

Green Synthesis of ZnO Nanoparticles: A Sustainable Approach for Wound Care

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Abstract: Cutaneous wound healing is a complex process regulated by molecular and cellular mechanisms. Conditions such as diabetes, obesity, and metabolic syndrome reduce this process, often leading to chronic wounds. These types of wounds remain a global health challenge due to prolonged healing, high infection risk, and poor response to conventional therapies. Zinc oxide nanoparticles (ZnO NPs) have gained attention in biomedical research because of their antimicrobial, anti-inflammatory, and antioxidant activities. While conventional synthesis methods often involve toxic reagents and high energy consumption, green synthesis using biological sources such as plants, fungi, and algae, offers safer and more sustainable alternatives. Furthermore, incorporating zinc oxide into biocompatible matrices enhances its therapeutic potential by promoting direct interaction with wound tissues. This review highlights recent advances in the green and biocompatible synthesis of ZnO NPs and explores their types and physical, chemical, and biological characteristics. Particular emphasis is placed on the use of green nanotechnology as a cost-effective and sustainable approach for developing next-generation wound healing materials reported the last five years in free-download through the literature.

Keywords: green synthesis, nanomaterials, wound healing, ZnO nanoparticles

Introduction

The skin, the largest organ in the human body, acts as a protective barrier for the body against the external environment. Continuous contact to environmental factors requires efficient mechanisms for carrying out repair processes to maintain barrier integrity. Skin repair and regeneration is a complex and multifactorial process involving highly sophisticated molecular pathways and cellular events that are activated after injury. The immune system plays a critical role in wound healing, in coordinating tissue repair and providing defense against pathogens that may enter through damaged skin. However, these processes can be altered under conditions such as malnutrition, stress, metabolic syndrome, diabetes, and obesity. Such impairments in repair mechanisms can lead to prolonged wound healing phases or excessive inflammatory responses resulting in chronic wounds, which affect health and quality of life.^{1–3} Chronic wounds represent a global public health challenge, and a silent epidemic that demands significant healthcare resources. At present, therapeutic options remain limited, and no intervention can fully prevent or reduce the morbidity and mortality associated with this condition. In this context, the development of new preventive and therapeutic approaches is attractive, and at the same time, can be made accessible to low-income and middle-income countries.⁴ The initial approaches were focused on the systemic administration of antimicrobial agents as antibiotics or local applications of drugs. Nevertheless, these strategies are often limited by poor drug penetration into skin tissues and the increasing problem of antimicrobial resistance, which results in failed wound healing.

Emerging therapeutic options include the use of nanomaterials, stem cell therapy, phototherapy, and microbiome-based therapy.⁵ In the field of nanomaterials, approaches have demonstrated remarkable efficacy in enhancing wound healing, using many types of nanomaterials such as nanoparticles (NPs), nanofibers, nanogels, and nanoemulsions.^{5–7}

Metal oxide NPs, such as iron oxide (Fe_3O_4), copper oxide (CuO), titanium dioxide (TiO_2), cerium dioxide (CeO_2), and zinc oxide NPs, have gained attention due to their biocompatibility, long shelf life, and cost-effectiveness.^{8,9} Typically, nanoparticles are produced using two methods: 1) Top-down [breaking down bulk materials into NPs] and 2) Bottom-up [assembling atoms or molecules into NPs].¹⁰ Nanotechnology is leading the way in creating multifunctional nanomaterials that can be utilized across a wide range of fields, including biomedicine, energy, food, cosmetics, and textiles. However, the principal disadvantages are high cost, poor eco-friendliness, and low energy efficiency.^{11,12}

To address these challenges, green-synthesized nanomaterials have emerged as a promising approach and sustainable alternative. Green-synthesized NPs are not only eco-friendly and cost-effective but also exhibit enhanced biocompatibility and functional versatility. In the biomedical domain, NPs exhibit antimicrobial, antioxidant, and anticancer properties, making them suitable for drug delivery, tissue engineering, and wound-healing applications. For instance, green-synthesized silver nanoparticles (Ag NPs) have demonstrated strong antibacterial activity against both Gram-positive and Gram-negative bacteria as well as antifungal and antiviral properties. Additionally, green-synthesized gold nanoparticles (Au NPs) have been explored in cancer therapy because of their selective cytotoxicity towards cancer cells and their ability to enhance chemotherapeutic drugs.^{13,14} Among metal oxides, zinc oxide nanoparticles (ZnO NPs) highlight their potential because of their small particle size. Recognized as safe (GRAS) by the Food and Drug Administration (FDA), ZnO NPs exhibit low toxicity, small particle size, and multifunctional biological properties, including antibacterial, antioxidant, and anticancer activities.^{15,16} According to scientific findings, traditionally synthesized ZnO NPs significantly accelerate the wound healing process. Firstly, their strong antimicrobial action reduces the risk of infection by creating an aseptic environment. Secondly, during the angiogenic stage, ZnO NPs are also able to promote revascularization through the characteristic production of reactive oxygen species (ROS), which initiates the MAPK/AKT signaling pathway. A major result of this activation is the release of nitric oxide (NO) that promotes endothelial cell growth and migration. On the other hand, the angiogenic properties of ZnO NPs are increased by the up-regulation of certain essential growth factors such as vascular endothelial growth factor-A (VEGF-A) and fibroblast growth factor-2 (FGF-2). Finally, during the remodeling stage, ZnO NPs enhance the activity of certain matrix metalloproteinases (MMPs), facilitating the clearance of collagen fragments from necrotic tissue. Moreover, free zinc ions (Zn^{2+}) promote the formation of new collagen fibers and induce the expression of other genes associated with tissue remodeling.¹⁷

In this context, the present review provides an overview of the green synthesis of ZnO NPs, emphasizing their biomedical applications in wound healing approaches and highlighting recent advances in their use for wound-healing purposes.

Green Synthesis and Types of ZnO NPs

The approach of green chemical synthesis for nanoparticle formation is an ecofriendly and cost-effective method compared to classical production methods. It centers on the use of processes and materials that minimize waste, toxicity, and energy consumption, thereby reducing reliance on chemicals and solvents. This strategy uses plant extracts, whole plants, or microorganisms to reduce and stabilize metal salts into nanoparticles, utilizing secondary metabolites that exhibit a wide range of properties, mostly antioxidant activity. The principles of green chemistry encourage a model of chemical design and implementation in which the challenge for chemists is to emphasize waste prevention rather than remediation. This begins with the development of synthetic routes that provide a high degree atom economy, that is to say, featured reagents are designed to become components of the final product and minimize byproduct formation. These methods should prefer the use and production of compounds having low or no human toxic effects as well as toxicity to the environment (design of effective, but safer chemicals and products). Energy should be saved and the use of auxiliary substances, including solvents, should be avoided or require special precautions for safety reasons.¹⁸ Wherever feasible, processes should prioritize the use of renewable raw materials and highly selective, often recyclable catalytic reagents rather than stoichiometric reagents. In addition, chemicals should be developed to biodegrade into safe products after use rather than persist in the environment. To achieve this, real-time analysis must be employed to prevent contamination before it occurs. The selection of all substances should inherently minimize the risk of chemical accidents and ensure a more equitable lifecycle – from inception to degradation. Over the last 20 years, green synthesis of nanomaterials has

been an innovative approach, originating from the adoption of inventive routes governed by the twelve basic principles of green chemistry. These principles provide a coherent scientific understanding and conceptual knowledge for the development of novel methods and products with optimized efficiency and sustainability. These guidelines must work to reduce environmental patterns and optimize construction of the next-generation materials. The principles involved include hazardous waste minimization, the use of processes that maximize product quality and performance, and the elimination of toxic reagents. They also facilitate the development of safe, biocompatible materials, environmentally benign solvents (such as water) and energy-conserving processes.^{19,20} Zinc oxide nanoparticles (ZnO NPs) have emerged as promising nanomaterials in the fields of regenerative medicine and tissue engineering due to their unique combination of antimicrobial properties, biocompatibility, and ability to promote tissue regeneration and stimulate regenerative processes. In general, the green synthesis of ZnO nanoparticles involves exposing a zinc ion solution to vegetal or biological extracts (aqueous or alcoholic), followed by incubation under controlled conditions and subsequent heat treatment (see Figures 1 and 2). The resulting nanoparticles retain some of the functional groups derived from the biological extracts, providing interesting properties, such as a positive surface charge, biocomposites with biological activity, and varied morphologies (see Figure 3).

