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Silver Nanoparticles: Biomedical Applications and Future Perspectives

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ABSTRACT

Silver nanoparticles (AgNPs) have attracted significant attention in the biomedical field because of their unique physicochemical characteristics and versatile applications. This review explores the remarkable potential of AgNPs in various biomedical applications, including their roles in drug delivery systems, cancer therapy, imaging and diagnostics, wound healing, and dental applications. The exceptional properties of AgNPs, like their high ratio of surface area to volume and enhanced reactivity, contribute to their effectiveness in combating infections and promoting tissue regeneration. Recent advancements in synthesis methods have further improved the biocompatibility and efficacy of AgNPs. We discussed the synthesis and mechanisms of AgNPs. Additionally, we reported the challenges associated with the biomedical application of AgNPs. Future perspectives are provided, focusing on optimizing synthesis techniques, improving safety profiles, and exploring novel applications in personalized medicine. This comprehensive overview underscores the transformative role of silver nanoparticles in modern healthcare and their potential to address critical health challenges.

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1. Introduction

A particle known as a nanoparticle (NP) has a size between 1 and 100 nanometers. Small-sized, large carrier capacity, high reactivity, high surface-to-volume ratio, and simple surface property variation distinguishes these NPs from others [1]. Nanoparticles of noble metals such as silver, gold, titanium, and platinum are commonly used in biomedicine [2]. Because of their unique characteristics, such as chemical stability, excellent conductivity, and catalysis, silver nanoparticles (AgNPs) have gained significant interest in biomedical applications. As a result of these attributes, AgNPs are remarkably effective as biomaterials in a variety of medical applications, including antibacterial, antiviral, antifungal, and anti-inflammatory applications [3].Various functions can be performed by smaller AgNPs because of their distinctive properties [4]. These are the reasons why silver nanoparticles are being investigated in biomedical applications, especially in medicine (wound dressings, medication delivery, biosensors, medical diagnostics, orthopedics) [5]. Materials containing AgNPs remain a significant source of significance in nanotechnology, particularly biomedicine, because of the fascinating, promising features they offer [6]. Depending on the synthesis, these NPs have a varied surface-to-volume ratio, making them distinctive. Compared to larger AgNPs, smaller AgNPs are superior antimicrobial agents because they have a greater surface-to-volume ratio, more silver cations are released [7]. Because of the amount of medication they can carry, larger AgNPs that are larger than 100 nm have a lower surface-to-volume ratio and are typically utilized in drug delivery [8].

Furthermore, AgNPs have been shown to enhance collagen synthesis, proliferation of fibroblasts, and anti-inflammatory qualities when paired with biomaterials. Their use in dental adhesive resins, composites, filling supplies, implants, and orthodontic materials has also been enhanced by their antibacterial and antibiofilm properties [9-11]. The creation of antithrombotic and anticoagulant medications, which can lower the dangers of embolism and hemorrhages in managing cardiovascular illnesses, has also been studied for biomaterials and implants made of silver nanoparticles [12, 13]. AgNP-based biomaterials have also been investigated to create scaffolds to regenerate damaged peripheral nerves and treat nerve injuries. AgNPs are excellent agents for photothermal therapy in tumor treatment and malignancies because of their high photothermal conversion efficiency [14, 15]. Additionally, various biosensors that use localized surface plasmon resonance (LSPR) and surface-enhanced Raman scattering (SERS) to detect cancer biomarkers, cholesterol, glucose, and other substances have been developed due to AgNPs' sensitivity, reactivity, and electrochemical, optical, and colorimetric characteristics [16, 17]. AgNPs continue to cause cytotoxicity, which restricts their direct applicability in vivo biomedical settings. To reduce the toxicity of the NPs, more studies are necessary to investigate various coatings and production techniques [6].

This review aims to give a broad overview of the status of research on silver nanoparticles, with a focus on their biological uses and an exploration of potential future directions. This article will discuss the latest research and developments in the field of biomedical nanoparticles and their potential for transformation. Comprehending the mechanisms of action of AgNPs and optimizing their production to enhance biological applications will be crucial.

2. Synthesis of Silver Nanoparticles

There are two thorough methods for NP synthesis: bottom-up and top-down. In contrast to the latter, which is immoderate and stable, the former uses atomic-size particles self-assembling to produce nano-sized particles. Chemical and physical methods can be used to accomplish this [18]. Silver nanoparticles have been synthesized and stabilized using various physical, chemical, and other techniques, which are covered below (Fig.1).

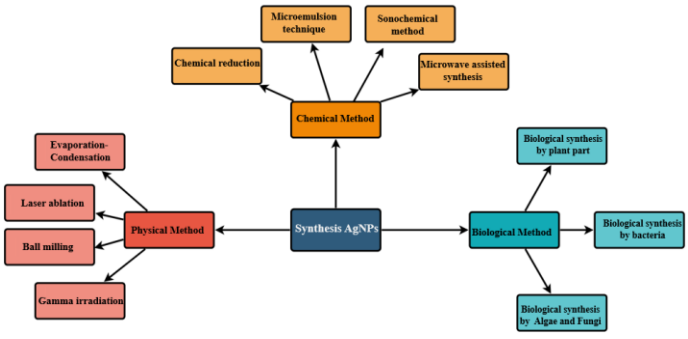

Fig.1. Synthesis of Silver Nanoparticles.

2.1. Chemical Methods

The most common technique for creating AgNPs is the chemical approach. Aqueous or organic agents can be used as the media for synthesis. Chemical synthesis uses toxic and dangerous compounds that may be bad for the environment. Synthesis-related compounds may be non-biodegradable and combustible [19]. If utilized in medicinal applications, the nanoparticles might absorb these harmful substances and have harmful side effects [20]. Chemical reduction, the microemulsion method, sonochemical synthesis, and microwave-aided synthesis are examples of chemical synthesis [21].

