

The following manuscript was accepted for publication in Pharmaceutical Sciences. It is assigned to an issue after technical editing, formatting for publication and author proofing

Citation: Umar NM, Parumasivam T, Toh S. An Overview of Cutaneous Wounds and the Beneficial Roles of Medicinal Plants in Promoting Wound Healing, Pharm Sci. 2021, doi: 10.34172/PS.2021.16

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

Nura Muhammad Umar^{1*}, Thaigarajan Parumasivam¹, Seok-Ming Toh¹

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

Running title: Beneficial Roles of Medicinal Plants in Promoting Wound Healing

Corresponding authors details:

Name: Nura Muhammad Umar

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

Email address: chemistnuratbw@gmail.com

Phone number: +2347030504044

ABSTRACT

It is undeniable that many patients worldwide suffer from various types of wounds, especially from 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.

Keywords: Wound healing, medicinal plants, chronic wounds.

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.¹ Skin is essentially elastic, with mucous membranes lining the surface of the body.²

Skin is composed of three layers (Figure 1), namely the epidermis, dermis, and hypodermis (subcutaneous tissue).² 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.³ 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.⁴

According to the Wound Healing Society (WHS), wounds are injuries inflicted by physical, chemical, or microbial agents that disrupt the anatomic structure of healthy skin and loss of its function.⁵ 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,⁵ and they continue to significantly affect the quality of life

and the cost of healthcare services.⁶ Most chronic wounds are ulcerative, including vascular ulcers, diabetic ulcers and pressure ulcers.^{5,7}

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.⁸ It is estimated that around 1 - 2 % of people in the developed countries will have a chronic wound during their lifetime.^{9,10} In the United States of America (USA) alone, it is estimated that over 6 million people suffer from chronic wounds¹¹⁻¹⁴. In comparison to the United Kingdom (UK), Walton¹⁵ reported that 1 % of the UK population has a chronic wound.

Moreover, it is reported that 10 - 25 % of patients who have diabetes would develop chronic foot ulcers,^{16,17}. Hence, in the USA, diabetes remains the primary cause of nontraumatic leg amputations (up to 90 %).¹⁸ 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.^{4,19} As a result, North America has spent over \$25 billion per year managing chronic wounds²⁰ 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.^{15,21} 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.¹¹ 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, ScienceDirect, 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.^{5,22-25} 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.²⁶

Studies conducted by Aly,²⁷ and Guo & DiPietro²⁸ 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 supply²⁹ and microbial infection,³⁰ 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.^{31,32} 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.^{33,34} 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.³⁴ Other medications including glucocorticoid steroids (e.g., cortisol and dexamethasone)^{35,36} and chemotherapeutic drugs (e.g., Avastin, methotrexate and nitrogen mustard)³⁷ interfere with blood clotting or platelet function, or inflammatory responses and cell proliferation that significantly delay wound healing.²⁸

ii. Diabetes mellitus

Diabetes mellitus causes oxidative destruction of cellular membranes, and redox imbalance within the cells called oxidative stress³⁸ 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.⁵ They, in turn, cause tissue injury by lipid peroxidation of membranes and oxidation of essential proteins and enzymes,²⁴ which may lead to delayed healing or chronic wounds.⁷ 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.²⁸

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.³⁹ Studies have revealed that chronic wounds are commonly found among elderly patients aged 65 and above.^{7,40} The delayed wound healing in the elderly population is also associated with a decreased inflammatory response, delayed re-epithelisation, collagen formation and angiogenesis.^{28,41}

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.⁴² Often, a more significant amount of carbohydrate, protein, fat, vitamins, and minerals are required for patients with chronic or non-healing wounds.⁴³

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.⁴⁴ For instance, plants containing carotenoids and polyphenolic flavonoids have demonstrated powerful antioxidant and wound healing properties.⁶ 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.^{24,45} 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.⁴⁶ Besides, active chemical phytochemicals were only identified in a couple of cases.^{45,47} 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.⁴⁸

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.⁴⁹ The dried leaves of the plant are prepared as a poultice to treat bedsores and wounds, with its juice added to oil or lime, to treat a variety of skin disorders.⁵⁰

A study carried out in India, investigated the biochemical and molecular rationale behind the healing potential of *A. indica* on dermal wounds in male Wistar rats.⁵¹ The plant extracts (40 mg/kg) were applied topically once a day on full-thickness excision wounds and various biochemical, biophysical, and histopathological changes were investigated. The treatment showed mitigation in the oxidative stress and decreased lipid peroxidation, which consequently and interestingly results in increased ascorbic acid tissue concentration. Enhanced wound contraction rates, epithelialisation, elevated shrinkage temperature, and high tensile strength were also recorded in the extract-treated rats. Improved cellular proliferation and increased

TNF- α (tumour necrosis factor-alpha) levels were also observed during the early stages of wound healing, which up-regulated TGF- β 1 (transforming growth factor-beta) and elevated collagen synthesis. Hence, the authors attributed the mechanism of wound healing of *A. indica* via increasing the collagen synthesis and antioxidative potential.

