Chapter 8

Plant-Derived Medicines with Potential Use in Wound Treatment

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Additional information is available at the end of the chapter

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Abstract

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

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

1. Introduction

The human body consists of several organs, of which the skin is the largest. The human skin plays an important role in the bodies defensive processes, since it represents the first line of defence [1]. Two other important roles of the skin that also contribute to the defensive mechanisms are regulation and sensation. All mentioned provide a crucial set of functions such as enable protection from mechanical impacts and pressure, restrict the influence of temperature changes, lower the potential impact of microorganisms, limit radiation effects and diminish the entrance of different chemicals. Other important skin functions include the regulation of body temperature (e.g. through sweat glands and hair), control over the peripheral circulation and fluid balance, and in the synthesis of vitamin D. Through its extensive nerve cell network, it enables detection and relaying of changes in the environment (e.g. heat/cold, touch and pain). Damage to these networks is called a neuropathy and impairs the sensation of the mentioned functions in the affected areas. The preservation of skin integrity is due to all mentioned functions crucial for maintaining a healthy body [2].

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

2. Mechanism of wound healing

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

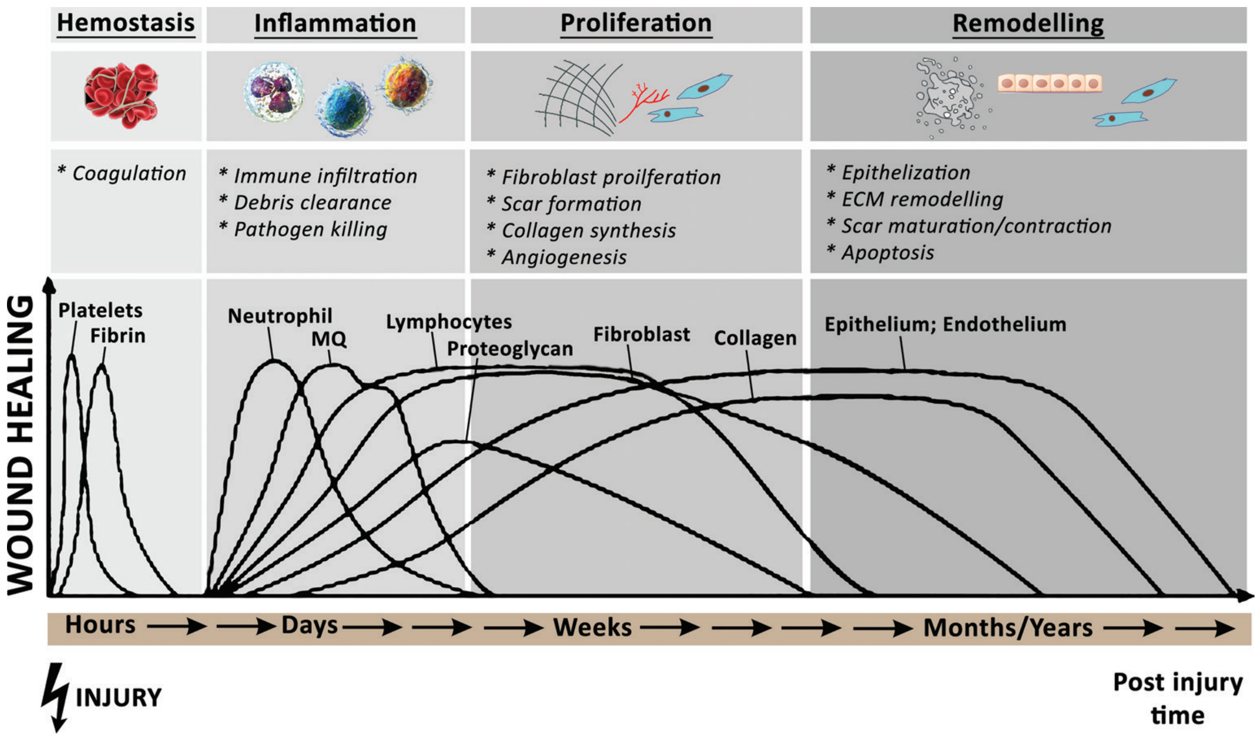

Figure 1. Schematic depiction of distinct phases during wound healing.