Recent advances since 2020 in the green synthesis of these nanoparticles have enabled the development of safer and more efficient green-synthesized ZnO nanoparticle systems, as demonstrated. For example, studies using *Cymbopogon oliveri* plant extracts have been used to produce ~28 nm spheroidal nanoparticles with potent activity against skin pathogens²¹ or puerarin extracts to obtain 200–400 nm nanoparticles with antiangiogenic properties.²² These sustainable methods not only avoid the use of harsh chemicals but also confer additional biological properties through the phytocompounds adsorbed on the nanoparticle surfaces; the interactions between phytocompounds and zinc ions are illustrated in Figures 1 and 2. In addition, the determination of the physicochemical and biological properties of nanoparticles can be performed using common phytocompounds, as exemplified in Figure 2.

The antimicrobial mechanism of ZnO nanoparticles is multifactorial and involves the release of Zn^{2+} ions, which interfere with microbial metabolic processes; the generation of reactive oxygen species (ROS), such as hydroxyl radicals ($\text{OH}^\cdot$) and hydrogen peroxide (H_2O_2), which induce oxidative stress, and electrostatic interactions between the positively

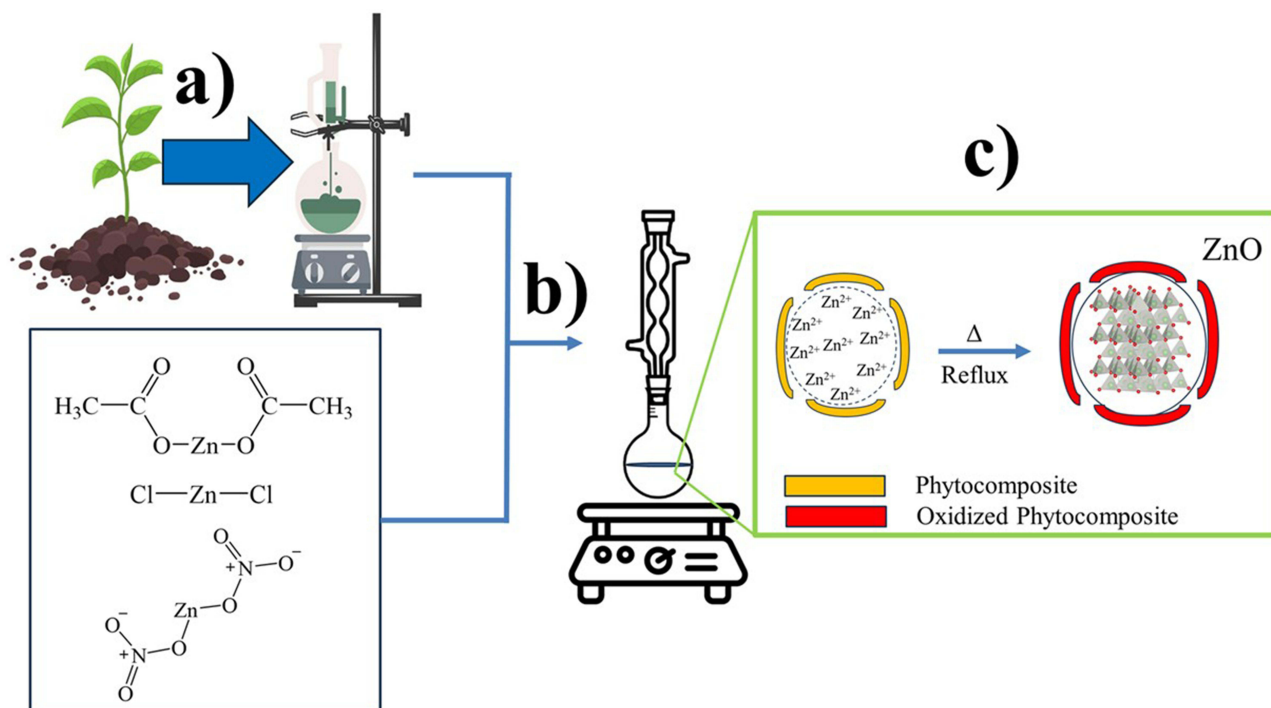


Figure 1 Schematic diagram of the green synthesis process of ZnO nanoparticles. The process involves three main steps: (a) preparation of the plant extract, (b) mixing the extract with a zinc salt precursor, and (c) the proposed reaction and nucleation mechanism involving phytocompounds and Zn^{2+} ions.

Green synthesis of ZnO nanoparticles

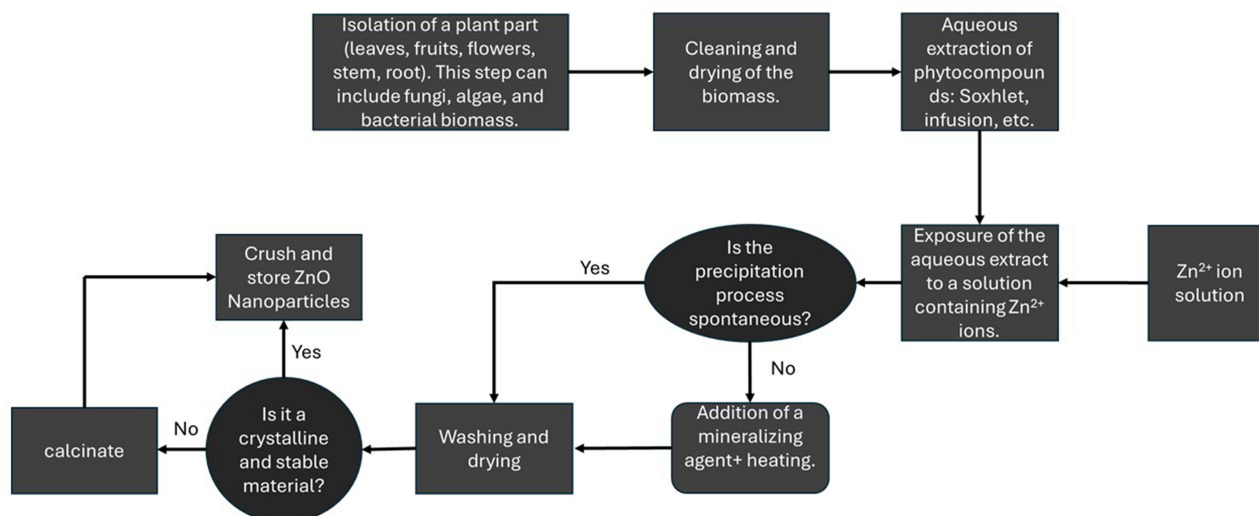


Figure 2 Schematic diagram illustrating the general route for the green synthesis of ZnO nanoparticles.

