tetracyclin 2 mg/disc | 4–12 μg/disc | No activity | [16] |
| *S. aureus* | Agar inoculation | MIC | None | No information | 5.0 mg/mL | [17] |
| *S. aureus* | Agar diffusion method | Inhibition zone | None | 0.1–1.0 mg/mL | >0.5 mg/mL (1–4 mm) | [35] |
| *S. aureus* | Agar diffusion method | Inhibition zone | Cloramphenicol 10 mg/mL (35.0 mm) | 100–200 mg/mL | 9.0–10.75 mm | [36] |
| *S. aureus* | Disc diffusion method | Inhibition zone | None | 1 g/mL | 9.7–19.9 mm | [37] |
| *S. aureus* | Disc diffusion method | Inhibition zone | None | No information | 16.15 mm | [18] |
| *S. aureus* | Disc diffusion method | Inhibition zone | Tetracyclin 10 μg/disc (38.8 mm) | 10 mg/mL | 11.22–15.07 mm | [19] |
| *S. aureus* | Broth dilution | MIC | Tetracyclin (MIC 2.5 μg/mL) | 10 μg/mL | 250 μg/mL | [19] |


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| Strains | Bioassay | Results expresion | Positive control | Active concentration | Main results | Reference |
|---|---|---|---|---|---|---|
| *S. aureus* | Disc diffusion method | Inhibition zone | No information | No information | 11–21 mm | [24] |
| *S. aureus* | Agar well diffusion, agar tube dilution | No information | No information | No information | Inhibition | [44] |
| *S. aureus* | Agar well diffusion | Inhibition zone | None | 120 μg/mL | 4.0–11.0 mm | [20] |
| *S. aureus* | Broth dilution assay | MIC | Tetracyclin 100 μg/mL (75%) | 50 mg/mL | 0–76% | [4] |
| *S. aureus* | Disc diffusion method | Inhibition zone | Tetracyclin 100 μg/mL (17 mm) | 50 mg/mL | 9–18 mm | [4] |
| *S. aureus* (salted white cheese) | Agar diffusion method | Inhibition zone | Cephalotin 30 μg/mL (24 mm) | 10 mg/mL | 16 mm | [9] |
| *S. aureus* ATCC 12600 | Paper disc diffusion method | Inhibition zone | Chloramphenicol 30 mcg (27 mm) | 50 μl/disc | No activity | [25] |
| *S. aureus* ATCC 25922 | Agar well diffusion | Inhibition zone | Penicillin | 320 mg/mL | 10.4 mm | [39] |
| *S. aureus* ATCC 43300 | Disc diffusion method | Inhibition zone | Erythromycin 50 μg/well | 40 μg | 7.5 mm | [27] |
| *S. aureus* ATCC 6530 | Broth dilution assay | MIC | None | No information | No activity | [22] |
| *S. aureus* ATCC 6538 | Broth dilution assay | MIC | Cloramphenicol (0.063 μM) | No information | 5.0 μM | [13] |
| *S. aureus* ATCC 6538 | Broth dilution assay | MIC | None | S, S/2 | No activity | [40] |
| *S. aureus* ATCC 6538 | Agar diffusion method | Inhibition zone, MIC | Erythromicin 1.0 μM. Cefixime 1.0 μM | 26 mg/mL | No activity | [8] |
| *S. aureus* ATCC 6538 | Disc diffusion method | Inhibition zone | Control (8 mm) | 1500–2000 μg/mL | 0–12 mm | [22] |
| *S. aureus* ATCC 6538 | Broth inhibition method | % Inhibition | None | 1500–2000 μg/mL | 5.1–97.9% | [22] |
| *S. aureus* ATCC 6538 | Agar diffusion method | Inhibition zone | None | 1 mg/mL | >1 mg/mL | [38] |
| *S. aureus* KCTC 1916 | Disc diffussion method | Inhibition zone | Control (8 mm) | 500–2000 μg/mL | 8.5–13.5 mm | [24] |
| *S. aureus* KCTC 1916 | Broth dilution | % Inhibition | None | 500–2000 μg/mL | 98.1–100% | [24] |
| *S. aureus* KCTC 3881 | Disc diffussion method | Inhibition zone | Gentamicin 0.2 mg/disc (20.1 mm) | 0.5–3.0 mg/disc | 6.8–16.5 mm | [45] |
| *S. aureus* NCTC 8178 | Broth dilution assay | MIC | None | 2 mg/mL | 375 μg/mL | [14] |

| Strains | Bioassay | Results expresion | Positive control | Active concentration | Main results | Reference |
|---|---|---|---|---|---|---|
| *S. aureus* UPCC 1143 | Agar well diffussion | Inhibition zone, antimicotic index | Chloramphenicol (20 mm, 2.3) | 30 μg | No activity | [9] |
| *S. australis* | Broth dilution assay | Growth | None | 10–10,000 ppm | No activity | [46] |
| *S. cerviseae* | Broth dilution assay | MIC | Tetracyclin 100 μg/mL (50%) | 50 mg/mL | 0–64% | [4] |
| *S. cerviseae* | Disc diffussion method | Inhibition zone | Tetracyclin 100 μg/mL 18 mm) | 50 mg/mL | 12–15 mm | [4] |
| *S. dysgalactiae* | Disc diffusion method | Inhibition zone | None | 1 g/mL | 13.8–9.6 mm | [37] |
| *S. enterica sorovar typhimurium* ATCC 13311 | Broth dilution assay | MIC | Cloramphenicol (0.001 μM) | No information | 5.0 μM | [13] |
| *S. enteriditis* | Disc diffussion method | Inhibition zone | No information | No information | No activity | [24] |
| *S. epidermis* KCTC 1917 | Disc diffussion method | Inhibition zone | Gentamicin 0.2 mg/disc (24.4 mm) | 130–200 mg/mL | 7.3–16.7 mm | [45] |
| *S. fiexneri* | Disc diffusion, broth dilution | Inhibition zone, MIC | Erythromicin | 10–500 μg/mL | No activity | [34] |
| *S. haemolyticus* | Agar diffusion method | Inhibition zone | Gentamicyn 1 mg/disc, Tetracyclin 2 mg/disc | 4–12 μg/disc | Weak activity, not indicated | [16] |
| *S. marscens* | Agar inoculation | MIC | None | No information | 1.0–5.0 mg/mL | [17] |
| *S. sonnei* ATCC 11060 | Broth dilution assay | MIC | Cloramphenicol (0.001 μM) | No information | 2.5 μM | [13] |
| *S. tiphimurium* SARB 69 | Broth dilution assay | MIC | None | 2 mg/mL | No activity | [14] |
| *S. typhi* | Agar well diffussion, agar tube dilution | No information | No information | No information | Inhibition | [44] |
| *S. typhi* (food poisoning patients) | Agar diffusion method | Inhibition zone | Cephalotin 30 μg/mL (18 mm) | 10 mg/mL | 14 mm | [9] |
| *S. typhi* H. | Agar diffusion method | Inhibition zone | Gentamicyn 1 mg/disc, Tetracyclin 2 mg/disc | 4–12 μg/disc | No activity | [16] |
| *S. typhimurium* Reference collection B-69 | Microtiterd method | MIC | None | 2 mg/mL | No activity | [15] |
| *Salmonella poona* NCTC 4840 | Disk diffusion method | Inhibition zone | Ciprofloxacin 5 μg/disc | 130–200 mg/mL | >200 mg/mL | [12] |