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

3. Wound healing management

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

Shortly after the injury, it is during the acute inflammatory response that different cytokines are formed. These are crucial for orchestration of the specific tissue growth, its repair, and hence regeneration [15]. Nevertheless, if this inflammation step persists, it can negatively affect the wound process, namely it leads to vicious cycle of ongoing inflammation, preventing the wound to reach the remodelling phase. If this happens, delays in wound closure occur, which are often accompanied with the increased sensation of pain in the wounded area and its surroundings that can additionally hinder the healing process [16]. Based on these findings about the wound healing physiology, a lot of research has focused on the development of therapeutic approaches that would provide an anti-inflammatory and pain relieving activity to wound dressings [17].

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

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

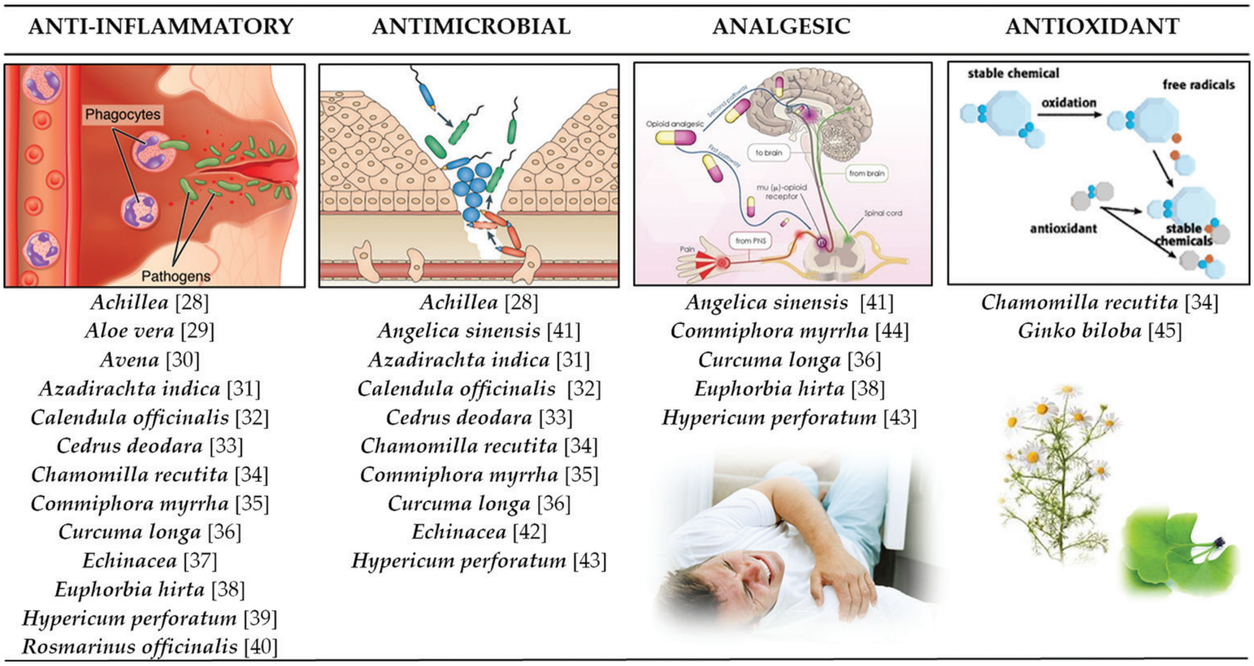

Figure 2. A diagram showing the most important beneficial properties that are desired in wound treatment (and some of the already known plants used in traditional medicine for this purpose). Anti-inflammatory: *Achillea* [28], *Aloe vera* [29], *Avena* [30], *Azadirachta indica* [31], *Calendula officinalis*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

