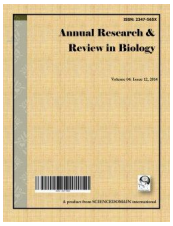

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Wound Healing: Contributions from Medicinal Plants and Their Phytoconstituents

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Author's contribution

The sole author designed, analyzed and interpreted and prepared the manuscript.

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ABSTRACT

Wound is an inescapable condition in one's lifetime that may arise due to physical injuries that can result in an opening or break of skin or chemical means. Wounds represent a significant burden on patients and can affect the physical and mental health of millions of patients thereby imposing a significant cost on them. Wounds are major cause of physical disabilities. The wound area is an ideal medium for the manipulation of many infecting organisms. The injured skin, therefore, remains vulnerable to invasive microbial infections. The primary objective of wound care, therefore, is to prevent or minimize infection and promote healing. Various materials and methods, especially antibacterial drugs are employed. Some of these wound care methods employed include the topical antimicrobial therapy of plant extracts. The present article, therefore, focuses on the review of the role medicinal plants play in wound healing with special attention on plants that have demonstrated both wound healing and antioxidant properties. Further attention was given to isolated compounds from wound healing plants that exhibited wound healing properties.

Keywords: Wounds healing; microbial infections; plants; antioxidants; phytoconstituents.

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1. INTRODUCTION

A wound comes through surgical operations or accidentally in our life and is inescapable and that may arise due to physical injuries that result in an opening or break of skin or chemical means [1]. The wound is defined as a disruption of cellular, anatomical, and functional continuity of a living tissue. Wounds are the result of injuries to the skin that disrupt the soft tissue. It may be produced by the physical, chemical, thermal, microbial, or immunological insult to the tissue.

Wounds represent a significant burden on the patients and healthcare professionals worldwide. Wounds affect the physical and mental health of millions of patients and impose a significant cost on patients. Wounds are a major cause of physical disabilities. Current estimates indicate that worldwide nearly 6 million people suffer from chronic wounds [2]. This has drawn the attention of many scientists to identify potential means and sources of wound care. This review classified wound and identified some impediment including microorganisms that cause wound infections to wound healing. To care for the wound and fight against infections, many medicinal plants have been identified to possess wound healing activity and found useful in the treatment of wounds. This paper reviews some of these medicinal plants that have been identified and used in wound management.

2. METHODOLOGY

As source and search strategy, I searched the available electronic databases. The search was performed using the keywords and some familiar botanical names. Online available published articles on wound healing and antioxidant properties since 2005 till now were consulted. Much emphasis and considerations were given to wound healing plants that were subjected to in vivo or in vitro wound models and demonstrated antioxidant properties. Additionally, those plants whose phytoconstituents have demonstrated wound healing activity were considered.

3. LITERATURE REVIEW

3.1 Classification of Wound

The wound can be classified based on the underlying cause of wound creation. When skin is torn, cut or punctured it is termed as an open wound and when blunt force trauma causes a contusion, it is called closed wound, whereas the burn wounds are caused by fire, heat, radiation, chemical, electricity, or sunlight. The wound can also be clinically categorised according to the time frame of healing [3]. Wound is said to be acute when the healing process occurs within the expected time frame and in an orderly manner. It is a chronic wound when it either requires a prolonged time to heal, does not heal, or recur frequently. A chronic wound is a major cause of physical disability. Local infection, foreign bodies and systemic problems such as diabetes mellitus, malnutrition, immunodeficiency or medications are the most frequent causes of chronic wounds [4,5].

3.2 Impediments to Wound Healing

Wound healing is a process of filling up of gaps and maintains the anatomical structure and function. Humans and all animals have in situ capabilities of healing wounds in their body parts through continuous tissue repair and tissue regeneration. However, such capabilities are impaired by age, stress situation, obesity, sex, habits of the patient (such as smoking , alcoholism etc.), conditions of health and immunity status, severity and types of wounds, patient's medication status , disastrous nature of the assault- environment around the site of the wounds and potentials of serious microbial infection [6,7]. Wound healing is a continuous process. However, deficiency of certain vitamins, trace elements and proteins may delay the process [1].