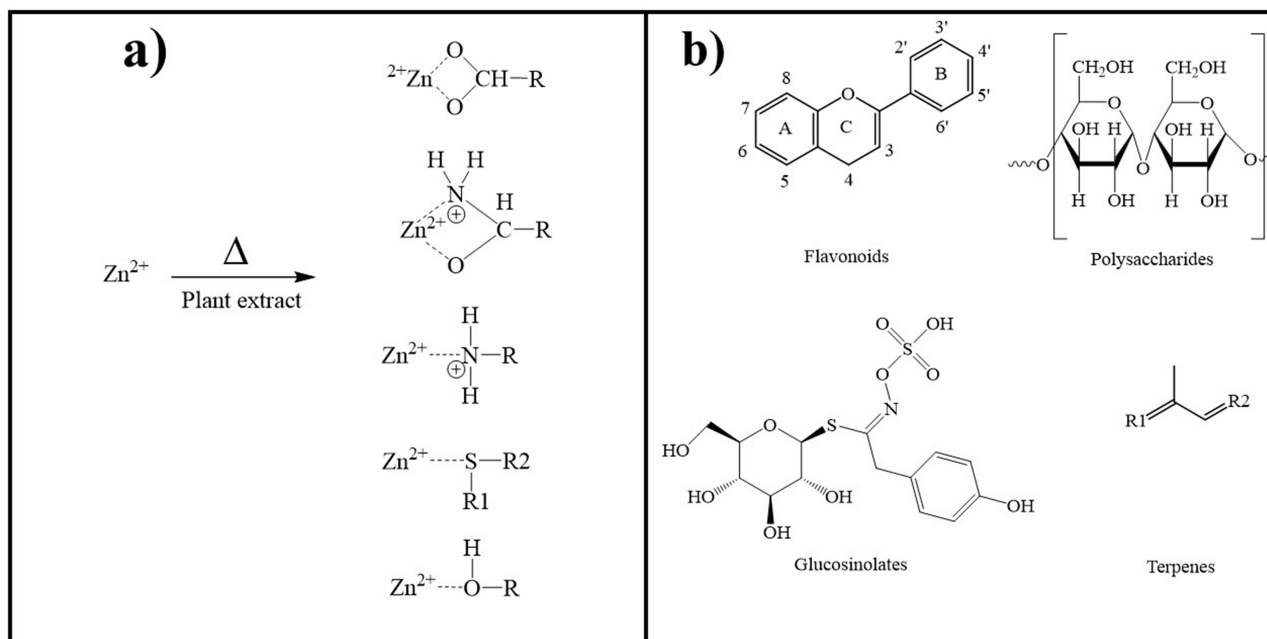


Figure 3 (a) Possible chemical interactions between the functional groups of phytocompounds and zinc ions (Zn^{2+}). (b) Common phytocompounds present in plant extracts used in green synthesis: flavonoids, polysaccharides, glucosinolates, and terpenes.

charged surface of ZnO nanoparticles and negatively charged bacterial membranes (see Figure 4). Studies by Viswanathan et al have shown that the use of agents such as didodecyltrimethylammonium bromide (DDAB) can enhance this positive surface charge, significantly increasing antimicrobial efficacy, particularly against Gram-negative bacteria.²³

ZnO nanoparticles with different morphologies and sizes have been synthesized using green synthesis routes.²⁴ For example, Naïel et al used *L. prunosum* extract to synthesize zinc oxide nanoparticles from hexagonal/cubic ZnO nanoparticles. These nanoparticles demonstrated significant anticancer activity in skin, as well as notable antimicrobial

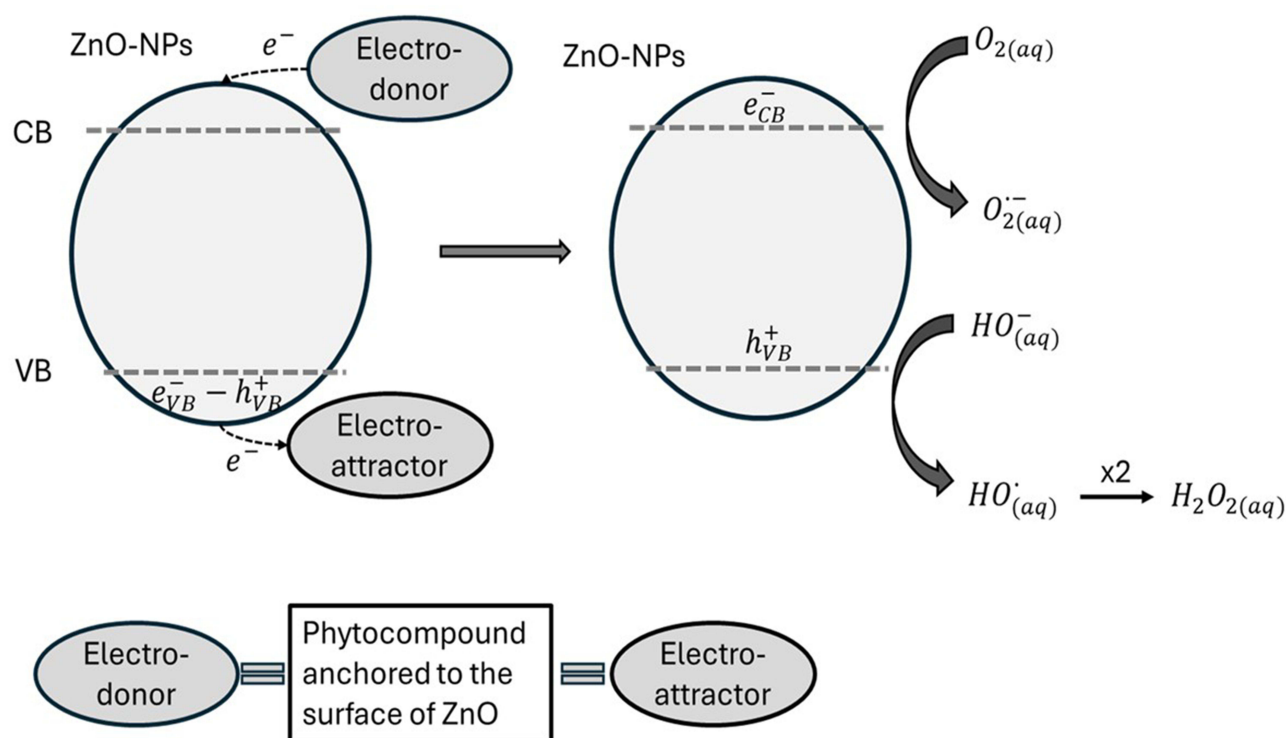


Figure 4 Schematic illustration of reactive oxygen species (ROS) generation on the surface of ZnO nanoparticles under dark conditions. Phytocompounds (or parts thereof) anchored on the ZnO nanoparticle surface can act as electron donors, populating the conduction band, while electron-accepting (partially oxidized) phytocompounds trap electrons in the valence band, promoting electron-hole pair separation. In the aqueous medium, dissolved oxygen captures electrons from the conduction band (e_{CB}^-) forming superoxide radical $O_{2(aq)}^-$, while $HO_{(aq)}^-$ ions capture holes (h_{VB}^+) from the valence band generating hydroxyl radicals ($HO_{(aq)}^\cdot$).