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

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

4. Plants with potential use in wound healing

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

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

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

When we describe the beneficial effects of plant-derived molecules on human health, mostly it is the secondary plant metabolites, producing pharmacological and/or toxicological effects, that we are discussing [48]. Secondary metabolites are produced within the plants and are regarded as by-products of biochemical reactions in the plant cells. As such, these molecules are not part of any crucial daily functioning of the plant, hence are not important for the plants main biosynthetic and metabolic routes that yield products with major significance for the plant growth and/or development [50]. Although this means that these molecules are not key to the plants basic functions, this does not mean that they do not importantly contribute to the success of the plants overall survival in its ecosystem. For example, several of them play important roles in the living plants´ protection, attraction or signalling [51]. It seems that most plant species are capable of producing at least some of these compounds. But before we describe the most important groups of these secondary metabolites, let us first define the related term bioactive compounds. By definition, bioactive compounds in plants are compounds, produced by plants having pharmacological or toxicological effects in man and animals [52].

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

4.1.1. Phenolic compounds

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

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

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

4.1.1.1. Flavonoids

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

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

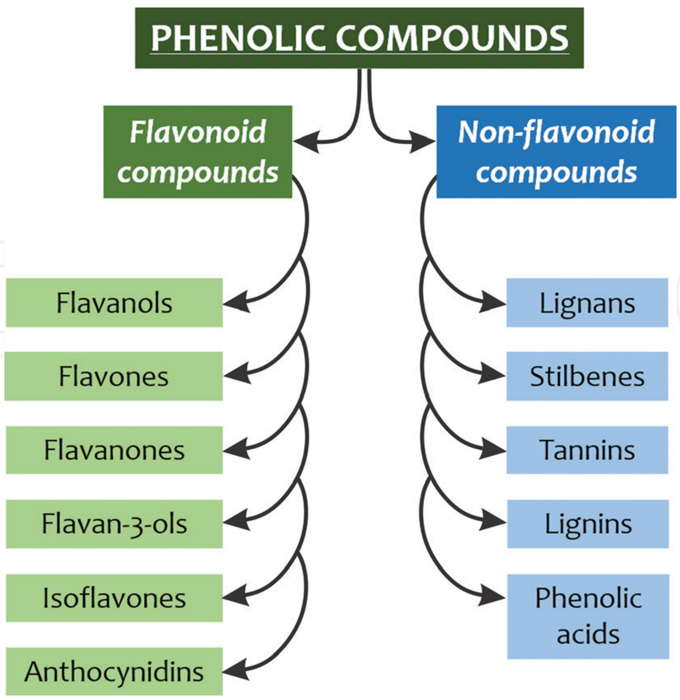


Figure 3. A diagram showing the classification of phenolic compounds.

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

4.1.1.2. Non-flavonoid polyphenols

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

4.1.2. Essential oils

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

4.1.2.1. Lavender oil

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

4.1.2.2. Chamomile oil

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

4.1.2.3. Tea tree oil

The tea tree (*Melaleuca alternifolia*) oil is an essential oil derived from the leaves of the tea tree that are used as a complementary therapy in Australia. The latter is mostly related to its known antiseptic, antibacterial, antifungal and anti-inflammatory activities [82]. Several studies report about its potential use in wound healing applications. Halcon and Milkus, for example, tested the tea tree oil as an antimicrobial agent in the case of *Staphylococcus aureus* infections [88]. Although this study was based only on a small clinical trial combined with case studies, the authors nevertheless showed the potential of the tea tree oil treatment of osteomyelitis and in chronic wound healing [88]. Another study was performed by Hammer et al., who investigated the effect of tea tree oil on transient and commensal skin flora *in vitro* [89]. They compared the effectiveness of different concentrations to induce bactericidal action and found the tea tree oil to be effective against *Staphylococcus aureus* and most Gram-negative bacteria (reduction to 0.25%), but was less effective against coagulase-negative staphylococci and micrococci (8%) [89]. Two groups of researchers tested also commercially available products based on tea tree extracts (including the essential oil). Sherry et al. claimed that the antimicrobial preparation from extracts of tea tree oil and eucalyptus showed an activity against methicillin-resistant *Staphylococcus aureus* (MRSA) [90]. Faoagali et al. evaluated the activity of another commercially available tea tree oil-based cream against different bacteria and confirmed its effectiveness against *Staphylococcus aureus* and *Escherichia coli* [91].

