Mini Review

An Overview of Cutaneous Wounds and the Beneficial Roles of Medicinal Plants in Promoting Wound Healing

Nura Muhammad Umar, Thaigarajan Parumasivam, Seok-Ming Toh

1School of Pharmaceutical Sciences, Discipline of Pharmaceutical Technology, Universiti Sains Malaysia (USM), 11800, Pulau Pinang, Malaysia.

Abstract

It is undeniable that many patients worldwide suffer from various types of wounds, especially chronic wounds. The complex and intricate process of wound healing has a severe impact on the patient's quality of life as well as causing an economic burden on healthcare institutions. Although various new therapies have become available for treating patients with acute and chronic wounds for the past decade, the available therapies are often expensive or accompanied by undesirable side effects. Hence, the discovery of a new arsenal for wound healing remains a hot topic of research. Recently, plants or herbs and their derivatives have garnered significant attention as a source of therapeutic agents to treat wounds. This is because plants provide a rich reservoir of phytochemicals that could potentially become effective and affordable therapeutic agents. Thus, the present review attempted to outline wound healing mechanisms and analysed some renowned medicinal plants with potential wound healing properties from the existing literature from various electronic databases. This review also sheds light on the plant's underlying molecular mechanisms and, wherever available, acknowledges the biologically active substances found in these plants.

Article Info

Article History:
Received: 12 October 2020
Accepted: 24 March 2021
ePublished: 1 April 2021

Keywords:
-Chronic wounds
-Medicinal plants
-Wound healing

Introduction

Skin is the human body's largest organ, accounting for about 15% of the total body weight. It has many essential roles, including defence against physical, chemical and biological agents, and to prevent excess loss of water from the body and a significant role in thermoregulation. Skin is essentially elastic, with mucous membranes lining the surface of the body.

Skin is composed of three layers (Figure 1), namely the epidermis, dermis, and hypodermis (subcutaneous tissue). The epidermal layer is the outermost layer and is composed of a particular collection of cells, called keratinocytes. These cells synthesise a long, thread-like protein known as keratin which forms a protective layer on the skin. The dermis is the middle layer that lies just beneath the epidermis and is made up of collagen. The hypodermis or subcutaneous tissue is made of small lobes of fat cells known as lipocytes and connective tissue. The thickness of these layers varies considerably, the dermis being the thickest, around 30-40 times thicker than the outer epidermal layer. The skin serves as a protective barrier against environmental assault. Hence, if the skin's structural integrity is compromised, its primary responsibility to the immune system is affected, leading to severe morbidity and mortality.

According to the Wound Healing Society (WHS), wounds are injuries inflicted by physical, chemical, or microbial agents that disrupt the anatomical structure of healthy skin and loss of its function. Thus, proper wound healing is necessary to restore tissue integrity and physiological function. Wounds are generally classified as open or closed wounds (based on their aetiology), and acute or chronic wounds (based on the physiology of the wound healing process).
Chronic wounds are a substantial public health issue, yet little is understood about their actual burden on the healthcare system, and they continue to significantly affect the quality of life and the cost of healthcare services. Most chronic wounds are ulcerative, including vascular ulcers, diabetic ulcers and pressure ulcers. Often disguised as a co-morbid condition, chronic non-healing wounds remain a silent epidemic that affects a significant fraction of the world’s population. It is estimated that around 1 - 2 % of people in the developed countries will have a chronic wound during their lifetime. In the United States of America (USA) alone, it is estimated that over 6 million people suffer from chronic wounds. In comparison to the United Kingdom (UK), Walton reported that 1 % of the UK population has a chronic wound. Moreover, it is reported that 10-25 % of patients who have diabetes will develop chronic foot ulcers. Hence, in the USA, diabetes remains the primary cause of nontraumatic leg amputations (up to 90 %). Besides, the global prevalence of pressure ulcers is increasingly alarming and has recently been reported to be in the range of 3.4 - 32.4%, where 50 - 80% of the cases are reported to be hospital-acquired. As a result, North America has spent over $25 billion per year managing chronic wounds while 4% (over £1 billion) of the annual National Health Service (NHS) expenditure in the UK is spent on care for patients with pressure ulcers. It is evident that the treatment of chronic wounds has a significant economic impact on the public. Generally, wound dressings, skin grafting, debridement, compression therapy, casting, and other varieties of topical products are primarily used in cutaneous wound management to create and maintain a moist environment for proper healing conditions. They are, however, often expensive or ineffective and may cause undesirable side effects. Hence it has become necessary to search for a cheaper and more effective alternative to manage and cure such wounds, preferably of plant origin. Plants and their processed products exhibit high potential in managing and treating such internal and external wounds. Such phyto-medications do not only have proven therapeutic benefits but are also relatively safer. This paper attempts to briefly review wound healing mechanisms and analyse some medicinal plants with potential wound healing properties, with the help of the existing literature searched via electronic databases such as Pubmed, Scopus, and Google Scholar. Searched terms used include wound healing, chronic wounds, medicinal plants, and phytotherapy. The review also sheds light on the plant’s underlying molecular mechanisms and acknowledges the biologically active substances found in these medicinal plants, wherever available.

Factors Affecting Wound Healing
Although wounds may be caused by diverse reasons, almost all types of injuries follow a common innate healing mechanism. Wound healing is a complex biological process that requires a series of concurrent physiological processes, such as haemostasis, inflammation, proliferation, and remodelling. These seemingly straightforward processes, in reality, it is a complex series of events that are strictly regulated by several biochemical and environmental factors that can impact the outcomes. Any alterations that may disrupt these controlled healing processes may lead to extensive tissue damage and improper skin repair. Studies conducted by Aly and Guo and DiPietro discovered systemic factors such as diabetes mellitus, age, obesity, smoking, alcoholism, medication, and nutrition deficiency might lead to impaired wound healing. Other local factors, such as depleted oxygen supply and microbial infection, are reported to harm wound healing. A few of these factors are briefly described below.

I. Medication
Despite enormous advances in the pharmaceutical industry, only a limited number of drugs can stimulate the wound healing process. The ability of commonly prescribed and over the counter drugs (such as ibuprofen, aspirin, and other non-steroidal anti-inflammatory drugs (NSAIDs)) to interfere with the inflammatory phase of wound healing results in delayed healing. Reviewed literature suggests that these drugs could inhibit the cyclooxygenase (COX) enzymes. These enzymes convert arachidonic acid into prostaglandin, prostacyclin and thromboxane, vital in the inflammatory process. Other medications including glucocorticoid steroids (e.g., cortisol and dexamethasone) and chemotherapeutic drugs (e.g., Avastin, methotrexate and nitrogen mustard) interfere with blood clotting or platelet function, or inflammatory responses and cell proliferation that significantly delay wound healing.

II. Diabetes mellitus
Diabetes mellitus causes oxidative destruction of cellular membranes, and redox imbalance within the cells called oxidative stress which increases free radicals’ production and decreases the antioxidant defence mechanism in the body. Oxygen-free radicals are produced principally in inflamed or ischemic tissues during the inflammatory response. They, in turn, cause tissue injury by lipid peroxidation of membranes and oxidation of essential proteins and enzymes, which may lead to delayed healing or chronic wounds. Diabetic foot ulcers and pressure ulcers are prime examples of this scenario as they are always accompanied by hyperglycemia and hypoxia, both of which increases the levels of oxygen-free radicals.

III. Age
The skin’s anatomical structure and function are affected during the ageing process and, consequently, upsets the wound healing phases. As a person gets older, the skin gets thinner and more prone to injury, and heals slower. Studies have revealed that chronic wounds are commonly found...
among elderly patients aged 65 and above. The delayed wound healing in the elderly population is also associated with a decreased inflammatory response, delayed re-epithelisation, collagen formation and angiogenesis.

**IV. Nutrition**

Malnutrition may significantly affect wound healing because a wound may not heal entirely if certain essential nutrients (such as vitamin C and Zinc) are lacking for cell repair and growth purposes. Often, a more significant amount of carbohydrate, protein, fat, vitamins, and minerals are required for patients with chronic or non-healing wounds.

