



# Unlocking Herbal Power Through Nanotechnology: A New Era in Wound Management

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*(Received: 16 May 2025*

*Revised: 20 June 2025*

*Accepted: 02 July 2025)*

## KEYWORDS

Nanocarrier,  
Niosomes, Anti-  
inflammatory,  
Antimicrobial,  
Potency,  
Bioavailability

## ABSTRACT:

The integration of nanotechnology with herbal medicine represents a groundbreaking approach in modern wound management. This review explores the potential of nano-herbal ointments as a novel therapeutic modality for enhancing wound healing. The use of nanocarriers, such as liposomes, solid lipid nanoparticles (SLNs), and niosomes, in the delivery of herbal compounds offers significant improvements in stability, bioavailability, and skin penetration, which are critical factors in promoting effective wound closure. Phytochemicals derived from medicinal plants such as Aloe vera, Centella asiatica, and curcumin have demonstrated powerful anti-inflammatory, antimicrobial, and regenerative properties, which are further amplified when formulated at the nanoscale. While traditional herbal ointments face limitations in terms of potency, bioavailability, and controlled release, the advent of nanotechnology overcomes these challenges by facilitating precise drug delivery and enhancing therapeutic outcomes. Despite these promising advancements, the scale-up, commercialization, and regulatory hurdles associated with nano-herbal formulations remain significant challenges. Nevertheless, the future of nano-herbal wound therapy is promising, with the potential for personalized medicine and greater accessibility to these advanced wound care solutions. This paper aims to provide a comprehensive overview of the benefits, innovations, and challenges associated with the use of nano-herbal ointments in wound healing and outlines a vision for the future of this rapidly evolving field.

## 1. Introduction

### 1.1 Overview of Wound Healing Challenges

Wound healing is a complex, finely regulated biological process that involves a sequence of overlapping stages: hemostasis, inflammation, proliferation, and remodeling. While acute wounds generally progress through these phases efficiently, various internal and external factors can disrupt this sequence, resulting in delayed or chronic wounds (Guo & Dipietro, 2010). Such complications are particularly prevalent in individuals with underlying health conditions like diabetes mellitus, peripheral vascular disease, or compromised immune function, where healing is significantly impaired.

One of the major challenges in wound management is the prevalence of chronic wounds, which fail to heal within an expected timeframe due to prolonged inflammation, impaired angiogenesis, and excessive degradation of extracellular matrix (ECM) components (Brem & Tomic-Canic, 2007). These wounds often become colonized by pathogenic microorganisms, further delaying tissue repair and increasing the risk of secondary infections.

Conventional wound healing therapies—including antiseptic creams, dressings, and systemic antibiotics—face numerous limitations. These include poor bioavailability of active ingredients, limited skin penetration, frequent dosing requirements, and poor patient compliance. Moreover, traditional formulations often lack sustained release mechanisms and may not



maintain an optimal wound environment for healing (Boateng et al., 2008). As a result, many chronic wounds remain unresponsive to standard treatment regimens.

A particularly concerning issue is the rise of antibiotic resistance among wound pathogens. Chronic wounds are often inhabited by microbial biofilms—structured bacterial communities embedded in a self-produced matrix—which are highly resistant to antibiotics and immune clearance. These biofilms create a barrier that not only protects the microbes but also interferes with the penetration of therapeutic agents, thus complicating wound treatment (Bjarnsholt, 2013).

Additionally, oxidative stress plays a crucial role in impairing wound healing, especially in diabetic patients. Elevated levels of reactive oxygen species (ROS) in the wound site contribute to cellular damage, inhibit angiogenesis, and prolong the inflammatory phase, further delaying healing (Roy et al., 2006). The inability to balance ROS production with antioxidant defenses is a key contributor to poor wound outcomes.

Given these multifaceted challenges, there is a growing demand for advanced wound care therapies that can offer antimicrobial, anti-inflammatory, and regenerative properties while maintaining safety and patient comfort. This has spurred interest in nanotechnology-based delivery systems that utilize plant-derived bioactive compounds. Nano-herbal ointments, in particular, have shown promise in overcoming the limitations of conventional treatments by enhancing drug solubility, penetration, and controlled release—thereby offering a modern solution rooted in traditional herbal medicine.