2.1.1. Chemical Reduction

Chemical reduction by organic and inorganic substances is the most often utilized technique in chemical synthesis. The reducing agents are polyethylene glycol (PVP), sodium citrate, sodium borohydride, and Tollen reaction. In aqueous and non-aqueous solutions, these chemicals are employed to decrease the condition of oxidation from Ag^{+} to Ag^{0}. The high rate of reaction caused by the introduction of these reducing chemicals resulted in a significant number of metal nuclei that generated minuscule particles [22]. Particles will aggregate if the process proceeds slowly. Stabilizers are used to reduce silver nitrate ($AgNO_3$) to prevent the growth of NPs through aggregation. According to a publication, ascorbic acid, thiosulfate, sodium citrate, and polyethylene glycol can all be used as reducing agents to create a particular form of AgNPs. These substances generate spherical AgNPs [23]. Smaller AgNPs are produced when a more potent reducing agent is used [24]. The most effective and simple technique for creating AgNPs without aggregation is chemical reduction, Using inorganic and organic reducing agents, resulting in a high yield and inexpensive preparation expenses [25].

2.1.2. Microemulsion Technique

The synthesis of AgNPs utilizes the microemulsion technique, where controlling the dispersion of two immiscible liquids, such as oil in water or water in oil, is essential. This method produces AgNPs within a microemulsion, leading to nanoparticles of uniform size and shape. Various surfactants can be utilized to create the microemulsion, including cationic surfactants like PVP and cetyltrimethylammonium bromide, non-ionic surfactants such as Triton X-100, and anionic surfactants like sodium dodecylbenzene sulfonate (SDS), bis(2-ethylhexyl) sulfosuccinate, and lauryl sodium sulfate. This variety of surfactants allows for precise control over the synthesis process, enhancing the stability and properties of the resulting nanoparticles [23].

2.1.3. Sonochemical Method

AgNPs are created via the sonochemical process, which uses ultrasonic energy to create a localized hot spot. Originally developed to create iron nanoparticles, this technique has now been utilized to create a wide range of metals, including silver [26]. The creation, expansion, and collapse of bubbles are the most crucial of the several sonochemical synthesis techniques [27]. A solution may have bubbles due to acoustic fields bursting when subjected to ultrasonic radiation. When the vaporization bubble bursts, a shock movement is created that quickly strikes the particle surface [28]. The synthesis is affected by temperature, pH, pressure, microjet speed, and cooling rate [29].

2.1.4. Microwave Assisted Synthesis

AgNPs synthesis in contrast to traditional heating. A combination may also be mixed entirely and microwaved for microwave-assisted synthesis. Because microwaves produce consistent heating, fine, thin, and uniformly sized nanocrystals are formed. AgNPs generated by microwave-aided synthesis have a more constrained size distribution, are smaller, and have a greater level of crystallization than AgNPs produced by traditional oil bath heating, according to Nadagouda et al. [30]. This technique showed better control over the AgNPs' nucleation and growth phases. Furthermore, microwave-assisted synthesis can heat materials quickly and evenly, cutting down on the amount of time needed for synthesis [31].

2.2. Physical Methods

AgNPs can be made physically by evaporation, condensation, laser ablation, ball milling, and gamma irradiation.

2.2.1. Evaporation–Condensation

A tiny ceramic heater or an atmospheric pressure tube furnace is needed to create AgNPs using the evaporation condensation process. This method is commonly employed to create AgNPs.

Three main processes create the evaporation condensation process: (I) material is sublimated or evaporated to create a vapor phase; (II) material is moved from the source to the substrate; and (III) nucleation and subsequent growth produces particles and/or films. When the vapor cools quickly, tiny AgNPs are formed in large quantities [32]. This approach also needed a particular amount of time to establish a steady temperature and a specified kilowatt of electricity from a standard furnace [33]. Two of evaporation condensation's drawbacks are the process's long duration and the massive energy consumption [34].

2.2.2. Laser Ablation

One method for producing metal colloids without requiring chemical reagents is laser ablation. This technique focuses intense laser pulses on an Ag target submerged in a liquid [35]. AgNPs might be produced by laser ablation of metallic bulk materials in the solution [36]. In addition, the length of the alcohol chain affects the size of the Ag-NPs that are produced. Compared to short-chain alcohols like methanol and ethanol, the alcohol whose chain length is more prolonged (from C-3 to C-5) produced more diminutive and more steady particles [37]. A few variables affect the properties of the AgNPs that are produced, such as the laser's wavelength, the length of its pulses (femto-, pico-, or nanoseconds), the laser's fluence, the removal time useful medium, and the existence of surfactants [38]. AgNP concentration increases with ablation time until saturation is achieved [39]. AgNPs can also get smaller when the concentration of surfactant is increased [38]. Using this technique, AgNPs may be produced cheaply, with less heat transfer, and with reduced environmental toxicity [40]. However, the primary drawbacks of this approach are the production of low concentrations of silver nanoparticles in the solution and the utilization of energetic lasers, which will ultimately raise the synthesis cost and compromise the antibacterial action of the nanosized silver [41].

2.2.3. Ball Milling

A form of physical synthesis called ball milling creates smaller AgNPs by dropping the ball in a container and spinning it horizontally. Particle aggregation is caused by the greater surface energy of smaller AgNPs [29]. Synthesis uses a variety of mechanical mill types, including planetary, uni-ball, attritor, and vibratory mills [26]. The milling duration, rotating speed, and ball size all affect the dispersion quality [42]. Temperature affects the produced AgNPs' phase and diffusivity during the ball milling process [43]. Many factors, such as the ball-to-powder proportion,

temperature, atmosphere, time, speed, dispersion, and dimensions of the crushing medium, affect the quality of goods that are ball-milled [44].

