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RECENT ADVANCES IN WOUND HEALING ACTIVITY WITH HERBAL EXTRACT

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ABSTRACT

This research paper explores the recent advancements in wound healing facilitated by herbal extracts, highlighting their pharmacological properties and mechanisms of action. The study reviews a variety of herbal compounds known for their anti-inflammatory, antimicrobial, and antioxidant effects, which are crucial in promoting tissue regeneration and accelerating the healing process. Experimental results demonstrate the efficacy of specific herbal extracts in enhancing wound closure rates and improving skin integrity, offering a comparative analysis with conventional treatments. The paper also addresses the potential of these natural remedies to minimize scarring and improve patient outcomes, while discussing the implications for future research and clinical applications. By synthesizing current literature and presenting new experimental data, this work aims to contribute to the growing body of evidence supporting the integration of herbal medicine into modern wound care practices.

Keywords*:* Herbal extract, wound healing activity, conventional treatment.

INTRODUCTION

Physical disabilities are most commonly caused by wounds. A wound is a tissue condition that has been disturbed by an insult that is physical, chemical, microbial, or immunological. usually linked to the loss function[1]. The Wound Healing Society defines wounds as physical injuries that cause the skin to open up or break, disrupting the normal structure and function of the ski. Injured tissues regain their strength and structural and functional integrity as a result of a complex cascade of cellular and biochemical processes known as wound healing. involves ongoing cell-to-cell and cell matrix interactions that enable the process to proceed in various overlapping phases and processes, such as wound contraction, inflammation, tissue re-epithelialization, re-modelling, and formation [2].

Stages of the Healing Process

A number of things happen during the wound healing process, including the repair, particularly when activated platelets are present and active. macrophages and neutrophils. Angiogenesis and increased vascular permeability are the results of the healing process, which involves the recruitment of several cellular and cytokine-mediated processes. Secreted soluble factors from the activated cells, such as fibroblast growth factors, transforming growth factors, epidermal growth factors, and vascular endothelial growth factors, among others, cause the endothelial cells to become more active. The vascular wall's contents also activate the platelets; the kick-off is caused by the primary activators, which include fibronectin, fibrillar collagen, and other matrix proteins.

The repair of wounds is facilitated by a number of processes, particularly the presence and activity of activated platelets, neutrophils, and macrophages. Angiogenesis and increased vascular permeability are the results of the healing process, which involves the recruitment of several cellular and cytokine-mediated processes. Secreted soluble factors from the activated cells, such as fibroblast growth factors, transforming growth factors, epidermal growth factors, and vascular endothelial growth factors, among others, cause the endothelial cells to become more active. The vascular wall's contents also activate the platelets; the kick-off is caused by the primary activators, which include fibronectin, fibrillar collagen, and other matrix proteins.

Several prostaglandins are released by the inflammatory skin tissues at the wound site, some of which are thought to act as platelet mediators. functioning and activation. Following activation, the platelets begin adhesion and aggregation; at the same time, they release a number of mediators, such as adhesive proteins and chemotactic factors. Every element contributes to the healing cascade. Histamine proteases, tumor necrosis factor, leukotrins, and cytokines are released by the mast cells that encircle the blood vessels at the wound site. These function as chemotactic cues to draw leukocytes or white blood cells to the wound site. Vasodilation and inflammation are signs of the repair process of polymorphonuclear cell migration, whereas blood coagulation and vasoconstriction at the wound site are finished in a matter of minutes[3].

The primary role of the skin is to act as a protective barrier against environmental factors. When this barrier is compromised due to trauma, whether from an accident or an intentional procedure, wound healing becomes essential in restoring its integrity[4].

Wound healing is the physiological process which mainly includes the three successive steps i.e,

- Haemostasis
- Inflammatory phase
- Proliferative phase
- Remodelling phase

These phases overlap with one another. The first phase involves achieving hemostasis, followed by the aggregation of platelets and damaged parenchymal cells at the injury site. These cells release growth factors and other chemical mediators that initiate the healing process by attracting and activating inflammatory cells and fibroblasts. As a result, vasodilation and increased capillary permeability allow neutrophils to migrate to the site, where they perform phagocytosis of bacteria and cellular debris. During the proliferative phase, re-epithelialization begins, and the formation of granulation tissue is stimulated by the release of vascular endothelial growth factor (VEGF) and other growth factors from activated macrophages. The final phase involves the remodeling of the collagen matrix by fibroblasts to enhance tissue strength, followed by wound contraction [5-6].

