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Antibacterial Wound Healing Application of Bio-Inspired Green Silver Nanoparticles: A Review

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Abstract

There is a high demand for silver nanoparticles (AgNPs) as a highly effective antimicrobial agent due to its unique properties. However, conventional synthesis methods utilizing toxic chemical reducing agents impose limitations on its applications. Besides, the infected wound by bacteria could increase treatment cost burdening the low-income communities. To address this challenge, a greener approach employing bioresources such as plant extracts as reducing agents has been explored, with the potential to facilitate the utilization of AgNPs in human wound healing applications. This paper reviews development of biosynthesized AgNPs as antimicrobial wound healing agent. The biosynthesized AgNPs using bioresources such as plant extract and microorganisms are effective antimicrobial agent against various types of bacteria related to the wound such as Gram-positive *Staphylococcus aureus*, Gram-negative *Escherichia coli* and *Pseudomonas aeruginosa*. At the same time, these biosynthesized AgNPs could accelerate the wound healing process as proven by the in vitro cell study and in vivo animal testing, as compared to the control samples. Hence, the biosynthesized AgNPs could be applied as antimicrobial wound healing agent.

Keywords Silver nanoparticles, biosynthesis, antibacterial, wound healing

1.0 INTRODUCTION

When it comes to treating bacterial infections, wound care management can be very expensive (Sheehan et al., 2022). Because infected wounds take longer to heal, more time and money are required for treatment. Due to the necessity for additional medical treatments and trips to healthcare institutions, the overall cost is raised. Numerous tests, such as wound cultures, are carried out to detect and track these infections, but they can be rather expensive, particularly if repeated tests are required. In addition, antibiotics are frequently needed to control the infection, and these prescriptions can be expensive if the bacteria that were causing the infection are resistant (Ennab et al., 2022). Surgery may be required in extreme circumstances, which would acquire extra costs for the operating room, post-operative care, and prolonged hospital stays. When bacterial infections are present, each of these factors contributes to the high cost of wound care management.

To deal with the high costs of wound care, it's important to focus on preventing infections in the first place such as practicing good wound hygiene and taking proper care of wounds. If an infection does occur, it's crucial to intervene early and manage it promptly. This can help reduce complications and ultimately lower treatment costs. By using antibiotics and antimicrobial agents more wisely, we can avoid the need for more expensive medications in cases of resistant bacteria. Exploring advanced wound care technologies is also beneficial. These innovative techniques and treatments can facilitate faster healing and potentially reduce overall expenses by shortening the duration of treatment and hospital stays. One strategy is to use antimicrobial wound material to treat the wound. This material has two functions: it can either kill pathogenic microorganisms or prevent their growth while also healing the wound. Therefore, this paper discusses the development of biosynthesized silver nanoparticles (AgNPs) specifically for antimicrobial wound healing agent.

2.0 NANOMATERIALS

Nanoparticles, like silver, gold, zinc, or copper nanoparticles, have been found to possess antimicrobial properties (Gudkov et al., 2021, Ab Razak et al., 2021). These small particles have demonstrated efficacy against a variety of harmful bacteria and fungi. They are regarded as inorganic antibacterial agents because of their capacity to prevent these microbes from growing and surviving. Silver nanoparticles (AgNPs), for example, have been extensively studied for their antimicrobial activity (Ab Razak et al., 2021). They have demonstrated the ability to disrupt the cell membranes of bacteria and fungi, leading to their death (Waiezi et al., 2022). Similarly, gold, zinc, and copper nanoparticles have also shown antimicrobial effects through various mechanisms, such as interfering with cellular processes or generating reactive oxygen species that are toxic to microorganisms (Samsulkahar et al., 2022). The advantage of using nanoparticles as antimicrobial agents lies in their small size, which allows them to penetrate and interact with microbial cells more effectively. They have a larger surface area compared to its bulk materials, enabling a higher contact area with microorganisms and enhancing their antimicrobial activity. These nanoparticles have shown promising potential in various applications, including wound dressings, coatings for medical devices, and water purification systems (Jamkhande et al., 2019). By incorporating these nanoparticles into such products, it is possible to harness their antimicrobial properties to prevent or control infections caused by pathogenic bacteria and fungi. The use of nanoparticles as antimicrobial agents carries significant dangers, and further study is still required to fully understand these risks and their long-term implications. Safety considerations and regulatory frameworks need to be carefully addressed before widespread implementation in medical and consumer products.