2.2.4. Gamma Irradiation

The high energy of gamma irradiation makes it suitable for the synthesis of AgNPs [45]. One technique in which the Ag^+ solution causes the conversion of Ag^+ into metallic Ag is gamma irradiation. When Ag is irradiated, the irradiation samples undergo a color shift from colorless to golden yellow [46]. Furthermore, the reducing agent may be evenly dispersed throughout the solution, and the produced AgNPs are highly stable and pure [47]. Because AgNPs are uniformly dispersed and devoid of solvent-based contaminants, physical synthesis techniques are superior to chemical-based synthesis protocols. When using the physical method, The tube furnace has a large surface area, requires a lot of energy (more than a few kilowatts), and takes longer to reach thermal stability when the temperature increases above ambient levels [48]. The manufacture of AgNPs at significant concentrations, stable NPs, easy operation, and toxicity inhibition are all made possible by physical methods, though [49].

2.3. Biological Synthesis of AgNPs

Biological synthesis is the easiest, safest, and most environmentally responsible way to create high-quality NPs [8]. Compared to physical and photochemical processes, which are hazardous, combustible, and cause environmental disruption, biogenic synthesis, commonly referred to as "green synthesis," is a rapid, simple, economical, and ecologically benign procedure. In addition, it requires less time and energy than photon and physical approaches. Other advantages include high density, natural stability, excellent solubility in water, and abundant biological resources [50]. Furthermore, single-step AgNP synthesis, like biological synthesis, has more stability, variety, and appropriate dimensions [8]. Microorganisms (such as bacteria, fungi, and yeast) and various plant tissues (such as fruit, peel, latex, leaves, stems, and roots) can be employed in green synthesis to produce AgNPs. Various naturally occurring substances found in plants and also generated by microorganisms, such as proteins, polyphenols, enzymes, amino acids, etc., serve as capping and reducing agents. In addition to being less expensive, using microorganisms and agricultural waste is also better for the environment [51, 52]. Fig.2 shows a schematic of the biological synthesis of silver nanoparticles.

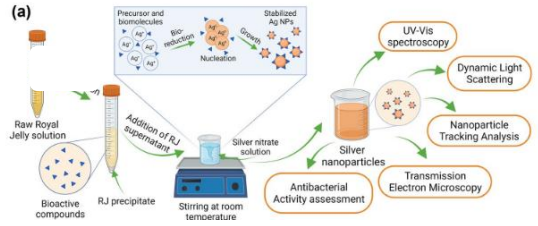

Fig.2. Scheme of the biological synthesis of Ag NPs using Royal Jelly [53].

2.3.1. Biological Synthesis of AgNPs by Plant Parts

Since plants are more plentiful than other biological resources, biological synthesis techniques that employ them as AgNP synthesizers are preferable to additional biological techniques [54]. AgNPs can be synthesized quickly, cheaply, environmentally, and non-pathologically using green plants [55]. Plant extracts, including leaves, stems, roots, seeds, and latex, are used to create AgNPs [56-58]. The chemical composition and concentration of AgNPs, the concentration of $AgNO_3$, the extraction solvent utilized, the extraction duration and temperature, and the response time and temperature all affect the size, shape, and concentration of AgNPs that plants generate [59]. The biological synthesis of AgNPs using plants is shown in Fig.3.

Biomolecules that are environmentally benign and have therapeutic uses, including polysaccharides, tannins, alkaloids, amino acids, vitamins, polyphenols, terpenoids, and saponins, are found in plant extracts and contribute to the stability and decrease in silver ions [60]. AgNPs' size and form are greatly influenced by the amount of plant extract, the focus of silver, the pH, the response duration, and the mixture's pH amount [61]. The NP content of a combination is significantly impacted by its pH. Changes in pH impact the chelating and reducing ability of plants because they cause a charge shift in their metabolism. Variations in the synthesis's shape, dimension, and yield may arise from this. Small, consistent-sized particles are created by raising the reaction mixture's pH [62-64]. Another essential element influencing the characteristics of AgNP during synthesis is temperature. Increased nucleation rate at high temperatures undoubtedly results in smaller AgNPs. The type and capacity for decrease vary among metabolites. Comparing the polyphenol family to other accessible metabolites, they have all the positive traits. These qualities include a strong reducing/antioxidant power, a suitable molar concentration, and direct engagement in the plant detoxification process for heavy metals. The flavonoid subclass is the most prevalent kind of polyphenol. Typically, flavonoids serve various biological purposes, including phytopathogen and ultraviolet (UV) radiation defense, potent antioxidant action, and fruit and floral coloring [65].

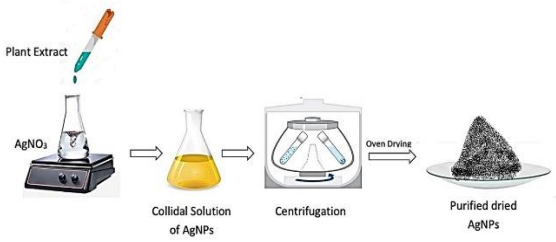

Fig.3. Scheme of AgNPs synthesis using plant [66].

2.3.2. Biological Synthesis of AgNPs by Bacteria

It has been acknowledged that one of the fastest-growing areas of green nanotechnology research is the biological synthesis of AgNPs using microorganisms. AgNPs, thought to be a substitute for traditional chemical and physical methods, have been continuously synthesized by various microbial entities. The production of AgNPs involved the utilization of several bacterial species, including Morganella morganii RP42, Bacillus stearothermophilus, Escherichia coli, Serratia nematodiphila, Pseudomonas proteolytica, P. meridiana, B. brevis, and others. Furthermore, it has recently been shown that several other bacteria, such as Novosphingobium sp., Brevibacterium frigoritolerans, and B. methylotrophicus, are efficient in producing AgNPs. In broth culture, bacteria secrete many enzymes, including a number of reductases that carry out the production of AgNPs [67]. Bacterial cells serve as lowering objects during this process because they lower the levels of metal ions (Ag^+) to metal NPs (AgNPs), which extracellularly induces the nucleation and capping of NPs [68]. Due to their rapid rate of reproduction and straightforward culture method, bacteria can provide a wide range of chances for the synthesis of AgNPs. The first bacteria utilized to

synthesize AgNPs was Pseudomonas stutzeri (AG259) [67]. Bacillus megaterium (NCIM 2326), Bacillus cereus, Bacillus licheniformis, Bacillus amyloliquefaciens, Bacillus marisflavi, Bacillus flexus, and Bacillus subtilis were also used in the synthesis of the AgNPs [69].

