

A review on Antimicrobial Activity of Silver Nanoparticles (AgNPs) from Lactic Acid Bacteria

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Abstract: *The tremendous diversity of natural compounds offered by nature possessing promising antimicrobial constituents have been explored and more are still being discovered. Antimicrobial properties of natural products have been reported to be very effective in enhancing the quality and safety of the health of humans and animals, as well as the quality and shelf life of food products. The benefits of microbially synthesized silver nanoparticles including the effective cost of production, less toxicity, ease of production, and environmentally friendly make it a keen interest of research in the food, pharmaceutical, and clinical settings. Lactic acid bacteria (LAB) have numerous advantages for the biosynthesis of silver nanoparticles. The beneficial roles of LAB-mediated AgNPs are not limited to food spoilage prevention and safety alone but also to human health when administered in the right proportion. Silver nanoparticles demonstrated a wide range of antimicrobial activities against bacteria, fungi, viruses, and protozoans. The current review is aimed at exploring and summarizing the antimicrobial activities of silver nanoparticles synthesized using lactic acid bacteria.*

Keywords: Antimicrobial, Biosynthesis, Lactic acid bacteria, Silver nanoparticles,

1.Introduction

Alexander Fleming in his lecture in 1945, being aware of the possibility of bacteria resisting antimicrobials, cautioned on the disastrous effect of bacteria developing resistance to the newly discovered penicillin. Today, this prediction has become a major challenge in the field of medicine. In the World Health statistics, antimicrobial resistance (AMR) is the leading threat to human health and well-being (Letek, 2020). The adverse effects of antimicrobial resistance are both on therapeutic and clinical outcomes, having repercussions that range from failures in treatment and the demand for costly and safer proxy medications to the cost higher rates of morbidity and mortality, high healthcare costs, and being hospitalized for a longer duration (Faheem et al., 2022).

The health problem created by antimicrobial resistance is becoming alarming because bacteria are developing resistance to antibiotics faster and discoveries are being made. Also, the potential of antibiotic resistance to cross borders and disseminate intercontinental with constrained treatment options makes it a major problem in healthcare (Ugwu et al., 2020). Microbes resisting antimicrobial agents occur both in community and hospital settings. The acquisition and dissemination of resistance genes contribute to antimicrobial resistance but the continuous indiscriminate use and misuse of antibiotics by humans and in agriculture accelerate the evolution of antibiotic resistance by bacteria (WHO, 2022). In addition, the increase in multidrug resistance (MDR) bacteria is linked to the dissemination of resistance genes between and among bacterial species (Haworth et al., 2021).

Pharmaceutical industries refrain from investing in the discovery of new antimicrobial agents since they consider that microbes will sooner or later develop resistance, thereby rendering these new drugs ineffective. Also, they think that research for new antimicrobials generates very low profit (CBO, 2021). Furthermore, the global reports of increasing rates of antimicrobial resistance urgently demand not only the quest to discover new antibiotics but also to come up with approaches to curb the spread and counter the advent of antibiotic-resistant pathogens. An estimate of 700, 000 mortality has been attributed to the ineffective treatment of bacterial infection as a result of antibiotic resistance annually with a projection of 10 million deaths yearly by 2050 (Strathdee et al., 2020). These deadly prognoses make it mandatory for innovations in antimicrobial medication technology and the evaluation of new treatments to restrain the hazard coursed by the superbug; antibiotic resistance.

Green chemistry has been the best choice for improving and protecting the environment. The pharmaceutical application of nanoparticles (NPs) in biomedical sciences has been the most promising approach to combat the menace of antimicrobial resistance (Gurunathan et al., 2015). The size range of 1-100nm has enabled silver nanoparticles to exhibit a higher surface (area-to-volume ratio) and greater capacity in contrast to bulk silver. They are eco-friendly and cost-effective. They are now used more and more in many fields including food, medical, healthcare, industrial, and consumer purposes due to their special properties which include electrical, optical and thermal, high electrical conductivity, and biological properties. Remarkably, biologically synthesized AgNPs demonstrate high stability, solubility, and high yield (Galatage et al., 2020; Yaqoop et al., 2020). The exceptional antibacterial activity possessed by AgNPs against various infectious and pathogenic microbes, and multi-drug resistance bacteria inclusive has been a major attraction to industries and researchers (Siddiqi et al., 2018). The broad-spectrum antimicrobial activity of silver

nanoparticles enables its usage against pathogenic and non-pathogenic microbes in numerous industrial setups and packaging of food (Ipe et al., 2020).

