

## Plant-Extract-Mediated Silver and Copper Nanoparticles for Wound Healing Applications: A Comprehensive Review

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### ABSTRACT

The increasing incidence of chronic and infected wounds has highlighted the limitations of conventional antimicrobial and wound-care therapies, necessitating the development of safer and more effective alternatives. Green nanotechnology has emerged as a promising approach for biomedical applications by integrating plant-derived bioactives with metal nanoparticles (NPs). This review critically evaluates the potential of polyherbal-mediated synthesis of silver and copper NPs using *Pereskia aculeata* (barbados gooseberry), *Trachyspermum ammi* (ajwain), and *Sphagneticola trilobata* (bay), three medicinal plants with well-established ethnopharmacological relevance in wound healing and infection control. The phytochemical constituents of these plants, including phenolics, flavonoids, terpenoids, and polysaccharides, play a dual role as reducing and stabilizing agents during NP synthesis while imparting additional antimicrobial, antioxidant, and anti-inflammatory properties. This review summarizes current knowledge on green synthesis strategies, antimicrobial and antioxidant mechanisms of silver and copper NPs, and their influence on key wound-healing processes. Evidence from in vitro and in vivo studies indicates that plant-mediated NPs exhibit enhanced biocompatibility and reduced toxicity compared to chemically synthesized counterparts, particularly for topical wound applications. Furthermore, the polyherbal approach offers potential synergistic effects that may improve therapeutic efficacy and stability. Challenges related to standardization, reproducibility, toxicological assessment, and regulatory approval are discussed, along with future perspectives for translating polyherbal-based nanomaterials (NMs) into clinically viable wound-healing formulations. Overall, this review underscores the promise of polyherbal-derived silver and copper NPs as sustainable and multifunctional platforms for advanced wound management. ..

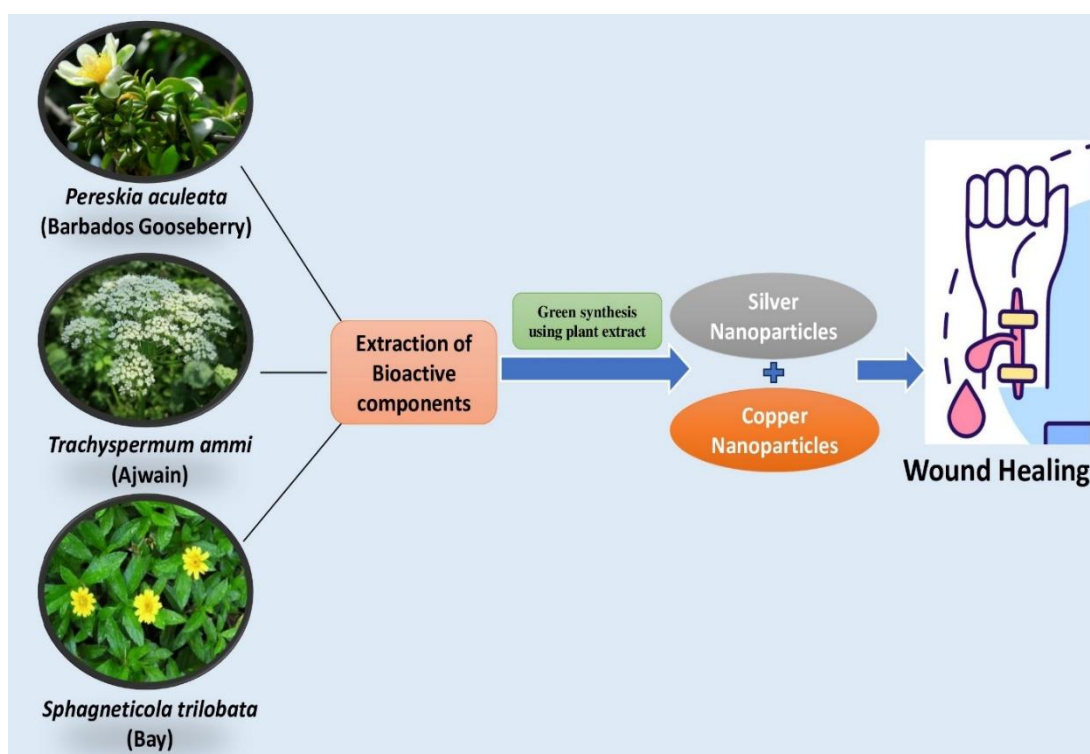
**Keywords:** Green Synthesis; Silver nanoparticles; Copper nanoparticles; Wound healing; Medicinal plants.