2.3.3. Biological Synthesis of AgNPs by Algae and Fungi

Since NPs have been synthesized from both living and dead dried biomasses, algae, a classification of freshwater or marine microorganisms are often regarded as bio-nano factories [70]. Apart from algae, fungi are also crucial for the green synthesis of AgNPs. As lowering agents, algae and fungus operate in an eco-friendly manner to produce AgNPs in a sustainable and non-toxic manner. Most of the algae used for this goal come from types such as Sargassum plagiophyllum, Chlorococcum humicola, Amphora-46, Caulerpa racemose, Padina pavonica, and Chaetomorpha linum, among others, and the fungal mycelium, which includes Aspergillus fumigates, Penicillium fellutanum, A. flavus, Fusarium semitectum, and Alternaria alternata. The advantages of fungal-based AgNPs over bacteria include greater organism growth rates, simple cultivation techniques, high releases of extracellular enzymes, enhanced NPs forbearance (protein coating), and superior stability with elevated levels of NP [71]. The synthesis of appropriate biocompatible AgNPs has lately involved an extensive study on massive fungal flora, such as Trichoderma reset, A. niger, F. oxysporum, and Phytophthora infestations. In biogenic synthesis, for example, Penicillium oxalicum has certain advantages because of its physiologically active compounds, which include antibacterial, antioxidant, immunomodulating, and anti-cancer activities [72]. Cladosporium cladosporioides, F. oxysporum, F. semitectum, F. acuminatum, F. solani, and T. asperellum are among the other fungi that may produce AgNPs for a variety of uses [73]. Fig.4 shows a schematic of the synthesis of silver nanoparticles using Fungi.

The synthesis of AgNPs from algae requires three steps: (I) heating or boiling water or an organic solvent and algal extract for a predetermined amount of time; (II) creating a metal precursor solution; and (III) continuously stirring the precursor and algal extract while incubating it under carefully monitored circumstances. After that, the $AgNO_3$-algal extract mixture's color shift was tracked to see if AgNPs had developed [74-76]. Blending and washing are examples of preparation procedures that take place outside of the cell in extracellular mode. Various proteins (enzymes), metabolites, pigments, ions, and non-protein components, including lipids, DNA, RNA, and antioxidants, all play a part in the process [21].

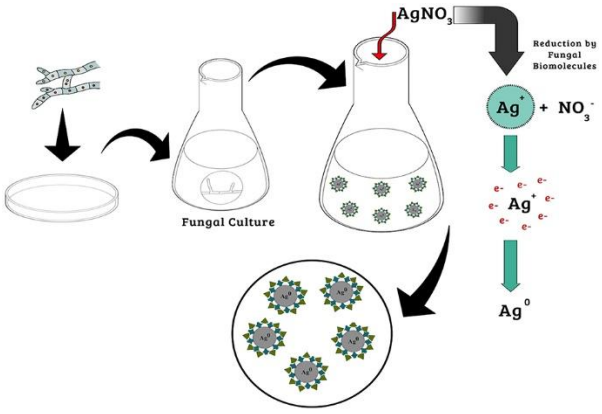

Fig.4. Scheme of AgNPs synthesis using Fungi [77].

3. Mechanisms of Silver Nanoparticles

Researchers are currently investigating how silver nanoparticles eliminate microorganisms, particularly viruses. Various studies reveal that silver nanoparticles typically function by binding antiviral drugs to proteins on the virus's surface, thereby hindering their activity or altering their structure [78]. This strategy prevents the virus from spreading inside the host cell early in the process and is very helpful in limiting the proliferation of viral-mediated infections [79].

3.1. Antimicrobial Properties

AgNP has encouraging benefits in the battle against infections caused by bacteria. Their powerful antibacterial activity results from improved interactions with bacteria made possible by their compact size and high surface area to volume ratio[80]. Furthermore, AgNP's distinct physical characteristics cause bacterial cell membranes to rupture and impede vital biological functions. These substances are noteworthy for their broad-spectrum effectiveness against a variety of bacteria, such as both gram-positive and gram-negative organisms, which helps to overcome the limits of conventional therapies and the developing problem of antibiotic resistance. The promise of silver as a useful weapon in the battle against bacterial diseases is highlighted by its comeback in the nanoscale age [81].

AgNPs can have antibacterial action that depends on size, shape, concentration, duration, and charge in addition to the bacterial strains. Generally, the antibacterial activity of AgNPs significantly increases as the particle size decreases. [7]. AgNPs exhibit superior antibacterial action, particularly at sizes less than 10 nm [82]. Increasing the duration of AgNPs' treatment can significantly boost their antibacterial impact, and the structure of AgNPs may also affect their antibacterial activity [83]. AgNPs with a spherical form had a better antibacterial impact than those with a triangular, linear, or cubic shape, according to a comparison of their antibacterial activity. According to this phenomenon, AgNPs with a greater surface-to-volume ratio associated with a larger reaction surface and a higher effective contact may exhibit more potent antibacterial activity [84].

