REVIEW

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Application of green synthesized silver nanoparticles in Burn therapy: a review

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Received December 28, 2023, accepted April 26, 2024

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Pharmazie 79: 42-48 (2024) *doi: 10.1691/ph.2024.3045*

Silver nanoparticles (AgNPs), owing to their unusual characteristics, have been used in various pharmaceutical, cosmetic, and healthcare products. AgNPs, with their exceptional biological potential, exhibit antibacterial, antifungal, antiviral, anti-inflammatory, anticancer, and wound healing properties and have been extensively used in burn therapy. Several studies have established the use of silver nanoparticles in the treatment of burn injuries, resulting in reduced inflammation, quick tissue regeneration, and the remarkable creation of collagen fibers. Conventional physical and chemical techniques have synthesized AgNPs, but they appear to be highly costly and hazardous. Recently, there has been considerable interest in the synthesis of AgNPs using the green chemistry approach because of its tremendous benefits, including being non-toxic, low energy consumption, pollution-free, economical, environmentally friendly, and more sustainable. This review emphasizes the green synthesis of AgNPs using bacteria, fungi, plants, and other microorganisms and the current research related to the application of green synthesized AgNPs in burn therapy, including the biological aspects of AgNPs, their mode of action, and any possible detrimental effects.

1. Introduction

Nanotechnology is a rapidly expanding field that enables the creation of nanoscale structures. Nanoparticles (NPs) are particles ranging from 10^{-9} to 10^{-7}m in size. They can be made of different materials and have different forms (Baig et al. 2021; Khan et al. 2019). Because of their numerous uses in a range of industries, including medication delivery, cancer therapy, biomarkers, cell labeling, diagnostics, and antimicrobial agents, nanoparticles have drawn a lot of attention in recent years (Elangovan et al. 2015). Because they are between 10 and 10,000 times smaller than cell organelles, exogenous (surface) and intrinsic pharmacological and medical treatments prefer to use nanoparticles (Moue-Tynga et al. 2014). In general, there are three types of nanoparticles: organic-based, carbon-based, and inorganic-based. Organic-based nanomaterials, including liposomes, dendrimers, micelles, and ferritin, are frequently utilized as vehicles for the targeted release of active pharmaceutical components (Zahoor et al. 2021). All of the components of carbon-based nanomaterials, including carbon nanotubes, carbon nanofibers, carbon black, graphene, and fullerenes, are entirely composed of carbon (Das and Roy 2020). Metal oxide and metallic nanoparticles are examples of inorganic-based nanomaterials that include no carbon atoms in their composition (Zahoor et al. 2021). Metallic nanoparticles with pore sizes, expanded surfaces, spherical and cylindrical shapes, crystalline and amorphous structures, surface charge densities, and colors, such as those of copper, lead, cobalt, aluminum, cadmium, iron, zinc, gold, and silver, can exhibit intrinsic properties (Karuppaiya et al. 2019; Zahoor et al. 2021). Among them, the physical, chemical, and biological characteristics of silver nanoparticles (AgNPs), which differ in size, form, function, crystallinity, and structures, have been the subject of much investigation (Gurunathan et al. 2015). Owing to their unusual characteristics, they have found use in a wide range of industries and products, such as pharmaceuticals, food, medical device coatings, optical sensors, cosmetics, industrial, household, and healthcare products; they have also been employed as antibacterial agents in consumer products, anticancer agents, and have even improved the ability of anticancer drugs to kill tumors (Chernousova and Epple. 2013). AgNPs have become widely used in wound dressings, biomedical equipment, and the textile industry (Li et al. 2014). Because of its exceptional biological potential, including antibacterial, antiviral, antifungal, anti-infectious, anti-inflammatory, and wound-healing capabilities, silver has been dubbed "dynamic" (Lateef et al. 2018; Aina et al. 2019).

