

Review Article

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Application of AgNPs in biomedicine: An overview and current trends

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Abstract: Silver nanoparticles (AgNPs) can provide excellent, reliable, and effective solutions for anti-microbial, drug-loading, and other purposes due to their extraordinary physical, chemical, and biological characteristics. Different methods have been used in the synthesis and characterization of AgNPs, and AgNPs have been applied in various fields of biomedicine, including dentistry, oncology, diabetology, neurodegenerative disorders, and so on. However, the cytotoxicity of AgNPs has not been solved during their application, making them controversial. The aim of this review is to summarize the capabilities, synthesis, and characterization methods, and the application of AgNPs in various biomedicine fields. In addition, the toxicity of AgNPs is explicated, and the methods of enhancing the benefit properties and reducing the toxicity of AgNPs are demonstrated. In the end, the perspective of AgNPs' research and application are proposed for the great potential in biomedicine contributing to human health.

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1 Introduction

Nanotechnology is a fast-growing emerging technology, providing materials in nanometer size with excellent physicochemical and mechanical properties. Silver nanoparticles (AgNPs) are metal silver particles with a small size of 1–100 nm, large surface area volume ratio, superior carrier capacity, high reactivity, and flexible surface [1]. Silver is an ancient and safe antibacterial agent. Humans have a long history of using silver to fight bacterial infections. It was used in ointments and dressings for burns as silver nitrate or silver sulfadiazine [2,3]. With the advent of the era of nanotechnology, it is meaningful to explore the application of the antibacterial ability of AgNPs. Meanwhile, they are also popular in the food packaging industry, electronic manufacturing industry, and agriculture [4–6].

AgNPs, owing to their distinguished physicochemical properties, are the most popular and widely used nanoparticles (NPs) [7]. There are various biological activities of AgNPs, such as antibacterial, antiviral, anti-inflammatory, antifungal, antioxidant, anticancer, and antidiabetic [8–13]. AgNPs, the new antibacterial agent, are considered against a variety of pathogenic and infectious microorganisms, including multidrug-resistant bacteria. To be specific, AgNPs have outstanding antibacterial activity against Gram-positive and Gram-negative bacteria [14]. In this review, we concluded the application of AgNPs in dentistry, such as the prevention of caries, restoration of tooth defects, root canal therapy, periodontology, implantology, orthodontic brackets, oral cancer, as well as its outstanding performance in the treatment of other cancers, diabetes, neurodegenerative diseases, and other biomedical fields [15]. In addition, we delved into the cytotoxicity of AgNPs and proposed the future research directions to explore the integration of AgNPs with biomedicine.

2 Capabilities of AgNPs

AgNPs have made remarkable contributions to biomedicine and processed high prospects for commercial use due to their antibacterial, antiviral, anti-inflammatory, anticancer, and antidiabetic activities [7]. Their possible mechanisms of action are shown in Figures 1–3.

2.1 Antimicrobial activity

2.1.1 Antibacterial capability

Nowadays, the research on the antibacterial mechanism of AgNPs is not sufficient, and the regularization of different bacteria may be distinguished in Figure 1. Taken as an example, the oral cavity is a complex environment inhabiting a variety of microorganisms. For example, *Streptococcus mutans* (*S. mutans*), *Porphyromonas gingivalis*, and *Fusobacterium nucleatum* are the main etiological agents

of caries and periodontal diseases [16]. Zorraquin-Pena *et al.* [17] demonstrated the antimicrobial activity against oral pathogens of AgNPs. Moreover, some studies found that the inhibition of *Staphylococcus aureus* was carried out by disturbing respiratory chain dehydrogenase, interfering with bacterial growth and cell metabolism; the inhibition of *Escherichia coli* was done by destroying the integrity of the bacteria by depolarization and membrane instability; the inhibition of *Pseudomonas aeruginosa* by AgNPs was done through the production of free radicals that destroyed the cell membrane, and the interaction of reactive oxygen species (ROS) with the cell wall and cell membrane [18–20].

Over the past few decades, the frequent and widespread use of antibiotics led to the antibiotic-resistant bacteria development. Resistance to pathogenic microorganisms threatened global public health [21]. Research has found that the combination of AgNPs with conventional antibiotics could improve the antibacterial effect and reduce the use of antibiotics to hinder the development of drug resistance of pathogenic bacteria [22].

