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# Green synthesis of silver nanoparticles and their antibacterial effects

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Antibacterial resistance is by far one of the greatest challenges to global health. Many pharmaceutical or material strategies have been explored to overcome this dilemma. Of these, silver nanoparticles (AgNPs) are known to have a non-specific antibacterial mechanism that renders it difficult to engender silver-resistant bacteria, enabling them to be more powerful antibacterial agents than conventional antibiotics. AgNPs have shown promising antibacterial effects in both Gram-positive and Gram-negative bacteria. The aim of this review is to summarize the green synthesis of AgNPs as antibacterial agents, while other AgNPs-related insights (e.g., antibacterial mechanisms, potential toxicity, and medical applications) are also reviewed.

KEYWORDS

**antibacterial resistance, silver nanoparticles, green synthesis, antibacterial activity, sustainability**

## 1 Introduction

Along with the long-term use of antibiotics for bacterial treatment, bacteria evolve in order to survive, leading to bacterial drug resistance (McManus, 1997; Munita et al., 2015). Bacterial resistance is a symptom of bacteria becoming resistant to previous effective antibiotics. Bacterial resistance is a growing threat to global public health since patients with drug-resistant bacterial infections have worse clinical outcomes, face a higher risk of death (Antoniadou et al., 2007), and consume more healthcare resources than patients with non-drug-resistant bacterial infections. For example, *Staphylococcus aureus* (MRSA) is a common cause of serious infections in health facilities and communities (David and Daum, 2010), whereas resistance to the first-line drugs used to treat these infections is universal. Estimated survival rates for patients with methicillin-resistant MRSA infections are 64% lower than for uninfected patients (Sabbagh et al., 2019). Whilst the emergence of bacterial resistance is a natural phenomenon, other main reasons for speeding up the spread of bacterial resistance including the lack of hygienic measures to prevent and control infections, the excessive and inappropriate use of antibiotics.

As a result, many proactive strategies for bacterial resistance have been proposed, including calling for rational use of antibiotics (Solomon and Oliver, 2014), strengthening health systems and regulatory capacity (Courtenay et al., 2019), and tapping into new antibiotics and other

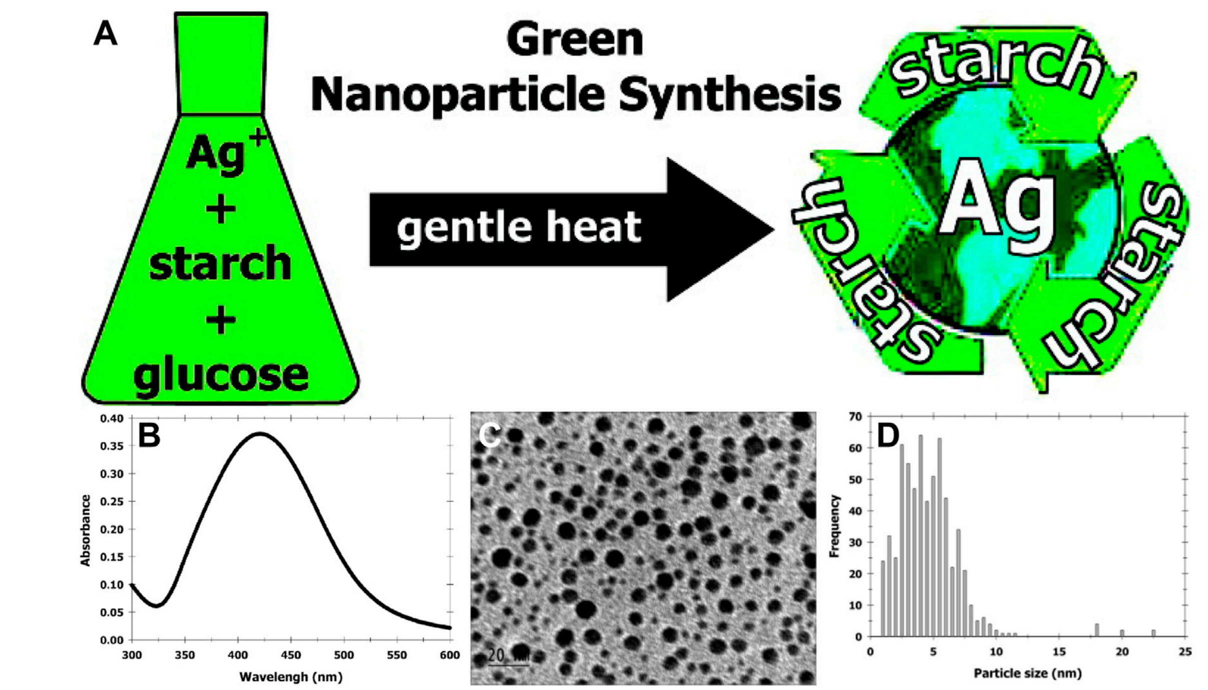


FIGURE 1
**(A)** Schematic of completely "green" synthesis of AgNPs. **(B)** The surface-plasmon absorbance spectrum of AgNPs formed in the aqueous starch dispersion ($\lambda_{max}$ = 419 nm). **(C)** Typical TEM image of starched AgNPs. The scale bar corrresponds to 20 nm. **(D)** Histogram showing the size distribution of the AgNPs (the average particle size = 5.3 nm and σ = 2.6 nm). The total number of particles counted for the histogram is 624. Reproduced with permission from ref (Vigneshwaran et al., 2006). Copyright 2003 American Chemical Society.

antibacterial drugs (World Health, 2012). AgNPs are currently gaining widespread attention as antibacterial agents (Alt et al., 2004; Silver et al., 2006) as it is very difficult for AgNPs to generate bacterial resistance. Also, it is crucial to manufacture nanomaterials in a safe, environmentally friendly and economical manner for further clinical translational applications. Among the many preparation methods for AgNPs, green synthesis with environmentally friendly catch our attention. Here, we overviewed the green preparation methods of AgNPs, including saccharide-based, irradiation-reduction and biosynthesis methods, and gave a systematic comparison of the advantages and disadvantages of these three methods. We also introduced the antibacterial mechanisms and potential side effects of AgNPs for balancing the efficacy and toxic effects of AgNPs in antibacterial therapy. Lastly, a summary of their medical applications is presented, reflecting their potential medical applications.

## 2 Preparation of AgNPs by green synthesis method

### 2.1 Saccharide-based method

Compared with traditional methods for the preparation of AgNPs, the glycosylation method as the first emerging green preparation strategy demonstrates many advantages. Water is used as environmentally friendly solvent throughout the synthesis process, and sugars are used as reducing and stabilizing agents, which fully embodies the concept of green chemistry. In addition, the weak binding interaction of release of silver and is suitable for biomedical applications.

Raveendran and others (Raveendran et al., 2003; Raveendran et al., 2006) first reported a green method for preparing AgNPs (Figure 1A). Silver nitrate ($AgNO_3$) and starch were dissolved in water, and β-D-glucose was added and the reaction was stirred at 40°C for 20 h. Starch and β-D-glucose functioned as stabilizing and reducing agent, respectively. The reaction conditions were mild and no organic solvents or toxic substances were involved. The mixture turned light yellow indicating the formation of AgNPs. The absorption maximum was at 419 nm (Figure 1B) due to the surface plasmon resonance of AgNPs and the size of AgNPs was around 10 nm (Figures 1C,D). In addition, many saccharide-based methods were then developed to synthesize AgNPs, including exploiting different polysaccharides, optimizing the concentration of silver salts and polysaccharides and optimizing the reaction conditions. For example, Many different polysaccharides including heparin (Huang and Yang, 2004), sucrose (Lee S. H. et al., 2014), corn starch (Valodkar et al., 2010) and cellulose (Mohammad et al., 2022) were also explored as reducing and stabilizing agents for

TABLE 1 Summary of saccharide-based AgNPs synthesis method.