Silver, a non-toxic inorganic antibacterial agent, can eradicate about 650 distinct kinds of disease-causing microbes (Bhuyar et al. 2020; Adebayo et al. 2019). AgNPs have been synthesized using a variety of techniques. Conventional physical and chemical techniques appear to be highly costly and risky in general (Gurunathan et al. 2009; Gurunathan et al. 2015). It's interesting to note that biologically produced AgNPs have great stability, solubility, and yield. Biological methods seem to be straightforward, quick, dependable, environmentally friendly, and safe among the several synthetic procedures for AgNPs. Under ideal circumstances, they can produce well-defined size and morphology for translational research. Ultimately, a green chemical strategy for AgNPs production appears quite promising. The green synthesis method lowers costs and improves safety in nanoparticle mass manufacturing (Munir et al. 2021). Green synthesis is a nontoxic and environmentally friendly way of creating nanoparticles from natural ingredients. In green synthesis, extracts from a variety of plants, algae, bacteria, fungi, and yeast are mostly utilized as reducing and stabilizing agents (Teimouri et al. 2018; Rahimzadeh et al. 2022). Recently, there has been much interest in the synthesis of nanoparticles using the green chemistry approach because of some of its benefits, including being non-toxic, free from pollution, having fewer energy requirements, being environmentally friendly, economical, and additionally sustainable (Qiao and Qi 2021; Ahmed et al. 2022; Bhardwaj et al. 2020). Furthermore, compared to other approaches, green chemistry produces nanoparticles that are comparatively safer and more stable (Gour and Jain. 2019).

Burn injury is one of the most significant public health problems due to the serious harm received by the patient and the result of increased treatment expenditures for burn wound dressing, drugs used for the treatment, and surgical operations (Sharma et al. 2020). The severity of burn injury is evaluated by assessing the depth of the burn damage and by evaluating the percentage of total body surface area effected by the burn. Burn wounds are classified into first to fourth degrees, depending on the depth of the tissue damage. Third- and fourth-degree burns are serious injuries that necessitate prompt surgical treatment (Lee and Jun. 2019). The burn damage healing process involves four overlapping biological phases: homeostasis, inflammation, proliferation, and remodeling. The conventional approach to wound healing includes transferring healthy tissue, such as skin replacements, to the site of damage. However, the scarcity of donor sites, the high risk of infection, and the susceptibility to scarring and contraction all led to an increased interest in exploring therapeutics with anti-infectious and anti-inflammatory effects (Odeniyi et al. 2020; Banasiuk et al. 2020). The focus of this review is on the green synthesis of AgNPs using bacteria, fungi, plants, and other microorganisms, as well as the current research on the use of these green synthesized AgNPs in burn therapy. This includes an examination of the biological aspects of AgNPs, their mode of action, and any potential adverse effects.

2. Pathophysiology and mechanism of action of AgNPs in burn injury

The pathophysiology of burn injuries implicates inflammation and infection. In the initial response, mast cells, macrophages, neutrophils, monocytes, and dendritic cells migrate to the injury site. This causes receptors to recognize damaged and pathogen-associated molecular patterns. This leads to the activation of inflammatory mediators such as IL-1, IL-6, IL-8, IL-18, and TNF-α, resulting in continuous inflammatory responses (Kelly et al. 2022). Whereas infection is the result of a compromised immune system due to suppression of T-cells and IL-2, disruption of neutrophils leading to phagocytosis, which results in reactive oxygen species (ROS) and neutrophil extracellular traps, makes them susceptible to infection. Burns damage skin barriers, causing bacteria to form colonies and proliferate around the injury. The source of infection could be the burned skin itself, hospital premises, and equipment used, such as ventilators, inserted tubes, and catheters, leading to a respiratory tract infection or a urinary tract infection (Lang et al. 2019). So, the infection and the systemic inflammatory responses cause cytokines to be released. This can cause systemic inflammatory response syndrome, which can damage multiple organs (Jeschke et al. 2020; Mulder et al. 2020).