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| Strains | Bioassay | Results expresion | Positive control | Active concentration | Main results | Reference |
|---|---|---|---|---|---|---|
| *Scedosporium apiospermum* QC 7870 | Disk diffusion method | Inhibition zone | Ciprofloxacin 5 μg/disc | 130–200 mg/mL | >200 mg/mL | [12] |
| *Serratia marcescens* | Disk diffusion method | Inhibition zone | Ciprofloxacin 5 μg/disc | 130–200 mg/mL | >200 mg/mL | [12] |
| *Serratia/Rahnella* sp. | Disk diffusion method | Inhibition zone | Ciprofloxacin 5 μg/disc | 130–200 mg/mL | >200 mg/mL | [12] |
| *Staphylococcus* | Diet | CFU count | Control | No information | Inhibition | [8] |
| *S. aureus* (MRSA) 43,300 | Disk diffusion method | Inhibition zone | Ciprofloxacin 5 μg/disc | 130–200 mg/mL | >200 mg/mL | [12] |
| *S. aureus* (MSSA) 25,923 | Disk diffusion method | Inhibition zone | Ciprofloxacin 5 μg/disc | 130–200 mg/mL | >200 mg/mL | [12] |
| *S. aureus* NCTC 6571 | Disk diffusion method | Inhibition zone | Ciprofloxacin 5 μg/disc | 130–200 mg/mL | >200 mg/mL | [12] |
| *Staphylococcus epidermidis* NCTC 14990 | Disk diffusion method | Inhibition zone | Ciprofloxacin 5 μg/disc | 130–200 mg/mL | >200 mg/mL | [12] |
| *T. longifusus* | Agar well diffusion, agar tube dilution | No information | No information | No information | Inhibition | [45] |
| *T. mentagrophytes* UPCC 4193 | Agar well diffusion | Inhibition zone, antimicotic index | Canesten (55 mm, 4.3) | 30 μg | 12 mm, 0.2 | [9] |
| *V. albo-atrum* | Broth dilution assay | IC50, MIC, Morphological changes | None | 15 μM | >15 μM; >15 μM; – | [10] |
| *V. albo-atrum F-2437* | Microtiterd method | IC56 | None | 15.6–250 μg/mL | No activity | [11] |
| *V. cholera* ATCC 11623 | Agar diffusion method | MIC | Erythromicin 1.0 μM. Cefixime 1.0 μM | 27 mg/mL | 12.5 μM | [8] |
| *V. parahaemolyticus* KCTC 2471 | Disc diffusion method. Broth Inhibition method | Inhibition zone. % Inhibition | Control (8 mm). None. | 500–2000 μg/mL | 9.5–15 mm. 5.1–97.9% | [21] |
| *V. parahaemolyticus* KCTC 2471 | Disc diffusion method. Broth dilution. | Inhibition zone. % Inhibition | Control (8 mm). None. | 500–2000 μg/mL | 9.5 - 15 mm. 84.0–97% | [23] |
| *X. campestris* VKM −608 | Broth dilution assay | IC50 (50% growth inhibition) | | 6–10 μM | 1.0–1.2 μM | [5] |

**Table 1.** Principal types of bioassays carried out to determine the antimicrobial activity of the genus *Taraxacum* and their respective results.

used as a preliminary check for antibacterial activity prior to more detailed studies. In the agar well test diffusion method, the extract is deposited into wells cut into the agar and can be used as a screening method when large numbers of extracts or large numbers of bacterial isolates are to be screened. In the agar dilution method, a known concentration of the extract is mixed with the agar prior to strain inoculation. In some cases, the inoculated plates or tubes are exposed to UV light to screen the presence of light-sensitizing photochemicals. In the broth dilution method, different techniques exist for determining the end-point, such as an optical density measurement or the enumeration of colonies by viable count. Antimicrobial activity can also be analyzed by a spore germination assay in broth or on glass slides. *In situ* antifungal activity can be achieved by electron microscopy techniques such as scanning and transmission, as well as by confocal laser scanning microscopy [2].

Direct tissue inoculation is the least used testing method, probably due to the inherent characteristics of the substrate (fruits, vegetables, etc.) that can affect the final results and the standardized laboratory conditions needed for proper result comparisons. Authors also indicate certain restrictions regarding the use of a specific technique. For instance, diffusion techniques seem to be inadequate for non-polar extracts, although many reports with these techniques have been published. Furthermore, when only a small amount of sample is available, diffusion techniques can be considered more appropriate [3]. The disc diffusion method is quick and easy but has several serious shortcomings, such as false positives and negative results due to poor test substance solubility and diffusion through the semi-solid nutritive medium [1].

The agar diffusion and microdilution broth methods are the two most common techniques for determining the antimicrobial activities of *Taraxacum* extracts, but the results are not always reproducible; factors, such as the volume and concentration of the extract placed on the paper disc and the solvent used, vary considerably between studies. When results are compared, the different sensitivities of the assays make antimicrobial activity highly dependent on the selection of the proper test. For example, aqueous fractions of *T. officinale* showed no activity in the disc diffusion test but moderate toxicity against *E. coli* and *B. subtilis* in the broth dilution test [4]. Considering this issue, a list of the bioassays used for testing *Taraxacum* extracts against every strain identified, including the main results, is presented in **Table 1**.