The nanomaterials can be produced, prepared or synthesized using two approaches namely bottom-up and top-down approaches, and also either via chemical, physical or biological approaches. Smaller atoms or molecules react to form larger particles as part of the bottom-up method of creating nanomaterials, as in the reduction reaction of Ag^+ to Ag^0. While the top-down strategy involves using laser ablation to reduce larger materials, like silver plate, to tiny particles to create nanomaterials (Menazea, 2020). The laser ablation technique is a physical approach, and the reduction reaction using a chemical reducing agent is considered a chemical approach. The use of toxic and dangerous chemical-reducing agents during the synthesis process necessitates special safety measures and requires the removal of chemical waste that is not environmentally friendly, among other issues, making the chemical approach problematic (Ab Razak et al., 2022). Furthermore, the physical synthesis of nanomaterials requires expensive equipment, high energy requirements, and is risky for human use. Therefore, creating the nanomaterials using biological methods is one way to overcome these difficulties.

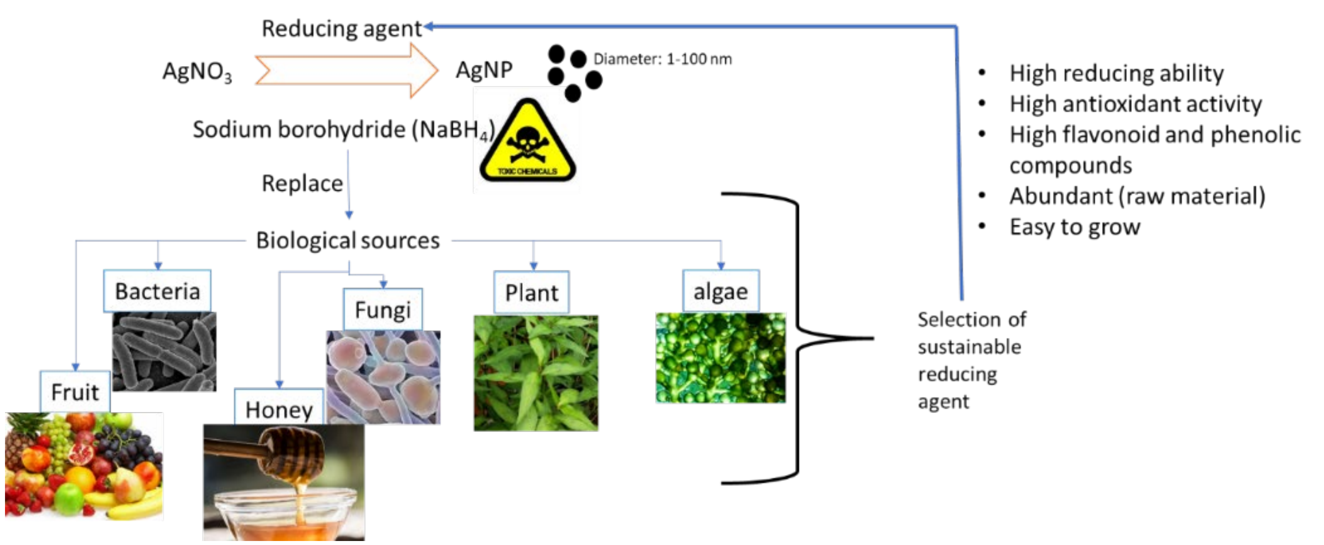

Figure 1 Synthesis process of AgNPs using a chemical reducing agent that can replace biological sources.

In the bottom-up method, the biological approach to nanomaterial synthesis uses suitable bioresources that can take the place of chemical reducing agents. The bioresources can come from a variety of sources, including bacteria, microalgae, honey, fungus, fruit and plant extracts. Not all bioresources can be utilised in the synthesis of nanomaterials as bioreducing agents. They must be highly antioxidant active and capable of acting as a reducing agent. The active compounds found in the bioresources serve as the foundation for these abilities. Utilizing this biological method has the advantage that the bioactive compounds can also serve as a capping agent, stabilising the nanomaterials so they cannot aggregate or agglomerate forming larger particles. The biological synthesis technique is just based on one single approach and requires no additional chemicals, in contrast to the chemical synthesis technique which requires additional chemicals for stabilising the nanoparticles. Additionally safe for people and the environment, the bioresource solution eliminates the need for waste management.

