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A review: the therapeutic power of natural extracts in wound recovery

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Abstract



Natural extracts from plants, herbs, and other biological sources have demonstrated substantial potential in wound healing through their diverse biochemical activities, primarily attributed to active compounds such as alkaloids, flavonoids, phenols, and terpenoids. These compounds facilitate wound healing across various stages, including hemostasis, inflammation, proliferation, and remodeling, by modulating cellular responses, promoting tissue regeneration, and minimizing scar formation. During the hemostasis phase, natural extracts enhance platelet aggregation and fibrin formation, creating an initial matrix conducive to cell migration. In the inflammation phase, these extracts exhibit antioxidant and anti-inflammatory effects, reducing the production of pro-inflammatory cytokines and reactive oxygen species (ROS) and contributing to chronic inflammation. This anti-inflammatory activity accelerates the transition to the proliferative phase, where active compounds stimulate fibroblast and keratinocyte proliferation, promoting collagen synthesis and angiogenesis critical for new tissue formation. During the remodeling phase, natural extracts aid in collagen reorganization and maturation, improving tissue strength and elasticity while minimizing excessive scarring. However, despite the benefits, challenges such as limited bioavailability, stability, and inconsistent dosing hinder clinical applications. Advanced delivery systems, including nanofibers and hydrogels, are being explored to improve the stability and efficacy of these bioactive compounds. This review synthesizes recent research on the biochemical mechanisms of natural extracts in wound healing, outlines the clinical challenges, and highlights future directions for enhancing their therapeutic utility.

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INTRODUCTION

Wound healing is a complex, dynamic process essential for restoring skin integrity and function after injury. This process involves a highly coordinated series of biological and molecular events, traditionally categorized into four overlapping phases: hemostasis, inflammation, proliferation, and remodeling [1]. Each phase is crucial in repairing damaged tissue and re-establishing a functional barrier against environmental threats. However, the intricacies of wound healing can be easily disrupted by infection,

chronic inflammation, and oxidative stress, leading to delayed healing, chronic wounds, and excessive scarring [2]. Consequently, there is a significant demand for therapeutic interventions that can support and enhance each stage of the wound-healing process. Natural extracts from plants, herbs, and other biological sources have long been used in traditional medicine for their healing properties, primarily attributed to their diverse bioactive compounds [3]. Historically, civilizations across Asia, Africa, and South America utilized herbal formulations for treating wounds and skin ailments, with plants like *Aloe vera*, *Curcuma longa* (turmeric), and *Calendula officinalis* (marigold) recognized for their therapeutic effects [4]. With modern pharmacology and analytical techniques, the active constituents within these extracts—such as flavonoids, alkaloids, terpenoids, phenols, and saponins, have been identified, isolated, and extensively studied [5]. These compounds interact with cellular and molecular pathways to modulate inflammation, promote cell proliferation, enhance collagen synthesis, and improve tissue remodeling, contributing to an accelerated and more efficient wound-healing process [6].

In the hemostasis phase, natural extracts have been shown to facilitate blood clotting by enhancing platelet aggregation and fibrin formation, which are essential for preventing excessive blood loss and providing a structural scaffold for incoming cells [7]. During the inflammation phase, these extracts are critical in regulating oxidative stress and reducing pro-inflammatory mediators, which are crucial for preventing chronic inflammation and transitioning to the proliferative phase. Phenolic compounds, particularly those found in plants like *Camellia sinensis* (green tea) and *Echinacea purpurea*, are noted for their antioxidant properties, which mitigate the damaging effects of reactive oxygen species (ROS) that otherwise impede the healing process [8].

The proliferative phase involves the formation of new tissue through the activation of fibroblasts, keratinocytes, and endothelial cells, processes that are significantly enhanced by bioactive compounds in natural extracts. Flavonoids and terpenoids, for example, stimulate collagen synthesis and angiogenesis, both essential for establishing a vascular network and

strengthening the newly formed tissue. This phase is further supported by saponins, which are known to promote angiogenesis by inducing endothelial cell migration and proliferation [9]. Finally, in the remodeling phase, the reorganization and maturation of collagen fibers contribute to more muscular, more elastic tissue with minimized scarring. Compounds in natural extracts, such as those found in *Allium cepa* (onion), assist in collagen alignment and reduce fibrosis, enhancing the structural integrity of the healed tissue [10].