**Plants as wound healing agents**

Plants have been used to treat and prevent diseases in both traditional and modern medicine for centuries. Topical applications of plants with free radical scavenging properties have been shown to improve wound healing and protect against oxidative stress. For instance, plants containing carotenoids and polyphenolic flavonoids have demonstrated powerful antioxidant and wound healing properties. Flavonoids as natural, free radical scavengers, have been reported to inhibit lipid peroxidation and promote vascular relaxation to accelerate wound healing in an animal model. The wound healing activities of plants have been scientifically screened and evaluated in various pharmacological models, although their clinical potential has yet to be explored. Besides, active chemical phytochemicals were only identified in a couple of cases. A summary of these medicinal plants found in the tropical and sub-tropical regions with potent wound healing properties is presented in Table 1. The mechanism of wound healing of twelve heavily studied and most promising plants is discussed in the following sections. Based on the studied literature, it was observed that regardless of the wound healing model under study, the most typical practice was that after the infliction of the wound, medicinal plant extracts were administered orally or topically in the form of crude extract suspension, gel, cream, ointment, lotion, or paste. The extract formulation was usually at a concentration ranging from 100 to 500 mg/kg/day for systemic and 1 to 10% w/w once a day for local application. Noteworthy was the observation that all the surgical procedures were performed under aseptic and anaesthetic conditions, and no local or systemic antimicrobial was given after wound infliction. The wounds are evaluated over an average period of 21 days post-injury or until the fall of the wound scar.

**Acalypha indica**

*Acalypha indica*, also known as the Indian Copperleaf, belongs to the family Euphorbiaceae and is widely distributed throughout the plains of India. The plant is renowned for treating conditions such as pneumonia, asthma, rheumatism, and several other chronic ailments. The dried leaves of the plant are prepared as a poultice to promote vascular relaxation to accelerate wound healing properties have been shown to improve wound healing and anti-herpetic activity.

**Aloe vera**

*Aloe vera*, is a juicy plant species of the genus *Aloe*, belonging to the Liliaceae family and cultivated for agricultural, medicinal and cosmetic purposes. *A. vera* preparations include fresh gel, juice or formulated products. Numerous literature has reported that the plant possesses beneficial pharmacological properties such as anti-inflammatory, antimicrobial, antitumour, antioxidant, and wound healing benefits. Chithra et al. assessed the wound healing potential of *A. vera* gel in incisional and excisional diabetic wound models in male Wistar rats. The study showed a faster rate of wound contraction (treated group 82.7% - 85.6% vs. untreated group 70.7%) at 16 days, shorter epithelisation period (treated group 20 - 22 days vs untreated group 25 days), and significant tensile strength in the *A. vera* treated group compared to the control group. A significant increase in collagen, DNA, and total protein contents were also recorded in the granulation tissue of the *A. vera* treated group. Decreased level of hexosamine content was also noted after the treatment suggesting better collagen crosslinking for a more robust extracellular matrix. Hence, the authors suggested that *A. vera* may influence wound healing phases such as fibroplasia, collagen synthesis and contraction for faster healing.

**Alternanthera brasiliana Kuntz**

*Alternanthera brasiliana* Kuntz, also known as Brazilian joy-weed, is a flowering plant belonging to the Amaranth family, native to Central and South America’s forests. It is mainly harvested from the wild for agricultural and medicinal purposes. Studies have shown that its extracts exhibit antinociceptive effects, antimicrobial effects, and anti-herpes simplex viruses activity.
Table 1. Literature search for Plants found in tropical and sub-tropical regions reported with wound healing properties within 1999 - 2020.

| Plant: Common name (scientific name) | Plant part used | Extraction solvent used | Formulation | Wound model studied | Ref. |
|-----------------------------------|----------------|-------------------------|-------------|---------------------|------|
| Golden Trumpet (*allmanda cathartica*) | Leaves | Water | Crude extract | Excision and incision | 26   |
| Axlewood (*anogeissus latifolia*) | Bark | Ethanol | Crude extract | Excision and incision | 45   |
| Golden shower (*cassia fistula*) | Leaves | Ethanol | Ointment | Excision | 63   |
| Seabuckthorn (*hippophae rhamnoides*) | leaves | Water | Crude extract | Excision | 64   |
| Indian Copperleaf (*acalypha indica*) | Whole plant | Ethanol | Crude extract | Excision and incision | 65   |
| Indian heliotrope (*heliotropium indicum*) | Whole plant | Ethanol | Crude extract | Excision and incision | 65   |
| Chitrak (*plumbago zeylanicum*) | Whole plant | Ethanol | Crude extract | Excision and incision | 65   |
| Bael (*aegle marmelos*) | Leaves | Methanol | Ointment | Excision and incision | 66   |
| Worm Killer (*aristolochia bracteolata*) | Leaves | Ethanol | Crude extract | Excision, incision and dead space wounds | 67   |
| Mexican poppy (*argemone mexicana*) | Leaves | Ethanol | Crude extract | Excision, incision and dead space wounds | 68   |
| Air plant (*bryophyllum pinnatum*) | Leaves | Water | Crude extract | Excision, incision and dead space wounds | 69   |
| Flame of the forest (*butea monosperma*) | Bark | Ethanol | Crude extract | Excision | 70   |
| Carray Cheddle (*canthium parviflorum*) | Leaves | Ethanol and water | Ointment | Excision | 71   |
| Silver cock's comb (*celosia argentea*) | Leaves | Ethanol | Ointment | Rat burn wound | 72   |
| Cinnamon (*cinnamomum zeylanicum*) | Bark | Ethanol | Crude extract | Excision, incision and dead space wounds | 73,74 |
| Swine cress (*coronopus didynamous*) | Whole plant | Ethanol and water | Crude extract | Incision | 75   |
| Nut Sedge (*cyperus rotundus*) | Rhizomes | Ethanol | Ointment | Excision, incision and dead space wounds | 76   |
| Thorn Apple (*datura alba*) | Leaves | Ethanol | Ointment | Burn rat wound | 77   |
| Trefle Gros (*desmodium triquetrum*) | Leaves | Ethanol | Crude extract | Excision, incision and dead space wounds | 78   |
| Elephant's Foot (*elephantopus scaber*) | Leaves | Ethanol and water | Gel | Excision, incision and dead space wounds | 79   |
| Tasmanian bluegum (*eucalyptus globulus*) | Leaves | Ethanol | Crude extract | Excision, incision and dead space wounds | 80   |
| Clustered yellowtops (*flaveria trinervia*) | Leaves | Methanol | Ointment | Excision and incision | 81   |
| Yellow gentian (*gentiana lutea*) | Rhizomes | Ethanol and petroleum ether | Crude extract | Excision, incision and dead space models | 82   |
| Licorice (*glycyrrhiza glabra*) | Root | Ethanol | Crude extract | Excision | 83   |
| Gamhar (*gmelina arborea*) | Leaves | Ethanol | Crude extract | Excision, incision and dead space wounds | 84   |
| St John's wort (*hypericum hookerianum*) | leaves | Methanol | Ointment | Incision and excision | 85   |
| Mysore St John's Wort (*hypericum mysorense*) | Leaves | Methanol | Ointment | Excision and incision | 86   |
Table 1 Continued.

| Plant Name                                      | Part Used | Extract/Preparation | Application | Wound Type                  |
|------------------------------------------------|-----------|---------------------|-------------|-----------------------------|
| Yellow mosqueta (Hypericum patulum Thumb)      | Leaves    | Methanol            | Ointment    | Excision and incision       |
| Pignut (Hyptis suaveolens)                     | Leaves    | Ethanol             | Crude extract | Excision, incision and dead space |
| Birdsville indigo (Indigofera enneaphylla)     | Aerial    | Ethanol             | Ointment    | Excision and incision       |
| Jungle geranium (Ixora coccinea)               | Flowers   | Ethanol             | Crude extract | Dead space                 |
| Big sage (Lantana camara)                      | Leaves    | Hydro-alcohol       | Crude extract | Excision                   |
| Henna (Lawsonia alba)                          | Leaves    | Chloroform, Ethanol and petroleum ether | Crude extract | Excision and incision         |
| Thai umb (Leucas hirta)                        | Leaves    | Methanol and water  | Ointment gel | Excision, incision and dead space |
| Isphagua (Plantago ovata)                      | Seeds     | Ethanol             | Ointment    | Excision and incision       |
| Holy basil (Ocimum sanctum)                    | Leaves    | Ethanol             | Crude extract | Excision, incision and dead space |
| Creeping wood sorrel (Oxalis corniculata)      | Whole plant | Ethanol and petroleum ether | Crude extract | Excision, incision and dead space |
| Egyptian star cluster (Pentas lanceolata)      | Flowers   | Ethanol             | Crude extract | Excision                   |
| Emblic (Phyllanthus emblica)                   | Leaves    | Ethanol             | Crude extract | Excision                   |
| Indian liverwort (Plagiochasma appendiculatum) | Thalli    | Chloroform, Acetone, Ethanol and Water | Crude extract | Excision and incision         |
| Pomegranate (Punica granatum)                  | Peels     | Methanol            | Gel         | Excision                   |
| Aleppo Oak (Quercus infectoria)               | Galls     | Water               | Crude extract | Excision, incision and dead space |
| Purple teeprosia (Tephrosia purpurea)          | Aerial    | Methanol            | Ointment    | Excision, incision and dead space |
| Arjun (Terminalia arjuna)                      | Bark      | 50% Ethanol         | Ointment    | Excision and incision       |
| Chebulic myrobalan (Terminalia chebula)        | Leaves    | Ethanol             | Crude extract | Incision and In vitro      |
| Portia tree (Thepesia populnea)                | Fruits    | Water               | Crude extract | Incision and excision       |
| Orange climber (Todalia asiatica)             | Stem bark | Ethanol, petroleum ether, chloroform and acetone | Crude extract | Excision and incision         |
| Climbing nettle (Tragia involucrata)           | Roots     | Methanol            | Crude extract | Excision                   |
| Vanda orchid (Vanda roxburghii)                | Whole plant | Water              | Crude extract | Excision                   |
| Tree vernonia (Vernonia arborea)               | Leaves    | Methanol and water  | Ointment    | Excision, incision and dead space |