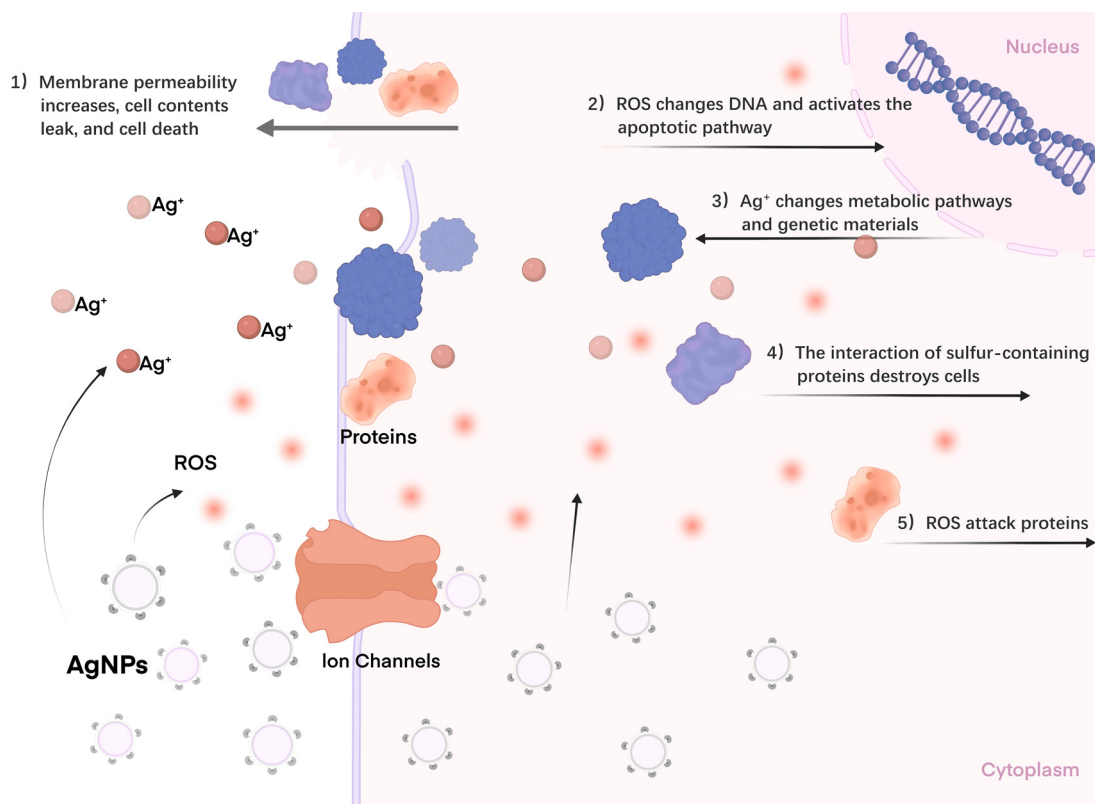


Figure 1: Antibacterial mechanism: (1) AgNPs increased membrane permeability and induced leakage of cell contents, leading to cell death. (2) Oxidative stress changes the structure and function of DNA and proteins, causes damage to intracellular machinery, and activates the apoptotic pathway. (3) The release of silver ions, due to their size and charge, can change metabolic pathways and genetic materials after interacting with cell components. (4) The interaction between AgNPs and sulfur-containing proteins in bacterial cell walls leads to the structural damage of cell wall rupture. (5) ROS attack proteins.

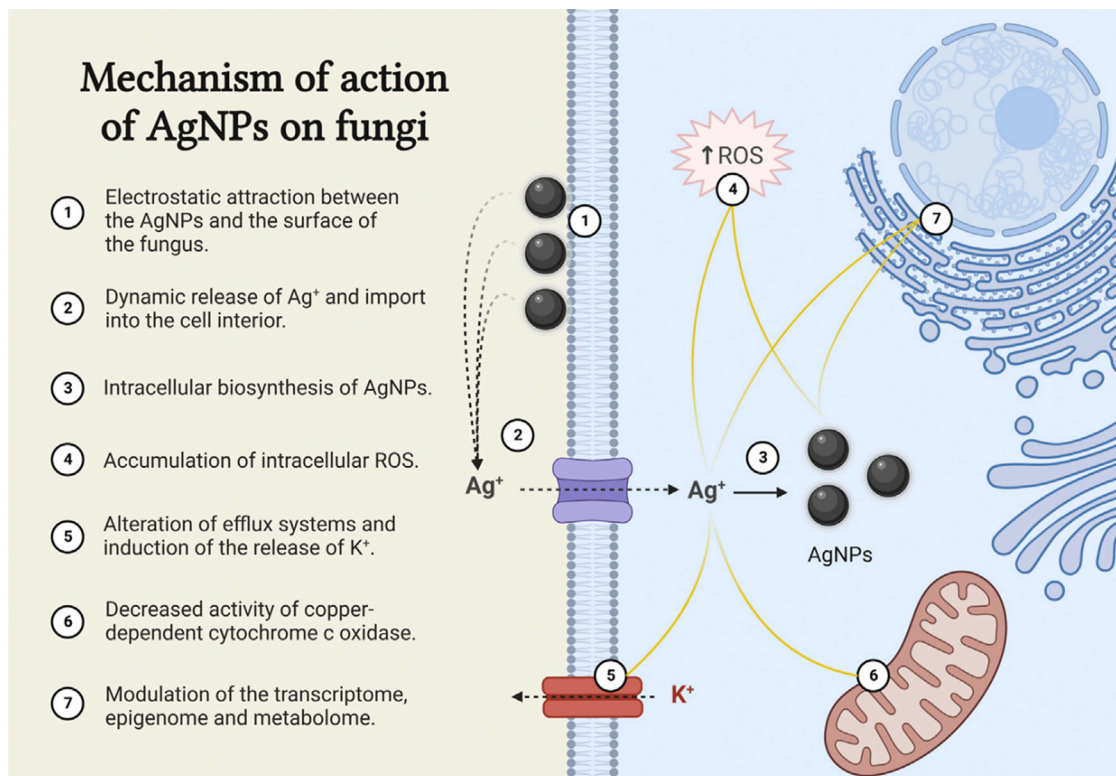


Figure 2: Antifungal mechanism of AgNPs. Reproduced with permission from Ref. [28] (Copyright 2022 Frontiers).