3.3 Wound Infection

One of the most commonly encountered and clinically important impediments to wound healing is wound infection. Impaired immunity and exposure or poor hygiene result in a wound becoming infected. The injured skin remains vulnerable to invasive microbial infections of all kinds of subsequent development of wound sepsis until complete epithelial repairs have occurred [8]. A wound or injury becomes infected when the wound area constitutes an ideal medium for the manipulation of the infecting organism.

Wound infection is one of the most common diseases in developing countries because of poor hygienic conditions [9,10]. All wounds contain bacteria and even if the wound is healing normally, a limited amount of bacteria will be present. The wound becomes infected when the bacteria count rises. Bacterial overload in a

wound can lead to a serious infection that requires antibiotic treatment. A wound that is not healing may probably indicate a sign of infection. In the wound, the following symptoms indicate an infection: odour, increased exudate, abscess or abnormal granulation tissue and increased pain. Additional clinical symptoms may arise if the infection spreads to the healthy tissue surrounding the wound. Depending on the type of bacteria, the wound exudate may become more puss-like, and the peri-ulcer skin may be tender, red and painful.

3.4 Organisms Responsible for Wound Infections

All wounds contain a variety of microorganisms. Table 1 shows a number of bacteria that may potentially cause wound infection.

Some important organisms causing wound infections are *Methicillin Resistant staphylococcus* aureus (MRSA), *Staphylococcus aureus, Eschericia coli, Pseudomonas aeruginosa, Vancomycin Resistant enterococci, Streptococcus pyogenes* and *Corynebacterium sp*. These infections represent the main causes of illness and mortality around the world especially, Enterococcus and Staphylococcus species. According to the literature [11], between 1995 and 1998, coagulase-negative staphylococci, S. aureus and Enterococcus spp. were the leading causes of nosocomial bacteraemia across the USA, accounting for 60% of such cases with Enterobacteriaceae being the major causes of hospital-acquired infections.

3.5 Wound Care and the Fight against Wound Infections

The primary objective of wound care is to prevent or minimize infection and promote healing. Unfortunately, there is non-availability of specific wound healing agents, except the use of antibiotics, anti-inflammatory and analgesic drugs in the allopathic system of medicines [13]. This is the major reason for the quest to undertake research in wound healing agents. Some of these wound care methods employed include the topical antimicrobial therapy of commercial antibiotics. Topical antimicrobial therapy is one of the most important methods of wound care [14]. Some of the antibiotics normally used include ampicillin capsules, penicillin ointment, chloramphenicol, a combination of ampicillin and mebendazole. These chemicals that are commonly used as antimicrobial and disinfectant agents are successful to fight these infections. Unfortunately, the future effectiveness of antimicrobial therapy is somewhat in doubt. Microorganisms, especially bacteria, are becoming resistant to more and more antimicrobial agents. In addition, these chemical agents are expensive and pose side effects.

Wounding and wound healing is a continuous process that takes place in all tissues and organs of the body. Healing of wounds proceeds through common basic phases of hemostasis, inflammation, proliferation, fibroplasia, collagen deposition, epithelisation, contraction, remodelling and maturation [3]. Wound repair process follows a set of biochemical reactions. At the wound site, increased amounts of superoxide anion radicals are produced by activated platelets, neutrophils and the macrophages as well as by the fibroblasts, stimulated by the pro-inflammatory cytokines during the inflammation phase. These radicals constitute part of the immune system which destroys the invading microbes at the wound site. However, the over production of these radicals leads to oxidative stress that requires careful manipulation and control as it is detrimental to the surrounding tissues and can cause heavy accumulated