Depending on the wound healing parameters to be evaluated, different wound healing models have been employed in evaluating the effectiveness of medicinal plants in cutaneous wound healing. The excision wound model is used to evaluate healing parameters such as collagen content, percentage wound contraction, and period of epithelialisation. A full-thickness (2 mm depth) excisional wound of around 200 to 500 mm² diameter is inflicted on the dorsal region of the animal, usually rats or mice. The incision wound model is commonly employed to evaluate the tensile strength (breaking strength) of the skin of the healed wound, which is not only associated with the tensile strength of the wound tissue, but also indicates the degree of wound healing often associated with the organisation, content, and physical properties of the collagen fibril network. Two long paravertebral incisions of about 4 - 5 cm were made with a sterile surgical knife on the vertebral column of the animal and stitched afterwards. The dead space wound model was employed to study the formation of granuloma tissue. The dead space wound is created by a cylindrical pith (a sterilised, shallow, metallic ring) with the size of 2.5 × 0.3 cm on each side beneath the dorsal paravertebral lumbar skin surface of the animal. The burn wound model is used to measure hydroxyproline content, wound contraction, and period of epithelialisation. A full-thickness burn wound is inflicted using a special hot (100 °C) metal plate (2 x 2 cm) on the dorsal area of the animal.
Barua et al., in an interventional study, investigated the wound healing activity along with the antioxidant enzyme profile after topical application of 5% w/w ointment of methanol extract of A. brasiliana leaf in immunocompromised rats. Healing potential was evaluated after twice-daily topical application of the ointment preparation on cutaneous excisional wounds for ten consecutive days. A significant elevation in enzymatic and nonenzymatic antioxidant parameters in the treated group was noted after the treatment period compared to the control group. Histopathological study revealed angiogenesis, development of basement membrane, collagen deposition, and fibroblast proliferation in the extract ointment treated group. The percentage of wound contraction was also recorded to be significantly higher in the extract-treated group (77.10%) in comparison with the negative control (39.25%) and positive control (60.00%) groups.

Amaranthus spinosus

Amaranthus spinosus belongs to the Amaranthaceae family and is commonly known as Pigweed. This perennial herb is native to tropical America, India, and Ghana. The plant has a long history of usage against diseases like bilious complaints, cough, worms, jaundice, fever, inflammation, rheumatism, anaemia, and vermiﬁuge. It is also found to be helpful in wound healing and rheumatism. A. spinosus is reported to be rich in proteins (12.6 to 18.0%), fat (5 to 8%), saccharides (60 to 65%), and crude ﬁbre (3 to 5%). The stem bark of this medicinal herb has also been reported to possess high levels of phenolic acids. Paswan et al. studied wound healing activity of the ethanolic extract ointment of A. spinosus (whole plant) on excisional wounds infected with 108 CFU/ml of Staphylococcus epidermidis (MTCC-3382), Salmonella typhi (MTCC-733), and Salmonella typhimurium (MTCC-3224) in a mixed-sex Sprague Dawley rat model. The animals were treated with different concentrations (5% and 10% w/w) of A. spinosus extract ointment, while soframycin was used as a positive control. The study showed that extract ointment (10% w/w) signiﬁcantly restored wound tissues in both infected and non-infected animal groups. A complete contraction was achieved, and the epithelisation period was reduced to 12 days compared to 25 days in the control group. A. spinosus extract was also reported to be bactericidal against various bacterial strains (Staphylococcus epidermidis, Salmonella typhi and Salmonella typhimurium) and fungal strains (Candida krusei and Aspergillus fumigatus).

The authors attributed the plant’s wound healing and microbial activity to gallic acid, ferulic acid, protocatechuic acid, and chlorogenic acid identiﬁed in the plant’s extract.

Azadirachta indica

Another renowned medicinal plant is A. indica or the neem tree that belongs to the mahogany family Meliaceae. Native to the Indian subcontinent and dry areas of South Asia, all parts of the neem tree show tremendous therapeutic benefits for treating numerous ailments. For instance, the bark, seed, leaves, fruit and ﬂower are employed as an analgesic, antipyretic, cough suppressant, antiasthmatic, anthelmintic, and for urinary disorders, diabetes, leprosy, ophthalmological conditions, epistaxis, anorexia, skin ulcers and cancer.

Neem leaves contain active ingredients such as nimbidin, sodium nimbidate, nimbin, and nimbidol which possess anti-inﬂammatory, antibacterial, antifungal, antiviral, and wound healing properties. Besides, neem leaf extract contains a signiﬁcant amount of amino acids, vitamins, and minerals essential in the formation of collagen and angiogenesis in the proliferation phase of wound healing. Studies have also shown that neem leaf extracts can result in the same rate of wound healing as povidone-iodine; hence, they can be used as an effective alternative. Maan et al. investigated wound healing properties of aqueous extract ointment from the stem bark of A. indica in male Swiss Albino mice using excision and incision wound models. Their study revealed that the animals treated with the ointment exhibited a faster rate of wound contraction (93.39%), increased hydroxyproline (13.31 ± 6.65 mg/g), DNA (20.99 ± 0.68 μg/100 mg) and protein (100.53 ± 7.88 mg/g) contents, and increased nitric oxide level (3.05 ± 0.03 mMol/g), as well as signiﬁcant wound tensile strength (289.40 ± 29.45 g) when compared to the untreated control group (wound contraction 78%; hydroxyproline 7.76 ± 0.03 mMol/g). The effect of the ointment was also shown to be comparable to the povidone-iodine treated positive control group.

Cassia fistula

Cassia fistula, belonging to the family Caesalpinioideae, is also known as Indian laburnum and has been extensively used for centuries in Ayurvedic medicine to manage various ailments. Multiple practitioners report it to possess hepatoprotective, anti-inﬂammatory, antitussive, antifungal, antibacterial, antipyretic and wound healing properties. The leaves of C. fistula exhibit laxative activity and can also be externally applied as an emollient for insect bites, swelling, rheumatism, facial paralysis, skin eruptions, and eczema. A study conducted by Kumar et al. evaluated the wound healing property of 10% w/w ointment of C. fistula leaves extract on excisional wounds in a male Wistar albino rats model infected with S. aureus and P. aeruginosa. Their ﬁndings revealed that rats treated with the ointment of C. fistula leaf extract showed better-wound closure, improved tissue regeneration, increased protein and collagen content evident by enhanced migration of ﬁbroblast cells, epithelial cells, and synthesis of the extracellular matrix. On the other hand, decreased wound healing activity was observed in the control group due to bacterial contamination at the wound site.