4.1.2.4. Thyme oil

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

4.1.2.5. Ocimum oil (basil)

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

4.1.2.6. Other oils

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

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

4.1.3. Other compounds with wound healing properties

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

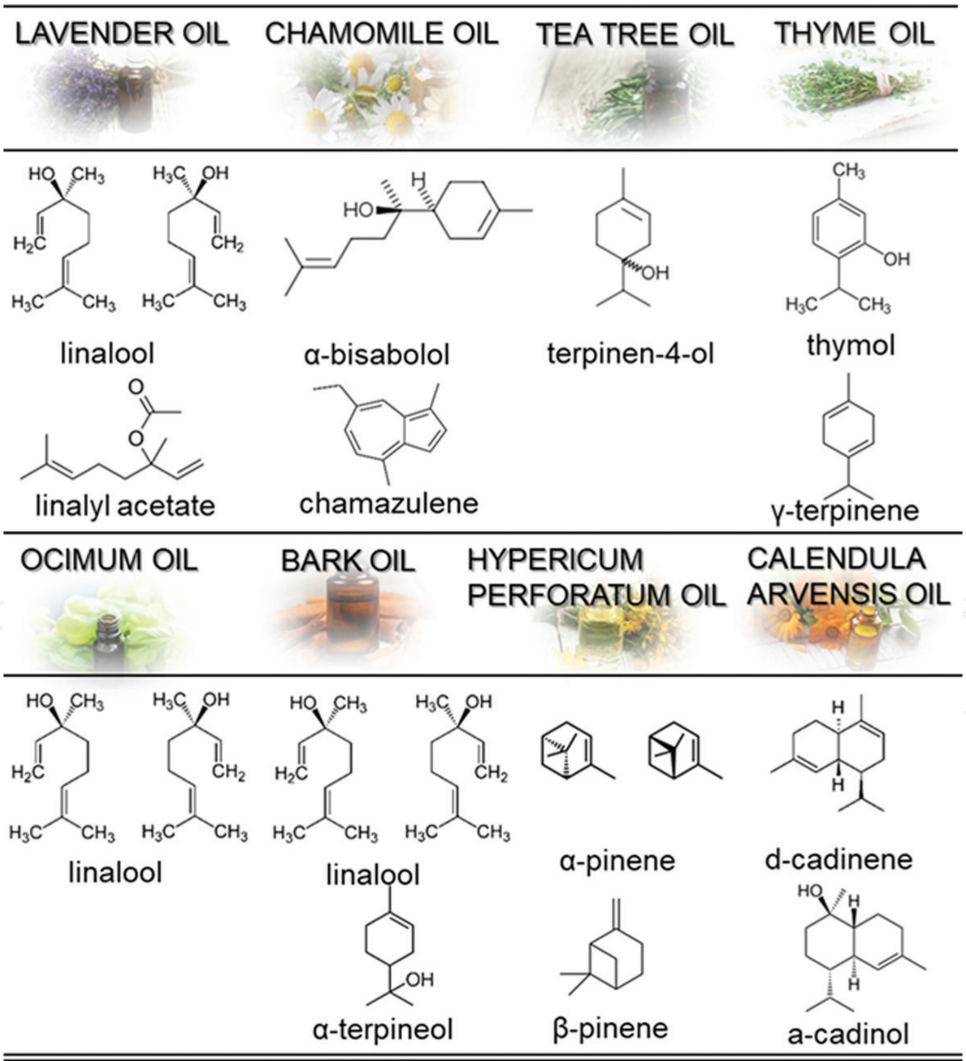


Figure 4. An overview of chemical structures of the above mentioned essential oils.

4.1.3.1. Alkaloids

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

4.1.3.2. Resins

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

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

4.1.3.3. Compounds with antimicrobial activity

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

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

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

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

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

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

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

Aloe vera (Family: *Liliaceae)*. *Aloe vera* has been used for medicinal purposes in several cultures for millennia: Greece, Egypt, India, Mexico, Japan and China [133]. 3500 years ago, Egyptians used this herb in treating burns, infections and parasites [134]. Its gel has the ability to heal different kinds of wounds including ulcers and burns by forming a protective coating on the affected areas and speeding up the healing process. Various constituents of *Aloe vera* stimulate wound healing and have anti-inflammatory activity [29].

