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Herbal Extracts in Wound Healing: Performance, Delivery Systems, and Future Directions

Sujit Ghosh[1,*], **Mahmuda Parveen**[2] **and Jitendra Mahato**[2]

[1] *Jagannath Kishore College, Purulia-723101, West Bengal, India.*
[2] *Department of Botany Sidho-Kanho-Birsha University, Purulia-723104, West Bengal, India.*

[*]Corresponding Author. E-mail address: sujit@jkcprl.ac.in

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Abstract: Herbal medicines have been used for over 5,000 years with minimal negative effects, but the precise evaluation of their benefits for human health remains uncertain. Wound healing involves four stages: hemostasis, inflammation, epithelialization, and remodelling. Plant extracts such as *Aloe vera*, *Curcuma longa*, *Centella asiatica*, and *Calendula officinalis* play vital roles in wound care due to their antibacterial, antifungal, antioxidant, and anti-inflammatory properties. Because each herbal extract is active in a specific phase of wound healing, sequential distribution of herbal extracts is being studied to maximize therapeutic benefits while preventing potential interactions. Furthermore, herbal extracts and growth factors are being evaluated concurrently for enhanced wound repair, as growth factors act most effectively during the re-epithelialization stage. The release rate and duration of herbal extracts can be adjusted using polymers, especially hydrogels, which provide a moist environment, biocompatibility, biodegradability, and controlled release of bioactive components, thereby supporting wound healing. Various techniques are employed, including selective bruising, membranes with different permeability, adhesives with variable contact times, and penetration enhancers that improve the delivery of herbal extracts. Nanotechnology is also being explored to overcome transport barriers of plant extracts to wound sites through nanofibers, vesicular structures, nanoencapsulation, nanoparticles, nano emulsions, and nanogels. These methods offer advantages in terms of biocompatibility, stability, and controlled release kinetics.

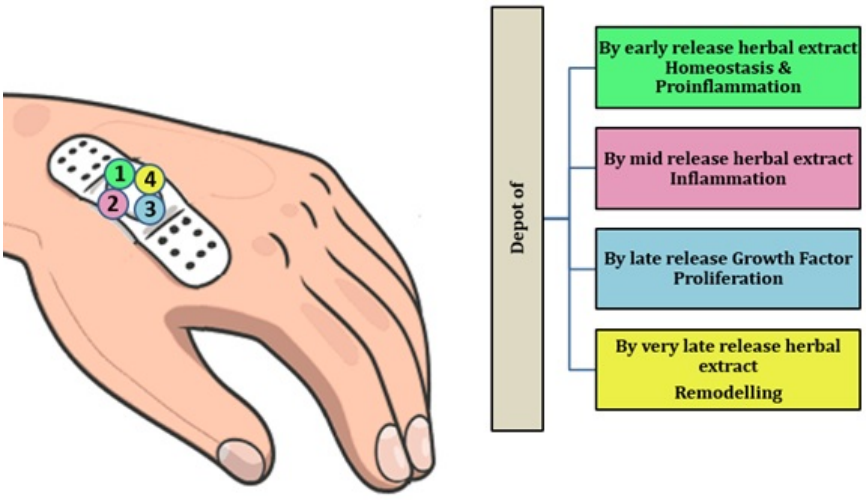

Figure 1: Graphical Abstract

Key words: Hemostasis; Inflammation; Re-epithelialization; Growth Factors; Herbal Extracts.

1 Introduction

Wound healing is an incredibly complex and intricate biological process that involves multiple phases. Wound management is the continuous care of a wound by creating an adequate environment for healing through both direct and indirect approaches, as well as the prevention of skin disintegration [1]. Wounds typically heal in four to six weeks on average, but some wounds may become chronic due to various factors that impair healing. Herbal remedies have long been used for their therapeutic properties in wound healing and offer a natural alternative to conventional treatments.

The wound healing phases are as follows: hemostasis and early inflammatory response, inflammatory, proliferative, and remodelling [2]. Depending on the phase of wound healing, different herbs are recommended. For example, Calendula (*Calendula officinalis* L.) is particularly effective in the inflammatory phase due to its anti-inflammatory properties. Similarly, Comfrey (*Symphytum officinale* L.) is often recommended for the proliferative phase due to its ability to stimulate cell growth.

A variety of herbs have been found to aid in the wound healing process. These include Calendula, *Aloe vera* (L.) Burm. f. (Aloe vera), Comfrey, and *Matricaria chamomilla* L. (Chamomile), among others. Different herbs can be extracted using various methods, such as solvent extraction. Once the herbs have been extracted, they can be purified to isolate the active phytoconstituents.

In addition to single herbs, a multi-herb formula can also be effective in promoting wound healing. These formulas may include a combination of herbs with complementary healing properties. For example, a traditional wound-healing polyherbal formula includes medicinal herbs such as *Achillea millefolium* L., *Hyssopus officinalis* L. (*Dracocephalum officinale* (L.) Y.P. Chen & B.T. Drew), *Equisetum arvense* L., and *Echinacea purpurea* (L.) Moench [3].

Growth factors, such as epidermal growth factor (EGF), play a critical role in wound healing. Molecular cloning can be used to manufacture a variety of growth factors, which can be paired with herbal remedies for optimal outcomes. A transdermal patch containing EGF, for example, has been shown to improve wound healing [4]. Furthermore, certain medicinal plants, such as *Centella asiatica* (L.) Urb., enhance the synthesis of specific growth factors.

Because wound healing occurs in phases, a polyherb formulation or a combination of polyherbal extracts and growth factors that work sequentially at each step of wound healing may provide superior outcomes. However, a sequential delivery and release mechanism is required to allow each herbal extract to operate at the appropriate stage. This also necessitates considering the reservoir, which includes the conjugate polymer and nanomaterials that govern the release mechanism.