Synthesis of nanoparticles involves various methods such as chemical, physical, and biological methods. The limitation of these methods is that some of the chemicals used are toxic, flammable, and not easily remediated, thereby threatening human health and polluting the environment (Naseer, 2022). The most promising method of nanoparticle synthesis is biosynthesis, it is eco-friendly, cost-effective, safe, and time-efficient. Nanoparticles are produced from various biological organisms for instance actinomycetes, bacteria, yeast, fungi, algae, and plants. Among many, bacteria used for the biosynthesis of silver nanoparticles include *Lactobacillus plantarum*, *Lactobacillus casei*, *Escherichia coli*, *Bacillus cereus*, *Aeromonas* sp, *Pseudomonas proteolytica*, *Bacillus subtilis*, *Bacillus amyloliquefaciens*, and *Bacillus indicus*. The biosynthesis of nanoparticles differs in every bacterium. It is either through intracellular or extracellular synthesis (Ijaz et al., 2020; Mughal et al., 2021; Alnehia, 2022).

Lactic acid bacteria (LAB) are collections of Gram-positive, nonsporulating, catalase-negative, acid-tolerant, aero-tolerant, and fermentative rods or cocci bacteria that are generally recognized as safe (GRAS), microbes promoting health, and natural bio-protective (Ben Said et al., 2019; Abdelhamid & El-Dougdoug, 2020). Examples of lactic acid bacteria genera include *Streptococcus*, *Lactobacillus*, *Vagococcus*, *Leuconostoc*, *Oenococcus*, *Lactococcus*, *Carnobacterium*, *Weissella*, *Enterococcus*, *Pediococcus*, and *Tetragenococcus* (Plavec and Berlec, 2020). These bacteria have been greatly utilized in the food industry to ferment various food products. They are also considered as a biological alternative to food preservation. Their metabolites also possess antimicrobial properties that have been applied to promote human health (Ayivi., 2020; Laslo et al., 2020). It has been reported that bio-protective cultures efficiently reduce bacterial loads and inhibit foodborne pathogens (FBP) in vegetables and meat products (Tamang et al., 2016). In addition, LAB inhibits the growth of bacteria, molds, and yeast on bread. They also prevent the replication of spoilage microorganisms such as *Listeria monocytogenes*, and *Clostridium* sp. in dairy products and sea foods (Ben Said et al., 2019; Lerner et al., 2019). The metabolites produced by lactic acid bacteria range from simple organic acids to complexes such as antimicrobial peptides that are characterized for their potential to inhibit foodborne pathogens and spoilage microorganisms (Plavec & Berlec, 2020; Siedler et al., 2019). Hence, this review aims to explore and summarize the antimicrobial activities of AgNPs synthesized from LAB.

2. Approaches to the Synthesis of Silver Nanoparticles

Primarily, there are two main approaches to the synthesis of silver nanoparticles which include: (i) the top-down approach and (ii) the bottom-up approach. The top-down approach employs techniques such as etching, sputtering, milling, laser ablation, and electro-explosion. The bottom-up approach makes use of plasma spraying synthesis, laser pyrolysis, aerosol process, superficial fluid synthesis, and green synthesis. The green biosynthesis of silver nanoparticles intracellularly or extracellularly harnesses microbial metabolites and plant constituents as essential bio-reducing agents (Arokiyaraj et al., 2017; Tariq et al., 2022).

2.1. Biosynthesis of Silver Nanoparticles

The production of silver nanoparticles using the green synthesis techniques signifies a paradigm shift in the field of nanotechnology which offers a sustainable and eco-friendly alternative to conventional methods. Small-scale inorganic substances that are of economic importance are synthesized by nature. The synthesis of nanoparticles is made up of natural phenomena in bacteria, plant, and fungal biosystems. Different organisms have been harnessed to produce silver nanoparticles with diverse chemical compositions: bacteria have been harnessed to synthesize zinc sulfide, iron sulfide, cadmium sulfide, and silver nanoparticles; ribosomes produce gold nanoparticles; yeasts have been used to explore to generate gold nanoparticles (Shivashankarappa & Sanjay, 2020).