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

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

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

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

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

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

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

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

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

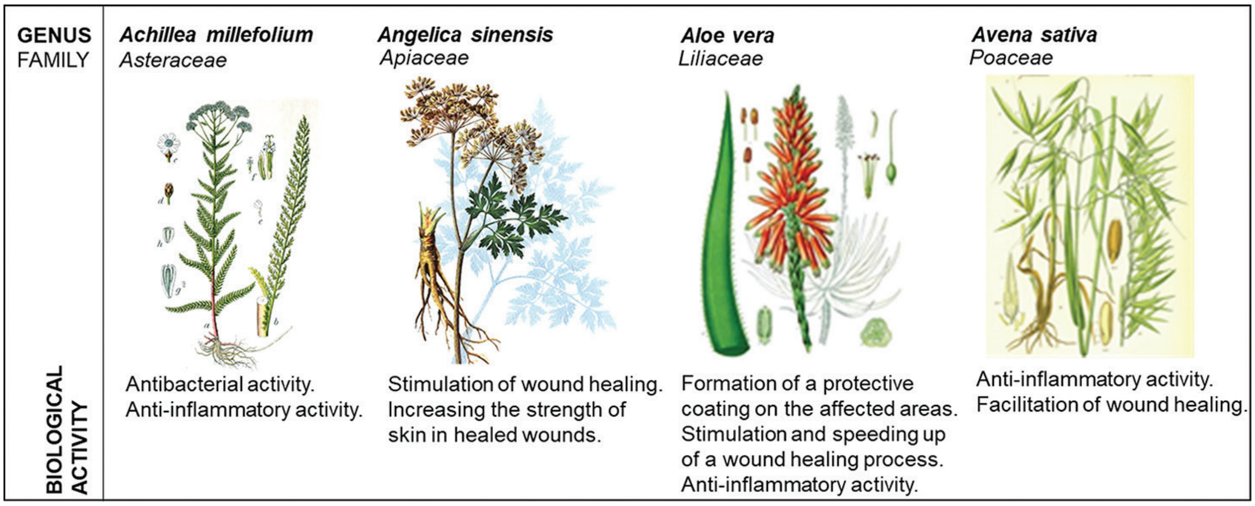
Curcuma longa (Family: *Zingiberaceae*). Turmeric possess anti-bacterial, anti-fungal, analgesic and anti-inflammatory activities [149]. Its anti-inflammatory properties, presence of vitamin A, as well as several proteins were shown to have a beneficial effect on the early formation of collagen fibres,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

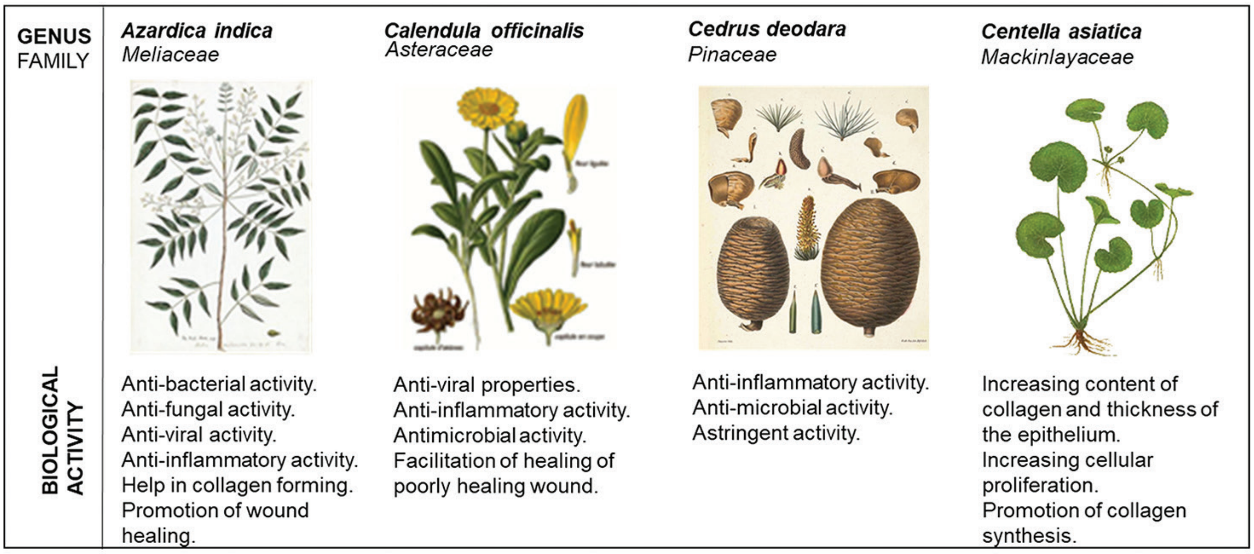
Echinacea (Family: *Asteraceae*). *Echinacea* species and various preparations thereof have one of the longest reported histories of use in the American people's medicine [150]. The most used species include *E. purpurea, E. angustifolia*, *E. palida*, *E. simulata* and *E. paradoxa* [151]. The documented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