Wound healing management depends on various factors and requires different products. These include ointments, creams, lotions, gels, gauzes, and transdermal patches. Ointments are greasy substances that stay on the skin and prevent moisture loss. They are suitable for minor wounds, burns, or infections. Creams are smooth substances that absorb into the skin and soften or hydrate it. They are useful for dry skin, rashes, or lesions. Lotions are light substances that cover large areas of skin and hydrate and plump it. They are suitable for skin types ranging from normal to oily. Gels are clear substances that provide a cooling effect and promote drying. They are recommended for oily skin, acne, or inflammation. Transdermal patches are adhesive systems that deliver drugs into the body over time. They are useful for pain relief, nicotine replacement, or hormone therapy, but not for open wounds. Gauzes are fabrics that protect wounds from infection, absorb fluids, and promote healing. They can be plain or impreg-

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nated with antiseptics or antibiotics. The choice of product depends on the type of wound and its characteristics, such as exudate level, tissue condition, and healing stage [5].

In conclusion, herbal remedies provide a natural and effective means of supporting the wound healing process. By harnessing the power of nature, healing can be promoted through the use of individual or multiple herbs that aid in various stages of wound healing. The sequential delivery of these applications is an important consideration. In the near future, this approach may become a preferred choice for wound healing.

2 Wound management

Wound management is the continuous care of a wound by creating an adequate environment for healing through both direct and indirect approaches, as well as the prevention of skin disintegration [1]. Chronic wounds are defined as those that do not heal within four to six weeks. Poor healing can be caused by a variety of factors, including restricted oxygen availability in a part of the body (ischemia), bacterial colonization, reperfusion damage (inability to restore blood flow to ischemic tissue), altered cellular responses, and collagen synthesis abnormalities. These are the main contributors [2]. Thus, optimal wound healing should meet the following criteria: gaseous transfer, clotting, restoration of blood flow, microbial growth limitation, strong cellular response, collagen production, and preservation of moisture surrounding the wound.

The following steps are involved in wound management:

1. **Hemostasis** - the process of halting bleeding.
2. **Cleansing** – the process of cleaning the wound, removing foreign substances, and irrigating with saline.
3. **Analgesia** – pain alleviation provided by local anesthetic infiltration or systemic analgesia.
4. **Skin closure** – using skin adhesive strips, tissue adhesive glue, sutures, or staples.
5. **Dressing** – covering the wound with a proper dressing that protects it from infection, absorbs exudate, maintains moisture, and permits gas exchange and evaporation.
6. **Follow-up** – monitoring the wound for infection symptoms, healing progress, and complications, as well as changing the dressing when required.

Wound dressings should be selected in accordance with wound characteristics, such as exudate level, infection risk, depth, location, and pain level, as well as patient preferences and resources. Topical agents include antimicrobials, antiseptics, growth factors, honey, and herbal compounds. These agents are applied directly to the wound surface to influence the wound environment. Topical agents should be used only when necessary and with caution, since they might impair wound healing due to cytotoxicity, allergies, drug resistance, or cost [6].

3 Physiology of wound healing

The physiology of wound healing includes the following phases: hemostasis, inflammation, proliferation, and remodelling [2]. Following an injury, the coagulation cascade is activated to stop blood loss, neutralize bacteria, and remove dead tissues. Neutrophils infiltrate the wound site during and after platelet plug formation and fibrin matrix deposition. Monocytes migrate to the wound after two to three days and differentiate into macrophages, which coordinate the next step of wound healing.

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3.A. Hemostasis and Proinflammation phase

Coagulation begins immediately after injury. During this phase, the wound is flushed and cleansed by blood and lymph released from damaged vessels [7]. Soon after, the injured blood vessels undergo vasoconstriction (constriction of vessels reducing blood flow), mediated by thromboxane and serotonin. This allows locally acting substances from mast cells to remain in the wound. Vasoconstriction lasts for five to ten minutes [8].

Vasodilation follows, mediated by histamine released from basophils, mast cells, and platelets [9]. This facilitates the passage of intravascular cells and fluid into the extravascular space. Platelets then interact with wound fluid and form a clot [10]. The clot provides not only hemostasis and infection control but also a provisional extracellular matrix for migrating neutrophils, macrophages, and connective tissue cells [11]. However, the fibrin clot provides minimal tensile strength [12]. The scab itself has little wound strength and eventually sloughs. The arrival of leukocytes into the wound marks the beginning of the inflammatory phase.

Proinflammation refers to the innate immune response mediated by various cell types, including neutrophils, basophils, eosinophils, monocytes, natural killer cells, macrophages, mast cells, and dendritic cells. These act rapidly to generate an antimicrobial state and remove debris. Innate immune cells (macrophages and neutrophils) produce cytokines such as TNF-α, IL-1β, and IL-6, initiating inflammation. Chemokines like monocyte chemotactic protein-1 regulate the release of these cells from bone marrow during infection.

3.B. Inflammatory phase

Inflammation is the second stage of wound healing and begins soon after blood vessel damage. This causes the release of their contents, leading to local edema. The inflammatory stage typically lasts 24 to 48 hours and can extend up to a week. The primary goals of this stage are to control bleeding, prevent bacterial infection, and remove cell debris from the wound.

According to Barrientos et al. [13], wound healing processes are regulated by a complex cocktail of growth factors and cytokines released by platelet- granules. Platelets (PLTs) have diverse functions, encompassing not only the prevention of blood loss but also tissue regeneration, collagen synthesis, angiogenesis, and the initiation of immune responses through the release of growth factors and cytokines.