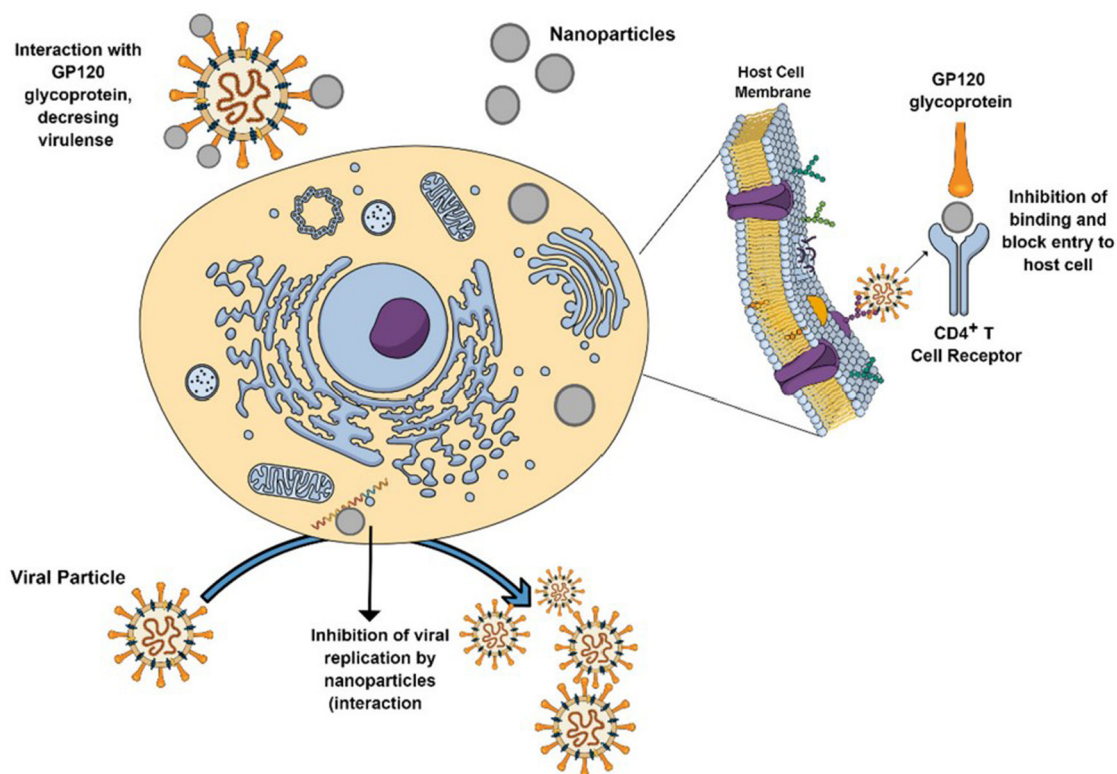


Figure 3: Antiviral mechanism of AgNPs. Reproduced with permission from ref. [31] (Copyright 2021 MDPI).

The development of drug resistance was done by changing the target side, degrading the enzyme, reducing membrane permeability, and activating the efflux pumps [23,24]. Bruna *et al.* [3] demonstrated that AgNPs can inhibit the growth of bacteria, showcasing an increased ability to penetrate their membranes with decreasing dimensions of NPs. Moreover, the antibacterial efficiency of AgNPs against Gram-negative bacteria was higher than that of Gram-positive bacteria.

2.1.2 Antifungal capability

The primary antifungal mechanism of AgNPs operates through structural modifications at the biofilm level. Numerous studies have demonstrated that the accumulation of reactive oxygen species in cells can trigger apoptosis. Furthermore, Babele *et al.* [25] discovered that AgNPs profoundly influence vital functions of fungal cells, including the regulation of the transcriptome, epigenome, and metabolome. Vazquez-Munoz *et al.* [26] considered AgNPs reduction process after the release of silver ions outside the fungus induced cell death. Rozhin *et al.* [27] demonstrated that potential antifungal mechanisms could be attributed to genes involved in maintaining cell wall or membrane integrity, entosis, vesicular transport activity, oxidative metabolism, cell respiration, and copper homeostasis (Figure 2).

2.1.3 Antiviral capability

AgNPs have high antiviral activity to inhibit virus infection or inactivate viruses, such as herpes simplex virus, respiratory syncytial virus, adenovirus type 3, and the influenza A virus [29,30], but the mechanism remains uncertain. AgNPs possess a large surface area and dominant size, promoting contact and penetration with viruses. AgNPs can adhere to the glycoprotein on the surface of viruses, interfere with the interaction between viruses and cell membranes, and prevent viruses from penetrating the cell membrane. They can also inhibit the nucleocapsid of the viral entity, ultimately destroying the viral genome and inhibiting its replication [29]. AgNPs exhibit antiviral potential, but it is still a challenge to design specific antiviral agents that only target viruses. It can also damage the viral lipid membrane, inhibit cellular replication, assembly, and release of virions, and have inhibitory effects at different stages of viral replication (Figure 3) [31,32].

2.2 Anti-inflammatory capability

Tyavambiza *et al.* [33] showed AgNPs had anti-inflammatory properties, as AgNPs decreased the levels of proinflammatory cytokines (IL-6, IL-1 β , and TNF- α) in macrophages. Another study reported that the anti-inflammatory activity was equivalent to that of the standard anti-inflammatory drug diclofenac [34]. This suggested that AgNPs had the potential to become an anti-inflammatory drug to control chronic inflammatory diseases [35]. In a mouse model of rheumatoid arthritis (RA), Yang *et al.* [36] used folic acid-modified AgNPs to treat RA, which showed a strong therapeutic effect without tissue accumulation and appreciable long-term toxicity.

2.3 Delivery drugs/medication nanocarriers

Recently, nanoparticle drug delivery systems (NDDS) deserve extensive attention and further research [37]. Asl *et al.* [38] believed most synthetic or semi-synthetic anticancer drugs can be toxic due to their insoluble accumulation at the absorption site. Moreover, the hydrophobicity of traditional drug delivery has limited the use of anticancer drugs [39]. In this regard, NPs have advantages in size, representing a solution to overcome these drawbacks, so that they can interact with lipids, proteins, and nucleic acids. The use of NPs to synthesize drugs increases the solubility and surface stability of the compound, enabling them to be transported across membranes, increasing blood drug concentration, reducing drug dosage, and thereby improving the efficiency of drug delivery to the target organ or tissue [40].

2.4 Photothermal therapy (PTT) and photodynamic therapy (PDT)

PTT is the use of near-infrared light to induce heat therapy, PTT is also widely used in antibacterial therapy, but it has the disadvantage of excessive temperature damaging normal cells. Zhu *et al.* [41] combined a mixture of sodium alginate and AgNPs modified polydopamine NPs to prepare a new hydrogel that can treat bacterial infections at low temperatures. In addition, Chang *et al.* [42] proved that the nano-composite hydrogel functional wound dressing prepared by the combination of AgNPs and PTT could alleviate inflammation and promote the healing of

infected skin wounds. Moreover, Ag-Te NPs synthesized by Ahn *et al.* [43] with Te nanorods can be used for the treatment of breast cancer *in vitro* and *in vivo* through the ablation of hyperthermic cancer cells by photothermal conversion and can play a role in eliminating breast tumor bacterial cells.

Photodynamic therapy (PDT) is to irradiate the lesion with a specific wavelength of laser, which can activate the photosensitive drugs selectively gathered in the lesion tissue and trigger a photochemical reaction to destroy the lesion [44]. PDT can effectively treat melanoma by coupling AgNPs with photosensitizer drug molecules, selectively induce apoptosis or necrosis of cancer cells, and target drug delivery to specific sites [45].

