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MINI-REVIEW ARTICLE

Discovering the Potential of Plants in Wound Healing: A Mechanistic Review

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Abstract:

Plants are admired for their taste, fragrance, and therapeutic characteristics. Herbs are used in multiple traditions, including cooking, medicine, and spirituality. Medicinal plants have been used to treat a number of illnesses and disorders from ancient times to the present day. The main reason for this is that therapeutic plants have no negative side effects. With a diverse spectrum of plant species and widespread access to traditional medical practices, India is one of the world's largest biodiversity reservoirs. According to WHO data and other relevant sources, herbal medicinal products are used by more than 80% of the world's population. The goal of this review article is to describe the importance of herbal agents in therapeutics, such as the use of crude plant extract for the medicinal purpose. Complex interaction of blood cells, tissues, soluble mediators, cytokines, and numerous growth factors is required for wound healing, whether it is accidental or surgical. Plants have enormous potential for wound management and therapy, as well as regeneration of damaged tissues, due to the presence of a variety of useful active phytoconstituents. This review presents comprehensive data on some important plants and their extracts used in wound healing along with their mechanism of action and the scientific research reported on these plants.

Keywords: Wound healing, Blood cells, Cytokines, Growth factors, Regeneration, Plant extract.

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1. INTRODUCTION

The relationship between humans and plants has its origins in historic civilizations and is a well-established one [1]. Traditionally, medicines are obtained primarily from plants, in basic forms from various plant parts, and in further developed forms as crude extracts or their combinations. Currently, a large variety of medications produced from plants are extremely successful in treating various life-threatening disorders [2]. Most of the plant components identified are active ingredients specific to the medicinal plant or its modifications. Plant-based or plant-derived therapeutic medications account for over a quarter of all therapeutic pharmaceuticals in developing nations, and their medical usage is widely recognized among the indigenous people of rural regions in various nations [3, 4]. Our ancestors' analysis of plants' healing powers was the product of numerous hits or misses, but the efficacy of herbal plant therapies based on hundreds and thousands of years of empirical results is impressive [5]. Due to inadequate hygiene, infection of the wounds is one of the most prevalent illnesses in developing nations [6]. Wounds are physical injuries that cause the opening or the disruption in the continuity of the epithelium of the skin, and the destruction of the functional and structural integrity of the underlying normal tissue [7, 8]. Wounds can be caused by a contusion, hematoma, laceration, or abrasion. As a result, adequate healing procedures are required for the re-establishment of normal skin and physiological conditions. Healing of wound begins the instant the damage occurs and progresses at the rate at which the four stages are completed: depending on the level of injury, the homeostasis, inflammatory, proliferative, and remodeling phase define the look and strength of the repaired tissue [9]. The regeneration process is disrupted by metabolic abnormalities and illnesses, which cause the healing mechanism to be delayed; it places a significant financial burden on both emerging and developing countries. As a result, alternative and inexpensive therapies based on herbal medicines have been investigated [10].

2. SKIN

The skin acts as a life-sustaining barrier between the body and the outside world, possessing immune neuroendocrine processes that support the body's homeostasis and protect it from physical damage, infection, and fluid loss [11]. The epidermis and dermis are the two layers that make up the skin structure. Keratinocytes, melanocytes, dendritic cells, Langerhans cells and other immune cells, tactile axons, and the epidermal-dermal cellular layer can be seen in the epidermis [12, 13]. The skin appendages, mast cells, fibroblasts, antigen-introducing dermal cells, and immune cells are present in the

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dermis [14]. Dermis also houses the extracellular matrix complex responsible for intercellular connections, cellular mobility, cytokine, and growth factor actions.

2.1. Skin Injury

The production of clots and local inflammation as a result of skin injury is characterized by neutrophils and phagocytes infiltrating the wound sites. These alterations characterize the inflammatory phase of wound healing. The inflammatory response is hypothesized to be involved in the delivery of growth factors, cytokines, and chemokines that coordinate the cell movement essential for wound healing [15]. Wound healing is a complicated procedure that attempts to restore injured tissue's cellular structures and layers to their original form as precisely as feasible [16]. Wound contraction occurs at many stages of the process of healing, initiating with the fibroblastic stage [17].

3. WOUND HEALING

One of the growing disciplines in current biomedical science is wound healing agents' study. Many traditional healers, specifically in India and China, have valuable knowledge of a variety of obscure and previously undiscovered wild herbs that may be used to treat wounds and burns. Conservative forms of medicine, which have been used for millennia in Africa and Asia, are being researched for the possibility of treating wounds [18].

3.1. Classification of Wounds

Wounds are categorized based on how long they take to heal. Acute wounds heal within a reasonable amount of time, following the typical process of healing. During wound healing, normal tissue's anatomical and functional integrity is re-established. Chronic wounds, on the other hand, take a long time to heal and do not go through the regular phases of wound healing. Chronic wounds are divided into four types based on their complexity: pressure, venous, diabetic, and arterial insufficiency ulcers.

Wounds can also be classed as open (those involving skin rupture) or closed (those involving underlying tissue damage but intact skin). Incisions (cut-like wounds), lacerations (tear-like wounds), abrasions (scraping of the outer skin layer), puncture and penetration wounds (produced by an object entering or departing the skin surface), and gunshot wounds are all examples of open wounds. Exposure of the underlying tissues to the outside environment in case of open wounds leads to bacterial and fungal infections. The difficulty of treating these infections due to antibiotic resistance increases the morbidity and burden of these wounds [19].

Class 1 wounds are classified as clean wounds. They are non-infectious, un-inflamed, and are mostly closed. If drainage of these wounds is required, a closed draining procedure is used. Penetration of the respiratory, alimentary, vaginal, or urinary system is not done by these wounds.