The biological resources could take the place of sodium borohydride as a reducing agent, according to **Figure 1**. Although sodium borohydride is an efficient reducer, its high concentration could cause other issues with waste management and handling hazardous chemicals (Ab Razak et al., 2022). The choice of an appropriate bioreducing agent is also crucial, and the resources chosen must be abundant, simple to grow, high yielding, have high reducing ability, antioxidant activity, and flavonoid and phenolic content. This might result in a green and sustainable method of synthesising AgNP.

3.0 BIOSYNTHESIZED SILVER NANOPARTICLES AS ANTIMICROBIAL WOUND HEALING AGENT

The bioactive components from the plant extract are what makes employing bioresources as reducing agents in the synthesis of nanomaterials so attractive. The bioactive components, which have biological properties like antioxidant, antimicrobial, anti-inflammation, and other useful activities, contribute to the bioactivity of the produced nanoparticles. As a result, in addition to the AgNP's inherent antimicrobial activity, the biosynthesized nanomaterial, in particular AgNPs will also have other convenient activities. By selecting a suitable plant extract, one could combine the bio-activity of the plant extract with the AgNPs. That is the reason why the biosynthesized AgNPs could be used as an antimicrobial wound-healing agent because some of the plants possess anti-inflammation activity and can heal the wound faster while inhibiting bacterial growth (Xu et al., 2023). Figure 2 shows an illustration of how the bioactive compound from the plant extract can act as a reducing agent in the synthesis of AgNPs and then, as a capping agent for the AgNPs. As a capping agent, the organic compounds can prevent the aggregation or agglomeration of the nanoparticles and stabilize them. At the same time, the bioactive compounds could also contribute to the wound-healing process.

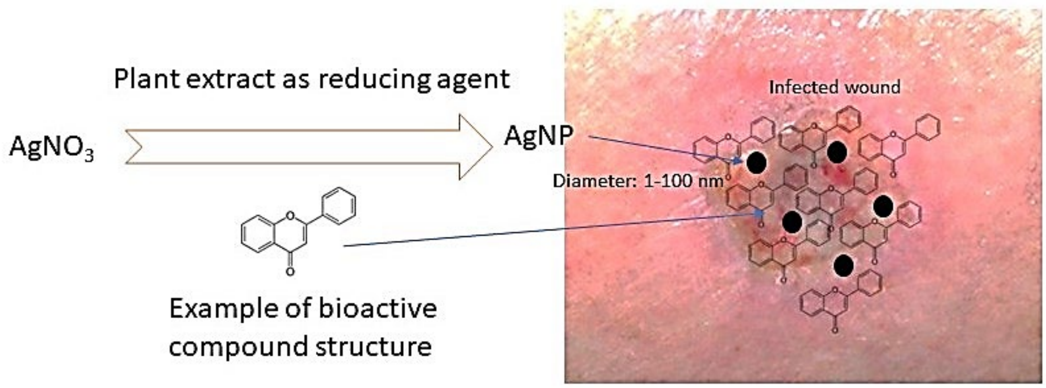

Figure 2 A possible mechanism on how the bioactive compound from the plant extract could become reducing and capping ageing from the AgNPs.

Table 1 shows some studies on the application of biosynthesized AgNP using plant extract and their analysis on antimicrobial and wound healing activities. Various plants can be used as bioreducing agents including the herbal plant *Persicaria odorata* or kesum in Malaysia, the famous neem plant (*Azadirachta indica*), *Melia azedarach* (Chinaberry) and *Catharanthus roseus* (Kemuning Berry). The formation of AgNP from plant extract showed maximum UV-Vis absorbance peak at around 400 to 440 nm and the particle diameter is within 10 to 50 nm. Almost all of the biosynthesized AgNPs have heterogeneous spherical shapes due to the various bioactive compounds that are responsible for reducing and capping agents.

