ejpmr, 2022,9(1), 191-200

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

INSIGHTS INTO THE EMERGING WOUND HEALING POTENTIALS OF SOME IMPERATIVE INDIAN AND GLOBAL PLANTS

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Article Received on 16/11/2021 **Article Revised on 06/12/2021** **Article Accepted on 26/12/2021**

ABSTRACT

The process by which skin heals itself is known as cutaneous wound healing. The four stages of cutaneous wound healing are universally accepted: hemostasis, inflammation, proliferation, and remodelling. Keratinocytes in humans quickly re-form a functioning epidermis (reepithelialization), sealing the lesion and restoring tissue homeostasis. Dysregulation in any step of the wound healing cascade slows healing and may lead to a variety of skin conditions, such as non-healing or chronic ulceration. Indigenous and traditional medicines make considerable use of natural goods and natural product derivatives, accounting for more than half of all medications utilized globally today. Recognizing the continuing importance of traditional medicine, we conducted a comprehensive review of the literature on the use of medicinal plants and plant-based products for cutaneous wounds. The active components, bioactivities, clinical applications, formulations, production techniques, and therapeutic value of 55 medicinal plant species are all described. Several species stand out as popular wound-healing remedies utilized by people of various cultures and ethnicities. Traditional traditions' popularity and evidence of continuous usage imply that there are still lessons to be gained from them. There are undescribed reagents, undiscovered combinations, and adjunct compounds hidden among the plethora of natural products and derivatives from natural products that might have a place in today's therapeutic inventory.

KEYWORDS: Wound, Healing, Plants, Herbal, Extract, Phytochemicals.

1. INTRODUCTION

1.1. Skin

Sensing the environment, maintaining physicochemical and thermal homeostasis, functioning as a store of necessary nutrients, providing passive and active defense, and reacting to shock and damage are all important functions of our skin. Protecting the skin against stress and insult, as well as repairing and replacing important skin functions when they are injured or lost, need strong and effective systems. For millennia, humans have been healing their wounds. Traditional wound care is limited by what is readily available or can be bought locally, such as water, dirt, and plant and animal items, and is usually supplemented with ceremony and ritual as a last resort. Traditional remedies made from local plants, animals, and natural products are the backbone of wound care for millions of people throughout Asia, Africa, the Middle East, and Latin America; for others, it is the sole source of wound treatment.[1]

1.2. Cutaneous Wound Healing

Acute wound healing is governed by a logical series of overlapping, interdependent physiological processes. In juveniles, this process may take a few days to complete, whereas, in adults, it might take many weeks. In less than four weeks, most wounds heal without complications and recover homeostasis, skin barrier function, pliability, and physiological processes. Clinical research suggests that wound closure times that are shorter are related to less fibrosis and scarring. Full-thickness wounds and wounds that take a long time to heal, on the other hand, are linked to increased fibrosis, which may lead to hypertrophic scars and keloids in certain people. Wounds that do not heal in 6 weeks, whether deep, full-thickness, or partial-thickness, seem to "stall" and fail to advance through the stages of healing. These difficult-to-heal lesions are known as "chronic" wounds. For a variety of causes, including underlying illnesses including diabetes, vascular disease, hyperglycemia, ischemia, and neuropathy, difficult-to-heal wounds become "chronic." Diabetic foot ulcers, venous leg ulcers, arterial leg ulcers, and pressure ulcers are all terms used to characterize the wound's underlying origin.[2]

1.3. Traditional Medical Practices

Yet it comes to wounds, practitioners of "modern" (western) medicine sometimes use dubious phrases like "alternative," "non-conventional," "indigenous," and "complementary," when many of "modern" medicine's

approaches and practices are little different from traditional ones. Traditional methods rely nearly totally on natural resources such as water, plants, animals, and minerals, and they are still highly valued and extensively used by the majority of the world's population. Traditional Chinese medicine (TCM) is founded on the Five-Phase theory and the Yin-Yang theory, both of which are documented in ancient Chinese medical texts such as "Shen Nong Ben Cao Jing" and "Ben Cao Gang Mu." TCM makes considerable use of botanicals in many, but not all, cases, ensuring that it is effective, inexpensive, and accessible. Surprisingly, natural compounds accounted for around 54 percent of novel anticancer medicines produced between 1940 and 2002. According to another survey, around 73 percent of all modern pharmaceutical medications include chemicals obtained from natural materials. Natural compounds created inside the plant impart therapeutic action to many traditional medicines; as a result, the efficacy of TCM preparations varies greatly and is dependent on the genotype, environmental, and growth circumstances faced by each source plant. The need for "off the shelf" TCM medications with uniform composition, quality, and clinical performance has grown as cities and pharmaceutical engineering have become more industrialized. Concurrently, industrialization has brought forth more stringent product testing for biological activity and clinical effectiveness.[3]

2. Plants for Wound Healing

Recent literature has revealed that common plants present in various parts of India as well as the World are one of the most privileged resources that are provided by the nature to mankind for wound healing.[4-12]

2.1. *Aegle marmelos*

Bael (*Aegle marmelos*) is a slender, fragrant, medium-sized tree with a height of 6.0-7.5 metres and a girth of 90-120 cm that grows wild across India's deciduous woods. Bael leaves are used topically to cure wounds. *A. marmelos* leaf extracts are high in antioxidants and function as an antigenotoxicant to help heal wounds. The active components in *A. marmelos* root extract speed wound healing and provide the healed wound breaking strength. *A. marmelos* fruit pulp has wound-healing properties by increasing collagen determinants and decreasing inflammation.