AgNPs, due to their extensive antimicrobial and anti-inflammatory properties, could prevent infection and inflammation that cause systemic inflammatory response syndrome and multiple organ failures in burn injuries. AgNPs exert their antimicrobial action in several ways, including by disrupting the lipid bilayer, enhancing permeability, disrupting transport activity, causing cellular content leakage, and inflicting cell wall damage. The second mechanism is by producing reactive oxygen species (ROS), which cause cellular oxidative stress in cells and lead to the production of free radicals. AgNPs also cause disruption and mutation of genes by interacting with nucleic acids. AgNPs complexes with DNA prevent bacterial replication and multiplication. It was also evidenced that AGNPs interrupt RNA transcription and alter gene expression (Mikhailova. 2020; Bruna et al. 2021). Moreover, several studies have reported AgNPs anti-inflammatory activity. AgNPs prevent COX-2 and MMP-3 expression and reduce the levels of TNF-α and IL-1β. Moreover, AgNPs also prevent the production of pro-inflammatory cytokines by inhibiting the activation of NF-kB in macrophages (Mikhailova. 2020). Thus, AgNPs play a significant role in the treatment of burn wounds due to their cogent anti-microbial and anti-inflammatory properties (Yesaya and Lewa. 2023).

3. Green synthesis of AgNPs

Ideally, there are two ways to obtain silver nanomaterials: "top-down" and "bottom-up" (Deepak et al. 2011). The bulk metals are mechanically milled, chemically etched, thermally or laser-ablated, sputter-treated, evaporated, condensed, and arc-discharged which represents "top-down" methods. Consequently, colloidal protective agents are used to stabilize the process. Sono-decomposition, chemical reduction, electrochemical processes, and pyrolysis are examples of "bottom-up" techniques (Habeeb Rahuman et al. 2022). In both aqueous and non-aqueous solutions, different chemical and inorganic agents have been employed to reduce the metal ion, including sodium borohydride, ascorbate, N-dimethyl formamide (DMF), tollens reagent, and polyethylene glycol (Iravani et al. 2014). Figure 1 represents different ways to synthesize AgNPs. In addition to being economical, the bottom-up approach can quickly generate several significant nanoparticle forms. Another term for it is the "self-assembly method," in which nanoparticles are created by atomic growth at the nucleation center. Consequently, the green synthesis of AgNPs frequently employs the bottom-up approach due to its benefits. This method also provides a higher yield compared to physical methods.

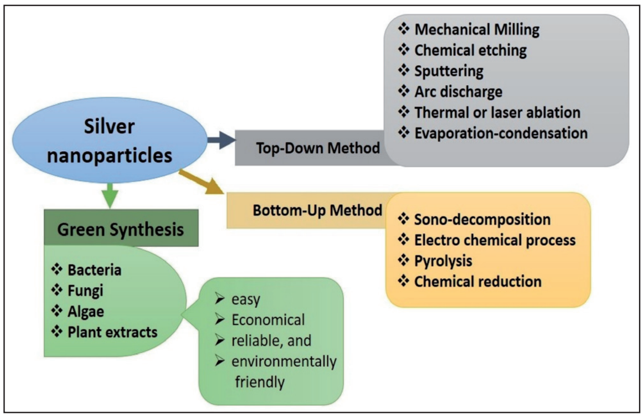

Fig. 1: Different approaches to synthesize AgNPs.