| Saccharide | Precursor | Size (nm) | Particle shape | References |
|---|---|---|---|---|
| Starch | $AgNO_3$ | 10 | isotropic in shape | Raveendran et al. (2003) |
| Heparin | $AgNO_3$ | 10–50 | Spherical | Huang and Yang, (2004) |
| Sucrose | $AgNO_3$ | 38–61 | Spherical | Lee et al. (2014a) |
| Corn starch | $AgNO_3$, $Ag_2$ $SO_4$ | 20–25 | Spherical | Valodkar et al. (2010) |
| Cellulose | AgNO | 42 | Spherical | Mohammad et al. (2022) |

the synthesis of AgNPs (Table 1). Vigneshwaran et al. (Vigneshwaran et al., 2006) used starch to obtain stable AgNPs by optimizing the resugars with AgNPs facilitates the action conditions. The mixture was incubated in an autoclave at a pressure of 15 psi and a temperature of 121°C for 5 min. Tai et al. (Tai et al., 2008) obtained small and homogeneous AgNPs using a rotating disc reactor. Subsequently, higher quality AgNPs were gradually obtained by adjusting the starch concentration, $AgNO_3$ concentration and reactor parameters. Besides, several studies have developed the usage of polymers as stabilizers, such as poly (ethylene glycol) (PEG) (Luo et al., 2005; Shameli et al., 2012). The chain length of the polymer affected the reaction rate and the size of AgNPs, specifically, longer polymer chains (e.g., PEG 2000) have higher reactivity than PEG 200 or ethylene glycol. Meanwhile, the large amount of oxygen in the longer PEG chain provided the coordination saturation of the dangling bonds on the surface of the AgNPs, helping to prevent the agglomeration of AgNPs and obtain stable AgNPs (Luo et al., 2005).

## 2.2 Irradiation-reduction method

Irradiation reduction is another method for green preparation of AgNPs. This method does not require additional reducing agents, and the reaction rate induced by irradiation can be clearly defined, which facilitates the control of the reaction process. At the same time, complete and homogeneous AgNPs can be obtained when prepared by this method (Zhang et al., 2003), avoiding the cumbersome post-treatment to remove unreacted silver ions.

The main mechanism for the preparation of AgNPs by irradiation reduction is that water is decomposed by irradiation to produce hydrated electrons, which subsequently reduce silver ions to silver and thus promote the formation of silver clusters (Karim et al., 2007; Long et al., 2007). Therefore, this method generally requires the addition of a cluster stabilizer to prevent silver agglomeration caused by direct irradiation reduction (Shin et al., 2004). The main process for synthesis of AgNPs by irradiation reduction was first to dissolve a certain amount of $AgNO_3$ and biocompatible macromolecules as stabilizer in water, such as amphiphilic polymers (Zhou et al., 1999; Zhang et al., 2003) or natural polysaccharides (Chen et al., 2007). Subsequently, the mixed solution was degassed with nitrogen bubbling for about 30 min, sealed and irradiated at a certain dose at room temperature. Related studies focus on the optimization of radioactive sources and the selection of stabilizers. A variety of radioactive sources can be used to prepare AgNPs, including ultraviolet light (Zhou et al., 1999), visible light (Zhang et al., 2003; Zhang et al., 2010), microwaves (Seku et al., 2018), and high-energy rays (Karim et al., 2007; Lee et al., 2007) (Table 2). Among them, microwaves as a radiation source can greatly reduce the synthesis time because microwaves provide uniform nucleation and growth conditions for nanoparticles (Chen et al., 2008; Hu et al., 2008). In addition, light emitting diode (LED) as radiation sources can control the size, morphology and optical properties of AgNPs. Stamplecoskie et al. (Stamplecoskie and Scaiano, 2010) explored the differences in the size, morphology and optical properties of AgNPs obtained for radiation at wavelength of 405 nm, 455 nm, 627 nm and 720 nm (Figure 2). Under irradiation with 405 nm LED, the particle size of AgNPs gradually increased with irradiation time (Figure 2B). Irradiation of AgNP seeds with a 455 nm LED induced spectral changes, and subsequently transformed their morphology into dodecahedra with narrower polydispersity (Figure 2C). In contrast, AgNPs with a larger distribution of nanoplates and nanorods were obtained with 627 and 720 nm light irradiation (Figures 2D,E). Further, the radiation dose also affects the physicochemical properties of AgNPs. Chen et al. discussed the effect of radiation dose on the size distribution (Chen et al., 2007). They used chitosan as a stabilizer, which degraded into small fragments upon γ-irradiation, and then its interaction with silver through amino chelation prevented silver agglomeration. They found that a slightly lower irradiation dose (~27 kGy) produced AgNPs with a narrower particle size distribution, while a slightly higher irradiation dose (~75 kGy) produced AgNPs with a wider particle size distribution (Chen et al., 2007). Liu et al. proposed the concept of AgNPs with "clean" surfaces (no surfactant or polymer contamination) and obtained the desired clean AgNPs by adjusting the γ-irradiation dose (Liu et al., 2007). This would be a great advantage for no other reagents involved during the preparation, which complying with the concept of green chemistry.

TABLE 2 Summary of irradiation-reduction AgNPs synthesis method.

| Types of irradiations | Irradiation conditions | Precursor | Size (nm) | Particle shape | References |
|---|---|---|---|---|---|
| Ambient light | 2.43 $W/m^2$ | $[Ag(NH_3)_2]^+$ aqueous solution | 10–20 | spherical | Zhang et al. (2003) |
| γ-rays | 10 kGy | $AgNO_3$ | 8 | spherical | Long et al. (2007) |
| Ultraviolet light | | $AgNO_3$ | 15–20 | Nanorods | Zhou et al. (1999) |
| Microwaves | 750 W, 50–90 s | $AgNO_3$ | 9 ± 2 | spherical | Seku et al. (2018) |

## 2.3 Biosynthesis method

Biosynthesis of AgNPs has been extensively studied as an emerging preparation strategy (Table 3). Biosynthesis is a very environmentally friendly process because it does not involve high temperature, high pressure, energy consumption and toxic chemicals, which gives it a great advantage over conventional synthesis methods. The general process of biosynthesis is to isolate the desired raw material from a natural resource and boil it, after which the bioactive components are extracted and then incubated with a silver ion solution to produce AgNPs.

### 2.3.1 Microorganism

Microorganisms are commonly used for the biosynthesis of AgNPs, including bacteria (Lateef et al., 2015; Wang et al., 2016; Saravanan et al., 2018; Ameen et al., 2020), fungi (Guilger-Casagrande et al., 2019; Hamad, 2019; Hu et al., 2019), and algae (Sinha et al., 2015; Muthusamy et al., 2017; Massironi et al., 2019). Microbial-based biosynthesis strategies are generally classified into intracellular and extracellular synthesis. In principle, AgNPs with more uniform size and shape distribution can be obtained by intracellular synthesis, but the collection and post-processing of the products are relatively cumbersome and expensive. Therefore, most studies on the biosynthesis of AgNPs have focused on the extracellular pattern.

Silver-resistant bacteria are the main microorganisms for microbial-based synthesis of AgNPs. A bacterial strain-*Weissella oryzae* DC6, isolated from mountain ginseng, has been first used for green and convenient synthesis of AgNPs, the secreted proteins and enzymes are responsible for the reduction of silver ions (Singh et al., 2016). Gandhi and others (Gandhi and Khan, 2016) also synthesized AgNPs via *Escherichia coli*, incubation of silver ions in the supernatant of *Escherichia coli* leaded to the extracellular reduction of metal ions and the formation of AgNPs (Figure 3). In addition, synthesis of AgNPs in fungi offers many advantages, as fungi grows rapidly and can secrete large amounts of enzymes, which producing abundant raw material for the synthesis. Furthermore, fungi can withstand the agitation and flow pressures of bioreactor. Laryssa et al. first reported that AgNPs were synthesized extracellularly using nematophagous fungus *Duddingtonia flagrans*. They obtained the cell-free fungal filtrates from *Duddingtonia flagrans*, and analyzed the total protein content and chitinase activity in the filtrates, which could act as a reducing agent for the synthesis of AgNPs. This method produced high yield of AgNPs with good stability (Costa Silva et al., 2017). Singh et al. prepared AgNPs on the endophytic fungus *Alternaria* sp. Isolated from healthy leaves of *Raphanus sativus*, which showed effective antibacterial effect against human pathogenic bacteria (Singh et al., 2017).

Microbial-based method for the preparation of AgNPs has many advantages, as it is a complete green reaction process without using industrial chemical reagents, and simple operations with low energy consumption. In addition, the prepared AgNPs are naturally coated with proteins secreted by biomass, showing high stability and excellent biocompatibility for further applications (Chowdhury et al., 2014).