Table 1. Summary of examples of bacteria that can infect wounds

Types of microorganism	Examples
Gram-positive cocci	Beta-heamolytic *Streptococcus* (*Streptococcus pyogenes*)* *Enterococcus* (*Enterococcus faecalis*) *Staphylococcus* (sensitive *Staphylococcus aureus* and resistant *Staphylococcus aureus* (MRSA)*
Gram-negative aerobic rods	*Pseudomonas aeruginosa**
Gram-negative facultative rods	*Enterobacter* species, *Escherichia coli* *Klebsiella* species, *Proteus* species
Anaerobes	*Bacteroides*, *Clostridium*
Fungi	Yeasts (*Candida*), *Aspergillus*

**Microorganisms most commonly associated with causing wound infection [12]. (Collier, 2004)*

damage. While the system has its checks and measures in place and utilizes superoxide dismutases, catalases, glutathione peroxidases and peroxiredoxins, secreted by the adjoining cells, the impairment of such cells in certain wounds calls for the use of extraneous agents that are more appropriate radical scavengers, working in synergy or independently.

3.6 Wound Healing Potency of Plants

Various plant products have been used in management and treatment of wounds over the years. Many plants can be cited in the literature showing different degrees of wound healing potentials when taken through different wound healing models. Data collected on phyto-extracts for the past 20 years identified about 450 plant species having wound healing properties [6]. Table 2 presents examples of plants cited in literature to have been used to treat wound infections.

Wound healing activity studied on *E. guineensis* (Arecaceae) leaf extract showed potent wound healing capacity as evident from the better wound closure ($P < 0.05$), improved tissue regeneration at the wound site, and supporting histopathological parameters pertaining to wound healing. The results thus confirmed the efficacy of *E. guineensis* in the treatment of the wound [30].

Similarly, *Milicia excelsa* (Moraceae) ointment using the excision wound model by Udegbunam et al., was found to have shown an enhanced wound contraction, epithelialization and fibroplasias on daily application. Different concentrations ranging between 12.5 mg/ml to 100 mg/ml of this ointment successfully inhibited the growth of *S. aureus* but not *P. aeruginosa* [31].

A study conducted on *Boesenbergia kingii* (Zingiberaceae) extract to investigate wound healing property of its compounds in order to support its traditional uses led to the conclusion that *B. kingii* was responsible for wound healing property via antioxidative effect, stimulation of fibroblast proliferation and migration as well as enhancement of collagen production [32].

The aqueous extract of *Allamanda cathartica* L. (Apocyanaceae), a perennial shrub used in traditional medicine for treating malaria and jaundice, was found to have promoted wound healing activity significantly in both Excision and incision wound models studied. High rate of wound contraction ($P<.001$), decrease in the period of epithelialisation (10.2±0.13), high skin breaking strength (440.0±4.53), significant increase in the weight of the granulation tissue ($P <.001$) and hydroxyproline ($P<.001$) content were observed in the Sprague Dawley rats treated with the aqueous extract of *Allamanda* [33].

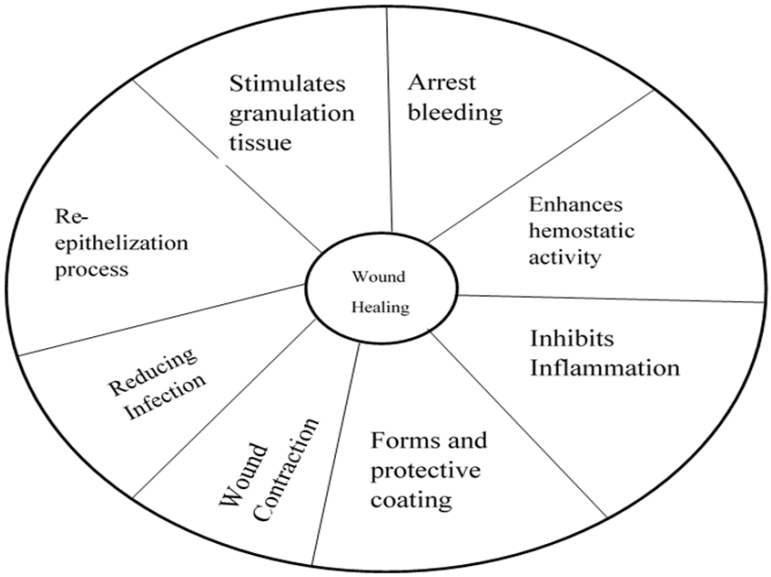


Fig. 1. Various phases of wound healing displayed by plants

Table 2. List of example of plants cited in literature that have been used to treat wound infections