and antioxidant properties. Furthermore, these nanosystems showed no cytotoxicity or adverse effects on normal cells (WI-38) at concentrations up to 250 $\mu\text{g/mL}$, supporting their biocompatibility.²⁵

Similarly, Ebadi et al employed cyanobacterial cell extracts to synthesize 3D star-shaped ZnO nanoparticles. These nanoparticles exhibited excellent antibacterial, antibiofilm, and antifungal activities against clinically relevant bacterial isolates, including *Escherichia coli* (*E. coli* 25922), *Pseudomonas aeruginosa* (*P. aeruginosa* PAO1), and *Staphylococcus aureus* (*S. aureus* 25923). The activity of these 3D star-shaped ZnO systems was associated with ROS generation in the exposed bacterial cells.²⁶ Hameed et al synthesized spheroidal ZnO nanoparticles, with an average diameter of approximately 45 nm in the wurtzite phase, by a coprecipitation method using a green algae extract (*Spirogyra hyaline*). These nanoparticles exhibited potent antimicrobial effects against both Gram-negative and Gram-positive bacteria.²⁷

El-Belely et al obtained ZnO nanoparticles with a diameter of approximately 43 nm using an alcoholic extract of the cyanobacterium *Arthrospira platensis* (*A. platensis*). The antimicrobial activity of the ZnO nanoparticles was evaluated using *P. aeruginosa*, *Bacillus pumilus* (*B. pumilus*), *S. aureus*, and *E. coli*, showing strong antibacterial activity against Gram-positive bacteria, particularly *S. aureus*.²⁸ However, their efficacy can vary depending on particle size, morphology, and concentration. Mohamed et al synthesized a ZnO/CuO cluster in the presence of *Penicillium chrysogenum* (*P. chrysogenum*) extract, which displayed potent antimicrobial and antibiofilm activities against *S. aureus*. The authors reported that ZnO/CuO exhibited potent antimicrobial activity due to the presence of proteins and enzymes on the fungal extract surface.²⁹

Thi et al investigated another plant-based synthesis method, using an orange peel (*Citrus sinensis*) extract to obtain ZnO nanoparticles. This approach aimed to minimize the use of toxic chemicals while improving the nanoparticles' antibacterial properties and biomedical potential. The resulting ZnO nanoparticles exhibited different morphologies, including quasi-spherical and rod-shaped structures, with sizes ranging from 15 nm to 200 nm, depending on the extract

concentration. These nanoparticles demonstrated strong antibacterial and antifungal activities, as well as preservative effects, indicating their potential for applications in food packaging.³⁰

Sedefoglu synthesized ZnO nanoparticles using a green approach with extracts from the *Myrtus communis* plant, varying the precursor type and calcination temperature. This study demonstrated that morphological variations in ZnO nanoparticles such as hexagonal shapes with acetate, pyramidal, and rod-shaped structures could be achieved by adjusting the precursors and calcination temperatures, particularly through heat treatment. Nanoparticle sizes also depend on the synthesis parameter conditions. Additionally, ZnO nanoparticles exhibited strong photocatalytic performance, achieving up to 99% degradation of the methylene blue dye under UV irradiation.³¹

In the context of fungal-based synthesis, Nehru et al reported the synthesis of ZnO nanoparticles using the endophytic fungus *Xylaria arbuscula*, isolated from *Blumea axillaris* Linn. X-ray diffraction (XRD) and microscopic analyses revealed that the ZnO nanoparticles exhibited a hexagonal wurtzite phase and spherical morphologies, with sizes ranging from approximately 30 to 50 nm. The nanoparticles demonstrated antimicrobial, anti-inflammatory, and antidiabetic properties. In vitro cytotoxicity was evaluated using L929 fibroblast cell lines, indicating an improvement in the wound healing process. Overall, these findings highlight the potential biomedical applications of ZnO nanoparticles, particularly as antifungal and antibacterial agents.³²

In a recent study, Alprol synthesized ZnO nanoparticles using the brown seaweed *Padina pavonica* extract as a natural reducing agent and stabilizer. The study aimed to enhance the adsorption capacity and photocatalytic activity of the nanoparticles for dye removal, thereby reducing environmental and health risks. The nanoparticles demonstrated a high adsorption capacity ($Q_m = 192.308$ mg/g) and high removal efficiency (>98%) for the dye methylene blue. These results were like low concentrations of methylene blue (20–60 ppm) and zinc oxide nanoparticles as an adsorbent at concentrations of 0.5 g/L (total volume = 100 mL). Furthermore, ZnO nanoparticles demonstrated antimicrobial properties against various bacteria, suggesting their potential application in both biomedical and environmental remediation fields.³³

As demonstrated in the studies discussed above, the use of different biological extracts results in ZnO nanoparticles with diverse morphological characteristics and improved biomedical properties. Table 1 summarizes the different green synthesis approaches and the corresponding ZnO nanoparticle morphologies reported in the literature. The following section describes these properties in detail, with particular attention to their applications in wound healing.

Table 1 Green-Synthesis of ZnO NPs

Source	Nanoparticle Size (nm)	Morphology	Extraction Part	Synthesis Method	Reference
<i>Arthrospira platensis</i>	43–54	Ovoid	Alcoholic extract	Green synthesis	[28]
<i>Citrus sinensis</i> (Orange)	15–200	Quasi-spherical / Rod-like	Fruit peel	Sol-gel	[30]
<i>Limonium pruinosum</i>	30–45	Hexagonal/Cubic	Leaf extract	Green synthesis	[25]
<i>Myrtus communis</i> (Myrtle)	40–60	Hexagonal/Pyramidal/Rod-shaped	Leaf extract	Green synthesis and calcination	[31]
<i>Nostoc</i> sp. (Cyanobacteria)	~24	3D Star-shaped (Wurtzite phase)	Cellular extract	Green synthesis	[26]
<i>Padina pavonica</i>	20–30	Spherical / irregular	Algal extract	Green synthesis	[33]
<i>Penicillium chrysogenum</i>	10.5–59.7	ZnO/CuO clusters (spherical)	Fungal biomass	Green synthesis	[29]
<i>Spirogyra hyalina</i>	45	Spheroidal (Wurtzite phase)	Whole algae	Co-precipitation	[27]
<i>Xylaria arbuscula</i>	30–50	Hexagonal (Wurtzite phase), Spherical	Fungal filtrate	Green synthesis	[32]
<i>Cymbopogon olivieri</i>	~28	Spheroidal	Leaf extract	Green synthesis and Precipitation	[21]
<i>Pueraria lobata</i>	~300	Spheroidal	Purified from root extract	Green synthesis	[22]

Abbreviation: NR, no reported.

Promissory Advances in Wound-Healing Applications of Green-Synthesized ZnO NPs

This section provides an analysis of recent advances over the past five years in the application of green-synthesized ZnO NPs for wound healing. The studies, presented in chronological sequence, reveal a clear evolution in the complexity of the research and highlight the key properties responsible for therapeutic efficacy. The main wound healing results of ZnO NPs synthesized by green protocols are summarized in Table 2, while the possible mechanisms behind their wound healing effects are schematized in Figure 5.

