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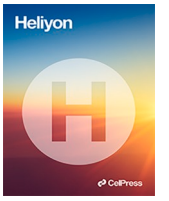

Review article

Recent advances in green synthesized nanoparticles for bactericidal and wound healing applications

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ABSTRACT

Nanotechnology has become an exciting area of research in diverse fields, such as: healthcare, food, agriculture, cosmetics, paints, lubricants, fuel additives and other fields. This review is a novel effort to update the practioneers about the most current developments in the widespread use of green synthesized nanoparticles in medicine. Biosynthesis is widely preferred among different modes of nanoparticle synthesis since they do not require toxic chemical usage and they are environment-friendly. In the green bioprocess, plant, algal, fungal and cyanobacterial extract solutions have been utilized as nucleation/capping agents to develop effective nanomaterials for advanced medical applications. Several metal salts, such as silver, zinc, titanium and other inorganic salts, were utilized to fabricate innovative nanoparticles for healthcare applications. Irrespective of the type of wound, infection in the wound area is a widespread problem. Microorganisms, the prime reason for wound complications, are gradually gaining resistance against the commonly used antimicrobial drugs. This necessitates the need to generate nanoparticles with efficient antimicrobial potential to keep the pathogenic microbes under control. These nanoparticles can be topically applied as an ointment and also be used by incorporating them into hydrogels, sponges or electrospun nanofibers. The main aim of this review is to highlight the recent advances in the Ag, ZnO and TiO_2 nanoparticles with possible wound healing applications, coupled with the bactericidal ability of a green synthesis process.

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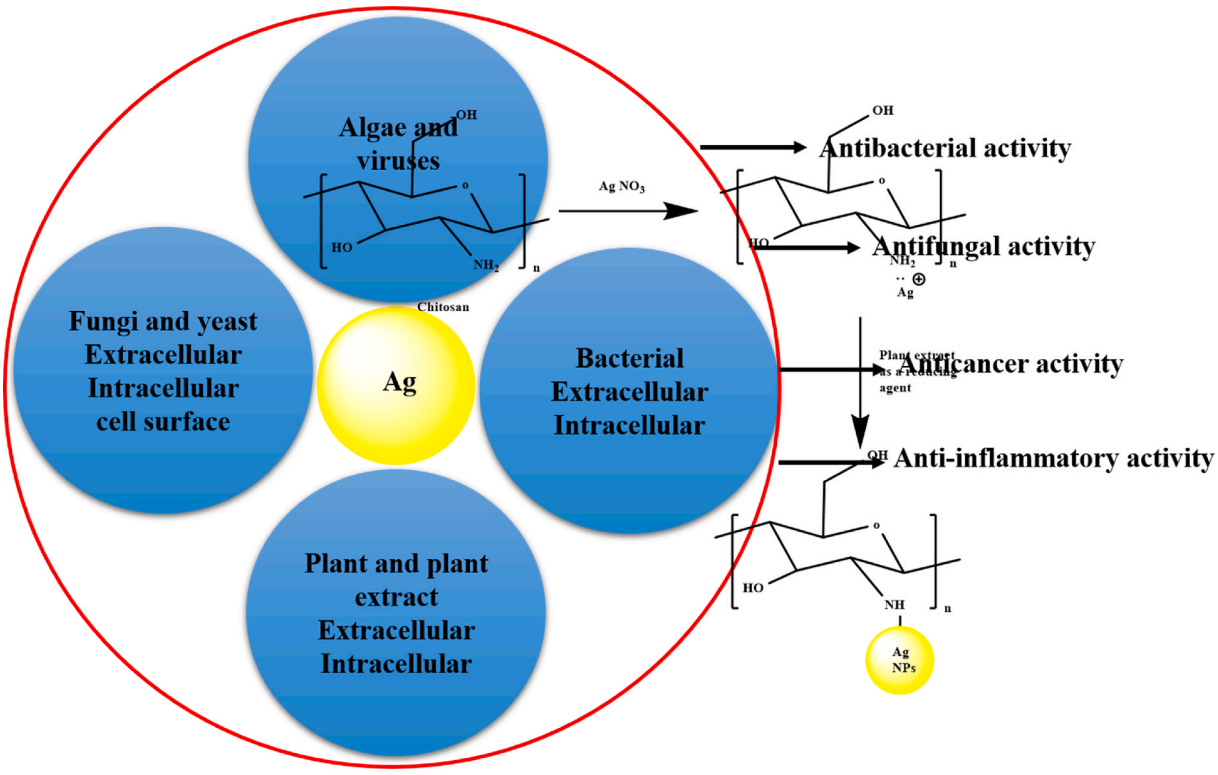
1. Introduction

The usage of nanomaterials, synthesized *via* nanotechnology, has become part of the routine life of humans in the 21st century. Since the advent of nanotechnology in the late 1950s, the realization of its enormous potential has been actualized through a rapid increase in its applications in almost all domains of life, and in particular, health-related and biomedical fields [1]. Nanotechnology comprises the yield and application of physical, chemistry and biological systems, with dimensions ranging from individual atoms or molecules to submicron levels [2,3]. Nanoparticles synthesized by physical and chemical routes, involve high voltage, high temperatures, expensive reagents, high-end apparatus and toxic solvents, which can leave hazardous residues which escalate environmental as well as human safety and health concerns [4]. Several synthesis techniques for the formulation of new nanomaterials have been developed in recent years. These include: the sol-gel route, solvothermal synthesis, hydrothermal technique, chemical vapour deposition (CVD) approach, electro-deposition, direct oxidation and green synthesis. However, the task of eradicating the harmful effects of many chemical processes has led to widespread support for green synthesis routes. There is an urgent need for such procedures by using biologically safe, ecologically-benign and economically accessible avenues, whilst minimizing or eliminating the higher costs and environmentally detrimental effects of the routinely employed synthetic approaches. Because green technology lessens and potentially prevents harmful environmental effects, it is immensely desirable for many real-world uses [5]. Phyto-nanotechnology, which uses extracts from plant parts (such as: roots, leaves, barks, fruits etc.) [6–9], bacteria, viruses, algae and fungi, etc. are gaining significant attention as a simple, rapid, high-yielding, easily scalable, eco-friendly and cost-effective avenues for synthesis of bioactive nanoparticles for diverse biomedical applications [1,10,11]. When reacting with metal oxides, the phytocompounds present in plants, serve as reducing or capping agents. Scheme 1 explains about the mechanism of capping agents found in plants for the preparation of Ag NPs. Therefore, plant-based methods significantly improve the nanoparticle synthesis protocol, yield, product bioactivity & functionality, simultaneously ensuring that the entire process is eco-friendly [12]. However, green synthesis has been instrumental in stabilizing bioactive nanoparticles, potentially minimizing their harmful actions in human cells, thereby enhancing their applicability in the management of human diseases [13].

Skin is the most significant body organ of human beings; it is most importantly, responsible for protecting the body against pathogenic microbes. Wound healing in the skin occurs commonly with minimal intervention or without it [14]. Generally, wound healing occurs over four sequential phases, *viz*: haemostasis, inflammatory, proliferative and maturation stages [15,16]. Several factors significantly, affect wound healing, including exuberant granulation, immoderate scar formation, defective contraction or enormous contraction [13]. Skin wounds are commonly caused due to skin diseases, burns, surgeries and traumas; this becomes a source of physical and physiological stress to the patient. Hence, there is a need to develop potent biomaterials to improve wound closure; moreover, the possibility to incorporate antimicrobial agents, should also be explored as infections seem to be the major cause of



Scheme 1. Phyto-constitutes acting as the capping agents during the synthesis of Ag NPs.

wound complications [17–20].

Both excessive use as well as misuse of antibiotics leads to antibiotic resistance in bacteria. Therefore, there is a need to develop new antimicrobial agents that are cost-effective, non-toxic to normal cells and proffer minimal resistance in bacteria; the novel green-synthesized agents also must have greater efficacy against antibiotic-resistant bacteria [21]. According to reports, skin wounds can be healed with inorganic (CuO, CoO, AgO, Ag, ZnO, TiO_2) nanoparticles, which are synthesized *via* the green processes [22–27]. Among them, silver nanoparticles (AgNPs) have gained significant popularity in the biomedical field, due to their versatile activity against a broad range of pathogenic bacteria and little or no toxicity towards mammalian cells [28]. In addition, nanosilver-based materials are beneficial prophylactic and therapeutic agents for the prevention of wound colonization by organisms. Therefore, nanosilver has been used for several applications, such as: dressings for wound healing, antimicrobial gel formulations, orthopedic applications, medical catheters, instruments, implants, contact lens coatings and 3D & 4D printing applications [28,29].