## 2. *Taraxacum* extracts versus commercial antibiotics

When comparing *Taraxacum* extracts to commercial antibiotics, *C. jejuni* adhesion was controlled by a *Taraxacum* extract with an IC50 value of 2.7 mg/mL, slightly less compared to the 3.4 mg/mL obtained with 3′-sialyllactose [28]. In another study, a *T. officinale* extract showed MIC values of 0.004 mg/mL, similar to chloramphenicol with MIC values of 0.001–0.06 mg/mL but considerably lower than amphotericin B with MIC values of 0.4 –0.8 μg/mL for different Gram positive and Gram negative bacteria, respectively [13]. The MIC value of 1.0 mg/mL for *M. luteus* was similar for a methanolic extract and for erythromycin and cefixime, but considerably lower than the MIC value of 12.5 mg/mL obtained for *V. cholera* [8]. In the same work, the inhibition percentage for *Aspergillu*s spp. and *Rhizoctonia* spp. was 37–84%, relatively lower than terbinafine at 12 mg/mL and 100% inhibition.

Generally, researchers select only one technique for evaluating the antimicrobial performance of *Taraxacum*. Few studies have assessed agar disc diffusion and broth dilution in parallel, even when the limitations and advantages for both bioassays have been already stated, as indicated above. An example of this includes the antibacterial properties of an ethanolic extract of the *T. mongolicum* flower, whose fractions were examined by both bioassays [19]. The authors indicated that at 0.1 mg/disc, inhibition results were relatively lower for the plant extract compared to gentamicin and tetracycline, with values between 7.12 and 19.4 mm for the plant extracts and 18.9–38.8 mm for the antibiotics. However, MIC values of 0.06–0.5 mg/mL were obtained for plant extracts against the tested strains. Antibiotics had much lower MIC values of 3.0–5.0 μg/mL, which reaffirms the fact that different bioassays need to be performed in parallel to accurately evaluate the antimicrobial effectiveness of an extract.

The weak activity that some authors have indicated could be improved by higher concentrations, which are needed to reach quantifiable antimicrobial activity under different conditions and assays. For instance, concentrations of *T. officinale* extracts at 130–500 mg/mL were needed to achieve the effect of amphotericin B at 0.2–0.4 μg/mL against Candida strains [26]. In the cases of mancozeb, carboxin, thiram, and benomyl, only 1 mg/disc was effective in inhibiting the growth of *R. solani*, *F. oxysporum*, and *C. sativus*, while the *Taraxacum* extract needed a concentration of 5 mg/disc to achieve the same effect [31]. For *H. pylori* and *C. jejuni*, growth was inhibited by ampicillin and gentamicin at concentrations of 0.5–5.0 μg/mL, while an extract of 500 mg/mL was needed to achieve this inhibition [29]. Considering the disc assay method, an extract of ethyl acetate at 10 mg/mL showed minor inhibition zones (14–18 mm) against *A. hydrophila*, *S. typhi*, *S. aureus*, *B. cereus*, and *E. coli* as compared to cephalothin at 0.03 mg/mL (18–24 mm) [9]. In this study, inhibition diameters were only 20–25% smaller than those reached by the synthetic antibiotic, but the extract concentration was more than 300 times higher, as well as 100 times higher than what would normally be indicated for an attractive natural antibiotic in a commercial setting. In a similar study, the inhibition zones of chloramphenicol at 0.02 mg/mL (10.7–23.5 mm) against *E. coli* and *S. aureus* were lower compared to an ethanolic extract *of T. officinale* at 200 mg/mL (25–30 mm) [36]. In this case, the extract showed higher activity but its concentration was 10,000 times higher than its respective antibiotic. Moreover, methanolic extracts of *T. officinale* at 50 mg/mL resulted in inhibition similar to tetracycline at 0.1 mg/mL using broth dilution and disc assay methods against *E. coli*, *S. aureus*, and *B. subtilis*, among others; that is, a concentration 500 times greater than the antibiotic was necessary to obtain a similar effect [4].

In several studies, different *Taraxacum* extracts exhibited no activity under the tested conditions. For instance, embedded discs with 50 μL of an ethanolic extract of *T. officinale* were not active compared to controls, such as ticarcillin, at 75 μg/disc, and chloramphenicol, at 30 μg/disc [26]. Another study, using a similar extract at 2.5 mg/disc, was inactive against certain strains, as compared to gentamycin, at 1.0 mg/disc, and tetracycline, at 2.0 mg/disc [16]. Different extracts of *T. officinale* leaves and roots (chloroform, methanol, and water) were not active towards *Mycobacterium* compared to streptomycin at 1.14 μg/mL [43]. An ethanolic extract of *T. phaleratum* was also inactive against the same strain compared to rifampin at 0.005–0.01 μg/mL, isoniazid at 0.05–0.1 μg/mL, and kanamycin at 2.5–5.0 μg/mL [44]. A leaf

and root extract of *T. officinale* at 150–200 mg/mL was inactive against 24 bacterial strains, but ciprofloxacin at 5.0 μg/disc showed high antimicrobial activity [12].

The conclusion of these studies may be misleading if slight dilutions or excessively high concentrations are tested. For example, experiments with quantities higher than 1.0 mg/mL for extracts or 0.1 mg/mL for isolated pure compounds should be avoided, whereas the presence of activity is very interesting when concentrations are below 0.1 μg/mL for extracts, and 0.01 mg/mL for isolated compounds [1]. Even when promising results have been achieved, the extracts have also shown contradictory results and can mislead the actual potential of this plant extract if no further investigation is pursued.

In general, active concentrations of *Taraxacum* extracts that achieve inhibitions similar to the synthetic antibiotics are 100–10,000 times higher, which makes *Taraxacum* extracts unsuitable for pharmaceutical development at the moment. However, this is expected since synthetic antibiotics are pure, concentrated compounds, whereas plant extracts are a mixture of different, dilute compounds that act synergistically or antagonistically. Because this situation is common and a characteristic of plant extracts, some authors indicate the possibility of using antibiotics synergistically with plant extracts to improve the action mechanisms against antibiotic-resistant bacteria. No research regarding the synergistic use of *Taraxacum* genus has yet been performed [47].

At present, only commercial and synthetic antibiotics, such as kanamycin, amphotericin B, terbinafine, chloramphenicol, and cephalothin, among others, have been considered as positive controls for establishing strain sensitivity. Comparisons of *Taraxacum* with natural, commercially available antibiotic compounds (such as propolis and other honey products) have been neglected: only one study, regarding antibacterial agents for dental care, contains a comparison with propolis [41]. The comparison with natural antibiotics, for example, honey, might be more realistic in traditional medicine due to the similar vegetable origin and characteristics. As long as no pure compound extraction or purification of *Taraxacum* extracts can be performed reliably for testing antimicrobial activity, the real potential of the *Taraxacum* genus as a source of natural therapeutic agents cannot be established.