Class 2 wounds are classified as clean-contaminated wounds. There is no abnormal contamination in these wounds. They affect the respiratory, alimentary, vaginal, or urinary systems, and usually infiltrate these tracts under regulated circumstances.

Class 3 wounds are classified as contaminated wounds. Fresh, open wounds may occur as a result of an insult to sterile procedures or gastrointestinal system leaks into the wound. Incisions resulting in acute or nonpurulent inflammation are also considered as class 3 wounds.

Class 4 wounds are classified as dirty-infected wounds. These are typically the consequence of traumatic wounds not adequately cared for. The presence of microorganisms in perforated viscera or the operating field is the most common cause of class 4 wounds, which manifest devitalized tissue.

3.2. Wound Healing Process

The following stages are involved in the wound healing process.

3.2.1. Hemostasis

The process of wound healing by clotting is called hemostasis. It starts when blood flows out of the body. The first step of hemostasis is the constriction of blood vessels to restrict the flow of blood. Next, sticking together of platelets to seal the break in the wall of the blood vessel takes place. Platelets also release growth factors and cytokines, like platelet-derived growth factor (PGDF), transforming growth factor-β (TGF- β), and epithelial growth factor, which are vital for wound healing. They encourage the collection of neutrophils, macrophages, fibroblasts, and myofibroblasts at the injury site, promoting further phases of wound repair. Finally, coagulation occurs for reinforcing the platelet plug with fibrin fibres, which resemble a molecular binding agent to form a mesh. The hemostasis stage of wound healing takes place very rapidly [20, 21].

3.2.2. Inflammatory

The second stage of wound healing is inflammation. This stage is the body's initial response to injury, and it makes way for the other two stages. The injury swells, and the blood flows out, which is a fundamental instrument for eliminating cell debris. Wound protection and hemostasis require coagulation. Inflammatory cells infiltrate the wound site shortly after an injury, and a fibrin plug forms. Platelets embedded in polymerized fibrinogen, fibronectin, vitronectin, and thrombospondin make up this plug. This stage fights microorganisms and also offers protection temporarily. Aggregation of platelets and release growth factors, such as platelet-derived growth factor (PDGF) and transforming growth factor (TGF), takes place as they converge within the plug. Inflammatory cells, like neutrophils, mast cells, monocytes, and macrophages, aid in wound debridement and removal of bacteria and other necrotic tissue. Neutrophils are attracted to the injury site by cytokines, like interleukin-1 (IL-1), tumor necrosis factor-α (TNF- α), and bacterial endotoxins. They secrete important growth factors and mediators that aid in the healing process. Dermal and inflammatory cells at the injury site produce an array of cytokines and growth factors in 2-3 days following the injury. TGF-β released from activated macrophages is predominant in

initiating the proliferative phase. Activated macrophages also release certain pro-inflammatory chemicals, like IL-1, IL-6, and TNF- α, and some growth factors, like vascular endothelial growth factor (VEGF) and PGDF. The presence of macrophages, fibroblasts, and endothelial cells stimulates wound contraction from earlier granulation. This phase lasts for 4-6 days. A typical feature of this phase is erythema, edema, and pain [22, 23].

3.3.3. Proliferative (Cell Proliferation)

The proliferative phase of wound healing results in the rebuilding of wound with new tissue consisting of collagen and extracellular matrix (ECM). The collagen is cross-linked by lysyl oxidase, an enzyme. Activation of fibroblasts, keratinocytes, macrophages, and endothelial cells leads to wound closure, angiogenesis, and matrix deposition. In response to TGF- β and PGDF, fibroblasts replace the fibrin-rich matrix with granulation tissue. In this phase, the wound contracts as new tissues are generated. In addition, neovascularization must take place so that the granulation tissue may be healthy and receive an adequate supply of oxygen and nutrients. Hypoxia induces angiogenesis that causes the release of VEGF, a factor important for neovascularization. Macrophages influence the behavior of microvascular endothelial cells, and thus support angiogenesis. Myofibroblasts cause the wound to shrink by gripping the wound edges and pulling them together using a mechanism similar to that of smooth muscle cells. The formation of a permeability barrier (*i.e.*, re-epithelialization), the establishment of an optimum blood flow (*i.e.*, angiogenesis), and the augmentation of the wounded dermal tissue are the key events during this phase (*i.e.*, fibroplasia). The formation of epithelial cell layers is accelerated in a moist and hydrated environment. This stage lasts for 4-24 days [24 - 26].

3.3.4. Remodeling

This phase is synonymous with the maturation stage of wound healing. In this phase, the collagen is remodeled from type III to type I, and the wound closes completely. During this stage, the newly formed tissue becomes strong and flexible. The cells that have played a role in the repair of wound, but are no longer required, are eliminated by apoptosis or programmed cell death. When the laying down of collagen is done during the proliferative phase, it is disorganized, causing the wound to be thick. In this phase, collagen is organized along the stress lines of the wound. The metalloproteinases secreted by fibroblasts, macrophages, and endothelial cells promote the remodeling of type III collagen to type I and also remove cell debris. It occurs throughout the wound healing process in which the granulation tissue rich in type III collagen and blood vessels replaces the fibrin clot formed during the initial inflammatory phase and then by a collagenous scar dominated by type I collagen with much less mature blood vessels. The adjustment of extracellular lattice synthesis is one of the highlights of wound redesigning. Collagen fibres make up around 80% of the dry weight of normal human dermis and are the main proteins that provide dermal tissue shape, strength, and stiffness. The resulting scar has about 80% of tensile strength in comparison to the original tissue. This phase lasts from 21 days to up to 2 years (Fig. **1**).

Factors that affect the wound healing process are the location of the wound, its severity, age, metabolic deficiencies, infection, metabolic disorders, like diabetes, nutritional status, and immune status [27].