Zinc oxide (ZnO) is another useful inorganic material, which exhibits potential biocidal activity due to its photocatalytic effects [30, 31]. Nano ZnO and their derivative biomaterials, possess surfaces which generate free radicals when they are in contact with light. The active radicals thus generated have been demonstrated to inhibit micro-organisms. Moreover, they are non-toxic, biocompatible, inexpensive, eco-friendly and transparent materials and these properties make them ideal for advanced medical applications [32,33]. Their high surface area-to-volume ratio and their high adsorption properties make them to be effective adsorbents [13]. In addition to these desirable characteristics, green synthesis can improve the nano ZnO's functionality, photocatalytic activity and size. The biogenic nano ZnO has effective degradation, higher biocompatibity with human red blood cells, improved antioxidant capacity and superior antibacterial activity [34]. Therefore, the loading of green synthesized nanoparticles onto wound dressings, can be a potentially useful approach for the development of non-toxic and biocompatible wound dressings [35]. Thus, biosynthesis of inorganic metals and metal oxide nanoparticles from plant, fungi and bacterial extracts, is strongly suggested herein, as a possible mode of fabricating biocompatible nanoparticles with desirable antimicrobial activities [36]. This evaluation provides insights into green synthesized inorganic (Ag, ZnO, TiO_2) nanoparticles, their antimicrobial and wound healing applications and the underlying mechanisms thereof this review attempts to enlighten researchers and practioneers, of the current developments in the widespread use of green synthesized nanoparticles in the fields of medicine and biotechnology.

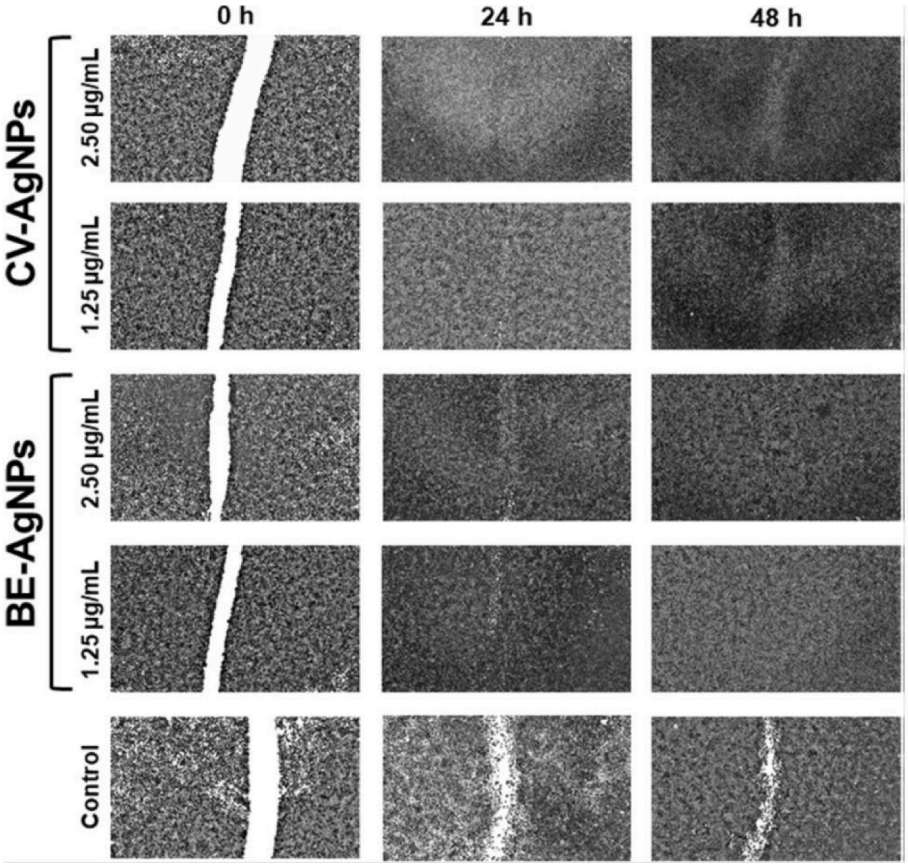


Fig. 1. In vitro wound healing efficacy of CV-AgNPs and BE-AgNPs at 2.50 g/mL and 1.25 g/mL in L929 cell line during 24 and 48 h (Adapted from O. Kaplan et al. 2021 [38]).

2. Green synthesized AgNPs

In the green process, bioactive AgNPs have been synthesized by using secondary metabolites, with active functional groups, such as: phytocomposites, alkaloids, flavonoids, saponins, steroids, tannins and other nutritional compounds which serve as nucleating and stabilizing agents [37]. Lately, AgNPs with *Coriolus versicolor* (CV-AgNPs) and *Boletus edulis* (BE-AgNPs), were synthesized by coupling AgNPs with extracts from *C. versicolor* and *B. edulis m*ushrooms *via* the microwave-assisted green synthesis technology [38]. The average diameter of CV-AgNPs and BE-AgNPs is ~86.0 ± 3.8 and ~87.7 ± 0.8 nm, respectively. These NPs have negative zeta potential on their surfaces, which improves their stability. These nanoparticles exhibit promising antimicrobial activity against gram-positive bacterial strains (*Staphylococcus aureus* and *Enterococcus faecalis)* and gram-negative bacterial strains (*Pseudomonas aeruginosa* and *Klebsiella pneumoniae*). Although both these nanoparticles exhibited significant inhibitory effects in fungal strains of *Candida utilis,* they were ineffective against *Candida albicans*. CV-AgNPs and BE-AgNPs demonstrated anti-proliferative activity in MCF-7, HUH-7 and HT- 29 cancer cell lines, in a dose and time-dependent manner. From the MTT cell proliferation assay results, BE-AgNPs were found to possess higher anti-proliferative activity than CV-AgNPs in all three cell lines at 48 h. CV-AgNPs and BE-AgNPs could cause the migration of L929 cell lines (murine fibroblast cells) and effectively heal wounds at low concentrations. When L292 cells were treated with 2.50 μg/mL and 1.25 μg/mL of CV-AgNPs and BE-AgNPs, migration of fibroblast cells was more significant than the control at 24 and 48 h. These nanoparticles have antibacterial, antifungal, anticancer and wound-healing properties (Fig. 1 [38]). AgNPs were green synthesized by using the non-heterocystous, filamentous *Cyanobacterium phormidium* sp. AgNPs improved the activity of chloramphenicol against methicillin-resistant *Staphylococcus aureus* (MRSA) strain. 20 μg/mL of AgNPs, when used alone and in combination with 0.5% chloramphenicol, yielded 1.3-fold and 1.86 fold (nearly double) antimicrobial activity than 0.5% chloramphenicol alone (positive control). The AgNPs showed topical effectiveness in different wound types, such as: incision, excision and burn. There was no bleeding, microbial contamination or pus formation in the NPs-treated wounds. Wound healing potency of AgNPs were confirmed by an increase in the rate of wound closure, hydroxyproline content and a reduction in the period of epithelialization. The escalation of inflammatory cytokines and enzymatic antioxidant levels, assisted the wound repairing effect of the as-prepared AgNPs. The antimicrobial AgNPs had wound-healing abilities that were helpful for advanced medical applications [39].

Aqueous extract of *Azadirachta indica* (*AI*) leaves, yielded fabricated spherical-shaped AI-AgNPs with 33 nm particle diameter [40]. Leaf extract of *AI* contained terpenoids, terpenes, phenolic compounds and flavonoids. Futhermore, When *AI* extract is added to $AgNO_3$, the colour of the solution changes from transparent to brown, indicating the formation of AIAgNPs. Toxicity study confirmed the normal egg-laying capacity and the eclosion of the F1 generation of *Drosophila* which were administered 100 mg/mL of AI-AgNPs. 500 mg/mL of the as-prepared NPs, affirmed the excellent radical scavenging effect in 2,2-diphenyl-1-picryhydrazil (DPPH) radical (65.17%) and {2,2′-Azinobis-(3-ethylbensothiazoline-6-sulfonic-acid)} (ABTS) radical (66.20%) scavenging assays. AI-AgNPs demonstrated antibacterial activity against *Bacillus cereus, Escherichia coli, Pseudomonas aeruginosa* and *Staphylococcus aureus* with a zone of inhibition of: 17.7, 18.7, 10.3 and 17.7 mm, respectively. The reason for higher bacterial suppression by AI-AgNPs than AI-extract, was the significant damage, caused to the bacterial cell wall, the disintegration of the cell membrane and the intercellular content outflow by AI-AgNPS [40].

