OCTAHEDRON
Drug Research
Vol. 7
Review Article

Silver nanoparticles in nanomedicine: Synthesis, biomedical applications and safety considerations

Hend Diaa Abdullah*[1], Abd El hakim Ramadan[1] , Rawda Mofed Gamal[2], Esraa Mohamed Helmy[1], Asmaa Mohamed Mokhtar[1], Omnia Emad Khedr Abozeid[1], Aya Elgaraihy Tawfeek[1], Basma Elsayed Hegazy[1], Basant Khaled Elzoghby[1], Radwa Yasser Elsherbeny[1], Rana Elsebaey Ahmed[1], Sahar Tawakul Mohamed[1], Sohair Adel Abdellateef[1], Faten Mohsen Elsaysd[1], Marwa Akram Naser[1], Menna Mansour Elsharkawy[1], Nada Saad Ahmed Hashem[1], Nada Saad Sadat Glala[1], Noran Ayman Mohamed[1], Norhan Elsayed Younis[1], Norhan Abdelkader Metwaly[1], Haidy Hany Mohamed[1], Hend Ayman Mohamed[1], Islam Kamal[1]

[1]Department of pharmaceutics, Faculty of pharmacy, Port Said University, Port Said 42515, Egypt.
[2]Department of clinical pharmacy and pharmacy practice, Faculty of pharmacy, Port Said University, Port Said 42515, Egypt.
*Correspondence: email: henddiaa169@hotmail.com Tel: 01281444978

ARTICLE INFO

Article history :
Received 29 April 2025
Received in revised form
23 May 2025
Accepted 23 May 2025
Available online 1 June 2025

Keywords: Green Synthesis; Silver Nanoparticles; Antimicrobial; Antibacterial; Antifungal.

ABSTRACT

Silver nanoparticles have emerged as a crucial component in nanomedicine due to their unique physicochemical properties and broad therapeutic potential. This review focuses on the chemical synthesis and the green synthesis of silver nanoparticles using eco-friendly biological methods, such as plant extracts, microbial processes, and biopolymer-assisted and enzyme-assisted synthesis. The green synthesis approaches offer sustainable alternatives to traditional chemical methods while ensuring biocompatibility and minimizing toxicity. The review highlights the diverse biomedical applications of silver nanoparticles, particularly their antibacterial, antibiofilm, anticancer, antifungal, and antiviral properties. Furthermore, silver nanoparticles demonstrate potential in the management of diabetes, osteomyelitis, and vector control (malaria). Despite these advantages, concerns regarding the potential toxicity and long-term accumulation in the body. Studies indicate possible neurotoxic effects, cytotoxicity, and off-target toxicity. The review highlights the necessity for refined synthesis techniques, specific applications, and comprehensive clinical research to guarantee the safe and effective use of it in the medical and industrial sectors

1. Introduction

Nanotechnology is a rising discipline of research with multiple applications in science and technology, particularly in the improvement of various nanomaterials and nanoparticles. Nanoparticles (NPs) are small in length, from one to hundred nanometers, and have gained attention because of their utilization in diverse fields such as biomedicine, agriculture, pharmaceutics, textile, meals technology, catalysis, sensors, mechanics, electronics, and optics (1). Silver nanoparticles (AgNPs) are used in medicine, food, household, health care, and industrial purposes due to their unique physical and chemical properties, including optical, thermal, high electrical conductivity, and biological properties. For example, they are widely used in medical device coatings, optical sensors, cosmetics, diagnostics, orthopedics, drug delivery,

Doi: 10.21608/odr.2025.379922.1049

antibacterial, antiviral, and anticancer agents. Recently, AgNPs have been frequently used in many textiles, keyboards, wound dressings, and biomedical devices (2).