Most of the plant extracts are safe and compatible with humans, especially those herbal plants. However, other bioresources mainly microorganisms either bacteria or fungus are not suitable to be used for human purposes, although they can be used as bio-reducing agents for the formation of AgNPs. **Table 2** shows two papers report on the biosynthesized AgNPs using microorganisms (cyanobacteria and endophytic fungus) acting as antimicrobial wound healing agents. Both microorganisms are rich in bioactive molecules and considered safe for humans, as compared to other microorganisms (Shahbaz et al., 2023).

One way to enhance the effectiveness of the bioactive compounds for healing the wound is by embedding, incorporating or immobilizing them on suitable materials. This strategy needs to be done to control the bioactive compounds' release, protection of the molecules, as a support system and ease of application. Embedding bioactive compounds onto materials can facilitate their application to wounds. This ensures efficient delivery of the bioactive compounds, improves patient compliance, and simplifies the overall wound healing process. Hence, there are also studies on the immobilization of the biosynthesized AgNPs onto other materials such as zeolite (inorganic aluminosilicate) (Asraf et al., 2022), chitosan (Zhou et al., 2021) and cotton fabric. Table 3 shows some research that has been done in immobilizing the biosynthesized AgNPs onto a suitable carrier system. Various bioresources such as herbal *Orthosiphon aristatus* (Misai Kucing) (Asraf et al., 2022), *Curcuma longa* (Turmeric) (Maghimaa et al., 2020) and *Scutellaria barbata* (Chinese herb) (Veeraraghavan et al., 2021), as well as, lipopeptides (iturin) (Zhou et al., 2021) produced by bacteria *Bacillus subtilis* were used as bioreducing agent for AgNP. These bioresources were selected because they contain bioactive compounds that act as reducing agents, and capping agents and also to accelerate the wound healing process.

Table 1 Biosynthesis of AgNPs using plants and studies for its antimicrobial and wound healing activities.

Type of plant	Characteristics of the biosynthesized AgNPs	Antimicrobial and wound healing tests	Reference
P. odorata (Kesum) leaves	Maximum UV-Vis absorbance was at 440 nm, with spherical forms and a mean diameter of 11±3 nm.	AgNPs inhibited *Staphylococcus epidermidis* and methicillin-resistant *Staphylococcus aureus* (MRSA) in a dose-dependent manner based on disc diffusion test (DDT) and minimum inhibitory concentration (MIC) analysis. Compared to untreated cells, AgNPs are not harmful to normal cells and can increase cell motility (in vitro study).	Lubis et al., 2022
A. indica (Neem plant)	The highest UV-Vis absorbance peak at 400 nm, spherical, 33 nm-diameter particles	Zone of inhibition on DDT: *Pseudomonas aeruginosa* (10.3 mm), *S. aureus* (17.7 mm), *Bacillus cereus* (17.7 mm), *Escherichia coli* (18.7 mm). The wound contraction rate in mice was markedly accelerated by applying AI-AgNPs-PF127 hydrogel to the wound sites.	Chinnasamy et al., 2021
M. azedarach (Chinaberry)	Absorbance peak at 420 nm. 14–20 nm in diameter, uniformly scattered, and crystallised.	Zone of inhibition on DDT: human pathogenic Gram-negative *E. coli* (37 mm) and Gram-positive *Bacillus cereus* (34 mm). The human dermal fibroblast cell scratch experiment demonstrated potential AgNP wound healing action.	Chinnasamy et al., 2019
C. roseus (Kemunting Cina) leaf extract	Maximum absorbance at 425 nm. Crystals with grains about 10-88 nm in diameter.	Antibacterial activity against clinical isolates of bacteria (*S. aureus*, *E. coli*, *Klebsiella pneumonia*, *P. aeruginosa, Citrobacter koseri*,) and the fungus *Candida albicans.* Based on a male albino mouse excision wound model, animals treated with AgNPs demonstrated improved wound-healing activity in comparison to either negative- or positive-control groups.	Al-Shmgani et al., 2017

Table 2 Biosynthesis of AgNPs using microorganisms and its evaluation on antimicrobial and wound healing activities.

