Chapter 4

Natural Compounds for Wound Healing

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Additional information is available at the end of the chapter

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Abstract

Many plants or plant-derived compounds with high levels of antioxidants and anti-inflammatory, immunomodulatory, and antimicrobial properties could be of great benefit for wound healing. Several studies have documented the use of plant extracts for the development of bioactive wound dressings. The purpose of this chapter is to give an update about the vegetal and bee products, which can be used as bioactive substances in wound dressings or in other formulations for wound healing. The adverse effects of plant and bee extracts, such as contact allergies, are also presented. In order to better exploit the huge reservoir of pharmacologically active plant-derived compounds and extracts, standardized methodology and clinical trials are necessary to give more concrete evidence supporting the use of traditional medicine in wound management.

Keywords: wound healing, essential oils, plant compounds, propolis, antimicrobial, immunomodulatory, antioxidant, wound dressings, dermatitis

1. Introduction

Wound healing is a complex and dynamic process which is not fully understood [1]. Leg ulcers are caused by circulatory problems and are characterized by the lack of skin substance, having a chronic evolution and delayed healing [2]. The causes of ulcers are (i) a prolonged or excessive inflammatory phase [3], (ii) persistent infections produced by microbial biofilms resistant to treatment, and (iii) failure of the epidermal or/and dermal cells to respond to the reparatory stimuli [4]. The characteristics of ulcers are an increased enzymatic activity of the matrix proteases, a low response to growth factors, and increased cell death [1].

Wounds and ulcers affect the patients' life quality with an annual cost of $25 treatment [5].

Medicinal plants have been used for thousands of years, worldwide, as traditional treatments for numerous diseases. For example, 65 herbs were used in the traditional Persian medicine, a holistic system of medicine, providing valuable information on natural remedies [6]. Almost 80 % of the population of developing countries, but also economy leaders as China and India, use traditional medicine for the treatment of a wide range of diseases [7, 8]. The naturally derived products from medicinal plants have proven to be an abundant source of biological active compounds, of which many have been used to start the development of new chemicals for the pharmaceutical industry.

There are approximately 500,000 species of plants in the world of which only 1 % have been phytochemically analyzed demonstrating a great potential for the discovery of new bioactive compounds [9]. Phytochemicals are nonnutritive substances present in plants, enhancing tissue remodeling when applied on wounds and acting as pro-angiogenic agents for wound healing [7]. From the 1184 new chemical entities introduced between 1981 and 2006, approximately half of them (48 %) were natural products, semisynthetic analogs of the natural products, or synthetic compounds based on the natural pharmacophores. Over 70 % of the therapeutic agents developed between 1981 and 2006 for bacterial and fungal infectious diseases have been derived from natural compounds [10, 11].

The therapeutic properties of vegetal extracts include the following effects, which are due either to some specific phytocompounds or to their synergic actions: anti-infectious, anticancer, antioxidant, immunomodulatory, actions on the central nervous system and on the cardiovascular system, and hemotropic activity.

Regarding the infectious diseases, the increased resistance of known pathogens to the currently used therapeutic agents, such as antibiotics and antiviral agents, has led to regaining the interest for the discovery of novel natural compounds with anti-infectious activity. The increasing appreciation of the different biological effects of the natural compounds has led to a reevaluation of the possible roles that these compounds play in plants, especially in the context of ecological interactions [12].

Besides the principal metabolites which assure the plant's viability, the plants produce many organic compounds, known as secondary metabolites, which do not participate directly to the growth and development of the plants. These are distributed differently in the taxonomic groups of the plants regnum. Many of their functions are not known, although they are remarkable through the complexity of their chemical structures and the biosynthesis pathways.

Many of these compounds are recognized, presently, as being involved in the plant's defense, having an insecticide, antimicrobial, and repellent effect; in reproduction, they have a role of attractant for pollinators and act as allelopathic agents. These ecological functions affect the survival of the plants and, apparently, the secondary metabolites of plants' act, mainly, on other species, being known the fact that invasive plants produce compounds that stop the development of autochthonous species in the clonal area [12].

This chapter is a synthesis of original results published in the PhD works of the chapter coauthors and also of research articles available from PubMed, using the following key words:

"wound healing" in association with one of the following "alternative methods" for "plant-derived compounds," "essential oils," "propolis," "*Calendula officinalis*," "aloe vera," "curcumin," "side effects," and "wound management."

2. Biological activities of plant compounds useful in the wound-healing process

2.1. Volatile oils

The volatile oils are products of the secondary vegetal metabolism, secreted by specialized cells, organized in different organs, and deposited in vacuoles, bags and secretory channels, or in the glandular hairs under the form of volatile liquids, oily, with nice, flavored scent. They are mixtures of different chemical compounds with different therapeutic properties [13]. Out of the 100,000 secondary known metabolites, the essential oils represent over 3000, of which approximately 300 have a commercial interest and are used in the food, cosmetic, and pharmaceutical industries [14].

2.1.1. The mechanisms of the antimicrobial action of the volatile oils

Over time, several mechanisms of action of the volatile oils on microbial cells have been proposed. The volatile oils can affect the cell wall and the cytoplasmatic compounds. Their hydrophobic character is, apparently, responsible for the perturbation of the bacterial structures. The mechanisms of action of the volatile oils include the degradation of the cell wall; the deterioration of the cytoplasmatic membrane; the cytoplasmatic coagulation; the deterioration of the membrane's proteins; and the increase of the permeability, which leads to the loss of the cellular content, reducing the proton force; and the intracellular ATP by decreasing the ATP synthesis [15].

The effect on the cellular membrane fatty acid profile: the adaptation of the microbial cells to a concentration lower than the minimal inhibitory concentration has been shown to lead to an increase of the percentage of the unsaturated fatty acids responsible for the membranes' fluidity. Also, timol, carvacrol, and eugenol led to an increase of the saturated fatty acid C_{16} and C_{18} concentration and to a decrease of the production of the unsaturated C_{18} fatty acids [16].

The inhibition of protein activity, which has as a consequence the perturbation of the cellular division (cinnamaldehyde, timol, eugenol, carvacrol). Timolol can also affect the expression of the proteins involved in the energetic metabolism [15].

The effect on the production of ATP and ATPase. The production of ATP in prokaryotes takes place in the cellular wall and in the cytosol through glycolysis. The volatile oils perturb the cellular membrane and modify the intracellular and extracellular ATP balance, so the ATP is lost through the disorganized membrane. This effect has been seen to be induced by terpenes with phenolic structure in the *E.*[i] *coli* and *L. monocytogenes* strains [15].