2.2. *Allium sativum*

The lily *Allium sativum* L. (Amaryllidaceae) includes large quantities of alliin, allyl cysteine, allyl disulfide, and allicin, as well as potent antioxidant properties. Farahpour *et al*. discovered that topical use of *A. sativum* promoted wound healing by boosting collagen production and up-regulating angiogenesis, as well as raising the intra-cytoplasmic carbohydrate ratio.

2.3. Aloe vera

Acemannan, a primary mucopolysaccharide (mesoglycan) found in Aloe vera, stimulates the synthesis of pro-inflammatory mRNAs such as IL-1, IL-1, IL-6, TNF-α, PGE_2, and nitrous oxide, and is a strong macrophage and T-cell activator. Endogenous mitogen inhibitors and reactive oxygen species bind and trap mesoglycan moieties, resulting in phagocytosis. By working on the cyclin D1 and AKT/mTOR signal pathways, topically administered acemannan has been shown to drastically shorten wound healing time in a rat wound healing model. Aloe vera glycans have also been shown to promote de novo granulation tissue formation via an unidentified method.

2.4. *Arctium lappa*

Burdock, also known as *Arctium lappa*, is a perennial plant that is extensively planted. *A. lappa* is used to treat sore throats and skin diseases such as boils, rashes, and acne throughout North America, Europe, and Asia. *A. lappa* root extract enhances dermal ECM metabolism, changes glycosaminoglycan turnover, and minimizes visible wrinkles in human skin, according to in vivo research. *A. lappa* has been demonstrated to influence cell adhesion and gene expression in canine dermal fibroblasts by modifying the Wnt/β-catenin signaling pathway, which is considered to be a key regulator of wound healing. A Burns and Wounds topical ointment commercial product containing *A. lappa* was demonstrated in a pilot study to manage pain and healing of first-degree and second-degree burns in humans better than the control treatment.

2.5. *Astragalus propinquus* and *Rehmannia glutinosa*

Urinary retention and edema are treated using the root of *Astragalus propinquus* in traditional Chinese medicine. *Rehmannia glutinosa* root has a long history of usage in hemorheology and diabetes. Initially, a combination of *A. propinquus* root and *R. glutinosa* root was shown to be clinically helpful in the treatment of diabetic foot ulcers. In diabetic rats, this result was confirmed. Tam *et al*. found that the roots of *A. propinquus* and *R. glutinosa* improve angiogenesis and reduce tissue oxidative stress in diabetic rats, promoting wound healing and postischemic neovascularization. According to studies, *A. propinquus* root and *R. glutinosa* induce enhanced ECM deposition in human skin fibroblasts by activating the TGF-1 signaling pathway.

2.6. *Ampelopsis japonica*

The roots of *Ampelopsis japonica*, which grow across eastern Asia and eastern North America, are used as a traditional cure for burns and ulcers, among other things. *A. japonica* has been shown to exhibit a variety of pharmacological properties, including neuroprotective, antibacterial, and anticancer properties. Ethanol extracts from dried roots of *A. japonica* hastened the healing of cutaneous scald damage in rats, according to Lee *et al*. The levels of tumor necrosis factor-alpha (TNF-α) and tumor growth factor-1 (TGF-1) were found to be higher two days after the injury and to decrease as healing continued. Interleukin-10 (IL-10), on the other hand, was shown to be raised after 14 days, coinciding with wound

closure. Topical therapy with ethanolic *A. japonica* increased re-epithelization, granulation tissue development, vascularization, and collagen deposition when compared to wounds treated with Vaseline® (petroleum jelly) or silver sulfadiazine.

2.7. *Andrographis paniculata*

Green chiretta, also known as *Andrographis paniculata*, is used to treat fever, snake bites, diarrhea, infections, wounds, and itching. Wound closure in rats was found to be significantly improved following treatment with a 10% aqueous leaf extract of *A. paniculata* in one research. In the healed wounds of animals treated with *A. paniculata*, there was decreased inflammation, scarring, enhanced angiogenesis, and more collagen fibres. Andrographolide, a bicyclic diterpenoid derived from *A. paniculata* leaves, has been proven to aid with a variety of auto-immune illnesses in clinical studies.

2.8. *Anethum graveolens*

The Apiaceae plant *Anethum graveolens* L. (dill) is one of the most widely used medicinal herbs in the world. Antimicrobial, antidiabetic, and anti-inflammatory activities of *A. graveolens* have been shown to aid wound healing. Dill essential oil contains many main components such as *cis*-carvone, limonene, β-phellandrene, and anethofuran. Other important components in dill essential oil include alpha-phellandrene, which is thought to be useful in infected wounds because it inhibits bacterial development and colonization.

2.9. *Angelica sinensis*

Angelica sinensis is a dried root used in TCM for feminine illnesses, inflammation, headaches, mild anemia, tiredness, and hypertension. The role of *A. sinensis* in angiogenesis remains unknown, despite many studies revealing inconsistent effects of *A. sinensis* on *de novo* blood vessel creation. An aqueous extract of *A. sinensis* was demonstrated to enhance blood vessel formation by activating JNK1/2 and p38 phosphorylation, resulting in increased VEGF production. Bioactive n-butylidenephthalide from *A. sinensis*, on the other hand, inhibits cell cycle progression, induces apoptosis, and lowers angiogenesis.

2.10. *Astragalus membranaceus*

Polysaccharides, saponins, flavonoids, amino acids, and trace elements are found in astragalus, also known as Huang Qi in China. In a wound-healing model, *Astragalus* exhibited a high potential for wound healing, and its method was to avoid inflammation, accelerate cell cycle, and promote the release of repair components.