The actual processes behind AgNPs' antibacterial, antifungal, and poisonous properties are a hotly contested subject. According to specific theories, Ag^+ ions are essential for antibacterial action. In addition to preferentially interacting with the phosphate group of nucleic acids rather than their nucleosides, silver ions may create a variety of complexes with nucleic acids, including DNA and RNA. Along with positively charged nanoparticles, certain studies demonstrate the electrostatic interaction between negatively charged bacterial cells, making this the most effective bactericidal agent that has been proposed [85]. Subsequently, it has been demonstrated that they both diffuse and collect inside the membrane, denaturing the bacterial wall or membranes. The Ag atom is suggested to form a stable S-Ag connection with thiol-containing structures by binding to the enzyme's thiol groups (-SH). It can suppress the cell membrane's enzyme activity, which transfers energy in addition to ions. Additionally, it was believed that Ag-I ions may penetrate the cell membrane and intercalate between purine and pairings of pyrimidine bases, causing the hydrogen bonds between the two antiparallel strands to be distorted and instantly denaturing DNA molecules. The ability of nanoparticles to alter the phosphor-tyrosine profiles of bacterial peptides can restrict the development and proliferation of microorganisms by influencing signal transduction. Unlike antibiotics, the antibacterial action is dosage-

dependent and unaffected by the development of bacterial resistance [86]. Hermanto et al. [87] reported that silver nanoparticles can be synthesized electrochemically at low cost using green tea leaf extract, making the nanoparticles more stable and less cytotoxicity. It also shows high purity and excellent antimicrobial activity against E. coli and S. aureus. In this way, AgNP-based antibacterial agents can be synthesized in large quantities. Ohiduzzaman et al. [88] investigated the synthesis of silver nanoparticles with banana pulp extract by examining the effect of various factors on electrochemical cells based on pulp extract over time, including current, voltage, power generation, voltage regulation, and changes in load resistance. Based on the results, the AgNPs-based bioelectrochemical cell (Cell-P) exhibited higher power and average voltage, enabling it to operate at a low voltage and have a longer lifetime than other cell types. Moreover, it showed that these nanoparticles could improve the performance of bioelectrochemical cells and be used for antibacterial applications. It was reported that Rammatian et al. [89] synthesized silver nanoparticles from Echinophora platyloba (E.P) plant extract and tested for antibacterial activity using phenolic and alcoholic compounds. Plant extracts reduce and stabilize agents because of their phenolic and alcoholic compounds. At pH 7 and higher, when phenolic and alcoholic substances are active, plant extracts reduce Ag ions to AgNPs. Further, silver nanoparticles were found to be antibacterial against Escherichia coli (E. coli) (G^-) and Staphylococcus aureus (S. aureus) (G^+).

3.2. Cytotoxicity and Biocompatibility

A chemical or physical synthetic AgNP binds to viruses and host cells by releasing chemical functional groups that prevent agglomeration and improve stability [90, 91]. Having synthetic origins, these functional groups interfere with viruses' capsid proteins and suppress them. Nanoparticles also disintegrate into silver ions, release reactive oxygen species, increase oxidative stress, and inhibit viruses [92].Additionally, the silver nanoparticle disrupts viral genomes, prevents them from growing in the host, and directly binds to them [93]. It is noteworthy that the biogenic synthesized silver nanoparticle acts similarly to a virus that does [94]. AgNPs, however, manufactured by physical or chemical methods may be toxic to contaminated cells due to their chemical-based functional groups [95]. The toxic functional groups may reduce or halt the metabolic activity of infected host cells, causing severe cytotoxicity complications [96].

Some researchers have also shown the toxic effects of chemically synthesized AgNPs on rats' brains and livers, based on the chemical functional group, dosage, and concentration [97-99]. As part of the biogenic AgNP function, the biomolecules act as an effective team that aids the AgNPs in entering host cells that are contaminated, thereby improving their compatibility with biomaterials [100]. Moreover, the Biological molecules have antiviral performance, which inhibits viral infections by combining synergistically [101, 102]. Furthermore, Biological molecules might act as building blocks for cells or to boost host cell defenses, which is particularly useful in treating viral infections [103]. The antioxidant properties of AgNP synthesized using eco-friendly methods, like plant extracts, enable it to counteract oxidative stress and free radicals in biological systems efficiently [104].

AgNPs were produced by Krishnamurthy et al. [105] using Argyreia nervosa leaves. According to experimental studies, the nanoparticles' modest size (1–10 nm) improves their reactivity and contact with radicals while providing a high surface area. Through a synergistic effect, bioactive phytochemicals increase their antioxidant capacity. Furthermore, silver nanoparticles mediated by A. nervosa exhibit antidiabetic, antibacterial, antioxidant, and anti-inflammatory properties. According to Bazrgaran et al. [106] , ASG-AgNPs were synthesized from A. sarcocolla extract and were shown to be more reactive to radicals. Furthermore, the bioactive compounds in gum extract enhance the scavenging capacity of nanoparticles and produce a synergistic antioxidant effect.

4. Biomedical Applications

Silver nanoparticles have been used in a wide range of biomedical applications, including cancer treatment, dental technology, bio-imaging, and so on (Fig.5).

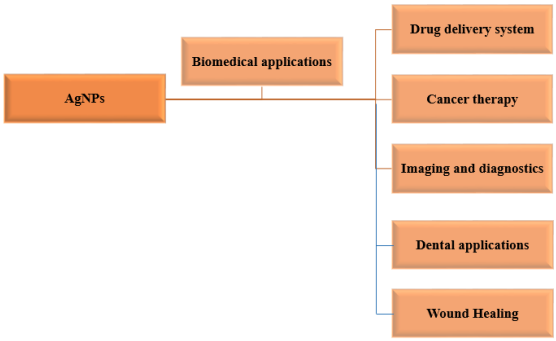

Fig.5. Schematic of Silver nanoparticles applications.

4.1. Drug Delivery Systems

In medicine, pharmaceuticals and pharmacodynamics are equally important .In recent years, nanoparticles have become increasingly popular for the development and use of novel and cutting-edge drug delivery techniques [107]. It is crucial to determine the methods used to distribute a specific medicinal component to human or animal species to give certain healing benefits. Chemically combined AgNPs can be used to create highly contagious, thermally adaptable, and anti-inflammatory drug delivery systems [108].