There are different types of agents that are used in wound healing, which include antibiotics and certain synthetic and natural agents.

The medicinal plants and their parts used in wound healing are as follows (Tables **1**-**6**):

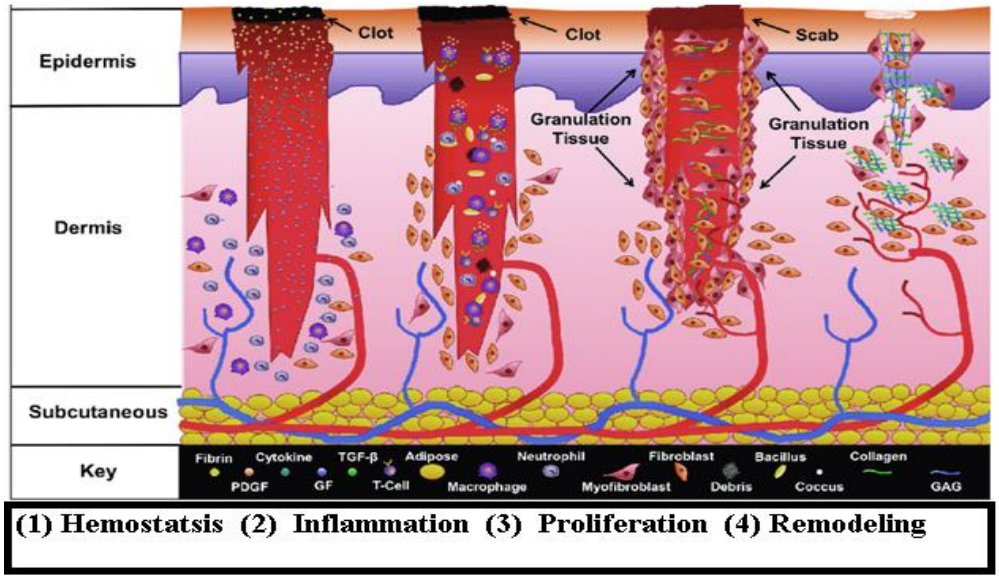
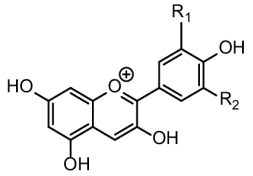
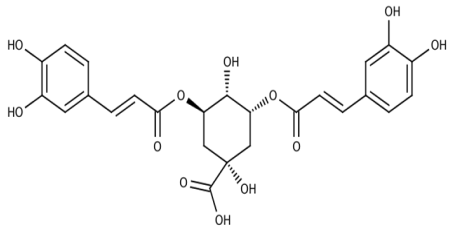
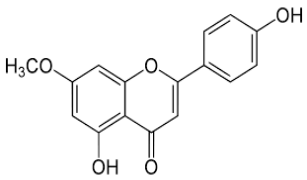
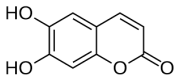


Fig. (1). Phases in wound healing.

Table 1. Flowers used in wound healing.

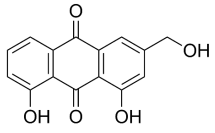
Common Name	Botanical Name	Family	Active Constituent	Chemical Structure of Active Constituents
China rose	*Hibiscus Rosasinensis*	Malvaceae	Anthocyanins	
Japanese honeysuckle	*Lonicera japonica*	Caprifoliaceae	Dicaffeoylquinic acid	
Lilac daphne	*Daphne genkwa*	Thymelaeaceae	Genkwanin	
Pot Marigold	*Calendula Officinalis*	Asteraceae	Aesculetin	

4. FLOWERS

4.1. Pot Marigold

Calendula officinalis is a widely used herb that is used to manage various skin disorders, including wounds, burns, and dermatitis [28]. However, the particular processes involved in its wound-healing effects are unclear. Extracts of its flowers are especially useful in accelerating wound healing. Carotenoids, coumarins, quercetin, protocatechuic acid, faradiol, oleanolic acid, betaamyrin calenduladiol, narcissin, and other phytochemicals are found in *Calendula officinalis* flowers. The carotenoids, which include ß-carotene, lycopene, flavoxanthin, lutein, and others, are the most important components. These chemicals' antioxidant activity may be a factor contributing to their wound-healing abilities. The wound-healing function of the *C. officinalis* flower extract may be related to the promotion of connective tissue synthesis, improved cross-linking, and impediment of enymes involved in collagen degradation, free-radical scavenging, and prevention of inflammation attributed to its antimicrobial activity. *Calendula officinalis* extract increases fibroblast movement and expansion in a PI3K-subordinate way, as per studies using human and murine fibroblast cells [29]. In excisional injuries of BALB/c mice, it has been studied that flower extract of Calendula officinalis prompts granulation tissue advancement by changing the state of connective tissue development factor (CTGF) and smooth muscle actin (SMA) [30]. The chicken chorioallantoic film (CAM) method and a cutaneous injury mending model in rodents have both shown that Calendula officinalis enhances angiogenesis *in vivo* [31, 32]

Table 2. Leaves used in wound healing.

Common Name	Botanical Name	Family	Active Constituents	Chemical Structure of Active Constituents
Aloe vera	*Aloe barbedensis*	Asphodelaceae	Aloe-emodin	

(Table 2) contd.....