Immune cells release pro-inflammatory cytokines such as IL-1, IL-6, and TNF-α in response to tissue injury. These cytokines aid in the recruitment of additional immune cells to the site of injury and activate inflammatory pathways that kill microbes and damaged tissue. TGF-β, an anti-inflammatory growth factor, stimulates the formation of extracellular matrix proteins and the proliferation of fibroblasts, while IL-10 inhibits pro-inflammatory responses and promotes tissue repair.

The balance between pro-inflammatory cytokines and anti-inflammatory growth factors is critical for wound healing. While an appropriate inflammatory response is necessary for tissue repair, excessive inflammation can delay healing and lead to tissue damage. Proper regulation of these molecules ensures an effective and timely healing response.

During the inflammatory stage, neutrophils and monocytes are the main active cells, both acting as phagocytes that kill invading microbes. Activated neutrophils release free oxygen radicals and lysosomal enzymes, including neutral proteases, elastase, and collagenase, which remove degraded cell and tissue debris and aid in host defense. Macrophages can differentiate into two functional types: inflammatory macrophages and reparative macrophages. These regulate extracellular connective tissue degradation through enzyme secretion and phagocytosis and

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contribute to wound matrix remodelling. Macrophages also control wound healing through the production of growth factors such as platelet-derived growth factor (PDGF).

During this initial phase, PDGF and vascular endothelial growth factor (VEGF) are released. PDGF stimulates the proliferation and chemotaxis of granulocytes and macrophages, while VEGF supports the formation of new blood vessels. Thus, both pro-inflammatory cytokines and anti-inflammatory growth factors cooperate to regulate the inflammatory response and promote tissue repair. Different growth factors, their activity, and sources are summarized in Table 1.

3.C. Proliferative phase

The epidermis, dermis, and subcutaneous layer constitute the three main layers of the skin. The digestion of dispase enzyme separates the dermis from the epidermis. Melanocytes and keratinocytes (over 95% of skin cells, producing keratin) are distinguished by differential digestion of the epidermis with trypsin. Collagenase treatment of the dermis isolates fibroblasts (located in the inner skin layer, synthesizing collagen and extracellular matrix) and endothelial cells (lining blood and lymphatic vessels).

During the proliferative phase, cell growth and division increase the number of cells. This stage is responsible for wound closure, which involves fibroplasia (formation of fibrous tissue), angiogenesis, and reepithelialisation. The aim is to shrink the injured area through contraction and matrix production.

Following inflammation, granulation tissue develops, marking the onset of wound healing. This tissue forms on wound surfaces and consists of newly generated connective tissue and capillaries. Healthy granulation tissue appears light red to dark pink, soft, moist, bumpy, and painless. Its granular appearance is due to the presence of small blood vessels and inflammatory cells in a loose extracellular matrix. Granulation tissue acts as a scaffold for epithelial cell migration and supports the restoration of tissue integrity.

Granulation tissue typically contains:

I. Proliferating blood vessels (cells of varying shapes and sizes with lumens filled with RBCs),

II. Fibroblasts producing and remodelling collagen and extracellular matrix components (proteoglycans, collagen, elastin, fibronectins, laminins),

III. Inflammatory cells (neutrophils, monocytes, and leukocytes).

After granulation tissue formation, various cell types replicate and migrate to restore tissue structure and function:

- **Keratinocytes:** Main epidermal cells. They proliferate and migrate from wound edges and hair follicles to form new epidermis [14]. They also secrete growth factors and cytokines that modulate inflammation, angiogenesis, and remodelling. Growth factors influencing keratinocyte migration include EGF, keratinocyte growth factor (KGF), and hepatocyte growth factor (HGF) [13].
- **Fibroblasts:** Principal dermal cells. They produce collagen, elastin, and extracellular matrix components that provide skin strength and elasticity [14]. Growth factors influencing fibroblast activity include TGF-β, FGF, and PDGF [13].
- **Endothelial cells:** Lining blood vessels, they form new capillaries by angiogenesis, essential for oxygen and nutrient supply [14]. Their activity is regulated by VEGF, angiopoietin, and nitric oxide (NO) [13].

Growth factors such as PDGF, EGF, FGF, and TGF-β regulate fibroblast collagen and fibronectin release. TGF-β and EGF stimulate fibroblasts to synthesize fibronectin and collagen, respectively. Matrix metalloproteinases convert collagen III (weaker, early protein) to collagen

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I (stronger, scar-associated protein) in a zinc-dependent process known as tissue remodelling.

Granulation tissue sets the stage for epithelial tissue to be laid down on top of the wound bed, having three primary tasks, namely: Immune: The wound surface is protected against microbial invasion and additional harm. Proliferative: Fills the wound with new tissue and vasculature from the bottom up.

Endothelial cells move and multiply across a healed wound to initiate angiogenesis. Capillaries arise through budding from pre-existing capillary networks, which is driven by angiogenesis factors like FGF. TGF-α may also promote endothelial cell development. Endothelial cells then allow capillaries to link, establishing a capillary network in the healing wound. Angiogenesis is important in wound healing because it offers a pathway for new healing elements to enter the site. Angiogenesis ceases when the wound obtains enough blood flow and may be controlled by oxygen tension.

The process of epithelialization commences with the proliferation of cells at the edge of the wound. Epithelial cells use contractile proteins to migrate over the wound surface, predominantly composed of collagen and fibronectin. This progression continues until the wound is covered with thickened, fully matured skin. Scar contraction begins as the wound matures. A number of proteins are involved in cell adhesion, including fibronectin and laminin.