Despite the recognized benefits of natural extracts in wound healing, challenges persist in their clinical application. One significant limitation is the bioavailability of active compounds; many phytochemicals exhibit low solubility, rapid metabolism, and limited stability, which reduce their therapeutic efficacy when applied *in vivo*. Additionally, variability in plant sources, extraction methods, and compound concentration can lead to inconsistent outcomes, complicating the development of standardized treatment protocols [11]. Emerging research on advanced delivery systems, such as hydrogels, nanofibers, and controlled-release formulations, aims to address these limitations, enabling better control over dosage, stability, and targeted delivery of bioactive compounds [12].

This review aimed to provide a comprehensive overview of the role of natural extracts in wound healing, focusing on the biochemical mechanisms through which these compounds modulate each phase of the healing process. By synthesizing findings from recent *in vitro* and *in vivo* studies and clinical trials, we aim to elucidate the therapeutic potential of natural extracts and highlight the challenges and future directions in this field. Understanding the mechanisms by which these bioactive compounds interact with cellular pathways not only advances the field of wound healing but also informs the development of novel, plant-based therapeutics that could complement or replace conventional treatments, offering safe, cost-effective alternatives for wound management.

METHODOLOGY:

This review employs a comprehensive literature analysis approach, systematically examining peer-reviewed articles, clinical trials, and relevant

Table 1 Identification of Studies via Data Bases and Registers

Identification of Studies via Data Bases and Registers		
Stage	Particulars	Number (n)
Identification	Records identified from:	500
	Databases Registers	200
	Records removed before the screening: Duplicate records removed	150
	Records marked as ineligible by automation tools	50
	Records were removed for other reasons	30
Screening	Records screened	470
	Records excluded	200
	Reports sought for retrieval	270
	Reports not retrieved	20
	Reports assessed for eligibility	270
	Reports excluded: Reason 1 Not relevant to wound healing Reason 2 Insufficient data quality Reason 3 Duplicates not previously identified	50 30 20
Included	Studies included in review	170
	Reports of included studies	170