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.⁵²⁻⁵⁴ *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.⁵⁵⁻⁵⁸

Chithra *et al.*⁵⁵ 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 brasiliiana* 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.⁵⁹ Studies have shown that its extracts exhibit antinociceptive effects,⁶⁰ antimicrobial effects,⁶¹ and anti-herpes simplex viruses activity.⁶²

Barua *et al.*,⁵⁹ 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 vermifuge.⁶³ It is also found to be helpful in wound healing and rheumatism.⁶⁴ *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.⁶⁵

Paswan *et al.*⁶⁶ 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.⁶⁷

Neem leaves contain active ingredients such as nimbidin, sodium nimbidate, nimbin, and nimbidol which possess anti-inflammatory, antibacterial, antifungal, antiviral, and wound healing properties.⁶⁸ 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.⁶⁸

Mann *et al.*⁶⁷ 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 μ g/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 ± 3.88 mg/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 Caesalpinaceae, 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.⁶⁹ 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.⁷⁰

A study conducted by Kumar *et al.*⁷¹ 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 show 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 found commonly in tropical countries, and this plant has been medicinally used as a remedy for various conditions, from headache to diabetes.⁷² In Malaysia, it is locally called *Kemunting Cina*.⁷³ With 400 identified alkaloids present, the plant has some approved medicinal use as an antineoplastic agent to treat leukaemia, Wilms' tumour, malignant lymphomas, rhabdomyosarcoma, neuroblastoma, and other cancers.⁷²⁻⁷⁴

Nayak & co-workers⁷⁴ investigated antimicrobial and wound healing activity of the ethanol flower extract of *C. roseus* using excision, incision and dead space wound models in Sprague Dawley rats. Oral and topical applications of 100 mg/kg of the ethanolic extract for 15 days showed that *C. roseus* promoted wound healing as it significantly enhanced wound tensile strength, epithelialisation, and rate of wound contraction compared to untreated controls. The ethanol extract was also bactericidal against *Pseudomonas aeruginosa* and *Staphylococcus aureus* that were tested in the study.

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.⁷⁵ The plant is also recommended as an antipyretic, antirheumatic, diuretic, antimicrobial drug, also to relieve anxiety, and improve cognition.⁷⁶

Shukla *et al.*⁷⁷ 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 epithelisation 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.⁷⁸ The healing potency of asiaticoside isolated from the plant has proven efficient in delayed-type wound healing.^{77,79-}

81

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.⁸² The ayurvedic practise also claims it to be good for skin ailments, blood purification, wound

cleansing, and effective against body toxins, and intestinal worms.⁸³ The extract of *C. longa* contains high levels of mineral dyes, curcumin, curcuminoids, phenolic compounds, and volatile oils such as turmerone, atlantone and zingiberene.^{84,85}

A study demonstrated the wound healing activity of *C. longa* rhizome extract on the 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 epithelisation rate, wound contraction, and complete healing in the treated animals compared to the positive control.⁸² However, the study did not evaluate the wound tensile strength.

In a similar study, Kundu *et al.*⁸⁶ 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 and reticulin fibre formation were significantly higher in the turmeric paste treated group compared to the control group. Likewise, faster wound contraction and epithelisation 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.⁸⁷

Seabuckthorn is therapeutically used to fight diseases and conditions like flu, cardiovascular disease, mucosal injuries, and skin disorders.⁸⁸ 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.⁸⁹

A preclinical study by Gupta *et al.*⁹⁰ 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.

Hypericum perforatum

Hypericum perforatum, known as St John's wort, is a 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*.⁹¹ 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.⁹²

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.⁹³

Samadi & co-workers⁹⁴ 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 10th-day post-caesarean section using the REEDA (redness, oedema, ecchymosis, discharge, and approximation) scale. The researchers noticed accelerated wound healing on the 10th day and lower scar formation (90% patients satisfaction) on the 40th 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.⁹⁵ 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.⁹⁶ 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.⁹⁵⁻⁹⁷

A study compared the efficacy of herbal ointment (100 mg/g) prepared with *N. imperialis* extract with a standard antibiotic Cicatrin® 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® 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.⁹⁸

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, curcumene, 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.

Acknowledgement

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).

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 ¹	Reference
Golden Trumpet (<i>allmanda cathartica</i>)	Leaves	Water	Crude extract	Excision and incision	[26]
Axlewood (<i>anogeissus latifolia</i>)	Bark	Ethanol	Crude extract	Excision and incision	[45]
Golden shower (<i>cassia fistula</i>)	Leaves	Ethanol	Ointment	Excision	[71]

¹ 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.^{26,145} 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.^{137,146} 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.^{103,137} 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.⁴⁸