The creation of ecologically friendly nanoparticles using natural materials like bacteria, fungi, plants, and other microorganisms is known as "green chemistry." Hereafter, this development process is called "green synthesis" (Pal et al. 2019). Several bacteria employed in the biosynthesis of AgNPs include *Bacillus licheniformis*, *Pseudomonas stutzeri* AG259, *Brevibacterium casei*, *Escherichia coli* (E. coli), and Lactobacillus strains. A few examples of fungi such as *Penicillium verrucosum, Ganoderma neo-japonicum Imazeki, Fusarium oxysporum, Aspergillus terreus,* and small biomolecules such as amino acids and vitamins were also employed for the biosynthesis of defined-size AgNPs. Biosynthesis of nanoparticles has recently been shown to be an easy, economical, reliable, and environmentally friendly approach. Plants are suitable for large-scale nanoparticle production and seem to be the best candidates among the biological materials discussed so far. When compared to other biological materials, nanoparticles synthesized via plant extracts have several advantages. One such advantage is that the kinetics of synthesis utilizing a plant-based technique are significantly higher than those of other biosynthetic approaches. Moreover, the method is cost-effective and ecologically sustainable, as it eliminates the need for intermediary base groups. The removal of toxins and contaminants from waste produced in environmentally friendly ways has also shown tremendous potential with plant extracts (Carolin et al. 2017). Furthermore, using plant extracts for nanoparticle production is more advantageous than using microorganisms because of their accessibility and lack of need for a labor-demanding cell culture maintenance procedure (Makarov et al. 2014). Because they end up in the form of non-aggregated nanoparticles, nanoparticles made from plant extracts are also more stable when stored for extended periods of time (Jayaprakash et al. 2017). Plants have a long history of producing natural chemical compounds at an affordable cost, and they have enormous potential for detoxifying hazardous substances and heavy metals (Eljounaidi and Lichman. 2020). Figure 2 depicts the green synthesis process for AgNPs fabrication.

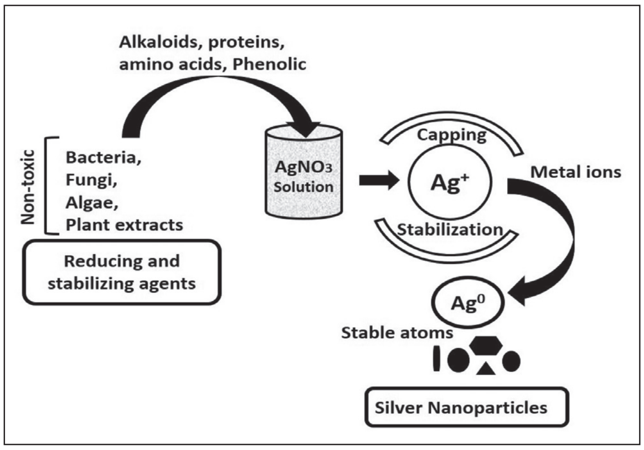

Fig. 2: Green synthesis of silver nanoparticles.

Phytochemicals from plant extracts obtained from roots, stems, leaves, fruits, and flowers act as reducing and stabilizing agents in the biosynthesis of nanoparticles (Narayanan and Sakthivel 2011). Small portions of these plants are chopped up and extracted with the proper solvents. Filtration and centrifugation are used to refine the extracts. After the extract is combined with $AgNO_3$ saline solution, metal ions (Ag^+) are reduced to atoms (Ag^0), and stable nanoparticles are formed in the presence of metabolites and redox enzymes. AgNPs formation is shown by color changes in the solution. For the formation of AgNPs, plant extracts function as mediators that cap and reduce the compound (Mikhailova 2021; Javed et al. 2020). The plant extract-mediated green synthesis of AgNPs involves three main steps as follows: (i) metal ion reduction and the formation of nuclei at the activation stage; (ii) spontaneous creation of larger-sized particles from small adjacent nanoparticles in addition to thermodynamic stabilization during the growth stage; and (iii) the termination stage, which determines the final shape of the nanoparticles (Makarov et al. 2014). A wide variety of herbs has been utilized for green synthesis of AgNPs, such as *Calophyllum tomentosum* (Deepak et al. 2019), polysaccharide from *Sanghuangporus sanghuang* (Ran et al. 2019), *Azadirachta indica* (Ahmed et al. 2016), Arabinoglucan from *Lallemantia royleana* (Iram et al. 2021), *Gleichenia pectinata* (Femi-Adepoju et al. 2019), *Mimosa tenuiflora* (Martínez-Higuera et al. 2021), *Piper ningrum* seed (Kanniah et al. 2021), *Moringa oleifera* seed polysaccharide (Mehwish et al. 2021), *Berberis vulgaris* (Behravan et al. 2019), *Abelmoschus esculentus* (Mollick et al. 2019), Urtica dioica (Jyoti et al. 2016). Table 1 represents a few examples of green synthesized AgNPs by using natural resources like bacteria, fungi, plants, and other microorganisms.