### 2.3.2 Plants

Plant-mediated reduction systems have also been widely investigated due to their simplicity, eco-friendly and the potential medicinal value of the plants themselves (Sengottaiyan et al., 2016a; Sengottaiyan et al., 2016b; Escárcega-González et al., 2018; Wang et al., 2018; S.S et al., 2019). A major advantage of using plant extracts for synthesis of AgNPs is that complex cell culture processes can be avoided, facilitating the post-processing of the products and their further industrial application (Sudhakar et al., 2015). The biomolecules in plant extracts can act as both reducing agents and stabilizer during AgNPs formation and can even exert their own antibacterial effect (Ghorbani et al., 2015).

Wang et al. synthesized AgNPs using aqueous extracts from *Psidium guajava* L. They demonstrated that AgNPs could be formed in 10 min after the mix of $AgNO_3$ and extracts, and the reaction was basically completed after 2 h (Figures 4A,B) (Wang et al., 2018). The reduction rate of plant-based synthesis was significantly improved compared to biosynthetic methods based on fungi, bacteria, etc., which require about 24 h to obtain large amounts of AgNPs. Also, they found that the resulting AgNPs had excellent antibacterial effects against both common Gram-positive and Gram-negative bacteria (Figure 4C) (Wang et al., 2018). Selvam et al. used *Tinospora cordifolia* (Thunb.) Miers for eco-friendly synthesis of AgNPs. They studied the influence

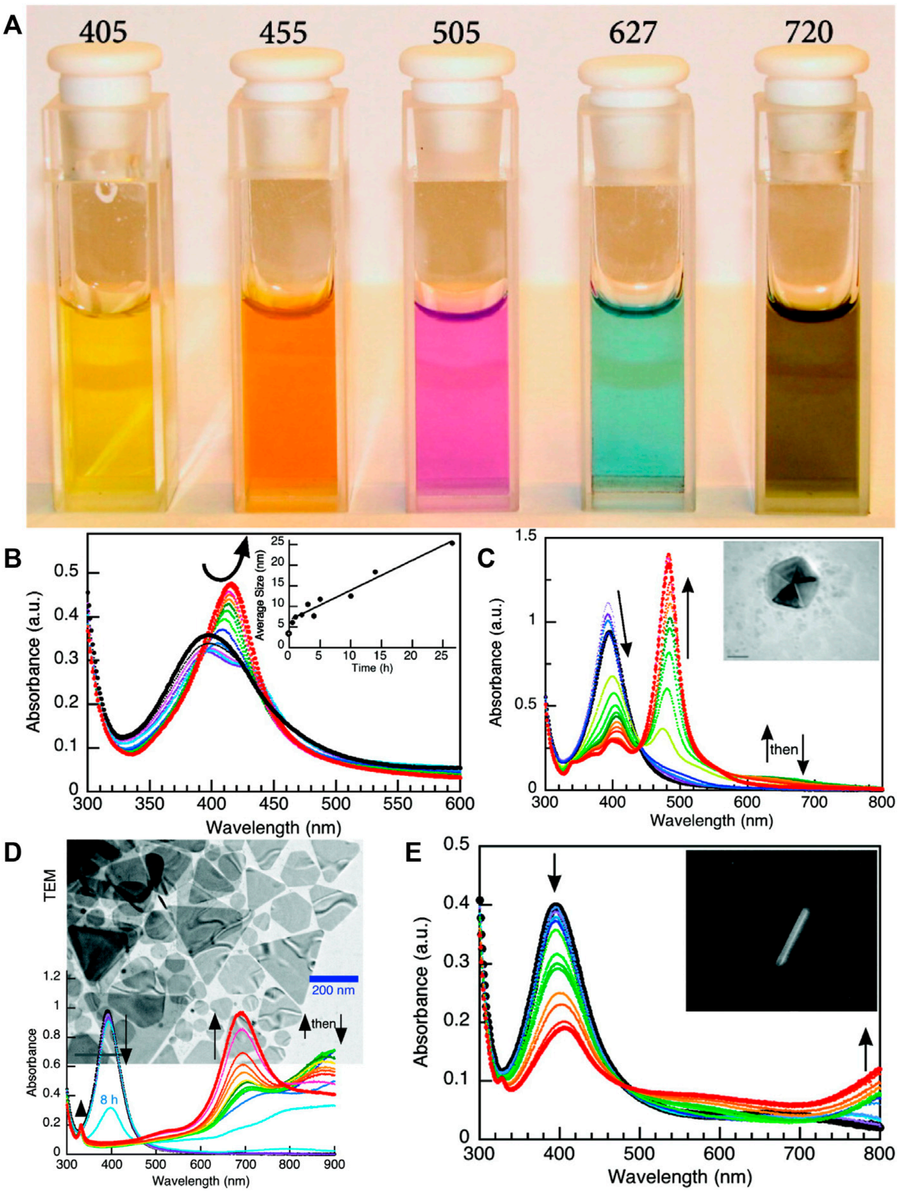


FIGURE 2
**(A)** Image of the various colloidal solutions produced under the corresponding LED irradiation at the wavelength indicated (in nm) at the top of each cuvette. **(B)** UV-vis spectral change upon 405 nm irradiation (initial in black, final in red) and (inset) change in particle size (determined by scanning electron microscopy (SEM)) against irradiation time. **(C)** UV-vis spectral change during 455 nm LED excitation (initial in black, final in red); note that at ~650 nm the maximum absorbance increases and then decreases at intermediate times (green) during conversion. The inset shows TEM image for a representative particle (size bar = 20 nm). **(D)** UV-vis spectral change and TEM image (background) during 627 nm LED excitation of AgNP seeds with ~900 nm absorption increase and then decrease during the overall conversion. **(E)** UV-vis spectral change during 720 nm LED irradiation as well as an exceptionally large aspect ratio nanorod (inset). Reproduced with permission from ref (Stamplecoskie and Scaiano, 2010). Copyright 2010 American Chemical Society.

factors ($AgNO_3$, leaf, incubation time, and pH) by response surface methodology of Box--Behnken design (BBD) to optimize synthesis conditions. Under optimal conditions, the silver ions were reduced to AgNPs within 30 min by heating (60 °C) of *T. cordifolia* extract mixed with silver ions (Selvam et al., 2017). In addition to plant leaves, flowers have also been studied for the biosynthesis of AgNPs (Aravinthan et al., 2015; Chinnappan et al., 2018; Ameen et al., 2019), bioactive components extracted from flowers can also exert antimicrobial effects. Aravinthan and others reported a rapid green synthesis of AgNPs using an aqueous extract of *Helianthus tuberosus* (sunroot tuber). The ability of the biomolecules

TABLE 3 Summary of biosynthesis AgNPs synthesis method.

| Types of biomaterials | | Precursor | Size (nm) | Particle shape | References |
|---|---|---|---|---|---|
| Microorganism | Bacteria | $AgNO_3$ | 10–50 | spherical | Lateef et al. (2015); Wang et al. (2016); Saravanan et al. (2018); Ameen et al. (2020) |
| | Fungi | $AgNO_3$ | 3–20 | spherical | Guilger-Casagrande et al. (2019); Hamad, (2019); Hu et al. (2019) |
| | Algae | $AgNO_3$ | 5–50 | spherical | Sinha et al. (2015); Muthusamy et al. (2017); Massironi et al. (2019) |
| Plants | Leafs | $AgNO_3$ | 25 | spherical | Wang et al. (2018) |
| | Flowers | $AgNO_3$ | 10–20 | spherical | Aravinthan et al. (2015); Chinnappan et al. (2018); Ameen et al. (2019) |
| | Seaweed | $AgNO_3$ | 20–30 | spherical | Valarmathi et al. (2020) |
| Food and agricultural waste | cow milk | $AgNO_3$ | 10–100 | spherical | Williams et al. (2022) |
| | Coffee | $AgNO_3$ | 25 | spherical | Chien et al. (2019) |
| | vegetable oilcake | $AgNO_3$ | 30–150 | polygonal | Singhal and Gupta, (2019) |
| | Peels | $AgNO_3$ | 10–50 | spherical | Soto et al. (2019) |
| | Wood | $Ag(NH_3)_2OH$, $AgNO_3$, $Ag(NH_3)_2NO_3$, $Ag_2O$ | 5–50 | spherical | Xue et al. (2018) |
| | other agricultural industrial wastes | $AgNO_3$ | 10–90 | spherical | Mythili et al. (2018) |