The effect on the microbial metabolism. The intracellular and extracellular metabolome presents many fundamental advantages through which this can provide important information about the functional genomics, metabolic engineering, the characterization of the strains, and

mechanism of cellular communication. The microbial metabolites can change depending on the weather conditions. Recently, many powerful analytical standard approaches, including NMR, microarray, GC-MS, and LC-MS, have been used to analyze the metabolome of the bacteria under stress. These techniques are more widely used to investigate the metabolic effects of natural molecules with bacteriostatic and/or bactericidal activity [15].

The impairing of the cellular morphology. The activity of the volatile oils and of its components differs according to the form of the bacteria studied, so there was a report that bacilli are more susceptible to volatile oils than cocci. For some strains of *S. typhimurium* and *E. coli*, which have a bacillary form with a smooth surface, respectively, those of *M. luteus* and *S. aureus*, which have a normal coccoidal form, after 24 h of treatment with mint volatile oil, the cellular lesions in bacilli were more pronounced compared to cocci [15].

The quorum sensing inhibitory activity. In this regard, the volatile oils can represent the biggest available reservoir of new therapeutic agents. Bacterial QS can be inhibited through different mechanisms, including (1) inhibition of the AHL synthesis, (2) inhibition of the transport and of the AHL secretion, (3) AHL antagonist action, (4) sequestration of AHL, and (5) inhibition of downstream targets of the binding receptor of AHL. Different volatile oils extracted from ornamental plants have proven efficient against biofilms formed by *Salmonella* sp., *Listeria* sp., *Pseudomonas* sp., *Staphylococcus* sp., and *Lactobacillus* sp., demonstrating their interference with the quorum sensing mechanism, which plays a pivotal role in biofilm development [17].

2.1.2. The anti-inflammatory activity of volatile oils

The *Ocimum sanctum*, *Baphia nitida*, *Aloe barbadensis*, *Illicium verum*, *Citrus aurantium*, *Cinnamomum zeylanicum*, *Juniperus communis*, *Cananga odorata*, as well as eucalypt, mint, rosemary, lavender, pine, and clove volatile oils are known for their anti-inflammatory activity. This activity is mediated through multiple mechanisms, such as the inhibition of lipoxygenase, prevention of leukotriene synthesis, inhibition of COX-2 enzyme, inhibition of the pro-inflammatory cytokines IL-1 and α tumor necrosis factor, and repression of pro-inflammatory gene expression [18].

2.1.3. The antioxidant activity of volatile oils

The free radicals and the reactive oxygen species induce the oxidation of biomolecules including proteins, amino acids, unsaturated lipids, and DNA, ultimately producing molecular modification linked to aging, atherosclerosis and cancer, Alzheimer disease, Parkinson disease, diabetes, and asthma. The human body has a defense mechanism which can neutralize the free radicals present in almost all the cells. If an imbalance between the production of free radicals and their removal through the antioxidant system of the organism occurs, it is accompanied by a phenomenon known as "oxidative stress." In this condition, an external source of antioxidants is necessary to ensure a balance between the free radicals and antioxidants [19].

The volatile oils, as natural sources of phenolic compounds, have an antioxidant activity or present the capacity to neutralize the free radicals. It was noted that volatile oils with a high content of timol, carvacrol, and α-tocopherol present a very good antioxidant activity, although still inferior to that of ascorbic acid. The antioxidant activity of volatile oils cannot be attributed only to the presence of phenolic compounds; the alcoholic monoterpenes, ketones,

aldehydes, hydrocarbons, and ethers from the volatile oil composition could contribute also to the neutralization of the free radical action (neral/geranial, citronellal, izomenton, menton, α-terpinen, γ-terpinen, α-terpinolenes, linalool, and 1,8-cineol). It is obvious that the volatile oils can be considered potential natural sources of antioxidants and can be, probably, used as daily supplements or additives to prevent the oxidative stress which contributes to many degenerative diseases [19].

2.2. Plant-derived compounds

The phytochemical studies on the plant extracts are currently headed toward the isolation and identification of the components from the complex mixtures with the purpose of establishing structure-biological activity and dose-effect correlations.

Based on the chemical structure of diverse essential oils, they are divided in two large, distinct groups: (i) terpenes (monoterpenes and sesquiterpenes) and terpenoids (isoprenoid) and (ii) the group of aromatic and aliphatic compounds [20].

2.2.1. Terpenes and terpenoids

The structural diversity and the different potential biological activities of sesquiterpenes, such as anticancer, anti-inflammatory, antitumoral, antimalaria, antiviral, antibacterial, antifungal, etc., have increased the researches' interest for the discovery of new drugs [21].

2.2.2. Carotenoids and carotenes

Carotenes are pigments of leaves, fruits, and flowers with yellow shades which are localized in the chromoplasts. In the plant organism, they could be found in free state or in combination with holoproteins and carbohydrates. The content in carotenoidic pigments depends on the species nature and the influence of environment's conditions [22]. Due to the hydrocarbon chemical structure, the carotenes are hydrophobic substances, soluble only in organic solvents, oils, and fats.

2.2.3. The aglicons of phenolic heterosides

2.2.3.1. Antimicrobial activity

Currently there are only a few studies regarding the antimicrobial action of polyphenolic compounds. For flavonoids a correlation between the chemical structure and their antimicrobial properties was realized, but these compounds can target different components and functions of the bacterial cells. It was noticed that the flavanone dihydroxylated 2, 4—and 2,6—at the level of B ring and 5,7-dihydroxylated at the level of the A ring have a significantly increased antimicrobial activity. The change of the six and eight positions with an aliphatic group with a long chain, such as lavandulil or geranil, leads to an improvement of the activity. An improvement of the flavan-3-ols activity with the substitution of some aliphatic chains C8 and C10 was noted [23].

Chalcones are more efficient against *S. aureus* than flavonones or flavones, the hydroxyl in 2—position being important for the antimicrobial activity of these compounds. For methoxylated flavonoids a drastic reduction of the antibacterial activity was reported. The substitution of

the B ring with the 3′-chloro, 4′-chloro, and 4′-bromo has led to an increase of the antimicrobial activity, being two times more efficient than the simple underived compound on the *S. aureus* strain and four times more active against *Enterococcus faecalis*. Also the 2′,4′-dichlor derivate presents a four to eight times improvement of the activity against the *S. aureus* strain and four times against *E. faecalis*. The 3-methyl-6-bromoflavanon compounds are less active; thus, the halogen substitution of the A ring decreases the antimicrobial activity [23].

Phenolic acids (garlic and ferulic) significantly changed the hydrophobicity and total charge of the cellular surface, as well as the secretion of K^+, leading to pore formation in the cellular membrane of both gram-positive and gram-negative microorganisms [24].

According to Cueva et al. [25], the number and position of the substituents in the benzenic nucleus from the phenolic acid structure and the length of the lateral saturated chains influence in different ways the antimicrobial potential. The antimicrobial activity for different polyphenolic acids decreased in the following order: 4-hydroxy- >> 3-hydroxy- > 4-hydroxy-3-metoxy- > 3,4-dihydroxy- > unsubstituted benzoic acids. For phenylacetic acids, the order of antimicrobial activity was unsubstituted> 3-hydroxy- > 4-hydroxy- >substituted 3,4-dihydroxy, while for phenylpropionic acids, the order was unsubstituted> 4-hydroxy > 3-hydroxy > 3,4-dihydroxy [25].