Pluronic F-127 (PF127) is a less toxic, biocompatible and biodegradable synthetic block copolymer and it was functionalized with AI-AgNPs to prepare viscous and spreadable hydrogels ~~for~~ with antimicrobial activity [40]. AI-AgNPs-PF127 hydrogel did not cause undesirable effects, such as: skin dryness or redness. Pristine PF127 hydrogel, 0.3 and 1 mg AI-AgNPs-PF127, attained wound

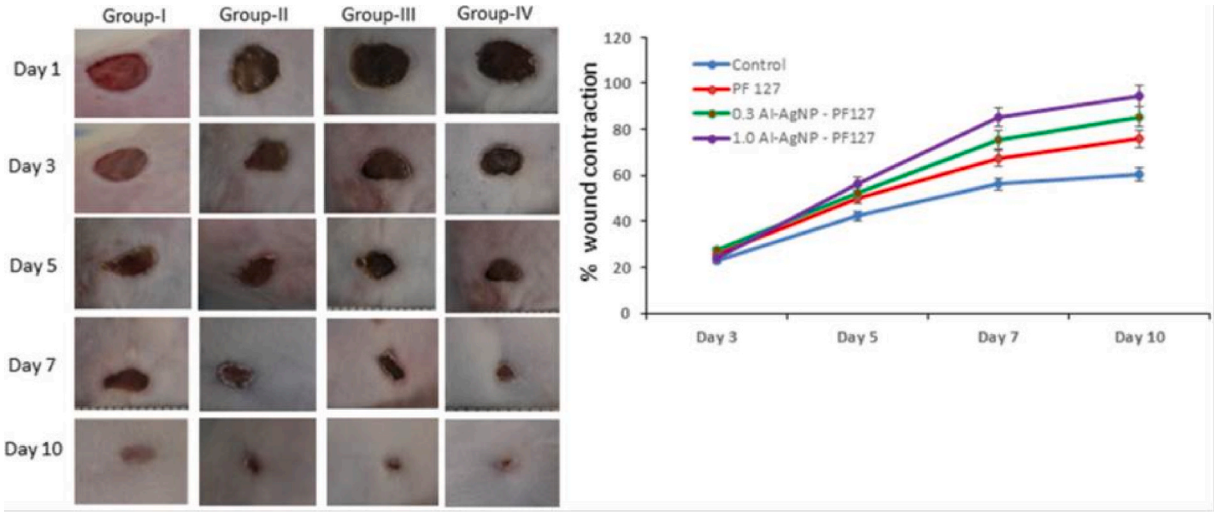


Fig. 2. Steps involved in wound healing in mice: (A) The image shows the effect on the control (group I), pure PF127 hydrogel (group II), 0.3 mg of AIAgNPsPF127 hydrogel (group III) and 1.0 mg of the hydrogel of AIAgNPsPF127 (group IV) and (B) percentage of wound contraction over time (Adapted from Chinnasamy et al., 2021 [40]).

contraction rates of: 75.77, 85.52 and 94.54 on the 10th day, respectively. AI-AgNPs-PF127 hydrogel increased the rate of wound contraction when applied topically on mice. Being less-toxic, it can be regarded as an eco-friendly delivery vehicle with the ability to heal wounds (Fig. 2A,B [40]).

Ethanolic bee propolis (pro) extract and chitosan (Csn), which had been extracted from the larvae of "black soldier fly (BSF), Hermetia illucens" was utilized for the fabrication of Ag-NPs. BSF-Csn was obtained with a final yield, deacetylation degree and molecular weight of: 1.56%, 91.3% and 88.600 Da, respectively. Pro, insect-derived Csn and Ag-NPs with Pro exhibited antimicrobial activity against bacteria *Staphylococcus aureus* and *Candida albicans,* but Csn/Pro/Ag-NPs composite, demonstrated superior antimicrobial activity. Csn/Pro/Ag-NPs composite produced inhibition zones of 26.3 mm (*S. aureus*) and 23.4 mm (*C. albicans*) for concentrations 35.0 and 45.0 μg/mL, respectively, which exceeded the activity of commercial antibiotics. Microbial contamination, bleeding or pus formation were not observed during the entire process of Csn/Pro/Ag-NPs composite-assisted wound healing, but remarkable signs of inflammation and infection were seen in the untreated wounds. In addition, Csn/Pro/Ag-NPs composite resulted in faster wound healing and significant wound size reduction within 14 days. The potent antimicrobial and wound healing action, exhibited by Csn/Pro/Ag-NPs supports their prospective suitability for disinfection, regeneration and skin protection applications [12].

Incorporating antibacterial AgNPs into cotton gauze (CG) will accelerate wound healing, but the leaching out of AgNPs from the cotton gauze fiber surface, is a significant hurdle. It leads to loss of antibacterial activity and other factors and side effects caused by AgNPs on the wound surface. In order to tackle this problem, Zwitterionic AgNPs were synthesized in alkaline condition with single step procedure by using poly(carboxybetaine-*co*-dopamine methacrylamide) copolymer-PCBDA and utilizing the mussel-inspired catechol/amino chemistry; the Zwitterionic PCBDA@AgNPs were immobilized onto cotton gauze (with amino-modified) through covalent and non-covalent interactions. The as-synthesized PCBDA@AgNPs- CG did show great antibacterial activity or excellent bacterial, anti-adhesive properties (owing to the ultra-low fouling character of carboxybetaine moieties), however, they inhibited biofilm formation. The rates of bacterial anti-adhesion for PCBDA-CG against *E. coli, S. aureus* and *MRSA* suspensions, are: 97.91%, 99.22% and 98.38%, respectively. Scanning electron microscopy results revealed a contact-killing activity against bacterial strains by the immobilized AgNPs. Besides, it had good cytocompatibility (L929 fibroblast cell viability was similar to the pristine CG) and hemocompatibility (haemolysis rate is lower than the pristine CG), and therefore, would be beneficial in wound dressing [41].

In-vivo wound healing assay, demonstrated that PCBDA@AgNPs-CG dressing had the potential to inhibit wound infection, decrease inflammation and support wound repair effectively [41]. The antimicrobial activity of iturin-AgNPs at lower content of AgNPs was considerably significant than that of the commercial AgNPs. Chitosan (CS)-based composite sponge dressing–loaded iturin-AgNPs was synthesized in order to study the antibacterial activity *in-vitro* and wound healing properties *in-vivo*. The CS-AgNPs prepared, possessed high porosity, water absorption and retention. The loaded iturin-AgNPs did not influence the three-dimensional structure of the porous packing chitosan dressing structure. The antibacterial activity of the CS prepared dressing, against *E. coli* ATCC25922 (Gram-negative bacteria) and *S. aureus* ATCC29213 (Gram-positive bacteria), was significantly elevated by the incorporation of iturin-AgNPs. Antibacterial activity against *E. coli* was higher than *S. aureus*. The inhibition of bacterial infection, the promotion of wound healing and the quality of the synthesized CS dressing were more effective than the *in-vivo* used commercial wound dressings, loaded with AgNPs. Mice wounds, treated with CS-AgNPs and AgNPs-gauze, healed into flat skin completely with new dorsal hair within 16 days. Wound healing was promoted due to the enhancement of re-epithelialization and collagen formation, with augmentation of antimicrobial activity. The prepared dressing material was non-toxic to any organ of mice and was deemed to be suitable for medical application. This study proposed an efficient means to improve the antibacterial activity of the synthesized chitosan dressing at low AgNPs toxicity [42].