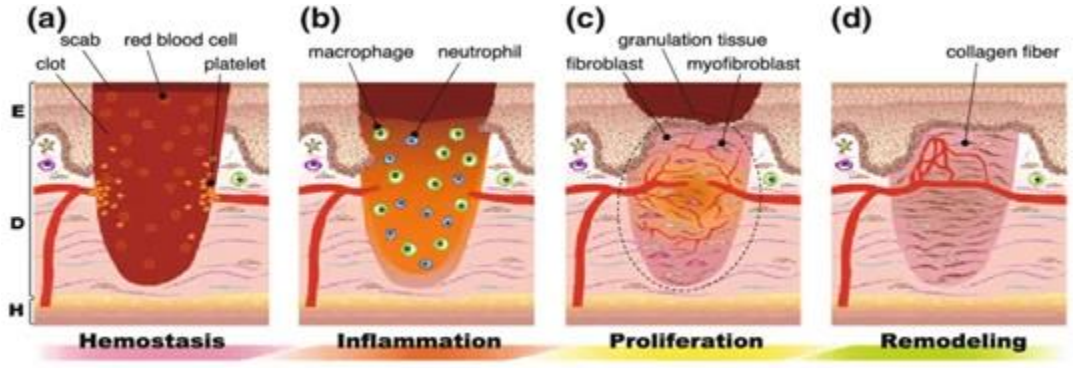

Figure 1: Stages of Wound Healing

Acute wounds and chronic wounds are the two primary categories of wounds.

CHRONIC WOUND

Chronic wounds are unable to move through all of the stages of wound healing because they become trapped in one. As a result, it may take longer than six weeks and continue for up to three months after the injury. All three layers of the skin—the epidermis, dermis, and subcutaneous fat tissue layer—are primarily destroyed. Regardless of gender, the impacted age group may include children, young people, and the elderly. Chronic wounds can occasionally arise as side effects of other medical conditions, such as pressure ulcers from spinal cord injuries or diabetic foot ulcers. Other factors contributing to chronic

or non-healing wounds include the presence of biofilm at the injury site, hypoxia within the wound bed, elevated levels of inflammatory mediators such as matrix metalloproteinases (MMPs), poor nutrition, and wound infections[7].

ACUTE WOUND

Acute wounds, which mainly affect the superficial layer of the skin and are typically associated with surgical incisions, thermal injuries, abrasions, lacerations, and similar conditions, generally require three to six weeks to heal. Acute wounds heal more quickly than chronic wounds because they essentially go through all four stages of wound healing: hemostasis, inflammation, proliferative phase, and remodelling[8].