The potential mechanism of action of the polyphenolic components:

- *The inhibition of nucleic acid synthesis*: the low concentration of polyphenols affects the activity of energy production-associated enzymes, while the high concentration has determined the protein precipitation. In a study using radioactive precursors, it was shown that the DNA synthesis was strongly inhibited in *Proteus vulgaris*, while the mRNA synthesis was most affected in the *S. aureus* strain. The polyphenolic compounds which present this activity have been robinetin, myricetin, and (−)-epigallocatechin [26].
- *The perturbation of the cytoplasmatic membrane*. Phenols can interact with the phospholipidic component from the cellular membrane increasing the cellular membrane permeability or causing significant modification of the fatty acid composition and phospholipids in the structure of the microbial membrane. For the phenolic compounds, it was proven that they can cause rapid swelling of the *P. aeruginosa* cells [27]. The effect on the cytoplasmatic membrane integrity of *S. aureus* was investigated also by measuring the intracellular potassium loss, observing an approximately 20 % loss comparing with the untreated cells with the studied phenolic compound. These data suggest that in the cytoplasmatic membrane, lesions are induced leading to the leak of intracellular potassium [23].
- *Inhibition of energetic metabolism*. It is well known that BHA, p-cumaric, and caffeic acids attack not only the cytoplasmatic membrane, perturbing the permeability and leading to intracellular constituent release, but also affecting the membrane functions responsible for electron transport, nutrient absorption, nucleic acid synthesis, and ATPase activity; in other words the bactericidal/bacteriostatic effect of phenolic compounds is the result of damages at two levels, i.e., the membrane and the cell wall integrity and the physiological state of bacterial cells [28].

Plaper et al. [29] have reported that quercetin binds to the GyrB unit of the DNA-gyrase of *E. coli* and inhibits the ATPase enzyme's activity. The flavonoids' binding site was bunked over those of ATP and novobiocin (antibiotic that blocks replication), because of the adding of these compounds which have interfered with the quercetin's fluorescence [23].

2.2.3.2. Immunomodulatory activity of polyphenolic compounds

The inflammation is the host's response to the invasion of a foreign body, such as infectious agents or inert foreign bodies. In this context, the inflammatory response is an acute protection reaction triggered in the course of irritation, lesions, or infections, characterized by erythema, heat, edema, and pain clinical signs. The redness and the heat result from a blood flux increase; the edema is associated with increased vascular permeability and plasma extravasation. The edema is pressing on the afferent endings of nerve fibers, leading to the appearance of the pain sensation, to which also contribute the small-size polypeptidic molecules called kinins. In normal conditions, these changes in the inflamed tissue serve to isolate and limit the negative effects on the organism [30]. The most secondary metabolites of plants such as phenolic acids, flavonoids, iridoids, monoterpenoids, and triterpenoids are known for their capacity to intervene directly or indirectly, in the following mechanisms: production of inflammatory mediators (metabolites of arachnoid acid (AA), peptides, cytokines, excitators or amino acids, etc.); the production and/or the activity of messengers (cGMP, cAMP), different protein kinases, and calcium; modification of the expression of the transcription factors, such as AP-1, NFkB, and proto-oncogenes (c-jun, c-fos, and c-myc); and the expression of key pro-inflammatory molecules, such as the NO synthase (iNOS), cyclooxygenase (COX-2), cytokines (IL-1β, TNF-α, etc.), neuropeptides, and proteases [30, 31].

2.2.3.3. The inhibition of the arachnoid acid pathway by polyphenolic compounds

One of the most important anti-inflammatory mechanisms is the inhibition of phospholipase A_2, cyclooxygenase, and lipoxygenase enzymes, thus reducing the prostaglandins (PGs) and leukotrienes concentration [32]. The arachnoid acid (AA) is released from membranary phospholipids by phospholipase A_2 cleavage (PLA_2), and it can be metabolized by cyclooxygenase pathway (COX) in prostaglandins (PGs) and thromboxane A_2 (TXA_2) or through the lipoxygenase pathway (LOX) in the hydroperoxyeicosatetraenoic (HpETEs) and hydroxyeicosatetraenoic (HETEs) acids and leukotrienes (LTs) [33]. Cyclooxygenase exists in two major isoforms (COX-1, COX-2) and a variety COX-3 [34]. COX-1 is expressed in many tissues, while COX-2 is known as an inducible enzyme which produces, in many cases, important quantities of prostanglandins. COX-2 is strongly expressed in inflammatory cells, which include macrophages and mast cells, after the stimulation with pro-inflammatory cytokines and/or lipopolysaccharides (LPS) [35]. LOXs are enzymes that participate in the formation of hydroxyl acids and leukotrienes from the arachnoid acid. The most known are metabolites resulted from the action of 5-lipoxygenase, an enzyme present especially in neutrophils. 5- and 12-LOXs produce 5-HETE and 12-HETE, which induce an inflammatory response. Prostaglandins and leukotrienes are present in the inflammatory exudate, and the agents that inhibit the cyclooxygenase exhibit an in vivo anti-inflammatory action [36].

The polyphenolic compounds have proven to inhibit the cellular enzymes, such as PLA_2, COX, and LOX, with the purpose to reduce the production of arachnoid acid, prostaglandins, and leukotrienes, thus exerting the anti-inflammatory action [33]. The polyphenolic compounds extracted from red wine and black tea have been capable to modulate the COX-2 activity and the genes' expression in different cell types [37]. For example, quercetin has reduced the mRNA expression of COX-2 in the Caco2 cells stimulated by IL-1β but also in unstimulated cells [38], in the peritoneal leukocytes of the rat [39] and in the guinea pig epiderma [40]. After the treatment of rabbit's articular chondrocytes with resveratrol, it was noted that the expression levels of cyclooxygenase (COX-2) and prostaglandin E2 (PGE2) have began to increase in 10 min, reaching maximal levels after 3 h, and then they began to decrease. Also, it was demonstrated that resveratrol provokes the phosphorylation of mitogen-activated protein kinases and Akt from rabbit's articular chondrocytes. The inhibition of mitogen-activated protein kinases and Akt with PD98059, SB203580, LY294002, and triciribin by resveratrol has led to the suppression of type II collagen induction and COX-2 expression [41]. It has been reported that other polyphenols from green tea, namely, prodelphinidin B-4,3′-O-galat and prodelphinidin B2 3,3′-di-O-galat, have the capacity to suppress mRNA, the COX-2 expression protein, and the release of PGE_2 in a dose-dependent manner. Moreover, (−)-epigallocatechin (EGC), (−)-gallocatechin (GC), galat-(−)-epicatechin (ECG), galat-(−)-catechin(CG), and galat-(−)-epigallocatechin (EGCG) have proven to have an inhibitory activity on COX-1/COX-2 for different human and mouse cell lines [42]. Also, kaempferol, a flavonoid present in different superior plants, has decreased significantly the production of PGE_2 by LPS stimulation of human cells in the culture whole blood [43].