The biosynthesis of AgNPs is not limited to bacteria alone but also some fungi such as *Fusarium oxysporum*, *Aspergillus flavus*, *Fusarium semitectum*, and *Verticillium* sp. has been useful. In addition, plants and algae have been utilized for the biosynthesis of silver nanoparticles; the plant extract of *Embllica officinalis*, *Acalypha indica*, *Aloe vera*, and *Pelargonium graveolens* have been utilized in the green synthesis of AgNPs. The exceptional antimicrobial activity against waterborne disease-causative organisms exhibited by these herbal plants makes them appropriate for the biosynthesis of AgNPs. The algae used include *Oscillatoria willei*, *Gelidiella acerosa*, and *Spirulina platensis*. The capacity of algae to accumulate metals and reduce metal ions makes them favorable for the biosynthesis of silver nanoparticles. Their advantages include swift and rapid growth, ease of handling, and a faster growth rate than that of plants (Patil & Kim, 2017; Mukherjee et al., 2021)

2.2. Microbial Synthesis of Silver Nanoparticles

Microbial synthesis of silver nanoparticles has generated lots of interest in recent years. Bacteria through the reduction of metal ions play a major role in the bioremediation of metals. The resistance property of *Pseudomonas stutzeri* against silver makes it a choice

for the intracellular buildup of silver crystals of about 200nm in diameter and of a definite shape and composition (Johnson and Prabu, 2015).

Bacteria has been considered the best microorganism for the synthesis of environmentally friendly and profitable silver nanoparticles. A study has reported that the optimized culture of *Bacillus* sp. produces rapid and high fabrication of silver nanoparticles. Saifuddin et al. 2009 cited in Bayene et al. 2017 show that nanoparticles range from 5-50nm in diameter. Research focuses more on the use of bacteria to synthesize nanoparticles due to their abundance and ability to adapt to harsh conditions, it is economical for cultivation, grows fast, and easily controlled growth conditions such as oxygenation, temperature, and incubation time. However, fungi due to their high amount of protein that amplifies the production of metallic nanoparticles and fungi, scale-up and downstream processes are very easy, which makes it cost-effective, and its larger mycelial surface area than that of bacteria Bayene et al. 2017.

Stable silver nanoparticles have also been reported to be synthesized by *Spirulina platensis* cell extracts with no toxicity, rapid reduction, environmentally benign, and economic viability. *Aspergillus terreus* at room temperature was also reported to synthesize silver nanoparticles extracellularly. The broad-spectrum antimicrobial activity of AgNPs shows a promising application in the food industry and clinical settings (Li et al., 2012 cited in Bayene et al. 2017).

The role of bacteria in the production of silver nanoparticles has extensively been dived into. An evident example included the synthesis of highly stable silver nanoparticles 40nm and 50nm in diameter in an aqueous solution through the bioreduction of silver ions using the supernatant culture of the bacterium, *Bacillus licheniformis*. Other bacteria reported to be useful in the synthesis of AgNPs are *Lactobacillus*, *Klebsiella pneumoniae*, and *Enterobacter cloacae* strains (Ibrahim et al., 2019).

3. Synthesis and Characterization of Silver Nanoparticles (AgNPs) from Lactic Acid Bacteria Metabolites

Lactic acid bacteria have the potential to produce antimicrobial substances of low molecular weight metabolites (such as reutericyclin, fatty acids, reuterin, and diacetyl), antibacterial substances, antifungal compounds, probiotics, and bacteriocins. They can be exploited industrially to biosynthesize compounds of industrial importance (Fidan et al., 2022). Examples of Lactic acid bacteria that have been reported for the biosynthesis of silver nanoparticles are *Lactobacillus brevis*, *Lactobacillus plantarum*, *L. fermentum*, *L. crustorum*, *L. pentosus*, *L. paraplantarum*, *Bifidobacterium* sp. (Sharma et al., 2022 a, b)

The interaction of microorganisms with metal ions makes them a nanofactory potential for the synthesis of nanoparticles. Studies on the biosynthesis of silver nanoparticles using lactic acid bacteria have been done severally. Reports from these studies show that lactic acid bacteria are a promising reducing agent for the production of AgNPs. The supernatant of *Lactobacillus acidophilus* produces spherical-shaped nanoparticles between 4-50nm. Also, various studies have shown that LAB supernatant serves as a reducing agent for the synthesis of silver nanoparticles (Rajesh et al., 2015; Dakhil, 2017; Viorica et al., 2017). Study shows that the downstream process would become more straightforward and effortless by manipulating the bacteria supernatant during the synthesis of silver nanoparticles (Das et al., 2014 cited in Mohd Yusof et al., 2020).