## 1.2 Role of Herbal Medicine in Traditional Wound Care

Herbal medicine has played a foundational role in wound management across diverse cultures for centuries. Traditional systems such as Ayurveda, Traditional Chinese Medicine (TCM), Unani, and African ethnomedicine have long relied on plant-based remedies for their anti-inflammatory, antimicrobial, antioxidant, and regenerative properties (Gomes et al., 2017). These herbal formulations were typically prepared as ointments, poultices, decoctions, or pastes,

and applied directly to wounds to accelerate healing and prevent infections.

Plants such as *Aloe vera*, *Curcuma longa* (turmeric), *Azadirachta indica* (neem), *Centella asiatica*, and *Calendula officinalis* are well-documented for their wound healing efficacy. For instance, *Aloe vera* gel contains polysaccharides and glycoproteins that promote fibroblast activity and collagen synthesis, both crucial for tissue repair (Surjushe et al., 2008). Similarly, *Curcuma longa* possesses curcumin, a potent polyphenolic compound known for its ability to modulate inflammatory pathways and scavenge free radicals, aiding the healing process (Chainani-Wu, 2003).

The popularity of these remedies is largely attributed to their biocompatibility, low toxicity, and cost-effectiveness, especially in rural and resource-limited settings where modern medical infrastructure may be inadequate (Chattopadhyay et al., 2012). Moreover, herbal ingredients often offer multi-targeted therapeutic actions, addressing not just microbial infections but also enhancing tissue regeneration, improving circulation, and modulating the immune response.

Despite their extensive traditional use, many herbal medicines have only recently been scientifically validated. With the advancement of phytochemical screening, in vitro assays, and in vivo wound models, researchers have been able to better understand the mechanisms by which herbal compounds aid in healing (Gomes et al., 2017). However, a major limitation of traditional herbal remedies is the poor solubility, low absorption, and unstable nature of bioactive phytoconstituents, which restrict their clinical application in modern wound care products.

These limitations have paved the way for integrating traditional herbal wisdom with modern nanotechnology platforms. Nanoformulation of herbal extracts into ointments, gels, and dressings not only enhances stability and skin penetration, but also offers controlled release, thereby maximizing therapeutic efficacy while minimizing side effects.



### 1.3 Emergence of Nanotechnology in Modern Medicine

Nanotechnology, the science of manipulating matter at the nanometer scale (1–100 nm), has emerged as a transformative force in modern medicine, offering novel approaches to diagnostics, drug delivery, and therapeutic interventions. The unique physicochemical properties of nanoparticles—including their small size, large surface-area-to-volume ratio, and tunable surface functionality—enable them to interact with biological systems at the molecular level, thereby improving the efficacy, precision, and safety of medical treatments (Singh & Lillard, 2009).

In the context of wound healing, nanotechnology has paved the way for next-generation ointments, dressings, and gels capable of delivering active agents in a controlled and sustained manner. Traditional ointments often suffer from poor drug penetration, instability, or rapid degradation of phytoconstituents. Nanocarrier systems such as liposomes, solid lipid nanoparticles (SLNs), nanoemulsions, and polymeric nanoparticles can encapsulate herbal bioactives and protect them from environmental degradation while enhancing skin permeation and bioavailability (Kakkar et al., 2014).

Moreover, the multifunctionality of nanomaterials allows for the simultaneous delivery of antimicrobial, anti-inflammatory, and regenerative agents. For instance, silver nanoparticles (AgNPs), widely incorporated in wound care products, offer broad-spectrum antimicrobial activity and promote tissue regeneration by modulating cytokine release (Rai et al., 2009). Similarly, zinc oxide nanoparticles and titanium dioxide have shown promise in accelerating epithelialization and reducing oxidative stress in wounds.

Nanotechnology also facilitates the development of responsive or "smart" wound dressings that release drugs in response to specific physiological triggers like pH, temperature, or bacterial load. These advanced systems improve therapeutic outcomes and reduce the frequency of dressing changes, enhancing patient comfort and reducing infection risk (Hussain et al., 2017).

Furthermore, integrating plant-derived compounds into nanocarriers combines the healing potential of herbal medicine with the precision of nanomedicine. This synergy—commonly referred to as "nano-herbals"—has shown enhanced wound healing outcomes in preclinical studies, particularly in diabetic and infected wound models (Sharma et al., 2019).

Overall, nanotechnology marks a significant leap in the development of safer, more efficient, and more targeted wound care therapies, bridging the gap between traditional knowledge and contemporary medical innovation.