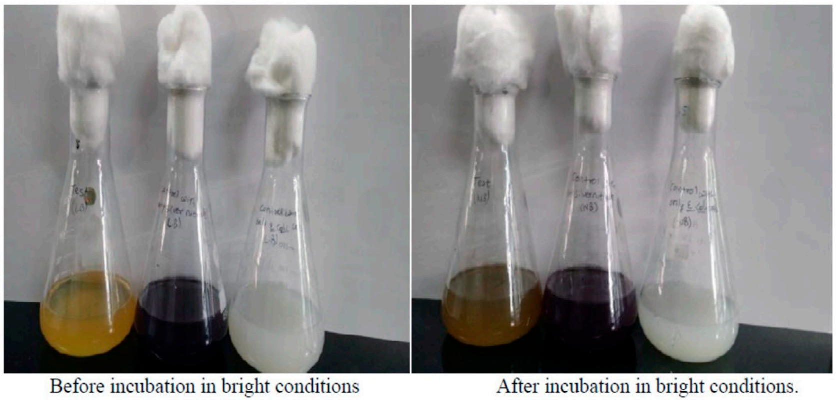


FIGURE 3
Color change from yellow to brown after incubation with *Escherichia coli* indicates presence of silver nanoparticles. Reproduced with permission from ref (Gandhi and Khan, 2016). Copyright 2016 Elsevier.

extracted from tuber reducing $Ag^+$ in solution was confirmed by the stretching vibrations of amines and alkaloids observed by fourier transform infrared spectroscopy (FTIR). They also investigated the antibacterial activity of AgNPs synthesized from tuber extracts against phytopathogenic bacteria, namely, *R. solanacearum* and *X. axonopodis*, and the results showed that the tuber extracts synergistically enhanced the antibacterial properties of AgNPs against the phytopathogenic bacteria (Aravinthan et al., 2015). Mango flower extract was also used as a bio-reducing agent for the synthesis of AgNPs. The obtained AgNPs were effective against Gram-negative bacteria *Klebsiella* sp., *P. agglomerans*, and *Rahnella* sp. At 10 mM of AgNPs (Ameen et al., 2019). In addition, other abundant seaweed extracts have also been developed for the synthesis of AgNPs, such as *Spyridia filamentosa* (Valarmathi et al., 2020), *Caulerpa racemose* (Kathiraven et al., 2015) and *Gracilaria birdiae* (de Aragão et al., 2019). The wide source of plants and their easy availability, and some plants possess antibacterial activity, all these contribute to the beneficial prospect of this method.

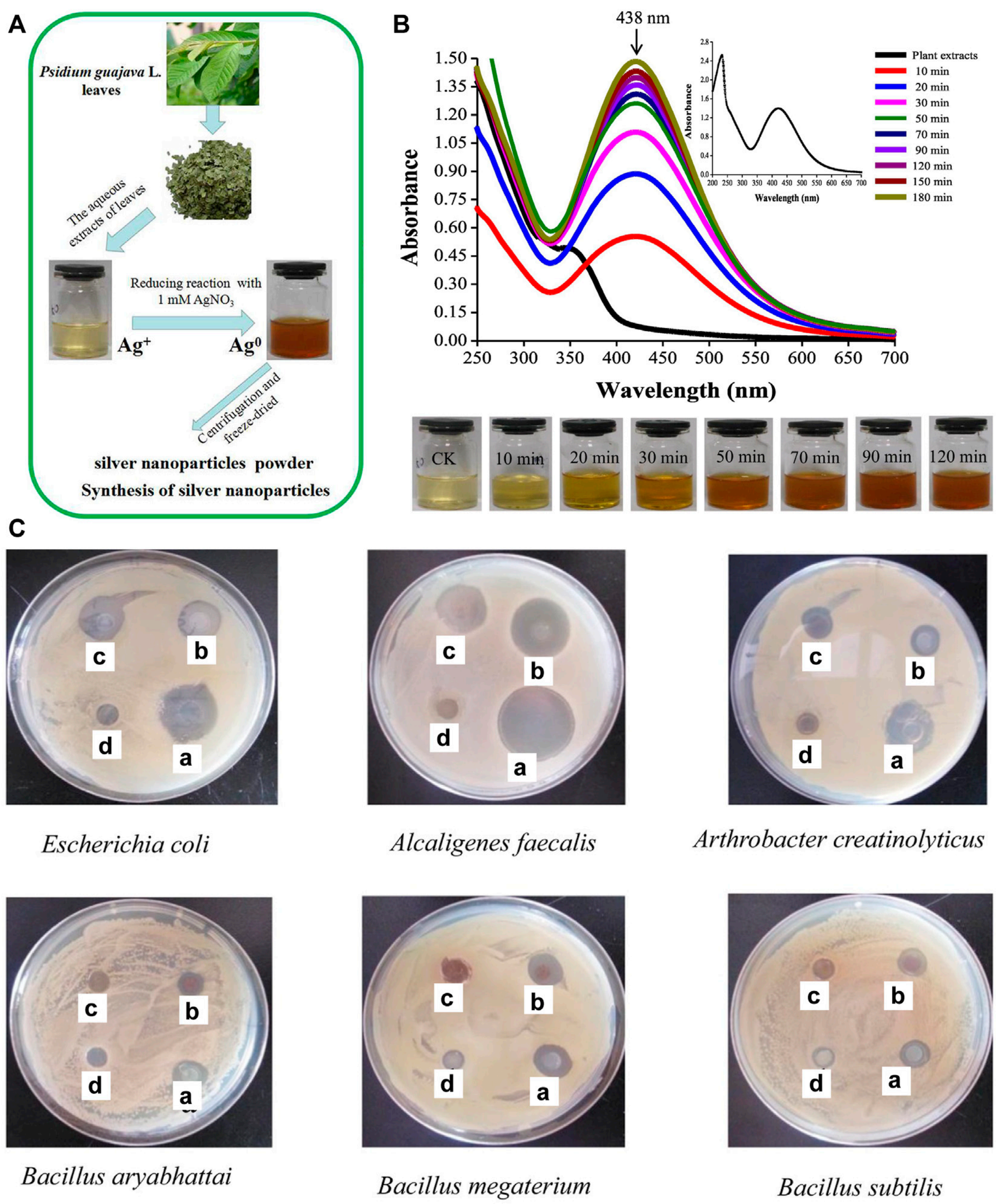


FIGURE 4
**(A)** Schematic of synthesis of AgNPs using *P. guajava* L. leaf extracts. **(B)** UV-vis spectra of the bioreduction kinetics in the range of 200–700 nm for a colloidal $AgNO_3$ solution with *P. guajava* L. leaf extracts; the inset upper right is the UV-vis spectra of *P. guajava* L. leaf extracts and the inset below shows the solution color changes over time. CK: the aqueous extracts of *P. guajava* L. leaf. **(C)** Activity of P-AgNPs formed by the reduction of $AgNO_3$ with aqueous extracts from *P. guajava* L. leaves against selected bacterials depicting zones of inhibition of (a) positive control-ampicillin, (b) P-AgNPs, (c) $AgNO_3$ control, (d) *P. guajava* leaf aqueous extracts. Reproduced with permission from ref (Wang et al., 2018). Copyright 2018 Elsevier.

### 2.3.3 Food and agricultural waste

The development of food and agricultural waste for the synthesis of AgNPs provides a sustainable way to effectively utilize the waste. In recent years, cow milk (Williams et al., 2022), coffee extracts (Chien et al., 2019), vegetable oilcake (Singhal and Gupta, 2019), peels (Soto et al., 2019), wood (Xue et al., 2018) and other agricultural industrial wastes (Mythili et al., 2018) have been widely developed for the synthesis of AgNPs.