Alternatively, instead of only utilizing a chemical antibiotic or a natural antibiotic, antimicrobial synergistic interactions between plant bioactives and some common antibiotics have been reported. There are many advantages to using antimicrobial compounds from medicinal plants, such as fewer side effects, better patient tolerance, lower expense, acceptance due to long history of use, and renewability [48].

## 3. Expression of results in antimicrobial studies

Regarding the expression of the results, the minimum inhibitory concentration (MIC), minimum bactericidal concentration (MBC), and inhibition percentage of growth are cited by researchers as the most common measurements of antimicrobial performance. In this sense, there are two primary categories for measuring an antimicrobial agent: bactericidal or bacteriostatic. Bacteriostatic refers to an agent that prevents the growth of bacteria and a bactericidal agent kills bacteria, but a complete separation of these definitions might be further pursued. This difference only applies under strict laboratory conditions and is inconsistent for a

particular agent against all bacteria; indeed, it can be influenced by growth conditions, bacterial density, test duration, and extent of reduction in bacterial numbers. Furthermore, bacteriostatic activity has been defined as an MBC/MIC ratio of 4, but numerous technical problems and other factors can affect the determination of that ratio and may have an important impact on the interpretation of the in *vivo* situation. Although MBC and MIC data may provide information on the potential action of antibacterial agents *in vitro*, it is necessary to combine this information with pharmacokinetic and -dynamic data to provide more meaningful predictions of efficacy *in vivo* [49]. Considering this information, no pharmacokinetic or -dynamic studies have been conducted involving the *Taraxacum* genus to date. The majority of the research (not only as an antimicrobial agent, but also as an important medicinal plant) has been performed from a traditional perspective, based on centuries of oral traditions. Only in recent decades has *Taraxacum* been subjected to a considerable amount of tests, principally due to its anti-inflammatory and anti-carcinogenic properties [50]. The antimicrobial properties of this genus have been widely known, but only very general studies have been performed to date, with information that is difficult to interconnect as the action mechanisms and the specific compounds involved have not yet been elucidated. Nevertheless, all the data gathered here provides a promising case for the advantageous commercial usage of this genus.

Considering this general approach, most of the research regarding *Taraxacum* indicates MIC values and inhibition percentages measured in relation to area (in solid cultures) or optical density (in broth cultures). The MBC values were not identified in the consulted references. An observation was made that the MIC definition sometimes differed between publications, another obstacle for data comparison. Some MIC definitions are: "the lowest concentration of the tested products that inhibited the development of microorganisms" [40]; "the lowest concentration required to show a marked inhibition of mycobacterial growth at 72 h" [43]; "the lowest concentration of the compound to inhibit the growth of microorganisms" [19]; and "the lowest sample concentration at which no pink color appeared" [15]. This indicates that MIC values are relative to each study and is compounded by the fact that the complete procedure (including extraction process and sample manipulation) is not standardized and varies considerably among the authors. Furthermore, due to the different solubilities and stabilities of the various compounds in the solvent and the sensitivity of the antimicrobial activity assay performed, directly comparing MIC values is difficult and sometimes confusing. As further examples, in three different studies, the authors reported MIC values in the 0.05–5.0 mg range for ethanol, methanol, or water extracts against *S. aureus* using broth microdilution or agar diffusion method as bioassays [13, 17, 34]. This meant that only MIC values could be used as a comparison against the positive control under the same conditions and may only be considered as an initial screening for further antimicrobial approaches; it cannot provide a reliable comparison between studies. The MIC/MBC ratio might be an option for making antimicrobial activity more independent of assay conditions if similar extraction conditions and sample manipulation have been performed.

## 4. Scaling up from in vitro to in vivo assays

Scaling up an antimicrobial assay from controlled, *in vitro* conditions to that of natural, *in vivo* conditions can be difficult if no proper considerations are taken. For instance, active concentrations

for *in vitro* conditions frequently cannot be reached *in vivo* because the infecting microorganisms are never exposed to constant concentrations of an antimicrobial agent. Microorganisms *in vivo* are subject to competition from other microorganisms present in the tissue, so decreased microbial activity might be due to this competition rather than directly related to the antimicrobial activity of the plant extract. Moreover, temperature, pH, and humidity are more difficult to control in an *in vivo* system. Another issue to consider is that microorganisms in a microtiter plate are in the form of a suspension, whereas bacteria associated with different illnesses naturally form biofilms (organ and tissue infections, dental plaque, etc.), representing an extra challenge for antimicrobial agents [1]. Until now, only studies regarding fruit and vegetable infections have shown a parallel between in vitro and *in vivo* responses to *Taraxacum* extracts (Chapter 1; see Section 2.2.2), but studies in animal tissues and organs have not yet been performed directly.

## 5. Factors affecting antimicrobial activity of extracts

The following sections are referred and discussed in accordance with the information provided in **Table 2** (see Chapter 1) and **Figure 1**. It should be noted that the impact of the parameters mentioned in these sections, except for solvent selection, on the antimicrobial properties of the *Taraxacum* genus has not yet been studied.

### 5.1. Plant material collection

Scientific criteria should be used in the selection of the sample material. To avoid the use of random criteria, the selection of plants should be made from an ethnopharmacological perspective. All the species tested need to be perfectly described and identified, including location, season, date, and time of day harvested. The use of commercial samples should be limited to cases of standardized extracts or defined phytomedicines [3]. The phytochemical composition of *Taraxacum* (and plants in general) is known to depend on the season in which

| ***Taraxacum* parts mentioned in the text** | **Number of extracts tested** | **Positive antimicrobial activity** | | **Negative antimicrobial activity** | |
|---|---|---|---|---|---|
| Root | 51 | 17 | 11% | 34 | 43% |
| Leaves | 38 | 28 | 18% | 10 | 13% |
| Flower | 13 | 10 | 7% | 3 | 4% |
| Honey | 6 | 4 | 3% | 2 | 3% |
| Herb | 3 | 3 | 2% | 0 | 0% |
| Aerial | 32 | 24 | 16% | 8 | 10% |
| Whole plant | 8 | 0 | 0% | 8 | 10% |
| No information | 81 | 66 | 43% | 15 | 19% |
| **Total** | **232** | **152** | | **80** | |