Tirozol, lycopene, and quercetin have inhibited the COX-2 and iNOS gene expression in RAW 264.7 macrophages stimulated in association with interferon-γ (IFN-γ), probably through NFkB pathway. These data suggest that these compounds can act as nontoxic agents by the control of pro-inflammatory genes involved in celiac disease [42].

2.2.3.4. Modulating cytokine production

Cytokines are the main local mediators of intercellular communication necessary for an integrated response to a variety of stimuli in the course of immune and inflammatory response [32]. Many cytokines have been identified in tissues in a series of inflammatory diseases with immunological substrate. More than that, a "balance" between the pro-inflammatory effects (IL-1β, IL-2, TNF-α, IL-6, and IFN-γ) and anti-inflammatory cytokines (IL-8, IL-10, IL-4, TGFβ) is considered a determinant factor in the disease evolution [42]. For this reason, the modulation of the cytokine profile represents an interesting objective for the development of anti-inflammatory drugs useful in the clinical practice. The polyphenolic compounds, which can interfere selectively with the production or/and function of cytokines, can offer an important alternative for the treatment of many inflammatory diseases [44]. With this purpose, it was observed that many polyphenolic compounds are capable to reduce the expression of different pro-inflammatory cytokines/chemokines, such as TNF-α, IL-1β, IL-6, and MCP-1, in many cell types, such as monocytes stimulated with phorbol-12-myristate-13-acetate (PMA) or phytohemagglutinin (PHA) [44], human activated astrocytes [45], human synovial cells [46], the human cellular line of activate mast cells, CMH-1 stimulated with calcium ionophore A23187 (PMACI) [47], fibroblasts of nasal mucosa, and bronchial epithelial cells A549 [48].

These studies sustain the fact that polyphenols have the capacity to modulate the immune answer through their anti-inflammatory potential [49]. However, the effects on the balance between the pro-inflammatory and anti-inflammatory cytokines have proven to be specific depending on the chemical structure of polyphenols [42]. The anti-inflammatory mechanism of quercetin consists in the inhibition of the expression of pro-inflammatory cytokines in the mast cell and in suppression of TNF-α [50].

2.2.3.5. The modulation of NFkB-dependent signaling pathways

From their discovery the transcription factors NFkB/Rel are considered responsible for chronic and acute inflammatory diseases. NFkB plays an essential role in the trigger of the inflammatory, stress, proliferative, and apoptotic responses [51]. NFkB coordinates the induction of a wide area of genes which encode the pro-inflammatory cytokines (IL-1, IL-2, IL-6, and TNF-α); chemokines (MIP-1α and MCP-1); cellular adhesion molecules (ICAM, VCAM, E-selectin); acute phase proteins; immune receptors; growth factors; inducible enzymes such as the growth factor of vascular endothelium (VEGF), COX-2, matrix metalloproteinase (MMP), and iNOS; and all the molecules involved in inflammation, cellular proliferation, cellular adhesion, migration, and invasion [52]. The inhibition of NFkB is generally considered a useful strategy in the treatment of inflammatory disturbances [51], this pathway being an important and attractive therapeutic target. It was observed that plant polyphenols can act as modulators of transduction pathways of the signal to trigger their beneficial effects [53]. The NFkB/Rel family is formed by five members: p65 (RelA), RelB, c-Rel, p50/p105 (NFκB1), and p52/p100 (NFκB2), these being DNA-binding proteins which recognize a common sequence [54]. In unstimulated cells, NFkB is sequestered in the cytoplasm in inactive form [55]. Polyphenols have proven to present an anti-inflammatory activity by modulating the NFkB activity. Through the influence of (−)-epigallocatechin galat polyphenolic component on the NFkB pathway, the inhibitory effect of this compound was demonstrated by counteracting IKK activation and IκBα degradation [42].

Flavonoids present the capacity to modulate the activation cascade of NFkB [56]. In RAW 264.7 cells activated with IFNγ, quercetin, tirozol, and lycopene have inhibited the iNOS, COX-2 expression, and pro-inflammatory genes, by the prevention of nuclear translocation of the subunits p50 and p65 of NFkB, STAT-1α, and IRF-1. These results suggest that lycopene, quercetin, and tirozol can be potential nontoxic agents in the control of bowel inflammation in the celiac disease trough the prevention of the activation of the signaling pathway of transduction [57]. The beneficial anti-inflammatory effects exhibited by quercetin, in vitro and in vivo, seem to be due to the inhibition of the phosphorylation protein IκBα, which, through the blocking of the NFkN pathway, leads to the counteraction of the cytokine expression and the induction of oxide nitric synthesis [44]. In a similar way, in the human mast cell line, quercetin has led to the decrease in the pro-inflammatory cytokine expression (TNF-α, IL-1β, IL-6) and anti-inflammatory cytokine expression (IL-8) through the degradation of IκBα and nuclear translocation of p65, blocking the activation of NFkB [47].

2.3. Propolis

Propolis, the so-called bee glue, is a natural product of double origin: vegetal and animal. Thus, the bees elaborate this product by adding glandular secretions and wax to the resinous

substances collected from different species of plants. Besides its mechanical purpose (sealing the holes and cracks, limiting the entry in the hive, reparations of the honeycombs), propolis has an antiseptic role in the hive's microclimate, being a real "chemical weapon" against the microorganisms [58, 59].

Since ancient times, propolis has been used in folk medicine, being one of the most efficient natural remedies. The active pharmacological compounds from propolis are present in variable quantities depending on the propolis sample, the way of dosing, and the nature of the extraction method [60]. The ratio of the organic compounds in propolis is very important for determining the biological effects [59]. The main constituents of propolis are phenolic compounds (flavonoids, phenolic acids, and their esters), aromatic acids, aliphatic acids and their esters, terpenoids, and bioactive compounds responsible for the biologic effect of propolis [61]. Flavonoids are considered to be responsible for the main therapeutic actions of propolis. It has been proven that the anti-infectious effects of propolis are different depending on the geographic area, botanical origin, and microbial species on which they act. Besides the therapeutic efficiency manifested in different diseases, propolis exercises also an immunomodulating action with an important role on the stimulation of the organism's capacity of defense. On an international level, the studies performed in some well-known pharmacology and medicine laboratories have confirmed the special role that this product plays for the human organism in the prophylaxis and the treatment of a wide variety of afflictions. In the natural state or in the extracted form, tinctures, and different pharmaceutical forms, propolis represents at this time one of the most important points of interest for the study and work of apitherapy. The international research has demonstrated that at the associated use with some antibiotics, the efficacy and length of action of the propolis extract are stressed and the studied microorganisms do not develop resistance to antibiotics. Due to the multiple chemical components, propolis is considered the most valuable bee product, with a wide variety of therapeutic actions: bactericidal, antiseptic, antiparasitic, antiviral, antioxidant, wound healing, anti-inflammatory, analgesic, antitumoral, regenerative, and immunomodulatory [62].