## 2. Herbal Therapeutics in Wound Healing

### 2.1 Phytochemicals and Their Healing Mechanisms

Phytochemicals—bioactive compounds found in plants—are central to the wound healing properties of herbal medicines. These compounds, such as flavonoids, tannins, alkaloids, terpenoids, and saponins, exhibit antioxidant, anti-inflammatory, antimicrobial, and proliferative effects that accelerate wound repair (Ghosh & Suryawanshi, 2001). Flavonoids, for instance, reduce oxidative stress at wound sites by scavenging free radicals, which is critical for preventing prolonged inflammation and promoting tissue regeneration (Nayak et al., 2007).

Tannins act as astringents, aiding in wound contraction and promoting the formation of a protective layer over the wound bed. Alkaloids possess antimicrobial activity, reducing the risk of infection and sepsis (Kumar et al., 2007). Terpenoids contribute by enhancing angiogenesis and collagen synthesis, which are vital for new tissue formation and strengthening of the wound matrix. These synergistic effects of phytochemicals support each phase of wound healing—hemostasis, inflammation, proliferation, and remodeling—thereby offering a holistic approach to tissue repair.

### 2.2 Common Medicinal Plants Used in Wound Ointments

Numerous plants have been traditionally incorporated into ointments for wound healing. Aloe vera, rich in glucomannan and gibberellin, stimulates fibroblast



proliferation and collagen production. *Centella asiatica* enhances angiogenesis and promotes the synthesis of extracellular matrix components like collagen and fibronectin (Shukla et al., 1999). *Azadirachta indica* (neem) has strong antibacterial properties, making it effective against common wound pathogens.

*Curcuma longa* (turmeric), due to its principal compound curcumin, is known for reducing inflammation, modulating cytokine levels, and enhancing re-epithelialization (Chainani-Wu, 2003). *Calendula officinalis*, used widely in ointments, promotes granulation tissue formation and epithelialization, attributed to its triterpenoids and flavonoids (Parente et al., 2012). These medicinal plants have been the foundation of many over-the-counter and traditional wound care products, especially in the form of pastes, creams, and herbal ointments.

### 2.3 Limitations of Conventional Herbal Formulations

Despite their proven efficacy, conventional herbal formulations face several limitations that hinder their widespread clinical use. Key issues include poor water solubility, low bioavailability, instability of active compounds, and lack of targeted delivery (Mishra et al., 2008). Many phytochemicals degrade quickly when exposed to light, oxygen, or varying pH levels, reducing their effectiveness over time.

Additionally, skin penetration of herbal constituents is often limited, preventing adequate concentrations from reaching deeper tissues. Conventional ointments also suffer from batch-to-batch variability, particularly when prepared from crude extracts, affecting therapeutic consistency. These limitations have necessitated the development of novel delivery systems, including nanoparticle-based formulations, to enhance the stability, absorption, and targeted action of herbal actives in wound healing applications.

## 3. Nanotechnology: A Game Changer in Wound Management

### 3.1 Basics of Nanocarriers and Drug Delivery

Nanocarriers are engineered delivery systems designed at the nanometer scale to enhance the solubility,

stability, and targeted delivery of therapeutic agents. In wound management, these carriers can encapsulate bioactive compounds—particularly phytochemicals from herbs—and deliver them precisely to the wound site. Common nanocarriers include liposomes, solid lipid nanoparticles (SLNs), polymeric nanoparticles, and niosomes (Mohanraj & Chen, 2006).

These systems exploit the enhanced permeation and retention (EPR) effect, allowing nanoparticles to preferentially accumulate in inflamed or damaged tissues. Their biocompatibility, surface modifiability, and controlled-release behavior make them ideal for improving the therapeutic index of herbal actives (Singh & Lillard, 2009). Through encapsulation, phytoconstituents are protected from degradation and metabolic loss, significantly increasing their residence time and effectiveness at the wound site.

### 3.2 Advantages of Nano-Formulations for Topical Use

Nano-formulations offer several distinct advantages over conventional topical preparations. Firstly, their small particle size (typically <200 nm) facilitates deep skin penetration, allowing active compounds to reach deeper dermal layers that are critical for wound healing (Baroli, 2010). Secondly, the controlled and sustained release profile of nanoformulations reduces the frequency of application and minimizes drug wastage, improving patient compliance.