2.11. *Azadirachta indica*

Neem is a tiny green-leaved evergreen tree that may reach a height of 100 feet. The neem tree, also known as Herbal Indian Doctor, is prevalent across India. The neem tree (*Azadirachta indica* A. Juss) is a prominent and ubiquitous tree in India, belonging to the Meliaceae family. The advantages of different portions of the neem tree have been recorded in the oldest Sanskrit medical works, bringing it closer to human culture and civilization since Vedic times. Active chemicals found in neem, such as nimbidin, nimbin, and nimbidol, have anti-inflammatory and antibacterial properties, which aid in wound healing. Neem also contains a lot of amino acids, vitamins, and minerals, all of which help in the wound healing process' proliferation phase. Eczema, ringworm, and scabies are all treated with a neem alcoholic extract. Antimicrobial activity of neem leaf extracts and seed oil has been shown. This protects any incision or lesion against subsequent infections caused by germs. Clinical tests show that neem works just as well as cortisone acetate in reducing inflammation, speeding up wound healing.

2.12. *Blumea balsamifera*

The traditional medicine *Blumea balsamifera* (also known as ngai camphor) is widespread across Asia's tropics and subtropics. Leaf extracts are used to treat eczema, dermatitis, skin damage, bruising, beriberi, lumbago, menorrhagia, rheumatism, and skin injury. Extracts from *B. balsamifera* have been demonstrated to have anti-malarial, anti-cancer, anti-fungal, and anti-obesity properties. According to Pang *et al*., oils from *B. balsamifera* stimulate angiogenesis, perfusion, collagen deposition, organization of granulation tissue, re-epithelialization, and wound healing in mice.

2.13. *Boswellia sacra*

In Africa, India, and the Middle East, frankincense, a resinous extract from the *Boswellia sacra* tree, is used to heal injuries and inflammatory illnesses including rheumatoid arthritis. ANBP enhances Smad-dependent pathways in the TGF-1 signaling cascade. Hou *et al*. demonstrated that ANBP lowers scar formation by lowering inflammation and speeding up the production of organized granulation tissue and re-epithelialization in a rabbit ear model of hypertrophic scarring. In addition, ANBP has been demonstrated to reduce collagen formation and accelerate the maturation of the collagen extracellular matrix, resulting in reduced scarring and faster skin tissue repair. Hou *et al*. recently discovered that ANBP had direct neovascularization effects in diabetic mice, which reduced wound closure time.

2.14. *Caesalpinia sappan*

The heartwood of *Caesalpinia sappan* is well-known for its coloring capabilities, and it has been used in Traditional Chinese Medicine to improve blood circulation, reduce edema, and alleviate pain. Surprisingly, the ethanol root extract from *C. sappan* promotes dermal fibroblast proliferation, migration, and collagen production, which aids cutaneous wound healing.

2.15. *Calendula officinalis*

Calendula officinalis, sometimes known as pot marigold, is a popular herb used to heal wounds, burns, and

dermatitis. *C. officinalis* has anti-inflammatory, antioxidant, antibacterial, antiviral, antifungal, and anticancer properties, to name a few. The actual processes behind its wound-healing effects, however, are unclear. *C. officinalis* extracts increase fibroblast migration and proliferation in a PI3K-dependent manner, according to studies performed on human and mouse fibroblast cultures. *C. officinalis* flower extracts induce granulation tissue development in excisional wounds of BALB/c mice *in vivo* via changing the expression of connective tissue growth factor (CTGF) and α-smooth muscle actin (α-SMA). The chicken chorioallantoic membrane (CAM) test and a cutaneous wound healing model in rats were used to show that *C. officinalis* may promote angiogenesis *in vivo*.

2.16. *Camellia sinensis*

Green tea, an aqueous extract made from *Camellia sinensis* leaves, is popular in Asia for its alleged health benefits. Keratinocyte proliferation and differentiation are aided by the major catechin (-)-epigallocatechin-3-gallate (EGCG). Klass *et al*. reported that EGCG inhibits TGF receptors in human dermal fibroblasts by altering TGF signaling, decreasing MMP-1 and MMP-2 expression, and reducing collagen type-1 formation. Because of these properties, EGCG might be employed as an anti-scarring agent. EGCG has also been demonstrated to prevent keloids' growth and degenerative properties by inhibiting STAT3 signaling, which causes keloids to shrink and shrink. Methanol extracts of *C. sinensis* are reported to increase fibroblast proliferation and collagen synthesis. *C. sinensis* also enhances wound healing in rats by increasing angiogenesis, according to *in vivo* studies. Extracts from *C. sinensis* have been found to improve wound healing in a diabetic rat model.

2.17. *Carthamus tinctorius*

Many countries use safflower seeds, or *Carthamus tinctorius*, as a source of cooking oil. *C. tinctorius*, a lesser-known species, has a long history of usage in TCM formulations to treat blood disorders. Safflower seed oil has been shown to reduce melanogenesis in B16 melanoma cells, making it a good alternative for skin whitening. HSYA, the major water-soluble monomer of safflower yellow pigments, has been discovered to protect against cerebral and cardiac ischemia due to its anti-oxidant, anti-inflammatory, pro-angiogenic, and apoptosis-inhibiting properties. Topical treatment of HSYA at a low dose (4 mg/mL) improves diabetic wound healing in streptozotocin-induced diabetic rats by enhancing neovascularization, re-epithelialization, and granulation tissue formation. At high doses (>10 mg/mL), however, wound healing is hampered.