Plant	Part used traditionally	Phytoconstituents	Mode of administration	Mechanism of action
Aloe vera (Liliaceae)	Liquid gel	Glycoproteins, vitamins, mineals	Gel is applied topically	Forms protective coating on affected areas and stimulating wound healing rate and reducing the chance of infection. Accelerates epithelization, wound contraction and wound closure [15, 16].
Azadiracta indica (Meliaceae)	Oil	Hydrocarbons, phenolic compounds, terpenoids, alkaloids, glycosides	Topical application	Inhibits inflammation to accelerate healing, enhanced wound closure rate and increases epithelization [17]
Calophyllum inophyllum Linn. Guttiferae or (Clusiaceae)	Seed oil, leaf	Flavonoids, tannins, saponins, steroids and triterpenes	Oil applied to burned skin	Stimulates wound contraction, decreases epithelialization period, and increases tensile strength and hydroxyproline content. [18, 19]
Calotropis procera W. T. Aiton (Asclepiadaceae)	Leaf latex, stem bark	steroids, triterpenes, proteins flavonoids, polyphenolic hydrocarbons	Leaf latex applied on fresh cut, to stop bleeding.	Increases collagen and epithelialization leading to a marked reduction in wound area [4]
Catharanthus roseus L. (Apocynaceae)	Leaf or flower	Alkaloids, tannins	Paste of dried or wet leaf and flower extracts applied to wound.	Increased the wound breaking strength, wound contraction and epithelization [4, 20]
Chromolaena odorata (Compositae),	leaf	Alkaloid, tannins, steroids, terpenoids, flavonoids and cardiac glycosides	Aqueous extract & decoction leaves are crushed and the decoction used in treating skin wounds	Enhances hemostatic activity, stimulates granulation tissue and re-epithelization processes [21]
Commelina diffusa Burn. F (Commelinaceae)	Leaf	Ascorbic acid, ß-carotene, tannins	Aqueous extract are applied to wound	Antioxidant and antifungal activities [22]
Pupalia lappacea (Amaranthaceae)	Leaf and fruit juice	Steroids, glycosides, saponins, alkaloids, sugar, tannins, penol	Leaf paste or fruit juice applied externally to wound	Wound contraction and wound epithelization [23]
Spathodea	Stem bark	Saponin, steroid, flavonoids,	Aqueous extract or paste	Increases wound contraction

Plant	Part used traditionally	Phytoconstituents	Mode of administration	Mechanism of action
campanulata Beav (Bignoniaceae)		glycoside, alkaloids, phenol, tannin, terpenoids, phlobatanin and anthraquinone.	applied to wound	[24, 25]
Tridax procumbens (Compositae)	Leaf juice	Flavonoids, alkaloids, tannins, phytosterols,	Systemic administration (intraperitoneal) of leaf juice	Arrest bleeding, increases epithelization and collagenisation [26]
Sida acuta (Malvaceae)	Leaf and root juice	Alkaloids, phytosterols, tannins, flavonoids, saponins,	Decoction of leaves to clean wound and root juice applied topically to wound	Increase in the tensile strength, epithelialize faster and the rate of wound contraction [27, 28]
Heliotropium indicum L (Boraginaceae)	Leaf	Alkaloids, glycosides, tannins, flavonoids, saponins,	Leaf paste over fresh cuts and wounds.	Increases in the granulation tissue weight and hydroxyproline content [4, 29]

The antibacterial and wound healing activity of the ethanolic leaf extract of *Carapa guianensis* (Meliaceae) was evaluated using excision, incision and dead space wound models in rats. The result indicated that the extract exhibited 100% reduction in the wound area when compared to controls (95%) after 15-days of treatment, with a significant decrease in the epithelialization period. The positive out of the evaluation empowered them to conclude that the increased rate of wound contraction, skin breaking strength and hydroxyproline content supports potential application of *C. guianensis* in wound healing [34].