Catharanthus roseus

Catharanthus roseus, also known as Madagascar periwinkle,
is a flowering plant belonging to the family Apocynaceae. It is commonly used in tropical countries, and this plant has been medicinally used as a remedy for various conditions, such as headache, digestive problems, and diabetes. In Malaysia, it is locally called Kemunting Cina. With 400 identified alkaloids present, the plant has received much attention as an antineoplastic agent to treat leukemia, Wilms’ tumor, malignant lymphomas, rhabdomyosarcoma, neuroblastoma, and other cancers. The rhizomes of Curcuma longa, known as Tiger grass, are widely grown and used in Asia, mainly in Pakistan and India, Equatorial Africa, and Central America. The medicinal use of C. asiatica has been documented throughout traditional medicine dates back centuries. It has a well-established therapeutic role in various dermatological conditions, such as scratches, wounds, burns, and eczema. The plant is also recommended as an antipyretic, antirheumatic, diuretic, antimicrobial drug, also to relieve anxiety, and improve cognition. The oil extracted from the fruit of the plant is frequently employed as a spice in food and medicinal use. It contains compounds such as curcumin, curcuminoids, phenolic compounds, and volatile oils such as turmerone, atlantone, and zingiberene. A study demonstrated the wound healing activity of C. longa rhizome extract on excision wound model in Wistar albino rats. An ointment of 5% w/w ethanolic rhizome extract was prepared and applied topically on the excision wounds of the animals. On the other hand, 5% w/w povidone-iodine was employed as a positive control. The findings revealed that the extract was more potent and had a more rapid onset in wound healing with a faster epithelialisation rate, wound contraction, and complete healing in the treated animals compared to the positive control. However, the study did not evaluate the wound tensile strength. In a similar study, Kundu et al. evaluated the potential efficacy of fresh turmeric (C. longa) paste to heal wounds in a preclinical study. The turmeric paste was applied on the experimentally created full-thickness circular excisional wound in 18 rabbits as a topical medicament under aseptic condition. Wound healing was assessed based on physical, histomorphological, and histochemical parameters. After treatment for 14 days, it was found that the wound tensile strength, collagen, and elastin in reticulin fibre formation were significantly higher in the turmeric paste treated group compared to the control group. Likewise, faster wound contraction and epithelialisation were observed.

**Centella asiatica**

_Centella asiatica_ belongs to the family Apiaceae and is also known as Tiger grass. The plant is commonly cultivated in Asia, mainly in Pakistan and India, Equatorial Africa, and Central America. The medicinal use of _C. asiatica_ in traditional medicine dates back centuries. It has a well-established therapeutic role in various dermatological conditions, such as scratches, wounds, burns, and eczema. The plant is also recommended as an antipyretic, antirheumatic, diuretic, antimicrobial drug, also to relieve anxiety, and improve cognition. Shukla et al. investigated the efficacy of topical applications of 0.2% solution of _C. asiatica_ extract on punch wounds in pigs. He observed a 56% increase in hydroxyproline, a 57% increase in tensile strength, increased collagen content, and effective epithelialisation after the subsequent treatment, concluding that _C. asiatica_ is efficient in healing cutaneous wounds. The main bioactive compounds responsible for wound healing activity of _C. asiatica_ are identified as asiaticoside, madecassoside, asiatic and madecassic acids. The healing potency of asiaticoside isolated from the plant has proven efficient in delayed-type wound healing.

**Curcuma longa**

_Curcuma longa_ Linn. is popularly known as turmeric and belongs to the family Zingiberaceae. _C. longa_ is a famous medicinal herb widely grown and used in Asia. The rhizomes of _C. longa_ are used as spices in food and are also known to possess antibacterial, anti-inflammatory, antioxidant, antiarthritic, antihepatotoxic, anticancer, and antiallergic properties. The ayurvedic practise also claims it to be good for skin ailments, blood purification, wound cleansing, and effective against body toxins, and intestinal worms. The extract of _C. longa_ contains high levels of mineral dyes, curcumin, curcuminoids, phenolic compounds, and volatile oils such as turmerone, atlantone and zingiberene. A study demonstrated the wound healing activity of _C. longa_ rhizome extract on excision wound model in Wistar albino rats. An ointment of 5% w/w ethanolic rhizome extract was prepared and applied topically on the excision wounds of the animals. On the other hand, 5% w/w povidone-iodine was employed as a positive control. The findings revealed that the extract was more potent and had a more rapid onset in wound healing with a faster epithelialisation rate, wound contraction, and complete healing in the treated animals compared to the positive control. However, the study did not evaluate the wound tensile strength. In a similar study, Kundu et al. evaluated the potential efficacy of fresh turmeric (C. longa) paste to heal wounds in a preclinical study. The turmeric paste was applied on the experimentally created full-thickness circular excisional wound in 18 rabbits as a topical medicament under aseptic condition. Wound healing was assessed based on physical, histomorphological, and histochemical parameters. After treatment for 14 days, it was found that the wound tensile strength, collagen, and elastin in reticulin fibre formation were significantly higher in the turmeric paste treated group compared to the control group. Likewise, faster wound contraction and epithelialisation were observed.

**Hippophae rhamnoides**

_Hippophae rhamnoides_ of the family Elaeagnaceae is a high altitude wild shrub that is commonly known as seabuckthorn. All parts of the plant are rich in bioactive substances such as vitamins (A, C, E, and K), carotenoids, flavonoids, organic acids, tannins, and triterpenes. Seabuckthorn is therapeutically used to fight diseases and conditions like flu, cardiovascular disease, mucosal injuries, and skin disorders. The oil extracted from the fruit and seeds of the _H. rhamnoides_ is frequently employed to manage burns, radiation skin lesions, scalds, and gastric and duodenal ulcers. A preclinical study by Gupta et al. determined the wound healing potential of aqueous leaf extracts of _H. rhamnoides_. After creating four full-thickness wounds in albino rats, the aqueous lyophilised extract of seabuckthorn leaves (0.5%, 1.0%, and 1.5% w/v) was applied at the wound site twice daily for seven days. The dose-dependent study found that the topical application of seabuckthorn leaf extract at a dose of 1.0% w/v was the effective baseline dose for wound-healing. The treated rats showed a significant reduction in wound area by 40% compared to the untreated group. It was further clarified that the extract promotes wound healing by increasing the antioxidant levels in the granulation tissue.
flowering plant of the family Hypericaceae, mainly cultivated for commercial use in herbal and traditional medicine. The herb has long been used to treat mild to moderate depression and related symptoms such as anxiety or insomnia. In recent advancements, the antibacterial activity of H. perforatum has been evaluated against various bacterial strains, including Streptococcus mutans, Streptococcus sobrinus, Lactobacillus plantarum, and Enterococcus faecalis.\textsuperscript{139} Today, various creams, and ointments prepared with the isolated compounds from H. perforatum are widely available to manage conditions such as viral and bacterial skin infections.\textsuperscript{140}

**In vivo** study of olive oil’s wound healing activity from the ethanolic extract of the aerial parts of H. perforatum was evaluated in excision and incision wound model in male Sprague Dawley rats. Remarkable wound healing and anti-inflammatory activities were recorded. Subfraction of the ethanolic extract on column chromatography revealed the presence of bioactive compounds including hyperoside, isoquercitrin, rutin, (-)-epicatechin, and hypericin.\textsuperscript{141}

Samadi and co-workers\textsuperscript{142} in a randomised, double-blind clinical trial determined the efficacy of 20\% w/w ointment from the flower extracts of H. perforatum in managing caesarean wounds and hypertrophic scars. The study assessed the wound healing on the 10\textsuperscript{th} day after caesarean section using the REEDA (redness, oedema, ecchymosis, discharge, and approximation) scale. The researchers noticed accelerated wound healing on the 10\textsuperscript{th} day and lower scar formation (90\% patients satisfaction) on the 40\textsuperscript{th} day postpartum with 20\% w/w H. perforatum extract ointment compared to the control groups (68\% patients satisfaction). Additionally, substantially lower pain and pruritus complaints were reported in the treatment group. However, one patient discontinued the treatment due to irritation at the wound site, which was resolved without any medical intervention.

**Napoleona imperialis**

*Napoleona imperialis* is a small evergreen popular Nigerian folklore plant of the family Lecythidaceae.\textsuperscript{143} “The juice of *Napoleona imperialis* obtained from the pods and leaf extracts is consumed, while its seeds are discarded due to their little to no industrial use.”\textsuperscript{144} This woody, several meters high, tropical rainforest plant is also known for its analgesic, tonic, antitussive, antiasthmatic, antibacterial, anti-inflammatory, antihypertensive and wound healing properties.\textsuperscript{143–145}

A study compared the efficacy of herbal ointment (100 mg/g) prepared with *N. imperialis* extract with a standard antibiotic Cicatrin\textsuperscript{*} for wound healing on inflicted excisional wounds in guinea pigs. The results recorded regarding the ointment's topical application revealed a comparable effect of a progressive decrease in the wound area and complete healing (100\%) on days 16, and 19 post-wounding in the herbal ointment treated and the Cicatrin\textsuperscript{*} treated group, respectively. Therefore, this study concludes that the *N. imperialis* extract, at the given concentration, has a better wound healing property than the standard antibiotic such as Cicatrin.\textsuperscript{146}

**Conclusion**

Wound healing is a complicated process involving various cell interactions. Hence, a better understanding of this complex interplay will provide the basis for designing new and effective wound healing therapies from natural sources to alleviate chronic wounds’ socio-economic effect on patients. Numerous preclinical studies have shown that various medicinal plants have the potential to be used for wound healing. This is not surprising as these plants have been reported to possess medicinal compounds such as curcumin, curcumen, germacrone, 1,8-cineole, hyperoside, isoquercitrin, rutin and (-)-epicatechin, hypericin, ellagitannins geraniin, and furosin. Although these results are quite promising, the use of plants for wound healing in clinical settings is still at the infancy stage and needs to be comprehensively and scientifically studied. Perhaps there are a few factors that could have led to this phenomenon: (i) compounds responsible for the wound healing activity in most of these plants have not been identified and isolated, and (ii) the few that have been isolated show that potent activity is often associated with low solubility and poor bioavailability.