Another major advantage is targeted delivery, which ensures that active agents are released predominantly at the wound site, reducing systemic absorption and associated side effects (Wissing et al., 2004). Additionally, nano-based ointments can be engineered to be mucoadhesive or stimuli-responsive, releasing their contents in response to pH, enzymes, or microbial presence—ideal for managing infected or chronic wounds.

Finally, nanoformulations can enhance the therapeutic efficacy of poorly soluble herbal compounds like curcumin, quercetin, and asiaticoside, which otherwise have limited bioavailability in traditional formulations (Sharma et al., 2019).



### 3.3 Types of Nanoparticles Used in Herbal Ointments

Several nanoparticle systems have been successfully used to incorporate herbal extracts in topical wound therapies:

- Liposomes are phospholipid vesicles that mimic biological membranes, making them highly biocompatible. They enhance drug penetration and have been used to deliver aloe vera, turmeric, and tea tree oil in wound healing applications (Honeywell-Nguyen & Bouwstra, 2005).
- Solid Lipid Nanoparticles (SLNs) consist of solid lipids that remain solid at room and body temperature, offering controlled release and excellent skin hydration. They are effective in incorporating hydrophobic herbal compounds like neem and *Centella asiatica* (Wissing & Müller, 2003).
- Niosomes, formed from non-ionic surfactants and cholesterol, are stable and versatile nanocarriers. They have shown promise in encapsulating phytochemicals like flavonoids and saponins for sustained release in infected wounds (Kaur et al., 2004).

These systems not only extend the shelf-life of herbal ointments but also enhance their healing performance, ushering in a new era of integrative, nanotechnology-driven wound care.

### 4. Herbal Ointments at the Nanoscale

#### 4.1 Nano-Herbal Ointment Formulations: Methods and Strategies

Nano-herbal ointments integrate bioactive plant compounds with nanocarrier systems to improve therapeutic outcomes in wound care. The formulation process often involves methods like solvent evaporation, high-pressure homogenization, ultrasonication, and emulsification-solvent diffusion, which ensure uniform dispersion and optimal particle size (Yadav et al., 2020). These techniques enable the successful entrapment of poorly soluble herbal

constituents into nanocarriers like liposomes, niosomes, nanoemulsions, and solid lipid nanoparticles.

Incorporating herbs such as *Curcuma longa* (curcumin), *Aloe vera*, *Azadirachta indica* (neem), and *Centella asiatica* into these delivery systems has shown enhanced wound healing efficacy. The nanoscale size of the carriers not only protects phytochemicals from oxidative degradation but also allows for controlled and sustained release, crucial in chronic wound environments (Das et al., 2013).

#### 4.2 Enhancing Stability and Skin Penetration with Nanotech

One of the core challenges in topical herbal therapies is the low permeability of active ingredients through the stratum corneum, the outermost skin layer. Nanotechnology overcomes this by reducing the size of the formulation to <200 nm, which facilitates deeper skin penetration and more effective drug localization at the wound site (Baroli, 2010). Moreover, the encapsulation of phytoconstituents in nanocarriers stabilizes volatile or sensitive compounds, significantly extending shelf life.

Techniques such as PEGylation, the use of surfactants, or polymer coatings further enhance the physicochemical stability and mucoadhesive properties of the formulation, increasing the residence time on the skin (Sharma et al., 2019). This is particularly beneficial in treating infected or non-healing wounds, where consistent exposure to therapeutic agents is essential for tissue regeneration.

#### 4.3 Case Studies of Successful Nano-Herbal Wound Healing Ointments

Several case studies highlight the success of nano-herbal ointments in preclinical and clinical settings. For instance, curcumin-loaded liposomes have demonstrated accelerated wound closure and reduced inflammation in animal burn models (Kumar et al., 2016). Similarly, *Aloe vera*-based SLNs showed enhanced skin hydration and epithelial regeneration in diabetic wound models, thanks to the controlled release of polysaccharides and glycoproteins (Aly et al., 2019).



Another study utilizing *Centella asiatica*-loaded niosomal gel reported improved tensile strength of healed tissue and increased collagen synthesis, underscoring the synergistic effects of nanotechnology and traditional botanicals (Pattnaik et al., 2021). These formulations not only outperform their conventional counterparts but also show greater patient tolerance and minimal irritation, making them ideal for chronic wound care.