AgNPs were bio-fabricated with leaf extract of *Parkia biglandulosa* (commonly referred to, as the badminton ball tree). Leaf extract from *P. biglandulosa* (Pb) serves as a reducing and a capping agent for Ag^{+} reduction. As observed from the transmission electron microscopy results, the AgNPs fabricated by using *P. biglandulosa* leaf extract had an average diameter of ~15 nm and were spherical. AgNPs were also chemically synthesized (cAgNPs) with a reducing agent (sodium borohydride) and were used for comparison with biosynthesized Pb-AgNPs. Pb-AgNPs exhibited the most antibacterial activity at a concentration of 0.02 M with ~12 mm of the zone of inhibition (ZIC) against *Bacillus cereus.* In contrast, *cAgNPs* exhibited mild antibacterial activity with 6.5 mm of ZIC. Alamar blue reduction assay confirmed the biocompatibility of PbAgNPs (99.82%) with human skin fibroblast cells and was more significant than the native nanoparticles (98.29%). The biosynthesis approach was single-step, rapid, facile as well as safe, and served as an effective alternative to the conventional physical and chemical methods [25]. *Echinophora platyloba* DC extract was used to prepare AgNPs and an eco-friendly method was employed to conjugate Chloroxine (COX), an antibacterial drug with AgNPs, forming COX-AgNPs. COX changed the shape of the AgNPs into flower-like. The biofabricated AgNPs synthesized in this study, were relatively smaller (19.77 ± 1.06 nm) than other AgNPs found in the existing literature. The as-synthesized AgNPs, possessed remarkable antibacterial and antifungal properties against several microorganisms. AgNPs, Chloroxine, COX-AgNPs and *Echinophora platyloba* DC extracts, exhibited antibacterial activity against bacteria *E. coli and S. aureus.* However, the efficiency of COX-AgNPs was higher than the rest, since it inhibited 100% bacterial growth at ≥ 0.25 μg/mL of concentration. *S. aureus* was more sensitive than *E. coli* in all of these cases. AgNPs, Chloroxine, COX-AgNPs and *Echinophora platyloba* DC extracts exhibited antifungal activity against *Aspergillus niger, Candida albicans* and *Trichophyton rubrumare* more effectively. Chloroxine and COX-AgNPs inhibited 100% fungal growth at a concentration of ≥0.125 μg/mL. The conjugation of nanoparticles with antibiotics and antibacterial drugs augmented biological activity w.r.t. to the free antibacterial and antibiotic molecules. Two ointments were taken to study wound healing ability, *viz*: ointment 1: Calendula flower oil-Vaseline and ointment 2: Calendula flower oil-Vaseline having COX-AgNPs. Ointments 1 and 2 exhibited wound contraction percentages of $95.60 \pm 0.33\%$ and $99.50 \pm 0.28\%$, respectively, on the 20th day. COX-AgNPs acts as a suitable platelet activator. The efficacy of the AgNPs was improved by conjugating the nanoparticles with chloroxine, whereby, COX-AgNPs had the potential to

Table 1
Mechanism of wound healing and bactericidal activities of different metal oxide NPs.

Plant materials	Nanoparticle	Wound healing mechanism	Bactericidal mechanism
Citrus lemon	Ag-NP	Fibroblast proliferation and collagenation, angiogenesis [45]	–
-	Ag-NP + Chitosan + propolis extract	Wound size reduction may be attributed to the antibacterial and anti-inflammatory properties of components. Prevention of wound microbial contamination, enabled the restoration of tissue integrity and supported the healing of the injury [47]	Distrups the cell membrane leading to cell lysis, release of internal cell contents and bacterial cell death [12].
Ilex paraguariensis	Electrospun polyacrylic acid and polyallylamine hydrochloride loaded ZnONP	–	Damages to the cell membrane, internalization of nanoparticles metal ions and ROS (Reactive oxygen species) affect the cell metabolism [48,49].
Aloe barbadensis	ZnONP + Silica gel	Improved the platelet activation, apoptosis, tissue necrosis, angiogenesis, re-epithelialization and stem cell activation occurred during wound repair [13]	Accumulation of ZnO NPs and the production of ROS [13].
Azadirachta indica	AgNP + PF127 hydrogel	Remodeling and re-epithelialization [50].	Cell membrane damage, shrinking of cytoplasm and outflow of cellular contents [40].
Lawsonia inermis L.	AgNP + Talc + Chitosan	Modulation in gene expression, induction of anti-inflammatory M2 phenotype, CD206, bFGF, IL-10 and collagen1A causing fibroblast migration [44].	Chitosan interacts with cell membranes, increasing the membrane permeability and killing the bacteria [51].
Parkia biglandulosa	AgNP	Supported cell proliferation [25].	Destabilization of the outer membrane, leading to the rupture of the plasma membrane, induction of alterations in the physical and chemical properties of cell wall and membrane, the reaction of AgNPs with sulphur containing proteins in the membrane or phosphorous-containing DNA, the release of silver ions destroyed the bacteria [25].
Boletus edulis (Mushroom)	AgNP	Migration of fibroblasts [38].	ROS release, which interrupted the electron transport chain, disrupted the cell integrity by reacting with phosphorus and sulfhydryl groups in the cell wall [52].
Coriolus versicolor (Mushroom)	AgNP	Migration of fibroblasts [38].	ROS release, which interrupted the electron transport chain, disrupted the cell integrity by reacting with phosphorus and sulfhydryl groups in the cell wall [52].
-	TiO_2 + heparin-polyvinylalcohol (H-PVA)	TiO_2 attacks bacteria's cell walls, causing an outflow of contents and the death of bacteria [53].	Fibroblast cell migration, epithelial cell development and blood flow restoration by training new blood vessels [27].
Echinophora platyloba DC	AgNP + Chloroxine	Improved re-epithelization, reduction of wound inflammation and modulated fibrogenic cytokines [43].	Penetrates the bacterial cell, interacts with and damages the sulphur and phosphorous-containing biomolecules, e.g., DNA [43].
Scutellaria barbata	AgNP	Induction of fibrobalast cell proliferation, differentiation and migration [46].	Silver cations disturbed the bacterial cell by binding to the thiol group of bacterial protein and led to bacterial death [54].
-	AgNP + poly (carboxybetaine-*co*-dopamine methacrylamide) (PCBDA) copolymer	Deposition of collagen and re-epithelization [41].	Contact-killing damages the cell membrane and kills the bacteria [41].
Prosopis cineraria	ZnPC	Collagen formation and re- epithelialization, neovascularization, increased fibroblast cell count. In addition, wound healing is supported by the synergetic effects of the anti-inflammatory phenolic compounds of *Prosopis cineraria* and ZnO [55].	–
Prosopis cineraria	FePC	Collagenation, re-epithelialization and keratinization. Wound healing is supported by the synergetic effect of the anti-inflammatory effect of phenolic compounds of *Prosopis cineraria* and Fe_3O_4 [55].	–
Phormidium sp. (cyanobacterium)	AgNP	Re-epithelialization and modulation of cytokines. Wound repairing was supported by an escalation of enzymatic antioxidants and attenuation of inflammatory cytokines [39].	Silver ions bind to DNA and inhibit bacterial enzymes. AgNPs prompt the damage of the cell walls and cytoplasmic membrane damage [56].
	AgNP + iturin + chitosan	Collagenation and re-epithelialization [42]	–

accelerate wound repair, coupled with its antimicrobial activity [43].