Evidence from herbal interventions:

- Aloe vera gel-coated poly-L-lactic acid nanofibrous scaffolds enhanced wound healing by increasing collagen production and reducing neutrophil levels (Jouybar et al., 2017) [15].
- Centella asiatica extract [0.5% methanol in carboxymethylcellulose (CMC)] promoted fibroblast proliferation, epithelialization, and increased collagen II and III expression, while reducing inflammation [16].
- Punica granatum peel extract demonstrated 94% wound closure after 14 days in animal models, with improved epithelialization, angiogenesis, and fibroblast activity [17]. Epithelization, neovascularization, fibroblast, PMN, and macrophage counts were investigated, and all showed positive results after 7 days starting from treatment [17].

3.D. Remodelling phase

The remodelling phase restructures granulation tissue into scar tissue with fewer cells and vessels but denser collagen. The main objective is to enhance tissue tensile strength. This is achieved by orchestrating extracellular matrix (ECM) reorganization, degradation, and resynthesis. A key feature is the replacement of collagen III with collagen I, producing thicker, parallel fibres that improve tensile strength.

Keratinocyte migration ceases as a stratified epidermis and basal lamina form from wound edges. Restoration of normal structure and function depends on this process. Over time, fibroblasts, vessels, and inflammatory cells regress through apoptosis or migration, leading to a less cellular scar.

A notable event is the differentiation of fibroblasts into myofibroblasts. These contractile cells promote wound contraction and accelerate closure. The ECM, containing structural proteins such as collagen and fibronectin, supports adhesion, migration, and other processes essential for tissue repair [18].

4 Herbal treatment for wounds

For decades, herbal remedies have been used to treat a variety of skin ailments, including wounds. They have significant benefits over traditional therapies, including fewer adverse side effects, lower costs, greater accessibility, and compatibility

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with cultural practices. Herbal remedies can aid in wound healing by cleansing, debriding, and moisturizing the wound while also boosting the natural healing process. Herbs that can heal wounds effectively include *Calendula officinalis*, garlic (*Allium sativum*), turmeric (*Curcuma longa*), and *Aloe vera* [19, 20, 4]. These herbs possess anti-inflammatory, antibacterial, antioxidant, and wound-healing properties that aid in wound closure while also preventing infection and scarring. Recent research has shown that herbal medicines and natural remedies can successfully treat wounds through various pathways.

a) Antimicrobial: Infection is a significant cause of wound complications, and the advent of multidrug-resistant organisms challenges the development of superior antibacterial wound dressings. Natural compounds and medicinal plant extracts have been demonstrated in studies to exhibit antibacterial activity against common bacteria in wounds, such as *Staphylococcus aureus* and *Pseudomonas aeruginosa*.

b) Antioxidants: By lowering the number of free radicals, antioxidants can help reduce wound oxidative stress and expedite healing. Vitamin E and C, grape seed extract, and glutathione are among natural antioxidants that encourage the growth of new tissue in wounds [21]. Herbal extracts rich in flavonoids, anthraquinones, and naphthoquinones also act as antioxidants that lower wound oxidative stress and accelerate healing. Wound repair requires low levels of oxidative stress and reactive oxygen species (ROS); however, high oxidant exposure hinders healing. NADPH oxidases (NOX), mitochondrial electron transport chain (ETC), xanthine oxidase (XO), and lipoxygenases (LOX) are enzymes that generate oxidants during normal metabolism or immune response. These enzymes produce ROS such as superoxide anion, hydrogen peroxide, and hydroxyl radicals, which can damage proteins, lipids, and DNA.

Protective enzymes such as superoxide dismutase, catalase, glutathione peroxidase, and glutathione reductase neutralize ROS [22]. ROS can also interfere with cellular signalling pathways; therefore, a balance between low and high ROS levels is critical for wound healing.

c) Anti-inflammatory: Cell division is necessary for the wounded area to heal; this is part of the proliferation phase, mediated by growth factor overexpression or growth factor receptor activation. One report described olive leaf extract inducing overexpression of VEGF, platelet-derived growth factor receptor (PDGFR), and VEGFR-1 [23].

The remodelling phase entails apoptosis of excess cells, repositioning of collagen fibres along stress lines, and restoration of blood vessels and neurons [24]. Some plants, such as Aloe vera and Centella asiatica, influence collagen synthesis, although the precise mechanism has not been reported. Herbs with active roles in various phases of wound healing are listed in Table 2.

5 Herbal Extracts and Their Development for Wound Healing

Herbal extracts, rich in bioactive compounds like flavonoids, alkaloids, and tannins, are promising for wound healing due to their antibacterial, anti-inflammatory, and regenerative properties [19]. These extracts are prepared, purified, tested for safety, and evaluated for pharmacological activity to develop effective topical formulations for wounds. This section outlines the key steps in this process, from extraction to therapeutic assessment.

Extraction Methods: Herbal extracts are obtained by processing plant material with solvents to isolate bioactive compounds. Common methods include maceration for heat-sensitive compounds (e.g., *Calendula officinalis* flavonoids), solvent extraction for concentrated extracts (e.g., *Aloe vera* phenolics), Soxhlet extraction for high yields, supercritical fluid extraction using CO_2 for purity (e.g., turmeric's cur-

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cumin), and microwave or enzyme-assisted extraction for efficiency [50, 51]. Solvent choice depends on compound polarity: polar solvents like ethanol extract flavonoids and saponins, while non-polar solvents like n-hexane target essential oils [52]. Table 3 lists solvents and their applications. The method and solvent affect extract quality, critical for wound-healing efficacy [51].