**Table 2.** Summary of the antimicrobial results regarding *Taraxacum* plant parts tested in main studies.

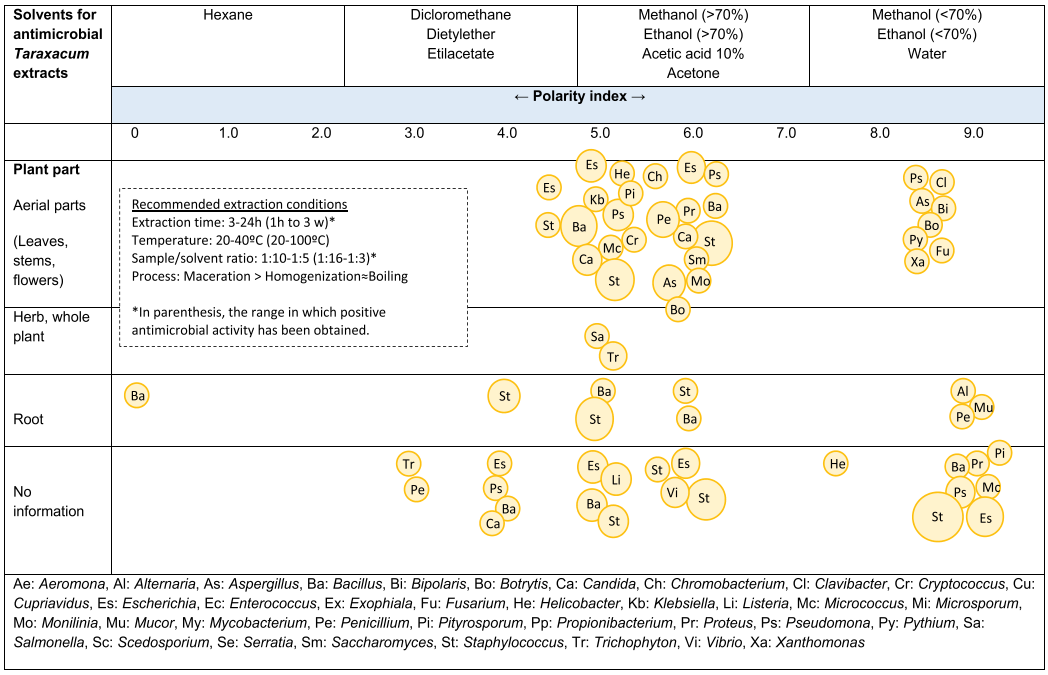


**Figure 1.** Reported extraction conditions to achieve positive antimicrobial results.

it is collected, as well as other ecological and climate factors. For example, sesquiterpene lactones are noticeable in the roots, particularly when harvested in the spring [51]. Sterols, which are present in the leaves throughout the year, are highest during the winter months, whereas levels of sitosterol and cycloartenol esters are highest during periods of sunshine [52]. Few authors indicated in which period of the year the plant was harvested, collected, purchased, or the collection site, another factor that could influence the final concentration of compounds in the extract, even when the same extraction conditions are applied. No *Taraxacum* studies have investigated a possible relationship between harvesting time or collecting site and its antimicrobial properties. Only one study indicated the environmental conditions in which the plant was grown and collected before the antimicrobial assay [27].

### 5.2. Species identification

Generally, there is a lack of taxonomic identification of the species characterized, mentioned occasionally as *Taraxi radix*, *Taraxi folium*, *Taraxi herba*, *Taraxacum* spp., or dandelion, especially when researchers use commercial preparations or purchase the plant from local markets [29, 33, 46]. Samples are commonly obtained in the wild, but the lack of proper identification makes the comparison for antimicrobial properties imprecise for determining the actual efficacy of *Taraxacum* extracts; therefore, only partial conclusions can be pursued and not always extrapolated. For instance, dandelion is used as a common name for several species: khur mang, a name for dandelion in Tibet, can be used for *T. officinale*, *T. mongolicum*, *T. tibetanum*, and *T. Sikkimense* [53]. As previously stated, environmental conditions affect the tissue composition of the plants, but few reports indicate the corresponding information for further

consultation. The importance of proper identification also relates to the risk of toxicity between morphologically similar, but chemically distinct, plants, which is a potential health risk for the communities that harvest medicinal plants in the wild. Only a small portion of the research available mentions proper, expert identification.

### 5.3. Plant part utilization

Reports indicate that compounds present in *Taraxacum* vary within parts of the plant, and even though there are common compounds across sections, these concentrations vary as well [54, 55]. A disadvantage that creates further uncertainties when comparing data is that a considerable amount of studies do not indicate which part of the plant was used. In general, aerial parts (leaves, flowers, and seeds), roots, and whole *Taraxacum* plants have been used in antimicrobial research. Only one *Taraxacum* study indicated differences between a root extract and a leaf extract, in which the root extract was active against *S. aureus* and *S. typhi.* Extracts of plant roots and herbs of different *Taraxacum* species endemic to Turkey displayed significant activity against *M. canis* and *T. longifusus* [44]. Few studies refer to the antimicrobial properties of *Taraxacum* derivatives. *Pseudomona* sp., *S. aureus*, and *E. coli* were inhibited in a disc diffusion assay, but *C. albicans* and *S. enteriditis* were not inhibited by *T. officinale* honey [24]. The pH of dandelion honey is considered the probable antibacterial component observed against *S. aureus* [56]. Analyzing the information gathered in this work (also see **Table 2**), *Taraxacum* root extracts are less effective at fungal and bacterial inhibition than the aerial parts and seem to be more effective on Gram positive than Gram negative bacteria.

### 5.4. Sample manipulation

Several authors propose that plants need to be dried and chopped before extraction. This is a consensus among researches due to the necessity of storing samples prior to processing; however, it is a central issue when testing biological activities because bioactive compounds are highly sensitive and react quickly to changes in environmental conditions. These types of changes are common: a sample is stored at room temperature, refrigerated, frozen, or freeze-dried. In rare cases, further sample manipulation has been reported prior to extraction. Specifically, the removal of lipids and proteins with solvents [31] could also affect the compound profile of the extract and the final antimicrobial activity. In one study, a fresh sample was also homogenized before tested [30]. In our research, sample manipulation seems to be just as adequate whether plant parts are dried under the sun or by oven prior to extraction, or used directly as fresh biomass in extract preparation. Due to the possibility that the material used in the extraction may be contaminated, a white control is considered in the activity bioassays, which is the sample not inoculated with the pathogen, to confirm sterility of the stored sample.