### 1. INTRODUCTION

Nanotechnology is a multidisciplinary field concerned with the manipulation of materials at dimensions typically between 1 and 100 nanometres (nm), where size-dependent physicochemical and biological properties emerge that are not observed in bulk materials. These nanoscale characteristics have enabled significant advances in biomedical applications, particularly in antimicrobial therapy and wound healing, where enhanced surface reactivity and biological interactions are critical (Rai et al., 2009). The conceptual origin of nanotechnology can be traced to Richard Feynman's visionary 1959 lecture, which emphasized the potential of controlling matter at atomic dimensions, while the term "nanotechnology" was later formally introduced by Norio Taniguchi in 1974 in the context of precision engineering (Taniguchi, 1974).

Among metal-based nanomaterials (NMs), silver and copper nanoparticles (NPs) have attracted sustained scientific interest due to their broad-spectrum antimicrobial activity and relevance to tissue repair. Silver has been used historically as an antimicrobial agent, and nanosilver exhibits enhanced bactericidal efficacy owing to its increased surface area and ability to disrupt microbial membranes and biofilms (Rai et al., 2009). Copper is an essential trace element involved in angiogenesis, extracellular matrix stabilization, and immune regulation, all of which are key processes in wound healing (Sen et al., 2002). These properties have positioned silver and copper NPs as promising candidates for advanced wound-care strategies.

## Graphical Abstract



Conventional NP synthesis methods often rely on hazardous chemicals and energy-intensive processes, raising concerns regarding environmental safety and biomedical applicability. In response, green synthesis approaches using plant extracts have emerged as sustainable alternatives, employing naturally occurring phytochemicals as reducing and stabilizing agents (Iravani, 2011). Plant-mediated synthesis is particularly advantageous for biomedical use because phytochemicals such as flavonoids, phenolics, and terpenoids not only facilitate NP formation but may also enhance biological activity through synergistic effects (Iravani, 2011). The present work focuses on three medicinal plants with documented traditional use and pharmacological relevance to wound healing: *Pereskia aculeata*, *Trachyspermum ammi*, and *Sphagneticola trilobata*.

*Pereskia aculeata* (Cactaceae), commonly known as Barbados gooseberry, is a climbing plant native to South America and traditionally consumed as a leafy vegetable in Brazil. Ethnopharmacological reports describe its use as an emollient for skin inflammation and wounds, which has been attributed to its mucilaginous content and nutritional richness, including dietary fiber, vitamins, and essential minerals (Takeiti et al., 2009; Pinto & Scio, 2014).

*Trachyspermum ammi* (ajwain), a member of the Apiaceae family, is a widely used medicinal seed spice in traditional Indian and Persian medicine. Its seeds have been employed for the treatment of infections, inflammation, and digestive disorders, and their biological activity is largely associated with volatile constituents such as thymol, which exhibits documented antimicrobial and anti-inflammatory effects relevant to wound management (Bairwa et al., 2012).

*Sphagneticola trilobata* (bay), belonging to the Asteraceae family, is a creeping perennial herb traditionally used across tropical regions for treating wounds, ulcers, and inflammatory conditions. Phytochemical investigations have identified sesquiterpene lactones and diterpenes associated with antimicrobial and anti-inflammatory activity, supporting its ethnomedicinal application in skin and wound-related disorders (Ali et al., 2024).

The convergence of these three medicinal plants with green-synthesized silver and copper NPs represents a rational polyherbal nanoformulation strategy for wound healing. By integrating traditional medicinal knowledge with nanotechnology-based enhancement of antimicrobial and regenerative properties, this approach holds potential for the development of safer and more effective wound-care systems.

#### Ethnopharmacological Relevance and Phytochemicals

Traditional medicinal plants have long served as a foundation for modern therapeutic discovery, particularly in the treatment of wounds and skin-related disorders. Plants used in ethnomedicine often possess a combination of antimicrobial, anti-inflammatory, antioxidant, and tissue-regenerative properties, which are critical for effective wound healing. In recent years, these same phytochemicals have gained attention for their role in green synthesis of metal NPs, where they function as natural

reducing and stabilizing agents (Iravani, 2011; Mittal et al., 2013).