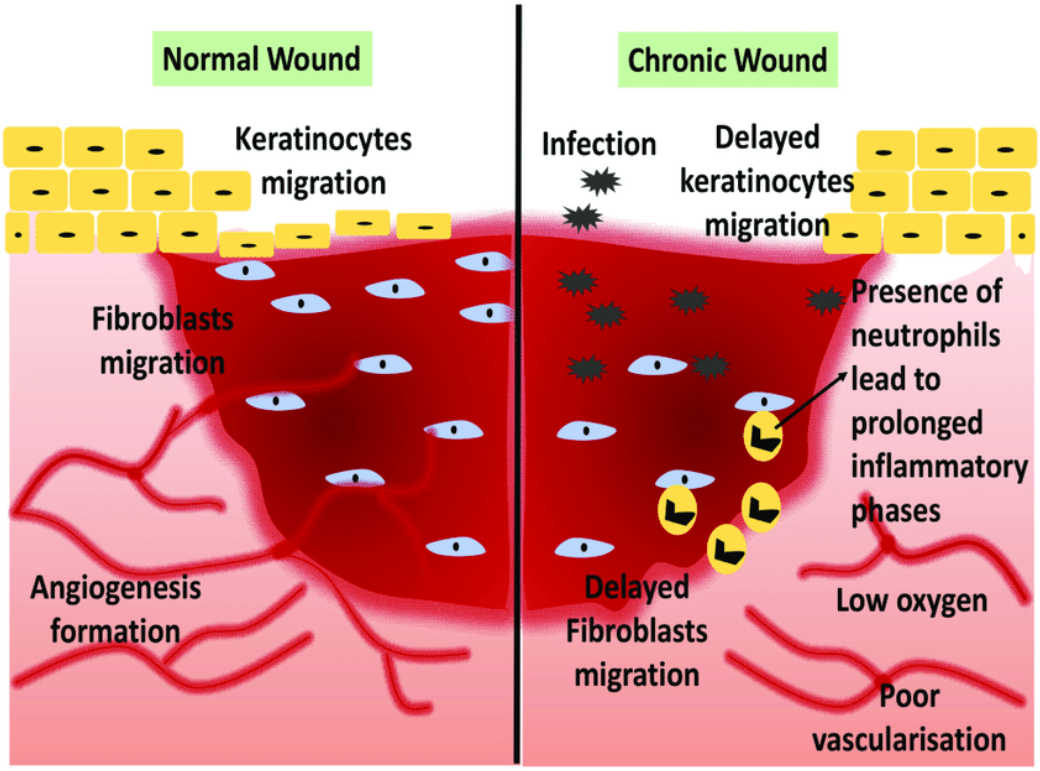

Figure 2: Acute And Chronic Wound

Natural Herbals and Spices in Wound Healing

Since ancient times, folk medicine has used herbal remedies to hasten the healing of wounds. Due to their enormous potential to influence wound healing, many plants and their various preparations have been used traditionally in relation to wound treatment. Through a number of mechanisms, plant-based extracts and/or isolates promote tissue regeneration, which frequently enhances the healing process as a whole. Many of these herbs' effectiveness and modes of action are currently well established. As a result,

natural products and their pure constituents are gaining popularity as alternative therapeutic agents for a variety of ailments, including wound healing[9].

Numerous studies on wound healing and management using medicinal products derived from plants have been conducted recently. The selection of herbs used here was based on their widespread use in wound care. The next subchapters will discuss the most recent studies from the last five years on the possible use of medicinal plants in wound healing[10].

1. Achillea millefolium

Achillea millefolium L., sometimes known as yarrow, is a major member of the Asteraceae family that has long been used in traditional medicine throughout Europe and Asia to treat many diseases, including cuts, wounds, abrasions, and diabetic ulcers[11]. The essential oils derived from yarrow flowers are considered the most potent component and are used as a hemostatic agent in wound care. Monoterpenes, which account for 90% of the essential oils in the volatile extract from Achillea flowers, are the primary representative metabolites. However, some reports indicate that sesquiterpene levels may actually exceed those of monoterpenes [12].

It has also been demonstrated that a wide variety of other chemical compounds are present in the methanolic extract of *A. millefolium's* aerial parts. More than 90% of the extract's constituents are flavonoids, including rutin, luteolin-glucoside, apigenin-glucoside, and chlorogenic acid[13]. The active ingredients isolated from *A. millefolium*, which are mostly ascribed to the presence of flavonoids, have demonstrated anti-inflammatory and antioxidant qualities in several in vitro and in vivo investigations. There are currently limited research on the benefits of yarrow extract on wound healing, despite the fact that yarrow has been used extensively in traditional medicine to treat skin inflammatory diseases and wound healing[14].

A recent study by Dorjsembe et al. investigated the effects of alcoholic extract from *Achillea asiatica* flowers on cutaneous wound healing using both in vitro and in vivo models. Their findings revealed that treatment with 3% YE significantly accelerated wound healing and enhanced epithelialization in a rat model. This impact was linked to elevated Akt and β-catenin expression. Furthermore, in vitro research revealed that YE treatments (25–50 mg/mL) enhanced collagen expression by activating transforming growth factor-β (TGF-β) in Hs68 fibroblasts and reduced the release of prostaglandin E2 and Nitric Oxide

(NO) in RAW 264.7 macrophages, suggesting anti-inflammatory activity. These findings support the hypothesis that yarrow flower extract has a positive impact on wound healing.

2. Aloe vera

Aloe barbadensis Miller, another name for the perennial green herb Aloe vera L., is a member of the Xanthorrhoeaceae family and features tubular, vivid yellow blooms. There are numerous uses for mucilaginous gel in both pharmacology and cosmetics. Minerals like zinc, copper, selenium, and calcium, sugars like glucomannans, acetylated mannans, and polymannans, polyphenols like anthraquinones, sterols like campesterol and lupeo enzymes like catalase, amylase, and peroxidase, vitamins A, C, E, and B12, and hormones like auxins and gibberellins are among its more than 75 different components. Historically, a variety of illnesses have been treated by A. vera's medical uses and associated pharmacological effects. Numerous skin diseases, such as wound healing, rejuvenation and other dermatological conditions like inflammation and burns, have been treated using this medicinal herb. [15-16].