2.18. *Celosia argentea*

Celosia argentea, also known as silver cock's comb, has been used in traditional medicine to treat skin lesions, eruptions, ulcers, mouth ulcers, and other skin disorders. Anti-oxidant, hepatoprotective, anti-diabetic, and anti-bacterial activities are all present in the leaf extracts of this plant. Priya *et al*. discovered that a *C. argentea* alcohol extract enhances collagen and hexosamine levels in granulation tissue wounds, speeding up burn wound healing in mice. After being treated to the extract, primary rat dermal fibroblasts multiplied and motiled more.

2.19. *Centella asiatica*

Centella asiatica, often known as Asiatic pennywort, has been used to promote wound healing for generations. In Sprague-Dawley rats, extracts from the aerial parts of *C. asiatica* were demonstrated to reduce the width, depth, and duration of chronic ulcers. Wounds linked with acute radiation dermatitis in rats healed quicker when they were treated with *C. asiatica* extracts than in the control group. Asiaticoside extracted from *C. asiatica* was shown to promote collagen deposition and epithelialization in a guinea pig punch wound model. Triterpenes isolated from *C. asiatica* promote collagen re-modeling and glycosaminoglycan synthesis in a rat wound model. Furthermore, oral therapy with *C. asiatica* madecassoside enhanced collagen synthesis and angiogenesis in a mouse wound model.

2.20. *Chamomilla recutita*

The chamomile plant, *Chamomilla recutita*, belongs to the Asteraceae family and is known as chamomile. It includes chemicals that have medicinal properties, including chamazulene, alpha bisabolol, bisabolol oxides, spiroethers, and flavonoids. It also has anti-inflammatory properties that help to reduce inflammation in infected wounds. Gholami Dogoury *et al*. discovered that applying *C. recutita* to the skin may reduce the inflammatory stage while increasing the proliferative stage. They also recommended that *C. recutita* be considered as a safe alternative to nitrofurazone ointment in wound healing.

2.21. *Cinnamomum cassia*

Cinnamomum cassia is a popular spice and flavouring ingredient, and the bark of *C. cassia* is also used as a painkiller and to improve blood circulation. *C. cassia* is one of the seven botanical components of Shexiang Baoxin pill (SBP), a well-known TCM recommended for chest pain and discomfort associated with coronary artery disease. SBP is now being studied in a randomized, double-blind clinical study for the treatment of non-revascularized coronary artery disease. The anti-inflammatory and anticancer properties of SBP, as well as its effects on hypertension, insulin resistance, and non-insulin-dependent diabetic mellitus, are all being studied. Cinnamaldehyde, a bioactive component of *C. cassia*, is a natural insecticide, antimicrobial, antidiabetic, antilipidemic, anti-inflammatory, and neuroprotective agent, and activates the PI3K/AKT and MAPK signaling pathways in human umbilical vein endothelial cells, increasing VEGF expression and stimulating angiogenesis, according to in vitro and in

vivo studies. In zebrafish, cinnamonaldehyde has been shown to promote wound healing.

2.22. *Commiphora myrrha*

Myrrh is a resinous exudate produced by the *Commiphora myrrha* plant with anti-oxidant, anti-inflammatory, anti-bacterial, and analgesic effects. Among other things, myrrh is used to treat gastrointestinal issues, fractures, arthritis, obesity, parasite infections, and as an anti-coagulant. Myrrh has been used topically to clean wounds, reduce edema, and alleviate pain (analgesia). Myrrh is often used with other substances. According to Galehdari *et al*., a combination of myrrh, *Adiantum capillus*-veneris, Aloe vera, and *Lawsonia inermis* significantly improved wound healing in diabetic mice. When administered for a short period of time, myrrh reduces pain and inhibits the recurrence of mouth ulcers in humans. *In vitro*, myrrh, like many other herbal medicines listed here, has been shown to modify TGF-1 and VEGF expression in mice dermal fibroblasts, suggesting a common mechanism of action.

2.23. *Curcuma longa*

Curcumin, an active component found in the root of the *Curcuma longa* plant, has long been utilized as a medicinal and culinary flavor. Traditional Ayurvedic medicine practitioners utilize curcumin to treat inflammation, lung issues, liver issues, and diabetes. In traditional Chinese medicine, curcumin is a common treatment for stomach pain. Curcumin is one of the well-studied nutraceuticals, having been utilized for millennia by a variety of ethnic groups. This pleiotropic molecule has been demonstrated to interact with essential physiological processes at the transcriptional, translational, and posttranslational levels. Some of the mechanisms targeted include pro-inflammatory cytokines, apoptosis, NF–κB, cyclooxygenase-2, 5-LOX, STAT3, C-reactive protein, prostaglandin E_2, prostate-specific antigen, cell adhesion molecules, phosphorylase kinase, transforming growth factor-β, ET-1, creatinine, heme oxygenase-1, AST, and ALT. More than 100 clinical trials and *in vivo* studies have been conducted on curcumin as a treatment for epithelial cancers. According to the findings of these *in vivo* and *in vitro* investigations, curcumin elicits the bulk of its beneficial effects through altering the pericellular and extracellular matrix. In cutaneous wound healing, curcumin stimulates fibroblast proliferation, granulation tissue formation, and collagen deposition, which is rather unsurprising.

2.24. *Daphne genkwa*

One of TCM's 50 important herbs, *Daphne genkwa*, grows in China's Yellow and Yangtze River basins. *D. genkwa* is treated with anti-convulsant, analgesic, diuretic, anti-tussive, expectorant, and mild sedative drugs. The primary bioactives found in *D. genkwa* include biflavonoids, coumarin, diterpenes, and triterpenes. These chemicals have anti-inflammatory, anti-tumor, immunoregulatory, and anti-melanogenesis effects. Flavonoids from *D. genkwa* flowers stimulate the ERK/MEK pathway, which regulates fibroblast proliferation and collagen expression (COL1A1 and COL3A1), resulting in improved wound healing.