The preparation of cell-free supernatant of Lactic acid bacteria is by inoculating single colonies of LAB in nutrient broth (Oxoid-England) and incubating at 37°C for 24 hours. Centrifuging of the culture is done after 24 hours at 4500rpm for 10 minutes. The precipitated cells at the bottom of the test tube are discarded and the cell-free supernatant is collected for the synthesis of silver nanoparticles (Chaudhari et al., 2012). 2mM of Silver trioxonitrate(iv) AgNO_3 is added to lactic acid bacteria cell-free supernatant in a ratio of 1:1 and thoroughly mixed in a dark environment to prevent the oxidation of AgNO_3 . The solution is incubated in a shaking incubator at a pH of 8.3. 150rpm at 37°C for 24 hours (Dakhil, 2017). The colour change is observed after incubation and the reacting mixture is centrifuged at 1000 rpm for 10 minutes. The supernatant is discarded, deionized distilled water is added, and re-centrifuged three times at the same speed and time to get rid of the residual supernatant. The deposited pellet at the base of the tube represents the silver nanoparticles and is dried at 40°C for 18–24 hours in an oven. The dried AgNPs powdered are collected and stored carefully in sample vials. Synthesized AgNPs are being characterized by transmission electron microscopy (TEM), X-ray diffraction (XRD), Fourier transform infrared (FTIR) spectroscopy, and UV-vis spectroscopy). (Chaudhari et al., 2012; Sarvamangala et al., 2013 cited in Syame et al., 2020).

4. Antimicrobial Activity of Silver Nanoparticles by LAB Metabolites

Antibacterial Activity of Silver Nanoparticles

Silver nanoparticles have been known for their potential to attack pathogens in multiple structures at a time and their bactericidal ability on diverse bacteria (Cheng et al., 2016 cited in Bruna et al., 2021). Metallic silver ions become activated from their inactive free state to active form once they come in contact with a reducing agent forming an ionic silver that binds to the bacterial cell wall, causing structural damage and changes in cell morphology. Silver nanoparticles cause denaturation of DNA and RNA replication leading to cell death. As a result of the bactericidal potential (oligodynamic) of silver nano-particles at a minimum concentration, it is largely used in medical products (Galatage et al., 2020; Altammar, 2023). Silver cations bind to the thiol groups of bacterial proteins and attribute bactericidal activity to silver nanoparticles with the capacity to disrupt the bacteria thereby resulting in necrobiosis (Burduşel et al., 2018).

There is an increase in the antibacterial activity of AgNPs when combined with antibiotics against multi-drug-resistant bacteria (Yuwen et al., 2018). *Salmonella typhimurium* growth was reported to be suppressed when kanamycin, enoxacin, neomycin, and tetracycline were combined with AgNPs (Deng et al., 2016). Also, the antibacterial activity of AgNPs against *Staphylococcus aureus* and *E. coli* is greatly enhanced with antibiotics such as vancomycin, gentamicin, streptomycin, ciprofloxacin, erythromycin, amoxicillin, and tetracycline. In addition, AgNPs in combination with ampicillin, chloramphenicol, and kanamycin showed synergistic potential against *E. coli*, *S. aureus*, *Enterococcus faecium*, and *S. mutans* (Saratale et al., 2017).

The culture-free supernatants (CFS) from *Lactobacillus casei* and *Lactobacillus fermentum* were used to biosynthesize silver nanoparticles (AgNPs), which demonstrated antibacterial effects against pathogenic microbes (Adebayo-Tayo et al., 2017). Similarly, AgNPs synthesized by *Lactobacillus plantarum* TA4 showed concentration-dependent antibacterial activity against both Gram-positive and Gram-negative bacteria (Mohd Yusof et al., 2020). The cell-free biomass of *Lactobacillus reuteri* was employed in AgNP synthesis, with the resulting nanoparticles displaying disc diffusion-based antibacterial activity against *Bacillus subtilis* and *Escherichia coli* (Tharani et al., 2020). Furthermore, AgNPs synthesized by the cell-free supernatant of *Lactobacillus bulgaricus* exhibited significant antibacterial effects against *Staphylococcus aureus*, *Staphylococcus epidermidis*, and *Salmonella typhi*, when compared with some antibiotics in the agar well diffusion assay (Naseer et al., 2021). Additionally, green synthesis of AgNPs using *Lactobacillus acidophilus* showed both antibacterial and antibiofilm activity against multi-drug-resistant *Escherichia coli* strains (Abishad et al., 2022). Furthermore, Sharma et al. (2022b) reported *L. pentosus*, *L. crustorum*, *L. plantarum*, and *L. paraplantarum* to possess strong antibacterial effects on *Listeria monocytogenes*, antibiotics-resistant *Staphylococcus aureus*, and *Bacillus cereus*.