There is no effective herbal medicine introduced yet to the market for wound healing. This suggests a critical need for more clinical, toxicity, and efficacy studies to be conducted. Besides, the demands for novel topical drug delivery systems should not be underestimated as it is crucial to improve the therapeutic potentials and delivery of new efficacious phytochemical-based formulations for wound healing and better patient care.

**Acknowledgements**

The authors would like to acknowledge that the work was supported by the Research University Individual (RUI) Grant from Universiti Sains Malaysia (Grant number: 1001/PFARMASI/8012341).

**Author Contributions**

NMU: concept and design, data acquisition and drafting manuscript. TP and SMT: data analysis/interpretation and critical revision of manuscript. All authors have read and agreed to the published version of the manuscript.

**Conflict of Interest**

The authors report no conflicts of interest.

**References**

1. Xu R, Luo G, Xia H, He W, Zhao J, Liu B, Tan J, Zhou J, Liu D, Wang Y, Yao Z, Zhan R, Yang S, Wu J. Novel bilayer wound dressing composed of silicone rubber with particular micropores enhanced wound re-epithelialization and contraction. Biomaterials. 2015;40:1-11. doi:10.1016/j.biomaterials.2014.10.077
2. Kanitakis J. Anatomy, histology and
Beneficial Roles of Medicinal Plants in Promoting Wound Healing

1. Beneficial Roles of Medicinal Plants in Promoting Wound Healing

2. Kolarsick PAJ, Kolarsick MA, Goodwin C. Anatomy and Physiology of the Skin. J Dermatol Nurses Assoc. 2011;3(4):203-13. doi:10.1097/JDN.0b013e3182274a98

3. Dreikle MB, Jayasuriya AA, Jayasuriya AC. Current wound healing procedures and potential care. Mater Sci Eng C. 2015;48:651–62. doi:10.1016/j.msec.2014.12.068

4. Singh S, Young A, McNaught CE. The physiology of wound healing. Surg (United Kingdom). 2017;35(9):473-7. doi:10.1016/j.jsurg.2017.06.004

5. Agyare C, Boakye YD, Bekoe EO, Hensel A, Dapaah SO, Appiah T. Review: African medicinal plants with wound healing properties. J Ethnopharmacol. 2016;177:85-100. doi:10.1016/j.jep.2015.11.008

6. Wong SY, Manikam R, Munirudd S. Prevalence and antibiotic susceptibility of bacteria from acute and chronic wounds in Malaysian subjects. J Infect Dev Ctries. 2015;9(9):936-44. doi:10.3855/jidc.5882

7. Sen CK. Human Wounds and Its Burden: An Updated Compendium of Estimates. Adv Wound Care. 2019;8(2):39-48. doi:10.1089/wound.2019.0946

8. Nussbaum SR, Carter MJ, Fife CE, DaVanzo J, Haught R, Nusgart M, Cartwright D. An economic evaluation of the impact, cost, and medicare policy implications of chronic nonhealing wounds. Value Heal. 2018;21(1):27-32. doi:10.1016/j.jval.2017.07.007

9. Järbrink K, Ni G, Sönnergren H, Schmidtchen A, Pang C, Bajpai R, Car J. Prevalence and incidence of chronic wounds and related complications: A protocol for a systematic review. Syst Rev. 2016;5:152. doi:10.1186/s13643-016-0329-y

10. Lordani TVA, De Lara CE, Ferreira FBP, De Souza Terron Monich M, Da Silva CM, Lordani CRE, et al. Therapeutic effects of medicinal plants on cutaneous wound healing in humans: a systematic review. Mediators Inflamm. 2018;2018:7534250. doi:10.1155/2018/7534250

11. Mathieu D, Linke JC, Wattel F. Non-healing wounds. In: Mathieu D, editor. Handbook on Hyperbaric Medicine. Dordrecht: Springer; 2006. p. 401-28. doi:10.1007/1-4020-4448-8-20

12. Menke NB, Ward KR, Witten TM, Bonchev DG, Diegelmann RF. Impaired wound healing. Clin Dermatol. 2007;25(1):19-25. doi:10.1016/j.clinmeth.2006.12.005

13. Mohanty C, Sahoo SK. Curcumin and its topical formulations for wound healing applications. Drug Discov Today. 2017;22(10):1582-92. doi:10.1016/j.drudis.2017.07.001

14. Walton EW. Topical phytochemicals: Applications for wound healing. Adv Ski Wound Care. 2014;27(7):328-32. doi:10.1097/01.ASW.0000450101.97743.0f

15. Margolis DJ, Hoffstad O, Nafash J, Leonard CE, Freeman CP, Hennessy S, Wiebe DJ. Location, location, location: Geographic clustering of lower-extremity amputation among medicare beneficiaries with diabetes. Diabetes Care. 2011;34(11):2363-7. doi:10.2337/dc11-0807

16. Ahmad J. The diabetic foot. Diabetes Metab Syndr Clin Res Rev. 2016;10(1):48–60. doi:10.1016/j.mpsyr.2014.10.006

17. Dargaville TR, Farrugia BL, Broadbent JA, Pace S, Upton Z, Voelcker NH. Sensors and imaging for wound healing: A review. Biosens Bioelectron. 2013;41(1):30-42. doi:10.1016/j.bios.2012.09.029

18. Anthony D, Alosoumi D, Safari R. Prevalence of pressure ulcers in long-term care: A global review. J Wound Care. 2019;28(11):702-9. doi:10.12968/jowc.2019.28.11.702

19. Shedoeva A, Leavesley D, Upton Z, Fan C. Wound healing and the use of medicinal plants. Evidence-based Complement Altern Med. 2019;2019:2684108. doi:10.1155/2019/2684108

20. Tricco AC, Cogo E, Isaranuwatchai W, Khan PA, Sammugalingham G, Antony J, et al. A systematic review of cost-effectiveness analyses of complex wound interventions reveals optimal treatments for specific wound types. BMC Med. 2015;13:90. doi:10.1186/s12961-015-0326-3

21. Reinke JM, Sorg H. Wound repair and regeneration. Eur Surg Res. 2012;49(1):35–43. doi:10.1159/000339613

22. Sikha A, Harini A, L HP. Pharmacological activities of wild turmeric (Curcuma aromatica Salisb.): a review. J Pharmacogn Phytochem. 2015;3(5):1–4.

23. Shetty BS. Wound Healing and Indigenous Drugs: Role as Antioxidants: A Review. Res Rev J Med Heal Sci. 2012;2(2):5-16.

24. Farjah MH, Farahpour MR. Efficacy of topical platelet-rich plasma and chitosan co-administration on C. albicans-infected partial thickness burn wound healing. Burns. 2020;46(8):1889-95. doi:10.1016/j.burns.2020.05.019

25. Nayak S, Nalabothu P, Sandiford S, Bhogadi V, Adogwa A. Evaluation of wound healing activity of Allamanda cathartica L. and Laurus nobilis L. extracts on rats. BMC Complement Altern Med. 2006;6:12. doi:10.1186/1472-6882-6-12

26. Aly UF. Healing in Diabetics. Int J Pharm Pharm Sci. 2012;4:76-77.

27. Guo S, DiPietro LA. Critical review in oral biology & medicine: Factors affecting wound healing. J Dent Res. 2010;89(3):219-29. doi:10.1177/0022034509359125

28. Bishop A. Role of oxygen in wound healing. J Wound Care. 2008;17(9):399-402. doi:10.12968/jowc.2008.17.9.30937

29. Edwards R, Harding KG. Bacteria and wound healing. Curr Opin Infect Dis. 2004;17(2):91-96. doi:10.1097/00001432-200404000-00004

30. Wang PH, Huang BS, Hornig HG, Yeh CC, Chen YJ. Wound healing. J Chinese Med Assoc. 2018;81(2):94-101. doi:10.1016/j.jcma.2017.11.002

Pharmaceutical Sciences, 2021, 27(4), 48-502 | 497
32. Das MK, Ahmed AB. Formulation and ex vivo evaluation of rofecoxib gel for topical application. Acta Pol Pharm - Drug Res. 2007;64(5):461-467.