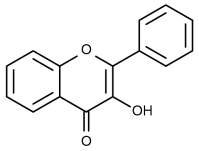
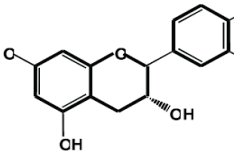
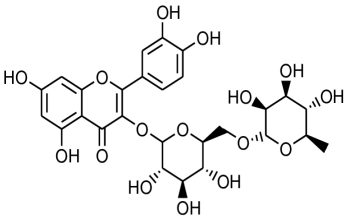
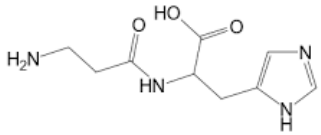
Common Name	Botanical Name	Family	Active Constituents	Chemical Structure of Active Constituents
Eucalyptus	*Eucalyptus citriodorata*	Myrtaceae	Eucamalol	
Neem	*Azadirachta Indica*	Meliaceae	Nimbidin	 nimbidin
Tea plant	*Camellia sinensis*	Theaceae	Epicatechin	

Table 3. Seeds used in wound healing.

Common Name	Botanical Name	Family	Active Constituents	Chemical Structure of Active Constituents
Chinese pepper	*Zanthoxylum bungeanum*	Rutaceae	Rutin	
Papaya	*Carica papaya*	Caricaceae	Papain	

4.2. *Hibiscus Rosa-sinensis*

It is a tropical South Eastern Asian evergreen plant. It is a glabrous shrub that is extensively grown in the tropical region. It contains anthocyanins and flavonoids, such as cyanidin-3, 5-diglucoside, cyanidin-3-sophoroside-5-glucoside, quercetin-3, 7-diglucoside, quercetin-3-diglucoside, quercetin-3-diglucoside, and quercetin-3-diglucoside [33]. This herb has traditionally been used to treat dysfunctional haemorrhage of the uterus and as a contraceptive *via* the oral route [34]. Hibiscus rosa-sinensis has been used to cure a number of ailments as well as enhance wound healing. Excision, incision, and dead space wound models were used to test the wound-healing ability of the ethanolic extract of Hibiscus rosa-sinensis flower in rats [35 - 37].

4.3. *Lonicera Japonica*

Chen *et al*. found that ethanolic concentrates of *Lonicera japonica* blooming aerial parts boost reepithelization, angiogenesis, granulation tissue improvement, and shrinking during cutaneous injury repair [38]. Although large amounts might cause neurological diseases, the plant can be taken as a "health food," offering some protection against gastrointestinal ulcers. Flavonoids, triterpenoids, and tannins, among other phytochemical elements found in plant extracts, have been shown to aid wound healing. The chemical components of *L. japonica* have been widely investigated as it is used and farmed in numerous countries. Its major components have been extracted and identified as essential oils, organic acids, flavones, saponins, iridoids, and inorganic elements. The active components of *L. japonica* are essential oil and chlorogenic acid, both of which have established pharmacological effects. Topical application of this plant on wounds reduced microbial invasion via the wound, resulting in wound protection against infection by numerous species. The wound-healing environment is affected by IL-10, which decreases the expression of proinflammatory/profibrotic mediators, providing less inflammatory cell infiltration at the wound site. Application of its plant extract enhanced blood IL-10 levels while decreasing TNF and IL-6 expression. TNF has been

shown to retard collagen and hydroxyproline production, both of which are essential for the final proliferative phase of wound healing [39, 40].

4.4. *Daphne Genkwa*

It is one of the 50 essential herbs in Traditional Chinese Medicine (TCM), growing in China's Yellow and Yangtze river valleys. Anticonvulsant, NSAID, diuretic, antitussive, expectorant, and moderate sedative agents are all utilised to treat wounds [41]. Biflavonoids, coumarin, diterpenes, and triterpenes are the main bioactives identified from Daphne genkwa, possessing anti-inflammatory, anti-tumor, immunoregulatory, and anti-melanogenesis properties. Flavonoids isolated from *Daphne genkwa* flowers activate the ERK/MEK pathway, which controls fibroblast proliferation and collagen expression (COL1A1 and COL3A1), leading to better healing of wounds [42].

5. LEAVES

5.1. Aloe Vera

Aloe vera, employed as a first-line therapy for burns, ulcers, and surgical wounds, has been used globally for over 5000 years. Anthraquinones, saccharides, vitamin E and C, zinc, enzymes, acetyl salicyclic acid, and other substances are found in it. The main carbohydrate fraction extracted from aloe vera leaves is acemannan. This fraction stimulates wound healing while also acting as an antiviral, anticancer, and immunological stimulator. The main hormones are auxins and gibberellins, which are responsible for wound healing and anti-inflammatory action. Epithelisation is a critical component of wound healing; proper hydration, oxygenation, and clearance of dead tissue are all essential. Aloe vera contains a lot of water (96%). This avoids wound desiccation and promotes epithelial cell motility. Aloe increases oxygenation by improving wound microcirculation. Catecholamines have varied effect on wound healing properties. Aloe enhances epithelisation by blocking catecholamine activity [43, 44]. Aloe vera enhances wound vascularity, which removes dead tissue and makes the site healthy, according to a histological study [45]. All of these mechanisms promote epithelial cell migration from the surrounding skin. Epithelisation also stimulates the formation of ground material [46 - 48].

5.2. Tea Plant

These pharmacological actions are generally attributed to catechins, which are polyphenolic chemicals found in *Camellia sinensis*. A significant catechin, (-) - epigallocatechin-3-gallate (EGCG), improves keratinocyte multiplication and differentiation [49]. In human dermal fibroblasts, Klass *et al*. found that EGCG decreases TGF receptors by changing TGF flagging, bringing down MMP-1 and MMP-2 articulation, and diminishing collagen type 1 creation. From these attributes, it can be inferred that EGCG may be utilized to prevent scarring [50]. Camellia sinensis methanol extracts have been shown to stimulate fibroblast proliferation and collagen production [51, 52]. In addition, *in vivo* investigations have shown that Camellia sinensis enhances wound healing in rats by boosting angiogenesis. Its extracts have also been shown to promote wound healing in diabetic mice model [53 - 55].