A consistent finding in the literature is the antibacterial activity of green-synthesized ZnO NPs against resistant pathogens. For instance, in 2021, Rasha et al synthesized ZnO NPs using *Acacia nilotica* aqueous extract, obtaining nanoparticles with an average size of 28 nm, hexagonal shape, and smooth surface. The antibacterial activity was evaluated using the well diffusion method, showing a significant reduction in the growth of *Klebsiella pneumoniae* carbapenemase (KPC) with an inhibition zone (ZOI) of 22.9 ± 1.96 mm at a concentration of 7.5 mg/mL of ZnO NPs, whereas the bacteria were resistant to the positive controls (imipenem and meropenem). The minimum inhibitory concentration (MIC) was 0.45 mg/mL, and minimum bactericidal concentration (MBC) was 1.14 mg/mL. Wound healing was evaluated in male Sprague–Dawley (SD) rats on day 7, and the infected rats treated topically with green ZnO NPs showed complete resolution of the infection and 98% wound healing by day 14. Histological evaluation revealed a decrease in inflammation; in contrast, the control group showed only 64% wound healing recovery and higher inflammation at the wound site. Elucidation of immune mechanisms or healing mechanisms could be improved to develop robust treatments that allow the resolution of chronic wounds.³⁵ These results are consistent with those reported

Table 2 Main Wound Healing Results of ZnO NPs

Plant Used for Extract	Type of Nanocomposite	Administration via	Wound Healing Evaluations	Mechanisms Elucidated	Reference
<i>Lawsonia inermis</i>	Carbopol 940 based gels	Topically	Donkeys and one horse show a significant reduction of wound size (93.6%) without infections, in animals treated with green ZnO NPs.	NR	[34]
<i>Acacia nilotica</i>	NR	Topically	Sprague-Dawley male rats show 98% of recovery after 14 days of treatment.	Histological evaluation shows a reduction of inflammation compared with non-treated rats	[35]
<i>Azadirachta indica</i>	Chitosan based hydrogel	NR	Hydorgel is capable of absorbing wound exudate, shows greater wound healing potential when administered to albino rats, with antimicrobial activity.	NR	[36]
<i>Calendula officinalis</i>	NR	NR	In vitro assays show wound closure of 69.1% compared with control (64.8%).	Antioxidant activity was shown in vitro assays.	[24]
<i>Caesalpinia spinosa</i>	NR	NR	In vitro, the assays showed a closed wound after 48 hours at concentrations of 0.625 µg/mL and 1.25 µg/mL of ZnO NPs.	Pro-inflammatory cytokines as IL-6 and TNF-α were reduced, production of anti-inflammatory cytokine TGF-β was shown.	[37]
Roots of <i>Moringa oleifera</i>	ZnO NPs loaded with ciprofloxacin and coated with polyethylene glycol	Topically	Promoting wound healing in albino mice, in addition, eliminates the infection of wound with <i>S. aureus</i> .	NR	[38]
<i>Salvia hispanica</i> L.	ZnO/Ag/Ag ₂ O nanocomposite	NR	Better wound healing capacity (96%) compared with control group (50%) after 10 days in mice.	Antioxidant activities were observed in vitro assays.	[39]

Abbreviation: NR, no reported.

Mechanisms that could favour wound healing process

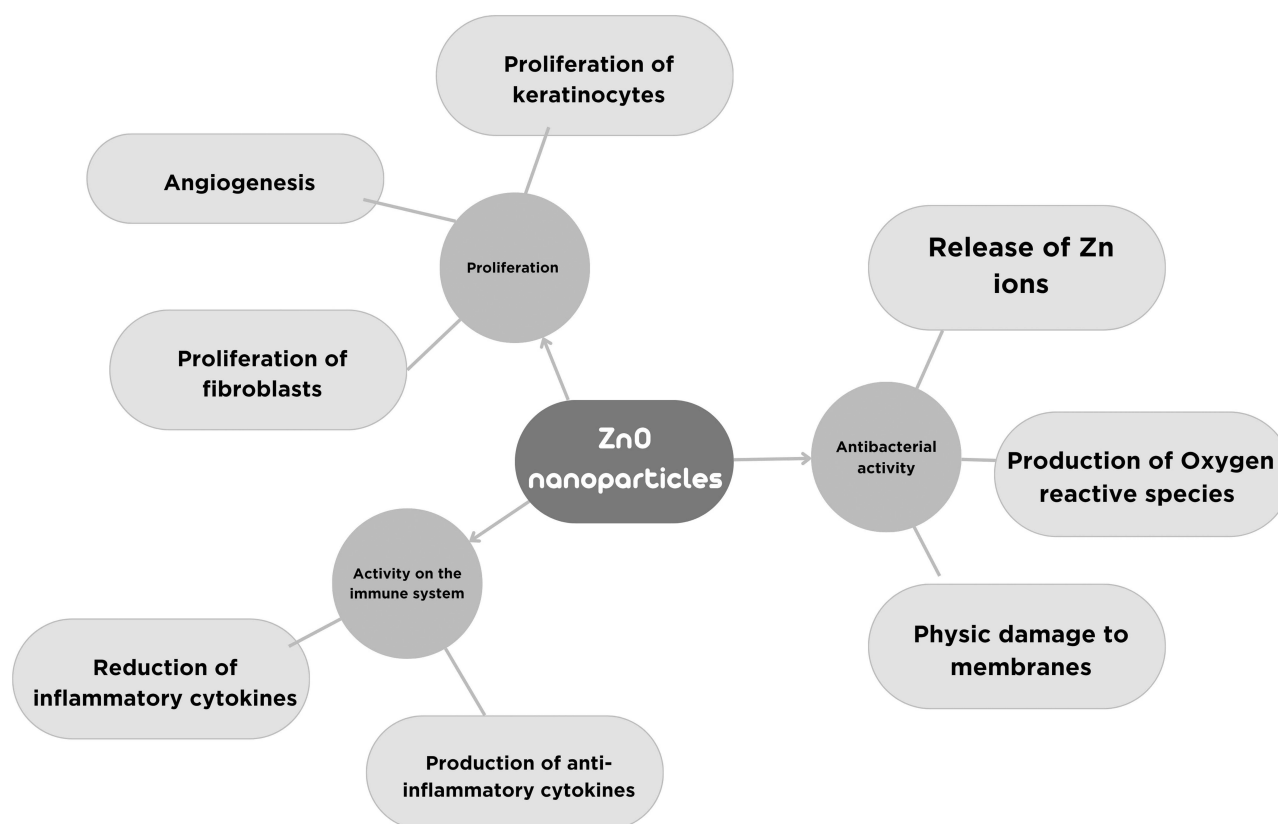


Figure 5 Schematic representation of the principal mechanisms underlying wound healing.