33. Abd Jalil MA, Kasmuri AR, Hadi H. Stingless bee honey, the natural wound healer: A review. Skin Pharmacol Physiol. 2017;30(2):66-75. doi:10.1159/000458416

34. Krischak GD, Augat P, Claes L, Kinzl L, Beck A. The effects of non-steroidal anti-inflammatory drug application on incisional wound healing in rats. J Wound Care. 2014;16(2):76-78. doi:10.12968/jowc.2007.16.2.27001

35. Carolina E, Kato T, Khanh VC, Moriguchi K, Yamashita T, Takeuchi K, et al. Glucocorticoid impaired the wound healing ability of endothelial progenitor cells by reducing the expression of CXCR4 in the PGE2 pathway. Front Med. 2018;5:276. doi:10.3389/fmed.2018.00276

36. Slominski AT, Zmijewski MA. Glucocorticoids Inhibit Wound Healing: Novel Mechanism of Action. J Invest Dermatol. 2017;137(5):1012-4. doi:10.1016/j.jid.2017.01.024

37. Charlotte W, Shoaib H, Suzanne T, David B, Alastair R, Samantha H, Keith H. Impact of medications and lifestyle factors on wound healing: A pilot study. Wounds UK. 2013;9(1):22-28.

38. Cheeseman KH. Mechanisms and effects of lipid peroxidation. Mol Aspects Med. 1993;14(2):191-7. doi:10.1016/0098-2997(93)90005-X

39. Wound Care Solutions. 7 Factors that Affect Wound Healing - Wound Care Solutions. 2017. Available at: https://www.woundcareinc.com/resources/factors-that-affect-wound-healing. Accessed 2020-08-12.

40. Ma J-WW, Tsoa TC-YY, Hsi Y-TT, Lin Y-CC, Chen YY, Chen YY, et al. Essential oil of Curcuma aromatica induces apoptosis in human non-small-cell lung carcinoma cells. J Funct Foods. 2016;22:101-12. doi:10.1016/j.jff.2016.01.019

41. Bonab FS, Farahpour MR. Topical co-administration of Pistacia atlantica hull and Quercus infectoria gall hydroethanolic extract improves wound-healing process. Comp Clin Path. 2017;26(4):885-92. doi:10.1007/s00580-017-2473-8

42. Sabale P, Bhimani B, Prajapati C, Sabalea V. An overview of medicinal plants as wound healers. J Appl Pharm Sci. 2012;2(11):143–150. doi:10.7324/JAPS.2012.21127

43. Arnold M, Barbul A. Nutrition and wound healing. Plast Reconstr Surg. 2006;117(7 Suppl):42S-58S. doi:10.1097/01.prs.0000225432.17501.6c

44. Kumar B, Vijayakumar M, Govindarajan R, Pushpagandan P. Ethnopharmacological approaches to wound healing: Exploring medicinal plants of India. J Ethnopharmacol. 2007;114(2):103-13. doi:10.1016/j.jep.2007.08.010

45. Govindarajan R, Vijayakumar M, Rao CV, Shirwaiker A, Mehrotra S, Pushpagandan P. Heating potential of Anogeissus latifolia for dermal wounds in rats. Acta Pharm. 2004;54(4):331-8.

46. Chopda M, Mahajan R. Wound Healing Plants of Jalgaon District of Maharashtra State, India. Ethnobot Leafl. 2009;2009(1):1-32.

47. Ahmad S, Ali M, Ansari SH, Ahmed F. Phytoconstituents from the rhizomes of Curcuma aromatica Salisb. J Saudi Chem Soc. 2011;15(3):287-90. doi:10.1016/j.jscs.2010.10.011

48. Thakur R, Jain N, Pathak R, Sandhu SS. Practices in wound healing studies of plants. Evidence-based Complement Altern Med. 2011;2011:438056. doi:10.1155/2011/438056

49. Kim J, Lee CW, Kim EK, Lee SJ, Park NH, Kim HS, et al. Inhibition effect of Gynura procumbens extract on UV-B-induced matrix-metalloproteinase expression in human dermal fibroblasts. J Ethnopharmacol 2011;137(1):427-33. doi:10.1016/j.jep.2011.04.072

50. Mutheeswaran S, Pandikumar P, Chellappandan M, Ignacimuthu S. Documentation and quantitative analysis of the local knowledge on medicinal plants among traditional Siddha healers in Virudhunagar district of Tamil Nadu, India. J Ethnopharmacol. 2011;137(1):523-33. doi:10.1016/j.jep.2011.06.003

51. Ganeshkumar M, Ponrasu T, Krithika R, Iyappan K, Gayathri VS, Suguna L. Topical application of Acalypha indica accelerates rat cutaneous wound healing by up-regulating the expression of Type I and III collagen. J Ethnopharmacol. 2012;142(1):14-22. doi:10.1016/j.jep.2012.04.005

52. Liao HM, Sheng XY, Hu ZH. Ultrastructural studies on the process of aloin production and accumulation in Aloe arborescens (Asphodelaceae) leaves. Bot J Linn Soc. 2006;150(2):241-7. doi:10.1111/j.1095-8539.2006.00452.x

53. Hashemi SA, Madani SA, Abediankenari S. The review on properties of aloe vera in healing of cutaneous wounds. Biomed Res Int. 2015;2015:714216. doi:10.1155/2015/714216

54. Gharaboghz MNZ, Farahpour MR, Saghieh S. Topical co-administration of Teucrium polium hydroethanolic extract and Aloe vera gel triggered wound healing by accelerating cell proliferation in diabetic mouse model. Biomed Pharmacother. 2020;127:110189. doi:10.1016/j.biopha.2020.110189

55. Chithra P, Sajithlal GB, Chandrakasan G. Influence of Aloe vera on the healing of dermal wounds in diabetic rats. J Ethnopharmacol. 1998;59(3):195-201. doi:10.1016/S0378-8741(97)00124-4

56. Lucini L, Pellizzoni M, Pellegrino R, Molinari G Pietro, Colla G. Phytochemical constituents and in vitro radical scavenging activity of different Aloe species. Food Chem. 2015;170:501-7. doi:10.1016/j.foodchem.2014.08.034

57. Pellizzoni M, Ruizickova G, Kalhotka L, Lucini L. Antimicrobial activity of different Aloe barbadensis Mill. and Aloe arborescens Mill. leaf fractions. J Med Plants Res. 2012;6(10):1975-81. doi:10.5897/
Beneficial Roles of Medicinal Plants in Promoting Wound Healing

58. Grindlay D, Reynolds T. The Aloe vera phenomenon: A review of the properties and modern uses of the leaf parenchyma gel. J Ethnopharmacol. 1986;16(2-3):117-51. doi:10.1016/0378-8741(86)90085-1

59. Barua CC, Ara Begum S, Talukdar A, Datta Roy J, Buragohain B, Chandra Pathak D, et al. Influence of Alternanthera brasiliana (L.) Kuntze on Altered Antioxidant Enzyme Profile during Cutaneous Wound Healing in Immuno-compromised Rats. ISRN Pharmacol. 2012;2012:948792. doi:10.5402/2012/948792

60. Macedo AF, Barbosa NC, Esquibel MA, Souza MM, Cechinel-Filho V. Pharmacological and phytochemical studies of callus culture extracts from Alternanthera brasiliana. Pharmazie. 1999;54(10):776-7.