5.3. Neem

Azadirachta indica (AI) is an evergreen tree with small green leaves that may reach a height of 100 feet. The neem tree, also known as Herbal Indian Doctor, can be found all across India. Active chemicals found in neem, such as nimbidin, nimbin, and nimbidol, have anti-inflammatory and antibacterial properties and aid in wound healing. Neem also contains a significant quantity of amino acids, vitamins, and minerals, which play an important part in the wound healing process' proliferation phase [56 - 58]. Eczema, ringworm, and scabies are all treated with neem alcoholic extract. Extracts from neem leaves and seed oil have been shown to have antibacterial properties. This stops bacteria from causing subsequent infections in any wound. Clinical investigations show that neem reduces inflammation just equally well as cortisone acetate, speeding up wound healing. The enhanced cross-linking of collagen fibres caused by the increase in hydroxyproline and total protein content of animals treated with extract improved collagen maturation. Because multiple healing phases, like inflammation, macrophagia, collagenation, contraction, and epithelization are interconnected, neem stem bark extract could affect the healing process by interfering with one or more of them. When statistically evaluated, total protein levels were shown to be considerably greater in animals treated with water extract formulation, while other groups also showed elevated protein levels, but not to a statistically significant level. Enhanced wound contraction in test-treated mice could be because of the action of fibroblasts [59].

Table 4. Resins used in wound healing.

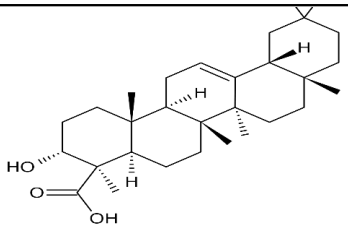
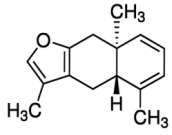
Common Name	Botanical Name	Family	Active Constituents	Chemical Structure of Active Constituents
Indian frankincense	*Boswellia sacra*	Primulaceae	Boswellic acid	
Myrrh	*Commiphoramyrrha*	Burseraceae	Furanoeudesma	

Table 5. Rhizomes used in wound healing.

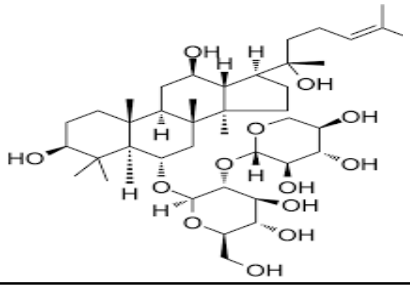
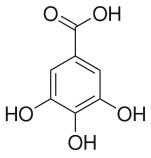
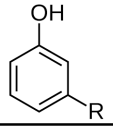
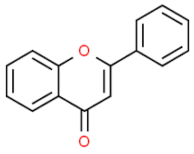
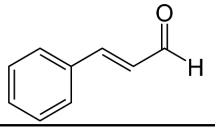
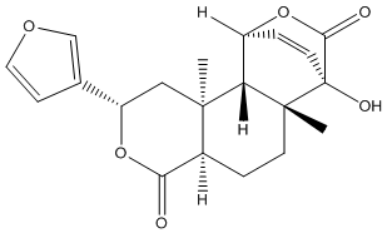
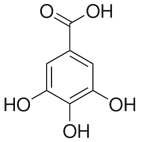
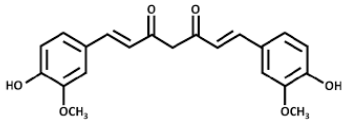
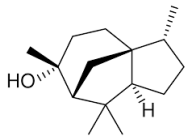
Common Name	Botanical Name	Family	Active Constituents	Chemical Structure of Active Constituents
Notoginseng	*Panax noto ginseng*	Araliaceae	Notoginsenoside	
Sedum	*Rhodiola Imbricata*	Crassulaceae	Gallic acid	

Table 6. Whole plant used in wound healing.

Common Name	Botanical Name	Family	Active Constituents	Chemical Structure of Active Constituents
Bael	*Aegle marmelos*	Rutaceae	Fordinol	
Bharangi	*Clerodendrum serratum*	Lamiaceae	Claroflavone	
Chinese cinnamon	*Cinnamomum cassia*	Lauraceae	Cinnamaldehyde	
Giloy	*Tinospora Cordifolia*	Menispermaceae	Tinosporin	
Tulsi	*Ocimum sanctum*	Lamiaceae	Gallic acid	
Turmeric	*Curcuma longa*	Zingiberaceae	Curcumin	

(Table 6) contd.....

Common Name	Botanical Name	Family	Active Constituents	Chemical Structure of Active Constituents
Red Sandal wood	*Pterocarpus santalinus*	Fabaceae	Cedrol	

5.4. Eucalyptus

Wounds, ulcers, burns, skin disease, blisters, cuts, and insect bites are all treated with it. It also strengthens the immune system and aids in the management of chicken pox, the common cold, flu, and measles. Topical and oral administration of *Eucalyptus citriodorais* is particularly effective for healing cutaneous wounds. All phases of wound healing are accelerated by these extracts [60]. At the proliferative stage, angiogenesis, collagen deposition, granulation tissue development, epithelization, and wound contraction have been hypothesized as mechanisms of action for these concentrates. The synergistic effects of phytochemicals, such as phenolic compounds, flavonoids, and tannins in the extract, are credited with these results [61]. 1,8-cineole, citronellal, citronellol, citronellyl acetate, p-cymene, eucamalol, limonene, linalool, -pinene, -terpinene, -terpinol, alloocimene, and aromadendrene are among the chemicals responsible for Eucalyptus extracts' antibacterial action [62, 63].