AgNPs were fabricated by the green method on the external talc layer surface in an aqueous solution, by utilizing a *Lawsonia Inermis* L. extract. It acted as both a reducing and stabilizing agent in this process. The negative layer of talc might act as a template and attract chitosan (cations) from the solution in order to form ~~a~~ layered hybrid structure Ag/Tlc/Csn nanocomposites (NCs) and Si–*O*–Ag bonds from its inorganic phase. At higher concentrations, Ag/Tlc/Csn is more cytotoxic than talc. The toxicity of the biologically-synthesized NCs was lower than the chemically synthesized NCs. Ag/Tlc and Ag/Tlc/Csn NCs exhibited better antioxidant properties than talc. The antibacterial activity of Ag/Tlc against *Staphylococcus aureus*, *Pseudomonas aeruginosa, Streptococcus pyogenes* and *Escherichia coli* was better than that of talc. However, there was no significant difference between Ag/Tlc and Ag/Tlc/Csn NCs. Ointments improved wound healing by influencing the anti-inflammatory M2 phenotype and bFGF, IL-10, collagen1A and CD206 production, which causes the migration of fibroblast and M2 macrophage that influenced wound closure. The ointment prepared from talc, which had been loaded

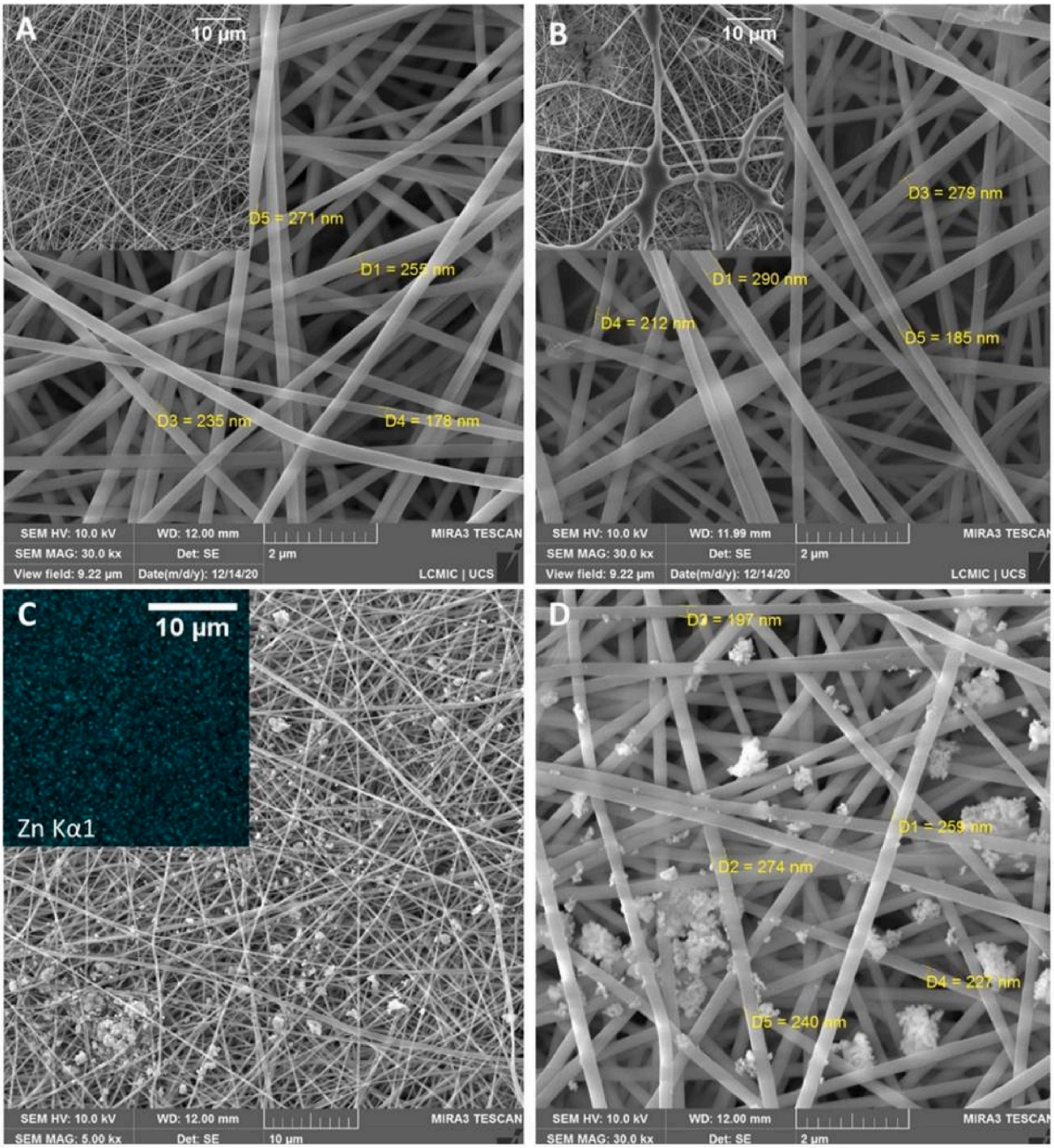


Fig. 3. Photomicrographs of (A) a thermally treated PAA/PAH fibre mat, (B) a thermally untreated PAA/PAH fibre, (C) a PAA/PAH fibre containing ZnONPs and elemental zinc EDS analysis, and (D) amplification of PAA/PAH fibres including ZnONPs (Adapted from Bandeira et al., 2021 [26]).

with both AgNPs and Csn, decreased the tissue bacteria colonization and its inflammation. Hence, Ag/Tlc/Csn can effectively treat infected wounds [44]. AgNPs were biosynthesized by utilizing $AgNO_3$ and aqueous *Citrus lemon* leaf extract under *in-vitro* conditions. Ag nanoparticles displayed excellent antioxidant activities against DPPH. The as-prepared AgNPs are non-toxic to human normal cell lines (HUVEC). When Ag-NP ointment was applied over a cutaneous wound, it increased the number of vessels, fibroblasts, fibrocytes and their ratio. It also increased the quantity of hexosamine and hexuronic acid and the wound contracture. At the same time, the number of the total cells, lymphocytes, neutrophils and the wound area, decreased. Keeping in view the antibacterial property and non-toxicity of Ag-NPs ointment containing Citrus lemon leaves, they may be used as a highly effective drug for cutaneous wound treatment in humans [45].

Scutellaria barbata is a herb, prescribed in Chinese medicine, to cure infections and inflammation and it is also a detoxifying agent. AgNPs with the aqueous extract of *Scutellaria barbata*, were synthesized. The as-prepared nanomaterials were coated with cotton fabric to test their efficacy against microbes and to prove their application. Transmission electron microscopy (TEM), Atomic force microscopy (AFM), Fourier Transform Infrared (FTIR) and X-ray diffraction (XRD) studies, confirmed that the synthesized Sb-AgNPs had ideal parameters, such as: shape and size for them to be used as a drug. 60% of the biofilm formation was inhibited by Sb-AgNs and their ability to, effectively, inhibit the biofilm formation in both sensitive and resistant bacterial strains, was confirmed by the XTT reduction assay. In antimicrobial sensitivity tests, synthesized Sb-AgNPs and cotton-coated Sb-AgNPs, exhibited effective antimicrobial activity against fungal, gram-positive and negative strains. The least and highest MIC for Sb–AgNP were reported with *Klebsiella pneumoniae* (2.2 mL) and *Pseudomonas aeruginosa* (3.1 mL), respectively. No bacterial growth was observed in the cotton-coated Sb-AgNPs and the zone of inhibition was also significantly higher than the Sb-AgNPs. MTT assay with L929 fibroblast cells, proved non-toxic, even at the highest 15 mg/mL concentration. Wound scratch assay confirmed the wound healing ability of the Sb-AgNPs by inducing the proliferation, differentiation and migration of fibroblast cells. Cotton-coated Sb-AgNPs were also non-cytotoxic and they had the potential to heal wounds. The synthesized AgNPs with extract of *Scutellaria barbata* can be a wound-healing drug [46]. The wound healing mechanism of different green synthesized NP's were given Table 1.

3. Green synthesized ZnO NPs

A novel antimicrobial material was fabricated by loading green synthesized zinc oxide nanoparticles (ZnO NPs) in an electronspun polyacrylic acid (PAA) and polyallylamine hydrochloride (PAH) polymeric fibers for wound healing application [26]. ZnO NPs exhibited high antimicrobial activity, covering a large variety of microorganisms that comprise, drug-resistant bacteria and are less cytotoxic against L929 fibroblast cells of the mouse. ZnO NPs were green-synthesized from *Ilex paraguariensis* leaf extract. The antimicrobial activity of ZnO NPs against *S. aureus* (Gram-positive) was higher than the *E. coli* (Gram-negative) and the minimum inhibitory concentration (MIC) for *S. aureus* was 35 g mL^{-1}, however, *E. coli* exhibited higher resistance, even at 100 g mL^{-1} concentration with a 70% viability. The resazurin viability assay demonstrated that PAA/PAH/ZnONPs have the potential to inhibit both bacterial strains, since no dye reduction was observed. Besides the antimicrobial property of ZnO NPs, they also mimic the morphology (extracellular matrix) of the skin tissue, thereby, assisting in cell attachment, growth and better wound healing. Despite the consistent dispersion of ZnO, particle agglomerates of varying sizes were observed and this drawback (particle agglomeration) needs to be addressed for successful usage in the future (Fig. 3a–d [26]). *Prosopis cineraria* (PC) leaf extract was used to biofabricate zinc oxide (ZnPC) and iron oxide (FePC) NPs, by the co-precipitation method.