The best activable and adaptable nanosystems for drug delivery applications must be easy to construct, have easy-to-access components, and be highly reactive. The drug delivery technology must also provide a flexible drug concentration and discharge characteristic. In addition, it should give maximal effectiveness of treatment at lower amounts than the primary substances, minimizing side consequences [109]. In this area, AgNPs have garnered much attention and are effective anticancer drug delivery systems [110]. It is necessary to modify AgNP surfaces with benevolent biological molecules to improve their bio-acceptability and add additional functionalities for clinical application before using them. Engineered AgNPs may solve clinical difficulties and significantly enhance drug delivery vehicles resistant to multiple drugs and pharmaceuticals that have improved bioavailability. The current use of AgNPs in nano pharmaceuticals as drug carriers includes conjugating them with antibodies, peptides, nucleic acids, and amino acids [111]. According to Koti et al. [112], they synthesized a nanocomposite consisting of cobalt ferrite, graphene oxide, and silver nanoparticles. After incorporation with the drug ciprofloxacin, the antibacterial activity of the composite was significantly improved, demonstrating a strong synergy between the drug and silver nanoparticles inside the composite. Aside from their strong antibacterial properties, these composites also have lower cytotoxicity and higher stability levels.

As part of his research, encapsulated curcumin (Cur) in silver nanoparticles. According to the results, Cur-AgNPs were less toxic

than plain Cur and demonstrated effective anticancer activity. Therefore, such environmentally friendly nanoparticles are used as anticancer agents in medical applications [113]. Vaccinations and medications could be delivered using AgNPs that are precise to cells or tissues. Silver nanostructured frameworks have excellent optical properties; recent improvements in the bioactivity and durability of AgNPs via surface modification indicate that silver nanostructured frameworks may make flexible, selective, and targeted drug delivery devices [114].

4.2. Cancer Therapy

There is a significant number of deaths caused by cancer and its secondary complications worldwide due to ineffective chemotherapeutic agents, severe side effects, and poor prognosis. In terms of cancer reports worldwide, breast cancer accounts for 13.3%, followed by colorectal cancer at 11.1% [115]. It is anticipated that 14 million new instances of cancer will receive a diagnosis by 2035, causing significant economic and social impact across the globe [116]. To reduce the adverse effects of cancer incidence, practical and advanced treatment methods must be developed. Common treatments incorporate surgery, chemotherapy, and radiotherapy. Nevertheless, traditional therapies have adverse consequences and limitations that can influence outcomes. In the case of standard chemotherapy, for example, there may be severe side effects, including thrombophlebitis and tissue necrosis, as well as systemic responses, such as the inhibition of myelos, liver and kidney malfunction, and immune suppression [117]. The evolution of novel drugs is necessary to improve the therapeutic effect of chemotherapy because cancerous growths may become multi-drug resistance (MDR) [118]. Recent years have seen a surge in interest in nanoparticles in cancer therapy, mainly because of their physical and chemical characteristics, resulting in the emergence of a new field of nanomedicine for cancer treatment [119].

When combined with drug candidates, metallic nanoparticles (MNPs) have potential use as innovative medicinal substances and drug carriers, and unwanted adverse effects are avoidable by targeting the treatment. As a result of these nanoparticles, AgNPs offer a promising therapeutic agent for cancer or tumors [120]. It is generally believed that AgNPs exhibit anticancer activity based on their size, dosage, and time dependence. AgNPs with reduced sizes can induce greater endocytosis and cause more significant cytotoxicity and genotoxicity. Because of the increased surface-to-volume ratio, spherical AgNPs have a higher cytotoxicity than other shapes [121]. According to studies, AgNP, which is produced using environmentally friendly methods, inhibits the proliferation of breast, lung, and prostate cancer cells significantly [122]. According to Nguyen and colleagues, AgNPs synthesized with Ganoderma lucidum (GL) were effective in addressing liver cancer (HepG2) and breast cancer (MCF-7). The researchers also found that small particles of AgNPs/GL (10.72 nm) inhibited HepG2 and MCF-7 proliferation [123]. According to Deeb et al. [124], silver nanoparticle production using metabolites of Arthrospira platensis, Microcystis aeruginosa, and Chlorella vulgarisactive was assessed in vitro, while in vivo, bio-AgNPs were tested for safety in albino mice and PBMCs. It was found that 0.1 mg/mL and 1.5 mg/mL concentrations of bio-AgNP were safe for use. Using Petroselinum crispum seed extract as a reducing agent, M.Z-Bidaki et al.[125] synthesized silver nanoparticles. It was found that these nanoparticles had significant antibacterial and antioxidant properties, making them a potential therapeutic agent. Moreover, they found that the nanoparticles demonstrated promising anticancer activity in MCF-7 cells, which suggests that these particles could be useful in cancer treatment.

4.3. Imaging and Diagnostics

Various biosensors can be employed with AgNP-containing nanoparticles, including those for detecting blood glucose, enzymes, molecular markers for pathogens, tumor cells, etc [126]. AgNPs have porous nanostructures and large surface areas; they can interact more readily with electrodes and glucose, which would improve the sensitivity of a biosensor by accelerating electron transfer. Even though AgNPs have good application prospects in biosensing due to their electrochemical properties and Raman scattering, the matrix composition affects their SERS and reduces their detection sensitivities. Consequently, AgNPs need to be modified in order to enhance their sensitivity when recreating platforms [127]. A study by Sun et al. [128] synthesized and deactivated silver nanoclusters with the GSH ligand. The results showed that GSH modulated AgNC specific ion recognition. They also have high blue stability and strong red fluorescence, so they are suitable for biological imaging and ion sensing in bloody environments. Guo et al. [129] developed silver nanoclusters by capping them with hybridized DNA duplexes, which have been applied in detection systems. These results demonstrate that this strategy can detect a broader range of single nucleotide differences.