6. SEEDS

6.1. Chinese Pepper

In traditional Western folk medicine, *Zanthoxylum bungeanum* is known as “toothache tree”, and is used to heal itch and chronic pain. TCM oils, powders, tinctures, elixirs, and tablets are typically made from the pericarp of the fruit berry [64]. Zanthoxylum bungeanum extracts are also used to manage skin diseases, such as acne, eczema, scalds, and wound healing [65]. Extracts from fruit husk of *Zanthoxylum bungeanum* have a unique characteristic of lifting skin wrinkles. The active constituent is rutin that promotes wound healing. Subcutaneous muscles relax when it is applied topically to the skin, minimizing skin wrinkles and attracting the attention of cosmetic makers. Inflammation, poor tissue repair, ECM deposition, and tissue contraction are all aided by pro-inflammatory cytokines released by a range of cells, including the epidermal and macrophages. ZBSO therapy decreased the levels of TNF-, IL-6, and IL-1, implying that ZBSO inhibited the pro-inflammatory response. Inactivated cells have NF-B complexed with its inhibitory protein IB in their cytoplasm. IB separates from NF-B and undergoes ubiquitination and destruction during activation, whereas NF-B migrates to the nucleus and is phosphorylated on serine 276 of its p65 subunit. It then encourages the production of a number of pro-inflammatory cytokines [66].

6.2. Papaya

The active constituent in *Carica papaya* is papain, a proteolytic enzyme that has an ulcer-protecting effect. It also has antibacterial, antioxidant, and anti-inflammatory properties. The wound healing activity of *C. papaya* is attributed to papain, which leads to enzymatic debridement and breakdown of proteins, an increase in collagen production, resulting in tissue formation and enhanced wound healing. Papain contains substances called proteolytic enzymes that help in the breakdown of protein. Proteolytic enzymes play a vital role in the normal wound healing process. Proteases are enzymes that act on proteins by breaking them down into peptides and amino acids. In wound healing process, the major proteases are the matrix metalloproteinases (MMPs). The other contributing element is L-ascorbic acid, a fundamental requirement for the change of proline to hydroxyproline [67, 68]

7. RESIN

7.1. Indian Frankincense

Frankincense, a resinous concentrate from the *Boswellia sacra* tree, is used to treat injuries and inflammatory disorders, including rheumatoid arthritis, throughout Africa, India, and the Middle East. It is an important ingredient in ANBP, a traditional Chinese medicine (TCM) comprised of pounded Agrimonia eupatoria (A), Nelumbo nucifera (N), Boswellia sacra (B), and Typha angustifoliae dust (P). In the TGF-1 signalling cascade, ANBP promotes Smad-dependent pathways [69]. ANBP has also been shown to inhibit collagen manufacturing and hasten the maturation of the collagen extracellular matrix, resulting in less scarring and better skin tissue restoration. Hou *et al*. recently reported that ANBP shortened wound closure time in diabetic mice by direct neovascularization effects [70].

7.2. Myrrh

Myrrh, a resinous exudate produced by *Commiphora myrrha*, has displayed antioxidant, antibacterial, and pain-relieving properties. The active ingredient of myrrh is furanoeudesma. It has been basically found to have wound healing properties. Myrrh, like numerous other herbal preparations discussed here, is reported to alter TGF-1 and VEGF expression in mouse dermal fibroblasts *in vitro*, implying a shared mechanism of action. Myrrh promotes the multiplication and differentiation of neutrophils, which aids in the healing of wounds. In comparison to untreated animals, Wistar rat models with skin injuries and wounds treated with myrrh demonstrated an increase in neutrophil proliferation and maturation during healing. The effect of myrrh on neutrophil influx into various tissues was also looked into. In an animal model, having septic shock with cecal ligation and puncture (CLP), administration of myrrh reduced CLP-induced mortality and inflammatory mediator levels [71].

8. RHIZOMES

8.1. Sedum

Rhodiola imbricata, a perennial herb found in the western Himalayas at high elevations (4000–5000 m), is characterized by having bioactive flavonoids, coumarins, and phenyl glycosides. Its active ingredient is gallic acid. When applied to excisional wounds in rats, ethanolic extracts of Rhodiola imbricata rhizomes trigger a vigorous wound-healing response [72]. Immunomodulation, antioxidation, hepatoprotection, radioprotection, and anticancer capabilities have all been documented as contributing to tissue healing. Wound contraction is mediated by granulation tissue's specialized myofibroblasts. The elevated levels of hydroxypyroline and hexosamine in treated rats likely contributed strength to the revived tissue, and elevated DNA and protein levels suggest that the extract has mitogenic potential. This could be attributed to cellular invasion as well as cell reproduction throughout the healing phase. The results of biochemical indicators matched the histological findings as well. *In vitro* investigations have recently revealed that *R. imbricata* rhizome extract has immunostimulatory properties, as seen by enhanced production of interleukin-6, tumor necrosis factor alpha, and other cytokines that aid wound healing [73 - 77]. However, more research into the primary mechanism of Rhodiola extract, which includes cellular growth, is needed.

8.2. Notoginseng

Panax notoginseng is utilized to prevent bleeding, lessen oedema and swelling, and reduce pain. Notoginsenoside is its active ingredient. It is not to be mistaken for Panax ginseng or different ginsengs. Panax notoginseng flower extracts have been reported to disrupt NF-B signalling [78], influencing the production of inflammatory cytokines, such as IL-6, which are known to contribute to keloid aetiology. PNS is the most essential component of Panax notoginseng, and it aids in wound healing. The activation of PI3K, AKT, and ERK by PNS increased wound fibroblast proliferation and migration and also the production of collagen and fibronectin. Wounds frequently result in inflammatory reactions in the damaged area, as well as a high level of inflammatory cytokines, like TNF-, IL-6, and IL-1. PNS reduced the inflammatory response and decreased the levels of TNF-, IL-6, and IL-1. These findings show that PNS possesses wound-healing properties [79].