2.5 Others

The synthesized AgNPs can be used to detect X-ray exposure and enhancement doses for further application in the field of radiotherapy and diagnostics [46]. AgNPs have been proven to increase cancer cell oxidative stress, and cell membrane fluidity and cause apoptosis [47]. In particular, in the treatment of gliomas after radiation therapy, observe their effects on promoting apoptosis and anti-proliferation of gliomas. Arif *et al.* [47,48] demonstrated the potential of AgNPs in bone healing. They found that AgNPs can enhance cell mineralization and differentiation, indicating promising applications in bone regenerative therapy. Furthermore, AgNPs promote wound healing by infiltrating a thick peptidoglycan layer in Gram-positive bacteria and a thinner layer containing lipopolysaccharide and acid in Gram-negative bacteria [49].

3 Synthesis and characterization of AgNPs

With the deepening investigation on AgNPs and the expansion of the application scope, the demand for AgNPs is also growing steadily, and the approach of AgNPs synthesis has become a matter of issue. Different methods of AgNPs synthesis have been studied, mainly including physical, chemical, and biological routes. Among them, the biosynthesis method has been extensively explored in recent years due to its low cost and low toxicity. To detect the presence of AgNPs, the synthesized AgNPs were characterized by means of UV-Vis, X-ray diffraction (XRD), transmission electron microscopy (TEM), scanning electron microscopy (SEM), and Fourier transform infrared spectroscopy (FTIR).

3.1 Physical synthesis

The physical method is to synthesize NPs from solid or atomized metallic silver to nanoscale utilizing laser ablation, ball milling, and sputtering to obtain stable AgNPs [3]. In general, the physical preparation uses physical energy to prepare AgNPs with fine-grained cycles. This method can effectively produce a large number of AgNPs in one process in ash form [50]. However, this synthesis requires external energy and complex equipment [51]. Although the physical synthesis method can produce plenty of AgNPs and the product is uniform, this method is costly, and there may be radiation [52]. Furthermore, it is still a major challenge to agglomerate with no capping agent or stabilizer.

3.2 Chemical synthesis

The chemical synthesis is lower in cost than the physical method, which can obtain NPs with clear spherical shapes, mainly including chemical reduction, electrochemistry, and sol-gel [53]. The materials of it require metal precursors, reducing agents, and stabilizers. The size of NPs is controlled by using capping agents, and their morphology is controlled by the growth and nucleation stages during the solution reduction process [50]. AgNPs with various shapes can be quickly obtained by chemical synthesis, but the use of irritating chemicals in the synthesis process may produce toxicity, which limits the application of AgNPs in medicine and may be harmful to the environment [51,54,55].

3.3 Biological synthesis

Biosynthesis is a method using reducing agents extracted from biological sources, which is noteworthy due to its fast, low-cost, and low-toxic effects on humans and the environment [56–59].

By multiple biotechnology tools, different natural resources are available, including fungi, bacteria, algae, viruses, plants, or their by-products such as proteins and lipids [60]. AgNPs from natural compounds like the bark of *A. nilotica*, *aloe*, *lemongrass*, *Mentha*, the aqueous leaf extract of *Psidium guajava*, and *Coriandrum sativum* are preferred because of their easier producing process and are cheaper and safer [56,61–64].

El-Naggar *et al.* [65] showed that AgNPs could be synthesized by reducing silver nitrate with phycoerythrin in cyanobacteria. Besides, the use of microorganisms such

as bacteria and fungi can induce the reduction required for metal nano synthesis and easily achieve high yield, providing an environmentally friendly and low-cost technology. For example, AgNPs can also be synthesized with *Aspergillus sydowii* and *Beauveria bassiana* [66,67]. Furthermore, it is achievable to use secondary metabolites to synthesize AgNPs, such as *Curcumin*, *Streptomyces* sp., and *Rhodococcus rhodochrous* [57,68,69].

Physical and chemical synthesis are mainly applied in AgNPs manufactured in large amounts for saving time. But the disadvantage was the possible production of toxic substances and environmental pollution [52]. Compared with others, biological synthesis is the easiest, the most non-toxic, and environmentally friendly method to produce high-quality NPs, which is still the most applied and investigated method nowadays. Overall, Biological synthesis is a promising alternative method for biocompatible stable NPs.

3.4 Characterization of AgNPs

The physicochemical properties of NPs on their behavior, biodistribution, safety, efficacy, *etc.*, need to be embodied by characterizing AgNPs to evaluate the functional aspects of the synthetic particles [70]. Different methods have been used to study the characterizations of AgNPs, including the size, morphology, surface area, surface charge, surface coating, and agglomeration behavior in the media. In the synthesis of AgNPs, silver ions are often obtained by reducing AgNO_3 , and the way to detect the success of reduction is by the change in the color of the mixture to dark brown due to the excitation of surface plasmon vibrations in AgNPs [51]. The synthesis of AgNPs was confirmed by ultraviolet-visible spectroscopy (UV-Vis), XRD, SEM, TEM, and FTIR. The optical absorption spectrum of metal NPs is mainly dominated by surface plasmon resonance and the absorption band is related to the particle size. XRD is one of the most widely used conventional techniques to characterize NPs to determine the crystal structure and morphology, including crystal structure, lattice parameters, phase properties, and crystal size [51]. The size, shape, and structure of the synthesized AgNPs are analyzed by SEM or TEM [51,71]. FTIR analysis is used to identify the functional groups in the compound and reveal functional groups actively participating in reduction [72]. Table 1 shows AgNPs characterization using UV-Vis, XRD, SEM, TEM, and FTIR.

4 Application of AgNPs in various fields of biomedicine

Due to the excellent characteristics of AgNPs, the applications in biomedicine have developed rapidly such as dentistry, cancer, diabetes, and neurodegeneration. The oral cavity is an external environment with enormous micro-organisms living in it. Dental caries and periodontitis are common oral diseases, and they will occur when the micro-environment niche is disturbed. Besides, it can also be used as a drug carrier for examination, diagnosis, and treatment (Figure 4, Table 2).

4.1 Dentistry

With the ability of antibacterial and anti-inflammation, AgNPs are widely used in dentistry, including dental caries therapy, periodontal and peri-implantitis prevention, orthodontic therapy, and oral cancer therapy.