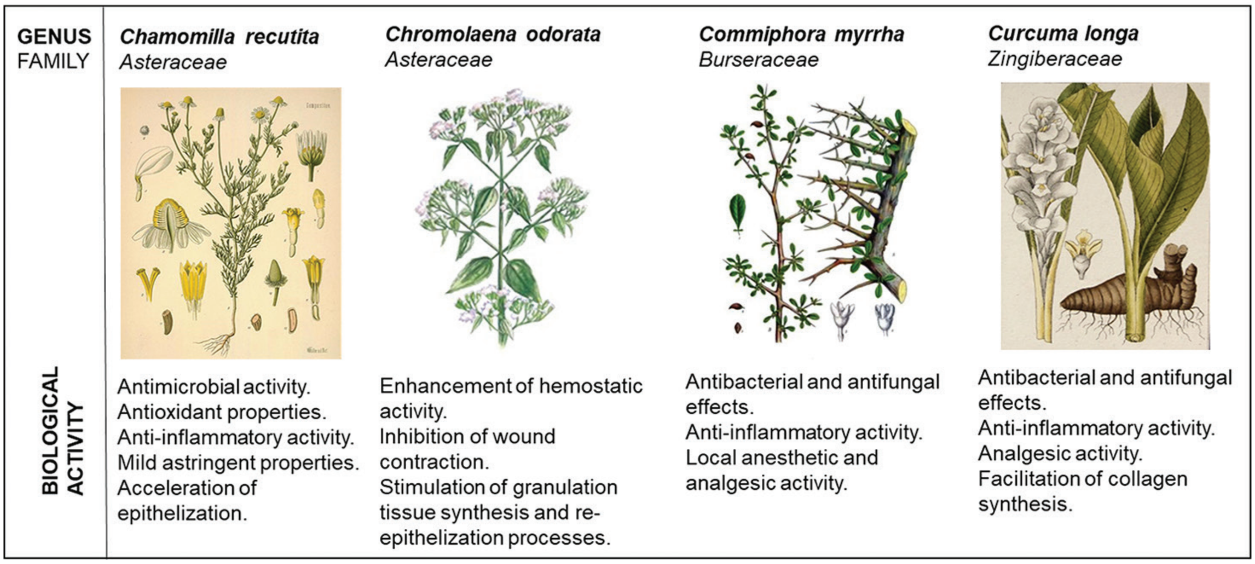
Euphorbia hirta (Family: *Euphorbiaceae*). The aqueous extract of the plant shows analgesic, anti-inflammatory activities and an inhibitory action on platelet aggregation. Ethanolic extract of the entire herb was found to possess significant wound healing activity [38].

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

Helianthus annuus (Family: *Asteraceae*). In traditional medicine, the sunflower herb is used by Indian tribes for treating inflammation of the eyes, sores, tiger bites, and to treat bone fractures [157]. The alcoholic extract of the whole plant of *Helianthus annuus* applied on the excised wounds of rats led to a significant reduction of the healing period which was indicated by earlier appearance and higher accumulation of mucopolysaccharides [158].