2.25. *Entada phaseoloides*

Entada phaseoloides, often known as St. Thomas bean, is a climbing vine from the pea family that may be found in lowland tropical woodlands and coastal forests in Africa, Australia, Asia, and the Western Pacific. The saponins and tannins present in *E. phaseoloides*' bark and seeds are used as analgesics, bacteriocide, hemostatic, and anti-cancer agents, as well as a topical treatment for skin lesions. Su *et al*. discovered that *E. phaseoloides* extracts combined with tannins accelerated the healing of infected wounds in rats. The increased wound healing was attributed to the anti-bacterial, pro-proliferative, and pro-migration actions of *E. phaseoloides* extracts.

2.26. *Eucalyptus citriodorais*

Topical and oral treatment of *Eucalyptus citriodorais* extracts is particularly effective for healing cutaneous wounds. All stages of wound healing are accelerated by these extracts. At the proliferative stage, angiogenesis, collagen deposition, granulation tissue development, epithelization, and wound contraction were hypothesized as mechanisms of action for these concentrates. The synergistic effects of phytoconstituents such phenolic compounds, flavonoids, and tannins in the extract are credited with these results.

2.27. *Hibiscus rosa-sinensis*

Hibiscus rosa-sinensis, sometimes known as shoeblack plant, is a tropical evergreen shrub native to Southeast Asia. The blooms of *H. rosa-sinensis* are tasty. Traditional literature claims that preparations made from plants and flowers promote hair growth and prevent greying. Women are claimed to benefit from alcoholic preparations of *H. rosa-sinensis* flowers in order to regulate their fertility. *H. rosa-sinensis* extracts have also been shown to have anti-bacterial and wound-healing properties. They decrease inflammation, boost fibroblast proliferation and collagen deposition, and up-regulate VEGF and TGF-1 expression in rat excisional wounds.

2.28. *Ganoderma lucidum*

In China, Korea, and Japan, the lingzhi fungus, *Ganoderma lucidum*, is known as "the mushroom of immortality". *G. lucidum* has immunological modulation, inflammatory modulation, anti-infective, anti-oxidant, cardioprotective, and anti-hyperlipidemia characteristics, and is utilized in TCM to enhance the patient's immune system. In diabetic rats, polysaccharide extracts from *G. lucidum* have been shown to improve wound healing by boosting fibroblast proliferation and migration, angiogenesis, and lowering oxidative stress. These reactions might, however, be indirect responses to *G. lucidum* as a result of its well-known humoral immune activation.

2.29. *Ligusticum striatum*

Another of TCM's 50 important herbs is *Ligusticum striatum* rhizome. So far, 174 chemical components have been discovered in *L. striatum*, the most numerous and pharmacologically active being phthalide lactones and alkaloids. In a rabbit ear scar model, essential oils from *L. striatum* were demonstrated to minimize cutaneous scarring.

2.30. *Linumu sitatissimum*

Flaxseed (*Linumu sitatissimum*) is an ancient cultivated plant used for its fiber and oil. Flaxseed and its derivatives are high in important fatty acids including alpha-linolenic acid, which are biological precursors of omega-3 and fatty acids like eicosapentaenoic acid, which may help with wound healing. According to Dogoury *et al*., topical use of *C. recutita* and *L. sitatissimum* reduced inflammatory phase and increased proliferative stage. They also suggested that *C. recutita* and *L. sitatissimum* be used as substitutes for nitrofurazone ointment in the wound healing process.

2.31. *Lindera erythrocarpa*

Luzidone is an antioxidant, anti-inflammatory, neuroprotective, and anti-vital chemical found in the *Lindera erythrocarpa* Makino plant. Human skin HaCaT cells treated with Lucidone show reduced oxidative stress and inflammation. Lucidone maintains human skin keratinocytes against UVA-induced DNA damage and mitochondrial dysfunction. Lucidone promoted wound healing by cooperation of keratinocyte/fibroblast/endothelial cell growth and migration and macrophage inflammation by PI3K/AKT, Wnt/β-catenin, and NF-κB signaling cascade activation.

2.32. *Lithospermum erythrorhizon*

The dried root of *Lithospermum erythrorhizon* is endemic to northeast China and has a variety of biological qualities, including anti-inflammatory, antibacterial, anti-angiogenic, and anti-tumor capabilities. Shikonin, a naphthoquinone derived from the root of *L. erythrorhizon*, stimulates the activity of caspases, poly-(ADP-ribosyl) polymerase (PARP), and reactive oxygen species (ROS) in cancer cell lines, resulting in programmed cell death. These qualities prompted scientists to investigate shikonin as a possible scar therapy. According to this study, Shikonin inhibits cell proliferation and collagen production in hypertrophic scar-derived human skin fibroblasts. Arnebin-1, a similar naphthoquinone derived from *L. erythrorhizon*, was found to synergize with VEGF in a rat diabetic model, resulting in markedly improved wound healing.

2.33. *Lonicera japonica*

Honeysuckle, or *Lonicera japonica*, has a long history of use in traditional Japanese, Korean, and Chinese medicine, where it has been used for thousands of years to treat infectious diseases. *L. japonica* was determined to have broad-spectrum antibacterial, anti-inflammatory, anti-pyretic, anti-oxidant, anti-cancer, hepatoprotective, and anti-hyperlipidemic activities after extensive pharmacological and clinical testing. Chen *et al.* recently discovered that ethanol extracts of *L. japonica* blooming aerial parts improve re-epithelization, angiogenesis, granulation tissue formation, and contraction during wound healing. The plant may be used as a "health food," providing some protection against gastrointestinal ulcers but also causing brain illnesses when consumed in high amounts.