61. Biavatti M, Bellaver M, Volpato L, Costa C, Bellaver C. Preliminary studies of alternative feed additives for broilers: Alternanthera brasiliana extract, propolis extract and linseed oil. Rev Bras Ciência Avícola. 2003;5(2):147-151. doi:10.1590/S1516-635X2003000200009

62. Lagrota MHC, Wigg MD, Santos MMG, Miranda MMFS, Camara FP, Couceiro JNSS, et al. Inhibitory activity of extracts of Alternanthera brasiliana (amaranthaceae) against the herpes simplex virus. Phythyr Res. 1994;8(6):358-61. doi:10.1002/ptr.2650080609

63. Kumar MS, Sripriya R, Raghavan HV, Sehgal PK. Wound healing potential of Cassia fistula on infected albino rat model. J Surg Res. 2006;131(2):283-89. doi:10.1016/j.jss.2005.08.025

64. Gupta A, Kumar R, Pal K, Banerjee PK, Sawhney RC. A preclinical study of the effects of seabuckthorn (Hippophae rhamnoides L) leaf extract on cutaneous wound healing in albino rats. Int J Low Extrem Wounds. 2005;4(2):88-92. doi:10.1177/1534734605277401

65. Reddy JS, Rao PR, Reddy MS. Wound healing effects of Heliotropium indicum, Plumbago zeylanicum and Acalypha indica in rats. J Ethnopharmacol. 2002;79(2):249-51. doi:10.1016/S0378-8741(01)00388-9

66. Jaswanth A, Akilandeswari, Loganathan V, Manimaran S, Ruckmani. Wound Healing Activity of Aegle marmelos. Indian J Pharm Sci. 2001;63(1):41-4.

67. Shirwaikar A, Somashekar AP, Udupa AL, Udupa SL, Somashekar S. Wound Healing studies of Aristolochia bracteolata Lam. with supportive action of antioxidiant enzymes. Phytotherapy. 2003;10(6-7):558-62. doi:10.1076/phbi.10.6-7.558.62

68. Patil MB, Jalalpure SS, Ashraf A. Preliminary phytochemical investigation and wound healing activity of the leaves of Argemone mexicana linn. (papaveraceae). Indian Drugs. 2001;38(6):288-93.

69. Khan M, Patil PA, Shobha JC. Influence of Bryophyllum pinnatum (Lim.) Leaf Extract on Wound Healing in Albino Rats. J Nat Remedies. 2004;4(1):41-6.

70. Sumitra M, Manikandan P, Suguna L. Efficacy of Butea monosperma on dermal wound healing in rats. Int J Biochem Cell Biol. 2005;37(3):566-73. doi:10.1016/j.biocel.2004.08.003

71. Mohideen S, Ilavarasan R, Hemalatha S, Anitha N, Sasikala E. Wound healing and diuretic activities of Canthium parviflorum Lam. Nat Prod Sci. 2003;9(2):102-4.

72. Priya KS, Arumugam G, Rathinam B, Wells A, Babu M. Celosia argentea Linn. leaf extract improves wound healing in a rat burn wound model. Wound Repair Regen. 2004;12(6):618-25. doi:10.1111/j.1067-1927.2004.12603.x

73. Kamath J V, Rana AC, Chowdhury AR. Pro-healing effect of Cinnamomum zeylanicum bark. Phyther Res. 2003;17(8):970-2. doi:10.1002/ptr.1293

74. Farahpour MR, Habibi M. Evaluation of the wound healing activity of an ethanolic extract of Ceylon cinnamon in mice. Vet Med (Praha). 2012;57(1):53-7. doi:10.17221/4972-VETMED

75. Prabhakar KR, Srinivasan KK, Rao PG. Chemical investigation, anti-inflammatory and wound healing properties of Coronopus didymus. Pharm Biol. 2003;40(7):490-3. doi:10.1076/phbi.40.7.490.14684

76. Puratchikody A, Devi CN, Nagalakshmi G. Wound healing activity of Cyperus rotundus linn. Indian J Pharm Sci. 2009;68(4):97-101. doi:10.4103/0250-474x.22976

77. Priya KS, Gnanamani A, Radhakrishnan N, Babu M. Healing potential of Datura alba on burn wounds in albino rats. J Ethnopharmacol 2002;83(3):193-9. doi:10.1016/S0378-8741(02)00195-2

78. Shirwaikar A, Jahagirdar S, Udupa AL. Wound healing activity of Desmodium trifidum leaves. Indian J Pharm Sci. 2003;65(5):461-4.

79. Singh SDJ, Krishna V, Mankanl KL, Manjunatha BK, Vidy SM. Wound healing activity of the leaf extracts and deoxyelephantopin isolated from Elephantopus scaber Linn. Indian J Pharmocol. 2005;37(4):238-42.

80. Hukkeri VI, Karadi R V, Akki KS, Savadi R V, Rajprakash B, Kuppast IJ, Patil MB. Wound healing property of Eucalyptus globulus L. leaf extract'. Indian Drugs. 2002;39(9):481-3.

81. Umadevi S, Mohanta G, Kalaiavelan V, Manavalan R. Studies on wound healing effect of Flaveria trinervia leaf in mice. Indian J Pharm Sci. 2006;68(1):106-8. doi:10.4103/0250-474X.22979

82. Mathew A, Taranalli AD, Torgal SS. Evaluation of anti-inflammatory and wound healing activity of Gentianella lutea rhizome extracts in animals. Pharm Biol. 2004;42(1):8-12. doi:10.1080/07088800390502883

83. Kishore Gnana Sam S, Senthil Kumar B, Ramachandran S, Saravanan M, Sridhar SK. Antioxidant and wound healing properties of Glycyrrhiza glabra root extract. Indian Drugs. 2001;38(7):355-7.

84. Shirwaikar A, Ghosh S RP. Effects of Gymelina arborea Roxb. leaves on wound healing in rats. J Nat Rem. 2003;3(1):45-8. doi:10.18311/jntr/2003/362

85. Mukherjee PK, Suresh B. The evaluation of wound-healing potential of Hypericum hookerianum leaf and stem extracts. J Altern Complement Med.
86. Mukherjee PK, Suresh B. Studies on in-vivo wound healing activity of leaf extract of Hypericum mysoresense with different wound model in rats. Nat Prod Sci. 2006;6(2):73-8.

87. Mukherjee PK, Verpoorte R, Suresh B. Evaluation of in-vivo wound healing activity of Hypericum putilum (Family: Hypericaceae) leaf extract on different wound model in rats. J Ethnopharmacol. 2006;70(3):315-21. doi: 10.1016/S0378-8741(99)00172-5

88. Shirwaiker A, Shenoy R, Udupa AL, Udupa SL, Shetty S. Wound healing property of ethanolic extract of leaves of Hystis suaveolens with supportive role of antioxidant enzymes. Indian J Exp Biol. 2003;41(3):238-41.

89. Hemalatha S, Subramanian N, Ravich V. Wound healing activity of indigofera enneaphylla linn. Indian J Pharm Sci. 2001;63(4):331-3.

90. Nayak BS, Udupa AL, Udupa SL. Effect of Isora coccinea flowers on dead space wound healing in rats. Fitoterapia. 1999;70(3):233-6. doi: 10.1016/S0367-326X(99)00025-8

91. Dash G, Suresh P, Ganapaty S. Studies on hypoglycaemic and wound healing activities of Lantana camara Linn. J Nat Remedies. 2001;1(2):105-110. doi: 10.18311/jnr/2001/16

92. Patil KS, Mandawgade SD. Wound healing activity of the leaves of Lawsonia alba Lam. J Nat Remedies. 2003;3(2):129-133. doi: 10.18311/jnr/2003/151

93. Daemi A, Farahpour MR, Oryan A, Karimzadeh S, Tajar E. Topical administration of hydroethanolic extract of Lawsonia inermis (Henna) accelerates excisional wound healing process by reducing tissue inflammation and amplifying glucose uptake. Kaohsiung J Med Sci. 2019;35(1):24-32. doi: 10.1002/kjm2.12005

94. Manjunatha B, Vidya S, Krishna V, Mankani K. Wound healing activity of Leucas hirta. Indian J Pharm Sci. 2006;68(3):380-4. doi: 10.4103/0250-474X.26681

95. Singh S, Singh R, Kumar N, Kumar R. Wound healing activity of ethanolic extract of Plantago Ovata (Isphagula) seeds. J Appl Pharm Sci. 2011;1(7):108-11.

96. Udupa SL, Shetty S, Udupa AL, Somayaji SN. Effect of Ocimum sanctum Linn. on normal and dexamethasone suppressed wound healing. Indian J Exp Biol. 2006;44(1):49-54.

97. Taranalli AD, Tipare S V, Kumar S, Torgal SS. Wound healing activity of Oxalis corniculata whole extract in rats. Indian J Pharm Sci. 2004;66(4):444-6.

98. Nayak BS, Vinutha B, Geetha B, Sudha B. Experimental evaluation of Pentas lanceolata flowers for wound healing activity in rats. Fitoterapia. 2005;76(7-8):671-5. doi: 10.1016/j.fitote.2005.08.007

99. Suguna L, Sumitra M, Chandrakasan G. Influence of Phyllanthus emblica extract on dermal wound healing in rats. J Med Aromat Plants. 2000;3:2-3.