4.1. Antifungal Activity of Silver Nanoparticles

Silver nanoparticles possess antifungal activity against various diseases caused by fungi. Biosynthesized AgNPs from the filtrate of *Lactobacillus* sp. strain LCM5 strongly inhibited the growth of *Aspergillus ochraceus*, *Penicillium expansum*, and *Aspergillus flavus* (Matei et al., 2020). Also, AgNPs synthesized biologically in synergy with fluconazole boosted antifungal activity against *Candida albicans* and *Phomaglomerata* sp. (Galatage, et al., 2021). *Bacillus-mediated* AgNPs were also reported to exhibit antifungal activity against *Fusarium oxysporum* and *T. asahii* at a concentration of 8 µg/ml and MIC of 0.5 µg/ml respectively (Xia et al., 2014). Ketoconazole enhanced by AgNPs had antifungal activity against *Malassezia furfur* (Javier et al., 2019).

4.2. Antiviral Activity of Silver Nanoparticles

Silver nanoparticles uniquely interact with viruses based on particular size ranges and shapes. The incorporation of AgNPs into polysulfone ultrafiltration membranes demonstrated antiviral activities against MS2 bacteriophage due to the increased membrane hydrophilicity. The transmission of cell-associated HIV-1 and cell-free HIV-1 isolates were prevented by polyvinyl pyrrolidone (PVP)-coated. Study shows that hepatitis B virus (HBV) was inhibited by AgNPs (Zhang et al., 2016). The mechanisms of antiviral activities of AgNPs are a result of their interaction with the virion core (Galatage et al., 2021).

5. Application of Silver Nanoparticles in the Food Industry

By exploring the antimicrobial potential of silver nanoparticles, food safety, production efficiency, and safety have been improved by nanoparticles globally. Biosynthesized AgNPs are considered safe and less toxic for possible application in food items (Shanker et al., 2014). Silver nanoparticles have been reported to elongate the shelf life of different food items using various protecting nanocoatings and appropriate packaging materials. The shelf life of vegetables and fruits is increased by incorporating AgNPs into sodium alginate to prevent microbial spoilage (Kondle et al., 2022).

Silvan et al (2018) also reported that AgNPs were effective against the multi-drug resistant *Campylobacter* strains isolated from chicken products and clinical patients. Study shows that packages of orange juice-impregnated silver nanoparticles derived from *Lactobacillus plantarum* had the greatest antimicrobial activity compared to the control (Simbine et al., 2019). Li et al. (2018) observed that the migration of AgNPs of polylactic acid (PLA) matrix infused with TiO₂ + AgNPs in Yunnan cottage cheese increased with storage time as determined by the European regulations for food contact material.

5.1 Health Benefits of Implementing Lactic Acid Bacteria Biosynthesized Silver Nanoparticles in Foods

Lactic acid bacteria are considered generally safe for human consumption as probiotics. They are largely harnessed in the industry as probiotics and starter cultures as a result of being safe and efficient cell factories for the manufacturing of high-value chemicals and being used as ingredients in food. The application of lactic acid bacteria for preservation (fermentation) in the food industry is one of the most studied methods (Hatti-Kaul et al., 2018). Consumers are all aware of and accept the health benefits of consuming fermented foods (Fidan et al., 2017), therefore using LAB metabolites for the synthesis of AgNPS for human consumption in the form of supplements is also safe for consumption with various health benefits.

6. Conclusion

The current review opined that the biosynthesis of silver nanoparticles from lactic acid bacteria offers numerous benefits to the medical, pharmaceutical, and food industries if properly harnessed. Also, LAB stops the growth of foodborne pathogens thereby prolonging the shelf life of foods. In recent years, researchers have been researching on the use of natural organic substances as an alternative to chemically inorganic preservatives and antimicrobial agents to improve the quality of human life. Lactic acid bacteria-mediated silver nanoparticles are safe and healthy for human consumption with numerous health and industrial benefits. Creating

consumer awareness of the health and nutrition benefits and monitoring the trend towards LAB-mediated biosynthesized AgNPs will result in the increase and acceptability of silver nanoparticles in society.

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