2.34. *Moltkia coerulea*

Moltkia coerulea is an important plant in the Boraginaceae subfamily of the Lithospermeae. Because of the huge levels of flavonoids and phenols, it is known to have various qualities such as antioxidant and antibacterial activities, which may speed wound healing. According to Farahpour *et al*., topical treatment of *M. coerulea* enhanced well-formed clots in wound areas, reduced inflammation by exerting antioxidant capabilities, boosted vascularization, and promoted collagen production by up-regulating fibroblasts and fibrocytes cell proliferation.

2.35. *Ocimum sanctum*

Ocimum sanctum is involved in the wound healing process at several levels, including antibody formation, hypersensitive reaction mediator release, and tissue response to these mediators in the target areas. The volatile oil in *O. sanctum* leaves contains limonene, borneol, copaene, caryophyllene, and elemol, as well as phenolic compounds (rosmarinic acid, apigenin, cirsimaritin, isothymusin), flavonoids (orientin, vicenin), and aromatic compounds (methyl chavicol, methyl eugenol) that aid wound healing. During the wound healing phase, *O. sanctum* compounds raise TNF-alpha levels. The presence of flavonoids in *O. sanctum* aids in free radical scavenging, which helps to reduce oxidative stress, which is linked to both acute and chronic inflammatory diseases, according to phytochemical screening. As a prohealer and aberrant healing controller, *O. sanctum* might be a cost-effective treatment for wound care.

2.36. *Paeonia suffruticosa*

Paeonia suffruticosa, often known as moutan peony, has been around for millennia and currently comes in over 1000 different kinds. The bioactive components used in TCM therapies originate from *P. suffruticosa*'s root bark. According to a pharmacological study, *P. suffruticosa* has antioxidant, neuroprotective, anticancer, anti-inflammatory, and anti-diabetic properties. The dried root of *P. suffruticosa* is commonly used to assist in healing and relieving pain in injured skin. When tested *in vitro* at modest dosages (10 μg/mL), *P. suffruticosa* enhances the survival and proliferation of human primary dermal fibroblasts and HaCaT keratinocytes, suggesting that it might be employed as a wound-healing therapy.

2.37. *Panax ginseng*

Panax ginseng is a popular medicinal plant that helps to improve thinking, attention, and memory. *P. ginseng* root extracts have been shown to protect C57BL mice's skin from acute UVB irradiation and enhance wound healing after laser burns and excisions. In human dermal fibroblasts, *P. ginseng* formulations have been demonstrated to increase keratinocyte migration, promote proliferation, and boost collagen synthesis *in vitro*. Choi also showed that the ginsenoside Rb2, derived from P. ginseng, promotes epidermal development in raft culture by boosting the synthesis of epidermal growth factor and its receptor, fibronectin and its receptor, keratin 5/14, and collagenase I, all of which are vital in wound healing.

2.38. *Panax notoginseng*

Not to be confused with Panax ginseng or other ginsengs, *Panax notoginseng* is used to halt bleeding, decrease edema, minimize bruising, and relieve pain. Terpene and saponins promote the synthesis of VEGF and angiogenesis, which facilitate wound healing. NF-B signaling has been demonstrated to be disrupted by *P. notoginseng* flower extracts, altering the production of inflammatory cytokines including IL-6, which are known to contribute to the development of keloid lesions. This finding emphasizes the significance of reagent preparation as well as the need for stringent quality control.

2.39. *Pistacia atlantica*

Pistacia atlantica is an anti-inflammatory, antibacterial, and antimicrobial plant that belongs to the Anacardiaceae family. *P. atlantica* has been shown to help burn wound healing, according to Haghdoost et al. According to Farahpour *et al*., varied quantities of *P. atlantica* reduced wound healing time, enhanced wound contraction, promoted neovascularization, and up-regulated hydroxyproline concentration. *P. atlantica* also boosted collagen deposition by up-regulating mast cell and fibroblast distribution at the same time, according to the researchers. Finally, the fact that greater doses of *P. atlantica* produced superior outcomes shows that bigger doses include more elements that play a key role in reducing healing time. Farahpour and Fathollahpour found that a flaxseed and pistachio oil ointment reduced polymorphonuclear and mononuclear cell distribution, enhanced new vascular creation, and fibroblast distribution in wounded rabbits in another investigation.

2.40. *Polygonum cuspidatum*

Coughs, hepatitis, jaundice, amenorrhea, leucorrhea, arthralgia, burns, and snake bites are all common uses for *Polygonum cuspidatum* root, which is frequently combined with a variety of substances. *P. cuspidatum* extracts were shown to stimulate TGF-1 expression and improve wound healing in rats in terms of re-epithelization, granulation tissue development, collagen production, and angiogenesis in a recent *in vivo* investigation. New anthraquinones produced from *P. cuspidatum* have been discovered to block tyrosinase, the rate-limiting enzyme in the formation of melanin, the pigment that gives skin its colour.

2.41. *Morinda citrifolia*

Noni or Indian mulberry is the *Morinda citrifolia* Linn (Rubiaceae) plant. Animals given the *M. citrifolia* extract showed a considerable increase in wound-healing activity when compared to those given a placebo. By reducing wound size and time to epithelialization, *M. citrifolia* extract enhances wound healing.