Many plants or plant-derived compounds with high levels of antioxidant properties also manifest wound-healing benefits. There are several studies that document the use of plant extracts in the development of bioactive wound dressings.

3. Plant extracts used in wound management

3.1. Essential oils

Oil extracts are widely used in skin care and treatment. A couple of oil extracts have proven antibacterial activities: oleo-gum-resin of *Commiphora guidotti* Chiov. ex. Guid. [63]; *Copaifera officinalis* and *Pentaclethra macroloba* [64], and the oily extract of *Rosa damascena* petals in combination with aqueous extracts of *Malva sylvestris* and *Solanum nigrum* leaves [65] (against *Staphylococcus aureus*). *Calophyllum inophyllum* L showed antibacterial activity against gram-positive bacteria by direct inhibition of mitotic growth and against gram-negative bacteria due to increased release of β-defensin 2 peptide by macrophages [66]. Moreover, the two Amazonian plants,

Copaifera officinalis and *Pentaclethra macroloba*, have proved well-documented anti-inflammatory, antimicrobial, emollient, moisturizing, and wound-healing activities [64]. An extracted oil from pumpkin seeds (*Cucurbita pepo* L.) can be a promising drug for healing wounds in animal studies (uniform wounds induced on the dorsum of rats) due to a high content of polyunsaturated fatty acids (linoleic acid, 50.88 ± 0.106 g/100 g of total fatty acids), tocopherols (280 ppm), and sterols (2086.5 ± 19.092 ppm) [67]. Several oil extracts have been successfully tried in burn wound models in rats. A poly-herbal cream containing aqueous extracts of *Malva sylvestris* and *Solanum nigrum* leaves and oily extracts of *Rosa damascena* petals, retrieved from Iranian traditional medicine, showed desirable reepithelialization with remarkable neovascularization with less inflammatory cells [65]. The oil extracted from the seeds of *Calophyllum inophyllum* L. (Calophyllaceae), an evergreen tree ethnomedically used along the seashores and islands of the Indian and Pacific Oceans, especially in Polynesia is traditionally used topically to treat a wide range of skin injuries from burn, scar, and infected wounds. The human keratinocyte cells were used to test the safety profile and wound-healing properties of the *Calophyllum inophyllum* L and proved efficient and safe in wound healing [66]. The oil extract (BBO) obtained from *Blumea balsamifera* (L.) DC (ainaxiang) was tested in deep second-degree burn model in rats. The plasma levels of interleukin-1 (IL-1) and tumor necrosis factor-alpha (TNF-α) decreased, but the tissue expressions of basic fibroblast growth factor (bFGF), vascular endothelial growth factor (VEGF), and transforming growth factor-beta (TGF-β) increased, so the healing accelerated after treatment with BBO in the burn injury rats [68].

3.2. *Calendula officinalis*

Marigold (*Calendula officinalis*) is an annual culture plant species, part of the daisy family (Asteraceae), rarely biannual, 40–80 cm tall, with a powerful balsamic scent [69, 70].

The *Calendula officinalis* extract contains different classes of compounds, such as triterpenoids, flavonoids, coumarins, quinones, volatile oil, carotenoids, and amino acids [71], but the active compound consists mainly of carotenoids (carotene, lycopene, flavoxanthin, lutein, and rubixanthin) and faradiol [72].

It is widely used in Romania as a universal, wonder cream. Many patients use it for its anti-inflammatory, anticancer, antibacterial, antifungal, antiviral, and wound-healing activity [71, 73, 74]. It is used in clinical applications such as wounds, leg ulcers, first-degree burns, contusions, and skin rashes (acute dermatitis during breast cancer treatment) [71, 75].

A study tried to link the angiogenic activity of *Calendula officinalis* L. grown in Brazil to the expression of VEGF but without success and suggested that maybe it is due to other pro-angiogenic factors (fibroblast growth factors (FGF) or angiogenic cytokines (interleukin-8 (IL-8), tumor necrosis factor-alpha (TNF-α), and transforming growth factor-β (TGF-β)) [76].

Studies on effects of *C. officinalis* tincture (CDOT) on cell viability and wound closure proved that it stimulated both proliferation and migration of fibroblasts in a statistically significant manner; in a PI3K-dependent pathway, the identified compounds are likely to be responsible for wound-healing activity [71]. Additionally, homeopathic preparations composed of *Arnica montana*, *C. officinalis*, *H. perforatum*, and *Symphytum officinale* have been shown to promote proliferation and migration of NIH-3T3 fibroblast cells [71].

Another preparation using marigold was designed for treating chronic ocular surface diseases. A formulation consisting of solid lipid nanoparticles (SLN), long-chain fatty acids (palmitic acid, stearic acid, or arachidic acid), Epikuron 200 (purified phosphatidylcholine), and bile salts (cholate, taurocholate, or taurodeoxycholate) has been prepared by dilution of a microemulsion. Then it was loaded with *Calendula officinalis* extract. Calendula-loaded SLN were nontoxic, with a good stability and a good lyophilization profile, probably useful for prolonged storage conditions [72].

3.3. Aloe vera

Aloe vera is a cactus-like plant [77] that belongs to Liliaceae family [78], originated in South Africa [79]. It has been shown to have benefits when used to accelerate wound healing [78].

There have been more than 75 active ingredients including aloesin, aloe emodin, acemannan, aloeride, methylchromones, flavonoids, saponin, amino acids, vitamins, and minerals [80].

The whole gel extract of aloe vera has been reported to promote wound, burn, and frost-bite healing, in addition to having anti-inflammatory, strong immunomodulatory and large spectrum antibacterial (*Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Salmonella typhi*, *S. pyogenes*, *S. mutans*, *A. actinomycetemcomitans*, *P. gingivalis*, *B. fragilis*, *Enterococcus bovis*, *A. hydrophila*, *Salmonella paratyphi*, *Bacillus subtilis*, *H. pylori*), antifungal (*Candida parapsilosis*, *Candida krusei*, *Candida albicans*), antiviral (herpes simplex virus type 2 strain, encephalomyocarditis virus, influenza A) activity, hypoglycemic, hepatoprotective effect, gastroprotective properties, laxative effects, antihyperlipidemic activity, and anti-aging effect [79, 81, 82]. Its healing property is related to a compound that is called glucomannan [78]. The mannose-6-phosphate increases wound contraction and collagen synthesis [79]. β-Sitosterol (found in aloe vera mucilage) increases angiogenesis and promotes a better healing of traumatic tissues by increasing the rate of genetic expression of VEGF and its receptor in the wound tissue [78]. The known targets and effects of available topical treatments in the processes of wound healing, skin scarring, and abnormal raised dermal scarring such as keloid and hypertrophic scarring are soothing/anti-inflammatory effect, hydration and moisturisation, and improved skin/scar condition [83].