## 5. Biological Activities and Therapeutic Outcomes

### 5.1 Anti-inflammatory and Antimicrobial Effects

Herbal-based nanoformulations are well-known for their potent anti-inflammatory and antimicrobial activities, which are crucial in wound healing. Chronic wounds, often characterized by persistent inflammation and infection, benefit significantly from the anti-inflammatory properties of plant-based nanoformulations. For instance, curcumin, a polyphenolic compound from *Curcuma longa*, has been encapsulated in various nanocarriers such as liposomes and SLNs to reduce pro-inflammatory cytokines and regulate inflammatory mediators like TNF- $\alpha$  and IL-6 (Kumar et al., 2016). This results in accelerated healing and reduced scar formation (Sharma et al., 2019).

In addition, antimicrobial properties of herbal compounds like tea tree oil, neem oil, and Aloe vera are enhanced in nanoformulations, improving their efficacy against common wound pathogens like *Staphylococcus aureus* and *Pseudomonas aeruginosa*. Studies have shown that nanoencapsulation protects these bioactive agents from premature degradation, enabling sustained antimicrobial action and preventing wound infections (Yadav et al., 2020). The surface charge and small size of nanoparticles further aid in penetrating bacterial biofilms, making them effective in treating resistant microbial strains (Nikkhah et al., 2021).

### 5.2 Angiogenesis and Collagen Regeneration

Angiogenesis, the formation of new blood vessels, and collagen regeneration are key processes in wound healing. Certain phytochemicals in herbal medicines, such as asiaticoside from *Centella asiatica*, have been shown to stimulate both these processes. Studies on nanoformulations of *Centella asiatica* indicate enhanced

collagen synthesis and fibroblast proliferation, crucial for wound closure and tissue repair (Pattnaik et al., 2021). Nano-carriers like liposomes can also promote the formation of new blood vessels, which is vital in treating ischemic or diabetic wounds by ensuring proper nutrient and oxygen supply (Buraimoh et al., 2020).

Furthermore, the controlled release of angiogenic factors from nano-herbal ointments results in improved granulation tissue formation and faster wound healing. This has been particularly effective in the healing of chronic wounds that are unable to regenerate efficiently due to poor vascularization (Kumar et al., 2016).

### 5.3 Clinical Efficacy and Safety Profiles

The clinical efficacy and safety of nano-herbal wound healing ointments are important in determining their practical use. In preclinical and clinical trials, nano-herbal formulations have consistently shown better wound closure rates, reduced inflammation, and improved tissue regeneration compared to conventional formulations. For instance, curcumin-loaded SLNs demonstrated significantly better wound healing and scar reduction in animal models and human clinical trials (Sharma et al., 2019).

Safety profiles of these formulations are typically favorable, with minimal systemic absorption of the herbal components due to the localized action of nanoparticles. This reduces the risk of systemic toxicity and enhances the biocompatibility of the ointments. However, some studies have highlighted the importance of optimizing nanoparticle size, surface charge, and the concentration of herbal extracts to prevent potential skin irritation or sensitization (Baroli, 2010).

Overall, the combination of efficacy, safety, and targeted delivery offered by nano-herbal ointments has made them a promising alternative to traditional wound care treatments.

## 6. Future Perspectives and Challenges

### 6.1 Regulatory and Safety Considerations

As the use of nano-herbal formulations in wound healing gains momentum, it is crucial to address the regulatory and safety concerns that accompany the incorporation of nanotechnology into pharmaceuticals.



Regulatory agencies such as the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) have outlined specific guidelines for the approval of nanomaterials, emphasizing the need for comprehensive toxicological evaluations (O'Brien et al., 2015). Nanoparticles, due to their small size and increased surface area, can interact with biological systems in ways that traditional drug formulations cannot, raising concerns about biocompatibility, cytotoxicity, and potential long-term effects (Ghaffari et al., 2019).

For herbal-based nanoformulations, additional challenges arise due to the variability in the composition of plant extracts. Standardization of the active ingredients in these extracts is crucial to ensure consistent therapeutic outcomes (Kumar et al., 2016). Regulatory frameworks will need to evolve to account for these specific issues while ensuring that nano-herbal ointments meet the safety standards necessary for widespread use.