4. Application of green synthesized AgNPs in burn therapy

Several studies demonstrated the use of silver nanoparticles in the treatment of burn injuries. Nanomaterials used to treat burn wound damage resulted in quick tissue regeneration with reduced inflammation. They also remark a higher production of collagen fibers, which generates a higher tensile force.

The biosynthesis and characterization of AgNPs produced by the filamentous *Cyanobacterium phormidium* sp. were demonstrated including their wound healing impact on several types of wounds, including burn wounds. Wound area contraction and epithelialization were used to evaluate burn wound healing. When compared to the negative control, topical administration of the positive control and AgNPs significantly shortened the epithelization duration and increased wound contraction (p 0.05). On day one, all the experimental animals burn wounds were swollen and bruised. On the sixth day, the animals treated with AGNPs showed thickening of the damaged skin, accompanied by dark reddening, while the positive control group showed no skin thickening. On the sixth

Table 1: Green synthesis of AGNPs by using various biomaterials

Source type	Source name	Activity	Formulation type	Outcomes	Reference
Tuber extract	*Amorphophallus paeoniifolius*	Antibacterial activity	AgNPs	Exhibited enhanced antibacterial activity against gram +ve and gram -ve bacteria with utmost zone of inhibition (20 mm) at a concentration of 25µL/disk against Pseudomonas aeruginosa.	(Nayem et al. 2020)
Leaf extract	*Clerodendrum inerme*	Antibacterial, antimycotic, antioxidant, cytotoxic, and biofilm inhibition activity	AgNPs	The developed AGNPs exhibited inherited biological functions. The biosynthesized nanoparticles showed improved antioxidant, antibacterial and antimycotic properties compared to commercial NPs.	(Khan et al. 2020)
Leaf and stem	*Aspalathus linearis*	Anticancer activity	AgNPs	The synthesized nanoparticles were more efficacious against Liver cancer cell (HepG2) and Human neuroblastoma. (SH-SY5Y).	(Akinfenwa et al. 2021)
Fruit extract	*Cornelian cherry*	Anti-inflammatory activity	AgNPs	UV light mediated biosynthesized AgNPs diminished apoptosis and inflammation in the early stage.	(Filip et al. 2019)
Bacteria	*Brevibacterium casei*	Anti-coagulant effect	AgNPs	The biosynthesized nanoparticles exhibited stable anti-coagulant effects.	(Kalishwaralal et al. 2010)
Bacteria	*Bacillus subtilis*	Antibacterial activity	AgNPs	The biogenic nanoparticles exhibited an enhanced antibacterial activity against multidrug resistant pathogens.	(Alsamhary. 2020)
Fungus	*Penicillium verrucosum*	Antifungal activity	AgNPs	The biogenic nanoparticles were found efficacious against *Fusarium chlamydosporum* and *Aspergillus flavus.*	(Yassin et al. 2021)
Fungus	*Aspergillus terreus*	Antimicrobial, antifungal and cytotoxic activity	AgNPs	Mycofabricated AgNPs exhibited bactericidal and fungicidal activity. Moreover, they also exhibited enhanced anti-cytotoxic activity against adenocarcinoma epithelial cells.	(Lotfy et al. 2021)
Algae extract	*Dunaliella salina*	Antibacterial activity	AgNPs	The biosynthesized AgNPs showed inherited biological activity against *Bacillus subtilis, Enterobacter tobbaci*, and *Escherichia coli*.	(Shantkriti et al. 2023)