later by Rasheed et al 2023 that describe the synthesis of ZnO NPs using a green chemical precipitation method, which resulted in a 21–300 average size range with a hexagonal shape. Their effectiveness against MRSA in wound healing was evaluated, and the findings demonstrate that ZnO NPs have significant antibacterial activity against this microorganism, with a MIC of 0.125 mg/mL. Similar results were found by well-diffusion agar when 0.03125 to 0.5 mg/mL of ZnO NPs are used. Additionally, in vivo experiments showed an improvement in wound healing in mice infected with *S. aureus*, treated with ZnO NPs, and showed complete regeneration after 12 days when compared with the positive control (mice with infected wounds without treatment). Infiltration of inflammatory cells, mostly neutrophils, in mice in the treated group was evidenced by histology, suggesting an effective immune response.⁴⁰ This consistency across independent studies strengthens the evidence for ZnO NPs potential in combating wound infections. The strategy of combining NPs with antibiotics, as demonstrated by Shoukani et al in 2024 reported the synthesis and evaluation of green-synthesized ZnO nanoparticles from *Moringa oleifera* (*M. oleifera*) root extract, these NPs were loaded with ciprofloxacin and coated with polyethylene glycol (CIP-PEG-ZnO-NPs). This nanocomposite demonstrated better ciprofloxacin encapsulation efficiency than the chemically synthesized nanoparticles (93 and 91%, respectively). The antibacterial properties of these NPs are strong against many bacteria, such as *Enterococcus faecalis* (*E. faecalis*), *E. coli*, *Klebsiella pneumoniae* (*K. pneumoniae*), and *P. aeruginosa*, and the nanoparticles were capable of inhibiting biofilm formation at concentrations between 2.5–5 µg /mL. Cytotoxicity evaluation showed that the nanoparticles did not significantly reduce cell viability. In vivo studies were performed in albino mice that were wounded with a surgical blade and infected with MRSA. Interestingly, in vivo assays demonstrated a 20% improvement in wound healing compared to the control group. In addition, these assays showed effective eradication of *S. aureus* from infected mice skin, further promoting wound

healing³⁸. This represents a significant advancement over earlier simple ZnO NP formulations, demonstrating enhanced efficacy and novel approach to circumvent antibiotic resistance complications.³⁸

Beyond antibacterial properties, the trend in recent studies is focused investigation of anti-inflammatory mechanisms. While Metwally et al in 2020 observed the disappearance of infection through the synthesis of ZnO NPs using an extract of *Lawsonia inermis* after gels at 0.2% were formed using Carbopol 940. In vivo assays were developed in nine donkeys and one horse, with wounds in different body parts, and ZnO gel was topically applied every other day doses for three weeks, after which the wound size of animals treated with green ZnO NPs drastically decreased, resulting in 93.6% wound contraction in the third week, when compared with animals treated with chemical ZnO NPs (90.6%). Interestingly, the infection in animal wounds treated with green ZnO NPs disappeared in the first week of treatment. The results shown by the authors reflect a promising approach for treating chronic wounds; however, more extensive studies should be performed to elucidate the mechanisms that promoting healing tissues.³⁴ Later, Abdelkader et al 2022 provided more detailed with molecular perspective, they reports the obtention of ZnO NPs using *Aspergillus niger* (*A. niger*) extract, the nanoparticles resulting in spherical morphology and 31.75 ± 4.38 nm, and the colloidal stability of the ZnO nanosuspension was evaluated by zeta potential, showing an adequate value of 26.6 ± 0.56 mV. In vitro antibacterial activity was observed at concentrations of 8–128 $\mu\text{g/mL}$, interestingly, the genes related to biofilm formation, such as *fnbA*, *fnbB*, *ebpS*, and *icaC*, were evaluated by Quantitative Reverse Transcription Polymerase Chain Reaction (qRT-PCR) and resulted in a decrease in these genes. In contrast, in vivo assays were performed in Swiss albino mice infected with subcutaneous (SC) injection of 2×10^7 UFC/mL of *S. aureus*, one day after the second administration, 5 mg/kg of ZnO NPs were intraperitoneally (IP) administered daily for 20 days. Significant decreases in UFC/g tissue in the liver and spleen were observed, and the survival rate increased compared to that in the control group. In addition, fibrosis and congestion of the liver and spleen were reduced, and these observations correlated with the reduction of inflammatory cytokines, such as IL-6 and IL-1 β , found in these organs. This approach shows important anti-inflammatory capabilities in addition to the antimicrobial properties demonstrated in other research studies and is positioned at ZnO NPs as a promising approach for biomedical applications.⁴¹ This was further corroborated by Sezen in 2023 in which ZnO NPs were obtained by green synthesis using *Caesalpinia spinosa* (*C. spinosa*) extract. Antimicrobial activity was demonstrated by a well-diffusion method, and the ZOI formed in *S. aureus* methicillin-resistant (MRSA), *Enterococcus faecium* (*E. faecium*), *Streptococcus mutans* (*S. mutans*) were 5, 8, and 9 mm, respectively. Interestingly, cell viability increased when the ZnO NPs concentration was 0.15625–1.25 $\mu\text{g/mL}$ compared to that of the control groups; however, toxic effects were observed when 2.5 $\mu\text{g/mL}$ was used. Through in vitro assays of wound healing were developed using different concentrations of ZnO NPs, cell bridges were observed around the 36 hours and totally closed in 48 hours when highest concentrations probed (0.625 $\mu\text{g/mL}$ and 1.25 $\mu\text{g/mL}$), when compared with the control groups the cell bridges still open at 48 h. Interestingly pro-inflammatory cytokines as IL-6 and TNF- α were reduced in cells treated with concentrations of 0.625 $\mu\text{g/mL}$ and 1.25 $\mu\text{g/mL}$. In addition, the production of the anti-inflammatory cytokine TGF- β increased when 0.625 and 1.25 $\mu\text{g/mL}$ of ZnO NPs were used compared with the control groups.³⁷ Their result clearly offer a link between ZnO NPs treatment and the resolution of the inflammatory phase of healing.

The field has also evolved from using simple ZnO NPs to developing more complex nanocomposites to enhance functionality. The 2021 work, of Iqbal et al first evaluated the antimicrobial properties of Ag-ZnO NPs and reported a greater bactericidal effect against cocci and *E. coli*. In addition, when these NPs were loaded in a chitosan hydrogel, they demonstrated swelling capacity in albino rats; however, this capacity was reduced compared to the chitosan hydrogel alone in the ability to absorb wound exudate. On the other hand, the evaluation of wound epithelization in rats with skin excision wounds 2 cm in diameter treated with chitosan hydrogel loaded with Ag-ZnO NPs resulted in safe properties and showed greater wound healing potential when compared with chitosan hydrogel alone or chitosan hydrogel loaded with ZnO NPs. Therefore, this report demonstrates green synthesis for generating functional nanoparticles, particularly Ag-ZnO NPs, with antibacterial and wound healing properties.³⁶

The combinatorial approach based on hydrogels and nanoparticles reported by Rafique et al in 2024³⁹, in which ZnO/Ag/Ag₂O nanocomposites were synthesized via green methods using *Salvia hispanica* L. (chia) seed extract and evaluated for anticancer, antibacterial, and wound-healing activity, can be considered a precursor to more advanced

composites. For this purpose, the authors first synthesized separate nanoparticles of ZnO and Ag/Ag₂O using an aqueous extract of chia seeds, after which a co-precipitation method was developed to obtain the nanocomposite ZnO/Ag/Ag₂O. The results showed that the average diameter of the nanocomposite (22.42 nm) was spherical. Antibacterial activity was evaluated against *S. aureus*, *Bacillus subtilis* (*B. subtilis*), and *E. coli* by a well-diffusion method, showing maximum inhibition growth at 3 mg/mL. Better results were obtained with the nanocomposite when compared with ZnO NPs or Ag/Ag₂O, with inhibition halo of 25.3 mm, 21 mm and 17.5 mm against *B. subtilis*, *S. aureus* and *E. coli* respectively. Interestingly, the nanocomposites showed better antioxidant activity than ZnO NPs and Ag/Ag₂O, as demonstrated by the reduction in power activity and DPPH free radical scavenging assays, suggesting a synergistic response. The anticancer activity was evaluated on MCF7 cell line, which showed 75.3% inhibition of proliferation; in addition, the wound healing capacity was assessed using the excision wound model in mice, which showed better capacity and after ten days 96% of the wounds healed; on the other hand, the control group only had approximately 50% healing.³⁹ This interesting report reflects the prominent role of ZnO NPs in the biomedical field, which demonstrated not only enhanced antibacterial activity and wound healing properties but also significant antioxidant and anticancer activities, showing multifunctional approach.