4.4. Wound Healing

One of the biggest problems in the medical industry is wound infections. These cause a significant amount of illness and mortality globally and result in measurable financial loss [130]. Wounds have been successfully treated with dressings based on AgNPs. Bacteria in the wound are interacting with and being destroyed by the AgNPs in the dressing [131]. Furthermore, AgNPs are essential for regenerating damaged skin [132]. It has been demonstrated that natural biopolymers can significantly improve wound healing when combined with AgNPs [133]. As a result of their remarkable role in wound healing, the United States Food and Drug Administration (FDA) has previously accepted many bio composites modified with AgNPs [134, 135]. Extracellular matrix and skin constituents must communicate extensively during wound healing. Various factors are involved in wound healing, including cell types, growth factors, vascular systems, cytokines, connective tissue, and coagulation factors. This has led to the development of wound treatment based on nanotechnology to treat chronic wounds. It is possible to use nanomaterials to deliver drugs for wound healing or to repair wounds [136]. Combining AgNPs and different biomaterials has shown more efficacy in healing wounds and preventing infection than their components. In addition to AgNPs well-established antimicrobial properties, biopolymers offer biodegradability and biocompatibility, making AgNP a potent wound healing agent [137].

The effect of oral silver nanoparticles on full-thickness wounds in mice was examined in vivo by Samii-Rad et al. Silver nanoparticles were shown to be effective for wound treatment, and the damaged cells were able to produce many mediators that accelerated wound healing as a result of these effects [138]. The researchers developed new formulations for antibacterial dressings by synthesizing PG/Ag-NPs. Also, antibacterial tests indicated that PG/Ag-NPs (1%) were highly bactericidal against Staphylococcus aureus and P. aeruginosa, and MTT tests indicated that PG/Ag-NPs accelerated fibroblast proliferation [139]. Additionally, Mariam et al. [140] reported that a combination of hydrogel films with mint and Ag-NPs improved wound healing in diabetic mice significantly.

4.5. Dental Applications

In some dental biomaterials, AgNPs are incorporated to reduce biofilm formation since they are antibacterial. It is common to fabricate dentures from polymethyl methacrylate (PMMA), sometimes referred to as composite resin and acrylic resin. However, the rough surfaces of dentures may attract harmful organisms. Dental materials can be improved by incorporating AgNPs. AgNPs present strong antibacterial properties in PMMA,

with continuous release of Ag^+ even after 28 days. AgNP loading in PMMA enhanced its mechanical properties as well [141]. It has been shown by Acosta-Torres et al. [142] PMM-AgNPs can effectively reduce Candida albicans adhesion and show no discernible cytotoxicity or genotoxicity. AgNPs encapsulated with carboxymethyl cellulose and sodium alginate were evaluated for their antibacterial and antibiofilm efficacies. In this study, carboxymethyl cellulose capped AgNPs were found to be more effective in inhibiting Gram-negative organisms, the primary cause of periodontal diseases.

Dental preventive treatment used AgNPs to penetrate unhealthy lesions, precipitate, and strengthen enamel. Studies conducted in vivo were done using Nano silver Fluoride with green tea extract (NSF-GTE) to stop cavitation-related lesions in preschoolers' teeth. 67.4% of primary teeth were successfully arrested for six months with dentin carious lesions [143]. AgNPs have excellent antimicrobial properties, as demonstrated by Paul et al. [144] who synthesized them with white pepper oleoresin. They were found to be effective against oral pathogens. In the same way, Umai et al. [145] used olive extract as a reducing agent for silver nanoparticle synthesis. These nanoparticles can prevent infection on conventional dental implants based on the results. In addition, they showed good antimicrobial and antifungal activity against oral pathogens. According to Almaza-Reyes et al. [146], silver nanoparticles can reduce the possibility of SARS-CoV-2 contamination in healthcare personnel and others who were exposed to COVID-19 as a mouthwash and nasal rinse solution. Another study showed that nanosilver fluoride and green tea extract (NSF-GTE) had comparable outcomes to silver diamine fluoride (SDF) at staving off active caries in primary teeth in fluoride-free communities. Primary teeth with caries can therefore be treated with this method [143].

5. Future Perspectives

In the last several years, metallic nanoparticles are becoming more and more common for their versatile applications in research. Therefore, new technologies, methods, and creative paths are being regularly investigated to increase their viability, affordability, sustainability, and convenience. In nanoscience and nanobiotechnology, the startling and brightly colored noble metallic AgNPs have gained significant attention. It is clear that there is a continual need for more enduring, reasonably priced, and multipurpose goods, which provides promising opportunities for biosynthesized AgNPs in the future [147].

5.1. Innovations in Synthesis and Applications

A physical and chemical approach is currently available for preparing stable, monodispersed, and 10 nm-sized AgNPs. Despite this, nanoparticles produced are non-specifically toxic, affecting host cells. Thus, it may be possible to investigate hybrid synthesis techniques to achieve equilibrium in the low toxicity and high stability of AgNPs. Silver nanoparticles and nanocomposites are also considered as potential antiviral agents to combat Coronaviruses [148-151].

The AgNPs have been used to inhibit IFV-A, H1N1, and H3N2 viruses. By attaching itself to the viral envelope glycoproteins, nanoscale AgNPs can prevent coronaviruses from entering host cells and/or inhibit neuraminidase (NA) and hemagglutinin (HA) activity. AgNPs were tested and demonstrated to prevent the inhalation of SARS-CoV-2 by Sarkar, Considering that upper respiratory tract infections usually begin [152]. Further, silver nanoparticles can be used as an inorganic antiviral agent to improve the suppression of viruses that cause pandemics and zoonotic infections, which can lead to severe sickness in humans by coating them on textiles and masks [153]. Moreover, Sportelli et al. [154] reported the usage of AgNPs in biomedical products that fight viruses, such as Covid-19 and, specifically, to slow and restrict contagions. Therefore, AgNPs or nanocomposites made using biological methods are very advantageous as antiviral agents capable of combating and eliminating numerous viral infections with minimal side effects and toxicity [155].