4.1.1 Dental caries

Dental caries not only affect oral health but also associate with systemic and inflammation-related diseases, like diabetes and respiratory diseases [82,83]. Therefore, the prevention and treatment of dental caries are common oral health problems, which have attracted wide attention. Early childhood caries (ECC) is the presence of one or more decayed, missing, or filled primary teeth in children aged 71 months (6 years) or younger [84]. ECC has become a significant health problem with high prevalence. Khubchandani *et al.* [85,86] found preparations containing AgNPs can prevent ECC and rampant caries due to their anti-caries activity against *S. mutans* and their abilities to invade and destroy biofilm matrix. The impact of synthesized AgNPs on *S. mutans* was tested by pore diffusion and microdilution techniques. Al-Ansari *et al.* [87] found the potent antibiotic action over *S. mutans* seen with the synthesized AgNPs. Yin *et al.* [88] reported that AgNPs could prevent dental caries by inhibiting the adhesion and growth of cariogenic bacteria and hindering the demineralization of enamel and dentin.

One study found that adding different concentrations of AgNPs to the bonding system could exert their antibacterial effect without increasing cytotoxicity [89]. Besides, the bonding strength of the tooth-bonding interface was

Table 1: AgNPs characterization using UV-Vis, XRD, SEM, TEM, and FTIR

Methods	Observed indexes	Material	Results
UV-Vis	Absorption band	<i>Curcumin</i>	The maximum absorption peak at 430 nm [57]
		<i>Ziziphus Jujuba</i> leaf	The spectrum band at 434 nm [73]
		Five plant leaf extracts (Pine, Persimmon, Ginkgo, Magnolia and Platanus)	The maximum absorbance occurs at 430 nm [74]
		<i>Nocardioopsis</i> sp. MBRC-1	A strong and broad peak at 420 nm [75]
		Trisodium citrate (TSC) as a reducing and stabilizing agent	One single extinction peak around 400 nm up to 425 nm [76]
		Liquid phase pulsed laser ablation (LPPLA) in TSC solutions	Increased plasmon absorption at 400 nm [77]
XRD	AgNPs peaks at 2θ angles	<i>Ziziphus Jujuba</i> leaf	The average crystallite size of 6 nm [73]
		<i>Caesalpinia ferrea</i> seed extract	30–50 nm [78]
		<i>Pandanus odorifer</i> leaf extract	10–50 nm [71]
		<i>Coriandrum sativum</i> L.	11.9 nm [79]
		<i>Nocardioopsis</i> sp. MBRC-1	45 ± 0.05 nm [75]
		TSC as a reducing and stabilizing agent	$21.1 \text{ nm} \pm 2.9$, $T = 80^\circ$ $14.64 \text{ nm} \pm 2.3$, $T = 120^\circ$ $20.7 \text{ nm} \pm 2.8$, $T = 140^\circ$ [76]
TEM	Images under TEM	Magnolia leaf Persimmon, Magnolia and Pine leaf	Spherical shape; average diameter of 32 nm [74]
		<i>Urtica dioica</i> (Linn.) leaf extract	20–30 nm [59]
		<i>Nocardioopsis</i> sp. MBRC-1	Spherical shape; average diameter of 45 nm [75]
		LPPLA in TSC solutions	Nearly spherical shape; The average size of about 13 nm [77]
SEM	Images under SEM	<i>Curcumin</i>	The average size of 51.13 nm [57]
		<i>Coriandrum sativum</i> L.	Ball shape [79]
FTIR	IR spectrum	TSC as a reducing and stabilizing agent	Near to spherical structure [76]
		<i>Nocardioopsis</i> sp. MBRC-1	The band at $2,923$ and $2,853 \text{ cm}^{-1}$ (C–H stretch)
			$1,460 \text{ cm}^{-1}$ (C–H bend)
			$1,655 \text{ cm}^{-1}$ (–C=C– stretch)
			685 cm^{-1} (–C=C–H:C–H bend) [75]
		<i>Coriandrum sativum</i> L.	3275.64 cm^{-1} (OH stretching)
			1632.43 cm^{-1} (C=O stretch)
			2919.43 cm^{-1} (C H extension and extension of alkanes with the C–H connection)
			1398.12 cm^{-1} (CH_3 stretching)
			1237.86 cm^{-1} (C–O and amine vibrations) [79]
		TSC as a reducing and stabilizing agent	$3,250 \text{ cm}^{-1}$ (O–H bond)
			$1,583 \text{ cm}^{-1}$ (anti-symmetric COO^- stretching)
			$1,393 \text{ cm}^{-1}$ (symmetric COO^- stretching) [76]

reliable and could improve the service life of the restoration [89]. Even with low concentrations of AgNPs incorporated into the composite resin, they could exhibit significant antibacterial properties without affecting inherent mechanical and biological properties [90]. In the realm of endodontic materials, the efficacy of AgNPs-based irrigants in eliminating *S. aureus* and *E. faecalis* is comparable to that of 5.25% NaClO. Furthermore, these irrigants exhibit an enhanced antibacterial effect when employed in root canal therapy [91].

4.1.2 Periodontal and peri-implantitis

Plaque control is the core of periodontal treatment. The effect of plaque control is crucial in periodontitis and peri-implantitis treatment. Antibiotics are required for patients with severe inflammation and periodontal surgery or implant surgery. However, antibiotics easily induce antibiotic resistance and reduce anti-microbial efficiency in plaque biofilms [92–94]. Nowadays, AgNPs have shown proposed application in the treatment of periodontitis and