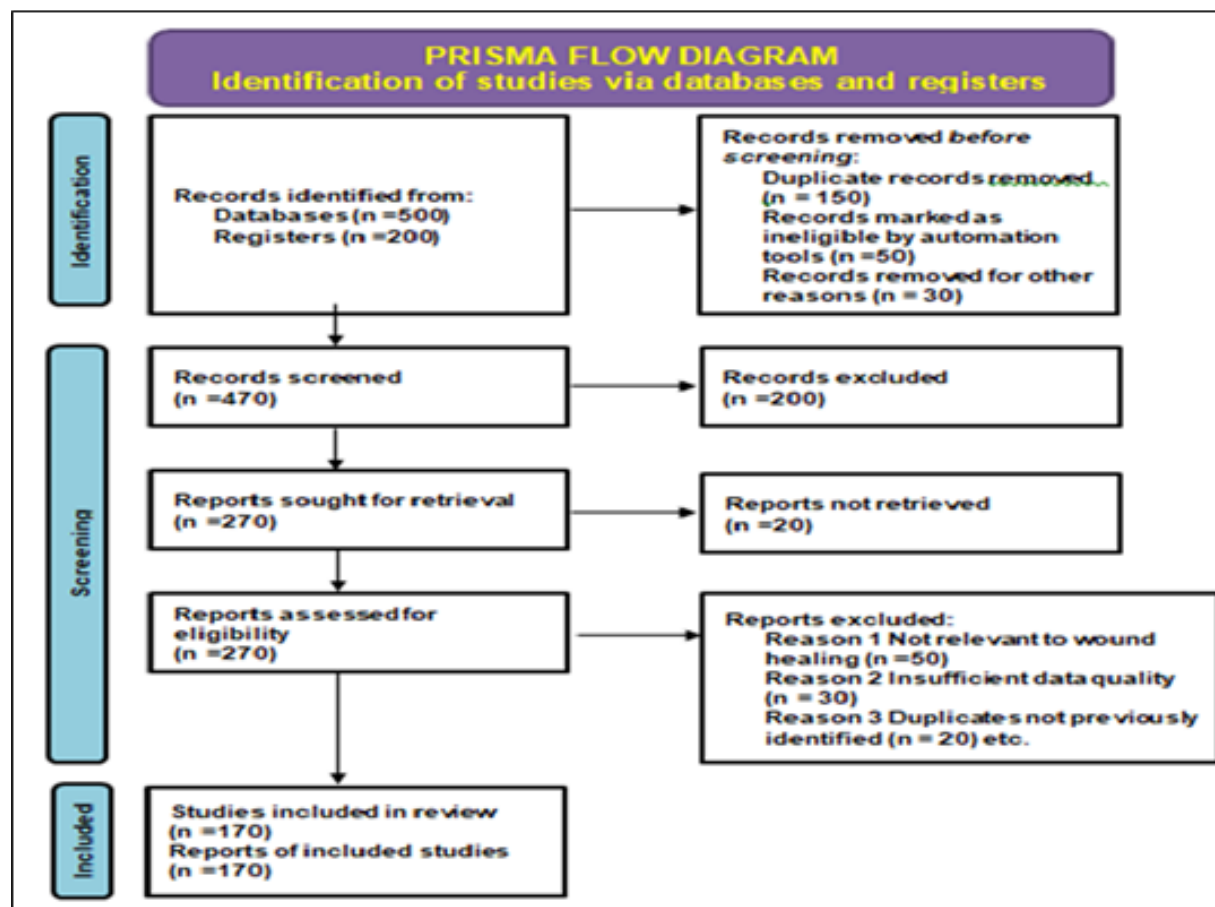


Figure 1 PRISMA Flow Diagram: Identification of Studies via Data Bases and Registers

preclinical studies on the role of natural extracts in wound healing. The literature search was conducted across major academic databases, including PubMed, Scopus, and Web of Science, using keywords such as "natural extracts," "wound healing," "phytochemicals," "inflammation," "proliferation," and "collagen synthesis." Publications from the last 10 years were prioritized to capture recent advancements, although seminal studies beyond this timeframe were included when relevant to provide foundational context [13].

Data extraction focused on identifying the specific bioactive compounds within these extracts, such as alkaloids, phenols, flavonoids, terpenoids, and saponins, and their documented biochemical activities about hemostasis, inflammation modulation, proliferation, and remodeling. Studies were critically analyzed using methodology, efficacy outcomes, and biochemical mechanisms to ensure comprehensive and objective coverage [14].

A PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart was utilized to organize and document the literature selection process, ensuring methodological transparency and replicability [15] (**Table 1 & Figure 1**).

RESULTS AND DISCUSSION

Hemostasis and Blood Clotting:

Numerous studies have demonstrated that natural extracts can promote hemostasis by affecting platelet aggregation and fibrin formation. For example, polyphenols and flavonoids in extracts from *Calendula officinalis* and *Curcuma longa* were found to accelerate clot formation by enhancing platelet activity and fibrin production. It has been reported that these compounds provide a matrix for cellular adhesion, essential for initiating the healing cascade.

This is supported by findings highlighting that bioactive compounds in plant extracts reduce blood loss and stabilize wound sites, aiding in faster recovery.

These studies underscore the role of natural extracts in facilitating hemostasis, which is particularly beneficial for acute injuries where rapid clotting is necessary to prevent blood loss and infection.

Anti-Inflammatory and Antioxidant Effects:

Natural extracts have been shown to modulate inflammation through several pathways, notably by reducing pro-inflammatory cytokine levels and ROS. Phenolic compounds and flavonoids, commonly found in *Camellia sinensis* (green tea) and *Echinacea purpurea*, inhibit the nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) pathway, which is critical for inflammatory signaling. It has been observed that polyphenols in these extracts decrease levels of inflammatory cytokines such as IL-6 and TNF- α , which are often elevated in chronic wounds. Additionally, antioxidants in these extracts reduce oxidative damage to cells, preventing prolonged inflammation and facilitating the transition to the proliferative phase. Studies confirmed these findings, reporting that extracts rich in antioxidants accelerate wound closure by reducing ROS-mediated cellular damage.

Proliferative Phase: Cell Proliferation, Angiogenesis, and Collagen Synthesis:

Natural extracts stimulate fibroblast and keratinocyte proliferation during the proliferative phase, crucial for new tissue formation. Bioactive compounds like terpenoids and saponins in *Centella asiatica* and *Aloe vera* have been shown to promote collagen synthesis and angiogenesis. For instance, these compounds stimulate fibroblast proliferation and collagen deposition, forming a stable extracellular matrix (ECM). Similarly, angiogenic factors stimulated by natural extracts enhance the vascular supply to the wound, supporting oxygen and nutrient transport to the regenerating tissue. This is supported that terpenoids promote endothelial cell migration, further improving vascularization and speeding up the healing process.