### 2.1 *Pereskia aculeata* (Barbados Gooseberry)

*Pereskia aculeata* (Cactaceae), is traditionally used in South American folk medicine for treating inflammation and skin wounds. The leaves are rich in mucilage, dietary fiber, vitamins, and minerals, contributing to both nutritional and therapeutic value (Takeiti et al., 2009; Ferreira et al., 2024). Several studies have reported antioxidant, anti-inflammatory, and wound-healing-related biological activities of *Pereskia aculeata* leaf extracts, supporting its traditional use in topical applications (Campos Pinto et al., 2015; Pinto & Scio, 2014). The presence of polysaccharides and phenolic compounds further suggests its suitability for NP synthesis and biomedical formulation.

### 2.2 *Trachyspermum ammi* (Ajwain)

Ajwain (*Trachyspermum ammi*), belonging to the Apiaceae family, is a widely used medicinal seed spice in traditional Indian, Persian, and Middle Eastern medicine. The seeds are known for their antimicrobial, anti-inflammatory, antioxidant, and antiseptic properties, primarily attributed to thymol-rich essential oil and other phenolic constituents (Bairwa et al., 2012; Baghel and Pal, 2024). Experimental studies have demonstrated the antibacterial and antifungal efficacy of ajwain extracts, reinforcing its relevance in infection control and wound-related applications (Paliwal et al., 2023). The abundance of volatile and non-volatile phytochemicals makes ajwain a suitable candidate for green synthesis of metal NPs.

### 2.3 *Sphagneticola trilobata* (Bay)

*Sphagneticola trilobata* (Asteraceae), commonly known as bay or trailing daisy, is a creeping perennial herb widely used in traditional medicine across tropical regions. Ethnomedicinal reports describe its use for wounds, ulcers, inflammation, and skin infections (Coe & Anderson, 1996). Phytochemical investigations have identified sesquiterpene lactones, diterpenes such as kaurenoic acid, and flavonoids, which exhibit antimicrobial, anti-inflammatory, antioxidant, and wound-healing-related activities (Zhang et al., 2004; Singhal et al., 2021; R et al., 2023). These findings support the therapeutic relevance of *Sphagneticola trilobata* in topical and NP-based biomedical applications.

### 2.4 Rationale for Polyherbal Use in NP Synthesis

Polyherbal formulations are a central concept in traditional medicine systems, where synergistic interactions among multiple plant constituents are believed to enhance therapeutic outcomes. In the context of green nanotechnology, polyherbal extracts may provide a broader spectrum of phytochemicals capable of improving NP reduction, stabilization, and biological performance (Mittal et al., 2013). The complementary properties of *Pereskia aculeata*, *Trachyspermum ammi*, and *Sphagneticola trilobata*, including antimicrobial, anti-inflammatory, antioxidant, and tissue-supportive activities, provide a strong ethnopharmacological and mechanistic rationale for their combined use in silver and copper NP synthesis aimed at wound healing.

## Green Synthesis of Silver and Copper NPs using Polyherbal Extracts

Conventional physical and chemical methods for NP synthesis often involve high energy input and toxic reducing or stabilizing agents, limiting their biomedical applicability. In contrast, green synthesis using plant extracts has emerged as an eco-friendly, cost-effective, and biologically safer alternative. Plant-mediated synthesis exploits naturally occurring phytochemicals, such as phenolics, flavonoids, terpenoids, alkaloids, proteins, and polysaccharides, which act simultaneously as reducing, capping, and stabilizing agents during NP formation (Iravani, 2011; Mittal et al., 2013).

Silver NPs and copper NPs synthesized through green routes have demonstrated enhanced antimicrobial, antioxidant, and wound-healing properties compared to their chemically synthesized counterparts, owing to improved surface biocompatibility and reduced toxicity (Khalifa et al., 2025; Ahmed et al., 2016). The interaction between metal ions and plant phytochemicals leads to controlled nucleation and growth, influencing NP size, shape, surface charge, and biological activity.

### 3.1 Role of Polyherbal Extracts in NP Formation

Polyherbal systems provide a chemically diverse pool of bioactive molecules, increasing the efficiency and stability of NP synthesis. Unlike mono-herbal extracts, polyherbal formulations offer synergistic interactions among phytoconstituents that enhance metal ion reduction, prevent agglomeration, and improve biological functionality (Mittal et al., 2013; Singh et al., 2018).

In the present context, the combined use of *Pereskia aculeata*, *Trachyspermum ammi*, and *Sphagneticola trilobata* is particularly advantageous. *Pereskia aculeata* contributes polysaccharides, vitamins, and antioxidant phenolics that support NP stabilization. *Trachyspermum ammi* supplies thymol and related phenolic monoterpenes with strong antimicrobial and reducing capacity, while *Sphagneticola trilobata* provides terpenoids and flavonoids associated with anti-inflammatory and

wound-healing effects. Collectively, these phytochemicals facilitate efficient NP synthesis while imparting therapeutic functionality to the NP surface.