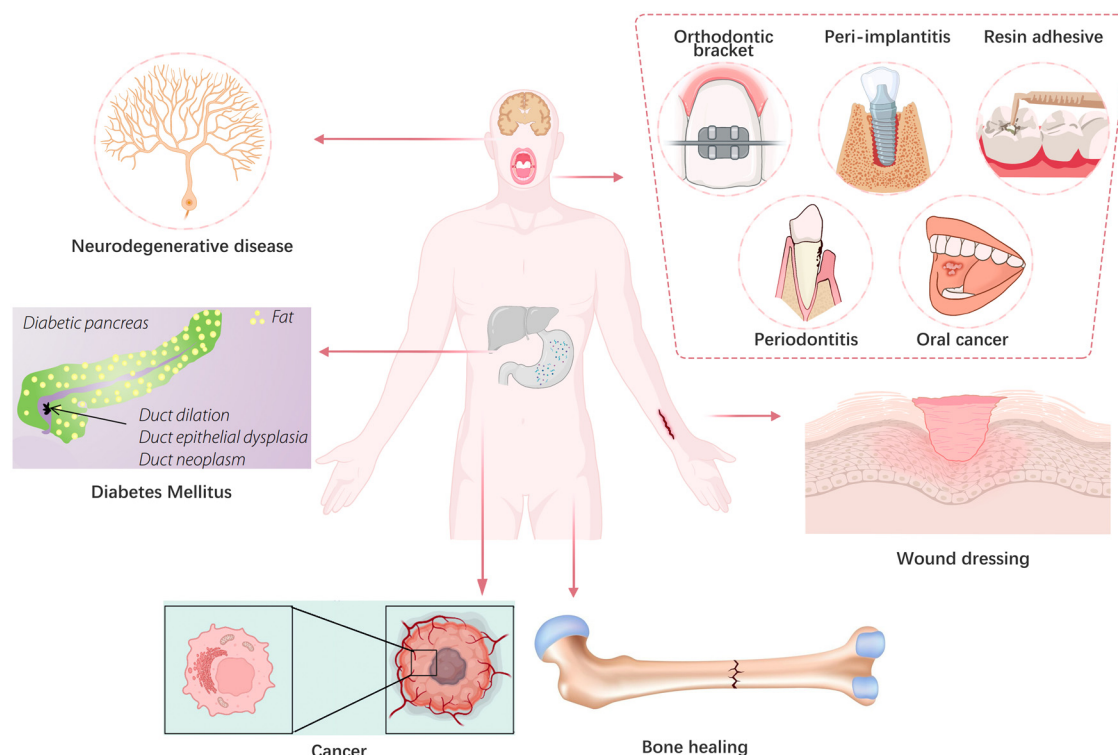


Figure 4: Application of AgNPs in various fields of biomedicine. Reproduced with permission from Ref. [80,81] (Copyright 2022 MDPI and WILEY 2017).

peri-implantitis or infection prevention due to their excellent antibacterial properties and resistance to induction [95]. Besides, Rani *et al.* [96] investigated the colonization and infiltration of specific bacteria (*S. mutans*, *Aggregatibacter actinomycetemcomitans*, *F. nucleatum*, and *Porphyromonas gingivalis*) on AgNP-impregnated guided tissue regeneration membranes. They believed that the incorporation of AgNPs may be valuable and worth studying

further. Habiboallah *et al.* [97] studied the effect of periodontal dressing with AgNPs on postoperative periodontal wounds and observed that the AgNPs group had less cell infiltration, more collagen synthesis, and cardiovascular formation.

Zhou *et al.* [98] studied the combination of antimicrobial peptides with osteogenic fragments with AgNPs and successfully achieved synergistically anti-bacterial and

Table 2: Functions of AgNPs in various biomedical fields

Function	Medical fields	Diseases	Ref.
Anti-caries and anti-bacteria	Oral medicine	Dental Caries	[82–91]
Anti-bacteria and anti-drug resistance		Periodontal and peri-implantitis	[92–99]
Anti-bacteria and reduce the surface sharpness and friction		Orthodontics	[100–103]
Anti-proliferation, cytotoxicity, and apoptosis-promoting effects		Oral cancer	[104–113]
Inhibit carbohydrate-digesting, key enzymes associated with diabetes, and promote wound healing		Diabetes mellitus	[114–118]
Inhibitory effect on amyloid fiber accumulation and biosensor construction	Nervous system	Neurodegenerative diseases	[119–128]
Small, highly targeted, and crossing the BBB	NDDS	Cancer and neurological disorders	[37–40]
Targeted therapy, drug resistance, cytotoxicity, and radiosensitivity	Cancer	PCa, ccRCC	[129–133]
Antibacterial activity, anti-inflammatory effect, and drug carrier effect.	Wound coating systems	Wound	[134–138]
Promote osteogenesis	Bone trauma	Bone healing	[139–142]
Toxicity	—	CVDs; neurodegenerative toxicity	[139–141]

osseointegration. The potential mechanism was the destruction of bacterial cell membranes and the production of ROS. Bone formation was due to the compound which was beneficial to the adhesion, diffusion, and proliferation of bone marrow stem cells on the surface, and promoted the expression of osteogenic genes and the secretion of collagen [98]. Titanium implants containing AgNPs can produce good bacterial protection, which is conducive to solving the problem of peri-implant inflammation. Gelatamp, a commercially available absorbable gelatin sponge imbued with colloidal silver, is extensively utilized in the dental field for procedures such as tooth extraction, oral and maxillofacial surgery, and periodontal surgery. It offers rapid hemostasis, reduces postoperative complications, and aids in wound healing [99].

4.1.3 Orthodontics

For patients undergoing orthodontic treatment, brackets on the surface of the teeth make it difficult to clean, resulting in the accumulation of plaque biofilms and the risk of tooth demineralization and mucosal diseases like white spot lesions [100]. Hernandez-Gomora *et al.* [101] found that AgNPs had plaque resistance and could improve the physical properties of orthodontic elastic plates, such as maximum strength, tension, and displacement. In addition, Yuan *et al.* [102] designed a new adhesive containing polycaprolactone–gelatin–AgNPs (PCL–Gelatin–AgNPs) composite fiber, which enhanced the antibacterial efficiency without affecting the bonding ability. In orthodontic treatment, the surface modification of the archwire by AgNPs can not only prevent the accumulation and development of plaque but also reduce the surface sharpness and friction between the archwire and the orthodontic bracket [103].

4.1.4 Oral cancer

The occurrence of cancer is a multi-factor, multi-step complex process, with abnormal cell differentiation and proliferation, growth out of control, invasion and metastasis, and other biological characteristics [65]. It has been reported that AgNPs had prominent anticancer activity in different types of cancers such as breast cancer, cervical cancer, colon cancer, ovarian cancer, and lung cancer [104–108].