The ethanol flower extract of *Catharanthus roseus* L was observed to have significantly ($p < 0.001$) increased the wound breaking strength in the incision wound model. In addition, the wounds were found to epithelialize faster and wound contraction significantly ($p<0.001$) increased in comparison to control wounds [4]. From the few examples cited above it is evident that plant products display all the phases of wound healing as shown in Fig. 1. Hence plants are alternative potential agents for wound healing and are largely preferred because of their widespread availability, low price with few complications and effectiveness as crude preparations [35,30].

Plant products are therefore used as alternative solution to the problem of wound treatment in developing countries.

The enhanced wound healing potency of various herbal extracts may be attributed to free radical-scavenging action and the antimicrobial property of the phytoconstituents present in the extract, and the quicker process of wound healing could be a function of either the individual or the synergistic effects of bioactive molecules [36, 37]. These active constituents promote the process of wound healing by increasing the viability of collagen fibrils, by increasing the strength of collagen fibers either by increasing the circulation or by preventing the cell damage or by promoting the DNA synthesis [37,38]. This affirms the statement that the wound- healing properties of plants, in most cases, are associated with their significant antioxidant activities [39]. Some plants extracts are believed to have strong antioxidant effects. Antioxidants play very important roles in cutaneous tissue repair as they significantly prevent tissue damage that stimulates wound healing process [40]. It has been mentioned that the antioxidant activity of plants might be due to their phenolic compounds [41]. The plant components having some such properties are the soluble compounds in the plant extracts. Among them are flavonoids, quinones, phenolic acids and phenyl propanoids. They have been found to possess considerable anti-microbial as well as antioxidant properties. Botanicals with antioxidant or free radical-scavenging activity thus can play a significant role in healing of wounds [42]. Many wound healing medicinal plants have been investigated to possess antioxidant properties. Table 3 presents the list of some examples of plants that exhibit both wound healing and antioxidant properties.

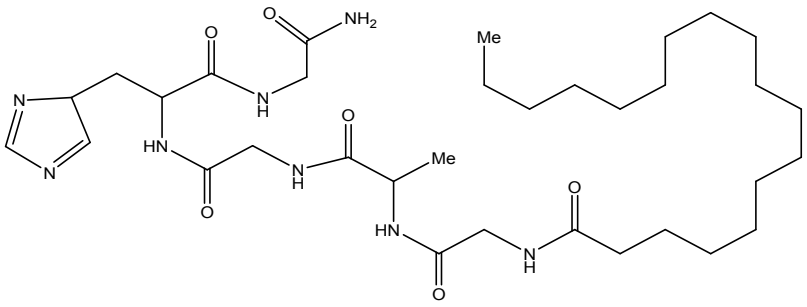
A number of secondary metabolites/ compounds isolated from plants have been demonstrated in animal models as active principles responsible for facilitating healing of wounds.

Table 3. List of some examples of wound healing plants with antioxidant properties

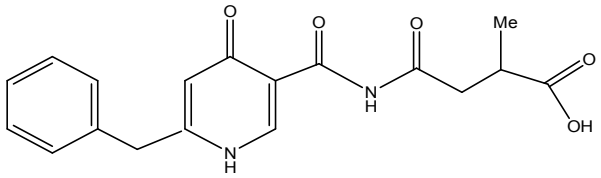
Name of plant	Botanical name and part used	Reference
Achyranthes aspera Linn	(Amaranthaceae)	[43, 44]
Amaranthus spinosus	Amaranthaceae (root)	[45, 46]
Anogeissus leiocarpus	Combretaceae (Leaves)	[46]
Ipomea Carnea	Convolvulaceae	[47]
Corchorus olitorius	Tiliaceae (Leaves)	[48]
Mallotus oppositifolia	Leaves	[45]
Sida acuta	Malvaceae (Leaves, root juice)	[28]
Spathodea campanulata P. Beauv.	Bigoniaceae (Leaves)	[39]
Spondias mombin	Anacardiaceae (Leaves)	[49]
Terminalia chebula	Combretaceae (Leaves)	[50, 51]
Terminalia macroptera	Combretaceae (Leaves, root and stem bark)	[52]