Active Pharmaceutical Ingredients (APIs): APIs are specific compounds responsible for therapeutic effects, isolated via techniques like chromatography or crystallization. For example, Aloe vera's aloin promotes collagen synthesis, *Calendula officinalis's* lupeol enhances wound contraction, and turmeric's curcumin reduces inflammation [60, 62]. *Centella asiatica's* asiaticoside supports epithelialization, while garlic's allicin offers antimicrobial benefits but requires stabilization due to its instability [61, 64]. These APIs are purified to ensure potency and formulated into gels, creams, or patches for topical use.

Downstream Processing: After extraction, APIs undergo purification through capture (e.g., filtration to remove debris), intermediate purification (e.g., chromatography to isolate compounds), polishing (e.g., ultrafiltration for purity), and formulation (e.g., adjusting pH for stability) [65]. These steps ensure high purity and bioactivity while minimizing costs and environmental impact [66]. For instance, curcumin is concentrated using ethanol and purified via chromatography for use in wound dressings.

Toxicity Testing: Safety is critical for herbal formulations. In vitro tests like the MTT assay(3-(4,5-Dimethylthiazol-2-yl)-2, 5-Diphenyltetrazolium Bromide assay for measure cell viability and cytotoxicity) measure cytotoxicity, while in vivo studies evaluate acute and chronic dermal toxicity. For example, an ethanolic extract of *Melastoma malabathricum* showed no toxicity in rats after 28 days of topical application [67]. Skin irritation, corrosion, and sensitization tests ensure formulations don't cause erythema, necrosis, or allergic reactions, as seen with *Gymnanthemum amygdalinum* extract in rabbits [68].

Pharmacological Activity Evaluation: The Index of Pharmaceutical Activity (IPA) quantifies therapeutic potential using in vitro assays, animal models, and clinical trials. In vitro studies show Aloe vera and honey enhance fibroblast proliferation [69]. Animal models demonstrate *Centella asiatica* improves wound closure and collagen synthesis in rats [70]. A clinical trial found *Calendula officinalis* and *Hypericum perforatum* ointment accelerated post-cesarean wound healing [71]. An index ranking herbs by their effects on inflammation, epithelialization, and collagen synthesis could guide formulation development, though more clinical data are needed to optimize dosages and safety profiles [19].

6 Clinical Evidence for Herbal Wound Healing

Herbal extracts have been used traditionally for wound healing, but clinical evidence is essential to validate their efficacy and safety in modern medical practice [19]. While preclinical studies highlight the antimicrobial, anti-inflammatory, and regenerative properties of herbs like *Calendula officinalis*, *Aloe vera*, and *Centella asiatica*, clinical trials provide critical insights into their real-world effectiveness. This section summarizes key clinical studies on herbal extracts for wound healing, focusing on outcomes like wound closure, inflammation reduction, and patient recovery.

One notable clinical trial evaluated an ointment containing *Calendula officinalis* and *Hypericum perforatum* extracts in post-cesarean section patients [71]. The study found significant improvements in wound closure rates, reduced wound size, and decreased inflammation compared to conventional treatments. The herbal ointment accelerated healing without adverse effects, suggesting its potential as an adjunct therapy for surgical wounds. An-

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other study explored a biocompatible hydrogel loaded with *Aloe vera* gel and honey, applied to chronic wounds [105]. This formulation enhanced cell migration and collagen synthesis, leading to faster wound closure in patients with diabetic ulcers, with no reported toxicities.

Limited clinical data also exist for *Centella asiatica*. A trial involving topical application of its extract in patients with venous ulcers showed improved epithelialization and collagen deposition, though the sample size was small [16]. Similarly, a study on *Punica granatum* peel extract applied to minor burns demonstrated enhanced healing rates, with 94% wound closure after 14 days, attributed to its antioxidant and antimicrobial properties [17]. However, these studies often lack large-scale, randomized controlled designs, limiting their generalizability.

Despite these promising findings, clinical evidence for herbal wound healing remains sparse. Most trials are small-scale or lack rigorous controls, and few compare herbal treatments directly with standard therapies like silver sulfadiazine. Variability in extract preparation and dosing further complicates interpretation. Larger, well-controlled clinical trials are needed to establish standardized protocols and confirm the efficacy of herbal extracts across diverse wound types, such as chronic, acute, or burn wounds [6].

7 Delivery Systems for Herbal Extracts

Wound healing is a complex process involving four distinct phases—hemostasis, inflammation, proliferation, and remodeling—each requiring targeted therapeutic interventions [2]. Herbal extracts, with their antimicrobial, antioxidant, and anti-inflammatory properties, are promising for wound care but require effective delivery systems to optimize their therapeutic impact [19]. These systems, including ointments, creams, gels, transdermal patches, and advanced carriers like hydrogels and nanomaterials, ensure controlled release and enhanced penetration at the wound site [5]. This section explores the principles of drug delivery, polymer-based systems, membrane and adhesive technologies, growth factor delivery, and nanomaterials, highlighting their applications in delivering herbal extracts for wound healing.

7.A. General Principles of Drug Delivery

Delivering herbal extracts to wounds involves ensuring bioavailability, stability, and targeted release to maximize therapeutic effects while minimizing side effects [80]. Key delivery systems include ointments, which form a protective barrier for minor wounds; creams and lotions, which hydrate and deliver active ingredients to dry or oily skin; gels, which provide cooling effects for inflammation; and transdermal patches, which offer controlled release for sustained action [5, 73]. Sequential delivery, where different herbal extracts or drugs are released at specific wound healing stages, enhances efficacy by aligning with the physiological needs of each phase [77]. For example, anti-inflammatory herbs like *Calendula officinalis* can target the inflammatory phase, while growth factors support proliferation [19]. Factors such as drug solubility, diffusion coefficient, and membrane thickness influence release rates, with permeation enhancers like oleic acid or terpenes improving skin penetration [83, 85, 123].