NPs have been successfully applied to anticancer drugs due to their high surface volume ratio and high binding activity, and are easily diffusing into cells. As a new anticancer drug, AgNPs can also be applied to oral cancer. Subramanyam *et al.* [109] analyzed caspase activity by cell cycle test, apoptosis test, and flow cytometry. The

results showed that AgNPs had excellent anti-proliferation, cytotoxicity, and apoptosis-promoting effects on oral cancer cells. Another study also demonstrated the significant free radical scavenging activity and antibacterial activity of AgNPs and inferred that AgNPs had the potential to treat human oral cancer-derived diseases [110]. In addition, AgNPs are now widely used in the diagnosis and treatment of cancer due to their unique sterilization, therapeutic effect, and stability, as well as the improvement of nanotechnology and therapeutic agents [111,112]. Moreover, the combination of different anticancer drugs and metal particles have been proven to enhance the endoplasmic reticulum stress of cancer cells, which has become an innovative method to fight different cancers [113].

4.2 Diabetes mellitus

Diabetes mellitus is a disease of abnormal metabolism characterized by hyperglycemia, which is associated with a high risk of specific chronic complications. Studies have shown that AgNPs can inhibit carbohydrate-digesting and key enzymes associated with diabetes, thereby controlling blood sugar. Kanmani *et al.* [114] showed that AgNPs have antidiabetic properties, significantly inhibiting α -amylase (78.84%) and α -glucosidase (58.86%) at a 100 $\mu\text{g/ml}$ concentration, highlighting AgNPs' potential for diabetes management. Furthermore, AgNPs have been proven to have intensive hypoglycemic activity which was significantly dose-dependent. With their increase in surface area and decrease in NP size, anti-diabetic activity is stronger [115]. Due to the high blood glucose level, local hypoxia, impaired immunodeficiency, and other factors, diabetic wounds are difficult to heal. Dressings with AgNPs can accelerate wound healing and reduce scar formation. This is not only related to the antibacterial properties of AgNPs but also related to its anti-inflammatory and high surface volume ratio to enhance the penetration of the wound site [116]. Kong *et al.* [117] prepared a new type of AgNPs composite hydrogel. Polymer materials with the new dressing could improve the microenvironment, promote wound healing, and relieve pain. Khalil *et al.* [118] believed that the biosynthesis of AgNPs had stronger free radical scavenging activity in wound healing, due to the dual mode of action provided by the metal covered by plant components.

4.3 Neurodegenerative diseases

The pathogenesis of most neurological diseases is associated with up-regulation of amyloid-beta aggregation.

Dehvari and Ghahghaei [119] found that biosynthesized AgNPs had a significant inhibitory effect on amyloid fiber accumulation. In addition, research has found that AgNPs can be used to combat neurological diseases caused by protein misfolding, such as Parkinson's disease and Alzheimer's disease (AD) [120]. Owing to their optimal size, anti-inflammatory, antibacterial, antioxidant properties, and sustained drug delivery capabilities, AgNPs can effectively transport therapeutic drugs across the Blood-Brain Barrier (BBB), thereby offering a promising approach for treating neurological disorders [121–123].

AgNPs can also be used for biosensor construction of nervous system-related diseases. In recent years, based on the great progress of nanoscience, biosensors for detecting the main biomarkers of AD have been significantly developed [124]. Microglia are resident immune cells in the brain, which are associated with neurodegenerative diseases. Experiments have shown that citrate-coated AgNPs formed inactive silver sulfide (Ag_2S) and released Ag^+ , eventually reducing inflammation and neurotoxicity of microglial [125]. However, some studies have shown that AgNPs may change the morphology of astrocytes, and increase neuronal inflammation and degeneration [126,127]. Recent studies have found that AgNPs induced oxidative stress in a coating-dependent manner and disrupted the antioxidant system in the hippocampus, which may be a potential cause of neurodegeneration and cognitive impairment [128].

4.4 Cancer

Thapa *et al.* [129] developed AgNPs embedded graphene oxide with coupled MTX(MTX-GO/AgNPs) and found that this combined system can be used for folate receptor targeted cancer therapy. Other studies have shown that AgNPs can also be used to treat drug-resistant forms of cancer, such as prostate cancer (PCa) that is resistant to hormone therapy or metastatic disease. Morais *et al.* [130,131] found that synthetic AgNPs can produce cytotoxicity through endocytosis for the treatment of castration-resistant prostate cancer. Morais *et al.* [130] went further and found that AgNPs showed new potential in radiological anticancer treatment strategies. They treated clear cell renal cell carcinoma (ccRCC) with AgNPs combined with Everolimus because it can sensitize cells to radiation while showing potential cytotoxicity in ccRCC tumor models. The role of nanomaterials in drug delivery in cancer treatment has been mentioned above in NDDS. In addition, Haque *et al.* [132] found that AgNPs can be used as a non-invasive imaging tool based on near-infrared to treat cancer. From this point of view, AgNPs

show tremendous potential in exploiting new fields for cancer therapy. In cancer disease theranostics, Mukherjee *et al.* [133] found that the red fluorescence of biologically synthesized AgNPs could serve as an imaging enhancer for detecting the localization of drug molecules within cancer cells.

4.5 Wound coating/dressing

AgNPs have excellent antibacterial activity, anti-inflammatory effect, and drug carrier effect [134]. Combined with other composite materials, AgNPs are incorporated into gels to form new wound dressing systems and develop unique new bandages. It can promote wound healing, control the growth of multi-drug resistant bacteria, reduce inflammation, and enhance immunity [135]. Scientists have developed and commercialized AgNPs-based wound dressings that can cover large areas of burns and improve wound healing activity (ACTICOAT: Smith and Nephew, UK) [136]. Popescu *et al.* [137] demonstrated that composite hydrogels embedded with AgNPs and ibuprofen can play an antibacterial role in wound dressings, support healing and proliferation processes, and reshape the ultimately damaged tissue. In the context of cancer gene therapy, pegylated AgNPs are used as carriers of small interfering RNA that exhibit apoptosis in leukemic line cells [138].