### 3.2 Mechanism of Plant-Mediated Reduction and Stabilization

The green synthesis process generally involves three key stages: (i) reduction of metal ions ( $\text{Ag}^+$  or  $\text{Cu}^{2+}$ ) to their zero-valent state, (ii) nucleation and growth of NPs, and (iii) stabilization by surface-bound phytochemicals. Phenolic hydroxyl groups, aldehydes, and carboxyl groups donate electrons to metal ions, initiating reduction, while proteins and polysaccharides adsorb onto the NP surface, preventing aggregation (Ahmed et al., 2016; Rani et al., 2023).

For wound-healing applications, the presence of bioactive capping agents is particularly beneficial, as they enhance antimicrobial efficacy, reduce oxidative stress, and improve cellular compatibility. This biofunctionalization is a distinct advantage of green-synthesized NPs over chemically synthesized systems. **Table 1** represents phytochemicals from selected medicinal plants and their role in NP synthesis and wound healing.

**Table 1. Phytochemicals from Medicinal Plants and their Role in NP Synthesis and Wound Healing**

Sr. No.	Plant species	Major phytochemicals	Role in NP synthesis	Wound-healing relevance
1.	<i>Pereskia aculeata</i>	Polysaccharides, phenolics, vitamins A & C	Stabilization, size control, surface capping	Antioxidant, tissue regeneration
2.	<i>Trachyspermum ammi</i>	Thymol, carvacrol, flavonoids	Strong reducing agents, antimicrobial surface coating	Antibacterial, anti-inflammatory
3.	<i>Sphagneticola trilobata</i>	Terpenoids, flavonoids, sesquiterpene lactones	Reduction and biofunctionalization	Anti-inflammatory, antimicrobial, wound repair

### Biomedical Relevance of Green-Synthesized Silver NPs and Copper NPs in Wound Healing

Wound healing is a complex biological process involving inflammation, proliferation, and tissue remodeling. Microbial infection and oxidative stress are major factors that delay healing and increase chronic wound burden. Silver NPs and Copper NPs synthesized via green routes have shown promising results in accelerating wound closure by controlling microbial load, modulating inflammatory responses, and promoting angiogenesis (Rai et al., 2009; Dizaj et al., 2014).

Silver NPs are widely recognized for their broad-spectrum antimicrobial activity, effective against both Gram-positive and Gram-negative bacteria, including antibiotic-resistant strains. Copper NPs, in addition to antimicrobial action, play a role in collagen synthesis and neovascularization, making them particularly valuable in wound repair (Borkow & Gabbay, 2005). When synthesized using medicinal plant extracts, these NPs demonstrate enhanced biocompatibility and reduced cytotoxicity, further supporting their application in wound-care formulations.

### Antimicrobial and Antioxidant Mechanisms of Polyherbal-derived silver and copper NPs

Microbial infection and excessive oxidative stress are two major factors responsible for delayed wound healing and the progression of chronic wounds. Green-synthesized silver and copper NPs derived from medicinal plant extracts exhibit dual antimicrobial and antioxidant functions, making them particularly suitable for wound management applications.

#### 5.1 Antimicrobial Mechanisms

Silver NPs exert antimicrobial activity through multiple, non-specific mechanisms, which significantly reduce the likelihood of microbial resistance development. These mechanisms include disruption of bacterial cell membranes, increased membrane permeability, generation of reactive oxygen species (ROS), interaction with thiol groups of essential enzymes, and interference with deoxyribonucleic acid (DNA) replication (Morones et al., 2005; Rai et al., 2009). The small size and high surface area of silver NPs facilitate close interaction with microbial cell walls, leading to structural damage and cell death.

Copper NPs demonstrate comparable antimicrobial efficacy, primarily through oxidative stress induction, protein dysfunction, and membrane lipid peroxidation. Copper ions released from copper NPs can penetrate microbial cells and

participate in redox cycling, resulting in intracellular damage (Borkow & Gabbay, 2005; Grass et al., 2010). Importantly, copper-based NPs also show activity against drug-resistant bacterial strains commonly associated with wound infections.