7.B. Polymer-Based Delivery Systems

Polymers are critical for controlled drug release, offering biocompatibility and customizable release kinetics. Natural and synthetic polymers are widely used to deliver herbal extracts, ensuring sustained therapeutic effects at the wound site.

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7.B.1. Natural Polymers (Hydrogels)

Hydrogels, derived from natural sources like chitosan, alginate, gelatin, and cellulose, are ideal for wound dressings due to their biocompatibility, moisture retention, and ability to mimic the extracellular matrix [99]. Chitosan-based hydrogels loaded with *Calendula officinalis* extract enhance wound closure by promoting collagen synthesis and reducing inflammation [100, 107]. Similarly, gelatin-gellan hydrogels with tannic acid exhibit antibacterial properties, accelerating healing in mouse models [102]. A carboxymethyl cellulose (CMC) hydrogel delivering *Centella asiatica* extract improved fibroblast proliferation and epithelialization in mice [16]. Curcumin-loaded chitosan/gelatin sponges also support wound healing by enhancing angiogenesis and tissue regeneration [109]. These hydrogels provide a moist environment, protect bioactive compounds, and enable sustained release, making them effective carriers for herbal extracts [110].

7.B.2. Synthetic Polymers

Synthetic polymers like poly(lactic-co-glycolic acid) (PLGA), poly(ethylene glycol) (PEG), and poly(N-isopropylacrylamide) (pNIPAM) offer tunable properties for drug delivery. PLGA forms biodegradable microspheres or nanoparticles that release herbal extracts like curcumin over time, though initial burst release can be a challenge [111]. PEG enhances the stability of liposomes and micelles, improving the delivery of hydrophobic compounds like curcumin by increasing circulation time and immune evasion [112]. Chitosan-pNIPAM nanogels have been developed to overcome curcumin's low solubility, providing stimuli-responsive release (e.g., pH-sensitive) for enhanced wound healing [113]. Synthetic polymers allow precise control over release kinetics, making them suitable for delivering complex herbal extracts to specific wound healing phases.

7.C. Membrane and Adhesive-Based Delivery Systems

Membranes and adhesives facilitate controlled drug release and skin permeation, critical for transdermal delivery of herbal extracts. Lipid bilayer membranes, mimicking the stratum corneum, form liposomes or transfersomes that enhance penetration of herbal compounds like curcumin through intercellular and transfollicular routes [115]. Artificial membranes, such as cellulose acetate, are modified with enhancers like fatty acids to improve drug permeability, as seen in curcumin-loaded nanostructured membranes [117]. Adhesive polymers like polyisobutylene (PIB), acrylics, and silicones are used in transdermal patches to control release rates. For example, a patch with *Rhodiola rosea* extract used an acrylic adhesive for sustained delivery [119]. Permeation enhancers, such as oleic acid, menthol, or azone, further improve drug transport by increasing lipid fluidity or disrupting skin barriers [123, 125]. These systems ensure herbal extracts reach the wound site effectively, with adhesives like silicones enabling stimuli-responsive release (e.g., pH or temperature) [122].

7.D. Growth Factor Delivery

Growth factors, such as epidermal growth factor (EGF) and platelet-derived growth factor (PDGF), enhance wound healing by promoting cell proliferation and angiogenesis but face challenges like short half-lives and rapid degradation [75]. Combining growth factors with herbal extracts can amplify therapeutic effects. For instance, a transdermal patch with *Centella asiatica* extract and PDGF enhanced angiogenesis and collagen synthesis in rats [96]. Hydrogels, such as zwitterionic sulfobetaine methacrylate, deliver fibroblast growth factor (FGF2) to promote tissue formation and collagen deposition [129]. A chitosan-gelatin implant with *Salvia miltiorrhiza* extract and FGF-1 accelerated burn wound healing by stimulating fibrob-

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last proliferation and angiogenesis [97]. These systems protect growth factors and ensure their release aligns with the proliferative and remodeling phases, complementing the anti-inflammatory and antimicrobial effects of herbal extracts [76].

7.E. Nanomaterials in Wound Healing

Nanomaterials, with their high surface-area-to-volume ratio, enhance the bioavailability and controlled release of herbal extracts [131]. Electrospun nanofibers loaded with *Calendula officinalis* or *Centella asiatica* extracts exhibit antimicrobial and antibiofilm properties, promoting collagen organization and wound closure [107, 134]. Liposomes and metal-based nanoparticles (MNPs) deliver herbal compounds like curcumin, improving permeability and antibacterial efficacy [136]. For example, chitosan-based nanofibers with *Premna microphylla* and *Centella asiatica* extracts provided hemostatic and regenerative effects in wound models [95]. Carbon-based nanomaterials, such as graphene, support cell migration and collagen regeneration [136]. These nanoformulations overcome transport barriers, ensuring sustained delivery of herbal extracts to enhance angiogenesis, reduce inflammation, and accelerate healing [130, 133].

8 Molecular Docking Studies to Investigate the Therapeutic Potential of Herbal Active Principles

Herbal active principles are becoming more popular as a result of their possible therapeutic advantages and the potential for discovering new molecules. It has been discovered that herbal active components interact with specific receptors and enzymes in the human body. Understanding these interactions via computational docking research provides useful information for drug design. Docking studies focus on the computational prediction of a ligand's binding affinity and mode of interaction with a receptor or enzyme. These investigations give a structural foundation for understanding molecular interactions and can help in the design of new drugs.

The interaction between curcumin (derived from turmeric) and the nuclear factor-kappa B (NF- B) receptor was examined in a study by Cheemanapalli et al. [141]. According to the study, curcumin binds to the receptor's active region and prevents its activation and the subsequent downstream signalling. These results imply that curcumin may have therapeutic potential for inflammatory disorders.