Plant Common name (scientific name)	Plant part used	Extraction solvent used	Formulation	Wound model studied¹	Reference
Seabuckthorn (<i>hippophae rhamnoides</i>)	leaves	Water	Crude extract	Excision	[90]
Indian Copperleaf (<i>acalypha indica</i>)	Whole plant	Ethanol	Crude extract	Excision and incision	[99]
Indian heliotrope (<i>heliotropium indicum</i>)	Whole plant	Ethanol	Crude extract	Excision and incision	[99]
Chitrak (<i>plumbago zeylanicum</i>)	Whole plant	Ethanol	Crude extract	Excision and incision	[99]
Bael (<i>aegle marmelos</i>)	Leaves	Methanol	Ointment	Excision and incision	[100]
Worm Killer (<i>aristolochia bracteolata</i>)	Leaves	Ethanol	Crude extract	Excision, incision and dead space	[101]
Mexican poppy (<i>argemone mexicana</i>)	Leaves	Ethanol	Crude extract	Excision, incision and dead space wounds	[102]
Air plant (<i>bryophyllum pinnatum</i>)	Leaves	Water	Crude extract	Excision, incision and dead space	[103]
Flame of the forest (<i>butea monosperma</i>)	Bark	Ethanol	Crude extract	Excision	[104]
Carray Cheddle (<i>canthium parviflorum</i>)	Leaves	Ethanol and water	Ointment	Excision	[105]
Silver cock's comb (<i>celosia argentea</i>)	Leaves	Ethanol	Ointment	Rat burn wound	[106]
Cinnamon (<i>cinnamomum zeylanicum</i>)	Bark	Ethanol	Crude extract	Excision, incision and dead space	[107,108]
Swine cress (<i>coronopus didynamous</i>)	Whole plant	Ethanol and water	Crude extract	Incision	[109]
Nut Sedge (<i>cyperus rotundus</i>)	Rhizomes	Ethanol	Ointment	Excision, incision and dead space	[110]
Thorn Apple (<i>datura alba</i>)	Leaves	Ethanol	Ointment	Burn rat wound	[111]
Trefle Gros (<i>desmodium triquetrum</i>)	Leaves	Ethanol	Crude extract	Excision, incision and dead space	[112]
Elephant's Foot (<i>elephantopus scaber</i>)	Leaves	Ethanol and water	Gel	Excision, incision and dead space	[113]
Tasmanian bluegum (<i>eucalyptus globulus</i>)	Leaves	Ethanol	Crude extract	Excision, incision and dead space	[114]
Clustered yellowtops (<i>flaveria trinervia</i>)	Leaves	Methanol	Ointment	Excision and incision	[115]
Yellow gentian (<i>gentiana lutea</i>)	Rhizomes	Ethanol and petroleum ether	Crude extract	Excision, incision and dead space models	[116]
Licorice (<i>glycyrrhiza glabra</i>)	Root	Ethanol	Crude extract	Excision	[117]
Gamhar (<i>gmelina arborea</i>)	Leaves	Ethanol	Crude extract	Excision, incision and dead space	[118]
St John's wort (<i>hypericum hookerianum</i>)	leaves	Methanol	Ointment	Incision and excision	[119]

Plant Common name (scientific name)	Plant part used	Extraction solvent used	Formulation	Wound model studied ¹	Reference
Mysore St John's Wort (<i>hypericum mysorense</i>)	Leaves	Methanol	Ointment	Excision and incision	[120]
Yellow mosqueta (<i>hypericum patulatum Thumb</i>)	Leaves	Methanol	Ointment	Excision and incision	[121]
Pignut (<i>hyptis suaveolens</i>)	Leaves	Ethanol	Crude extract	Excision, incision and dead space	[122]
Birdsville indigo (<i>indigofera enneaphylla</i>)	Aerial	Ethanol	Ointment	Excision and incision	[123]
Jungle geranium (<i>ixora coccinea</i>)	Flowers	Ethanol	Crude extract	Dead space	[124]
Big-sage (<i>lantana camara</i>)	Leaves	Hydro-alcohol	Crude extract	Excision	[125]
Henna (<i>lawsonia alba</i>)	Leaves	Chloroform, Ethanol and petroleum ether	Crude extract	Excision and incision	[126,127]
Thumbai (<i>leucas hirta</i>)	Leaves	Methanol and water	Ointment gel	Excision, incision and dead space	[128]
Ispaghula (<i>Plantago Ovata</i>)	Seeds	Ethanol	Ointment	Excision and incision	[129]
Holy basil (<i>ocimum sanctum</i>)	Leaves	Ethanol	Crude extract	Excision, incision and dead space	[130]
Creeping woodsorrel (<i>oxalis corniculata</i>)	Whole plant	Ethanol and petroleum ether	Crude extract	Excision, incision and dead space	[131]
Egyptian starcluster (<i>pentas lanceolata</i>)	Flowers	Ethanol	Crude extract	Excision	[132]
Emblic (<i>phyllanthus emblica</i>)	Leaves	Ethanol	Crude extract	Excision	[133]
Indian liverwort (<i>plagiochasma appendiculatum</i>)	Thalli	Chloroform , Acetone, Ethanol and Water	Crude extract	Excision and incision	[134]
Pomegranate (<i>punica granatum</i>)	Peels	Methanol	Gel	Excision	[135]
Aleppo Oak (<i>quercus infectoria</i>)	Galls	Water	Crude extract	Excision, incision and dead space	[136]
Purple tephrosia (<i>tephrosia purpurea</i>)	Aerial	Methanol	Ointment	Excision, incision and dead space	[137]
Arjun (<i>Terminalia arjuna</i>)	Bark	50% Ethanol	Ointment	Excision and incision	[138]
Chebulic myrobalan (<i>terminalia chebula</i>)	Leaves	Ethanol	Crude extract	Incision and In vitro	[139]
Portia tree (<i>thespesia populnea</i>)	Fruits	Water	Crude extract	Incision and excision	[140]
Orange climber (<i>toddalia asiatica</i>)	Stem bark	Ethanol, petroleum ether, chloroform and acetone	Crude extract	Excision and incision	[141]