100. Singh M, Govindarajan R, Nath V, Rawat AKS, Mehrotra S. Antimicrobial, wound healing and antioxidant activity of Plagiochasma appendiculatum flowers for wound healing in rats. J Med Aromat Plants. 2000;3(2):2-3.
Beneficial Roles of Medicinal Plants in Promoting Wound Healing

doi:10.1186/1472-6882-12-166

115. Paswan SK, Srivastava S, Rao CV. Wound healing and antimicrobial activities of ethanolic extract of *Amaranthus spinosus*. Int J Sci Technol Res. 2020;9(3):6606-10.

116. Paswan SK, Srivastava S, Rao CV. Wound healing, antimicrobial and antioxidant efficacy of *Amaranthus spinosus* ethanolic extract on rats. Biocatal Agric Biotechnol. 2020;26:101624. doi:10.1016/j.bcab.2020.101624

117. Maan P, Yadav KS, Yadav NP. Wound Healing Activity of *Azadirachta indica* A. Juss Stem Bark in Mice. Pharmacogn Mag. 2017;13(50):S316-20. doi:10.4103/0973-1296.210163

118. Chundran NK, Husen IR, Rubianti I. Effect of Neem Leaves Extract (*Azadirachta Indica*) on Wound Healing. Althea Med J. 2015;2(2):199-203. doi:10.15850/amj.v2n2.535

119. Gupta RK. Medicinal and Aromatic Plants. New Delhi: CBS publishers and distributors; 2010. p. 234-499.

120. Danish M, Singh P, Mishra G, Srivastava S, Jha KK, Khosa RL. Cassia fistula Linn. (Amulthus)-An important medicinal plant: A review of its traditional uses, phytochemistry and pharmacological properties. J Nat Prod Plant Resour. 2011;1:101-18.

121. Gajalakshmi S, Vijayalakshmi S, Rajeswari D V. Pharmacological activities of *Centella asiatica*: A perspective review. Int J Pharma Bio Sci. 2013;4(2):431-9.

122. Loh K. Know the Medicinal Herb: *Catharanthus roseus* (Vinca rosea). Malaysian Fam physician  Off J Acad Fam Physicians Malaysia. 2008;3(2):123.

123. Nayak BS, Pinto Pereira LM. *Catharanthus roseus* flower extract has wound-healing activity in Sprague Dawley rats. BMC Complement Altern Med. 2006;6:41. doi:10.1186/1472-6882-6-41

124. Bylka W, Znajdek-Awiżeń P, Studzińska-Sroka E, Brzezińska M, Bylka W, Znajdek-Awiżeń P, Studzińska-Sroka E, Brzezińska M. *Centella asiatica* in cosmetology. Postepy Dermatol Alergol. 2013;30(1):46-9. doi:10.5114/pda.2013.33378

125. Gohil KJ, Patel JA, Gajjar AK. Pharmacological review on *Centella asiatica*: A Potential herbal cure-all. Indian J Pharm Sci. 2010;72(5):546-56. doi:10.4103/0250-474X.78519

126. Shukla A, Rasik AM, Jain GK, Shankar R, Kulkhrestha DK, Dhawan BN. In vitro and in vivo wound healing activity of asiaticoside isolated from *Centella asiatica*. J Ethnopharmacol. 1999;65(1):1-11. doi:10.1016/S0378-8741(98)00141-x

127. James I, Dubery I. Identification and quantification of triterpenoid centeloids in *Centella asiatica* (L.) Urban by densitometric TLC. JPC-J Planar Chromat. 2011;24(1):82-7. doi:10.1556/jpc.24.2011.1.16

128. Shukla A, Rasik AM, Dhawan BN. Asiaticoside-induced elevation of antioxidant levels in healing wounds. Phyother Res. 1999;13(1):50-4. doi:10.1002/(SICI)1099-1573(199902)13:1<50::AID-PTR368>3.0.CO;2-V

129. Lee J, Jung E, Kim Y, Park J, Park J, Hong S, et al. Asiaticoside induces human collagen I synthesis through TGF beta receptor I kinase (TbetaR1 kinase)-independent Smad signaling. Planta Med. 2006;72(4):324-8. doi:10.1055/s-2005-916227

130. Kimura Y, Sumiyoshi M, Samukawa K-I, Satake N, Sakanaka M. Facilitating action of asiaticoside at low doses on burn wound repair and its mechanism. Eur J Pharmocol. 2008;584(2-3):415-23. doi:10.1016/j.ejphar.2008.02.036

131. Purolat SK, Solanki R, Mathur V, Mathur M. Evaluation of Wound Healing Activity of Ethanolic Extract of *Carcuma longa* Rhizomes in Male Albino Rats. Asian J Pharm Res. 2013;3(2):79-81.

132. Farahpour MR, Peyman Emami SJG. *In vitro* antioxidant properties and wound healing activities of hydroethanolic turmeric rhizome extract (*Zingiberaceae*). Int J Pharm Pharm Sci. 2014;6(8):474-8.

133. Li S. Chemical composition and product quality control of turmeric (*Curcuma longa* L.). Pharm Crop. 2011;5(1):28-54. doi:10.2174/2120920601102010027

134. Lobo R, Prabhu KS, Shirwaikar A, Shirwaikar A. *Curcuma zedoaria* Rosc. (white turmeric): a review of its chemical, pharmacological and ethnomedicinal properties. J Pharm Pharmacol. 2008;61(1):13-21. doi:10.1211/jpp.61.01.0003

135. Kundu S, Biswas TK, Das P, Kumar S, Kumar De D. Turmeric (*Curcuma longa*) rhizome paste and honey show similar wound healing potential: A preclinical study in rabbits. Int J Low Extrem Wounds. 2005;4(4):205-13. doi:10.1177/1537473605281674

136. Kallio H, Yang B, Peippo P. Effects of different origins and harvesting time on vitamin C, tocopherol, and tocotrienols in sea buckthorn (*Hippophae rhamnoides*) berries. J Agric Food Chem. 2002;50(21):6136-42. doi:10.1021/jf020421v

137. Beveridge T, Li TSC, Oomah BD, Smith A. Sea buckthorn products: Manufacture and composition. J Agric Food Chem. 1999;47(9):3480-8. doi:10.1021/jf981331m

138. Xing J, Yang B, Dong Y, Wang B, Wang J, Kallio HP. Effects of sea buckthorn (*Hippophae rhamnoides*) pulp oil and pulp oil on experimental models of gastric ulcer in rats. Fitoterapia. 2002;73(7-8):644-50. doi:10.1016/s0367-326x(02)00221-6

139. Süntar I, Oyardi O, Akkol EK, Özcelik B. Antimicrobial effect of the extracts from *Hypericum perforatum* against oral bacteria and biofilm formation. Pharm Biol. 2016;54(6):1065-70. doi:10.3109/13880209.2015.1102948

140. Saddique Z, Naeem I, Maimoona A. A review of the antibacterial activity of *Hypericum perforatum* L. J Ethnopharmacol. 2010;131(3):511-21. doi:10.1016/j.jep.2010.07.034
141. Süntar IP, Akkol EK, Yılmazer D, Baykal T, Kirmizibekmez H, Alper M, et al. Investigations on the in vivo wound healing potential of *Hypericum perforatum* L. *J Ethnopharmacol*. 2010;127(2):468-77. doi:10.1016/j.jep.2009.10.011

142. Samadi S, Khadivzadeh T, Emami A, Moosavi NS, Tafaghodi M, Behnam HR. The effect of *Hypericum perforatum* on the wound healing and scar of cesarean. *J Altern Complement Med*. 2010;16(1):113-7. doi:10.1089/acm.2009.0317

143. Ben I, Etim O, Udo N. Anti-inflammatory effects of *Napoleona imperialis* P. Beauv. (Lecythidaceae) on rat model of inflammation. *Indian J Heal Sci*. 2016;9(1):89-95. doi:10.4103/2349-5006.183686

144. Chah KF, Eze CA, Emuelosi CE, Esimone CO. Antibacterial and wound healing properties of methanolic extracts of some Nigerian medicinal plants. *J Ethnopharmacol*. 2006;104(1-2):164-7. doi:10.1016/j.jep.2005.08.070

145. Nagori BP, Solanki R. Role of medicinal plants in wound healing. *Res J Med Plant*. 2011;5(4):392-405. doi:10.3923/rjmp.2011.392.405

146. Esimone C, Ibezim E, Chah K. The wound healing effect of herbal ointments formulated with *Napoleona imperialis*. *J Pharm Allied Sci*. 2006;3(1):294-9. doi:10.4314/jophas.v3i1.34994