Type of microorganism	Characteristics of the bioynthesized AgNPs	Antimicrobial and wound healing tests	Reference
Cyanobacteria *Phormidium* sp	UV-Vis maximum absorbance at 440 nm, particle size around 86.38 (± 3.364) nm	The AgNP has antibacterial activity against Methicillin-resistant S. aureus (MRSA) and increased its activity together with antibiotic chloramphenicol. The AgNP displayed topical efficacy in excision, incision, and burn wound models. AgNPs' ability to speed up wound healing was demonstrated by significant wound improvement, a rise in wound closure rate, hydroxyproline content, and a decrease in the time needed for epithelialization (in vivo study using Male Wister Rats)	Younis et al., 2021
Chinese medicinal herb *Orchidantha chinensis* (Endophytic fungus)	Maximal UV-Vis absorbance at 420 nm, well-distributed, spherical or almost spherical, with a diameter of 25 nm	Inhibitory effects against *P. aeruginosa* ATCC 27853, *S. aureus* ATCC 25923, and *E. coli* ATCC 25922. According to research on in vivo wound healing, the AgNPs significantly reduced bacterial growth on the wound tissue and improved the local environment for speeding up the healing process.	Wen et al., 2016

Studies on the biosynthesized AgNPs typically included a variety of bioactivity analyses, including those of antioxidant, anti-inflammatory, anti-bacterial, anti-biofilm, anti-fungal, anti-cancer, and in vitro and in vivo wound healing activities. In order to complete this cross-disciplinary study, experts from the fields of materials, biology, and medicine typically collaborate. The properties of the nanomaterials will be examined by the materials expert, and others will add to the nanomaterial's bioactivity.

Table 3 Immobilization or incorporation of AgNPs on other materials and its application as an antimicrobial wound healing agent.

Characteristics of the AgNPs	**Immobilizer/ composite**	**Antimicrobial and wound healing tests**	**Reference**
Biosynthesized AgNP using *Orthosiphon aristatus* leaves extract. Spherical with diameters 20.01 nm. AgNP incorporated inside the zeolite.	Synthesized zeolite A from raw natural kaolinite (SZ)	Antibacterial activity against *S. aureus* ATCC 6538 and *E. coli* ATCC 11229 Not cytotoxic to HSF 1184 and biosynthesized AgNP-SZ encourages cell migration and proliferation more than Ag+-SZ does.	Asraf et al., 2022
Biosynthesized AgNPs using lipopeptides (iturin) produced by *Bacillus subtilis.* UV-Vis maximum absorbance at 450 nm, particle size around 20 ± 10 nm.	chitosan (CS) composite sponge dressing–loaded iturin-AgNPs	Antibacterial activity against *E. coli* ATCC25922 and *S. aureus* ATCC29213. CS dressing–loaded iturin-AgNPs could effectively kill *E. coli* in wounds. Accelerated wound healing by encouraging the proliferation of fibroblasts and subcutaneous connective tissue, neovascularization, collagen fibre growth in wounds, and re-epithelialization of wounds.	Zhou et al., 2021
Biosynthesized AgNPs using *Curcuma lon*ga leaf.	Cotton fabric	Antimicrobial activity against the *S. pyogenes*, *S. aureus*, *C. albicans and P. aeruginosa.* Promoted the cell migration in the normal fibroblast (L929) cells .	Maghimaa et al., 2020
Biosynthesized AgNPs using *Scutellaria barbata.* sphere-shaped, 20–40 nm in size, and spherical in shape	cotton fabric	Increased zone of inhibition for *P. aeruginosa* (21 mm), *S. aureus* (20 mm), *E. coli* (21 mm) and *Klebsiella pneumoniae* (22 mm). It was not cytotoxic to L929 fibroblast cells, and it also promoted fibroblast cell migration and differentiation, which significantly reduced the size of the wound.	Veeraraghavan et al., 2021

Based on **Tables 1**, **2**, and **3**, biosynthesized AgNP produced by microorganisms and plant extract typically exhibits Surface Plasmon Resonance (SPR) at a wavelength of 400–440 nm, is heterogeneous spherical, and has a particle size between 10 to 50 nm. Transmission electron microscopy, X-ray diffraction, Fourier transform infrared spectroscopy, and UV-Visible spectrophotometer were the common instruments used to characterise the samples (TEM). These instruments, along with other instruments or experiments, can be used to gather data on the characteristics of the biosynthesized AgNPs. For instance, the AgNP's crystallinity and phase can be demonstrated using XRD, while the functional groups present in the bioresources can be demonstrated in the AgNPs using FTIR. Particularly for the biosynthesized AgNPs, the FTIR results can produce some remarkably useful information. This is because all bioresource extracts or isolates contain different functional groups that can be detected using an FTIR instrument. These functional groups are responsible for the formation of AgNPs along with the bioactive compounds from the bio-resources (Samsulkahar et al., 2022, Lubis et al., 2022). Therefore, using FTIR to analyse the biosynthesized AgNPs will show that the bioactive substances from the bioresources coexisted as capping agents in the AgNP samples.