9. WHOLE PLANT

9.1. Chinese Cinnamon

It is a typical spice and flavouring ingredient. Cinnamomum cassia’s bark is also used as an analgesic and to enhance blood circulation. In human umbilical vein endothelial cells, it generally animates the PI3K/AKT and MAPK flagging pathways, aiding VEGF articulation and driving angiogenesis. Cinnamaldehyde has also been shown to help zebrafish recover wounds. Cinnamon is a medicinal plant with a wide range of therapeutic effects. Cinnamon essential oil has anti-oxidant activity, according to Stefan *et al*,. Ceylon cinnamon essential oil inhibits hepatic 3-hydroxy-3-methylglutaryl CoA (HMG-CoA) reductase activity in rats and suppresses lipid peroxidation by increasing hepatic antioxidant enzyme activity, according to another study (Lee *et al*., 2003). Cinnamon's anti-inflammatory and antioxidant qualities may help to speed up wound healing. It is generally understood that inflammatory reactions can be triggered by a variety of methods. Eugenol has anti-inflammatory properties similar to a COX inhibitor, which aids wound healing [80].

9.2. Tulsi

It is the traditional plant of Ayurveda for curing various diseases. Urosolic acid is the main active ingredient in basil leaves. The main mechanism by which Ocimum sanctum compounds provide safeguard against cellular damage is their free radical scavenging activity [81]. *Ocimum sanctum* is involved in the repair of wounds at many levels of immunological processes, including antibody formation, hypersensitive reaction mediator release, and tissue response to these mediators in the target areas [82]. *Ocimum sanctum* leaves contain volatile oil, including limonene, borneol, copaene, caryophyllene, and elemol, as well as phenolic components (rosmarinic acid, apigenin, cirsimaritin, isothymusin), flavonoids (orientin, vicenin), and aromatic compounds (methyl chavicol, methyl eugenol) responsible for wound healing [83, 84]. During wound healing, Ocimum sanctum compounds raise TNF-alpha levels. The leaves of O. sanctum are anti-inflammatory, analgesic, and immunostimulatory. At very low concentrations, flavonoids extracted from *O. sanctum* scavenged free radicals *in vitro* and demonstrated antilipoperoxidant action *in vivo*. Plant flavonoids' ability to scavenge free radicals aids in wound healing. In rats, low antioxidant levels, along with elevated levels of free radical damage indicators, play a key role in wound healing. The ability of *O. sanctum* compounds to protect against cellular damage is mostly due to their free radical scavenging activity. *O. sanctum* may modulate humoral immune responses at several stages in the immunological system, such as antibody formation, the release of hypersensitive mediators, and the response of tissues to these mediators in the target organs, according to research in rats [85].

9.3. Giloy

Tinospora cordifolia preparations are commonly used in the traditional system to treat jaundice, rheumatism, intermittent fevers, eye and liver ailments, spasms, inflammation, diabetes, seminal weakness, urinary tract infections, and also act as an aphrodisiac. It is also a key ingredient in many Ayurvedic formulations, and it has been shown to have adaptogenic and immunomodulatory properties in the fight against infections. Tinosporin and jateorine are the active ingredients of *Tinospora cordifolia*. It primarily affects immune effector cells, cytokine production, mitogenicity, stimulation, and activation. Its extracts have been proven to cause an increase in the cytokine IL-6 level, resulting in acute damage responses, inflammation, and the activation of cytotoxic T cells and B cells, which also promote wound healing. Tinosporin basically helps to increase cytokine production, which leads to stimulation of interleukin and interferon that help in the activation of immune system and promote wound healing [86].

9.4. Turmeric

Turmeric (*Curcuma longa*) has been employed as an herbal medicine to cure a variety of diseases. Curcumin (a constituent of turmeric) has been displayed to be hostile to infections, oxidants, mutagenic and cancer-causing agents, and coagulants. In addition to other things, curcumin, the most dynamic part of the rhizome of *Curcuma longa* L. (normal name: turmeric), has long been used because of its prolific practical properties, particularly cell reinforcement, free radical scavenger, antimicrobial and calming action, which assume a pivotal part in the injury recuperating process. It hastens the wound-healing process at various stages. Edema and erythema are related to expansions in vascular porosity, leukocytic penetration, and extravasation of liquid from veins to tissues. Wound healing is related to the diminution of vascular penetrability, diminished leukocytic movement, fibroblast multiplication, epithelial hyperplasia, upgraded recovery, collagen conversion, and decreased ciliary cell degeneration. Curcumin can also aid in the production of granulation tissue, collagen deposition, tissue remodeling, and wound contraction [87]. Curcumin has been shown to hasten wound healing by generating growth factors important in the healing process [88].

Turmeric has the following features that help with wound healing:

- It prevents microbes from infecting the wound.
- It has anti-inflammatory properties, which means it helps to reduce inflammation.
- It reduces pain by acting as an analgesic.
- It assists in the formation of skin cells and wound healing [89].

9.5. Bael

It has been utilized by the people of the Indian subcontinent for about 5000 years. It is a plant that is native to the area. Its leaves, bark, roots, fruits, and seeds are widely utilized in Ayurveda and other traditional remedies to cure a variety of ailments. As indicated by reports, bael organic products have a wide scope, including free radical scavenging, cell reinforcement, lipid peroxidation restraint, antibacterial and antiviral action, diarrheal protection, gastroprotection against ulcerative colitis, hepatoprotection, protection from high sugar levels, cardioprotection, and numerous ethnomedicinal uses [90, 91]. *Aegle marmelos* leaf extract is high in antioxidants aiding in the healing of wounds [92]. The active components in *Aegle marmelos* root extract speed wound healing and offer the healed wound strength [93]. Aegle marmelos fruit pulp promotes wound healing by increasing collagen and reducing inflammation [94]. Different natural concentrates of the *A. marmelos* leaves have intense and subacute mitigating activity. These actions might be because of the presence of lupeol and skimmianine in the leaves, as the mixture of the components has shown similar effects in unadulterated form.