In 1990 the efficacy of aloe vera saturated polyethylene oxide (PEO) dressings for treating full-face dermabrasion wounds was proven [81]. An amorphous hydrogel dressing derived from the aloe plant (Carrasyn Gel Wound Dressing, Carrington Laboratories, Inc., Irving, TX) has been approved by the Food and Drug Administration for the management of Stages I through IV pressure ulcers being as effective as a moist saline gauze wound dressing [84]. A couple of studies performed by Silva et al. included sodium alginate/polyvinyl alcohol films loaded with aloe vera and vitamin E, capable of enhancing healing in burn wounds [81], and blended membranes composed of chitosan (CTS) and aloe vera gel, cross-linked with genipin to improve their properties (in vitro cell culture studies evidenced that the L929 cells have high cell viability) [85]. Another study on mice with burn wounds demonstrated the healing properties of aloe emodin in combination with resveratrol, without a cytotoxic to THP-1 macrophages [86]. Moreover a dressing film comprising 1.95 % w/v fibroin and 0.05 % w/v aloe gel [87] and an aloe vera-olive oil combination cream may find application in treatment of diabetic nonhealing skin ulcers [88]. Another bioactive dressing was designed using collagen-chitosan scaffolds supplemented with aloe vera [81].

3.4. Curcumin

Curcumin, a natural yellow phenolic antioxidant compound, is present in many kinds of herbs, particularly in *Curcuma longa* Linn. (turmeric), the main curcuminoid present in turmeric [89, 90].

It contains methoxy groups and phenols, which are responsible for its biological and pharmacological properties, being shown to possess significant anti-inflammatory, antioxidant, anticarcinogenic, anti-mutagenic, anticoagulant, and anti-infective effects [89, 91]. Curcumin has hepatoprotective, nephroprotective, cardioprotective, neuroprotective, anticancer, hypoglycemic, antirheumatic, and antidiabetic activities, and it also suppresses thrombosis and protects against myocardial infarction and treats many diseases including cough, rheumatism, diabetes, biliary disorders, anorexia, sinusitis, hepatic disorders, cancer, and Alzheimer disease [90, 92].

Curcumin has been used for wound healing [89] because of the anti-inflammatory activity due to the inhibition of TNF-α, COX-2, STAT, cyclin D1, NFkB signaling pathways; IL-1b, IL-8, IL-6 expressions; downregulation of the expression of MMP-8, and acute phase proteins [93]. Also the wound-healing potential of curcumin is attributed to its anti-infectious and antioxidant properties [89]. Curcumin is involved in tissue remodeling, granulation tissue formation, and collagen deposition and increases fibroblast proliferation and vascular density [89].

Moreover two new synthetic analogs of curcumin (C66 and B06) proved to reduce TNF-α and NO production; downregulated mRNA levels of IL-1b, TNF-k, IL-6, IL-12, COX-2, as well as iNOS; and prevented activation of JNK/NFkB signaling in high glucose stimulated primary peritoneal macrophages [93].

The antibacterial activity of curcumin is due to its action against the bacterial membrane [94]. Curcumin inhibited the growth of periodontopathic bacteria *P. gingivalis*, *Prevotella intermedia*, *Fusobacterium nucleatum*, *Treponema denticola* [95], foodborne bacteria *Bacillus cereus* and *Escherichia coli* [96], methicillin-resistant *Staphylococcus aureus* (*MRSA*) [97], *Enterococcus faecalis*, *Bacillus subtilis*, *Streptococcus mutants*, and *Pseudomonas aeruginosa* [94].

Curcumin has been used in different nanoformulations used to increased solubilization of curcumin but at the same time protect curcumin against inactivation by hydrolysis: liposomes, polymeric nanoparticles, polymeric micelles, conjugates, peptide/protein carriers, cyclodextrins, solid dispersions, etc. However, most nanoformulations are administered parenterally [90].

The compound glucosyl-THC increased the epithelialization and granulation tissue formation, with nonstaining, nontoxic, nonirritant, and non-skin-sensitive side effects. Thus the synthesized glucosyl-THC may act as a promising therapeutic agent in the future, in the management of excision wounds, and in cosmetic applications [98].

Curcumin has demonstrated its efficacy for healing of diabetic wound in a work that used curcumin (Cur)-loaded poly(-caprolactone) (PCL)/gum tragacanth (GT) scaffold membranes fabricated by electrospinning. The scaffold membranes obtained a controlled release of curcumin for over 20 days [92]. Another design implied chitosan (CTS)/chondroitin sulfate (CS)

nanoparticles, both pure and curcumin-loaded, synthesized by ionic gelation, investigated as a way to reduce the viability of human lung tumor cells [91].

To enhance the properties of curcumin, it has been combined with ginger, and the two were dissolved in dimethyl sulfoxide. A 500 μl of solutions containing 10 % curcumin, 3 % ginger extract, and topical dermatocorticoid were used as pretreatment on hairless rats. The pretreatment improved healing of subsequently induced abrasion skin wound-treated rats, maybe because the ginger extract increases vascularity and blood flow in the repairing tissue, while curcumin acts on matrix remodeling. Still, we should not overlook the anti-inflammatory properties of dermatocorticosteroids [99].

On the other hand, a cellular biomechanics approach where automated quantitative wound-healing assays were used did not identify significant effects of curcumin, aloe vera, and ginger on en-mass migration kinematics of fibroblasts in damaged cultures [100].

3.5. Other plant species used in wound healing

Many Brazilian plants have proven efficient in wound healing. *Struthanthus vulgaris*, *H. speciosa* leaves Gomes (Apocynaceae), *Casearia sylvestris* Sw. (popularly known as guaçatonga), *Achyrocline satureioid*es DC Lam., *Matricaria recutita* L., *Melia azedarach* L., and *Mirabilis jalapa* L. are the most recently evaluated, usually on fibroblasts, keratinocytes, and rats. The aqueous extracts from these plants demonstrated the ability to stimulate keratinocytes' growth up and also fibroblast proliferation resulting in a positive cell proliferation [101]. In an experimental wound model in rats, *Struthanthus vulgaris*, in a 5 % ointment, was capable of modulating the release of pro- and anti-inflammatory cytokines (IL-1α, TNF-α and IL-10, nitric oxide, and growth factors such as TGF-β), improving the quality of the scar tissue [102]. Also the ethanolic extract of *H. speciosa* leaves Gomes (Apocynaceae) demonstrated its effects on the release of the pro-inflammatory cytokine tumor necrosis factor (TNF-α) by lipopolysaccharide (LPS)-stimulated human acute monocytic (THP-1) cells. Moreover, *H. speciosa* showed an increase cell migration and proliferation of fibroblasts compared with control cells, as well as a reduced TNF-α release by LPS-stimulated THP-1 cells. All together, the results indicate that it can be used to treat wounds and inflammatory disorders [103]. Another hydroalcoholic extract of *Casearia sylvestris* Sw. showed benefits in the treatment of inflammatory conditions, in second-degree scald burn injuries, and in an experimental wound model, most likely due to its analgesic, antiseptic, and anti-inflammatory activities [104].