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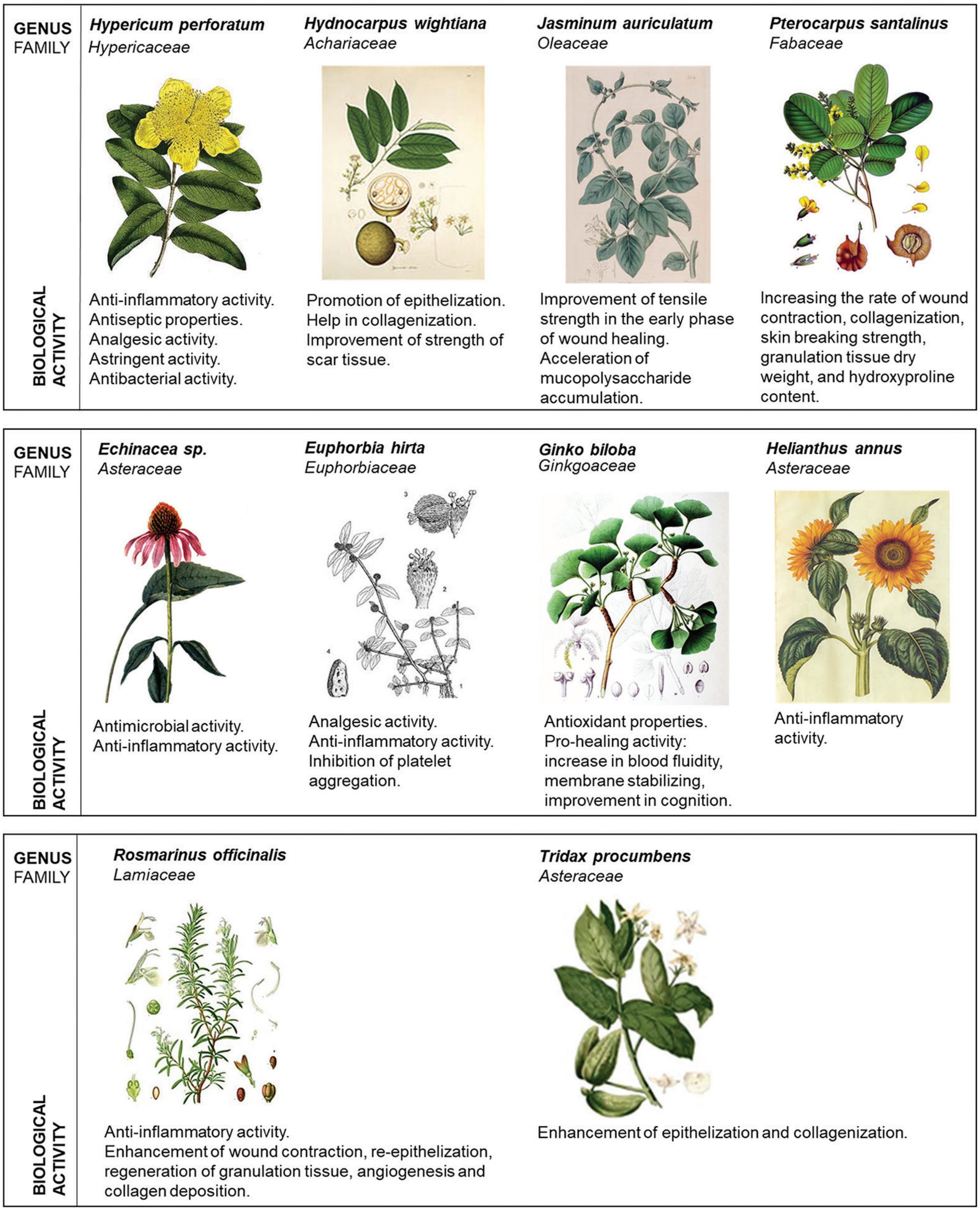

Figure 5. Overview of medical plants traditionally used in wound healing and their pharmacological activities (all plant images were obtained using the Google search engine with the enabled option for 'free use, share and modify').

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

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

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

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

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

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

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

6. Outlook and future development

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

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

7. Conclusions

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

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Conflict of interest

The authors declare no conflict of interest.

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