### 5.5. Extraction procedure

Traditional extraction techniques involve solid-liquid extraction with or without high temperatures (maceration, soaking, reflux, etc.), and are characterized by the use of high solvent volumes and long extraction times. These techniques often produce low bioactive extraction yields, low selectivity, and reproducibility can sometimes be compromised. In a common extraction procedure, plant parts are soaked in solvent for extended periods, the slurry is filtered, the filtrate may

be centrifuged multiple times for clarification, and the result may be dried under reduced pressure and re-dissolved in alcohol to a determined concentration. Solid-liquid extractions using soaking, maceration, and homogenization are the most used for *Taraxacum* (although, to a lesser extent, the Soxhlet procedure has been used). Pressurized liquid extraction, subcritical water extraction, and supercritical fluid extraction are presented as novel techniques with important advantages over traditional solvent extraction, such as rapidity, higher yields, and reduced solvent usage. Microwave-assisted extraction and ultrasonic-assisted extraction are pretreatments that can improve the extraction yield by releasing the compounds from the solid matrix [2]. No studies using these techniques have been conducted for the extraction of antibacterial compounds from *Taraxacum* because maceration, blending, and boiling are the most common extraction procedures for this genus. In one study, the sample was sonically treated prior to extraction but no conclusion regarding the effectiveness of this pretreatment can be pursued [22].

### 5.6. Relationship between temperature and extraction time

Temperature directly influences both the solubility equilibrium and mass transfer rate of an extraction process. When temperature is increased, the lower viscosity and surface tension of the solvent improves its diffusion inside the solid matrix, achieving a higher yield and extraction rate along with enhanced diffusivity and solubilization results. The primary disadvantages of applying a higher temperature are increased solvent boil-off and reduced effective contact area between solid and liquid phases. A high temperature can also decrease the cell barrier by weakening the integrity of the cell wall and membrane. Furthermore, bioactive compounds may decompose at high temperatures, which require research on the influence of temperature on the overall yield. Temperatures ranging from cold (4°C), room temperature (20–25°C), and solvent boiling point (50–100°C) have been reported for *Taraxacum*. The majority of the work was conducted in the range of 20–40°C, where the maceration process was proposed and, to a lesser extent, extraction under boiling temperatures has also been indicated (80–100°C, depending on the solvent). Our findings suggest that inhibitory activity is most probable when using a maceration process at mild temperatures (Chapter 1; See **Table 2**).

Determination of the duration of the extraction process required to extract the bioactive compounds, that is, the minimum time at which equilibrium of solvent concentration between inner and outer cells is reached, is important. Most bioactive compounds are sensitive to elevated temperatures and are susceptible to thermal decomposition outside of the original matrix. The extraction time mentioned in literature for *Taraxacum* ranged from 5 min for homogenization, 1–3 hours for boiling, and up to 3 weeks for maceration. A clear relationship between extraction time and antimicrobial activity was not observed in the data presented. However, it is possible that the antimicrobial compounds extracted are relatively stable when extracted by maceration at mild temperatures because numerous positive results regarding inhibitory activity were obtained with this process that included times ranging from 4 hours to 5 days.

### 5.7. Relationship between sample size, solid to solvent ratio, and agitation speed

The particle size of the plant material influences the extraction rate by affecting the total mass transfer area per unit volume, which increases as particle size is reduced. Several authors

| Polarity index | 9.0 | 8.2 | 7.7 | 7.4 | 6.3 | 6.3 | 6.2 | 6.0 | 5.9 | 5.6 | 5.5 | 5.4 | 5.1 | 5.1 | 4.4 | 4.1 | 4.0 | 3.1 | 0.0 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Genus/solvent** | **Water** | **Ethanol20%** | **Ethanol35%** | **Ethanol40– – 45%** | **Ethanol70–75%** | **Methanol70%** | **Aceticacid** | **Ethanol80%** | **Methanol80%** | **Ethanol90%** | **Methanol90%** | **Ethanol96–100%** | **Methanol100%** | **Acetone** | **Ethylacetate** | **Chloroform** | **Dietylether80%** | **Dichloromethane** | **Hexane** |
| *Aeromona* | | | | | | | | | | | | | | | — | | | | |
| *Alternaria* | | | | | | | + | | | | | | | | | | | | |
| *Aspergillus* | — | | | | | | + | | + | | | | | | | | | — | |
| *Bacillus* | –/+ | | | | + | + | + | + | | | | –/+ | –/+ | + | + | + | | + | –/+ |
| *Bipolaris* | | | | | | | –/+ | | | | | | | | | | | | |
| *Botrytis* | | | | | | | + | | + | | | | | | | | | | |
| *Campylobacter* | | | + | + | | | | | | | | | | | | | | | |
| *Candida* | — | — | | | | + | | | | | | –/+ | + | | | | | + | |
| *Chromobacterium* | — | | | | | | | | | + | | — | | | | | | | |
| *Cochilibus* | + | | | | | | | | | | | | | | | | | | |
| *Colletotrichum* | + | | | | | | — | | | | | | | | | | | | |
| *Cupriavidus* | — | | | | | | | | | | | | | | | | | | |
| *Clavibacter* | | | | | | | + | | | | | | + | | | | | | |
| *Enterobacter* | — | | | | | | | | | | | | — | | | | | | |
| *Enterococcus* | –/+ | | | | | | | | | | | | | | | | | | |
| *Escherichia* | –/+ | + | | — | + | + | | — | + | | — | –/+ | –/+ | + | + | + | | + | — |
| *Exophiala* | — | | | | | | | | | | | | | | | | | | |
| *Fusarium* | — | | | | | | –/+ | | | | | | — | | | | | | |
| *Helicobacter* | | | | + | | | | | | | | + | | | | | | | |
| *Klebsiella* | — | | | | | | | — | | | | | –/+ | | | | | | |


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| Polarity index | 9.0 | 8.2 | 7.7 | 7.4 | 6.3 | 6.3 | 6.2 | 6.0 | 5.9 | 5.6 | 5.5 | 5.4 | 5.1 | 5.1 | 4.4 | 4.1 | 4.0 | 3.1 | 0.0 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Genus/solvent** | **Water** | **Ethanol20%** | **Ethanol35%** | **Ethanol40– – 45%** | **Ethanol70–75%** | **Methanol70%** | **Aceticacid** | **Ethanol80%** | **Methanol80%** | **Ethanol90%** | **Methanol90%** | **Ethanol96–100%** | **Methanol100%** | **Acetone** | **Ethylacetate** | **Chloroform** | **Dietylether80%** | **Dichloromethane** | **Hexane** |
| *Listeria* | — | | | | | | | | | | | | + | | | + | | | |
| *Micrococcus* | | | | | | | | | | | | | + | + | | | | | |
| *Microsporum* | | | | | | | | | | | | + | | | | | | | |
| *Monilinia* | | | | | | | | | + | | | | | | | | | | |
| *Mycobacterium* | | | | | — | | | | | | | | — | | | | | | |
| *Mucor* | + | | | | | | | | | | | | | | | | | | |
| *Penicillium* | −/+ | | | | | | | | −/+ | | | | | | | | + | + | |
| *Pityrosporum* | | | | | | | | | | | | + | | | | | | | |
| *Phoma* | + | | | | | | + | | | | | | | | | | | | |
| *Phytophthora* | + | | | | | | | | | | | | | | | | | | |
| *Proteus* | — | | | | + | | | — | | | | | | + | | | | | |
| *Pseudomona* | −/+ | — | | | + | | + | — | | | | −/+ | −/+ | | | + | | + | |
| *Salmonella* | — | | | | | | | | | | | −/+ | | | | | | | — |
| *Saprolegnia* | | | | | | | | | | | | — | | | | | | | |
| *Pythium* | — | | | | | | + | | | | | | + | | | | | | |
| *Rhizoctonia* | + | | | | | | | | | | | | + | | | | | | |
| *Saccharomyces* | | | | | | + | | | | | | | | | | | | | |
| *Salmonella* | | | | — | | | | — | | | | | + | | — | | | | |
| *Scedosporium* | — | | | | | | | | | | | | | | | | | | |