Economical and readily available milk was reported to synthesize AgNPs, and the presence of proteins in milk may be responsible for the reduction of $Ag^{+}$. TEM results showed that AgNPs mainly existed in the form of aggregates, which might be caused by the presence of lipids in milk (Lee et al., 2013). However, this problem could be controlled by changing the reaction parameters, such as pH, temperature and reactant concentration (Nguyen et al., 2013). Due to reducing active ingredient chlorogenic acid (CGA), green coffee bean extracts have also been developed for the synthesis of AgNPs (Wang et al., 2017). Govarthanan et al. (Govarthanan et al., 2014) used a traditional Indian agricultural formulation panchakavya, a mixture of microorganisms, to synthesize AgNPs without any contamination. Coconut (*Cocos nucifera*) oil cake (COC) is a by-product that extracts oil from the dried copra. It contains starch, soluble sugar, protein, lipid and trace nitrogen, the reducing components of which can also be used for the synthesis of AgNPs (Govarthanan et al., 2016). And plant waste Sal deoiled seed cake (DOC) can also be used to extract AgNPs from discarded X-ray sheets (Singhal and Gupta, 2019). In addition, the synthesis of AgNPs using vegetable waste extracts from the market has also been reported (Mythili et al., 2018). The raw materials for this method are all waste, representing a promising sustainable route. This synthetic route is "green" in that: 1) waste is used as a resource for the synthesis of AgNPs, 2) non-critical environmental synthesis conditions make it energy-efficient and cost-effective, and 3) no organic solvents are involved, making it environmentally friendly and economical (Devadiga et al., 2015).

In short, several environmentally friendly green methods for the synthesis of AgNPs are presented in this section, including saccharide-based method, irradiation reduction method and biosynthesis method. The saccharide-based method as the first emerged green synthesis does not involve environmentally unfriendly materials in the whole process. However, as a preliminary attempt, there are some disadvantages, such as the need for high temperature and pressure, and the unclean surface of the obtained AgNPs, requiring suitable post-treatment for their further applications. While irradiation-reduction method shows some advantages, such as the high controllability of the reaction process. It allows the obtained AgNPs to be controlled in size and morphology, and even to achieve a completely clean surface, which is great beneficial for further applications. But it has special requirements for the equipment and the reaction process is more tedious. Specifically, the reducing and stabilizing agents used in the biosynthesis process come from nature, which are widely available and easily accessible for mass production. Among them, plant-mediated synthesis could significantly increase the reaction rate, and own medicinal value of extracted plants might be synergistic with AgNPs for efficient antibacterial purposes. While the food and agricultural waste method reflects the concept of economic benefits of waste utilization and sustainable development, which is very compatible with the concept of green synthesis. Altogether, each of these green synthesis methods has its own advantages and can be chosen specifically according to the purpose of application of AgNPs.

# 3 Antibacterial mechanisms of AgNPs

The resistance of bacteria to antibiotics is based on three general mechanisms (Kumarasamy et al., 2010; Wilson, 2014; Blair et al., 2015): 1) production of enzymes that degrade drugs, 2) alteration of drug targets, and 3) reduction of the permeability of bacterial cell membranes to drugs. Unlike the antibacterial mechanism of traditional antibiotics, the unique antibacterial mechanism of AgNPs effectively avoid the occurrence of bacterial resistance.

## 3.1 Release of silver ions from AgNPs

Many hypotheses have been proposed for the antibacterial mechanism of AgNPs, presenting that AgNPs are transformed into silver ions after entering bacterial cells and exert antibacterial effects by interacting with various intracellular biomolecules. For example, silver ions can bind to sulfhydryl enzymes within bacteria, thereby denaturing the enzymes, which are necessary for the normal metabolism of antibacterial drugs (Liau et al., 1997; McDonnell and Russell, 1999). Silver ions can also bind to the DNA of bacteria, changing the conformation of DNA, causing dysfunctional DNA and exerting antibacterial effects (Feng et al., 2000; Arakawa et al., 2001). In addition, silver ions can mediate the release of potassium ions from microbial plasma (Russell and Hugo, 1994b; Holt and Bard, 2005). It has also been reported that silver ions are associated with elevated intracellular ROS levels (Park et al., 2009). The interference of silver ions with the respiratory chain of bacteria increases the production of ROS and exhibits efficient bactericidal activity.

## 3.2 AgNPs-mediated destructive effect on bacterial membranes

Apart from releasing silver ions for antibacterial activity, AgNPs can also perform antibacterial functions by directly disrupting bacterial membranes and then penetrating to microorganisms, as evidenced by the forming "pits" on the membrane surface after treating with AgNPs (Sondi and Salopek-Sondi, 2004; Choi et al., 2008). Nevertheless, the size and shape of AgNPs have a significant effect on their ability to bind to bacterial membranes. AgNPs with {111} facets had been reported to interact directly with the bacterial surface (Morones et al., 2005), while the truncated triangular AgNPs with {111} lattice plane showed stronger bactericidal effects than other shape structures, such as spheres (Pal et al., 2007).

### 3.3 Other antibacterial mechanisms of AgNPs

Additional antibacterial mechanisms of AgNPs have been reported. For exsample, Kalishwaralal et al. (Kalishwaralal et al., 2010) explored the potential anti-biofilm activity of AgNPs with *Pseudomonas aeruginosa* and *Staphylococcus epidermidis*, which were the source of many chronic bacterial infections. More than 95% of biofilm formation were inhibited by treating these bacteria with AgNPs, resulting in inhibition of bacterial growth. The other well mentioned antibacterial mechanism is that AgNPs may induce an apoptosis-like response with bacteria (Lee W. et al., 2014), including phosphatidylserine externalization (early apoptosis) and DNA damage (late apoptosis) (Bao et al., 2015).

Taken together, AgNPs are different from conventional antibiotics that can trigger bacterial resistance. AgNPs are acting in a new antibacterial paradigm that contribute to breaking the dilemma of antibiotic-induced bacterial resistance.

## 4 Potential toxicity

AgNPs-containing products are widely used in daily life. Human being may be exposed to AgNPs-containing products in different ways (inhalation, skin contact and ingestion), thus unconsciously taking in heavy metal compounds and causing potential harm to the body. Ji et al. (Ji et al., 2007) exposed rats to certain concentrations of silver and showed no significant changes in lung tissue after 28 days, according to the current American Conference of Governmental Industrial Hygienists (ACGIH) silver dust limit (100 μg/m$^3$). Park et al. (Park et al., 2007) studied the cytotoxicity of AgNPs in alveolar epithelial cells and found that even at high concentrations of AgNPs (200 μg/ml), the apoptosis rate was less than 12% and the degree of DNA fragmentation was less than 2%, confirming the relatively low toxicity of AgNPs to the lung. From these works, it can be concluded that the effect of AgNPs on the lung is negligible, probably due to the high atomic mass of Ag. The effect of AgNPs on the skin has also been investigated. The cytotoxicity of AgNPs-containing antimicrobial wound dressings was evaluated with human epidermal keratin-forming cells and human fibroblasts, and it was found that AgNPs could not distinguish between healthy cells and pathogenic bacteria involved in wound healing and had a certain degree of cytotoxicity (Lam et al., 2004; Poon and Burd, 2004; Paddle-Ledinek et al., 2006; Arora et al., 2008; Samberg et al., 2010).

The liver and kidneys are the main organs that take up and metabolize nanoparticles, so it is crucial to assess the effects of AgNPs on these organs. To that end, the BRL 3A immortal rat liver cells were incubated with AgNPs for 24 h. Hepatocytes showed increased leakage of lactate dehydrogenase (LDH) and mitochondrial dysfunction, displaying marked cytotoxicity (Figure 5) (Hussain et al., 2005). And the depletion of reduced glutathione (GSH) in hepatocytes suggests that hepatotoxicity is related to oxidative stress, which is one of the antibacterial mechanisms of AgNPs. Cytotoxicity of AgNPs to HepG2 human hepatoma cells at high concentrations (>1 mg/L), but no apparent cytotoxicity below that concentration (Kawata et al., 2009). Moreover, gender differences in renal silver accumulation have been reported (Kim et al., 2008). Female rats showed large accumulation of AgNPs in all regions of the kidney (cortex, outer medulla and inner medulla), and the accumulation of AgNPs in cortical glomeruli was obviously higher in females than in males (Kim et al., 2009). These relevant studies illustrate the tendency of silver to accumulate in the liver and kidneys with toxic effects. There are also studies reported that AgNPs could accumulate in the brain and exhibit neurotoxicity. Tang et al. found that AgNPs could cross the blood-brain barrier. Long-term exposure to AgNPs might lead to neuronal lesions and necrosis (Tang et al., 2008). Lee et al. (Lee et al., 2010) investigated the effect of AgNPs on gene expression in the mouse brain using affymetrix mouse genome arrays and found that 468 genes in the brain and 952 genes in the cerebellum were sensitive to AgNPs. Given the potential hazards of AgNPs to humans, we need to take a critical view of the antibacterial activity and potential toxicity of AgNPs. It should prescribe appropriate doses for administration according to different therapeutic purposes. Importantly, the size and morphology of AgNPs can be modulated, their surface can be optimized modification to reduce cytotoxicity and enhance therapeutic effects.