day, treatment with AgNPs (50 µg/kg) revealed a wound contraction rate of 26.01 % compared to the positive control (25.81 %), showing no significant difference between the two groups. The healing effect of AgNPs lasts until the 18th day, showing 85.81 % of wound contraction. Burn wounds treated with varied AgNPs concentrations or positive control preparations exhibited greater wound contraction percentages than the negative control. On the 12th day, the wounds treated with various concentrations of AgNPs, or positive control preparations exhibited considerable exudation and hair development on the wound surface with scab covering. In comparison, there was no hair growth or scab covering in the negative control group. Furthermore, the burn wounds had a dry surface, gradual wound shrinkage, and enhanced hair growth when treated with varied doses of AgNPs. There was no significant difference in the mean epithelialization period between the varied doses of AgNPs, i.e., 30 and 50 µg/kg. The mean epithelialization period shown was 15.46±2.7 days in the AgNPs (30 µg/kg) treated groups compared to the negative control group showing 20.0± 1.2 days (Younis et al. 2021)**.**

A unique ointment for burn wounds made out of sheep's tails loaded with AgNPs was developed. The AgNPs were formed using a biological approach and the medicinal herb *Rhodiola rosea*. The AgNPs-loaded ointment was delivered to the BALB/c mice wound site; the wound healing effect was examined. When compared to negative control burn wounds, a reduction in wound size, epidermal layer thickness, and mast cell migration was seen. Furthermore, the green synthesized nanoparticles modulated gene expression in BALB/c mice (both pro- and anti-inflammatory), facilitating burn wound closure. The newly discovered AgNPs-loaded ointment finds its potential in biomedical applications. On burn wounds, the biosynthesized AgNPs suppressed pro-inflammatory cytokines (TNF, IL-1, and IL-6) and enhanced the production of anti-inflammatory cytokines (IL-10). The surface area and spleen length changes of the burn wound were measured to evaluate the effect of silver nanoparticle ointment on wound healing. The burn wound surface area closure showed a significant difference of 61±9 mm^2 and 5±4mm^2 for the control and treatment groups, respectively. The wound sites of all examined mice in the treatment group generated newborn hair follicles, while the control group formed scabs (Bold et al. 2022). Moreover, AgNPs hydrogel was synthesized by using *Mimosa tenuiflora extracts* for the treatment of second-degree burns. A second-degree burn injury model was analyzed for 14 days on a Wistar rat, and further skin samples were investigated to determine the burn wound healing process. A commercial gel containing silver nanoparticles (AgNPs) was made and used as a control in biological tests. Because of its antibacterial and anti-inflammatory properties, a silver nanoparticle hydrogel system produced with *Mimosa tenuiflora* was used as a viable therapeutic method for burn wound healing. After 14-day treatments in the 2nd degree burn model, wound repair ratios were found to be 61.22 %, 38.18 %, 31.95 %, and 32.51 % for the developed *Mimosa tenuiflora* AgNPs hydrogel system, for the control group, vehicle groups, and the plain AgNPs-gel, respectively. The wound healing ratios of *Mimosa tenuiflora* gel were found to be 52.15 %. The wound healing rates of the Mimosa *tenuiflora* AgNPs hydrogel system were higher than with eother therapies after 14 days of application, according to macroscopic and histological data. The microscopical results reveald that the developed hydrogel system reduces the percentage of wound contraction considerably (P 0.05) when compared to the other groups (P > 0.05). It was discovered that the group treated with *Mimosa tenuiflora* AgNPs hydrogel system heals wounds quicker than the other groups, which is supported by statistical analysis. After 14 days, skin samples from the control group revealed no histological changes in the epidermis, dermis, or hypodermis. Biopsies taken from rats given the vehicle indicate inflammation that spreads from the epidermis and reaches the hypodermis, indicating a cellular debris zone with fibrin and a hyaline crust. Biopsies from rats treated with a marketed nanoparticle gel demonstrate edema, necrosis with an inflammatory reaction, and the presence of newly developed blood vessels, which have been wrapped by a keratin layer showing scabs. A small inflammatory reaction, consisting of lymphocytes, detects severe dermoplasia and spreads to the hypodermis. The epidermis and dermis of rats treated with *Mimosa tenuiflora* gel