3. Bletilla striata

Bletilla striata, a plant of the Orchidaceae family, has been used in Traditional Chinese Medicine for over 1500 years to heal burns, ulcers, chapped skin, bleeding, bruising, and injury to the alimentary canal mucosa. 192 monomeric chemicals were found in B. striata during a phytochemical investigation. Anthocyanins, quinones, steroids, glucosides, bibenzyls, phenolic acids, phenanthrenes, biphenanthrenes, and dihydrophenanthrenes are the main triterpenoids found in these compounds that were extracted from B. striata tubers. According to pharmacology study, the plant has a variety of biological activities, including antioxidant, anti-inflammatory, and immune-regulating qualities [17-18].

Furthermore, several polysaccharides present in Bletilla striata have been identified as the primary active components of its dried tubers. These polysaccharides possess antiviral, antioxidative, antibacterial, and anti-aging qualities. In recent years, natural polysaccharides have become more and more prevalent in a

variety of biomaterials because to their high biocompatibility, low toxicity, and pharmacological biomedical action. Bletilla striata polysaccharides (BSP) can be used as natural biomaterials for drug administration and wound dressings, in addition to promoting wound healing. The most prevalent polysaccharide in BSP, glucomannan, has a high molecular weight and is composed of D-glucose and D-mannose[19].

4. Calendula officinalis

Calendula officinalis, a member of the Asteraceae family, is a widely used garden plant for medicinal purposes in Europe, China, the United States, and India. It is known by several common names, including Marigold and Pot Marigold. It has historically been applied externally to burns, minor wounds, and other skin conditions. *C. officinalis* can be used for various purposes, including treating herpes, wounds, scars, and in skin and hair products. It can be applied in the form of an infusion, tincture, liquid extract, cream, or ointment [20].

The most active ingredients include triterpenoids (both free and esterified), flavonoids, coumarins, quinones, volatile oils, carotenoids, polyunsaturated fatty acids such as calendic acid, and amino acids[21].

Most of the research on the role of *C. officinalis* in healing acute wounds has come from in vitro studies (using fibroblasts and keratinocytes) and in vivo studies (in rodent animal models). A recent study found that loading ethanolic CFE onto chitosan nanofibers as a wound-healing dressing resulted in more than a 90% reduction in both Gram-positive and Gram-negative bacteria. This demonstrated significant antibacterial properties. In vitro studies using fibroblast cells showed that the mixed film inhibited collagenase activity, leading to increased collagen production, as well as enhanced cell proliferation, growth, and adhesion. When applied to rat wounds in vivo, the dressing promoted collagen synthesis, re-epithelialization, and tissue remodelling, resulting in excellent wound-healing performance (87.5% wound closure after 14 days) [22].

5. Casearia sylvestris

The Salicaceae family includes the Brazilian herb *Casearia sylvestris*. In various Brazilian communities, *C. sylvestris*, also known as "guaçatonga," is applied topically to wounds, stomach ulcers, and to encourage skin healing. The leaves of C. sylvestris contain a variety of chemical constituents. These substances, which are mostly composed of triterpene content, volatile oils, and tannins, are in charge of a variety of biological processes, such as cytotoxic and antioxidant effects. Pharmacological studies have shown that extracts of *C. sylvestris* (including ethanolic, hydroethanolic, and aqueous extracts) and their bioactive compounds possess antitumoral, antiulcerogenic, anti-inflammatory, and wound-healing properties. The casearin-like clerodane diterpenes, such as ellagic acid, isolated from *C. sylvestris* leaves, have been associated with its anti-inflammatory and wound-healing effects.

A recent study combined natural latex from *Hevea brasiliensis* (Euphorbiaceae), which has angiogenic effects, with an ethanolic extract of *Casearia sylvestris* Sw. leaves (containing a diterpene-rich fraction and casearin J) that has anti-inflammatory and wound-healing properties to create membranes for wound-healing dressings. These topical systems show significant potential for the therapeutic use of *C. sylvestris* components, as demonstrated by the dermal penetration of phenolic compounds from the membrane with ethanolic extract and the penetration of casearin-like clerodane diterpenes from all membranes, according to penetration and retention assays.