| Polarity index | 9.0 | 8.2 | 7.7 | 7.4 | 6.3 | 6.3 | 6.2 | 6.0 | 5.9 | 5.6 | 5.5 | 5.4 | 5.1 | 5.1 | 4.4 | 4.1 | 4.0 | 3.1 | 0.0 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Genus/solvent** | **Water** | **Ethanol20%** | **Ethanol35%** | **Ethanol40– – 45%** | **Ethanol70–75%** | **Methanol70%** | **Aceticacid** | **Ethanol80%** | **Methanol80%** | **Ethanol90%** | **Methanol90%** | **Ethanol96–100%** | **Methanol100%** | **Acetone** | **Ethylacetate** | **Chloroform** | **Dietylether80%** | **Dichloromethane** | **Hexane** |
| *Serratia* | — | | | | | | | | | | | | | + | | | | | |
| *Shigella* | — | | | | | | | | | | | | + | | | | | | |
| *Staphylococcus* | –/+ | — | | — | + | + | | –/+ | | | — | –/+ | –/+ | + | + | + | | –/+ | — |
| *Trichophyton* | | | | | | | | | | | | + | | | | | | + | |
| *Vibrio* | | | | | | | — | | | | | | + | | | | | | |
| *Xanthomonas* | | | | | | | + | | | | | | | | | | | | |

(+) Positive antimicrobial activity report. (−) No antimicrobial activity reported. Empty cells indicate no study has been performed so far.

**Table 3.** Antimicrobial activity regarding the solvent tested with *Taraxacum* genus.


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chopped and ground *Taraxacum* plant material, but few indicate the mesh grain utilized in extract powder selection. Bioactive compounds are dissolved from the solid matrix into the solvent by a physical process under mass transfer principles and compound solubility. When the amount of extraction solvent is increased, the possibility of the bioactive compounds in the solid matrix coming into contact increases. However, the removal of solute from the solvent requires energy. Therefore, if more solvent than needed is used, there will be a higher energy consumption, needlessly increasing processing costs. In the literature reviewed for *Taraxacum*, the sample:solvent ratio ranged between 1:1 and 1:40 w/v. In light of the gathered data, this range has no direct impact on antimicrobial activity but certainly affects the economy of the process. Interestingly, most of the positive results have been achieved with ratios of 1:10–1:4.

A higher agitation speed in solid-liquid extraction is preferred, in accordance with mass transfer theory. In this process, the solute moves from inside the solid to the surface through diffusion or capillary action. Once the compound is on the surface, it is recovered by the solvent through convective mass transfer. Agitation rate affects the mass transfer coefficient (kL) and, at higher rates, improves the convective mass transfer rate, which facilitates the extraction process and leads to increases in extraction yields. For *Taraxacum*, the agitation speed is not usually mentioned in homogenization processes but the most cited value is 170 rpm. Similarly, for the solid: solvent ratio, no direct impact was found in comparisons of different studies.

### 5.8. Solvents

One critical parameter in extraction procedures is the solvent used for sequestering bioactives from the plant matrix. Extractants that solubilize antimicrobial compounds from plants have been ranked by factors such as biohazard risk and ease of solvent removal from fractions. Methanol was ranked second to methylene dichloride and superior to ethanol and water. Even though acetone was rated the highest, it is one of the least used solvents for bioactive extraction. Ethanol and methanol, in contrast, are both commonly used for initial extraction yet may not demonstrate the greatest sensitivity in yielding antimicrobial chemicals on an initial screening [57]. Solvents used for the extraction of bioactive compounds from plants are selected according to polarity and the compounds they are capable of solubilizing. Different solvents may modify results. Apolar solvents (cyclohexane, hexane, toluene, benzene, ether, chloroform, and ethyl acetate) primarily solubilize alkaloids, terpenoids, coumarins, fatty acids, flavonoids, and terpenoids; polar solvents (acetone, acetonitrile, butanol, propanol, ethanol, methanol, and water) primarily extract flavonols, lectins, alkaloids, quassinoids, flavones, polyphenols, tannins, and saponins [58].

The impact of solvent selection is recognized as extremely critical. For example, the gathered data indicate that growth inhibition on fungal strains can be reached by using ethanolic extracts but not aqueous extracts. Moreover, in the same study, inhibition of Gram positive and Gram negative bacteria using an aqueous extract was indicated but no inhibition was achieved using an acetone extract against the same strains [17]. However, it has also been reported that water extracts led to better activity than ethanolic extracts against acne strains, which can be useful in the skin care field [46]. Alcohol extracts tend to display better activity against bacteria and fungi than water extracts, the latter being generally ineffective. Crude *Taraxacum* extracts are commonly used in testing antifungal and antibacterial properties [57], but only a few reports involve the fractioning of the crude sample with other solvents to concentrate and isolate potential

| Solvents used in *Taraxacum* extracts | Number of extracts tested | Positive antimicrobial activity | | Negative antimicrobial activity | |
|---|---|---|---|---|---|
| Low polarity (0–3.0) | 47 | 22 | 9% | 25 | 10% |
| Medium polarity (3.1–6.0) | 100 | 70 | 28% | 30 | 12% |
| High polarity (6.1–9.0) | 101 | 38 | 15% | 63 | 25% |
| **Total** | **248** | **130** | | **118** | |

**Table 4.** Summary of the antimicrobial results regarding the polarity of the *Taraxacum* extracts tested in main studies.

compounds related to microbial activity [4, 15, 19, 22, 24, 42]. These authors agree that antimicrobial activity decreases as follows: ethyl acetate > dichloromethane ≈ chloroform > butanol ≈ hexane > water. This indicates that the antimicrobial compounds should be extracted according to the solvent polarities, showing effective extractions from solvents with a polarity index ranging from approximately 3.0 to 7.0 instead of too polar or apolar solvents. Data analysis indicates that solvents with low (0–3.0) and high (6.1–9.0) polarities are less active against microorganisms than medium polarity solvents (3.1–6.0). A list of the solvents used in research regarding *Taraxacum* antimicrobial activity is presented in **Tables 3** and **4**.