2.42. *Nelumbo nucifera*

Nelumbo nucifera is a member of the Nymphaeaceae family, which is known as Kamal in Hindi and Lotus in English. It has huge flowering mud and is widely utilized as a natural and traditional healer. Its leaves are said to offer wound-healing properties. It has been reported that using a methanolic extract of *N. nucifera* rhizomes in the creation of an ointment may help rats with various wound models. In varied doses of 5 and 10% w/w ointment, this impact was examined in the excision wound model, incision wound model, and dead space wound model. Both concentrations have the potential to greatly enhance wound models. Both concentrations may help with contracting activity, wound closure time, tensile strength, wound tissue regeneration, and lysyl oxidase activity. The observed effects were comparable to those of conventional medicines.

2.43. *Rheum officinale*

Rheum officinale, sometimes known as Chinese rhubarb, is a well-known pharmacologically active herbal remedy. Tang *et al*. found that TGF-1-related pathways improved wound healing in a rat excisional wound model. It's unknown what kind of active ingredient is responsible for this effect. The recognized regulators of pro-inflammatory cytokine and mitogenic kinase pathways, NF-κB, AP-1, and STAT3, have been demonstrated to interact directly with emodin in experiments.

2.44. *Ribwort plantain*

Ribwort plantain (Plantaginaceae) is a perennial plant with a broad range of ecological amplitude and global distribution. Antibacterial characteristics are also found to exist in it. *R. plantain* has been demonstrated in studies to speed up wound healing and epithelialization. Antioxidant qualities decrease inflammation and enhance wound contraction in rabbits, according to Farahpour and Heydari.

2.45. *Rhodiola imbricata*

Rhodiola imbricata, a perennial plant found in the western Himalayas at high elevations (4000–5000 m), is known to contain bioactive flavonoids, coumarins, and phenyl glycosides. Botanical herbal remedies often include these chemicals. When applied to excisional wounds in rats, ethanolic extracts of *R. imbricata* rhizomes trigger a strong wound healing response. Immunomodulation, antioxidation, hepatoprotection,

radioprotection, and anticancer characteristics, among others, have been documented as activities that may aid in tissue healing.

2.46. *Salvia rosmarinus*

Rosemary is a member of the mint family, and its components, which include carnosic acid, carnosol, rosmarinic acid, diterpene, triterpenoid, phenolic acid, and flavonoids, have been shown to have antioxidant qualities. It also has anti-inflammatory and antimicrobial properties, which might help in wound healing. Furthermore, it's essential oil includes significant amounts of terpenoids such as limonene, 1,8-cineol, carnosic acid, rosemarinic acid, and α-pinene, which may decrease inflammation and speed up the healing process by stimulating proliferation. In diabetic BALB/c mice, Abu-Al-Basal found that rosmarinus aqueous extract speeds wound healing by preventing wound closure and promoting full-thickness epidermal regeneration and organization. In an infected rat model, Nejati *et al*. found that topical treatment of rosemary ointment reduced inflammatory cells, enhanced fibroblast migration, and improved wound closure.

2.47. *Salvia miltiorrhiza*

TCM treats cerebrovascular and cardiovascular illnesses like stroke, coronary heart disease, and hyperlipidemia using the root of the perennial plant *Salvia miltiorrhiza* (often known as red sage). *S. miltiorrhiza* has been proven to improve skin flap survival and reduce ischemia and necrosis after mastectomy. Salvianolic acid B also inhibits the epithelial-to-mesenchymal transition, which is necessary for wound healing. Cryptotanshinone, a lipid-soluble terpenoid isolated from *S. miltiorrhiza*, has been demonstrated to inhibit HSF migration and contraction as well as downregulate the expression of COL1A1, COL3A1, and β-SMA in hypertrophic scar-derived fibroblasts (HSF), reducing fibrosis, and scarring.

2.48. *Sanguisorba officinalis*

Sanguisorba officinalis, sometimes known as great burnet, is a Rosaceae plant that grows extensively in Asia, Europe, and North America's colder northern areas. The roots of this plant include anti-oxidant, immunomodulatory, anti-inflammatory, and anti-allergy properties. *S. officinalis* has long been used to alleviate bleeding problems. It is used to treat scalds, burns, allergic skin problems, urticaria, eczema, and allergic dermatitis. Mast cell degranulation, as well as the activation of the STAT-1, Jak-2, p38, and JNK pathways and the generation of inflammatory cytokines, is suppressed by aqueous extracts produced from the root of *S. officinalis*. Furthermore, mice given the polysaccharide extract showed increased IL-1 and VEGF levels.

2.49. *Securigera securidaca*

Securigera securidaca, an Iranian natural herb, has long been used to cure diabetes in the southern region of the country. It's often used to help in wound healing. Flavonoids and coumarins, which operate as potent antioxidants, are widely employed as primary ingredients in aerial sections of *S. securidaca*. It's also believed to have antibacterial qualities that help infected wounds heal faster.

2.50. *Sophora flavescens*

Sophora flavescens is a Sophora species, a genus of over 50 plants native to Asia, Oceania, and the Pacific islands. The root of *S. flavescens* is used to treat heart, liver, intestinal, and skin issues. Experiments reveal that extracts from *S. flavescens* stimulate anti-cancer, anti-bacterial, anti-viral, anti-inflammatory, and anti-pruritic reactions, promoting wound healing. It is a potent inhibitor of tyrosinase, the enzyme responsible for melanin formation, according to a recent study, and hence has aesthetic promise as a skin whitener. Other research suggests that compounds contained in *S. flavescens* may aid those with androgenetic alopecia. In a recent study, Xu *et al*. discovered that a combination of *S. flavescens* and other herbs reduced perianal ulcers in a rat model, as well as the expression of prostaglandin E_2 and IL-8.