Additionally, biosynthesized AgNPs were used for degrading poisonous chemical substances and in several diseases such as cancer, diabetes, malaria, osteomyelitis, and neurodegenerative disorders (3-5). In cancer therapy, AgNPs offer advantages in drug targeting, thus overcoming the side effects of conventional anticancer therapy such as surgery, radiation, and chemotherapy. Not only can they be used in targeted drug delivery, but they are also used in tumor imaging as they can travel to the deepest areas of cancer cells (6). Additionally, nanotechnology improves biomolecular structures, which could discover cells, bacteria, fungi, and viruses, even severe illnesses that cause cancer and immunodeficiency as HIV and hepatitis viruses (7). Silver-containing formulations are also efficiently applied in the field of dentistry; they stop dental caries and have been utilized in the US and Japan for over 80 years (8, 9). Recently, nanostructured silver-based formulations were tested to be powerful antimicrobial additives in prosthetic materials (10), adhesives (11, 12), implants (13, 14); stop tooth decay (15), prevent biofilm formation (16), and support bone growth (osteogenic induction) (8, 9). AgNPs show antidiabetic activity and can be used in the treatment of diabetes mellitus by activating the hepatic glucose transporter-2 (GLUT-2) gene, raising serum insulin levels, and increasing liver glucokinase (GK) levels (17).

Moreover, Silver nanoparticles can be utilized in tissue engineering and regenerative medicine (TERM) to overcome the limitations of tissue and organ transplantation, including the shortage of donors, the risk of organ rejection, and the need for lifelong immunosuppressants. TERM combines biological, fabric, and engineering sciences to manufacture synthetic systems that resemble the natural organ (18). Using nanoparticles adjusts these systems by controlling the properties of scaffolds (19). Despite the advantages and applications of using NPs in the medical field, it is observed to cause some problems. For example, AgNPs in psychiatry may lead to neurotoxic effects, such as short-term memory loss and reduced learning ability (20). Moreover, when women are exposed to nanoparticles, it can impair fertility and fetal neurobehavioral development (21, 22) by the buildup of reactive oxygen species (ROS) in the hippocampus (23).

This review aims to provide an overview of AgNP preparation methods, including green and chemical approaches, applications in biomedical fields, and safety concerns. It also addresses some challenges regarding AgNPs and what are the prospects of enhancing their effectiveness and safety.

2. Synthesis of Silver Nanoparticles

2.1. Green Synthesis of Silver Nanoparticles

The main aim of green synthesis methodologies for silver nanoparticles is to produce sustainable and biocompatible nanomaterial, which will offer an eco-friendly alternative to conventional chemical synthesis while maintaining precise control over nanoparticle properties (1). We outlined the principal approaches with quantitative insights, advantages, disadvantages, and comparative analysis, as shown in **Table 1**.

2.1.1. Plant-mediated synthesis

The biological manufacture of silver and silver oxide nanoparticles using plant resources has gained significant prevalence in nanotechnology due to the exceptional features of these nanoparticles. Plants and their components encompass a variety of chemicals, including carbohydrates, lipids, pigments, alcohols, alkaloids, vitamins, polysaccharides, proteins, and other secondary metabolites. In the domain of nanoparticle synthesis from metal salts, these chemicals function as reducing agents, capping agents, or stabilizing agents, yielding low to no deleterious by-products. The exact mechanisms and molecules involved in plant-mediated synthesis remain unclear; nonetheless, it is hypothesized that electrostatic interactions between silver ions and compounds in plant extracts trigger bioreduction. Proteins in plant samples are responsible for reducing bulk silver. This reduction is facilitated by plant extracts, which establish interactions between the nanoparticle surface and biomolecules, thereby improving stability. Capping agents are essential in inhibiting aggregation and coagulation by adhering to the surface of silver nanoparticles. Although stabilizing agents resemble capping agents, their main purpose is to inhibit the oxidation of AgNPs. The high reactivity of silver can lead to oxidation, resulting in the development of unwanted silver oxides that compromise the stability and characteristics of nanoparticles. Reducing substances are essential in the transformation of silver ions (Ag^+) into silver nanoparticles (Ag_0) by donating electrons to Ag^+. In green synthesis, plant extracts act as abundant sources of these agents, actively engaging in the processes of AgNP reduction, capping, and stabilization (27).