In a study by Abou-Zeid and El-Mowafy [142], the docking of resveratrol, a natural compound found in grapes, with the estrogen receptor was investigated. The study demonstrated that resveratrol exists in two isomeric forms: trans- (E) and cis- (Z). The trans- (E) form binds to the estrogen receptor alpha, modulating its transcriptional activity and downstream signalling. This interaction has been implicated in the prevention and treatment of hormone-related cancers.

Docking studies also provide valuable insights into the molecular interactions between herbal active compounds and receptors/enzymes, which can guide the design of novel drugs. A study by Muhammad and Fatima [143] focused on the docking of quercetin, a flavonoid found in various fruits and vegetables, with the angiotensin-converting enzyme (ACE). The study revealed that quercetin binds to the active site of ACE, inhibiting its enzymatic activity. This suggests that quercetin derivatives could be potential candidates for the development of antihypertensive drugs.

By understanding the binding affinity and mode of interactions, researchers can design drugs with enhanced efficacy and specificity. Further research in this field is crucial to unlock the full potential of herbal medicine in modern drug discovery.

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9 Research Gap

Herbal medicine, involving medicinal plants and extracts, has been a significant part of human healthcare for millennia. The appeal of herbal remedies lies in their perceived safety and historical usage in traditional and complementary medicine. However, several research gaps persist, hindering the comprehensive integration of herbal medicine into mainstream healthcare practices. These gaps include the need for a more systematic and rigorous evaluation of the efficacy of herbal medicines, a dearth of well-controlled clinical trials comparing herbal medicines to conventional pharmaceutical treatments, and unexplored therapeutic mechanisms. Additionally, the safety and potential adverse effects of herbal medicines are crucial considerations, with concerns about potential herb–drug interactions and long-term safety. A multidisciplinary approach, involving rigorous clinical trials, mechanistic investigations, and robust safety assessments, is needed to fully harness the potential of herbal medicine and ensure informed and responsible integration into modern healthcare practices. Further scientific research is necessary to validate the effectiveness and safety of herbal medicines in wound healing and to gain deeper insights into their mechanisms of action [19,4].

10 Conclusion

Wound healing is a complex biological process encompassing a variety of cellular and molecular events. Herbal medicines have been used traditionally and are increasingly being studied for their potential therapeutic benefits in wound healing due to their multiple active components and properties, such as anti-inflammatory, antimicrobial, and antioxidant effects.

The development of multi-herbal drug delivery systems for wound healing could offer promising advantages, such as providing multiple therapeutic effects simultaneously, increasing the safety of treatment, and reducing the risk of microbial resistance and enterohepatic renal complications. Additionally, the use of transdermal patches or other formulations with sustained-release properties could provide benefits such as reducing the number of applications required, improving patient compliance, and minimizing side effects. The therapeutic potential of herbal active principles revealed by molecular docking studies provides fresh insights for drug development and shows promise in addressing a variety of health issues.

However, the development of a multi-herbal drug or an herbal drug combined with a growth factor for sequential delivery technologies in wound healing faces several challenges. The variability and complexity of the active components in herbal medicines could lead to difficulties in standardization, regulation, and quality control. Continued study in this area is critical to fully unlocking the potential of herbal substances and their interactions with receptors, enzymes, and transcription factors, thereby boosting current drug discovery. Furthermore, the interactions between multiple active components could affect the pharmacological properties, resulting in unpredictable or adverse effects.

Therefore, more research is needed to optimize the active principle ingredients of multi-herbal drug delivery systems for wound healing. This could include developing standardized extraction and formulation methods, determining the optimal combination and ratio of active components, and evaluating the safety and efficacy of such systems in animal models or clinical trials.

In conclusion, the future of multi-herbal drug delivery for wound healing holds great potential but also requires significant research and development efforts to overcome the challenges in establishing standardized and safe treatment options. Ultimately, advancements in this field could provide alternative or complementary therapies for wound healing that are more effective, convenient, and afford-

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able for patients.

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Table 1: Growth Factors and Their Characteristics

Growth Factor	Mitogenic / Mitogenic Inhibitor	Released From
Platelet-Derived Growth Factor (PDGF)	Mitogenic for vascular smooth muscle, fibroblast	Platelets, endothelial cells, or macrophages, vascular smooth muscle cells
Epidermal Growth Factor (EGF)	Mitogenic for epithelial tissue, endothelial cells, fibroblast	Platelets, almost all body fluids
Fibroblast Growth Factor (FGF)	Mitogen for mesenchymal cells, neural tissue	Fibroblast, endothelial cells, bone cells, astrocytes, smooth muscle
Vascular Endothelial Growth Factor (VEGF)	Mitogen for endothelial cells, but not for keratinocytes, smooth muscle, fibroblasts	From pituitary
Transforming Growth Factor – (TGF-)	Inhibits the replication of most cells: keratinocytes, endothelial cells, lymphocytes, macrophages, fibroblasts. May stimulate or inhibit	Platelets, fibroblast, lymphocytes, macrophages, bone cells, keratinocytes