Plant Common name (scientific name)	Plant part used	Extraction solvent used	Formulation	Wound model studied ¹	Reference
Climbing nettle (<i>tragia involucrata</i>)	Roots	Methanol	Crude extract	Excision	[142]
Vanda orchid (<i>vanda roxburghii</i>)	Whole plant	Water	Crude extract	Excision	[143]
Tree vernonia (<i>vernonia arborea</i>)	Leaves	Methanol and water	Ointment	Excision, incision and dead space	[144]

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-epithelialisation and contraction. *Biomaterials*. 2015;40:1–11. doi:10.1016/j.biomaterials.2014.10.077
- ² Kanitakis J. Anatomy, histology and immunohistochemistry of normal human skin. *Eur J Dermatology*. 2002;12(4):390–401.
- ³ Kolarsick PAJ, Kolarsick MA, Goodwin C. Anatomy and Physiology of the Skin. *J Dermatol Nurses Assoc*. 2011;3(4):203–213. doi:10.1097/JDN.0b013e3182274a98
- ⁴ Dreifke MB, Jayasuriya AA, Jayasuriya AC. Current wound healing procedures and potential care. *Mater Sci Eng C*. 2015;48:651–662. doi:10.1016/j.msec.2014.12.068
- ⁵ Singh S, Young A, McNaught CE. The physiology of wound healing. *Surg (United Pharmaceutical Sciences (Indexed in ISI and Scopus))*
<https://ps.tbzmed.ac.ir>

- Kingdom). 2017;35(9):473–477. doi:10.1016/j.mpsur.2017.06.004
- 6 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
- 7 Wong SY, Manikam R, Muniandy S. Prevalence and antibiotic susceptibility of bacteria from acute and chronic wounds in Malaysian subjects. *J Infect Dev Ctries.* 2015;9(9):936–944. doi:10.3855/jidc.5882
- 8 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
- 9 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
- 10 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(1):1–6. doi:10.1186/s13643-016-0329-y
- 11 Lordani TVA, De Lara CE, Ferreira FBP, De Souza Terron Monich M, Da Silva CM, Lordani CRF, Bueno FG, Teixeira JJV, Lonardoni MVC. Therapeutic effects of medicinal plants on cutaneous wound healing in humans: a systematic review. *Mediators Inflamm.* 2018;2018. doi:10.1155/2018/7354250
- 12 Mathieu D, Linke JC, Wattel F. Non-healing wounds. In: *Handbook on Hyperbaric Medicine.* 2006:401–428. doi:10.1007/1-4020-4448-8-20
- 13 Menke NB, Ward KR, Witten TM, Bonchev DG, Diegelmann RF. Impaired wound healing. *Clin Dermatol.* 2007;25(1):19–25. doi:10.1016/j.clindermatol.2006.12.005

- 14 Mohanty C, Sahoo SK. Curcumin and its topical formulations for wound healing applications. *Drug Discov Today*. 2017;22(10):1582–1592. doi:10.1016/j.drudis.2017.07.001
- 15 Walton EW. Topical phytochemicals: Applications for wound healing. *Adv Ski Wound Care*. 2014;27(7):328–332. doi:10.1097/01.ASW.0000450101.97743.0f
- 16 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):2363–2367. doi:10.2337/dc11-0807
- 17 Ahmad J. The diabetic foot. *Diabetes Metab Syndr Clin Res Rev*. 2016;10(1):48–60. doi:10.1016/j.mpmed.2014.10.006
- 18 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
- 19 Anthony D, Alosoumi D, Safari R. Prevalence of pressure ulcers in long-term care: A global review. *J Wound Care*. 2019;28(11):702–709. doi:10.12968/jowc.2019.28.11.702
- 20 Shedoeva A, Leavesley D, Upton Z, Fan C. Wound healing and the use of medicinal plants. *Evidence-based Complement Altern Med*. 2019;2019. doi:10.1155/2019/2684108
- 21 Tricco AC, Cogo E, Isaranuwatthai W, Khan PA, Sanmugalingham G, Antony J, Hoch JS, Straus SE. A systematic review of cost-effectiveness analyses of complex wound interventions reveals optimal treatments for specific wound types. *BMC Med*. 2015;13(1):1–16. doi:10.1186/s12916-015-0326-3
- 22 Reinke JM, Sorg H. Wound repair and regeneration. *Eur Surg Res*. 2012;49(1):35–43.