2.1.2. Microbial-mediated synthesis

Microorganisms such as bacteria, fungi, and algae use enzymatic pathways to reduce silver ions and synthesize

Doi: 10.21608/odr.2025.379922.1049

AgNPs. Although the incubation period may be longer and require strict sterility compared to plant-based methods, this method offers high specificity and control over particle formation. The use of different microorganisms can affect the properties of nanoparticles. For example, in bacterial synthesis, species like *Pseudomonas aeruginosa* and *Bacillus subtilis* produce nanoparticles in the 10–25 nm range. In fungal synthesis, *Aspergillus niger* and *Fusarium oxysporum* generate extracellular AgNPs ranging from 8 to 35 nm. In algal synthesis, algae such as *Spirulina platensis* typically yield particles in the 10–20 nm range (25).

2.1.3. Biopolymer-assisted synthesis

Utilizing natural polymers (e.g., chitosan, alginate, cellulose, starch) as both reducing and stabilizing agents not only facilitates nanoparticle formation but also enhances biocompatibility and stability. Particle sizes can be finely controlled within the 5–20 nm range, depending on polymer concentration. Nanoformulations are stabilized through electrostatic repulsion when their zeta potentials exceed ±30 mV (28). They can be used in biomedical scaffolds for advanced therapeutic applications. However, polymer concentration must be optimized to ensure uniform nanoparticle properties; besides, some biopolymers may introduce impurities that affect nanoparticle stability (26).

2.1.4. Enzyme-assisted synthesis

Enzymatic methods employ catalysts such as nitrate reductase, laccase, and peroxidase to reduce silver ions under mild physiologically compatible conditions. It operates under ambient temperature and pH, eliminating the need for harsh chemicals and enhancing biocompatibility. However, this method requires enzyme purification, stability optimization, and reaction conditions adjustment, which all affect enzyme activity (26).

2.2. Chemical synthesis

2.2.1. Chemical reduction

The predominant method for synthesizing silver nanoparticles is chemical reduction with organic and inorganic reducing agents. Various reducing agents, including sodium citrate, ascorbate, sodium borohydride (NaBH4), elemental hydrogen, the polyol process, Tollen's reagent, N, N-dimethylformamide (DMF), and poly(ethylene glycol)-block copolymers, are employed for the reduction of silver ions (Ag^+) in both aqueous and non-aqueous solutions. These reducing agents convert Ag^+ into metallic silver (Ag_0), subsequently resulting in agglomeration into oligomeric clusters. These clusters ultimately result in the production of metallic colloidal silver particles. Utilizing protective agents is crucial for stabilizing dispersive nanoparticles during metal nanoparticle synthesis and for safeguarding the nanoparticles from absorption or binding to surfaces, hence preventing agglomeration. The inclusion of surfactants with functions such as thiols, amines, acids, and alcohols facilitates interactions with particle surfaces, hence stabilizing particle development and safeguarding against sedimentation, agglomeration, or degradation of surface characteristics.

2.2.2. Microemulsion method

It can generate uniform and size-controllable silver nanoparticles. The creation of nanoparticles in two-phase aqueous organic systems relies on the initial spatial segregation of reactants (metal precursor and reducing agent) within two immiscible phases. The interface between the two liquids and the degree of inter-phase transport, mediated by a quaternary alkyl-ammonium salt, influence the rate of interactions between metal precursors and reducing agents. A coating of stabilizer molecules present in the non-polar aqueous medium stabilizes metal clusters at the interface. They are then transported to the organic medium via the inter-phase transporter. A significant drawback is the utilization of highly harmful chemical solvents (29).