When synthesized using polyherbal extracts, the antimicrobial activity of silver NPs and copper NPs is often enhanced due to the presence of bioactive phytochemicals on the NP surface. Phenolics, flavonoids, and terpenoids derived from *Pereskia aculeata*, *Trachyspermum ammi*, and *Sphagneticola trilobata* act synergistically with metallic cores, improving bacterial adhesion, membrane disruption, and intracellular targeting (Ahmed et al., 2016; Singh et al., 2018).

## 5.2 Antioxidant Activity and Oxidative Stress Modulation

Oxidative stress plays a crucial role in delaying wound repair by damaging cellular proteins, lipids, and nucleic acids. Controlled modulation of ROS is essential, as excessive ROS impairs tissue regeneration, while physiological levels support cell signaling and angiogenesis. Green-synthesized NPs capped with antioxidant phytochemicals can effectively scavenge excess free radicals while maintaining antimicrobial efficacy (Mittal et al., 2013; Naseer et al., 2020).

Plant-derived phenolic compounds and flavonoids adsorbed onto the surface of silver NPs and copper NPs enhance their radical-scavenging ability and reduce metal-induced cytotoxicity. Studies have shown that green-synthesized NPs exhibit higher antioxidant activity than chemically synthesized counterparts, attributed to the retention of plant bioactives on the NP surface (Rajeshkumar & Bharath, 2017).

The antioxidant potential of *Pereskia aculeata*, combined with the thymol-rich profile of *Trachyspermum ammi* and the flavonoid-terpenoid content of *Sphagneticola trilobata*, supports the development of NPs capable of mitigating oxidative stress at wound sites while simultaneously controlling microbial burden.

## 6. Advantages of Polyherbal-based Green NPs over Conventional Systems

Polyherbal-mediated NP synthesis offers several advantages over single-plant and chemically synthesized systems. The presence of multiple phytochemical classes enhances NP stability, biological efficacy, and reproducibility. Additionally, plant-capped NPs exhibit improved biocompatibility, reduced cytotoxicity, and enhanced therapeutic functionality, which are critical for clinical wound-care applications (Iravani, 2011; Ahmed et al., 2016).

Compared to synthetic antibiotics and topical antimicrobials, metal NPs provide broad-spectrum activity and reduced risk of resistance development. The incorporation of traditional medicinal plant knowledge into nanotechnology further bridges the gap between ethnopharmacology and modern biomedical innovation. Table 2 represents comparative properties of green-synthesized vs. chemically synthesized NPs.

**Table 2. Comparative properties of green-synthesized vs chemically synthesized NPs**

Sr. No.	Parameter	Green-synthesized NPs	Chemically synthesized NPs
1.	Reducing agents	Plant phytochemicals	Toxic chemicals
2.	Biocompatibility	High	Moderate to low
3.	Toxicity	Reduced	Higher
4.	Environmental impact	Eco-friendly	Hazardous
5.	Suitability for wound healing	High	Limited

## 7. In Vitro and In Vivo Evaluation of Green-Synthesized silver and copper NPs for Wound Healing

Preclinical evaluation of green-synthesized silver and copper NPs is essential to establish their efficacy and safety for wound-healing applications. In vitro assays are commonly employed as an initial screening platform to assess cytocompatibility, antimicrobial efficacy, antioxidant potential, and cell migration activity. Fibroblast and keratinocyte cell lines are frequently used to evaluate cytotoxicity and wound closure potential through scratch (cell migration) assays, which simulate re-epithelialization processes critical for wound repair (Liang et al., 2007; Rigo et al., 2013).

Several studies have demonstrated that plant-mediated silver NPs promote fibroblast proliferation and enhance cell migration at optimized concentrations, while exhibiting minimal cytotoxicity compared to chemically synthesized NPs (Ahmed et al., 2016). Copper NPs have also been reported to stimulate angiogenesis and collagen deposition, largely due to copper's role



as a cofactor in enzymes involved in extracellular matrix remodeling and vascular formation (Sen et al., 2002; Borkow and Gabbay, 2005).

In vivo wound-healing studies, typically conducted using excision or incision wound models in rodents, provide more comprehensive insights into tissue regeneration, inflammation control, and granulation tissue formation. Green-synthesized silver NP and copper NP-based formulations have been shown to accelerate wound contraction, enhance epithelial regeneration, and reduce microbial colonization at wound sites (Rai et al., 2009). Polyherbal-derived NPs are particularly promising, as synergistic phytochemical interactions may further improve healing outcomes by simultaneously addressing infection, inflammation, and oxidative stress.