doi:10.1159/000339613

- ²³ Sikha A, Harini A, L HP. Pharmacological activities of wild turmeric (*Curcuma aromatica* Salisb): a review. J Pharmacogn Phytochem. 2015;3(5):1–4.
- ²⁴ Shetty BS. Wound Healing and Indigenous Drugs: Role as Antioxidants: A Review. Res Rev J Med Heal Sci. 2012;2(2):5–16.
- ²⁵ Farjah MH, Farahpour MR. Efficacy of topical platelet-rich plasma and chitosan co-administration on *Candida albicans*-infected partial thickness burn wound healing. Burns. 2020;46(8):1889–1895. doi: 10.1016/j.burns.2020.05.019
- ²⁶ 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;6:1–6. doi:10.1186/1472-6882-6-12
- ²⁷ Aly UF. Healing in Diabetics. Int J Pharm Pharm Sci. 2012;4:76–77.
- ²⁸ Guo S, DiPietro LA. Critical review in oral biology & medicine: Factors affecting wound healing. J Dent Res. 2010;89(3):219–229. doi:10.1177/0022034509359125
- ²⁹ Bishop A. Role of oxygen in wound healing. J Wound Care. 2008;17(9):399–402. doi:10.12968/jowc.2008.17.9.30937
- ³⁰ Edwards R, Harding KG. Bacteria and wound healing. Curr Opin Infect Dis. 2004;17(2):91–96. doi:10.1097/00001432-200404000-00004
- ³¹ Wang PH, Huang BS, Horng HC, Yeh CC, Chen YJ. Wound healing. J Chinese Med Assoc. 2018;81(2):94–101. doi:10.1016/j.jcma.2017.11.002
- 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, Hamada H, Ohneda O. Glucocorticoid impaired the wound healing ability of endothelial progenitor cells by reducing the expression of CXCR4 in the PGE2 pathway. *Front Med*. 2019;5(SEP):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):1012–1014. 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):191–197. 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, Tsao TC-YY, Hsi Y-TT, Lin Y-CC, Chen YY, Chen YY, Ho C-TT, Kao J-YY, Way T-D Der. Essential oil of *Curcuma aromatica* induces apoptosis in human non-small-cell lung carcinoma cells. *J Funct Foods*. 2016;22:101–112. 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):885–892. doi:10.1007/s00580-017-2473-8
- 42 Sabale P, Bhimani B, Prajapati C, Sabale 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) 42S-58S. doi:10.1097/01.prs.0000225432.17501.6c
- 44 Kumar B, Vijayakumar M, Govindarajan R, Pushpangadan P. Ethnopharmacological approaches to wound healing-Exploring medicinal plants of India. *J Ethnopharmacol.* 2007;114(2):103–113. doi:10.1016/j.jep.2007.08.010
- 45 Govindarajan R, Vijayakumar M, Rao CV, Shirwaikar A, Mehrotra S, Pushpangadan P. Healing potential of *Anogeissus latifolia* for dermal wounds in rats. *Acta Pharm.* 2004;54(4):331–338.
- 46 Chopda M, Mahajan R. Wound Healing Plants of Jalgaon District of Maharashtra State, India. *Ethnobot Leaflet.* 2009;2009(1):1–31.
- 47 Ahmad S, Ali M, Ansari SH, Ahmed F. Phytoconstituents from the rhizomes of *Curcuma aromatica* Salisb. *J Saudi Chem Soc.* 2011;15(3):287–290. 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. doi:10.1155/2011/438056
- 49 Kim J, Lee CW, Kim EK, Lee SJ, Park NH, Kim HS, Kim HK, Char K, Jang YP, Kim JW. Inhibition effect of *Gynura procumbens* extract on UV-B-induced matrix-metalloproteinase expression in human dermal fibroblasts. *J Ethnopharmacol* 2011; 137(1):427–433. doi:10.1016/j.jep.2011.04.072
- 50 Mutheeswaran S, Pandikumar P, Chellappandian 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):523–533. 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):241–247. doi:10.1111/j.1095-8339.2006.00452.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. doi:10.1155/2015/714216
- 54 Gharaboghaz MN zadeh, Farahpour MR, Saghaie 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. 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;170:501–507. doi:10.1016/j.foodchem.2014.08.034
- 57 Pellizzoni M, Ruzickova 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):1975–1981. doi:10.5897/JMPR11.1680

- 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):117–151. doi:10.1016/0378-8741(86)90085-1
- 59 Barua CC, Ara Begum S, Talukdar A, Datta Roy J, Buragohain B, Chandra Pathak D, Kumar Sarma D, Saikia Bora R, Gupta A. Influence of *Alternanthera brasiliana* (L.) Kuntze on Altered Antioxidant Enzyme Profile during Cutaneous Wound Healing in Immunocompromised 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):776–777.
- 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, Costa SS. Inhibitory activity of extracts of *Alternanthera brasiliana* (amaranthaceae) against the herpes simplex virus. *Phyther Res.* 1994;8(6):358–361. doi:10.1002/ptr.2650080609
- 63 Victor Y. A. Barku, Yaw Opoku-Boahen, Ernest Owusu-Ansah, Nicholas T. K.D. Dayie FEM. In-Vitro Assessment of Antioxidant and Antimicrobial Activities of Methanol Extracts of Six Wound Healing Medicinal Plants. *J Nat Sci Res.* 2013;3(1):74–80.
- 64 Chaudhary MA, Imran I, Bashir S, Mehmood MH, Rehman N ur, Gilani AH. Evaluation of gut modulatory and bronchodilator activities of *Amaranthus spinosus* Linn. *BMC Complement Altern Med.* 2012;12(166):1–11. doi:10.1186/1472-6882-12-166
- 65 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):6606–6610.
- 66 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
- 67 Maan P, Yadav KS, Yadav NP. Wound Healing Activity of *Azadirachta indica* A. Juss Stem Bark in Mice. Pharmacogn Mag. 2017;13(50):S316–S320. doi:10.4103/0973-1296.210163
- 68 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
- 69 Gupta RK. Medicinal and Aromatic Plants. CBS publishers and distributors, 2010; 234-499.
- 70 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(1):101–118.
- 71 Senthil Kumar M, Sripriya R, Vijaya Raghavan H, Sehgal PK. Wound healing potential of *Cassia fistula* on infected albino rat model. J Surg Res. 2006;131(2):283–289. doi:10.1016/j.jss.2005.08.025
- 72 Gajalakshmi S, Vijayalakshmi S, Rajeswari D V. Pharmacological activities of *Catharanthus roseus*: A perspective review. Int J Pharma Bio Sci. 2013;4(2):431–439. doi:10.1.1.302.1823
- 73 Loh K. Know the Medicinal Herb: *Catharanthus roseus* (Vinca rosea). Malaysian Fam physician Off J Acad Fam Physicians Malaysia. 2008;3(2):123.

