Chapter 1

Are Herbal Products an Alternative to Antibiotics?

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Additional information is available at the end of the chapter

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Abstract

Medicinal plants have been widely used in the management of infectious diseases and by now, many of the ancient remedies have proven their value through scientific methodologies. Although the mechanisms underlying most plant-derived remedies are not well understood, the success of herbal medicine in curing infectious diseases shows that many plants have beneficial effects in various bacterial, fungal, viral or parasitic infections. The modern methodologies in the isolation, purification and characterization of the active compounds, has been a great impact for advancing *in vitro* and *in vivo* research, this step being crucial for further application in clinical trials. Many plant-derived compounds, for example, quinine and artemisinin, have been already successfully used in healing life-threatening infectious disease. The main limitations of plant medicine healing are lack of standardization and reproducibility of plant-derived products. Despite the paucity of clinical trials evaluating their efficacy, phytotherapy, adult plant uses and gemmotherapy, the use of embryonic stem cells should be reconsidered as valuable resources in finding new active compounds with sustained antimicrobial activity.

Keywords: phytotherapy, gemmotherapy, infection, herbal medicine, medicinal plants

1. Introduction

Traditional medicine used for a long time various medicinal plants for infectious diseases healing [1]. Ancient healers often combine medicinal plants with mysterious incantations, recipes being inherited together with the secrets of their employment. On traditional healing practices, the knowledge were orally communicated along with sophisticated protocols about harvesting plants, methods of preparation, applications, dosage, special diets and associations with other secret stories about the nature of illness. This chapter highlights some data on the use of herbal products in the treatment or prevention of infectious diseases. Our knowledge of the role of herbal products in the treatment of infectious diseases has not increased so rapidly

as studies on the discovery of new antibiotics, but the emergence of multi-drug resistant strains requires new therapeutic strategies. Analyzing the evolution of antibiotic resistance has proven challenging due to the countless of factors involved—the genetic adaptation of microorganisms depends not only on exposure to antibiotics [2, 3]. Nowadays, we often find ourselves in a deadlock in choosing effective anti-infective treatment for nosocomial infections [4]. For sure, bacteria are continuously adapted their defense mechanisms, and any new synthetic antibacterial compounds will be sooner or later ineffective. There are some notable exceptions, mentioning only the high activity of penicillin G against *Streptococcus pyogenes.*

Since ancient times, people have faced with infections, ranged from simple urinary tract infections to major epidemics. Obviously, they used their healing the most diverse substances, which included herbs or other natural products found nearby [5]. For instance, a recent paper demonstrates that a well-known natural product—honey has *in vitro* antibacterial activity against *Staphylococcus aureus* and *Streptococcus pyogenes* [6]. Also, many drugs have been discovered from ethnobotanical leads. The most well-known analgesic and anti-inflammatory drug—aspirin—was developed from the plant *Filipendula ulmaria* (queen of the meadow) [7].

The purpose of the paper is not to develop the history of empirical antimicrobial therapy, but only to recover the valuable results of ancient healing prescriptions that have led to current remedies. The origin of the particular history of healing with plants is lost in the dawn of mankind's history. People have always tried to understand and heal the diseases, just as they have tried to understand the human-nature relationship. We could say that they approached illness in a philosophical manner, seeking the causes and remedies in everything that meant life. In the past, people were more attentive, more patient and time was redeemed differently. They were ardent observers of the environments and were able to make amazing connections between the smallest details. How ancient people, without any medical device or epidemiological resources, masterminded the therapy strategies is beyond our understanding. A first observation of the ancient way of life is that they traveled far less than today—with some notable exceptions of ocean voyagers—and the commodity exchanges were not so extended, therefore they had had to use the local products to prepare their healing recipes. Undoubtedly plants, almost always wild plants, and animal products were widely used with more or less efficiency. For many of them, outstanding studies demonstrated their scientific value.

Many health care professionals draw a distinct border between allopathic medicine and complementary and alternative medicine, claiming the ascendance of reductionist approaches or, contrary, the naturalistic approaches. For some time, there is a more balanced point of views in identifying favorable aspects of both ways and taking advantages in health care provision [8]. Accurate studies about the efficacy complementary and alternative medicine methods of are scarce until now, but the positive perception of patients toward this way of healing, even for pediatric patients, will, inevitably, force us to analyze more carefully this field [9].

This chapter does not discuss the ascendancy of the various branches of herbal medicines against allopathic medicinal products, it only highlights herbal remedies with proven antimicrobial efficacy [10]. The chapter is not intended to be encyclopedic, but a synthesis of commercial plant products proven by substantial evidence as having biological activity in human infectious diseases. Further, research articles on plant extracts with antimicrobial activity have

been reviewed to find evidence that supports plants value in infectious diseases. Since this chapter is dedicated to health care professionals, in the following sections, the plant products are systematized according to their clinical conditions, without intending to cover all herbs and all infectious diseases. Phytotherapy and chemotherapy applications in infectious diseases will be described separately as there are differences in the healing process underlying these methods.