Some of the isolated compounds reported, which include glycosides, saponins, tannins, and phenolic compounds such as catechins, and isoflavonoids, have been previously documented in the literature as having a positive effect on wound healing that could potentially be new therapeutic agents to treat wounds [53]. These agents usually influence one or more phases of the healing process [54]. For instace, Dodehe et al. isolated two compounds from n-butanol fraction of *Heliotropium indicum* leaf. The structures of these two compounds were established by spectral analysis as Pestalamide and Glycinamide, N-(1-oxooctadecyl) glycyl-L-alanylglycyl-L-histidyl (Fig. 2). Both compounds indicated *in vitro* wound healing effect compared with Fetal Bovine Serum (FBS) as the control ($P<0.05$) [55]. There was progressively wound contraction when the compounds were used in the treatment of wound.

In a similar work, grandiflorenic acid (ent-kaura-9(11), 16-dien-19-oic acid) (Fig. 3) isolated from the leaves of *W. trilobata*, was taken through scientific wound healing activity. The results proved that grandiflorenic acid; the isolated compound had potential wound healing activity at a dose below 3 µg/ml. The wound healing activity was due to a combination of fibroblast and macrophage activity. The compound also showed no evidence of hemolysis up to 8 µg/ml [56]. Compounds that possess hemolytic effect may not be useful in pharmacological preparations for open wounds.

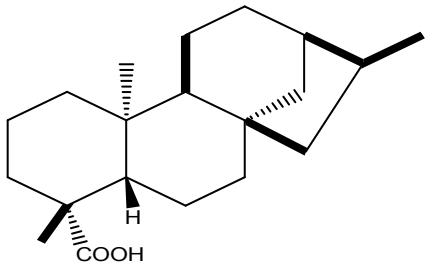


Glycinamide



Pestalamide

Fig. 2. Structure of glycinamide and pestalamide



Glandiflorenic acid

Fig. 3. Structure of glandiflorenic acid

A study by Nguye et al., led to the isolation of a phyto-constituent, calophyllolide (Fig. 4) (a non-steroidal anti-inflammatory agent) from *Calophyllum inophyllum* [19]. The isolated compound was found to be a good candidate for accelerating wound healing through its anti-inflammatory effects. The results obtained in the study showed that calophyllolide could reduce fibrosis formation and effectively promote wound closure in mouse model without causing body weight loss. As a result, the utilization of calophyllolide as a potent therapeutic for cutaneous wound healing was suggested [19].