Table 2: Biomedical application of AgNPs in burn therapy

Source type	Source name	Formulation type	Burn model	Outcomes
Bark extracts	*Mimosa tenuiflora*	AgNPs hydrogel	Second degree burn	Treatment with AgNPs hydrogel results in no visible inflammation, epidermal integrity, basal stratum hyperplasia, acanthosis, some hair follicles, and a desmoplasia zone rich in collagen fibers.
Root extract	*Onosma dichroantha*	AgNPs suspension	Burn wound	Exhibited bactericidal activity in treating burn wounds and injuries.
Green algae	Ulvan	AgNPs hydrogel film	Second degree burn	Enhanced healing by regulating the inflammatory process, improved the vascularization and re-epithelialization
Root extract	*Rhodiola rosea*	AgNPs ointment	Burn wounds	Resulted in reduced wound size, epidermal layer thickness, and mast cell migration.
Bacterial culture	*cyanobacterium Phormidium* sp	AgNPs ointment	Burn wound	AgNPs significantly shortened the epithelization duration and increased wound contraction.
Floral extract	kappa-carrageenan	Wound dressing	Second degree burn	The nano-floral polymeric complex wound dressing increased exudate absorption, promoted effective proliferation, with the emergence of compact fibrous arrangements, and the appearance of hair follicles, so facilitating healing of 2nd degree burn wounds.
Herb extract	*Aloe Vera*	Fish skin scaffold	Burn wound	The AgNPs loaded fish skin scaffold acts as a shielding barrier to the outside environment and forms a 3D framework for fibroblasts and keratinocytes to connect and proliferate, while AgNPs in the scaffold aid in fibroblast migration. Thus, the AgNPs-loaded scaffold functions as a biocompatible antimicrobial scaffold capable of improving burn wound healing.
Plant extract	*Ammania baccifera*	AgNPs gel	Burn wound infection	The green synthesized AGNPs gel was found to be equally effective bactericidal at 95% lesser concentration compared to marketed silver product and hence provides an alternative to the marketed products with least toxicity and better treatment option for burn infections.

show no pathological modifications, but there is a distinct inflammatory lesion within the inner regions of the dermis and hypodermis that extends throughout the whole lesion. Treatment with *Mimosa tenuiflora* AgNPs hydrogel system results in no visible inflammation, epidermal integrity, basal stratum hyperplasia, acanthosis, some hair follicles, and a severe desmoplasia zone rich in collagen fibers (Martínez-Higuera et al. 2021).

The potential of *Onosma dichroantha* herb root extract in the production of silver nanoparticles is proposed for bio-reduction and the development of stabilized silver nanoparticles exhibiting bactericidal activity in treating burn wounds and injuries (Nezamdoost et al. 2014). A polysaccharide from green algae, Ulvan, has been used to develop AgNPs hydrogel film for potential burn treatment. The second-degree burn wound healing test and *in-vitro* antimicrobial activity test were evaluated. The results indicated that Ulvan hydrogel film AgNPs significantly enhanced healing by regulating the inflammatory process and improving vascularization and re-epithelialization. Thus, the Ulvan-based AgNPs hydrogel film proved to be an effective tool to support second-degree burn wound healing and a suitable candidate for wound dressing (Sulastri et al. 2023).

The development of biosynthesized AgNPs for burn wound dressings demonstrated another innovative method, i.e. creating polysaccharide-based polymeric complexes from floral extracts. The treatment of silver salt with kappa-carrageenan and sodium alginate resulted in a stable polymeric complex. The wound closure diameter and histological examination were then measured to study the impact of the designed AgNPs wound dressings. The results indicated increased exudate absorption, promoting effective proliferation, the emergence of compact fibrous arrangements, and the appearance of hair follicles, thus facilitating the healing of 2nd degree burn wounds (Zia et al. 2020).