2. Phytotherapy

2.1. Overview

It can be said that phytotherapy is one, if not the oldest method, used in the treatment of infectious diseases. Many countries have a long tradition in herbal medicine [11–14]. People in countries where traditional medicine is widespread are more prone to continuing these practices [15, 16]. Nowadays, traditional healers are trying to treat contemporary infectious diseases (e.g., HIV) with herbs without any evidence of their efficacy or toxicity [17]. Moreover, certain associations of antibiotic plants are antagonistic, therefore the failure of antibiotic treatment may be the result of the addition of an apparently harmless plant product such as rose and pomegranate flowers [15]. Thorough out the world, there are many lost legends about traditional medicine, people lifestyle being intertwined with the plants cycle of life, but the subject is far more complex to be developed in the present chapter [7].

Phytotherapy uses the entire plant or parts of plants prepared by various methods. Presently, there are a wide range of plant products—oils, tinctures, plant extracts, mother tincture (TM), essential oils, powders, suppositories, syrups, inhalants and all sort of mixtures. There are studies that not only demonstrate the antibacterial effect of some plants, but also identify the possible target of action. *Juglans regia* (walnut) in combination with *Camellia sinensis* (tea plant, tea shrub) acts synergistically to inhibit multiple-resistance bacteria (MDR), most likely targeting the bacterial cell wall [18].

2.2. Phytotherapy in bacterial infections

Oral hygiene. Today there are thousands of commercial herbal mouthwash and dentifrices. People prefer natural products for oral hygiene, and dentists also agree to use effective alternatives to prophylactic products containing chlorhexidine or sodium fluoride [19]. Due to the interest of dental professionals, many clinical trials have been performed with promising results. Whereas washing with water and neutral soap proved to be the most efficient protocol against *Candida albicans* and *Staphylococcus aureus* biofilms on the maxillofacial silicone polymer, *Cymbopogon nardus* (citronella grass) and *Hydrastis canadensis* (goldenseal) are also efficaces [20]. *Ribes nigrum* (blackcurrant) and *Hippophae rhamnoides* (sea buckthorns) juices may reduce the risks for both tooth decay and gingivitis, by inhibition of bacterial grow [21] and by their anti-inflammatory effect [22]. The assessment of a paste containing *Myrtus communis* (myrtle) in the treatment of recurrent aphthous stomatitis, an idiopathic oral ailment, gave positive results [23].

Respiratory tract infections. Essential oils are widely used in respiratory illnesses. Although there are attempts to accurately characterize active principles, the results of specific identification of a single antibacterial compound are not promising. Among well-known plants with therapeutic potential in healing or prevention bacterial respiratory infections are *Urena lobata* (Caesarweed) [24], *Rosmarinus officinalis* (rosemary), *Thymus vulgaris* (thyme) or *Primula veris* (primula root) [10]. The essential oils mixtures—*Cinnamomum zeylanicum* (cinnamon), *Daucus carota* (wild carrot), *Eucalyptus globulus* (eucalyptus) and *Rosmarinus officinalis* (rosemary)—are also effective in treating influenza infection and bacterial complication of influenza [25].

The **urinary tract infections** are frequently encountered especially in woman, and many plants formulations have been used by centuries with both antibacterial and anti-inflammatory potential—*Astragalus membranaceus* (Mongolian milkvetch) root, *Sophora flavescens* (shrubby sophora), *Lindera aggregata* (lindera) root, *Oldenlandia diffusa* (snake-needle grass), *Phellodendron amurense* (Amur cork tree), *Desmodium styracifolium* (Guang Jing Qian Cao) [26]. Aqueous extract of *Calluna vulgaris* (common heather) and *Vaccinium vitis-idaea* (lingonberry, cowberry or bearberry) extract directly inhibit most uropathogenic strains or prevents biofilm formation [27, 28].

Cutaneous infections. Cosmetology widely uses herbs in various forms to treat other skin infections difficult to treat [29]. Treatment for acne—a chronic condition which deteriorates the quality of life—is discouraging, relapses and duration of treatment often lead both patients and doctors to use herbal medicines. Topical treatment with various plants or plant-drugs formulations is extensively used. Their antimicrobial efficacy is supported by numerous *in vitro* and *in vivo* studies showing that certain plant and essential oil extracts inhibit bacterial species encountered in cutaneous infections [30].

Digestive infections. Undoubtedly, the main plant species recommended in digestive infections is the *Vaccinium myrtillus* (bilberry) [31]. Gastritis due to *Helicobacter pylor*i infections could be treated with *Punica granatum* (pomegranate) [32]. A clinical trial shows the efficacy of traditional herbs used in Chinese medicine, Jiechang mixture, in the treatment of infantile mycosis enteritis [33].

