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Mini Review

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

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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.

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).

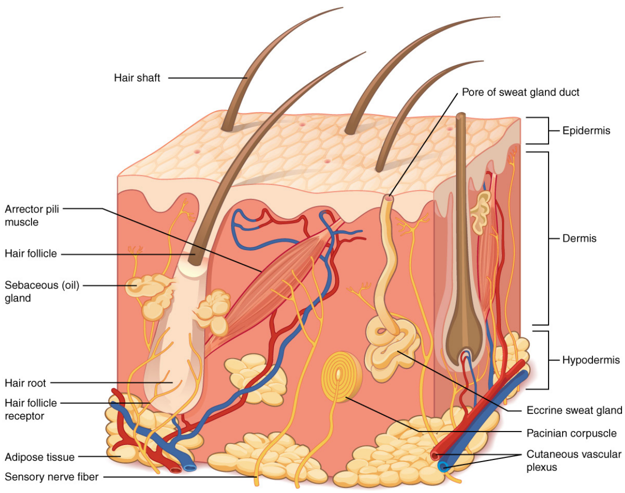

Figure 1. Cross-section of the skin structure showing epidermis, dermis and hypodermis. Adapted from Wikimedia commons (the free media repository). OpenStax College (https://commons.wikimedia.org/wiki/File:501_Structure_of_the_skin.jpg), "501 Structure of the skin", https://creativecommons.org/licenses/by/3.0/legalcode.

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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 wounds.[11–14] In comparison to the United Kingdom (UK), Walton[15] 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 wounds[20] 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, 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 and DiPietro[28] 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[29] 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 stress[38] 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-β1 (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 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.[59] Studies have shown that its extracts exhibit antinociceptive effects,[60] antimicrobial effects,[61] and anti-herpes simplex viruses activity.[62]

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[a]	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	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	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	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	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	78
Elephant's Foot *(elephantopus scaber)*	Leaves	Ethanol and water	Gel	Excision, incision and dead space	79
Tasmanian bluegum *(eucalyptus globulus)*	Leaves	Ethanol	Crude extract	Excision, incision and dead space	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	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.

Yellow mosqueta *(hypericum patulatum Thumb)*	Leaves	Methanol	Ointment	Excision and incision	87
Pignut *(hyptis suaveolens)*	Leaves	Ethanol	Crude extract	Excision, incision and dead space	88
Birdsville indigo *(indigofera enneaphylla)*	Aerial	Ethanol	Ointment	Excision and incision	89
Jungle geranium *(ixora coccinea)*	Flowers	Ethanol	Crude extract	Dead space	90
Big-sage *(lantana camara)*	Leaves	Hydro-alcohol	Crude extract	Excision	91
Henna *(lawsonia alba)*	Leaves	Chloroform, Ethanol and petroleum ether	Crude extract	Excision and incision	92,93
Thumbai *(leucas hirta)*	Leaves	Methanol and water	Ointment gel	Excision, incision and dead space	94
Ispaghula (*Plantago Ovata*)	Seeds	Ethanol	Ointment	Excision and incision	95
Holy basil *(ocimum sanctum)*	Leaves	Ethanol	Crude extract	Excision, incision and dead space	96
Creeping woodsorrel *(oxalis corniculata)*	Whole plant	Ethanol and petroleum ether	Crude extract	Excision, incision and dead space	97
Egyptian starcluster *(pentas lanceolata)*	Flowers	Ethanol	Crude extract	Excision	98
Emblic *(phyllanthus emblica)*	Leaves	Ethanol	Crude extract	Excision	99
Indian liverwort *(plagiochasma appendiculatum)*	Thalli	Chloroform , Acetone, Ethanol and Water	Crude extract	Excision and incision	100
Pomegranate *(punica granatum)*	Peels	Methanol	Gel	Excision	101
Aleppo Oak *(quercus infectoria)*	Galls	Water	Crude extract	Excision, incision and dead space	102
Purple tephrosia *(tephrosia purpurea)*	Aerial	Methanol	Ointment	Excision, incision and dead space	103
Arjun *(Terminalia arjuna)*	Bark	50% Ethanol	Ointment	Excision and incision	104
Chebulic myrobalan *(terminalia chebula)*	Leaves	Ethanol	Crude extract	Incision and In vitro	105
Portia tree *(thespesia populnea)*	Fruits	Water	Crude extract	Incision and excision	106
Orange climber *(toddalia asiatica)*	Stem bark	Ethanol, petroleum ether, chloroform and acetone	Crude extract	Excision and incision	107
Climbing nettle *(tragia involucrata)*	Roots	Methanol	Crude extract	Excision	108
Vanda orchid *(vanda roxburghii)*	Whole plant	Water	Crude extract	Excision	109
Tree vernonia *(vernonia arborea)*	Leaves	Methanol and water	Ointment	Excision, incision and dead space	110

[a]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 mm^2 diameter is inflicted on the dorsal region of the animal, usually rats or mice.[26,111] 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.[103,112] 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] 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]

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.[113] It is also found to be helpful in wound healing and rheumatism.[114] *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.[115]

Paswan *et al.*[116] 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.[117]

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.[118]

Maan *et al.*[117] 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 ± 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 Caesalpiniaceae, 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.[119] 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.[120]

A study conducted by Kumar *et al.*[63] 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.[121] In Malaysia, it is locally called *Kemunting Cina.*[122] 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.[123-125]

Nayak and co-workers[122] 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.[124] The plant is also recommended as an antipyretic, antirheumatic, diuretic, antimicrobial drug, also to relieve anxiety, and improve cognition.[125]

Shukla *et al.*[126] 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.[127] The healing potency of asiaticoside isolated from the plant has proven efficient in delayed-type wound healing.[126-130]

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.[131] The ayurvedic practise also claims it to be good for skin ailments, blood purification, wound cleansing, and effective against body toxins, and intestinal worms.[132] The extract of *C. longa* contains high levels of mineral dyes, curcumin, curcuminoids, phenolic compounds, and volatile oils such as turmerone, atlantone and zingiberene.[133,134]

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.[131] However, the study did not evaluate the wound tensile strength.

In a similar study, Kundu *et al.*[135] 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.[136] Seabuckthorn is therapeutically used to fight diseases and conditions like flu, cardiovascular disease, mucosal injuries, and skin disorders.[137] 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.[138]

A preclinical study by Gupta *et al.*[64] 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*.[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.[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.[141]

Samadi and co-workers[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 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.[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.[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.[143–145]

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.[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, 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.

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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.

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