## 5 Medical application of AgNPs

As described above, it is difficult for AgNPs to develop resistance to antimicrobial therapy because silver resistance requires a generation of bacteria to undergo three independent mutations in three different bacterial systems (Alt et al., 2004; Silver et al., 2006). Owing to the unique advantages, AgNPs are often employed as antimicrobial agents in medical applications to ward off infections (Table 4).

### 5.1 Wound dressing

Blisters repeatedly appear during wound healing after deep burns, which are prone to ulcerate and infect to form residual wounds (Huang et al., 2007). Additionally, local wounds are classified into acute and chronic wounds according to their nature and recovery time. Chronic trauma is a fertile ground

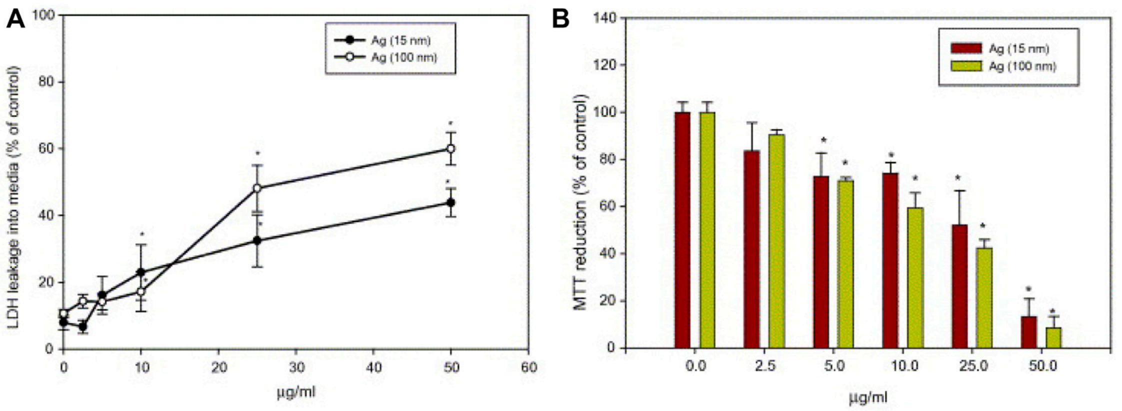


FIGURE 5
**(A)** Effect of AgNPs on LDH leakage in rat liver cells BRL 3A cells. **(B)** Effect of nanoparticles on mitochondrial function in rat liver cells (BRL 3A cells). Cells were treated with different concentrations of AgNPs for 24 h. Reproduced with permission from ref (Hussain et al., 2005). Copyright 2005 Elsevier.

TABLE 4 Summary of medical products containing AgNPs.

| Medical products containing AgNPs | Functions | Applications | References |
|---|---|---|---|
| Wound dressing | to inhibit biofilm formation and wound infection | wound dressing | Huang et al. (2007); Sacco et al. (2015) |
| Implants | to avoid infection | heart valves, bone graft devices, orthopedic implants | de Mel et al. (2012); Huang et al. (2017); van Hengel et al. (2020) |
| Medical catheters | for clinical care | indwelling catheters | Thokala et al. (2018); Bhargava et al. (2018) |
| Dental composites | to inhibit the adhesion and proliferation of pathogens | dental bone cements, titanium implants | Akhavan et al. (2013); Chladek et al. (2013); Ai et al. (2017); Chambers et al. (2017) |

for biofilm formation, which is one of the causes of bacterial resistance (Sacco et al., 2015). Over the past decades, AgNPs have been extensively studied in wound healing, and although silver is relatively inert and difficult to absorb by mammalian or bacterial cells, it is readily ionized by wound fluid or other secretions. When bound to proteins and cell membranes, ionized silver becomes highly active, inhibiting biofilm formation and wound infection (Atiyeh et al., 2007). Silver sulfadiazine has been considered the gold standard for the treatment of local burns, but subsequent studies have found that it delays the wound healing process and is accompanied by severe cytotoxicity (Russell and Hugo, 1994a; Atiyeh et al., 2007). Actually, ideal wound dressing should meet the following requirements: good mechanical strength and breathability, excellent exudate absorption, blood and cell compatibility, etc. AgNPs-containing antibacterial wound dressings prepared by electrostatic spinning and *in situ* reduction of surface silver ions using biocompatible macromolecules such as polymers (Hong et al., 2006; GhavamiNejad et al., 2015; GhavamiNejad et al., 2016; Unnithan et al., 2016; Augustine et al., 2018) and biomacromolecules (Lu et al., 2008; Madhumathi et al., 2010; Singh and Singh, 2014; Biswas et al., 2018; Wu et al., 2018) as substrates can achieve good therapeutic effects. For example, a wound dressing consisting of AgNPs and chitosan was prepared by self-assembly, which passed sterility and pyrogenic safety evaluations in tests with deeper thick wound Sprague-Dawley rat model (Lu et al., 2008). Further, MADO-AgNPs prepared by coating AgNPs on a novel electrospun nanofiber material, poly (methyl methacrylate-dopamine methacrylamide, MADO), exhibited good antibacterial activity *in vitro* and good wound healing ability *in vivo* (Figure 6) (GhavamiNejad et al., 2015).

## 5.2 Implants

Implants are widely used in clinical treatment, but since they are exogenous materials, they tend to trigger an immune response in the body and expose patients to infections. Bacterial infections