2.3. Phytotherapy in viral infections

Most herbal formulations with viral infection benefits are dedicated to respiratory diseases. Traditional Chinese herbal medicine (TCHM) formulas are by far the most used and play an important role in virus infectious diseases like **respiratory syncytial virus infections** [34]. TCHM formulas contain a long list of plants and its underlying mechanism is not yet elucidated. Do not forget that traditional Chinese medicine, due to its philosophical approach, is more profound and more sophisticated than the simple use of some curative formulations [35]. *Echinacea angustifolia* (narrow leaf echinacea), a versatile immunomodulator, is probably the best choice for **common cold** and prevention of **influenza** complications [36]. Essential oils, referred to bacterial infections, administered separately or in different mixtures, are also beneficial in preventing influenza complications. Infectious herpes simplex is other recurrent viral infections and the emergence of acyclovir-resistant clinical isolates

has made the treatment more difficult. Birch bark efficacy has been shown to inhibit the acyclovir-sensitive and acyclovir-resistant clinical isolates of **herpes simplex virus type 1** (HSV-1) in the early phase of infection [37].

2.4. Phytotherapy in parasitosis

Many parasitic infections are of major public health concerns, but the helminth infections are one of the most common infections [38]. The effectiveness of human parasitosis treatment is diminished by the resistance to parasite medication. Also, some parasitic diseases require high doses for long terms of drugs with substantial adverse effects. Therefore, it is not surprising that researchers are interested in healing parasitic infections with plant remedies with proven effectiveness [39]. Traditional herbal healing of parasitosis rely on well know plants like garlic, ramson or pumpkin seeds, but interesting studies show that innovative technologies can bring new insights into treating parasitic diseases [40, 41].

Allium ursinum TM (ramsons) stimulate the digestion and help at eliminating the **intestinal worms**. Alternatively, in pediatrics, suppositories may be recommended. *Nigella sativa L.* seeds (black cumin, fennel-flower and negrilla) has been used in the treatment of quite different clinical conditions—helminths infections, epilepsy [42] or preventing oral malodor [43]. Promising results were obtained in helminths infections—a new formula of highly antiparasitic compound silver doped titanium dioxide nanoparticles (TiAgNps) and *Nigella sativa* L. essential oil is very efficient on **cutaneous Leishmaniasis** [40]. A recent *in vitro* study shows that a nano emulsion of *Zataria multiflora* (Shirazi thyme) essential oil determines the decrease in the size, number and weight of **hydatid** (*Echinococcus granulosus*) cysts [41]. This species of thyme is also effective against the protozoan *Trichomonas vaginalis* [44]. *Artemisia annua* L. (sweet wormwood) may prolong survival of animals experimentally infected with *Acanthamoeba* sp., therefore can be used for general and local treatment of **acanthamoebiasis**, or in combined therapy with antibiotics [45]. **Malaria** has always been a challenge for health practitioners, even today, when attempts to develop a commercially available vaccine are already under way in clinical trials [46]. Nowadays, the main antimalarials originated from plants (quinin, artemisinin and newly lupane triterpenes) [47–49]. Since phytotherapy has a holistic approach of illnesses, the combination of antimalarials with curcurma oil has positive effects [50].

Many producers have developed several formulations, more simple to administrate especially, for children or elderly persons. In Romania, there are an antiparasitic mixture *Vermicin* (www.fares.ro) which consists of *Olea europaea* L. folium (olive leaf), *Thymus vulgaris* (thyme, thymi herba), dry extract of rhizome of *Hydrastis canadensis* (goldenseal), berberine sulfate (alkaloid derived from *Berberis aristata*) [51], *Inula helenium* L (Inulae radix) [52] and flower bud of *Eugenia caryophyllata* (Caryophylli flos). It is not recommended for pregnant women due to possible effects of stimulation of uterine contractions or women who are breastfeeding because active substances pass into breast milk and can alter the taste of milk. A formulation recommended by Ovidiu Bojor (www.plantextrakt.ro) is *Giardinophyt* and contains extracts of *Thymus vulgaris* (thyme, thymi herba), *Chrysanthemum vulgare* (tansy), seeds of *Anethum graveolens* (dill), *Eugenia caryophyllata* (cloves) and propolis cera. The producer claims that parasite removal is favored, along with other beneficial effects on the digestive system. Seven-day treatments are recommended to prevent relapses.