- 74 Nayak BS, Pinto Pereira LM. *Catharanthus roseus* flower extract has wound-healing activity in Sprague Dawley rats. *BMC Complement Altern Med.* 2006;6(41):1–6. doi:10.1186/1472-6882-6-41
- 75 Bylka W, Znajdek-Awizeń P, Studzińska-Sroka E, Brzezińska M. *Centella asiatica* in cosmetology. *Postep dermatologii i Alergol.* 2013;30(1):46–49. doi:10.5114/pdia.2013.33378
- 76 Gohil KJ, Patel JA, Gajjar AK. Pharmacological Review on *Centella asiatica*: A Potential Herbal Cure-all. *Indian J Pharm Sci.* 2010;72(5):546–556. doi:10.4103/0250-474X.78519
- 77 Shukla A, Rasik AM, Jain GK, Shankar R, Kulshrestha 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
- 78 James J, Dubery I. Identification and quantification of triterpenoid centelloids in *Centella asiatica* (L.) Urban by densitometric TLC. *JPC - J Planar Chromatogr - Mod TLC.* 2011;24(1):82–87. doi:10.1556/jpc.24.2011.1.16
- 79 Shukla A, Rasik AM, Dhawan BN. Asiaticoside-induced elevation of antioxidant levels in healing wounds. *Phytother Res.* 1999;13(1):50–54. doi:10.1002/(SICI)1099-1573(199902)13:1<50::AID-PTR368>3.0.CO;2-V
- 80 Lee J, Jung E, Kim Y, Park J, Park J, Hong S, Kim J, Hyun C, Kim YS, Park D. Asiaticoside induces human collagen I synthesis through TGF beta receptor I kinase (TbetaRI kinase)-independent Smad signaling. *Planta Med.* 2006;72(4):324–328. doi:10.1055/s-2005-916227
- 81 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 Pharmacol.* 2008;584(2-3):415–423. doi:10.1016/j.ejphar.2008.02.036

- 82 Purohit SK, Solanki R, Mathur V, Mathur M. Evaluation of Wound Healing Activity of Ethanolic Extract of *Curcuma longa* Rhizomes in Male Albino Rats. *Asian J Pharm Res.* 2013;3(2):79–81.
- 83 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):474–478.
- 84 Li S. Chemical Composition and Product Quality Control of Turmeric (*Curcuma longa* L.). *Pharm Crop.* 2011;5(1):28–54. doi:10.2174/2210290601102010028
- 85 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
- 86 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):205–213. doi:10.1177/1534734605281674
- 87 Kallio H, Yang B, Peippo P. Effects of different origins and harvesting time on vitamin C, tocopherols, and tocotrienols in sea buckthorn (*Hippophaë rhamnoides*) berries. *J Agric Food Chem.* 2002;50(21):6136–6142. doi:10.1021/jf020421v
- 88 Beveridge T, Li TSC, Oomah BD, Smith A. Sea Buckthorn Products: Manufacture and Composition. *J Agric Food Chem.* 1999;47(9):3480–3488. doi:10.1021/jf981331m
- 89 Xing J, Yang B, Dong Y, Wang B, Wang J, Kallio HP. Effects of sea buckthorn (*Hippophaë rhamnoides* L.) seed and pulp oils on experimental models of gastric ulcer in rats. *Fitoterapia.* 2002;73(7-8):644–650. doi:10.1016/s0367-326x(02)00221-6
- 90 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
- ⁹¹ Süntar I, Oyardi O, Akkol EK, Özçelik B. Antimicrobial effect of the extracts from *Hypericum perforatum* against oral bacteria and biofilm formation. *Pharm Biol*. 2016;54(6):1065–1070. doi:10.3109/13880209.2015.1102948
- ⁹² Saddiqe Z, Naeem I, Maimoona A. A review of the antibacterial activity of *Hypericum perforatum* L. *J Ethnopharmacol*. 2010;131(3):511–521. doi:10.1016/j.jep.2010.07.034
- ⁹³ Süntar IP, Akkol EK, Yilmazer D, Baykal T, Kirmizibekmez H, Alper M, Yeşilada E. Investigations on the in vivo wound healing potential of *Hypericum perforatum* L. *J Ethnopharmacol*. 2010;127(2):468–477. doi:10.1016/j.jep.2009.10.011
- ⁹⁴ 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):113–117. doi:10.1089/acm.2009.0317
- ⁹⁵ 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. doi:10.4103/2349-5006.183686
- ⁹⁶ 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):164–167. doi:10.1016/j.jep.2005.08.070
- ⁹⁷ 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
- ⁹⁸ Esimone C, Ibezim E, Chah K. The wound healing effect of herbal ointments formulated with *Napoleona imperialis*. *J Pharm Allied Sci*. 2006;3(1):294–299. doi:10.4314/jophas.v3i1.34994