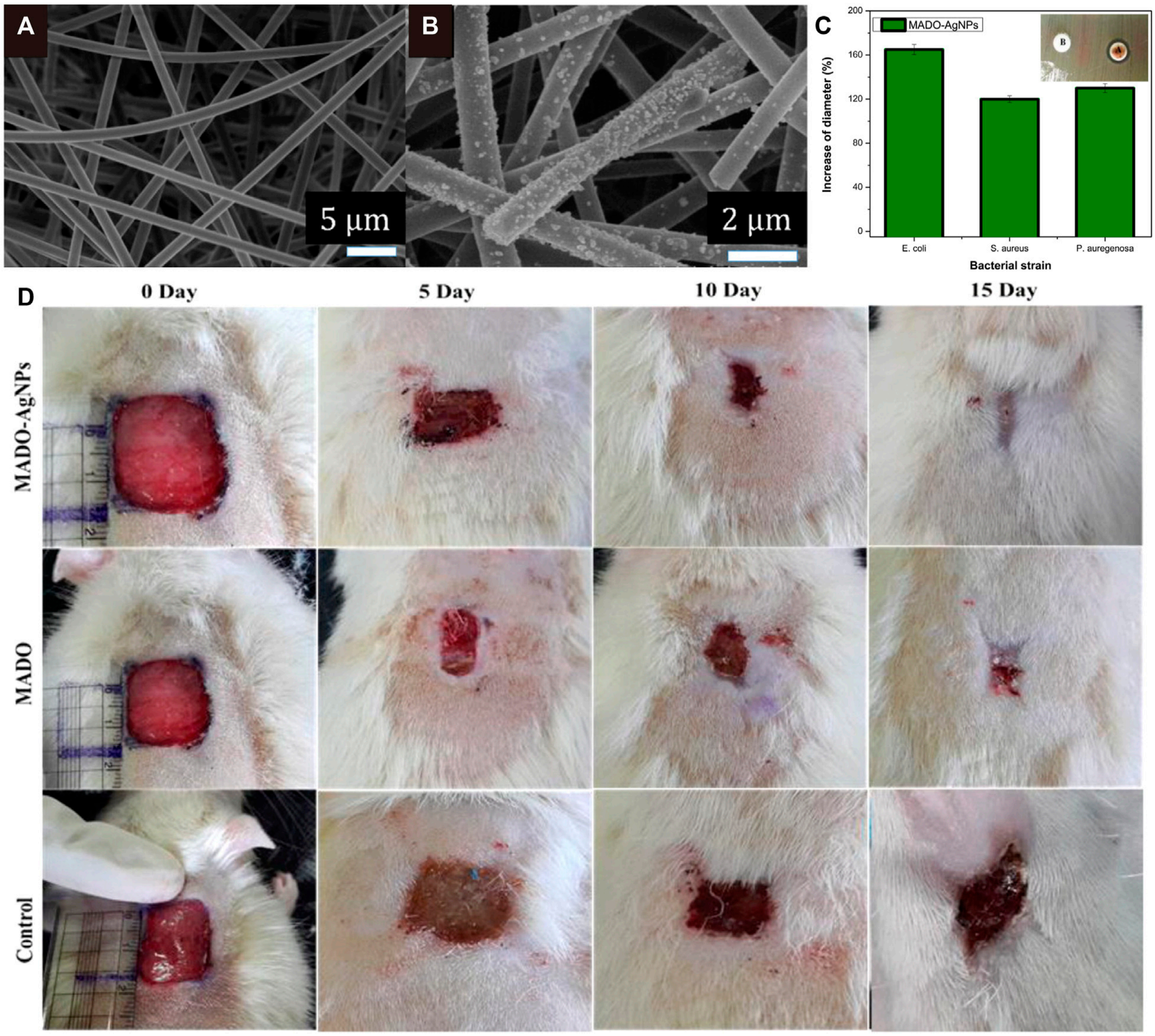


FIGURE 6
**(A)** and **(B)** Field emission scanning electron microscopy (FESEM) images of MADO nanofibers and MADO-AgNPs nanofibers. **(C)** Results of the antibacterial activity of MADO-AgNPs electrospun membranes against *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Escherichia coli*. The inset shows a comparison of **(A)** MADO-AgNPs nanofiber and **(B)**MADO nanofiber on a Lysogeny broth (LB)-agar plate covered with *Pseudomonas aeruginosa*. **(D)** Wound appearance at 0, 5, 10, and 15 days after grafting with MADO-AgNPs, MADO nanofiber, and bare. Reproduced with permission from ref (GhavamiNejad et al., 2015). Copyright 2015 American Chemical Society.

of implants are usually caused by *Staphylococci*, as the bacteria tend to adhere to the surface of the implants, forming biofilm and inducing infection (van de Belt et al., 2001). The use of high-dose antibiotics to prevent implant infection during transplantation has been attempted in the clinic, but the action duration is limited (Oliveira et al., 2018). Therefore, it is an urgent need to develop implants that are resistant to bacteria. A potential strategy is to deposit antimicrobial substances on the surface of the implant. AgNPs are excellent antibacterial agents with drug-resistant *Staphylococci*, widely deposited on the implant surface to avoid infection. To date, implants surface deposited with AgNPs have focused on various medical devices, such as heart valves (Grunkemeier et al., 2006; Ghanbari et al., 2009; de Mel et al., 2012), bone graft devices (Zheng et al., 2010; Travan et al., 2011; Zhao et al., 2011; DeVasConCellos et al., 2012; van Hengel et al., 2020) and orthopedic implants (Liu et al., 2012; Fordham et al., 2014; Huang et al., 2017). For example, Andara et al. developed a multi-component target pulse laser deposition process to prepare a diamond-like carbon-silver composites and validated their promising hemocompatibility as a coating for cardiovascular

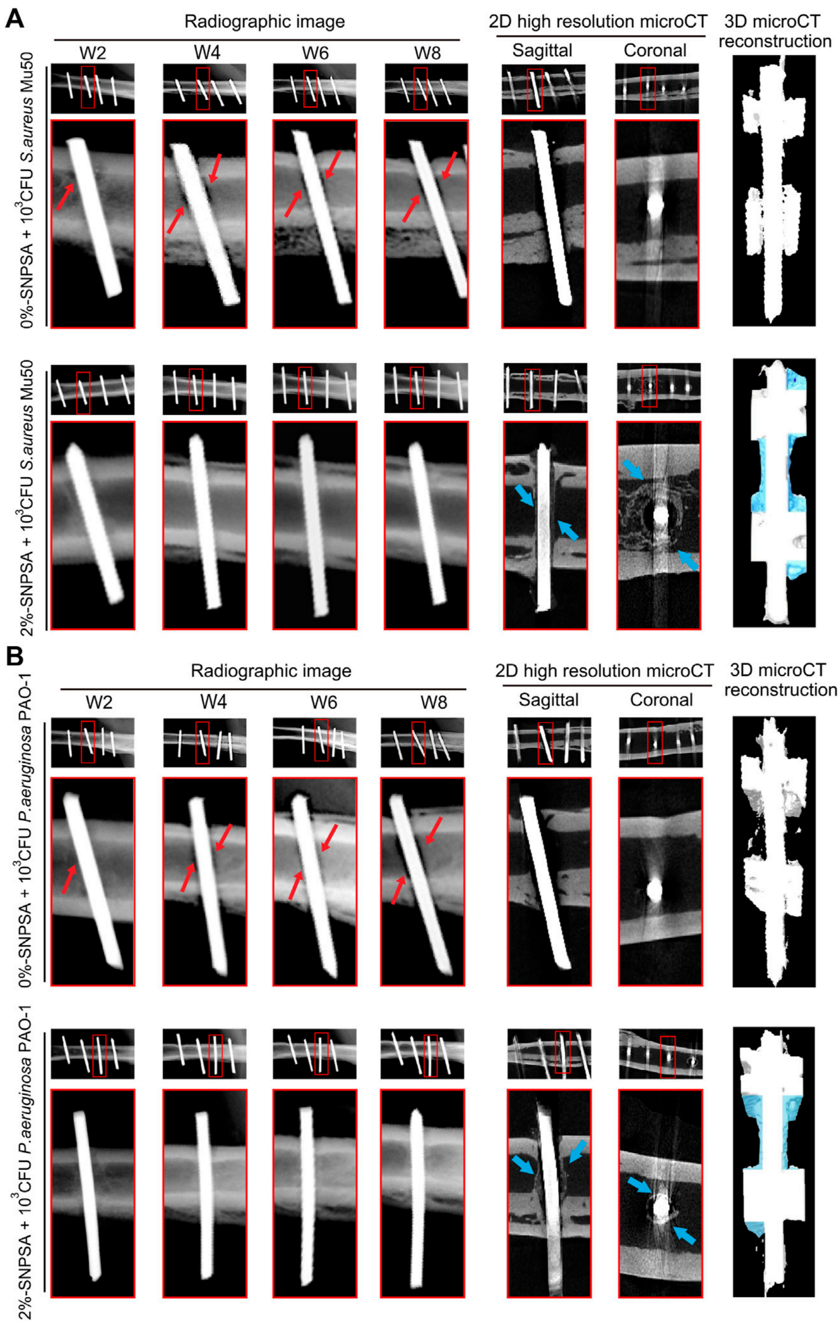


FIGURE 7
Radiographic images of contaminated 0 %- and 2 %-SNPSA implants in rat femoral canal (FC) model. $10^3$ CFU *S. aureus* Mu50 **(A)** or *P. aeruginosa* PAO-1 **(B)** in 10 μL PBS ($10^5$ CFU/ml) was pipetted into the canal before implantation for bacterial invasion. Radiographic evidence of osseous destruction (red arrows), without any obvious signs of bone formation up to 8 weeks post-surgery, was detected in the contaminated 0%-SNPSA group. In contrast, significant bone formation surrounding 2%-SNPSAs implanted in rat FCs at week eight post-implantation (shown as blue arrows in 2D resolution micro-computed tomography (microCT) images), without significant osteolysis, was detected. Newly formed bone around 2%-SNPSA implants was highlighted in 3D microCT reconstruction images (blue shading). Reproduced with permission from ref (Liu et al., 2012). Copyright 2012 Elsevier.

implants (Andara et al., 2006). Liu et al. reported AgNPs/poly (DL-lactic-co-glycolic acid)-coated stainless steel alloy (SNPSA) as a potential antibacterial implant material that exhibited strong antibacterial activity *in vitro* and *in vivo* without interfering with bone morphogenetic protein 2 (BMP-2) for bone formation (Figure 7) (Liu et al., 2012).