Table 2: Growth Factors and Their Characteristics

Name of the Herb	Homeostasis and Proinflammation	Inflammation	Epithelization	Remodeling	Reference
Acalypha indica L.	NR	Anti-inflammation	NR*	Up-regulating the expression of Type I and III collagen	[25],[26]
Aloe vera (L.) Burm.f.	Stimulate proinflammatory cytokines (TNF-alpha, IL-1 beta, IL-6)	Reverse inflammation	NR	NR	[27]
Curcuma longa L.	Stimulate production of pro-inflammatory cytokines IL-10	Anti-inflammatory	NR	NR	[28],[29]
Zingiber officinale Roscoe	(with gelatin and CMC producing a biocompatible hydrogel)	Decreasing pro-inflammatory cytokines (e.g., TNF- , IL-1)	NR	NR	[30]
Matricaria recutita L.	Decreasing pro-inflammatory cytokines (e.g., TNF- , IL-1)	Increasing anti-inflammatory cytokines (e.g., IL-10)	NR	NR	[30]
Centella asiatica (L.) Urb.	NR	NR	Epithelialization and collagen deposition in a punch-type wound	Collagen deposition	[31]
Calendula officinalis L. (Flower)	NR	Anti-inflammatory	NR	NR	[32]
Lawsonia inermis L.	Homeostasis via AhR pathway activation in keratinocytes	Increased expression of TGF- 1 and VEGF-A genes	NR	NR	[33]
Garcinia mangostana L.	NR	NR	Increased expression of TGF-1, VEGF-A, bFGF, PDGF-B decreased	NR	[34]
Ocimum sanctum L.	Cold aqueous extract of leaves	Anti-inflammatory	NR	NR	[35]
Phyllanthus emblica L.	NR	Anti-inflammatory; increases VEGF	NR	NR	[36],[37]

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Name of the Herb	Homeostasis and Proinflammation	Inflammation	Epithelization	Remodeling	Reference
Justicia flava L. (Leaves)	NR	Improving angiogenesis	Collagenation and reepithelialization	NR	[38]
Lannea welwitschii	NR	Improving angiogenesis	Collagenation and reepithelialization	NR	[38]
Camellia sinensis L. (green tea)	NR	Anti-inflammatory and angiogenic effects	NR	NR	[39]
Simmondsia chinensis (Jojoba) Seed	NR	Analgesic, anti-inflammatory, transdermal drug delivery	NR	NR	[39]
Alternanthera brasiliana L. Leaves (Methanol extract)	NR	Fibroblast proliferation, angiogenesis, basement membrane development	NR	Collagen deposition	[40,41]
Ampelopsis japonica (Roots)	NR	TNF- and TGF- 1	Improved reepithelialization, granulation tissue formation, vascularization, collagen deposition	NR	[4]
Blumea balsamifera (Leaf extract)	NR	NR	Promoting angiogenesis, perfusion, granulation tissue, reepithelialization, wound closure	Collagen deposition	[4]
Hibiscus rosa-sinensis L. (Alcoholic extracts)	NR	Attenuate inflammation, enhance fibroblast proliferation (upregulate VEGF and TGF-1)	NR	Collagen deposition	[4]
Tridax procumbens L.	Homeostasis and Proinflammation	NR*	NR	NR	[42]
Cucumis sativus L.	Homeostasis and Proinflammation	NR	NR	NR	[43]
Cucumis dipsaceus Wender. ex Steud.	Homeostasis and Proinflammation	NR	NR	NR	[44]
Chromolaena odorata (L.)	Homeostasis and Proinflammation	NR	NR	NR	[45]
Echinacea angustifolia D.C., Echinacea pallida	NR	Anti-inflammation	NR	NR	[46]
Geranium (Pelargonium)	NR	Anti-inflammation	NR	NR	[47]
Carissa edulis (Forssk.) Vahl	NR	Anti-inflammation	NR	NR	[48]
Boswellia serrata Roxb.	NR	Anti-inflammation	NR	NR	[49]

Table 3: Growth Factors and Their Characteristics

Solvent	Polarity	Examples of Compounds Extracted	From Plant	Compound Isolated	References
Water	High	Sugars, amino acids, organic acids, phenolic acids	Aloe vera	Phenolic acids	[53]
Methanol	High	Flavonoids, anthocyanins, tannins	Ginkgo biloba	Flavonoids	[54]
Ethanol	High	Flavonoids, alkaloids, saponins	Panax ginseng	Saponins	[55]

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Solvent	Polarity	Examples of Compounds Extracted	From Plant	Compound Isolated	References
Acetone	Medium	Flavonoids, carotenoids, chlorophylls	Calendula officinalis	Flavonoids	[56]
Ethyl Acetate	Medium	Flavonoids, phenolic acids, caffeic acid derivatives	Echinacea purpurea	Phenolic compounds	[57]
Chloroform	Low	Alkaloids, terpenoids	Catharanthus roseus	Alkaloids	[58]
n-Hexane	Low	Lipids, waxes, essential oils	Lavandula angustifolia	Essential oils	[59]

Table 4: Growth Factors and Their Characteristics

Technique	Materials Used	Main Function	Mode of Action	Reference
Core-Shell Nanoparticles	Organic chemicals, metals	Act as carriers for antimicrobials/drugs	1. Nanoparticles encapsulate antimicrobial/drug 2. Within a core and have a surface shell 3. Provides stability and controlled release	[137]
Surface Nanoengineering	Polymer coatings	Prevent biofilm formation and inhibit bacteria growth on medical devices	1. Coatings prevent bacterial growth or release 2. Antimicrobials are permanently active or activated upon stimulation	[138]
Carbon-Based Nanomaterials	Carbon dots, carbon nanotubes, graphene	Antibacterial and antibiofilm efficacy	1. Carbon nanotubes promote cell migration within hydrogels	[139]
Liposomes	Phospholipids	Deliver hydrophilic molecules for wound healing	1. Sustained release and better penetration of drugs to the targeted skin site	[140]
Metal (Loid)-Based Nanoparticles	Metal and metalloid atom-based nanoparticles	1. Antimicrobial efficacy, control planktonic cells 2. Eradication of biofilms, inhibition of biofilm formation	1. High surface area/volume ratio and surface-active properties enhance antimicrobial properties 2. Effective against planktonic cells and biofilms	[136]

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