3. Biomedical applications of silver nanoparticles

3.1. Antibacterial and antibiofilm applications

Silver nanoparticles have exhibited efficacy against methicillin-resistant Staphylococcus aureus (MRSA) and methicillin-resistant Staphylococcus epidermidis (MRSE). Thirty-six numerous research have proven the antibacterial efficacy of silver nanoparticles against microorganisms (30). The precise method by which silver nanoparticles exert their antibacterial activity remains unclear and is a subject of ongoing dispute. There are, however, several theories on the mechanism by which silver nanoparticles exert a microbicidal effect on bacteria. Silver nanoparticles can adhere to the bacterial cell wall and then infiltrate it, resulting in structural alterations to the cell membrane, such as increased permeability and cell death. Pits occur on the cell surface, accompanied by the deposition of nanoparticles on the cell surface. The generation of free radicals by silver nanoparticles may be regarded as an additional mechanism of cellular death. Electron spin resonance spectroscopy studies indicate that silver nanoparticles generate free radicals upon contact with bacteria, which can compromise the cell membrane's integrity, rendering it porous and potentially resulting in

Doi: 10.21608/odr.2025.379922.1049

cell death, as illustrated in **(Figure 1)** (31)**.** Biofilms consist of clusters of bacteria encapsulated within a self-produced extracellular matrix. Bacterial tolerance and resistance to antibiotics are governed by specific mechanisms impacted by factors such as the composition and structure of the biofilm, the stage of biofilm development, and the environment of growth. The biofilm's structure obstructs antibiotic penetration and may impede the formation of deadly bacterial levels throughout the biofilm (32). The antibiofilm efficacy of AgNPs has been evidenced in several research. A groundbreaking investigation was conducted to examine the interactions of AgNPs with Pseudomonas putida biofilms. The findings indicated that biofilms are influenced by treatment with AgNPs. The nanoparticles examined in the study were relatively large, exceeding 60 nm in size. Kalishwaralal *et al*. presented one of the initial findings on the antibacterial efficacy of AgNPs against P. aeruginosa and S. epidermidis, as well as their influence on biofilm development. The study examined two significant bacteria responsible for keratitis, revealing that a 2-hour treatment with AgNPs at a concentration of 100 μM resulted in a 95% and 98% reduction in biofilm formation. Consequently, the scientists determined that AgNPs can promote the detachment of P. aeruginosa and S. epidermidis swiftly and effectively, thereby presenting practical prospects for alternative therapy (33).

3.2. Antiviral applications

Viral infections provide considerable global health issues, particularly due to the advent of resistant viral strains and the detrimental side effects linked to extended usage, which hinder the implementation of effective antiviral medicines. This necessitates the development of safe and effective alternatives to traditional antiviral medications. Nanoscale materials have emerged as innovative antiviral drugs due to their distinctive chemical and physical features. Silver nanoparticles have primarily been investigated for their antibacterial efficacy against bacteria. However, they have also demonstrated activity against many viruses, including human immunodeficiency virus, hepatitis B virus, herpes simplex virus, respiratory syncytial virus, and monkeypox virus. AgNPs inhibit viral replication and fungal proliferation by binding to viral surface proteins to prevent host cell entry. This leads to antiviral activity that is applied in coatings for personal protective equipment (PPE) and air filters (3). Elechiguerra *et al*. were the pioneers in elucidating the antiviral properties of metal nanoparticles, namely discovering that silver nanoparticles exhibit size-dependent interactions with HIV-1. Their investigations examined the potential influence of nanoparticle interactions with a capping agent molecule on the physicochemical properties of nanoparticles. Consequently, they evaluated silver nanoparticles with three distinct surface chemistries: foamy carbon, poly(N-vinyl-2-pyrrolidone) (PVP), and bovine serum albumin (BSA). Foamy carbon-coated silver nanoparticles were incorporated into a foamy carbon matrix to prevent coalescence during synthesis. PVP-coated nanoparticles were produced with glycerin as the reducing agent and solvent. This process involves dissolving a metal precursor in a liquid polyol with a capping agent, such as PVP. The synthesis of BSA-conjugate silver nanoparticles was conducted in an aqueous solution. The interactions between silver nanoparticles and HIV-1 were investigated using high angle annular dark field (HAADF) scanning transmission electron microscopy technique. Sufficient evidence was obtained to ascertain that the interaction between HIV particles and silver nanoparticles is predominantly attributable to the size of the silver nanoparticles since only those within the 1–10 nm range were capable of binding to the virus. Specifically, nanoparticles were not randomly affixed to the virus; rather, all three nanoparticle species formed consistent spatial interactions with the viral envelope. The most likely interaction sites were identified as the sulfur-containing residues of the gp120 glycoprotein knobs, which, because of their limited quantity, may also account for the failure of bigger nanoparticles to attach to the virus. The ability of silver nanoparticles to impede the infectivity of a laboratory-adapted HIV-1 strain at non-cytotoxic concentrations was assessed by in vitro experiments, revealing a dose-dependent suppression of viral infectivity (34).