Remodeling Phase and Scar Reduction

In the remodeling phase, natural extracts contribute to collagen maturation and fiber reorganization, vital for scar reduction and tissue strength. Extracts from *Allium cepa* (onion) and *Calendula officinalis* have been shown to aid in collagen fiber realignment and improve tissue elasticity, resulting in minimal scarring. According to "Mechanistic Insights and Therapeutic Potential of Natural Products in Amelioration of Wound Healing, these extracts enhance the expression of

growth factors like epidermal growth factor (EGF), platelet-derived growth factor (PDGF), and transforming growth factor-beta (TGF- β 1), which are critical for fibroblast activity and collagen reorganization. It was corroborated that antioxidant compounds in natural extracts reduce oxidative stress during this phase, preventing the excessive collagen deposition that typically leads to hypertrophic scarring.

Antimicrobial Activity of Natural Extracts:

Preventing infection is essential for effective wound healing, and many natural extracts exhibit antimicrobial properties that reduce the risk of wound contamination. Polyphenols in *Echinacea purpurea* and *Aloe vera* reduce bacterial load at wound sites, creating a sterile environment conducive to healing. Broad-spectrum antimicrobial effects of alkaloids and terpenoids, particularly against common wound pathogens such as *Staphylococcus aureus* and *Pseudomonas aeruginosa*. This antimicrobial activity decreases the likelihood of infection-related complications, allowing for uninterrupted wound healing.

Challenges and Advances in Delivery Systems:

While natural extracts offer numerous benefits for wound healing, challenges such as low bioavailability, inconsistent dosing, and stability limit their effectiveness in clinical settings. Recent studies have explored advanced delivery systems to address these limitations. Hydrogels and nanofiber-based scaffolds enhance the stability and sustained release of active compounds, ensuring prolonged exposure to healing sites. These studies suggest that encapsulating natural extracts within biocompatible materials could improve their clinical applicability, offering controlled release, targeted delivery, and reduced degradation of bioactive compounds.

DISCUSSION:

The use of natural extracts in wound healing offers a promising, multifaceted approach due to the complex blend of bioactive compounds they contain, including alkaloids, flavonoids, terpenoids, and phenols. The findings from this review suggest that natural extracts significantly impact each phase of the wound healing process, hemostasis, inflammation, proliferation, and remodeling by interacting with distinct biochemical pathways that regulate tissue repair

and immune response. When understood and harnessed effectively, these interactions can yield safer, more accessible, and cost-effective alternatives or complements to conventional wound care therapies. However, translating the benefits observed in vitro and preclinical models into clinical practice poses unique challenges, including bioavailability, stability, and standardized dosing of these compounds.

In the initial phase of wound healing, hemostasis is crucial to prevent excessive blood loss and create a foundation for tissue repair. The ability of natural extracts to promote platelet aggregation and fibrin formation, as evidenced by studies on *Curcuma longa* and *Calendula officinalis*, highlights their potential to enhance early wound stabilization. This activity supports hemostasis and creates an extracellular matrix (ECM) that serves as a scaffold for cellular migration. While conventional hemostatic agents often focus on clot formation, natural extracts offer the added advantage of bioactive compounds that initiate concurrent anti-inflammatory and antimicrobial effects, providing a more holistic approach to wound management.

The anti-inflammatory effects of natural extracts were consistently documented across multiple studies, particularly in their ability to reduce ROS levels and inhibit the NF- κ B pathway, which is pivotal in the inflammation process. Compounds such as phenolic acids and flavonoids were shown to modulate cytokine activity, reducing IL-6 and TNF- α levels, which are often elevated in chronic wounds. This modulation is critical because unresolved inflammation can impair healing, leading to persistent wounds. By providing antioxidant and anti-inflammatory activities, extracts like those from *Camellia sinensis* and *Echinacea purpurea* appear to promote a smooth transition from the inflammatory to the proliferative phase. This transition is essential for maintaining a balanced healing environment, as prolonged inflammation can lead to tissue damage and delayed healing, particularly in diabetic or immune-compromised patients.

During the proliferative phase, the active compounds in natural extracts stimulate fibroblast and keratinocyte proliferation, essential for tissue regeneration. The presence of terpenoids and saponins in *Aloe vera* and *Centella*

asiatica extracts supports collagen synthesis and angiogenesis, further strengthening the new tissue. The promotion of angiogenesis by these extracts is particularly significant, as forming new blood vessels is critical for nutrient and oxygen supply to the growing tissue. These bioactivities accelerate wound closure and enhance the new tissue's structural integrity, leading to more substantial and resilient healing outcomes. These findings reinforce the potential of natural extracts as bioactive supplements to existing wound care treatments, particularly in settings where access to advanced therapies may be limited.