The anti-inflammatory activity of the as-prepared NPs was confirmed through the proteinase inhibition and albumin denaturation methods. By applying ZnPC and FePC regularly, the healing process had been hastened because of their anti-inflammatory effect, through reduction of proinflammatory cytokine levels. The 1,1-diphenyl-2-picrylhydrazyl (DPPH) method, confirmed the antioxidant properties and the free radical inhibiting efficiency of ZnPC and FePC in a concentration-dependent manner. The antioxidant effect of the biofabricated NPs, contributed to angiogenesis, collagenation, fibroblast proliferation, granulation tissue formation and maturation. ZnPC and FePC ointments were exposed to the dermis, at 0.10 and 0.16 $\mu g/cm^2$/hr of skin permeation rates for the zinc and iron contents that were observed, which entailed a very low penetration of the metal ions and non-toxicity. The wound-healing effect of the nanoparticles prepared, was supported by hydroxyproline content, enzymatic antioxidant profile and inflammatory markers. Topical application of ZnPC ointment demonstrated a quicker tissue injury healing than the application of FePC ointment. Swift wound healing property of the as-prepared nanoparticles, might be attributed to the synergistic effect of polyphenolic compounds of the PC leaves and metal oxides. This study proved the possibility of utilizing ZnPC and FePC-based nano-ointment for dermal total thickness wound healing topical application. The ZnPC-treated wound healed completely on 15th day when FePC showed a wound closure rate of 95.47 $\pm$ 1.25% in Wistar rats. Thus, the as-prepared ZnPC and FePC NPs can, effectively, be involved in wound healing [55].

ZnO NPs fabricated and stabilized with leaf extract of *Aloe barbadensis* act as an effective absorbent material for removing two carcinogenic dyes, *viz*: Malachite green (cationic azo dye) and Congo red (anionic azo dye). At the maximum quantity of 70 mg/mL of as-prepared ZnO NPs, an adsorption efficiency of 90.7% was obtained within 90 min for the Malachite green dye and 92.30% of adsorption efficiency was reported for the Congo red dye at 80 mg/mL maximum concentration of ZnO-NPs within 120 min. The study of the different parameters, such as: the amount of adsorbent, time and pH, through the batch process, showed that ZnO-NPs can be used effectively, as an adsorbent for both the azo dyes. The as-synthesized ZnO-NPs exhibited a potent antibacterial activity against four bacterial strains, viz., of *Bacillus subtilis*, *Bacillus licheniformis* (Gram-positive bacteria), *Escherichia coli* and *Klebsiella pneumoniae* (Gram-negative bacteria) and antifungal activity against two fungal strains, of *Candida albicans* and *Aspergillus niger*. The antimicrobial efficiency increases due to the accumulation of the as-prepared ZnO-NPs and the reactive oxygen species (ROS) production. ZnO-NP/silica gel dressing (ZnO-NP/SG-30 ppm), significantly reduced mouse skin wounds within 11 days of the study when compared to the ZnO-NP/SG-15 ppm and the control sample of ZnO-NPs. ZnO-NP/SG-30 ppm demonstrated a recovering percentage of 95%, which is

considerably, much more significant than the control sample (61%). The dressing also enhanced apoptosis, bacterial clearance, re-epithelialization and stem cell activation, during the healing process of wounds in mice. It showed a controlled degradation, blood clotting and swelling than the control samples. Wound healing and antimicrobial properties of the as-prepared dressings on the skin's surface, enhanced its practical application [13]. The process of wound healing, comprising four stages of: hemostasis, inflammation, proliferation and remodeling, is represented in Fig. 4(a,b) [57].

ZnO NPs were green synthesized with *Aloe Vera* extract and were surface-modified with polydopamine (PDA) by a one-step and straight approaches [58]. The as-prepared ZnO nanoparticles had rod-shaped morphology with a large surface area for bacterial contact and a uniform PDA layer (average thickness of 23 ± 2 nm). The PDA did not have any significant effect on the morphology of nanomaterials. PDA@ZnO NPs can effectively create blood clots due to their negative surface charge. In addition, BCI was halved after the surface modification of ZnO. PDA@ZnO NPs were non-toxic to human cells and they also promoted cell survival more than the ZnO NPs. PDA@ZnO NPs can thus, be employed for wound repairing applications [58]. The wound healing process, which includes four stages, *viz*: hemostasis, inflammation, proliferation and remodeling in general [57].

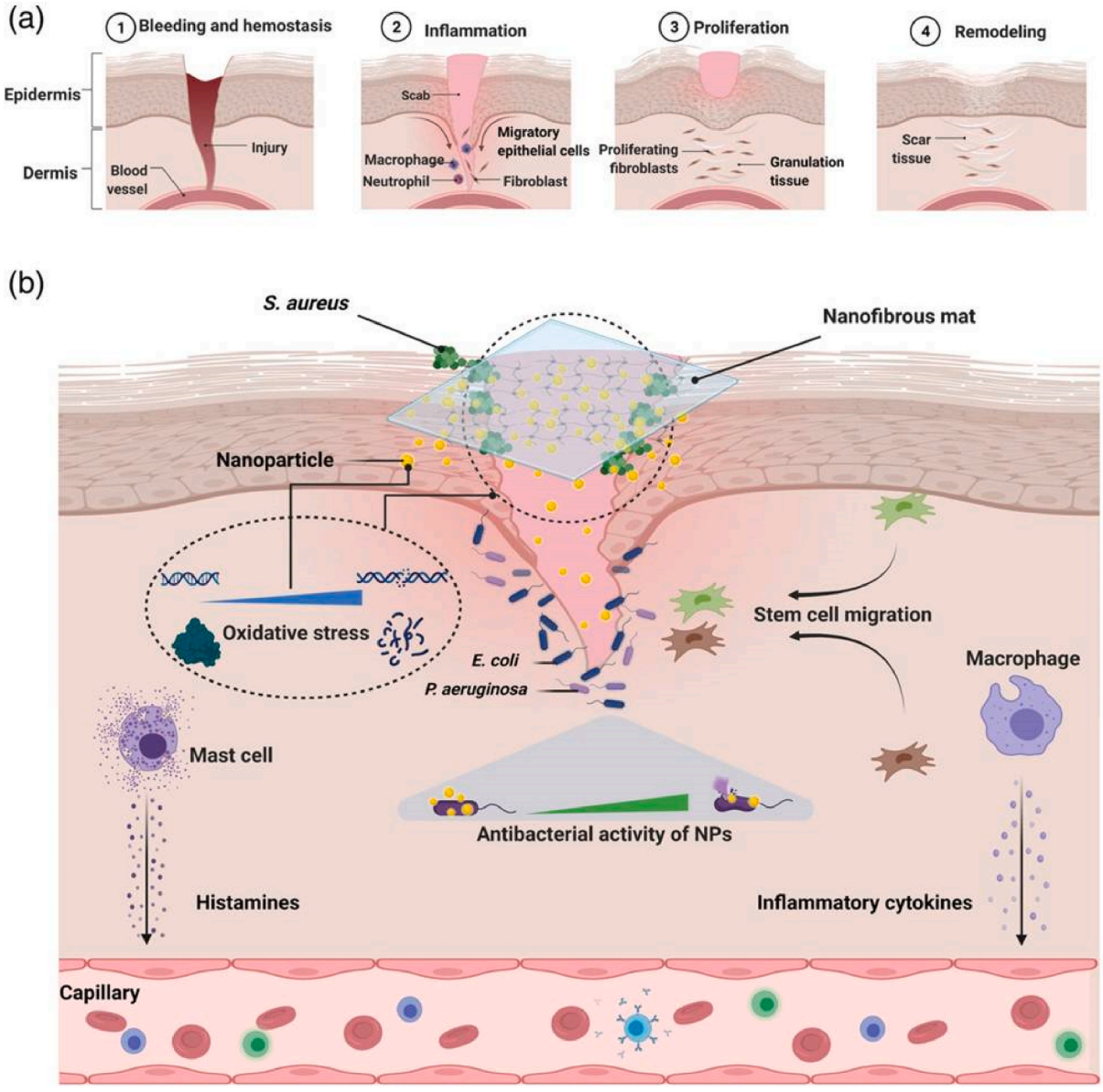


Fig. 4. Schematic illustration of (a) Wound healing stages diagram. (b) Schematic representation of antibacterial nanofibrous composite mats that activate wound healing cell migration (Adapted from Bagheri et al. 2021 [57]).