On the other hand, the biological models reveal a progression from observational to mechanistic research, earlier studies like Metwally et al in 2020 and Rasha et al in 2021 relied heavily on in vivo wound contraction measurements and histology, that are crucial evaluations,^{34,35} later studies incorporated sophisticated in vitro models to elucidate the mechanisms, in this sense Aydin-Acar et al 2023 described the green synthesis and characterization of Co-ZnO NPs using a *Calendula officinalis* (*C. officinalis*) flower extract, which resulted in an average crystallite size of 17.66 nm NPs. Cytotoxicity was evaluated by the authors using the MTT method, resulting in non-toxic nanoparticle concentrations of less than 10 µg/mL after 48 h. Subsequently, the in vitro wound healing response at 10 µg/mL of Co-ZnO NPs was evaluated, showing an increase in wound closure after 24 h when compared with the control group. These results were confirmed by the scratch wound assay, and the resulting NPs showed safe properties in vitro assays using the L929 cell line at concentrations less than 10 µg/mL, with an IC₅₀ of 25.96 µg/mL, resulted in enhanced cell migration, indicative of wound closure of 69.1%, in contrast to the control, which only showed 64.8%. In addition, antioxidant activity was evaluated using ABTS radical scavenging activity and DPPH radical scavenging activity assays, with values of 32.25 and 32.37%, respectively, at a concentration of 500 µg/mL. Acceptable antioxidant activity was observed only at high concentrations (1000 µg/mL).²⁴ These preliminary results are interesting; however, further studies are required to consolidate the observations of the authors.

Similarly, Sezen in 2023 used scratch assays and cytokine profiling, respectively, to evidence cellular and molecular effects.³⁷ Furthermore, studies began targeting specific clinical challenges; Nair et al in 2023 specifically reported the production of ZnO NPs by green synthesis using dark chocolate extract for use in the treatment of diabetic complications such as wound healing, in vitro assays to determine the inhibition of aldose reductase as a marker of intracellular sorbitol accumulation and associated complications of diabetes were performed. The use of chocolate-mediated ZnO NPS showed a dose-dependent inhibition of aldose reductase (AR), comparable to that of standard quercetin. Similarly, the evaluation of the production of advanced glycation end products (AGE) as a marker of oxidative stress shows a dose-dependent reduction in AGEs, suggesting the potential for reduced complications due to diabetes. This work reflects another promising approach for ZnO NPs, which can be used in chronic wounds developed in diabetic patients by examining aldose reductase inhibition and AGE reduction with a focused application that addresses a major unmet medical need.⁴²

Most recently, Elhabal et al in 2024 report for the successful green synthesis of ZnO-NPs with flower aqueous extract of *Althaea officinalis*, acting as both a reducing and stabilizing agent. The spherical particles obtained (~76 nm, +30 mV zeta potential) were inserted in 2% water suspension of chitosan (CS = A.O.-ZnO-NPs-CS formulation) to develop a new topic formulation. The main findings indicated that the biocompatible gel expressed good antioxidant (IC₅₀ 4.23 µg/mL) and antibacterial activities against clinically significant bacteria such as *Staphylococcus aureus*. More importantly, the formulation markedly promoted closure of diabetic wounds in rats by 98.1% after only 14 days. The anti-inflammatory activity of the nanosystem used herein derived from both the direct antimicrobial and antioxidant activities of ZnO-NPs as well as bioactive compounds such as quercetin (flavonoid) and gallic acid, which modulated inflammation by

profoundly suppressing innate immune activation. This was supported by the downregulation of pivotal pro-inflammatory factors (TNF- α , IL-6, and IL-1 β) and upregulation of anti-inflammatory factor IL-10 offering a tailored blockade to aberrant inflammatory signaling pathways involved in impaired healing. The study highlights that the green synthesized ZnO-NPs when conjugated with chitosan gel could be an innovative and multimechanistic as well as eco-friendly approach to wound therapy for better management of wounds.⁴³ It's important to note some discrepancies, for instance, reported safe concentrations of ZnO NPs vary considerably across studies. Sezen³⁷ observed toxicity at 2.5 $\mu\text{g/mL}$, while Aydin-Acar et al²⁴ reported an IC50 of 25.96 $\mu\text{g/mL}$, and other studies used much higher concentrations in vivo without reported adverse effects, this aligns with warnings about potential cytotoxic effects at high concentrations (>100 $\mu\text{g/mL}$).⁴⁴ The influence of synthesis methods, surface modifications, and the chosen biological model on NP biocompatibility, indicating a need for more standardized testing protocols to facilitate direct comparison between different ZnO NP formulations. This discrepancy underscores the need for strategies to improve safety profiles, such as the hyaluronic acid coatings⁴⁵ or magnesium dropping⁴⁶ mentioned in the recent literature, which could be directly applied to green-synthesized NPs to enhance their translational potential.

Insights Into the Wound-Healing Efficacy of Conventional ZnO Nanoparticles

Recent research in the field of tissue regeneration has revealed that ZnO NPs can act at multiple levels. Studies such as those by Hassan et al⁴⁷ demonstrated that these nanoparticles, at subcytotoxic concentrations ($\leq 50 \mu\text{g/mL}$), induced VEGF secretion in Human Umbilical Vein Endothelial Cells (HUVECs), promoting angiogenesis, a fundamental process for healing wounds. In this sense, Emam-Djomeh and Hajikhani⁴⁸ have shown that chitosan/ZnO dressings can increase the proliferation of human fibroblasts (HFF-1 cell line) by 40% by activating the MAPK/ERK signaling pathway through the released Zn²⁺ ions. Similar effect was also observed in vivo models, where PCL/ZnO nanofibers (5% w/w) reduced the healing time by 30% by stimulating the production of type I collagen.⁴⁹ The ability of ZnO NPs to modulate immune response was another significant finding identified that these nanoparticles in in vitro and in vivo models suggest that ZnO NPs can reduce chronic inflammation in wounds by polarizing macrophages towards the anti-inflammatory M2 phenotype through inhibition of the NF- κB pathway.¹⁷ This mechanism is particularly relevant for the treatment of chronic wounds and infected burns, where persistent inflammation delays healing.

The tissue engineering applications have been particularly diverse. For example, electrospun chitosan/collagen/ZnO membranes developed by Tiplea et al⁵⁰ achieved a 95% wound closure rate in 14 days, combining antibacterial activity with epithelialization stimulation. For bone regeneration, Fotouhi-Ardakani et al⁵¹ demonstrated a 200% increase in calcium deposition in vitro when PVDF/PCL/ZnO scaffolds were combined with dexamethasone. Biological evaluations of PC12 cells revealed that up to 5 WT% of ZnO nanoparticles synthesized by electrospinning in PLA matrices promotes a favorable environment for their proliferation.⁵² Despite these advances, studies such as those by Kad et al⁴⁴ warn of potential cytotoxic effects at high concentrations (>100 $\mu\text{g/mL}$), which have led to the development of strategies to improve their safety profile. These include the use of hyaluronic acid coatings⁴⁵ or magnesium doping,⁴⁶ which reduce cytotoxicity without compromising biological activity. The versatility of ZnO NPs is enhanced by their ability to be integrated into various controlled release systems. Cleetus et al⁵³ developed alginate/ZnO scaffolds with controlled porosity (100–200 μm) that not only improved vascularization in diabetic rat wounds but also showed sustained release of zinc ions for 14 days. This characteristic is particularly valuable for clinical applications that require prolonged action. In the clinical context, one of the greatest advantages of ZnO NPs over conventional antibiotics, as highlighted by Wiesmann et al⁵⁴ is that they do not induce bacterial resistance, which is a growing global health problem. Furthermore, their capacity to safely degrade in the body and be excreted makes them attractive alternatives for long-term use.