3. Gemmotherapy

3.1. Overview

Gemmotherapy is part of complementary and alternative medicine, being a form of herbal therapy which uses embryonic stem cell tissues of plants—inflorescences, buds, bark of the stalk, young branches of the spring plants, young roots, acorns, sap, seeds or bark of roots. Gemmotherapy, the youngest branch of herbal therapy, was developed by a group of homeopaths—Henry Pol, Max Tétau and O.A. Julian—and is characterized by a different approach to illness, health and life in general. Although this chapter is not dedicated to gemmotherapy, we can not ignore its fundamental principles. The most important intriguing concept is that then prior to any treatment, it is essential to understand that symptoms are considered an expression of energetic status of a certain organ. Therefore, the efforts are directed to restoring the dynamic balance of the affected organs rather than simply treating the pathological symptoms; in other words—a holistic approach to human being and disease.

Principle of preparation of the extracts used in gemmotherapy. The procedure involves two steps—the fresh harvested plants are first treated with alcohol, then a hydro-glycerin solution is added. In the first step, there is inhibition of enzymatic activity of the plant followed by further extraction and stabilization of active principles. The extracts are stored as concentrated glycerin macerate 1DH (dilution 1:10) in glass brown bottles at room temperature. The warranty period is 5 years [53].

Mechanism of action of the extracts used in gemmotherapy. The principles of gemmotherapy derived from the drainage concepts from homeopathy; for the very first time it was named in France as "drainage therapy". The main action of the extracts used in gemmotherapy is the rebalancing of cellular and tissue homeostasis, targeting the reticulohistiocytosis tissue. The most important characteristic of these products is their holistic activity, separated molecule do not have the same activity like the whole extract. Until now, we could not separate a certain molecule in order to accurately characterize its activity due to coordinated action of the active principles. The comprehensive studies about precise mechanism of action of extracts used in gemmotherapy are very rare, therefore, in my opinion, at this moment clinical observation is the most relevant way of validate gemmotherapy.

Treatment regimen in gemmotherapy. There is not a standardized therapeutic regimen in gemmotherapy, but the glycerine macerate 1DH are usually administrated 40–50 drops/1–2 times/day diluted in 100 ml water. Fernando Piterà explained that this water dilution not only releases active principles, but triggers crucial electronic exchanges between the molecules. If a complementary regimen is recommended, 50–70 drops/once a day are recommended. The association of different glycerine macerate 1DH are often proposed. Usually the treatment lasts for a month and can be repeated after at least 2 weeks. Some authors do not recommend the mixtures and administration of more than one extracts at once, although therapeutic regimens often includes more then one extract. The main argument for avoiding mixtures is that of avoiding reactions between different active compounds that can cause inactivation or even the formation of toxic compounds.

Since the scientific literature dedicated to gemmotherapy is so scant, recommendations on the application of gemmotherapy products to infectious diseases—bacterial infections, viral infections or parasitosis—are selected from the Fernando Piterà's *Compendio di gemmoterapia clinica (Meristemoterapia) con indice clinico,* 3rd edition, Genova [53]. Inflammatory response is a well-known feature of many infectious diseases, so most of the gemmotherapy regimens include *Ribes nigrum* (black currant) that reduces inflammation and stimulates and supports the adrenal glands. Also, *Juglans regia* (walnut) is considered to be the major stem cell plant-derived "antibiotic". Note that embryonic plant cell stem tissues are unique in structure and composition therefore their properties and clinical applications differ from the adult plant.

3.2. Gemmotherapy in bacterial infections

Oral hygiene. The aphthous stomatitis and gingivitis—a common and mild form of periodontal disease—are diseases commonly encountered characterized by frequent recurrences and the lack of specific treatment. Gemmotherapy may have a real benefit in preventing relapses of the oral ulcers or in gingivitis by admiration of *Alnus glutinosa* (alder) associated with *Vaccinium myrtillus* (bilberry), *Juglans regia* (walnut), *Ligustrum vulgare* (privet) and *Ulmus campestris* (elm). In paradontosis, *Abies pectinata* (silver fir), *Betula pubescens* (downy birch) or *Quercus pedunculata* (oak) could be prescribed.

Respiratory tract infections. Fernando Piterà claims that in recurrent tonsillitis and group A streptococcal pharyngitis *Vitis vinifera* (common grape vine) associated with *Juglans regia* (walnut), *Ampelopsis veitichii* (peppervine), *Ribes nigrum* (black currant) and *Rosa canina* (dog rose) can reduce the level of streptolysins and prevent the complications of rheumatic fever. In tuberculosis the dynamics of immune response greatly influence the clearance and dissemination of *Mycobacterium tuberculosis*, the heterogeneity of the disease being closely related to underlying immune dysfunctions [54]. Tuberculosis convalescence is a critical period for healing the illnesses, and gemmotherapy may help in this critical period by *Prunus spinosa* (blackthorn)—an excellent tonic which greatly stimulate the immune response—in combination with *Juglans regia* (walnut) and *Rosa canina* (dog rose).