6. Crocus sativus

A spice made from the dried stigmas of *Crocus sativus* L., a member of the Iridaceae family, is commonly referred to as saffron. Saffron is used in Traditional Chinese, Ayurvedic, Persian, and Unani medicines. In the first century A.D., the Greek physician Pedanius Dioscorides wrote *Materia Medica*, which documented the medicinal properties of saffron for healing. Contemporary pharmacological studies have shown that saffron extract and its bioactive components, including apocarotenoids, monoterpenoids, flavonoids, phenolic acids, and phytosterols, offer a variety of medicinal benefits. The primary carotenoids found in saffron extracts are crocin, crocetin, picrocrocin, and safranal (SE).

A recent in vivo study using a rat burn wound model compared the effects of saffron extract and silver sulfadiazine (SSD), the most commonly used topical treatment for burn injuries. On day 7, animals

treated with 20% saffron pomade showed significantly greater wound closure, including re-epithelialization and wound contraction, compared to both the SSD-treated and untreated groups (83.04 ± 1.36% vs. 57.57 ± 2.8% vs. 35.53 ± 3.5%, respectively; $p < 0.001$). In vitro studies, confirmed by the scratch test, validated saffron's positive effects on fibroblast migration and proliferation during the remodeling phase, as well as its anti-scarring and regenerative properties.

7. Curcuma longa

Curcuma longa, a herbaceous, perennial, rhizomatous plant in the Zingiberaceae family, is one of the many species in the *Curcuma* genus. The spice, known as "turmeric," is derived from the rhizome of *Curcuma longa* and contains antioxidant polyphenolic compounds. Turmeric has long been used to treat a variety of inflammatory illnesses in Ayurvedic and traditional medicine [23]. Turmeric's ability to reduce histamine production and extend the effects of the naturally occurring anti-inflammatory adrenal hormone cortisol accounts for its anti-inflammatory properties [24].

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The main component of turmeric, known as "curcumin," is an orange-yellow, lipophilic polyphenol compound that is generally responsible for its health benefits . One of the three curcuminoids found in turmeric, curcumin accounts for 2–5% of the spice and roughly 77% of the extract alone. Milobedska et al. first described the structure of curcumin (1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-hepadiene-3,5-dione) in 1910. Curcumin is a highly pleiotropic molecule [25]. Recent research has focused extensively

on curcumin's anti-cancer, anti-aging, antiviral, antibacterial, and wound-healing properties. Its wound-healing effects are believed to be attributed to its anti-inflammatory, antioxidant, and radical-scavenging properties [26].

8. Glycyrrhiza glabra L

The root of *Glycyrrhiza glabra*, a herbaceous perennial legume in the Fabaceae family, produces licorice, a sweet and aromatic flavoring. The licorice plant is used extensively in skin care products and as a herbal remedy. Antifungal, antibacterial, antiviral, and antioxidant properties are just a few of the potential therapeutic qualities that have been documented in numerous articles. For many years, licorice root extract has been used as a successful treatment for stomach ulcers. The primary biologically active compounds in licorice, responsible for its observed effects, include terpenoids such as triterpene saponins, chalcones, and glycyrrhizin, as well as flavonoids and isoflavonoids.

9. Malva sylvestris

Malva sylvestris, a species from the mallow genus in the Malva family, has long been recognized for its medicinal uses. It is recommended as an antiseptic and emollient, as well as an antimicrobial and anti-inflammatory agent for healing burn and cut wounds. Additionally, *M. sylvestris* is suggested for acne and skincare. The therapeutic properties of this plant are attributed to the mucilage and flavonoids found in its leaves and flowers. The pharmacological and biological activities of *M. sylvestris* flowers are attributed to the presence of anthocyanin, malvidin, flavones, flavonols, malvin, malvaline, niacin, and folic acid in their extract [27].

Recent studies have explored the effect of *M. sylvestris* extract incorporated into new polyurethane (PU)-based nanofibers used as diabetic wound dressings. The wounds in animals treated with *M. sylvestris* nanofibers showed a significantly smaller area compared to the control groups. Over the course of 85 hours, the progressive release of the herbal compound was tracked using a polymer blend that contained 15% w/w herbal extract of *M. sylvestris*. Treatments with extract-loaded wound dressings demonstrated satisfactory antibacterial activity against *Staphylococcus aureus* and *Escherichia coli*, enhanced collagen

deposition and neovascularization, and significantly reduced both acute and chronic inflammation compared to the control group.