2.51. *Stemona tuberosa*

Stemona tuberosa is another of TCM's 50 fundamental herbs. It is used to treat coughs and lung infections in traditional medicine. Alkaloid and stilbenoid extracted from the root of *S. tuberosa* have been discovered to exhibit wound healing, anti-inflammatory, and anti-bacterial activities, while dehydrotocopherol derivatives have been found to scavenge oxygen and free radicals.

2.52. *Trigonella foenum*

Trigonella foenum-graecum, generally known as fenugreek, is widely used in Ayurvedic remedies and is also known to have antiulcer and hypocholesterolaemic properties. Fenugreek is a popular condiment and ingredient in cooking. Fenugreek is well-known for its hypoglycemic properties. Diosgenin, yamogenin, gitogenin, tigogenin, and neotigogens are polysaccharides found in fenugreek seeds. Saponins have steroidal properties that may help to reduce inflammation in the body. Mucilage, volatile oils, flavonoids, amino acids, and alkaloids are some of the other bioactive ingredients of fenugreek. 4-hydroxyisoleucine is another active component in fenugreek. Fenugreek has been shown to release anti-inflammatory substances into wounds and reduce inflammation. Fenugreek's antibacterial qualities may also boost its anti-inflammatory effects. Because of their antibacterial qualities, flavonoids and triterpenoids have been demonstrated to aid wound healing in research. Antioxidant properties of fenugreek have been linked to faster wound healing. The kinetics of wound contraction and epithelialization was significantly enhanced when the fenugreek seed was applied topically.

2.53. *Vitis vinifera*

Vitamin E, linoleic acid, oligomer pro-anthocyanidins compounds, and phenolic compounds such as flavonoids, phenolic acids, and antioxidants stilbenes and anthocyanins are found in *Vitis vinifera*, which belongs to the Vitaceae family. Anti-inflammatory, wound-healing, antibacterial, and diabetic characteristics are among the active chemicals present. *V. vinifera* increased neovascularization, fibroblast migration, and epithelialization, and may encourage the enclosure of burn wounds, according to Nejati and Farahpour.

2.54. *Wedelia trilobata*

Wedelia trilobata, also known as *Sphagneticola trilobata*, is a plant that was formerly only found in the tropical Americas but has now spread across the tropics as one of the most invasive species on the planet. Alcohol extracts made from the leaves of *W. trilobata* have been used to treat rheumatism, stubborn wounds, and arthritic sore joints. Traditional healers employ the leaves of *W. trilobata* to treat skin wounds. Luteolin inhibits the synthesis of NF-κB-regulated pro-inflammatory cytokines, which are frequent in psoriasis and skin infections. In order to validate this traditional use, Balekar *et al*. extracted ethanolic extracts from the leaves of *W. trilobata* and examined them *in vitro*. Specific sub-fractions were discovered to improve fibroblast viability, proliferation, and migration. Different sub-fractions were also shown to be efficacious against *Staphylococcus aureus* and *Staphylococcus epidermidis*.

2.55. *Zanthoxylum bungeanum*

Zanthoxylum bungeanum is a flowering plant from China's eastern provinces that belongs to the Rutaceae family. It manufactures key culinary ingredients such as sichuan pepper. Skin infections such as acne, eczema, scalds, and wound healing are also treated using *Z. bungeanum* preparations. Fruit husk extracts from *Z. bungeanum* have the unique ability to lift wrinkles on the skin. When subcutaneous muscles are relaxed and applied topically to the skin, skin wrinkles are reduced, drawing the attention of cosmetic manufacturers. The capacity of *Z. bungeanum* essential oils to increase percutaneous drug delivery is another noteworthy feature.

CONCLUSION

We conducted a review of the literature to explain why numerous medicinal plants are utilized as traditional remedies for cutaneous wounds and clinical skin problems. From the dawn of time, medicinal plants have been used to cure trauma, infection, sickness, and damage. Humans have learned to recognize and convert plant resources from their local surroundings into food and medicine throughout millennia, and with the emergence of commerce. Many of these "traditional" and "ancient" medicinal plants have been shown to have therapeutic advantages, but not necessarily in controlled scientific research. The number of medicinal plants that manufacture comparable or nearly related chemicals was an unexpected result of validation investigations. As a result, it's not unexpected that unrelated species share many biological characteristics. Many biological targets and pathways are also common; many of these are also critical stages in the mammalian wound healing cascade. Many of the chemicals discovered target mitogenic pathways (e.g., AKT, PI3K, SMAD, and cyclins), the proinflammatory NF-κB pathway (e.g., caspases, interleukins, TNF-α, and TGF-1), angiogenesis (e.g., VEGF), extracellular matrix formation (e.g., MMPs), and differentiation pathways (e.g., β-SMA). While *in vitro* or *in vivo* tests have provided experimental data for each listed plant, not every mechanism of action has been confirmed. Several compounds, such as acemannan (Aloe vera), hydroxysafflor yellow A (*Carthamus tinctorius*), polysaccharide (*Ganoderma lucidum*), phthalide lactones, and alkaloids (*Ligusticum striatum*), saponins (*Panax ginseng*), shikonin and arnebin-1 (*Lithospermum erythrorhizon*), *Centella asiatica*, *Curcuma longa*, and *Paeonia suffruticosa*, in particular, are widely used medicinal plants in many parts of the world.

Conflict of Interest

No conflict of interest for the publication of this manuscript.

Funding Information

No agency provided funding for this work.

ACKNOWLEDGEMENT

Dinesh Kumar is thankful to the college management for immense help provided in form of computers and internet in the preparation of this manuscript.

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