- 99 Reddy JS, Rao PR, Reddy MS. Wound healing effects of *Heliotropium indicum*, *Plumbago zeylanicum* and *Acalypha indica* in rats. J Ethnopharmacol. 2002;79(2):249–251. doi:10.1016/S0378-8741(01)00388-9
- 100 Jaswanth A, Akilandeswari, Loganathan V, Manimaran S, Ruckmani. Wound Healing Activity of *Aegle marmelos*. Indian J Pharm Sci. 2001;63(1):41–44.
- 101 Shirwaikar A, Somashekar AP, Udupa AL, Udupa SL, Somashekar S. Wound healing studies of *Aristolochia bracteolata* Lam. with supportive action of antioxidant enzymes. Phytomedicine. 2003;10(6-7):558–562. doi:10.1078/094471103322331548
- 102 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):288–293.
- 103 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):41–46.
- 104 Sumitra M, Manikandan P, Suguna L. Efficacy of *Butea monosperma* on dermal wound healing in rats. Int J Biochem Cell Biol. 2005;37(3):566–573. doi:10.1016/j.biocel.2004.08.003
- 105 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):102–104.
- 106 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):618–625. doi:10.1111/j.1067-1927.2004.12603.x
- 107 Kamath J V., Rana AC, Chowdhury AR. Pro-healing effect of *Cinnamomum zeylanicum* bark. Phyther Res. 2003;17(8):970–972. doi:10.1002/ptr.1293
- 108 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):53–57.
doi:10.17221/4972-VETMED
- 109 Prabhakar KR, Srinivasan KK, Rao PGM. Chemical Investigation, Anti-inflammatory and Wound Healing Properties of *Coronopus didymus*. *Pharm Biol*. 2003;40(7):490–493. doi:10.1076/phbi.40.7.490.14684
- 110 Puratchikody A, Devi Cn, Nagalakshmi G. Wound healing activity of *cyperus rotundus* linn. *Indian J Pharm Sci*. 2009;68(1):97–101. doi:10.4103/0250-474x.22976
- 111 Priya KS, Gnanamani A, Radhakrishnan N, Babu M. Healing potential of *Datura alba* on burn wounds in albino rats. *J Ethnopharmacol* 2002;83(3):193–199. doi:10.1016/S0378-8741(02)00195-2
- 112 Shirwaikar A, Jahagirdar S, Udupa AL. Wound healing activity of *Desmodium triquetrum* leaves. *Indian J Pharm Sci*. 2003;65(5):461–464.
- 113 Singh SDJ, Krishma V, Mankani KL, Manjunatha BK, Vidya SM. Wound healing activity of the leaf extracts and deoxyelephantopin isolated from *Elephantopus scaber* Linn. *Indian J Pharmacol*. 2005;37(4):238–242.
- 114 Hukkeri VI, Karadi R V., Akki KS, Savadi R V., Jaiprakash B, Kuppast IJ, Patil MB. Wound healing property of *Eucalyptus globulus* L. leaf extract'. *Indian Drugs*. 2002;39(9):481–483.
- 115 Umadevi S, Mohanta G, Kalaichelvan V, Manavalan R. Studies on wound healing effect of *Flaveria trinervia* leaf in mice. *Indian J Pharm Sci*. 2006;68(1):106–108. doi:10.4103/0250-474X.22979
- 116 Mathew A, Taranalli AD, Torgal SS. Evaluation of anti-inflammatory and wound healing activity of *Gentiana lutea* rhizome extracts in animals. *Pharm Biol*. 2004;42(1):8–12. doi:10.1080/13880200390502883

- 117 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):355–357.
- 118 Shirwaikar A, Ghosh S RP. Effects of *Gmelina arborea* Roxb. leaves on wound healing in rats. J Nat Rem. 2003;3(1):45–48. doi:10.18311/jnr/2003/362
- 119 Mukherjee PK, Suresh B. The evaluation of wound-healing potential of *Hypericum hookerianum* leaf and stem extracts. J Altern Complement Med. 2000;6(1):61–69. doi:10.1089/acm.2000.6.61
- 120 Mukherjee PK, Suresh B. Studies on *in-vivo* wound healing activity of leaf extract of *Hypericum mysorensense* with different wound model in rats. Nat Prod Sci. 2000;6(2):73–78.
- 121 Mukherjee PK, Verpoorte R, Suresh B. Evaluation of *in-vivo* wound healing activity of *Hypericum patulum* (Family: Hypericaceae) leaf extract on different wound model in rats. J Ethnopharmacol. 2000;70(3):315–321. doi:10.1016/S0378-8741(99)00172-5
- 122 Shirwaikar A, Shenoy R, Udupa AL, Udupa SL, Shetty S. Wound healing property of ethanolic extract of leaves of *Hyptis suaveolens* with supportive role of antioxidant enzymes. Indian J Exp Biol. 2003;41(3):238–241. PMID:15267154
- 123 Hemalatha S, Subramanian N, Ravich V. Wound healing activity of *indigofera enneaphylla* linn. Indian J Pharm Sci. 2001;63(4):331–333.
- 124 Nayak BS, Udupa AL, Udupa SL. Effect of *Ixora coccinea* flowers on dead space wound healing in rats. Fitoterapia. 1999;70(3):233–236. doi:10.1016/S0367-326X(99)00025-8
- 125 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