3.3. Antifungal applications

The incidence of fungal infections has risen in recent years, and silver nanoparticles have emerged as possible antifungal medicines. Fungal infections predominantly occur in immunocompromised people resulting from cancer chemotherapy or viral infections. They are frequently incited by opportunistic strains that induce infections of the skin, nails, oral cavity, and vulva. Numerous fungal illnesses are attributable to different species of Candida. Silver nanoparticles demonstrate remarkable antifungal efficacy against C. albicans by compromising cell membranes and inhibiting the typical process of cell division. The antifungal efficacy of silver nanoparticles arises from the development of insoluble complexes with sulfhydryl groups in the fungal cell wall and the disruption of membrane-bound enzymes and lipids, leading to cell lysis. Damage to the cell wall and membrane results in heightened membrane permeability and the efflux of potassium ions (K^+). Furthermore, silver nanoparticles

Doi: 10.21608/odr.2025.379922.1049

impede cellular mechanisms associated with yeast budding, perhaps by compromising membrane integrity. Transmission electron microscopy verifies the interaction between silver nanoparticles and membrane architecture. Upon exposure to nanoparticles, C. albicans cells exhibit notable surface alterations, manifested as pits in their cell walls and pores in their cell membranes. Biogenic silver nanoparticles produced from an aqueous extract of Gymnosporia royleana Wall leaves exhibited low to moderate antifungal efficacy (4–8 mm ± 0.2) against C. albicans and Candida tropicalis. Synthesis of silver nanoparticles with an aqueous extract of Gymnema sylvestre R. Br. callus had notable antifungal efficacy against C. albicans, C. nonalbicans, and C. tropicalis, with inhibition zones measuring 15.4, 14.2, and 15.7 mm, respectively. The silver nanoparticles exhibited biocompatibility, were non-toxic to mammalian cells, and their antifungal efficacy was concentration-dependent (35).

3.4. Anticancer applications

AgNPs demonstrate significant anticancer properties by inducing apoptosis and enhancing drug delivery. Mechanisms of AgNPs in cancer management (shown in **Figure 2**): ROS generation that leads to mitochondrial dysfunction and apoptotic cell death; DNA damage by interaction with DNA resulting in cell cycle arrest; synergistic drug delivery by AgNPs carriers will improve the targeted delivery of chemotherapeutics, with some studies reporting up to a 40% improvement in tumor reduction; therefore, reducing the needed doses, and decreasing side effects (36). The cytotoxicity of AgNPs is contingent upon their dimensions and morphology. For instance, it was reported that AgNPs with diameters ranging from 100 to 160 nm, lengths between 1.5 and 25 μM, and spherical forms of 30 nm exhibited possible lethal effects on human lung epithelial A549 cells. The likely explanation for this is that, within this size and shape range, the AgNPs can directly interact with cell surfaces and induce cytotoxicity. Nanoparticles are benign at lower doses but can be hazardous at elevated doses. Typically, cells exposed to varying concentrations of nanoparticles exhibit a dose-dependent enhancement in cell inhibition. AgNPs in various formulations demonstrate varying dosage responses that may influence cytotoxicity or enhance anticancer efficacy (37).