## 6. Perspectives of potential bioassays

As stated above, reports have shown that the antimicrobial potential of different compounds depends not only on the chemical composition of the extract, but also on the targeted microorganism. Further evaluation of the activity of these plants required the study of different conditions. Different parts of the plant (flowers, leaves, stems, etc.), solvent selection (water, alcohol, and organic solvents), extraction procedure (temperature, pH, time, and equipment), bioassay selection (diffusion, dilution, bioautographic methods), and bioassay conditions (volume of inoculum, growth phase, culture medium used, pH of the media, incubation time, and temperature) among others, complicate the comparison of published data.

Studies of the identification and characterization of *Taraxacum* compounds are generally unrelated to a particular pharmacological property. Therefore, the extraction methods for identifying and quantifying extract compounds differ in sample manipulation:temperature, extraction time, and solvent (among others parameters), indicating that comparisons of the extraction methods utilized in antimicrobial activity assays are typically invalid. This complicates the establishment of a relationship between compounds isolated from *Taraxacum* parts and antimicrobial activities.

Nevertheless, *Taraxacum* has been proven effective against most known strains of bacteria, fungi, and protozoa that attack animals and plants through an *in vitro* or *in vivo* approach. All studies of *Taraxacum* extracts against microbes that cause important human diseases (*E. coli*, *S. aureus*, and *A. niger*, among others) were conducted *in vitro*, while microbes causing foodborne diseases with economic implications (*C. lagenarium* for cucumber or *S. australis* for salmonids) were also tested *in vivo*. For humans, only antimicrobial *in vitro* assays were conducted primarily due to the ethical issues of clinical trials. Several authors have mentioned that *Taraxacum,* despite being used as a well-known medicinal plant for centuries, suffers from a lack of *in vivo* evidence and

clinical trials supporting its use [58], which prevents this genus from attracting the possibility of economic development in the pharmacological industry.

Depending on the bioassay selected, diverse extraction conditions should be tested to study the influence of solvents, temperatures, and other parameters that might change outcomes in the extraction process employed. Authors often use non-standardized procedures derived from self-experience combined with bibliographic references, further complicating comparisons between investigations. Even though there are vast amounts of literature on *Taraxacum* biochemical composition and antimicrobial activity, few isolated compounds can be directly related to this activity because studies do not always identify the accurate active fraction and its associated components. In bioassays, the extract generally used is a mixture of compounds; therefore, there is a strong possibility that the activity may be due to the synergy of the compounds present in the extract and not related to a specific compound. The identification, extraction, and isolation of these active compounds are major areas of research that can be initially pursued to formulate a promising source of *Taraxacum* antibiotics. The next step is to test these extracts on *in vitro* and *in vivo* systems to establish pharmacodynamics and interactions, facilitating the commercial attractiveness of *Taraxacum* to the pharmaceutical industry.

The bioavailability, pharmacodynamics, and action mechanisms in *Taraxacum* bioactives have not yet been addressed. Considering that primarily *in vitro* and, to a much lesser extent, *in vivo* studies have been conducted using *Taraxacum* extracts, direct application is the only route that has been considered. If a bioactive compound is going to be suggested as a potential therapeutic agent, other application routes must be tested. Oral ingestion, injection, or inhalation have different characteristics that need to be considered, such as flavor, compound volatility, stability in stomach pH, and possible organ irritation, among others. Therefore, clinical trials are fundamental to evaluating the suitability of *Taraxacum* extract use in pharmacological approaches.

## 7. Conclusion

Only a minor fraction of the *Taraxacum* species has been tested against microorganisms that cause human, animal, and plant diseases. Considering that species can differ in composition due to environmental and genetic characteristics, the evaluated antimicrobial properties could also differ, which means that there is a considerable potential in establishing this genus as a commercial antimicrobial compound. Currently, this genus is considered to have a mild antimicrobial activity compared to other plants, but its worldwide presence and simple cultivation provide an advantage that needs to be assessed more accurately.

Generally, studies do not provide sufficient details concerning the sample manipulation, extraction procedure, or bioassay used, which are necessary for standardization and further statistical comparison. Therefore, despite the published data, it is not possible to conclude which solvent or which conditions provide the optimal results for antimicrobial activity; however, it is possible to set a range of operational parameters that can be used to maximize extract potential.

Isolation and purification of *Taraxacum* compounds needs to be further explored. Although synergy is an important characteristic of plant mixtures responsible for its antimicrobial activity and even though bioactive synthesis is difficult and expensive on a large scale, knowing the

nature of *Taraxacum* extracts and the associated antimicrobial mechanisms may provide important advantages in synthesizing specific structures with improved antimicrobial properties.

Contradictory information is available in the data analyzed; however, these discrepancies are probably the result of different procedures, particular considerations, or inaccurate process descriptions. These differences make it quite possible that the results are not directly related to the full antimicrobial potential of *Taraxacum* but to a limited scope. Therefore, extracts and bioassays must be conducted under a standardized protocol to provide reproducible studies and reliable data comparisons between published articles, which would empower research conducted by authors worldwide and allow for the interrelated study of this genus. In addition, the efficacy of reported biological activity *in vitro* could be validated with *in vivo* assays.

Standardization of the entire procedure (sample manipulation, extraction, and further bioassay) is necessary for comparisons of published data and establishing the exact potential of *Taraxacum*, or any other plant extract, as a commercial antimicrobial agent. The uniformity of an extract is highly susceptible to external factors that influence plant metabolism. This problem could be solved by performing plant breeding techniques with selected *Taraxacum* species grown under controlled environmental conditions.

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*Herbal medicine* is a multidisciplinary compilation of topics in herbal medicine that are designed to enlighten all who have a stake in healthcare. In light of the current trends and popularity of herbal medicine, cultural/societal differences and perception, and the relationship with modern healthcare this book presents selected topics to ensure that necessary information on herbal medicine in healthcare is provided. Apart from clarifying certain important complexities and misconceptions on herbal medicine, a general overview of herbal medicine, uses of herbs in the management of diseases, plant secondary metabolites, analytical techniques, applications in stem cell research, use as leads for conventional drug compound development, and research and development of herbal medicines for healthcare are among the major discussions in this book.

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