- 126 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
- 127 Daemi A, Farahpour MR, Oryan A, Karimzadeh S, Tajer 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
- 128 Manjunatha B, Vidya S, Krishna V, Mankani K. Wound healing activity of *Leucas hirta*. Indian J Pharm Sci. 2006;68(3):380–384. doi:10.4103/0250-474X.26681
- 129 Singh S, Singh R, Kumar N, Kumar R. Wound healing activity of ethanolic extract of *Plantago Ovata* (Ispaghula) seeds. J Appl Pharm Sci. 2011;01(7):108–111.
- 130 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. PMID:16430091
- 131 Taranalli AD, Tipare S V., Kumar S, Torgal SS. Wound healing activity of *Oxalis corniculata* whole plant extract in rats. Indian J Pharm Sci. 2004;66(4):444–446.
- 132 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):671–675. doi:10.1016/j.fitote.2005.08.007
- 133 Suguna L, Sumitra M, Chandrakasan G. Influence of *Phyllanthus emblica* extract on dermal wound healing in rats. J Med Aromat Plants. 2000;32:2–3.
- 134 Singh M, Govindarajan R, Nath V, Rawat AKS, Mehrotra S. Antimicrobial, wound healing and antioxidant activity of *Plagioclasma appendiculatum* Lehm. et Lind. J Ethnopharmacol. 2006;107(1):67–72. doi:10.1016/j.jep.2006.02.007
- 135 Murthy KNC, K VR, , Jyothi M V, Murthy UD. Short Communication Study on Wound

- Healing Activity of *Punica granatum* Peel. J Med Food. 2004;7(2):256–259.
- 136 Jalalpure SS, Patil MB, Alagawadi KR. Wound healing activity of the galls of *Quercus infectoria* olivier. J Nat Remedies. 2002;2(1):54–58. doi:10.18311/jnr/2002/345
- 137 Lodhi S, Pawar RS, Jain AP, Singhai AK. Wound healing potential of *Tephrosia purpurea* (Linn.) Pers. in rats. J Ethnopharmacol. 2006;108(2):204–210. doi:10.1016/j.jep.2006.05.011
- 138 Chaudhari M, Mengi S. Evaluation of phytoconstituents of *Terminalia arjuna* for wound healing activity in rats. Phyther Res. 2006;20(9):799–805. doi:10.1002/ptr.1857
- 139 Suguna L, Singh S, Sivakumar P, Sampath P, Chandrakasan G. Influence of *Terminalia chebula* on dermal wound healing in rats. Phyther Res. 2002;16(3):227–231. doi:10.1002/ptr.827
- 140 Nagappa AN, Cheriyan B. Wound healing activity of the aqueous extract of *Thespesia populnea* fruit. Fitoterapia. 2001;72(5):503–506. doi:10.1016/S0367-326X(01)00275-1
- 141 Kar DM, Mohanty A, Sethi RK, Dash GK. Antimicrobial and wound healing properties of stem bark of *Toddalia asiatica* Linn. Indian J Pharm Sci. 2005;67(2):220–223.
- 142 Perumal Samy R, Gopalakrishnakone P, Sarumathi M, Ignacimuthu S. Wound healing potential of *Tragia involucrata* extract in rats. Fitoterapia. 2006;77(4):300–302. doi:10.1016/j.fitote.2006.04.001
- 143 Nayak BS, Suresh R, Rao AVC, Pillai GK, Davis EM, Ramkissoon V, McRae A. Evaluation of wound healing activity of *Vanda roxburghii* R.Br (Orchidacea): A preclinical study in a rat model. Int J Low Extrem Wounds. 2005;4(4):200–204. doi:10.1177/1534734605282994
- 144 Manjunatha BK, Vidya SM, Rashmi K V., Mankani KL, Shilpa HJ, Jagadeesh Singh SD. Evaluation of wound-healing potency of *Vernonia arborea* Hk. Indian J Pharmacol.

2005;37(4):223–226. doi:10.4103/0253-7613.16567

- ¹⁴⁵ Joshi A, Joshi VK, Pandey D, Hemalatha S. Systematic investigation of ethanolic extract from *Leea macrophylla*: Implications in wound healing. *J Ethnopharmacol.* 2016;191(2016):95–106. doi:10.1016/j.jep.2016.06.034
- ¹⁴⁶ Dwivedi D, Dwivedi M, Malviya S, Singh V. Evaluation of wound healing, anti-microbial and antioxidant potential of *Pongamia pinnata* in wistar rats. *J Tradit Complement Med.* 2017;7(1):79–85. doi:10.1016/j.jtcme.2015.12.002

Accepted Manuscript