9.6. Bharangi

The plant's ethnomedicinal value has been described in several indigenous medical systems, such as Ayurveda, Siddha, and Unani for the management of a variety of life-threatening disorders, such as syphilis, typhoid, cancer, jaundice, and hypertension. D-mannitol, hispidulin, cleroflavone, apigenin, scutellarein, serratagenic acid, acteoside, verbascoside, oleanolic acid, clerodermic acid, sitosterol, cholestanol, clerosterol, campesterol, and 24-ethyl cholesterol are some of the main elements identified in the plant. It has also been used as an anti-rheumatic, anti-asthmatic, febrifuge, and in cephalalgia and ophthalmia in the past. C. serratum roots are also utilized as an anti-oxidant, anti-bacterial, and anti-fungal agent. Apart from this, the stems and leaves of this herbal plant have been shown to have antibacterial properties [95].

9.7. Red Sandalwood

It is also known as Lal Chandan; it is native and unique to India, occurring exclusively in the southern sections of the Eastern Ghats. The wood is in high demand both at home and abroad, particularly in East Asian countries. The wood consists of various medicinal properties, like astringent, tonic, and diaphoretic effects. The wood's paste is used for inflammation and headaches. In wound healing, it basically decreases the period of epithelialization. It also increases the rate of wound contraction [96]. Phytochemical examination of the plant showed the presence of starches, flavonoids, terpenoids, phenolic compounds, alkaloids, saponins, tannins, and glycosides; likewise, a few phytoconstituents present in heartwood powder were pterocarpol; santalin A, B, and Y; pterocarptriol; isopterocarpalone; pterocarpodiolones with β-eudesmol; and cryptomeridiol [97 - 100]. It is notable that T lymphocytes work by stimulating cells, like pole cells, eosinophils, neutrophils, and macrophages, leading to the creation of intermediary and supportive cytokines. Tumor necrosis factor (TNF)- α is one of the cytokines released in infective wounds. TNF-α creation in RAW264.7 cells was inhibited at 25 μg/mL level of savinin, a lignan compound. The inhibitory activity of the compound is because of its underlying similarity with that of a butyrolactone ring and its extremity on the C-9 position. Some lignans, specifically savinin, calocedrin, and eudesmin, were accounted for in the heartwood concentrate of P. santalinus. These mixtures were found to hinder TNF-α and further showed antiproliferative activity [101].

10. COMMERICAL HERBAL FORMULATIONS

Natural medication is still the backbone of around 75-80% of the total populace, predominantly in agricultural nations [102]. This is principally on account of the overall conviction that homegrown drugs are with minimal side effects and are easily locally accessible [103]. As indicated by the World Health Association (WHO), the utilization of herbal remedies all through the world surpasses ordinary medications by more than two times [104]. The following are some commercially available herbal formulations for wound healing (Table **7**).

Table 7. Some commercially available herbal wound healing preparations.

Brand Name	Ingredients	Company Name
New heal EK ointment	Teel oil, Vidarikand, Yashtimadhu, Amalki, Manjistha, Neem Patra, Haldi extract	Dabur
Quick heal cream	Extracts of Ghrita kumara, Paladu, Shatavari, Tambula Piper betel	Sri Sri Tattva
Healeviate cream	Yashtimadhu extract, Azadirachta indica, Lal Nagkeshara extract, Peelu extract	Surya Herbal
Scavon vet spray	Azadirachta indica, Euccalyptus, Curcuma longa	Himalaya
Herboheal ointment	Ocimum sanctum, Green tea, Rosemary, Mint	Udyan
Ruuh heal cream	Azadirachta indica, Shorea robusta, Ficus infectoria, Pongamia pinnata	Forest gold
Scortchnil ointment	Azadirachta indica, Ocimum sanctum, Santalum album, Berberis aristata, Glycyrrhiza glabra	Demega

CONCLUSION

A review of the literature explains why numerous herbal plants can be utilized as traditional remedies for cutaneous injuries and clinical skin issues. Humans have learned to recognize and transform plant resources from their immediate surroundings into food and medicine. Many of these “traditional” and “ancient” medicinal plants have been proven to have therapeutic advantages, but not necessarily in controlled scientific research. The number of medicinal plants that possess comparable or closely related chemicals was an unexpected result of validation investigations. Numerous natural targets and pathways are normal for herbal healing agents; a significant number of these targets are the basic stages in injury repair overflow. While *in vitro* or *in vivo* tests have provided experimental data for some listed plants, not every mechanism of action has been confirmed. To harness the full potential of herbal agents, more experimental and clinical studies need to be conducted for confirmation of the action of these plant-derived agents. These facts have been presented with the idea that traditional remedies still require a lot of exploration, and that some of them might certainly lead to effective treatments by overcoming today's therapeutic difficulties. It is recognized that the development of synthetic medications offers practical difficulties, and phytoconstituents can be a substitute for these synthetics or act as precursors for synthetic drugs, thus effecting a reduction in cost and time of development. With more scientific information on them, these may then act as the main line of treatment instead of being classified as alternative therapies, and we may soon see them as “present day medication” along with synthetic drugs.

LIST OF ABBREVIATIONS

(PDGF)	=	Platelet-derived Growth Factor
(TGF)	=	Transforming Growth Factor
(IL-1)	=	Interleukin-1
(TNF- α)	=	Tumor Necrosis Factor-α
(ECM)	=	Extracellular Matrix

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