4.6 Bone healing

AgNPs can promote the formation of fibrous joints, join the subsequent ends of the fracture, and upregulate the proteins of different bone morphogenesis [139–141]. Abd-Elkawi *et al.* [142], using a rabbit osteogenic model, further studied that the addition of platelet-rich fibrin and AgNPs to calcium carbonate nanoparticles (CCNPs) could reduce their absorption rate and improve their osteogenic and osteoinductive properties by promoting new bone formation.

5 Toxicity of AgNPs

As AgNPs have become widely used, research on their effects on human health and the environment has increased. But its toxicological mechanism remains unclear. Some experimental results on NPs toxicity suggest that the cytotoxic and genotoxic effects of AgNPs depend on their size, shape, concentration,

exposure time, administration routes environmental factors as well as capping agents. Scherer *et al.* [143] found that the smaller the particle size of AgNPs, the greater the toxicity, which may result from the larger specific surface area assisting in penetrating the cell membrane. The toxicity of AgNPs is also related to the specific surface area due to the shape of the particle, and the physical damage to the cell is more caused by irregular particles.

5.1 Possible toxicity mechanisms

AgNPs have the ability to continuously release silver ions (Ag^+) for a long time, and it has great potential in dermatology and wound care management. However, Ahlberg *et al.* [144] proved that the release of Ag^+ during the preparation and storage of NPs was the main reason for inducing intracellular ROS and related cytotoxicity by comparing AgNPs in O_2 and Ar. Another study evaluated the acute toxicity of metal/metal oxide NPs using a rat liver-derived cell line (BRL3A) *in vitro*. The results showed that when AgNPs decreased mitochondrial function, their cytotoxicity to hepatocytes may be mediated by oxidative stress [145]. Meanwhile, they studied the size and concentration-dependent cytotoxicity mechanism of AgNPs [56]. The results showed that AgNPs can cause cell damage by destroying the stability of the autophagy-lysosomal system, resulting in activation of NLRP3 inflammasome-dependent caspase-1, endoplasmic reticulum stress, lactate dehydrogenase release, and apoptosis [146]. In addition, an *in vitro* study has shown that short-term and low-dose AgNPs exposure can induce vascular endothelial(VE)-cadherin phosphorylation, thereby disrupting vascular integrity and increasing endothelial cell permeability, which is associated with cardiovascular diseases (CVD) [147]. In terms of neurotoxicity, Pavičić *et al.* [148] proved *in vitro* tests that no matter what coating agent AgNPs is, it will cause oxidative damage to neurons, attenuate mitochondrial activity, and ultimately affect neurodevelopment and neurodegenerative toxicity.

5.2 Methods to reduce toxicity

Changing coating is a method to reduce the cytotoxicity of AgNPs. Coating material on the metal surface can enhance the advantages of NPs like improving stability and reducing agglomeration, but uncoated AgNPs significantly will reduce cell viability in a time- and dose-dependent manner. Coating can also play an oxidative protection role and reduce the

release of silver ions. Moreover, the coating can even protect living cells from the cytotoxicity of AgNPs. The mechanism is by affecting the surface area, shape, and physical properties [149]. The material of the coating can be divided into organic and inorganic substances. With respect to organic substances, Travan *et al.* [150] promoted biosynthesis of AgNPs, polysaccharides-coated AgNPs possessed antimicrobial activity, but were non-toxic to eukaryotic cells. Another study has shown that natural clay as raw material to prepare silicate nanoplatelets loading with AgNPs provided good support for AgNPs, and reduced the inherent toxicity of AgNPs in clinical use [151].

Several studies have reported that selenium (Se) manages to resist AgNPs-induced toxicity by inhibiting oxidative damage and enhancing anti-inflammatory ability [152–155]. Ma *et al.* [156] recently found that Se had a protective effect on CVD caused by VE injury induced by AgNPs, which is attributed to inhibiting oxidative ROS and pro-inflammatory NF- κ B/NLRP3 inflammasome by activating Nrf₂ and antioxidant enzyme (HO-1) signaling pathways. Meanwhile, Hajtuch *et al.* [157] found that AgNPs coated with lipoic acid were more biosafe. In the oral field, studies by Niska *et al.* [158] showed that AgNPs with capping agents had less cytotoxicity and a wider range of antimicrobial activity against gingival fibroblasts.

6 Conclusion and perspectives

AgNPs have shown extraordinary functions in biomedicine due to their unique physicochemical properties and enhanced anti-bacterial activities. For example, AgNPs may provide new strategies for the treatment and prevention of dental infections, diabetes, and neurodegeneration. In addition, AgNPs have gradually been applied in other biochemistry, including environmental protection, monitoring, purification, medical treatment, and agricultural wastewater treatment through nanofiltration technology. In the coming decades, the application of AgNPs in nanomedicine, wound healing products, disinfectants, antibacterial nanocomposites, and antibacterial coatings is expected to have broad market prospects. However, although AgNPs have been maturely applied in various fields, the properties of AgNPs still need to be improved, and their toxicity remains unsolved.

In combination with this review, in order to enhance the capabilities and reduce the toxicity of AgNPs, the following strategies can be considered:

- 1) Changing the synthesis method: Using Green synthesis using biosynthesis: Using biosynthesis methods (such as using microbial or plant extracts) to produce AgNPs can result in safer and more environmentally friendly AgNPs.

These biosynthesized AgNPs generally have better biocompatibility and lower toxicity.

- 2) Changing traits to control the size and shape of AgNPs: The study found that the size and shape of AgNPs have a significant impact on their toxicity. In general, the smaller the size and the more irregular the shape of AgNPs, the more toxic it is. Therefore, by optimizing the synthesis conditions and controlling the size and shape of AgNPs, its toxicity can be effectively reduced.
- 3) Surface modification: Surface modification of AgNPs can change their activity and reduce toxicity.
- 4) Using drug-carrying AgNPs: AgNPs can be used as drug carriers to enhance their antibacterial or anticancer activity by combining with other drugs.
- 5) Combining with other methods: AgNPs can be combined with PDT, PTT, and radiology to promote the development of treatment and diagnostics.
- 6) In addition, to ensure the safe application of AgNPs, it is also necessary to conduct low-dose use of AgNPs and conduct more in-depth biocompatibility and toxicity studies, so as to reduce the toxic effects on non-target sites.

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