In **urinary tract infections**, the most important gemmotherapy products according to Fernando Piterà are *Calluna vulgaris* (common heather) and *Vaccinium vitis-idaea* (lingonberry, cowberry or bearberry). *Calluna vulgaris* has diuretic and disinfectant action on the urinary tract. The young branches of the spring plant of *Vaccinium vitis-idaea* have antiseptic, antimicrobial and anti-inflammatory effect on urinary tract. In acute cystitis, Fernando Piterà recommends *Calluna vulgaris* (common heather), *Vaccinium vitis-idaea* (lingonberry, cowberry or bearberry) and *Vaccinium myrtillus* (bilberry); in recurrent cystitis—*Calluna vulgaris, Vaccinium vitis-idaea* and *Juniperus*.

Genital infections. *Buxus sempervirens* (common box) is a small, always green and toxic shrub because of cyclobuxine. The glycerine macerate 1DH of young branches of *Buxus sempervirens* (common boxwood), harvested in vegetative stage, even have not a specific prescription, it appears to cure the syphilis sequelae. Vaginosis has several causes, but very often is associated to vaginal microbiota imbalance [55]. *Rubus idaeus* (raspberry) was already identified as

targeting the hypothalamic-pituitary-gonadal axis and along with *Calluna vulgaris* (common heather) and *Juglans regia* (walnut) have a beneficial impact on reestablishing the equilibrium of vaginal microbiota [56].

Digestive infections. *Vaccinium myrtillus* (bilberry) is strongly recommended in enteritis, diarrhea, dysentery and membranous colitis. *Juglans regia* walnut) and *Vaccinium vitis-idaea* (lingonberry, cowberry or bearberry) could be associated.

Cutaneous-mucosal infections. *Juglans regia* (walnut) is recommended in many cutaneous illnesses like acne, dermatoses, mycosis, tinea, blepharitis. There are several notable associations of *Juglans regia* in complicated infections—in pustular acne, furunculosis complicated with staphylococcal and streptococcal infection with *Ulmus campestris* (elm); in infected wounds with *Buxus sempervirens* L. (boxwood). *Juglans regia* is helpful in the treatment of superficial forms of panaritium along with *Ficus carica* (common fig). In oral candidiasis, the combination of the following three product—*Buxus sempervirens* L. (boxwood), *Ligustrum vulgare* (common privet) and *Rubus fructicosus* (blackberry)—is the best choice.

3.3. Gemmotherapy in viral infections

Ribes nigrum (black currant) is indispensable for the treatment of **viral respiratory infections** and may be associated with *Abies pectinata* (silver fir) and *Rosa canina* (dog rose) in the common cold and with *Alnus glutinosa* (alder), *Betula pubescens* (downy birch), *Lonicera nigra* (blackberried honeysuckle) or *Salix alba* (white willow) in the flu, the last one if hyperpyrexia and arthralgia accompanies the illness.

Juglans regia (walnut) with *Acer camestre* (field maple), *Ulmus campestris* (elm) and *Rosa canina* (dog rose) prevent relapses of **herpes simplex**. Also, *Acer camestre* may be combined with *Prunus spinosa* (blackthorn) in recurrent **herpes simplex keratitis**.

In Epstein-Barr virus infectious **mononucleosis**, one of the common viral infectious of young people around the world, gemmotherapy offers quite a long list of products: *Alnus glutinosa* (alder), *Betula pubescens* (downy birch), *Juglans regia* (walnut), *Juniperus communis* (common juniper), *Ribes nigrum* (black currant), *Tamarix gallica* (French tamarisk) and *Vitis vinifera* (common grape vine).

The *Radical Secale* (rye) root has a selective tropism for hepatic parenchyma, being recognized for its hepatocyte regenerative capacity. It is used in **acute viral hepatites** in combination with *Rosmarinus officinalis* (rosemary), *Berberis vulgaris* (barberry), *Corylus avellana* (hazel), *Lonicera nigra* (blackberried honeysuckle) or *Zea mays* (corn).

Radical Secale (rye) root, *Rosmarinus officinalis* (rosemary), *Berberis vulgaris* (barberry), *Corylus avellana* (hazel), *Juniperus communis* (common juniper), *Ribes nigrum* (black currant) and *Rosmarinus officinalis* (rosemary) are used in **chronic hepatites**. Note that *Rosmarinus officinalis* has a specific tropism for the liver, cholecyst, biliary tract, adrenal glands and gonads, which contributes to the liver regeneration.

The treatment of **warts**, common viral infections caused by the human papilloma virus, is discouraging for patients and physicians too, but gemmotherapy offers some alternatives:

Buxus sempervirens L. (boxwood), *Ficus carica* (fig), *Juglans regia* (walnut), *Rosa canina* (dog rose), *Taxus baccata* (yew), *Thuja orientalis* (Chinese thuja) and *Vitis vinifera* (common grape vine).

3.4. Gemmotherapy in parasitosis

The *Buxus sempervirens* (common boxwood), also used phytotherapy, in combination with *Alnus incana* (gray alder) and *Juglans regia* (walnut) may be an effective therapy in parasitoses.