Importantly, differences between the chemically synthesized ZnO nanoparticles that are biologically active in vivo and those that are synthesized green, we can draw a clear distinction between them. This can be seen most clearly in the preclinical trials of biocompatibility green ZnO NPs exhibit; though both types exhibit a strong antimicrobial effect, those whose extracts come from plants show far lower cytotoxicity to mammal cells than endogenous fibroblasts and keratinocytes. This safety profile is mainly attributed to the fact that the NPs are coated with biological compounds from

Table 3 Comparative Performance of the Wound Healing Activity of ZnO NPs for in vivo Experiments, NR: No Reported

Type of Nanocomposite	Concentration	% Wound Closure	Reference
<i>Lawsonia inermis</i> extract and Carbopol 940 based gels	0.2%	After 1 week - 45%; After 2 weeks 76% and After 3 weeks - 93.6%	[34]
NPs based on <i>Acacia nilotica</i> extract	5 mg/mL	After 2 weeks - 98%	[35]
NPs based on roots of <i>Moringa oleifera</i> extract and loaded with ciprofloxacin and coated with polyethylene glycol	20 mg/mL	After 10 days ~ 98%	[38]
ZnO/Ag/Ag ₂ O nanocomposite based on seeds of <i>Salvia hispanica</i> L. extract	100 µg/mL	After 10 days - 96%	[39]

the extract (such as flavonoids, terpenoids) that stabilize and slow release of Zn²⁺ ions, which cause cytotoxicity. The in vivo models for wound healing, it has been consistently found in animal studies that green ZnO NPs cause more rapid reepithelialization of wounds (see Table 3), deposit more collagen sooner, and result in a better organized tissue environment when compared with their traditionally counterparts. However, there is a significant constraint to the transfer of this evidence from in vitro experiments to clinical practice. In this sense, for green ZnO NPs, research evidence from such robust randomized controlled trials (RCTs) comparing therapeutic superiority in human-wounded healing just does not exist. The current prospects of green synthesis in clinical terms are carried forward chiefly by its finely preclinical biocompatibility and effect. It is a very promising alternative, but one that has not yet been tested for human use on a practical basis.

Conclusions and Future Perspectives

As reported in the literature, revised ZnO-NPs synthesized in this way are not only safe but, like traditional antimicrobial treatments, can also be used as another kind of treatment in the biomedical field. However, reports revised here show that ZnO NPs reduce the time taken to close wounds, but the mechanism has not been fully elaborated and there are some signs of anti-inflammatory properties that stem from production anti-inflammatory cytokines reduction cytokines such as IL-6 or IL-1β.^{35,37} In contrast, the swallowing of free radicals may be related to wound regeneration;²⁴ in addition, this power has special implications for diabetic patients with chronic wounds. Looking ahead, the clinical translation of this technology is critically dependent on overcoming key challenges in manufacturing and scalability. This aspect has been slightly covered in ZnO NPs synthesized by chemical methodologies using animal models such as mice, rats, rabbits and donkeys. Nanoparticle properties vary significantly from batch-to-batch sudden changes in size, shape, and surface charge during synthesis cannot be dismissed as mere technical points but constitute the main barrier to standardization and regulatory approval. Therefore, future research must focus on providing well-objectified green synthesis protocols that are both robust and reproducible and can be utilized in large-scale manufacturing; this is a prerequisite for translating in vitro results suggesting exciting prospects for safe, satisfactory new therapies. The true signature of these therapies' profound therapeutic impact may come from a combination of catalysts. Based on not all but some examples of synergy between ZnO NPs and biological adjuvants, such as growth factors, or more advanced delivery platforms like hydrogels and even biodegradable scaffolds: all these approaches are multi-targeted combination therapies. The convergence of these fields points the way to smart wound dressings, which lack only passive barrier functions but already help activate healing processes themselves. Such approaches represent a new epoch in handling chronic wounds, an area of very pressing medical need, particularly for diabetics. Realizing this potential will require a new form of integrated cooperation. The results of this study show that the green-synthesized ZnO NPs can get you another step closer to human cures. Apart from its antimicrobial effects, it gives effective, high-quality wound care. For example, other such indications on display here are thorough control and modulation of inflammatory responses through cytokine regulation, the facilitation angiogenesis and regeneration, as well as tissue growth that also make present elements for our future therapies. Thus, the functional paradigm of ZnO NP dressing has proceeded from simple protection against infections to a kind complex, artificially designed bioactive living system, which promotes this situation.

Abbreviations

ZnO, Zinc oxide; NPs, Nanoparticles; Fe₃O₄, Iron oxide; CuO, Copper oxide; TiO₂, Titanium dioxide; CeO₂, Cerium dioxide; Ag NPs, Silver nanoparticles; Au NPs, Gold nanoparticles; GRAS, Generally-recognized-as-safe; ZnO NPs, ZnO nanoparticles; ROS, Reactive oxygen species; OH·, Hydroxyl radicals; H₂O₂, Hydrogen peroxide; DDAB, Didodecyltrimethylammonium bromide; *E. coli*, *Escherichia coli*; *P. Aeruginosa*, *Pseudomonas aeruginosa*; *S. aureus*, *Staphylococcus aureus*; *A. Platensis*, *Arthrospira platensis*; *B. pumilus*, *Bacillus pumilus*; *P. Chrysogenum*, *Penicillium chrysogenum*; KPC, *Klebsiella pneumoniae* Carbapenemase; ZOI, Inhibition zone; MIC, Minimum inhibitory concentration; MBC, Minimum bactericidal concentration; SD, Sprague–Dawley; *A. niger*, *Aspergillus niger*; qRT-PCR, Quantitative Reverse Transcription Polymerase Chain Reaction; SC, Subcutaneously; IP, Intraperitoneal; *C. officinalis*, *Calendula officinalis*; *C. spinosa*, *Caesalpinia spinosa*; MRSA, *S. aureus* methicillin-resistant; *E. faecium*, *Enterococcus faecium*; *S. Mutans*, *Streptococcus mutans*; *M. oleifera*, *Moringa oleifera*; CIP-PEG-ZnO-NPs, ZnO NPs loaded with ciprofloxacin and coated with polyethylene glycol; *E. faecalis*, *Enterococcus faecalis*; *K. pneumoniae*, *Klebsiella pneumoniae*; AR, Aldose reductase; AGE, Advanced glycation end products; *B. subtilis*, *Bacillus subtilis*; HUVECs, Human Umbilical Vein Endothelial Cells; MAPK/AKT, Mitogen-Activated Protein Kinase/AMP-activated protein kinase.; VEGF-A, vascular endothelial growth factor A; FGF-2, fibroblast growth factor 2; MMPs, matrix metalloproteinases; MAPK/ERK, Mitogen-Activated Protein Kinase/Extracellular signal-Regulated Kinase; PCL/ZnO, poly(ϵ -caprolactone)/zinc oxide.

Data Sharing Statement

The authors confirm that data supporting the findings of this study are available within the article.

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Author Contributions

The problem can be resolved by adding the following sentence (if it is accurate): All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agreed to be accountable for all aspects of the work.

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