Traditional Turkish medicine has many important plants used to treat ulcers, burns, and wounds. *Hypericum perforatum* (HP) (St. John's Wort-Kantaron), widely for the treatment of burn injuries for many years in traditional Turkish medicine, was compared with silver sulfadiazine (SS) in the treatment of second-degree thermal burn created on the dorsal sites of rats. The measures of epidermal thickness and number of vessels demonstrated that HP administered four times a day within the first 24 h is clearly effective in wound healing in the experimental thermal second-degree burn and is significantly superior to SS treatment [105]. The roots and root barks of *Echium* sp. (*E. italicum* L, *E. vulgare* L., and *E. angustifolium*) have been also used to treat ulcers, burns, and wounds in traditional Turkish medicine. Thus an experimental study using ethanol root extract of *Echium* sp. on linear incision experimental

models showed remarkable wound-healing activity [106]. Three species—*A. coarctata* Poir. (AC), *A. kotschyi* Boiss. subsp. *kotschyi* (AK), and *A. lycaonica* Boiss. and Heldr. (AL) (genus *Achillea* L.)—were evaluated for their phenolic compositions, total phenolic contents, antioxidant properties, wound-healing potencies on NIH-3T3 fibroblasts, and cytotoxic effects on MCF-7 human breast cancer cells. AK was the most valuable source of flavonoids and chlorogenic acid with important antioxidant, wound-healing, and cytotoxic activities [107].

Various plant parts including leaves, fruits, stem bark, and root extracts of 61 African medicinal plants belonging to 36 families were reported to have scientifically demonstrated wound-healing properties [108]. Widely used in Ethiopia for treatment of wound, *Rumex abyssinicus* Jacq (Polygonaceae) has been evaluated as ointment (an extraction of the rhizomes of the plant with 80 % methanol) on an excision model in mice. The hydroalcoholic extract increased wound contraction, shortened the epithelization time, increased the hydroxyproline content, and also reduced the inflammation [109]. A hydroalcoholic leaf extract of *Combretum mucronatum*, a medicinal plant widely used in West African traditional medicine, proved beneficial effects for wound-healing and anthelmintic activity [110].

A herbal ointment containing 10 % *Salvadora persica* extract was compared with Solcoseryl jelly 10 % and blank Vaseline using excision wound-healing model in animals. The 10 % *Salvadora persica* extract and 10 % Solcoseryl jelly showed superiority in the acceleration rate of wound enclosure in rats [111].

The ethanolic extract of the bark of *Calotropis procera* was evaluated for the antioxidant potential and the wound-healing effect using excision and incision wound on normal and dexamethasone-suppressed wound-healing rodent models. It revealed a potential wound-healing agent due to improved collagen deposition and reduced inflammatory reaction [112, 113].

Moringa oleifera (MO), another herb used as a traditional folk medicine for the management of wound healing and associated conditions, has proven its efficacy by promoting fibroblast proliferation and migration through increasing the wound closure rate corroborating its traditional use [114].

Polygonum aviculare L. with ingredients such as quercitrin hydrate, caffeic acid, and rutin has been known for its antioxidant and anti-obesity effects. Moreover it accelerated the motility of HaCaT keratinocytes with the activation of Wnt/β-catenin signaling, without showing significant leading to efficiently reepithelized wounds generated on mice [115].

An extract of the leaves of *Porophyllum ruderale* and laser irradiation on the healing of burns were effective in decreasing the granulocytes during the repair process indicating a possible anti-inflammatory action of this extract of native flora [116].

Allium ascalonicum Linn., commonly called shallot, have been reported to be beneficial in wound healing due to its antibacterial (inhibiting the gram-positive *Staphylococcus epidermidis* and *Bacillus subtilis* ATCC 6633 strains) and antioxidant properties [117] on wound models in rats.

Ampelopsis radix has been used as a traditional Korean medicine for the treatment of burns and scalds. The healing effect of *A. japonica* root tuber ethanol extract (AJE) was shown on

induced cutaneous scald injury in Sprague Dawley (SD) rats, by decreasing the TNF-α and TGF-β1 levels and increasing the IL-10 levels [118].

The methanol extract of *Rubus ellipticus* leaves showed antioxidant activity and antitumor and wound-healing properties in incision, excision, and *Staphylococcus aureus*-induced-infected wound models and mice with Ehrlich ascites carcinoma [119].

A 10 % gel of unripe banana (*Musa sapientum*) peel used in treating surgical wounds in rats proved anti-inflammatory activity (the presence of mononuclear cells and the decreased presence of polymorphonuclear cells), fibroblast proliferation, so stimulated wound healing [120].

Broken rice maltodextrin showed better functionality properties than other maltodextrin sources with a beneficial role in wound healing due to its ability to proliferate the NIH 3T3 fibroblast-wounded cells without causing cytotoxic effect [121].

3.6. Propolis

Well known from ancient times as a remedy for disease, propolis is a complex resinous mixture collected by bees from exudates of plants, with high medicinal value [122, 123].

There are three possible sources for the organic compounds of propolis: plants, secreted substances from honeybee metabolism, and materials that are introduced during propolis formation [122].

Propolis is found in many parts of the world (Europe, North America, New Zealand, and temperate zones of Asia, Brazil (green and red propolis), Russia, Cuba, Venezuela, etc.). Based on physicochemical properties such as color, texture, chemical composition, and geographic origin, Brazilian propolis is classified into 13 types [123].

Propolis contains more than 180 separate compounds (typically 50 % resin and vegetable balsam, 30 % wax, 10 % essential and aromatic oils, 5 % pollen, and 5% other substances), and while its ingredients differ based on plants in different geographic regions accessed by propolis-making bees, the main active components are thought to be present in all forms of propolis [122, 124]. Although caffeic acid phenethyl ester (CAPE) and flavonoids are characteristic constituents of poplar-type propolis, the typical constituents of Brazilian green propolis (from *Baccharis dracunculifolia*) are caffeoylquinic and prenylated cinnamic acids, such as artepillin C and baccharin [125]. Since the content of flavonoid found in the red propolis extracts was higher than that observed in the green ones [126].