4. Active compounds from medicinal plants

The attempts to understand the antimicrobial effect of medicinal plants and precise mechanisms of action are delayed by two major obstacles. First, the antimicrobial effect is the result of the combined action of several factors, some of which do not have direct antimicrobial action but plays an essential role in achieving the therapeutic effect. Second, for the vast majority of medicinal plants, aside of antimicrobial effect, the active compounds have additional effects—for example, anti-inflammatory effect. In particular, gemmotherapy has stated that all active principles in embryonic cell stem tissues act in a coordinated manner, so attempting to divide the whole effect is useless. Even so, identifying of therapeutically active ingredients in order to obtain a pure compound is mandatory for further experimental tests and clinical trials [57].

Tracing connections between the active compounds and their degradation products is an issue more challenging than isolating a pure compound and to determine the structure of the pure substance. Nowadays, there exist extraction methodologies and accurate protocols for analyzing the physico-chemical features of pure substances, but considering all possible interconnections is much more complicated than that. Healing is the result of an entire network of substances, therefore very often the mechanism of action of plant products is not well-understood. What is really necessary is the feasible protocols to bioassay the reaction chain between the active compounds. The advance in recognizing the therapeutic effect of plant products begins with the precise characterization of the active compounds. Progresses made in nanotechnologies are encouraging in the direction of developing more effective, more stable and manageable plant-derived formulations. In the near future, the nanoparticles may find an immediate application in controlling side-effects, for example, toxicity, of some drugs used for the treatment of infectious diseases [40, 50, 58–60].

Herein some of plant active compounds are quoted.

1,8-cineole (ethyl-dimethyl-(3-sulfopropyl)azanium) ($C_7H_{18}NO_3S^+$) (PubChem CID 448830) is found in many essential oils, for example, *Eucalyptus globulus* (eucalyptus) oil, *Melaleuca alternifolia* (tea tree) or *Rosmarinus officinalis* (rosemary). It is one of the main active compound, which explains the antimicrobial effectiveness of essential oils [61].

Anthocyanins (2-phenylchromenylium) (Cyanidin: $C_{15}H_{11}O_6Cl$; Peonidin: $C_{16}H_{13}O_6Cl$; Malvidin: $C_{17}H_{15}O_7Cl$; Delphinidin: $C_{15}H_{11}O_7Cl$; Petunidin: $C_{16}H_{13}O_7Cl$; Pelargonidin: $C_{15}H_{11}O_5Cl$ or $C_{15}H_{11}O^+$) (PubChem CID 448830) are found in *Vaccinium myrtillus* (bilberry). A recent study about intestinal accessibility and bioavailability show that the colon is a significant site for anthocyanins and their degradation products [62].

Arbutin ((2R,3S,4S,5R,6S)-2-(hydroxymethyl)-6-(4-hydroxyphenoxy)oxane-3,4,5-triol) ($C_{12}H_{16}O_7$) (PubChem CID 440936) is found in plants from the families *Ericaceae*, *Asteraceae* and *Rosaceae*. It explains the antiseptic properties, but its relation with microorganisms are not enough studied, notably the mutagenic effect of its metabolites hydroquinone [63].

Allicin (3-prop-2-enylsulfinylsulfanylprop-1-ene) ($C_6H_{10}OS_2$) (PubChem CID 65036) found in family *Alliaceae*, has a broad spectrum antimicrobial and immunomodulatory activity, along with many other beneficial effects for human health [64, 65].

Artemisinin ($C_{15}H_{22}O_5$) (PubChem CID 68826) is one of the most celebre semi-synthetic plant-derived compound used in infectious diseases. The discovery of artemisinin, the active compound of *Artemisia annua* (sweet wormwood) has brought new hope for medical community [47, 48, 66]. The emergence of artemisinin-resistant *Plasmodium falciparum* explains the critical need to identify new antimalarials [67]. Hope comes again from herbal compounds—a recent paper describe **lupane triterpenes**, originated from *Buxus sempervirens* (common boxwood), as being the next antimalarials [49].

Benzoic acid ($C_7H_6O_2$) (PubChem CID 243), found in the fruits of *Vaccinium vitis-idaea* (lingonberry, cowberry or bearberry), has antiseptic effect which explains the preservation of jam.

Curcumin ((1E,6E)-1,7-bis(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-dione) ($C_{21}H_{20}O_6$) (PubChem CID 969516), an active compound extracted from aromatic *Curcuma aromatica* (wild turmeric), is not only a powerful antioxidant, anti-inflammatory and anticancer ingredient but also has antiparasitic activity, *in vitro* studies showed antimalarial, antileishmanial and antitrypanosomal activity [68, 69].

Essential oils are ethereal oils consisting of complex mixture of many volatile compounds. Even if research on their mechanism of action is lacking, their antimicrobial efficacy is demonstrated by the results of their use in infectious diseases [70].