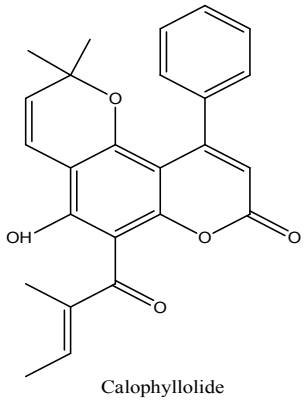
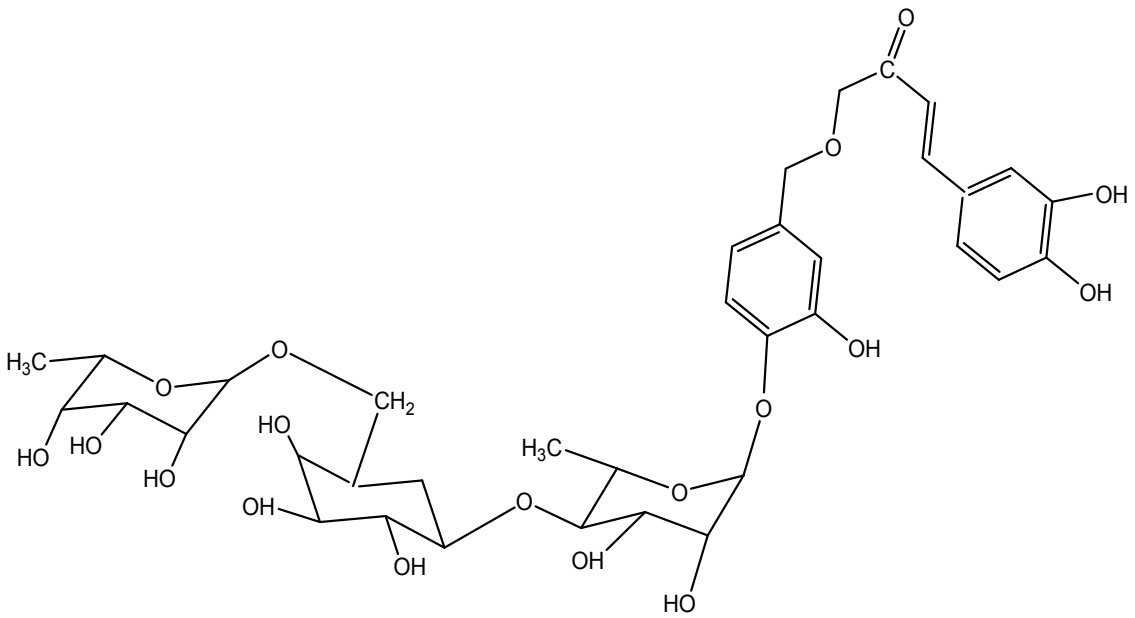


Fig. 4. Structure of calophyllolide

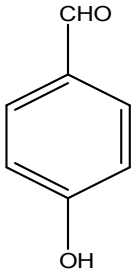
A significant increase in the wound-healing activity was observed in rats inflicted with excision and incision wounds when treated with Menthyl teucrol glycoside (Fig. 5), a chemical constituent isolated from *Mentha piperita* (L.) (Lamiaceae). In both models, the animals treated with the isolated compound showed a more rapid decrease in wound size and a decreased time to epithelialization. The Compound also indicated a significant breaking strength when the incision wound study was carried out to measure the tensile strength of the regenerated tissue [57].

A recent report on 4-Hydroxybenzaldehyde (4-HBA) (Fig. 6), an active compound isolated from *Gastrodia elata* (Tianma), which has long been used as a Chinese herbal medicine to treat headaches, migraines, as well as some neuralgias and nervous disorders, indicated that 4-HBA could be a candidate therapeutic agent with the potential to promote acute wound healing. It was found that 4-HBA treatment promoted wound healing and re-epithelialization in an in vivo excision wound animal model. In addition, 4-HBA significantly promoted keratinocyte cell migration and invasion by increasing focal adhesion kinase and Src activity [58].



Teucrol glycoside

Fig. 5. Structure of teucrol glycoside



4-Hydroxybenzaldehyde (4-HBA)

Fig. 6. Structure of 4-hydroxybenzaldehyde

Many other plant-derived phytochemical compounds (Fig. 7) have also been cited in literature that promote wound healing process. Some are Asiaticoside, a triterpene glycoside isolated from *Centella asiatica;* Curcumin, a phenolic compound isolated from *Curcuma longa* Linn; Chlorogenic acid, an ester of caffeic acid and quinic acid, the major polyphenolic compound in green coffee beans; Quercetin, a flavonoid compound found in many plants and herbs and Gallic acid a polyphenol with wide range of therapeutic and biological properties [59].