The remodeling phase is characterized by collagen maturation and reorganization, processes in which natural extracts play a supportive role by minimizing scarring and enhancing tissue strength. Extracts from *Allium cepa* and *Calendula officinalis* have been shown to improve collagen alignment and reduce fibrosis, which is crucial for functional and aesthetic recovery. By up-regulating growth factors like EGF, PDGF, and TGF- β 1, these extracts facilitate fibroblast proliferation and collagen remodeling, yielding more muscular, more elastic tissue with minimized scar formation. This finding is particularly interesting for applications in cosmetic surgery and treatments where scar minimization is a priority. Furthermore, the antioxidant properties of these extracts help reduce oxidative stress during this phase, preventing excessive collagen deposition that could otherwise lead to hypertrophic or keloid scarring.

Despite the compelling evidence supporting the efficacy of natural extracts, challenges related to their clinical application persist. Low bioavailability, rapid metabolism, and stability limitations hinder their therapeutic potential when administered *in vivo*. Recent advancements in drug delivery, such as encapsulation within hydrogels and nanofibers, provide promising solutions to these challenges. These delivery systems offer controlled release, targeted delivery, and prolonged stability of bioactive compounds, potentially improving clinical outcomes by maintaining therapeutic levels of the compounds at the wound site.

Future research should optimize these delivery systems and conduct large-scale clinical trials to

validate the safety, efficacy, and standardization of natural extracts in wound care. Additionally, investigating the synergistic effects of combining different natural extracts or pairing them with conventional therapies could lead to the development of more comprehensive wound-healing treatments. Standardized extraction methods, quality control protocols, and pharmacokinetic studies are essential for translating these promising preclinical findings into real-world applications. By addressing these challenges, natural extracts could become integral to wound care, especially in regions with limited access to synthetic drugs and advanced medical treatments. In summary, natural extracts show substantial promise in modulating each wound healing phase through various biochemical mechanisms. They represent a holistic, bioactive approach that supports healing and minimizes complications related to infection, inflammation, and scarring. While further research is necessary to overcome clinical translation challenges, these extracts offer a valuable addition to the current wound care arsenal, potentially enhancing outcomes for acute and chronic wounds.

CONCLUSION:

Natural extracts represent a promising frontier in wound healing, offering a range of bioactive compounds that interact with the cellular and molecular pathways of the healing process through enhancing hemostasis, modulating inflammation, promoting tissue proliferation, and aiding collagen remodeling, natural extracts such as those from *Curcuma longa*, *Aloe vera*, *Centella Asiatica*, and *Allium cepa* provide a practical, multi-phase approach to wound care. These extracts leverage the therapeutic potential of alkaloids, flavonoids, terpenoids, and phenolic acids to support wound stabilization, reduce oxidative stress, stimulate cell proliferation, and improve scar quality. Despite their promising bioactivities, bioavailability, stability, and standardized dosing challenges have limited their clinical applications. Advanced drug delivery systems like hydrogels and nanofibers offer a feasible solution by improving these extracts' stability and targeted delivery. Yet, additional research is necessary to optimize these methods.

To translate the benefits of natural extracts into clinical practice, further research should focus on

a few key areas. Firstly, large-scale, randomized clinical trials are necessary to validate the efficacy and safety of these extracts across various wound types and patient populations. Investigations into optimal dosing, potential side effects, and long-term outcomes would provide the clinical data for standardizing treatment protocols. Exploring synergistic combinations of different natural extracts could uncover potential additive or synergistic effects, enhancing their overall therapeutic potential. Thirdly, improved bioavailability and stability of natural extracts should be prioritized by developing and refining innovative delivery mechanisms, such as nano-encapsulation, liposomes, and controlled-release hydrogels, to enable sustained and targeted release at the wound site. Finally, research into the mechanistic pathways of these extracts will deepen our understanding of their roles in cellular signaling and immune response during wound healing, potentially unveiling new therapeutic targets. By addressing these research gaps, natural extracts could emerge as a reliable, practical addition to modern wound care strategies, providing functional and aesthetic benefits in acute and chronic wound management.

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Author Contribution

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