Quinine ((R)-[(2S,4S,5R)-5-ethenyl-1-azabicyclo[2.2.2]octan-2-yl]-(6-methoxyquinolin-4-yl) methanol)($C_{20}H_{24}O_2N_2$ or $C_{20}H_{24}N_2O_2$) (PubChem CID 3034034) originates from *Cinchona*. It was for decades the main cure in malaria, other active compounds of plant origin demonstrated their value.

Resveratrol (5-[(E)-2-(4-hydroxyphenyl)ethenyl]benzene-1,3-diol)($C_{14}H_{12}O_3$)(PubChem CID 445154) is best known for its antioxidant properties, but also has antimicrobial activity [71].

Thymoquinone (2-methyl-5-propan-2-ylcyclohexa-2,5-diene-1,4-dione)($C_{10}H_{12}O_2$) (PubChem CID 1028) is the main active compound of *Nigella sativa L.* seeds essential oil. It has not only an anti-inflammatory effect [72], but it is a versatile immunomodulator, novel mechanisms being recently discovered [73]. The role in activation cellular immunity, by stimulating CD4+ T lymphocytes and production of γ-interferon, explain the positive results of *Nigella sativa L.* seeds essential oil in viral infections [74].

5. Limitations of phytotherapy and gemmotherapy

The main limitation of phytotherapy and gemmotherapy, as well for any traditional healing treatment, is the lack of *standardization* of the treatment. This is one of the reasons for

the low credibility regarding the efficacy of medicinal plants, so most doctors do not even consider herbs as an alternative to antibiotics. Basically, they are right, does anyone have the courage to treat their own severe pneumonia only with thyme essential oil? On the other hand, the antibiotics overuse is a notable factor in emergence of MDR bacterial isolates. Very often patients claimed antibiotics even for uncomplicated common cold. Luckily, empirically antibiotics use is restricted by general health laws. Recently many studies have focused on the identification and isolation biologically active compounds, and this is the first step in the process of developing new drugs with clear mechanism of action and a standardize employment. Finding more about the pharmacology of plant-derived active compounds will surely lead to the standardization of the therapeutic regimens [33]. Health care professionals are accustomed to precise therapeutic protocols, and are more confident in prescribing certified medicines than to use a plant extract of uncertain composition. We must recognize that in the field of phytotherapy or gemmotherapy, prescribe a concise therapeutic regimen for a specific infection, adapted to the pathology of each patient, requires a well-trained professionals.

Another important limitation is the *reproducibility* of the composition of plant products—the same product may have different properties depending on the suppliers. Researchers are interested in analytical characterization and authentication of active compounds in order to establish quality control procedures. Once again, the step is a real challenge because of the various factors that need to be taken into account. DNA barcoding and metabarcoding are proposed for authentication single plant ingredient, and mixed plants products, respectively [75]. Poor characterization of plant products is the main reason for different clinical trial results. A plant product credibility started with a certified manufacturing method—International Food Standard, Community herbal monograph, German Homeopathic Pharmacopeia or other international recognized quality standards [76]. The major obstacle in the manufacturing plant products is the natural genetic variation of plant species. A product from the same supplier, obtained by the certified manufacturing method, could be different because of the origin of the raw materials. Plant quality depends very much on environmental conditions, pollution being an important variable.

Third, the *availability* of quality plant species, in particular exotic plants, is limited to a particular geographical area. Only ancient people relied solely on wild plants for healing, hence the interest in massive cultivation of medicinal plants. Concomitantly, there are other variables ranging from plant species to environmental conditions, that significantly influence the availability of quality medicinal plants [4, 77, 78]. At present, environmental pollution is a problem that seems to grow continuously, and it also seems hopeless to find a viable solution. Even if we can not change environmental conditions, we need to be aware that the place where plants grow is the first thing that affects the quality of a final product.

Finally, there are no extensive clinical trials evaluating the *effectiveness* of phytotherapy and gemmotherapy for infectious diseases and the determination of *adverse effects* [79]. Assessing the antimicrobial efficacy of plant products requires standardized tests and guidelines to compare experimental data. As for antibiotic and antifungals, we have standards provided by the Clinical and Laboratory Standards Institute (CLSI) [80] and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) (www.eucast.org), we lack consistent procedures to test plant products. Pure active compounds could easily be tested for minimal inhibitory concentration (MIC), but different methods are needed to test plant extracts or essential oils [81].