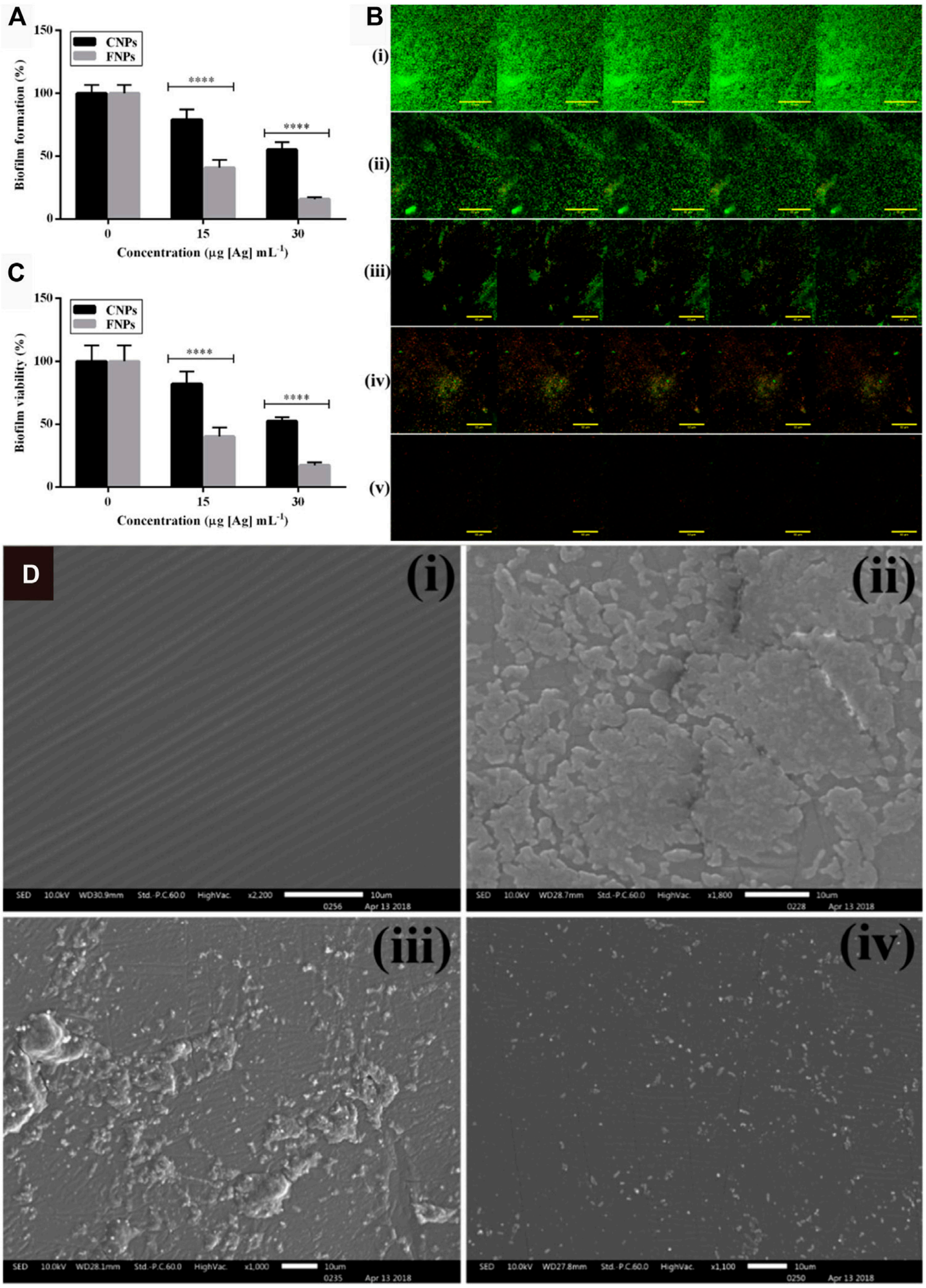


FIGURE 8
**(A)** Biofilm formation by bacterial cells exposed to CNPs and FNPs assessed by Crystal violet (CV) staining assay (n = 8). **(B)** Composite confocal laser scanning microscopy (CLSM)-stacked image of live/dead stained biofilm formed by cells exposed to CNPs and FNPs: i) Untreated/control, ii) 15 μg [Ag] mL$^{-1}$ CNPs, iii) 15 μg [Ag] mL$^{-1}$ FNPs, iv) 30 μg [Ag] mL$^{-1}$ CNPs, and v) 30 μg [Ag] mL$^{-1}$ FNPs. **(C)** Effect of CNPs and FNPs on the bacterial viability in established biofilm. **(D)** SEM imaging of the silicone rubber disc: i) blank, ii) control, iii) CNP- and (iv) FNP-loaded discs at a concentration of 80 μg [Ag] g$^{-1}$. Reproduced with permission from ref (Bhargava et al., 2018). Copyright 2018 American Chemical Society.

## 5.3 Medical catheters

The risk of chronic catheterization-related infections is extremely high, such as catheter-associated urinary tract infections (Thokala et al., 2018), intravascular infections (Hsu et al., 2010; Paladini et al., 2013) and cerebrospinal fluid infections (Lackner et al., 2008). AgNPs could also be utilized to coat catheters destined for clinical care. Roe et al. demonstrated that surfactant-modified AgNPs coated on the surface of catheters can reduce the risk of infectious complications in patients with indwelling catheters by continuously releasing sterilized silver at the implantation site (Roe et al., 2008). Besides, Zhang et al. developed a silver-tetrafluoroethylene nanocomposite coating with catheters by simple wet chemical method, which was able to decrease biofilm coverage up to 97.4% compared to commercial silicone tubes (Zhang et al., 2019). The colonization of fucose-functionalized silver nanoparticles (FNPs) on urinary catheters revealed superior biofilm resistance and antibacterial effect on silicone rubber compared to citrate-encapsulated silver nanoparticles (CNPs), attributed to their strong attachment capacity with bacterial and penetrating into bacterial cells (Figure 8) (Bhargava et al., 2018).

## 5.4 Dental composites

*Streptococcus mutans* is the main microorganism that causes tooth decay. Initial adhesion of specific oral bacteria to the tooth surface or artificial dental matrix is a prerequisite for the formation of pathogenic biofilms (Magalhães et al., 2012). Dental modification materials should preferentially manifest antimicrobial properties at an early stage in order to inhibit the adhesion and proliferation of pathogens. For this purpose, the incorporation of AgNPs into dental bone cements or silver plating on their surface can generate an antibacterial effect (Akhavan et al., 2013; Chladek et al., 2013; Ai et al., 2017; Chambers et al., 2017). A report evaluated the antibacterial activity of three AgNPs-modified dental bone cements (Sealapex, RelyX ARC and Vitrebond) and noticed that the antibacterial activity of Vitrebond was enhanced by the addition of AgNPs (Magalhães et al., 2012). With the aim of improving biocompatibility, a surface modification of AgNPs-coated titanium implants with hydroxyapatite was developed, showing optimum antimicrobial capacity and favorable biosafety (Salaie et al., 2020).

Evidently, AgNPs are currently widely used in clinical applications due to their unique antibacterial properties. Not only can they be used for antibacterial treatment of traumatic surfaces, but they can even be applied to materials such as implants and medical devices for the prevention of bacterial infections.

# 6 Conclusion

At a time when antibiotic resistance is rampant around the world, AgNPs are being extensively invented for their antimicrobial effects. Here, we systematically state the green method to prepare AgNPs for a sustainable development concept, including saccharide-based method, irradiation-reduction reduction method and biosynthesis method. Each of these methods has advantages in practical application for the preparation of AgNPs. Overall, the wide source of materials, the simplicity of operation, and the stability of the products are greatly in line with the principles of green chemistry and are instrumental in promoting AgNPs as antibacterial alternative therapeutics. Unlike conventional antibiotics, it combines multiple antibacterial effects which is effective for bacteria that have evolved resistance to antibiotics. Furthermore, AgNPs are equipped with the activity of inhibiting biofilm, which showing beneficial effect to the antibiotic-induced biofilm formation. However, it must take into account that synthesize AgNPs with batch-to-batch reproducibility and scale-up for the following pharmaceutical application. Finaly, the function behavior of AgNP should be reasonably designed to balance the therapeutic outcome and potential toxicity to normal cells and tissues, resulting from the heavy ion effect of metals.

# Author contributions

XX, CQ, LX, and QG wrote the manuscript together.

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# Conflict of interest

Author LX was employed by the company Enantiotech Corp., Ltd.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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