## 8. Toxicological Considerations and Safety Assessment

Despite their therapeutic potential, the safety profile of metal NPs remains a critical concern for biomedical applications. Toxicological effects of silver and copper NPs are influenced by particle size, surface chemistry, concentration, and duration of exposure. Excessive accumulation of metal ions can induce oxidative stress, mitochondrial dysfunction, and inflammatory responses in mammalian cells (Zhang et al., 2022).

Green synthesis using plant extracts has been widely reported to reduce NP-associated toxicity by providing natural surface coatings composed of biocompatible phytochemicals. These coatings not only stabilize NPs but also modulate metal ion release, thereby minimizing cytotoxic effects (Mittal et al., 2013; Singh et al., 2018). Comparative studies suggest that green-synthesized NPs exhibit lower hemolytic activity and improved cellular tolerance relative to chemically synthesized counterparts (Kharissova et al., 2013).

For wound-healing applications, topical administration significantly reduces systemic exposure; however, long-term safety, bioaccumulation, and environmental impact must still be carefully evaluated. Standardized toxicity testing, including dermal irritation, sensitization, and chronic exposure studies, is essential before clinical translation.

## 9. Challenges, Regulatory Aspects, and Future Perspectives

Despite encouraging preclinical evidence, several challenges limit the large-scale translation of polyherbal-mediated silver and copper NPs into clinical wound-care products. One major limitation is batch-to-batch variability in plant extracts due to differences in geographical origin, harvesting conditions, and phytochemical composition. This variability can influence NP size, stability, and biological performance, complicating standardization and regulatory approval (Iravani, 2011; Singh et al., 2018).

Regulatory frameworks for nanomedicines remain complex and evolving. Agencies such as the United States Food and Drug Administration (USFDA) and the European Medicines Agency (EMA) require detailed characterization of NP physicochemical properties, toxicity profiles, and manufacturing reproducibility. Currently, the lack of unified international guidelines for plant-based NMs presents an additional barrier to commercialization (Fadeel et al., 2018).

Future research should focus on mechanistic studies elucidating NP–cell interactions, optimization of polyherbal extract ratios, and integration of NPs into advanced wound dressings such as hydrogels, nanofibers, and bioactive scaffolds. The convergence of traditional medicinal knowledge with nanotechnology holds significant promise for the development of safe, effective, and affordable wound-healing therapies.

## 10. Conclusion

The integration of green nanotechnology with traditional medicinal knowledge offers a promising strategy for the development of advanced wound-healing therapies. This review highlights the potential of polyherbal-mediated synthesis of silver and copper NPs using *Pereskia aculeata*, *Trachyspermum ammi*, and *Sphagneticola trilobata*, three medicinal plants with well-documented ethnopharmacological relevance and bioactive phytochemical profiles. The phytoconstituents present in these plants not only facilitate eco-friendly NP synthesis but also impart additional biological functionality through surface capping, enhancing antimicrobial, antioxidant, and anti-inflammatory activities.

Silver and copper NPs synthesized via plant extracts demonstrate broad-spectrum antimicrobial efficacy, effective modulation of oxidative stress, and the ability to promote key wound-healing processes such as fibroblast proliferation, angiogenesis, collagen deposition, and re-epithelialization. Compared to chemically synthesized NPs, green-synthesized systems show improved biocompatibility and reduced toxicity, making them particularly suitable for topical wound-care applications. The polyherbal approach further strengthens therapeutic outcomes by exploiting synergistic interactions among diverse phytochemicals, reflecting principles long established in traditional medicine.

Despite encouraging preclinical evidence, challenges related to standardization, reproducibility, large-scale production, and

regulatory approval remain significant barriers to clinical translation. Variability in plant composition, lack of unified regulatory frameworks for nanomedicines, and insufficient long-term safety data must be addressed through rigorous mechanistic studies and well-designed in vivo investigations. Future research should prioritize optimization of polyherbal extract ratios, detailed NP–cell interaction studies, and incorporation of these NPs into advanced wound dressings such as hydrogels, nanofibrous scaffolds, and bioactive films.

Overall, polyherbal-derived silver and copper NPs represent a sustainable, multifunctional, and cost-effective platform for wound management. Continued interdisciplinary research bridging ethnopharmacology, nanotechnology, and biomedical sciences is essential to translate these promising systems from bench to bedside.

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## Authors Contribution

Neha Singh: Writing–Conceptualization, Original Draft and Investigation; Sonam Yadav: Writing–Review and Editing; Tanvi Jain: Conceptualization and Supervision..

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