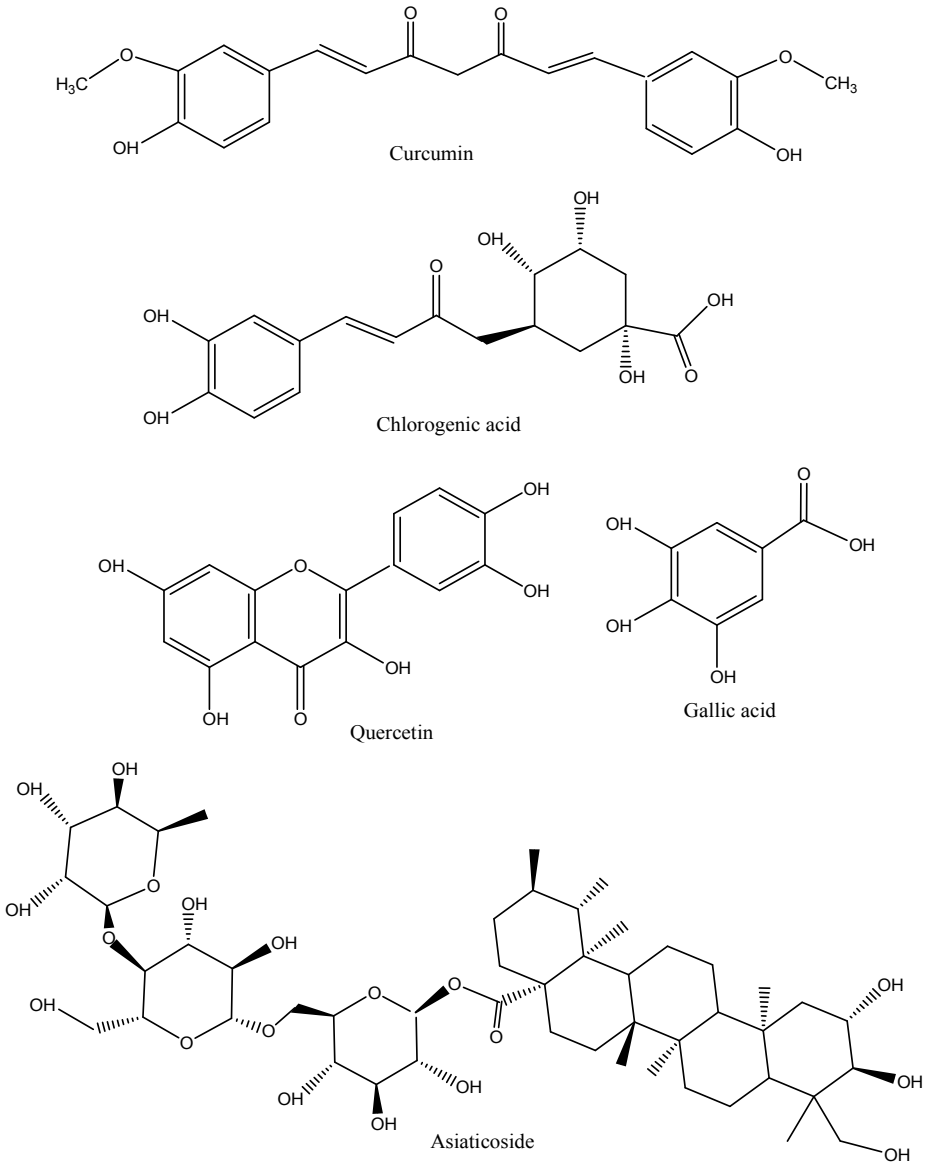


Fig. 7. Structures of examples of plant-derived wound healing phytochemical compounds [59]

4. CONCLUSION

The plant kingdom is rich in chemical constituents for acting especially as antimicrobial agents and also as free radical scavengers. These constituents of plant extracts modulate one or more of the wound healing stages or processes. Plants, therefore, have the immense potential for the management and treatment of wounds. Hence, a large number of plants are used by tribal and folklore in many countries for the treatment of wounds over the years and have proved to possess significant pro-healing properties in different types of wounds. This practice must, therefore, be encouraged and modernized to enhance the wound healing performance of plant extracts. More efforts must be made by combining the strengths of modern scientific techniques such as NMR, MS and chromatographic techniques to identify more of the phytoconstituents, the main architects of the medicinal potentials of plants, for development of wound healing drug and also, to provide new functional lead compounds with high therapeutic value. It is also necessary to protect our biodiversity to prevent the extinction of our essential plants of medicinal value.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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