4. Green synthesized TiO_2 NPs

A highly porous bandage of heparin-polyvinylalcohol hydrogel incorporated with TiO_2 (H-PVA@TiO_2) was fabricated by the freeze-drying route to treat burn injury. The dispersal of TiO_2 nanoparticles was uniform in the H-PVA hydrogel and the resultant bandage was flexible. The elongation and tensile modulus of H-PVA @ TiO_2 were greater than that of heparin, PVA and the H-PVA hydrogel, but its mechanical strength was lower. The interaction between H-PVA hydrogel and TiO_2, reduced the degradation rate of the composite bands. The TiO_2 NPs with different sizes, surface charges and morphologies, led to a higher swelling capacity of the H-PVA@TiO_2 NPs than of the pure H-PVA hydrogel. The as-prepared H-PVA@TiO_2 nanocomposite, exhibited an excellent antimicrobial efficiency against *Staphylococcus aureus* (Gram-positive) and *Escherichia coli* (Gram-negative) than the H-PVA hydrogel. TiO_2 when present, may attack the cell wall of bacteria and cause leakage of the cell contents, leading to the death of bacteria. The H-PVA@ TiO_2 nanocomposite bandage also demonstrated ~~the~~ viability of ~82%, ~86% and ~96% after 1, 4 and 7 days, respectively; its good biocompatibility with human dermal fibroblast cells (HFFF2)~~,~~ makes it suitable for biological applications. Improved wound healing was observed *in-vivo*, in experiments with Kunming mice. The wound area decreased significantly on the 7th day and the tissue loss associated with its removal, was achieved on the 14th day, resulting in a 95% of damaged depth fragments for H-PVA@TiO_2, whereas the wound did not heal at the end of 14th day in the control and the H-PVA-treated mice. High biocompatibility and anticoagulant properties of TiO_2 contribute to the improved wound healing ability of H-PVA@TiO_2 bandages. Synergistic (intense bactericidal activity, wound healing ability, cell proliferation, excellent hydrophilic design and biocompatibility) effects of H-PVA@TiO_2 nanocomposite make it a potential candidate for burn injury treatment (Fig. 5 [27]) and as well as the antibacterial mechanism of green

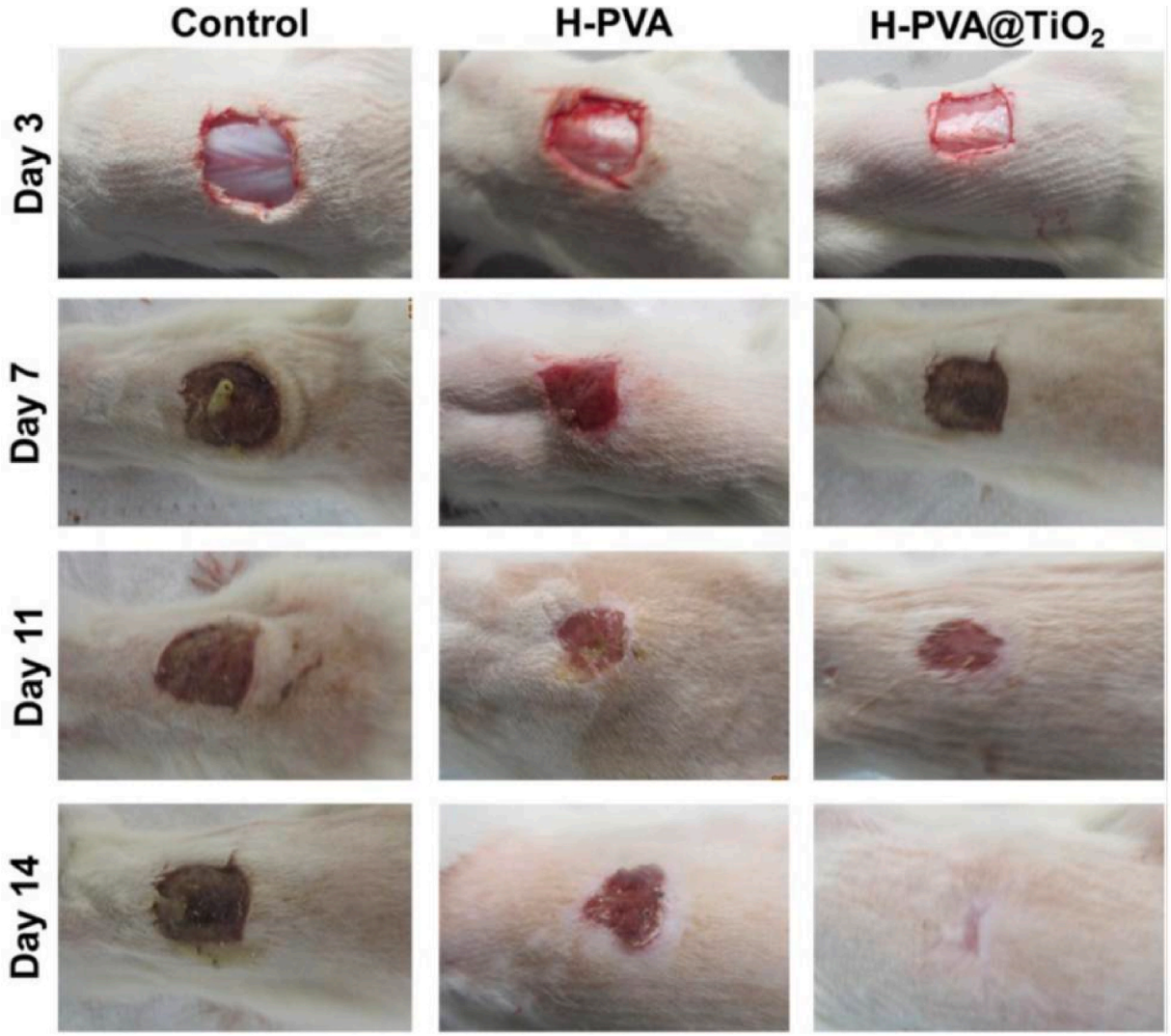


Fig. 5. On separate treatment days, wound pictures of all treated groups, including control, H-PVA, and H-PVA@TiO2 groups, were taken (3, 7, 11, and 14). In compared to the H-PVA group, H-PVA@TiO2 has pronounced healing effects (Adapted from Li et al. 2021 [27]).

synthesized MgO NP's were depicted in Fig. 6 [8]. Beyond medical applications, nanomaterials are also widely used in agriculture, [59]. In recent years, environmental nanotechnology has made enormous strides towards environmental conservation. Environmental applications in the field of water/air remediation, rank among the most promising contributions. The distinctive characteristics of NPs, such as: their nanoscale size, high flexibility for *in-situ* and *ex-situ* procedures, resistance to eco-factors and huge surface area-to-volume ratio, make them good candidates for various environmental applications. In order to remove eco-contaminants, many types of nanomaterials and nanotools are used. Due to their numerous qualities, including: ideal electronic band structure, high quantum efficiency, stability and chemical inertness, TiO_2 NPs are being used more frequently than other materials, as a remediating agents to clean water, purify the air and sanitise soil (see Fig. 7(a–c), [59–61].

5. Conclusion and future perspectives

The use of nanotechnology is quickly developing and leading to a plethora of new applications in the upcoming generation of the medical industry. It has undergone substantial research for drug delivery, cancer treatment, radiosensitizers, bioimaging, and wound healing. Attention is also being paid to the use of NPs in various other fields, including wastewater management, biosensors, and oil recovery. The potential for employing nanoparticles' absorption properties to clean up oil spills in the ocean, absorb greenhouse gases like carbon dioxide, and absorb microplastics from the air and water should all be investigated. They have lately become a key topic of research due to their small size and high surface area to mass ratio, which helps to overcome various constraints of conventional treatments.