Antimicrobial activity, typically antibacterial and antifungal activities, have been conducted for these biosynthesized AgNPs, specifically for its application as an antimicrobial wound healing agent (**Tables 1**, **2** and **3**). They frequently employed the minimum inhibition concentration (MIC) and disc diffusion technique (DDT) for the antibacterial activity against a variety of common bacteria associated with the wound. *S. epidermidis*, Methicillin-resistant *S. aureus* (MRSA), *B. cereus*, *E. coli*, *P. aeruginosa*, *S. aureus, K. pneumonia*, and *C. koseri* are among the common bacteria. On the plates containing these bacteria, the biosynthesized AgNPs exhibit an inhibition zone, demonstrating high antibacterial activity. AgNP's antibacterial mechanism may involve several mechanisms, such as the production of reactive oxygen species (ROS) that may eventually attack the bacteria, disruption of the bacterial cell membrane, denaturation of the bacterial protein, and harm to the bacteria's DNA (Yin et al., 2020). These mechanisms will hurt the bacteria, which will then either kill them or stop them from multiplying.

For the wound healing activity, most of the studies (**Tables 1**, **2** and **3**) performed either in vitro or in vivo assays. The in vitro assay involves using normal human cell culture, usually normal human fibroblast cells, that are responsible for wounds on the skin. Fibroblasts play a crucial role in wound healing by synthesizing and depositing extracellular matrix components, such as collagen, which provide structural support to the healing tissue. In addition, the effect on these cells will also give information on the toxicity aspect of the materials towards human skin. Lubis et al (2022) showed that the biosynthesized AgNPs using kesum leaf extract is non-toxic to normal cells and enhances cell migration in vitro. Cell migration is a common method to determine the ability of the AgNP in accelerating wound healing because it is based on the cells treated with the AgNP that can assist in in vitro wound closure. On the other hand, the in vivo assay can provide direct information on wound healing activities. Al-Shmgani et al. (2017) studied the in vivo wound healing activity of the biosynthesized AgNPs using Kemunting Cina leaf extract against albino mice based on an excision wound model. The results found that the AgNP-treated animals showed better wound healing activity compared to positive- and negative-control groups. In addition, Younis et al. (2021) demonstrated that the AgNPs effectively improve wound healing based on various models including excision, incision and burn against male Wister rats. Furthermore, the study also showed that the AgNPs effectively improved wound closure rate, the content of hydroxyproline and the epithelialization period reduction. The in vitro and in vivo necessitates experiments with control samples or groups including positive and negative controls. The positive controls are those that are proven to increase wound healing activity and accelerate its healing and are suitable to the sample such as silver nitrate or silver sulfadiazine (Demling and DeSanti, 2001). On the other hand, the negative control is those that are slower in the wound healing process or no treatment is performed on that cell (in vitro) or animals (in vivo). Hence, these control samples would indicate the efficacy of the in vitro and in vivo wound healing assay performed in comparison to the treated cells or specimens.

4.0 CONCLUSION

This review paper concludes that there are many studies on the biosynthesized AgNPs using various bioresources that can be used as antimicrobial wound healing agents. Most importantly is that the AgNPs can be synthesized using various bioresources and having bioactive compounds that are responsible for reducing and capping agents. On top of that, having other beneficial bioactivities such as antioxidant and antiinflammation activities that eventually contribute to accelerating the wound healing process. There are many futures studies can be done on the usage of biosynthesized AgNPs as antimicrobial wound healing agent including the utilization of other types of beneficial bioresources as bioreducing agents, the safety aspects of the produced material, a final product such as in the form of wound dressing, cream or colloid, and its innovative application.

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