Propolis has antioxidant and anti-inflammatory activity. The flavonoids and caffeic acid phenyl ester (CAPE) concentrated in propolis are powerful antioxidants [127] increasing the cellular immune response through the increase of mRNA synthesis for interferon-γ, activation of the production of other cytokines [128], and scavenging free radicals [125]. The anti-inflammatory activity has been attributed to the presence of active flavonoids (acacetin, quercetin, and naringenin) and cinnamic acid derivatives (caffeic acid phenyl ester (CAPE) and caffeic acid (CA)).CAPE and galangin, both being typical poplar propolis constituents,

exhibited anti-inflammatory activity and significantly inhibited carrageenan oedema, carrageenan pleurisy, and adjuvant arthritis inflammations in rats. Dietary propolis significantly suppressed the lipoxygenase pathway of arachidonic acid metabolism during inflammation in vivo. CAPE was a more potent modulator of arachidonic acid metabolism than caffeic acid, quercetin, and naringenin [128]. CAPE, a polyphenolic compound, with cytoprotective activities and protective effects enhanced the closure of diabetic wounds and decreased the levels of IL-1β, IL-6, TNF-α, and MMP9 [124, 127]. A study on diabetic mice with leg wounds showed that the protease MMP-9 in wound fluid has importance as a marker of foot ulcer healing in diabetes. High levels of active MMP-9 correlates with poor wound healing [124]. Propolis significantly enhanced the production of collagen via the TGF-β1/Smad 2,3 signaling axis in wounded tissues [129]. Brazilian green propolis (from *Baccharis dracunculifolia*) can suppress an important inflammatory component (cell influx) and reduces the vascular permeability, angiogenesis without compromising the repair process by reducing fibrosis and increasing the pro-inflammatory markers and cytokine (TNF-α) involved in fibrinolytic activity [125, 130]. Moreover, propolis has been used in combination with honey in a synergistic effect for wound healing [131], maybe due to the honey's hydrogen peroxide, high osmolality, acidity, non-peroxide factors, nitric oxide, and phenols [132].

The mechanism of antimicrobial activity of propolis is complex and could be attributed to the synergistic activity between phenolic and other compounds, mainly to the flavonoids, pinocembrin, galangin, and pinobanksin pinocembrin, pinobanksin, p-coumaric acid benzylester, and caffeic acid phenethyl ester (CAPE) [126, 128].

Many studies showed the antibacterial activity of propolis on *Staphylococcus aureus* [133], *Staphylococcus epidermidis*, *Micrococcus glutamicus*, *Bacillus subtilis*, *Pseudomonas aeruginosa*, *Streptococcus pyogenes*, *Streptococcus mutans*, *Sarcina lutea*, *Escherichia coli*, *Salmonella typhi*, *Listeria monocytogenes*, *Helicobacter pylori*, *Streptococcus pyogenes*, *Salmonella* sp., *Mycobacterium tuberculosis*, *Mycobacterium avium*, *Klebsiella pneumoniae*, *Enterobacter aerogenes*, *Moraxella catarrhalis*, *Haemophilus influenzae*, *Neisseria meningitides*, *Enterococcus* spp., and *Bacillus cereus* [134, 135]. Bee propolis in combination with chlorhexidine possesses high antimicrobial activity against *Streptococcus mutans*. Propolis in combination with chlorhexidine can suppress the pathogenic potentials of a dental plaque by inhibiting the adherence and accumulation of cariogenic streptococci on the tooth surface.

Propolis has shown fungicidal effects on *Candida albicans*; *C. tropicalis*; *C. glabrata*; *C. famata*; *C.kefyr*; *C. pelliculosa*; *C. parapsilosis*; *C. guilliermondii*; *C. lusitaniae*; *C. stellatoidea*; *Cladosporium cladosporioides*; *C. sphaerospermum* [58]; *Pichia ohmeri*; *Trichosporon* sp. including *T. asahii*, *T. ovoides*, and *T. cutaneum*; *Geotrichum candidum*; *Saccharomyces cerevisiae*; *Rhodotorula* sp. [128]; and *Aspergillus niger* [58].The fungicidal effect was associated with the presence of flavonoids. Propolis microparticles from Brazilian propolis have shown their positive effect in the treatment of vulvovaginal candidiasis [128].

Antiprotozoal activity has been documented in the following diseases in humans and animals such as trichomoniasis (*Trichomonas vaginalis*), toxoplasmosis (*Toxoplasma gondii*), giardiasis

(*Giardia lamblia*), Chagas' disease (*Trypanosoma cruzi*), leishmaniasis (*Leishmania donovani*), and malaria (*P. falciparum*, *P. vivax*, *P. ovale*, *and P. malariae*) [128].

3.7. Side effects associated with the use of plant compound in wound management

The immune system is involved in skin allergies induced by plants. There are two different contact reactions mediated by the immune system in individuals sensitized to plants or plant products: immediate (type I) or delayed hypersensitivity contact reactions [136].

Aloe vera is frequently found in emollients, along with lanolin and parabens. It has been named a skin sensitizer because it may lead to a delayed hypersensitivity reaction [137].

Also curcumin is reported to have caused a few cases of contact allergy as a color agent in food or in disinfectants used prior to surgery [138].

The flower belonging to the family Compositae, including also *Calendula officinalis*, has induced many allergies in senior patients [139]. However, a study performed for a perfume made 100 % of *Calendula officinalis* did not influence the patch tests of patients allergic to the flower family Compositae [70]. On the other hand, specialists recommend to test additionally the creams containing *Calendula officinalis* because there have been patients that tested negative to Comp mix. (included in the standard patch test), but positive to the creams made with *Calendulaofficinalis* [139].

A few topical traditional Chinese medicaments have been involved in contact dermatitis: Saw Hong Choon skin ointment, Tjin Koo Lin, Tiger balm, Eagle brand oil, Green grass oil, White flower oil, Zhen Gu Shui, Tiger oil, and Wong Cheung Wah UI oil [140].

Regarding propolis allergic reactions, there have been reported with using red and green propolis. In green propolis, esters of aromatic acids, e.g., dimethyl allyl caffeic acid ester and flavonoids, e.g. tectochrysin, have been incriminated in producing contact dermatitis [126].

4. Conclusion

Many plants or plant-derived compounds with high levels of antioxidant properties and immunomodulatory and antimicrobial activity may have benefits in wound healing, being used for the design of bioactive wound dressings or topical formulations. However, the used methodology is inconsistent among different studies, and there is a lack of reports regarding the adverse effects of these plants, such as dermatitis. Therefore, in order to better exploit the huge reservoir of pharmacologically active plant-derived compounds and extracts, standardized methodology and clinical trials are necessary to give more concrete evidence supporting the use of traditional medicine in wound management.

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