A novel antibacterial fish skin scaffold was developed using green-synthesized AgNPs. The AgNPs were biosynthesized using the *Aloe vera* plant and doped in decellularized fish skin scaffolds. This nanoparticle-loaded scaffold served as a protective barrier to the outside environment, forming a 3D framework for fibroblasts and keratinocytes to connect and proliferate, while AgNPs in the scaffold aid in fibroblast migration. As a result, the AgNPs-loaded scaffold functioned as a biocompatible antimicrobial scaffold capable of accelerating burn wound healing (Adhikari et al. 2023). Another study showed that green synthesized AgNPs gel worked better than a commercial product called Silverex™ (silver nitrate gel, 0.2% w/w) at treating an infection in a burn wound. The AgNPs were biosynthesized using *Ammania baccifera* plant extract, and the bactericidal activity was determined against a group of microbes causing burn wound infection. The study's findings showed that the green synthesized AgNPs gel was just as effective at a significantly lower concentration (0.03%) than the marketed product, offering a more effective and less toxic treatment for burn wound infections (Jadhav et al. 2016). Table 2 illustrates the biomedical application of AgNPs in burn therapy.

5. Cytotoxicity in humans

In today's era, the biomedical application of nanosystems has increased a lot, but there are many studies addressing adverse effects of these nanoparticles on human health (Ahamed et al. 2010). Studies also indicate that nanoparticles can interact with biological systems by invading cell membranes due to their strong oxidative activity (Akter et al. 2018). The silver ions from AgNPs released into the cell membranes induce genotoxicity, cytotoxicity, and even cell death (de Lima et al. 2012; Zhang et al. 2014). Prolonged exposure to AGNPs leads to liver and lung damage. AgNPs damage the human hepatoma cell viability by endocytosis and diffusion mechanisms (Vrček et al. 2016). Inside the cell cytoplasm, AgNPs ionize $Ag+$ ions, which causes oxidative stress and leads to the formation of ROS (reactive oxygen species) (Akter et al. 2018). AgNPs cause DNA damage, apoptosis, genotoxicity, and chromosomal aberration. Research has discovered that silver nanoparticles can be genotoxic (Rodriguez-Garraus et al. 2020). Large-size AgNPs are less cytotoxic than small-size AgNPs due to their higher surface area and higher release of $Ag+$ ions (Jaswal and Gupta 2023). However, the detrimental effects of AgNPs should be determined with respect to the concentration at which they provide maximum safety to humans and the environment.

6. Conclusion

The green synthesis of AgNPs from biomaterials has gained much interest due to their plentiful benefits, and among the various sources, plants are highly preferable for synthesizing nanoparticles due to the wide range of plant-based bioactive reducing metabolites compared to bacteria, fungi, algae, and other microorganisms. Green synthesized AgNPs are widely used in antibacterial, anticancer, anti-inflammatory, antifungal, antiviral, anti-angiogenic, anti-biofilm, anti-diabetic, anti-ulcer, anti-parasitic, antioxidant, wound healing, and burn therapy applications. Since ancient times, silver compounds have been used in different forms as key elements in the treatment of burn wounds. This review comprehensively emphasized the application of green synthesized AgNPs in burn therapy and provided an overview of burn wound healing mechanisms. Moreover, with respect to the toxicity caused by AgNPs to human health, more investigational studies should be performed, and the role of green synthesized AgNPs in reducing cytotoxicity, either by developing more stabilized or non-toxic forms of AgNPs, should be studied further.

Funding: This work was funded by the Deanship of Scientific Research at Najran University, Najran, Saudi Arabia, under the Research Priorities and Najran Research funding program grant code (NU/NRP/MRC/12/34).

Acknowledgment: The authors are thankful to the Deanship of Scientific Research at Najran University for funding this work under the Research Priorities and Najran Research funding program grant code (NU/NRP/MRC/12/34).

Conflict of interest: The authors declare no conflict of interest.

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