Although physical and chemical methods are employed to synthesis nanoparticles, green synthesis/biosynthesis of nanoparticles is gaining attention because of the growing environmental concerns of conventionally employed synthetic methods. Unlike the conventional methods, green synthesis is not costly, it is not time-consuming, it does not require complex reaction conditions and it employs simple routes. This method combines the antimicrobial effect of the plant extract with NPs and enhances their efficacy, leading to their successful applications. Moreover, a given metal (Zn/Cu/Ti/Fe) can combine with several secondary metabolites during green synthesis and lead to formation of chemically diverse NP formulations (depending on the microbe/plant species used for synthesis), with a wide array of biological actions. It is cost-effective, but using an extract of fungi or bacteria has the property of introducing toxic chemicals acquired by them. More research is required to ensure the bio-safety of the generated nanoparticles.

Most NPs also prove to be biocompatible with human fibroblast cells. Both acute and chronic wounds are commonly spotted in human beings and without stringent treatment, it might even lead to death. Bacterial and fungal infections in the wound area, delay and further complicate the wound healing process. The incorporation of NPs with antimicrobial properties, improves wound repairing. Different nanoparticles exhibit antibacterial properties through different mechanisms. AgNPs, with their inherent antimicrobial property, occupy an important area in medical research, but their high cost may make their accessibility difficult. The possibility of using other metals must be explored in order to find the hidden potentials. Nanoparticles with high antimicrobial properties against common pathogenic microbes, high efficiency of wound healing and non-cytocompatible, will improve their chances of practical medical application.

Future in focus, development and implementation of nano-based antiviral strategies Attracting the attention of a wide group of

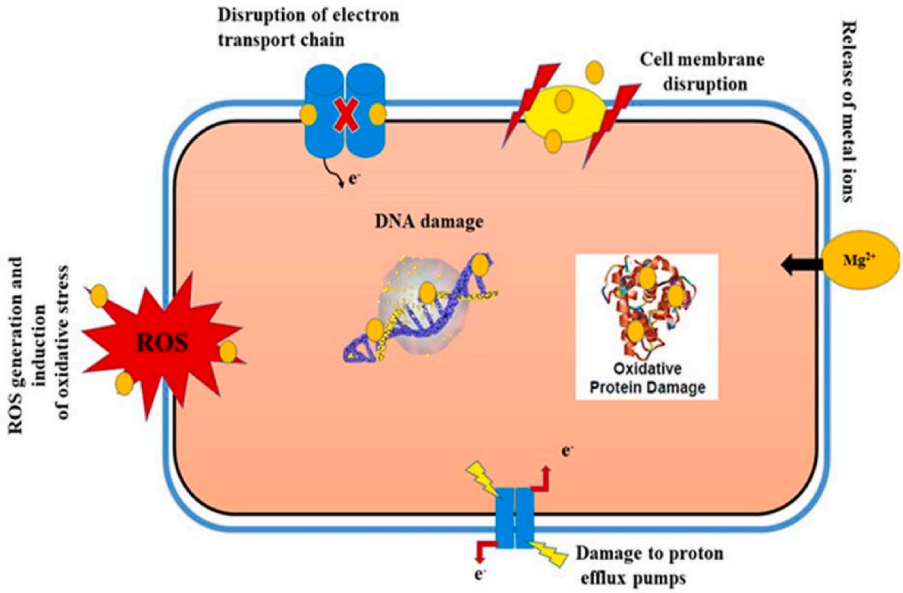


Fig. 6. The mechanism of MgO NPs is depicted in this diagram. MgO's antibacterial efficacy is achieved through a variety of mechanisms, including: (a) direct interaction with bacteria's cell wall, (b) the generation of reactive oxygen species (ROS), and (c) the initiation of intracellular defects, such as macromolecular interactions, such as proteins and DNA (Adapted from Karthikeyan et al., 2021 [8]).

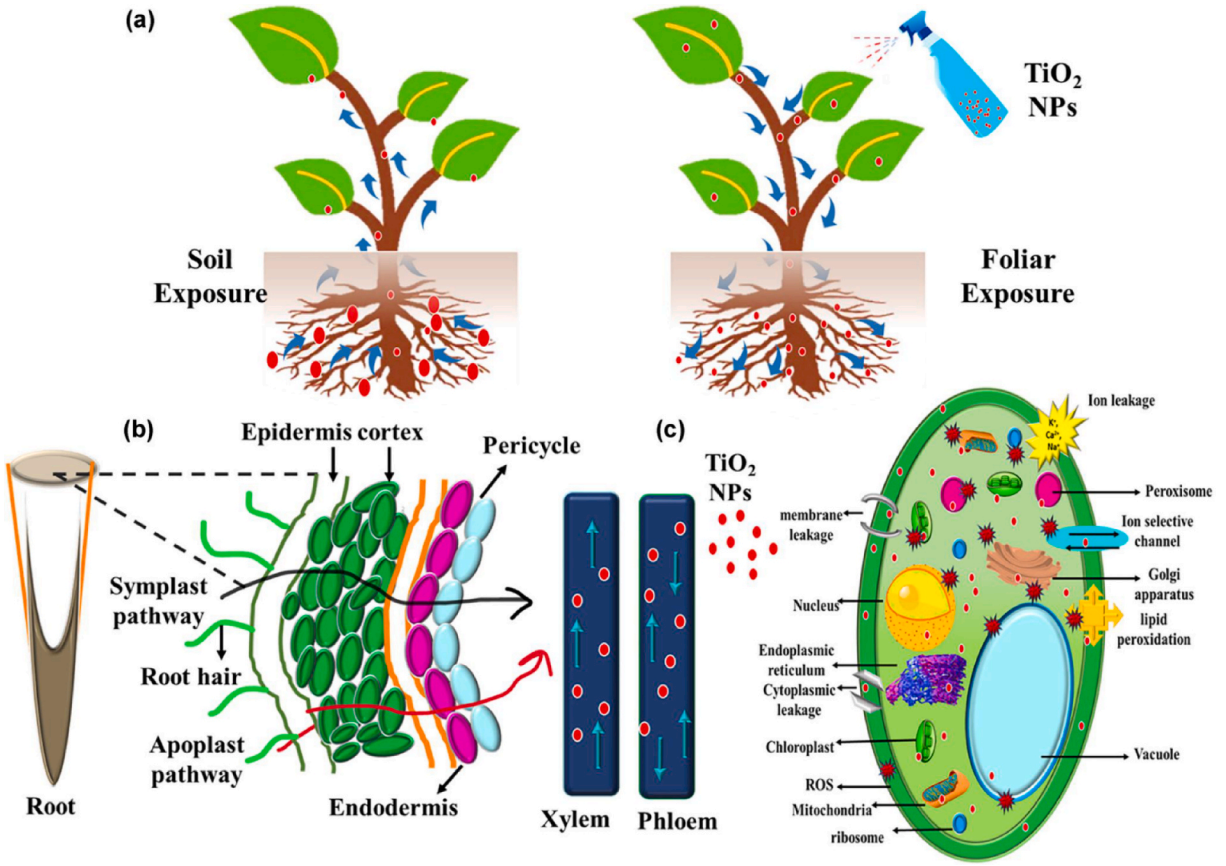


Fig. 7. Crop plants and TiO_2 NPs interaction, TiO_2 nanoparticles are exposed to crops in the following ways: (a) through soil medium and foliar spray; (b) through the apoplast and symplast routes, which allow them to penetrate plant cells; and (c) by regulating the oxidative stress response (Adapted from Javed et al., 2022 [59]).

plant/human biologists, pathologists and agricultural/biomedical engineers working together, Responding to the growing challenges in the agricultural sector and the biomedical field. Efforts should be focused on the exploration sustainability, eco-friendliness and durability. An orthogonal approach to optimizing crops/human protection and advance efforts to achieve global food security and human longevity should be a priority. In addition, the evaluation of the toxicity and toxicological pathways of metal oxide NPs is essential for the widespread use of these NPs in various fields. In short, the unique attributes of the percentage of metal oxide NPs that need improvement to complement existing knowledge should be rigorously, explored. The closing of gaps and need to overcome future challenges across the capabilities of these NPs in biotechnology need to be strongly emphasized.

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Data included in article/supp. material/referenced in article.

Declaration of interest's statement

The authors declare no competing interests.

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