10. Plantago

Plantago L. (Plantaginaceae) is a widespread genus that includes approximately 260 species of both annual and perennial herbs and shrubs. Phytochemical research has shown that the Plantago genus contains a diverse array of compounds, such as acteosides, iridoids, glucosides, phenylethanoid glycosides, flavonoids, tannins, triterpenes, saponins, sterols, and phenyl carboxylic acid derivatives. The *Plantago* genus is commonly used in folk medicine as an anti-inflammatory remedy for various conditions, including wound treatment. Fresh *Plantago* leaves have demonstrated antibacterial properties and are beneficial for wound healing. Crushed leaves are applied to treat chronic wounds, abscesses, and acne. However, there is limited research on the effects of *Plantago* species in wound healing. An in vitro study using human oral epithelial cell lines H400 revealed that the anti-inflammatory effects of *P. major* are attributed to the combined actions of polyphenols and water-soluble substances, such as polysaccharides. Treatments with varying concentrations of the aqueous fraction of *P. subulata* methanolic extract (PHE) (200, 400, 800, and 1000 μg/mL) protected fibroblasts against oxidative stress, although these effects were not directly related to PHE concentrations. Preincubating macrophages with 50 and 200 μg/mL of PHE reduced lipopolysaccharide-induced production of NO, PGE2, and TNF-α.

11. Rosmarinus officinalis (Syn. Salvia rosmarinus)

Commonly known as rosemary, *Rosmarinus officinalis* L. belongs to the Lamiaceae family. Recent evolutionary studies suggest that the genera *Salvia* and *Rosmarinus* have merged, with *Salvia* replacing *Rosmarinus officinalis*. Rosemary is a fragrant plant with needle-like leaves, cultivated globally and widely used in traditional medicine. Due to its content of carnosol/carnosic acid and ursolic acid, rosemary offers therapeutic benefits and is utilized in the cosmetics and pharmaceutical industries, primarily for its anti-inflammatory and antioxidant properties [29].

Rosemary contains a wide array of secondary metabolites, which have been identified through ultra- and high-performance liquid chromatography, as well as gas chromatography. These analyses revealed

substantial amounts of phenolic compounds, including diterpenoids and flavonoids, as well as volatile chemicals. Flavonoids found in rosemary, such as eriocitrin, luteolin 3′-O-D-glucuronide, hesperidin, diosmin, isoscutellarein 7-O-glucoside, hispidulin 7-O-glucoside, and genkwanin, were detected in various parts of the plant over time.

In an in vivo study, the group treated with rosemary essential oil showed significant improvements in angiogenesis, granulation tissue formation, and wound healing compared to the control group. Another study found that both diabetic and non-diabetic rats treated topically with 10% *R. officinalis* oil experienced faster wound healing. A recent in vivo investigation examined the wound-healing effects of three chitosan-based topical formulations, each containing tea tree essential oil, rosemary essential oil, or a combination of both, using a rat excision wound model. The results showed that the chitosan-based product with both essential oils significantly enhanced wound shrinkage compared to groups treated with individual oils or the control group. In conclusion, rosemary extract demonstrates substantial therapeutic potential and could aid in wound healing at various stages [30].

CONCLUSION

Wound healing is a complex but highly regulated process. Healing of all kinds of wounds follows common steps of recovery. Microbial colonization is often inescapable. Infections of wounds from potentially pathogenic bacteria in most situations of causation of wounds are inevitable. Therefore, the primary goal is to reestablish the balance between host and bacteria by thoroughly cleaning the wound, applying antimicrobial agents, and using moisture-retentive dressings. Additionally, since oxidative stress is elevated during the early stages of wound healing, another key objective is to apply agents that can neutralize the excess reactive oxygen species (ROS) produced at the wound site, helping to regulate their concentration for optimal healing. Other objectives are to stimulate the adjoining tissues in the wound so that the processes of cell proliferation, remodelling and maturation are facilitated. The plant kingdom is rich in chemical constituents for mitigating these objectives acting especially as antimicrobial agents as also as the free radical scavengers, and several compounds have since been isolated. The steps of tissue repair involving interactions of neutrophils, macrophages, fibroblasts and other cells at the wound site along with deposition of collagens with proper laying out around the wounds are complex processes and it requires an understanding of the complex interactions between multiple agents. At the same time, the formation of new blood vessels through angiogenesis essential for maintaining a steady supply of nutrients and healing factors also demands thorough insight. In all these processes, several compounds from the plant extracts would work synergistically to provide the desired effect and therefore such phytochemicals concentrated and blended in optimal concentrations from multiple sources are

expected to be available in the future years to carry out multi-tasking efforts in wound healing of all kinds as more knowledge about the properties of the key constituents and the healing processes are unveiled.

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