6. Discussions

To answer at the question of effectiveness of herbal products in infectious diseases, clear evidence should be stated before any other debate. Undeniably, some plant species contain antimicrobial substances, elaborated for their own defense against infections. Certainly, plant pathogens and human pathogens are not the same, and plant defense mechanisms are quite different from human defense mechanisms. But these differences should not be a reason to deny the efficacy of plants in certain infectious diseases. Conversely, the demonstrated antimicrobial effects of certain plants should not overestimate their capability and discontinue the therapeutic regimens of conventional drugs. However, one of the latest scientific certification of plant usefulness in infectious diseases is the discovery of artemisinin, which saved millions of lives, by Youyou Tu, a pharmacologist at the Chinese Academy of Chinese Medical Sciences in Beijing, who received the Nobel Prize in 2015 [47, 48, 66].

With the abundance of all range of over-the-counter herbal products, more or less expensive, it looks like it is not difficult to break into natural products market. People are more prone to try something accessible, cheaper and presented as without side effects. By adding a professional advertise, the suppliers' success is guaranteed. Where does this confidence in herbal products come from? We can only guess that the first reason is we use plants in daily life in the form of tea, spices or simply as soft drinks—lemonade, mint water and so on. Hot tea with lemon and honey is almost always indispensable in the treatment of the flu, so we can think that there is nothing wrong with the administration of herbal products such as, for example, essential thyme oil. Nothing wrong at first sight, but should not forget the main problem of the therapy with herbal products—standardization. We are talking not only about dose standardization but also especially about the standardization of the therapeutic regimen when two or more herbal products are recommended. It is noteworthy that mixed herbal products are presented as a simpler alternative when several plants are included in therapeutical regimen. Any reasonable person should admit that we cannot blend any kind of substances without alter the effect of each component. An herbal product is already a mixture and its effect is the result of the subtle interactions of its molecules, which is why random mixing of several plants can even lead to the cancelation of the therapeutic effect. Due to the lack of accurate studies on plant interactions, at this time we cannot understand the complexity of the network formed in a recipient which contain more than one species of plant. Most plant products has not been evaluated by the Food and Drug Administration (FDA) and the lack of clear-cut studies on the safety of certain herbs, for example, echinacea and elderberry, suggest that certain risk groups, such as pregnant women, should not be treated with them [82]. Very often, natural products are considered superpower remedies, but recent studies have shown that they should be used with caution in the absence of accurate evidence of their effectiveness [83]. However, there are certain clinical situations when plant-derived products can have a real benefit—in infections characterized by frequent recurrences such as simplex hepatic infections or when immune modulation is important for complete recovery, for example, flu or tuberculosis. In pediatrics or in geriatric, parasitic infections are one of the most common infections, especially in nurseries or day care centers. Considering that relapses are quite frequency in such care centers, plants could be of real benefits in cure and prevention. We are now able to study herbal products by analytical methods that separate into individual components, but in my opinion the physico-chemical analysis of all plant components cannot answer the main question: we can

ever synthesize antimicrobial substances that have similar effects to their natural counterparts. It is like trying to listen to a symphony by isolating the sounds of each instrument. Fernando Piterà argues that this approach neglects that the effects of each natural component depend fundamentally on the entire plant. He describes a plant as a "phytocomplex"—a biological unit with internal dynamics. In fact, this is the doctrine of gemmotherapy. One may say that conventional research methods are not suitable in clinical trials of phytotherapy or gemmotherapy. Experienced doctors in complementary medicine argue that it is not impossible to find research methods that meet the rigor of conventional medicine [84].

It is not exaggerate to remember here the title of a famous etching of Goya "El sueño de la razón produce monstruos" ("The sleep of reason produces monsters"). When it comes to the success or failure of treating a disease, reason is all the more important. Health care providers are aware of the consequences of a wrong therapeutic regimen for the treatment of infectious diseases. If the immediate consequences are therapeutic failure, the long-term consequences are resistance to antibiotics and the spread not only in clinical wards but also in the environment of these antibiotic resistance genes.

7. Conclusions

The ancient herbal therapeutic schemes differ from one geographic region to another, influenced directly by the flora existing in those regions. The folklore is the foundation of medicinal herbs, and the references to relevant bibliographies are rare. In countries with a strong tradition of plant healing, people are more confident in using plant products. Even so, the current trend in antimicrobial resistance has convinced many research teams to orient their resources toward selecting and standardizing plant treatments beneficial to healing or preventing infectious diseases. Embryonic stem cells used in gemmotherapy are often multiple organotropic, the products recommended for infectious diseases are more immunomodulatory than genuine antimicrobial agents. Also, embryonic stem cells have different characteristics from adult plants. The positive outcomes of many plant-based products or plant-derived compounds in healing of infectious diseases justify the reconsideration of their therapeutic potential. The emergence of bacterial, viral or parasitic resistant to various drugs and the toxicity of synthetic drugs are only two reasons for designing precise *in vitro* and *in vivo* studies targeting the antimicrobial efficacy of plants. There are so many unexplored features of the plant's therapeutic potential, that somewhere behind these unknown features is some hidden evidence of the mechanisms of action but evidence of new plant uses.

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