5.2. Challenges and Limitations

Silver nanoparticles are highly toxic to plants, aquatic animals, and, most importantly, humans, which could be the primary obstacle to their development in many fields [156]. A plant's physiology and concentration determine how toxic silver nanoparticles will be, as well as the length of time it will be exposed to particles. According to the toxicity mechanisms of silver nanoparticles, they could cause cardiovascular diseases, immunotoxicity, and neurotoxicity in humans [157]. Studies using silver nanoparticles have increasingly relied on green synthesis techniques to overcome the numerous drawbacks of NP applications, especially toxicity, in recent years [158]. Green synthesis of silver nanoparticles features reduced energy use, environmentally positive responses, and more straightforward, more dependable, and less complex processes [159]. It is necessary to carefully control silver NPs' physicochemical properties via synthesis techniques and optimize the dosage to prevent bacteria from becoming resistant to silver NPs. Various mechanisms can be used by bacteria to fight silver nanoparticles, such as agglomeration, suppression of dissolution, avoidance of particle contact, removal of silver ions from cells, etc [160]. Surface alterations and co-administration strategies may be able to help overcome resistance mechanisms. It is crucial to remember that resistance mechanisms can differ based on silver NP size and surface modification [161]. In addition to overcoming resistance mechanisms, surface modification of silver nanoparticles is also an effective tool for lowering possible toxicity and maintaining stability so as in order to avoid agglomeration. A silver NP's efficiency can be significantly affected by the amount of silver ions released, depending on the environment. Furthermore, it is important to emphasize that studies using silver nanoparticles as bioimaging or biosensing materials are sensitive to agglomeration. Agglomeration accumulates large particles, affecting the particle's stability and efficiency [162]. Silver nanoparticles are widely applied, but optimizing cost-effective manufacturing presents a significant challenge. Physicochemical properties of silver nanoparticles are greatly impacted by the synthesis process, so determining dimensions and form in large-scale manufacturing is a significant challenge. Clinical applications of silver nanoparticles are hindered heavily by inconsistency in large-scale production procedures and the inability to predict therapeutic results [163]. It is unclear how silver nanoparticles are distributed within the human body in the future. The surface alteration and chemistry of silver nanoparticles can substantial affect how they interact with biological systems, as mentioned previously [164]. For better predictions of undesirable outcomes, silver nanoparticles need to be studied in biological systems [165, 166].

5.3. Emerging Trends in Nanomedicine

It is expected that AgNPs will continue to thrive due to their distinct uses in many facets of life, such as medical applications, antimicrobial, antibacterial, anti-angiogenic, antifungal, anticancer, anti-inflammatory, antiviral, anti-protozoal, and antiparasitic applications, repair of the environments, and electronics and energy

applications [167, 168]. Nanoparticles such as copper, platinum, silver, nickel, iron, and gold especially AgNPs, are effective against parasites when used after drugs and vaccines fail [169].

It is necessary to use nanosized drugs to enter the parasite cuticle and treat parasites within cells. For controlling ruminant helminths like H. contortus and F. hepatica in animals and humans, research is being conducted. The use of AgNPs as an anthelmintic therapy for parasites can be used [170]. AgNPs are significantly effective at killing Cryptosporidium parvum (waterborne protozoan) oocysts at concentrations that chlorine disinfectants do not kill them [171]. Nanoparticles are mostly targeted at ticks, which transmit zoonotic diseases and pests to cattle. With titanium dioxide nanoparticles, AgNPs have toxic impacts on ticks, and different eco-friendly nanoparticles worked well against R. microplus [172]. AgNPs coupled with rifampicin are also effectively produced chemically [173]. In addition, nanoparticles can be used as vaccines against veterinary parasites, especially F. hepatica [174]. Nanocarrier drugs stay in the kidneys, spleen, and liver for a long period because they are protected from metabolism [175]. By reducing albendazole's toxic effects, include necrosis, elevated liver enzymes, and steatosis, albendazole's effectiveness against Echinococcus granulosus hydatid cysts can be improved by using silver nanoparticles [176]. Therefore, anthelmintic (such as albendazole, mebendazole, etc.) loaded AgNPs offer a lot of promise in combating parasites [177]. Additionally, hemoglobin can be used as a biomarker for parasitic diseases, however specific antigens are required to use it as a biosensor [178]. A variety of nanoparticle-loaded drugs such as vincristine , paclitaxel, curcumin, resveratrol, doxorubicin, salvianolic acid B, silymarin, artemisinin, honokiol, and camptothecinare available on the market [179].

6. Conclusions

Silver nanoparticles have become a versatile and promising element in the biomedical field due to their unique physicochemical properties, including antimicrobial, anti-inflammatory, and anticancer activities. Their applications span many areas, such as wound healing, drug delivery, diagnostic imaging, and biosensing. The ability of AgNPs to combat multidrug-resistant pathogens has positioned them as a potential solution to one of modern medicine's most pressing challenges. Despite their immense potential, challenges remain in the widespread adoption of silver nanoparticles in clinical practice. Issues such as toxicity, biocompatibility, and long-term environmental impact need to be thoroughly addressed through rigorous research and standardization. Advances in green synthesis methods and surface functionalization strategies pave the way for safer and more effective applications.

Future research should focus on developing safer synthesis methods, enhancing biocompatibility, and exploring targeted delivery mechanisms. By overcoming these hurdles, silver nanoparticles could play a pivotal role in shaping the future of biomedical innovation.

Authors' contribution

Samira Ranjbar: Writing—Original Draft Preparation, Investigation, Resources, Writing—Review and Editing**, Ameneh Bakhtiari:** Writing—Original Draft Preparation, Investigation, Writing—Review and Editing, **Negin khosravi*:*** Writing—Original Draft Preparation, Writing—Review and Editing, **Shima Jafari Ashkavandi:** Writing—Original Draft Preparation, Writing—Review and Editing, **Fariba Azamian*:*** Writing—Original Draft Preparation, Writing—Review and Editing, **Mahfam Alijaniha:** Writing—Original Draft Preparation, Writing—Review and Editing. **Mojtaba karbalaee:** Writing—Original Draft Preparation, Writing—Review and Editing.

Declaration of competing interest

The authors declare no conflicts of interest.

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