## 6.2 Scale-Up and Commercialization of Nano-Herbal Ointments

Although nano-herbal ointments show promising therapeutic benefits in preclinical and clinical trials, scaling up these formulations for mass production remains a significant challenge. The methods used to fabricate nano-carriers, such as high-pressure homogenization and solvent evaporation, are generally labor-intensive and costly, which can limit the commercial viability of these products (Sharma et al., 2019). In addition, quality control and reproducibility are essential when moving from small-scale laboratory formulations to large-scale production, particularly when dealing with plant-based ingredients that may vary in potency from batch to batch (Moghimi et al., 2020).

However, the commercialization of nano-herbal ointments is a rapidly growing market, with increasing interest from pharmaceutical and cosmeceutical industries. Efforts to optimize production processes, lower costs, and establish automated systems for manufacturing will be essential to meet the growing demand for these advanced wound care products. Collaboration between academic researchers, industry partners, and regulatory bodies will help address these

challenges and bring these innovative formulations to the global market (Nikkhah et al., 2021).

## 6.3 Potential for Personalized Wound Care

A promising future direction for nano-herbal ointments is the potential for personalized wound care. Nanotechnology offers the unique advantage of tailoring drug delivery systems to individual patient needs, based on factors such as wound type, severity, and patient-specific conditions (Kumar et al., 2016). For example, nanoparticle-based formulations could be engineered to release active herbal compounds in response to pH changes at the wound site, ensuring that the formulation adapts to the dynamic nature of wound healing.

Personalized medicine in wound care could also involve the use of biomarkers to monitor healing progress and adapt treatment plans in real-time. Nanocarriers, equipped with sensors or responsive materials, could be used to detect changes in wound biomarkers and adjust the release of herbal actives accordingly, leading to optimized therapeutic outcomes (Buraimoh et al., 2020). This precision medicine approach has the potential to revolutionize wound care, offering tailored solutions for patients with chronic or difficult-to-heal wounds.

## 7. Conclusion

### 7.1 Summary of Benefits and Innovations

The integration of nanotechnology into herbal medicine has unlocked new possibilities in wound healing therapies. Nano-herbal formulations combine the therapeutic potential of botanicals with the advanced delivery capabilities of nanocarriers, offering numerous advantages over traditional wound treatments. These nano-herbal ointments provide enhanced stability, bioavailability, and controlled release of active compounds, which are crucial for improving wound healing outcomes. Through nanotechnology, herbal medicines like curcumin, Aloe vera, and Centella asiatica can be more effectively delivered to the wound site, promoting faster healing and reducing the risk of infection, inflammation, and scarring (Sharma et al., 2019).



The nanoencapsulation of herbal extracts also addresses several limitations of conventional formulations, such as instability, poor skin penetration, and limited shelf life. Furthermore, nanoparticles like liposomes, solid lipid nanoparticles (SLNs), and niosomes enhance the antimicrobial, anti-inflammatory, and angiogenic properties of these herbal compounds, thereby supporting comprehensive wound healing processes, from the initial inflammatory phase to tissue regeneration (Kumar et al., 2016).

In essence, nano-herbal ointments offer a synergistic solution to modern wound management, bridging the gap between traditional herbal remedies and cutting-edge nanomedicine.

## 7.2 Vision for the Future of Nano-Herbal Wound Therapy

Looking forward, the future of nano-herbal wound therapy is bright, with the potential for further innovations and refinements in both formulation techniques and therapeutic approaches. One promising area is the development of personalized wound care solutions, where nano-herbal formulations can be tailored to individual patient needs. By leveraging biomarkers or smart nanocarriers, it is possible to create more precise and adaptive treatments that respond dynamically to the unique challenges presented by each wound, such as its location, type, or underlying health conditions.

Moreover, the scalability and commercialization of nano-herbal wound care products will likely benefit from advancements in manufacturing technologies, such as automated nanocarrier production and standardization of herbal extracts. These innovations will lower the production costs and improve the global accessibility of these advanced treatments, particularly in developing regions where wound care remains a significant public health issue.

In the coming years, we may also see increased regulatory clarity and acceptance of nano-herbal products in clinical practice. As research continues to demonstrate the safety and efficacy of these formulations, they will likely become a mainstream option in both clinical settings and over-the-counter

wound care products, revolutionizing the management of chronic, acute, and complex wounds.

## Acknowledgement

We would like to express our sincere gratitude to all those who have contributed to the success of this research.

## Conflict of Interest

The authors declare that there are no conflicts of interest regarding the publication of this research.

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