3.4.1. Silver Nanoparticles in Skin Cancer Management

Skin cancer includes a spectrum of malignancies, primarily melanoma and non-melanoma skin cancers (NMSC), such as basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) (38). Melanoma originates from melanocytes, with mutations in oncogenes such as B-Rapidly Accelerated Fibrosarcoma (BRAF) and mitogen-activated protein kinase (MAPK) pathway- both are important in regulating cell division and growth (39-41). BCC and SCC develop from epidermal keratinocytes; in BCC, mutations in the Hedgehog signaling pathway involving PTCH1- the brake- and SMO- the accelerator- lead to dysregulation in cell growth (42, 43). Ultraviolet (UV) radiation-induced DNA damage remains the primary modifiable risk factor for skin cancer (38, 44).

3.4.2. Nanotechnology-Enhanced Therapeutic Strategies in Cancer Management

Innovative nanotechnology has enabled the design of drug-delivery systems that improve anticancer efficacy. AgNPs can be conjugated with ligands (e.g., EGFR antibodies) to achieve selective binding to tumor cells, increasing local drug concentrations while reducing systemic exposure (45, 46). Moreover, Incorporation into liposomes, polymeric nanoparticles, or solid lipid carriers enhances tissue penetration and improves pharmacokinetics. These platforms support theranostic applications also by combining therapy with real-time imaging for treatment monitoring (47, 48).

3.5. In diabetes mellitus management

Diabetes mellitus, a worldwide health issue characterized by dysfunctional insulin activity and elevated blood glucose levels, has prompted novel treatment research, including the application of nanotechnology. Silver nanoparticles have emerged as viable contenders in this endeavor. Recent investigations demonstrate their capacity to influence critical pathways in diabetes etiology, improving insulin sensitivity, diminishing oxidative stress, and bolstering pancreatic beta-cell activity. Their antibacterial qualities are especially advantageous for diabetic people susceptible to infections. Furthermore, employing silver nanoparticle-based carriers for antidiabetic medications enhances drug bioavailability and diminishes adverse effects, potentially augmenting the efficiency of conventional treatments. Nonetheless, it is imperative to address safety and toxicity concerns. Current studies aim to optimize the size, shape, and surface changes of nanoparticles to improve biocompatibility and reduce negative effects (49).

3.5.1. Benefits of AgNPs in diabetic animal models

Diabetic models treated with AgNPs show significant reductions in fasting blood sugar (FBS) ($P < 0.001$) compared to controls (50). Although plasma insulin increases are variable, a positive trend in insulin is observed (50, 51). Improvements in lipid profile, such as increased high-density lipoprotein (HDL) and reduced cholesterol/triglyceride levels, have been reported (50-53).

Doi: 10.21608/odr.2025.379922.1049

Table 2 provides a summary of animal studies investigating AgNPs in diabetes mellitus.

Method	Size (nm)	Reaction time	Advantage	Disadvantages	Ref.
Plant-mediated	5-30	30-60 min	Eco-friendly and cost-effective.	Variability in composition and scalability issues.	(24)
Microbial-mediated	8-35	Hours-days	High control over characteristics.	Long incubation time and aseptic conditions requirement.	(25)
Biopolymer-assisted	5-20	Variable	High biocompatibility and stable colloids.	Expensive and slow reaction rates.	(26)
Enzyme-assisted	5-15	1-4 hours	Mild conditions, biocompatible.	Enzyme cost, slow reaction, and sensitivity issues.	(26)
Green chemical	10-25	20-40 min	Simple, fast, and scalable.	Stability issues and limited control over size.	(1)

Table 2. Summary of animal studies investigating AgNPs in diabetes mellitus.

Animal model & Gender	Dose (μg/kg)	Duration & Route	Main Outcomes	Ref.
Wistar albino rats, male	1-100μg/kg (50 μg/kg)	21-30 days Oral/Intraperitoneal	Significant FBS reduction ($P < 0.001$); the trend toward increased insulin; improved lipid profile.	(50)
Albino mice, Male	11-80μg/kg	14-30 days Orally	Marked FBS reduction; minimal pancreatic histopathological alterations.	(51)
Wistar albino rats, male	100μg/kg	28 days Intraperitoneal	Significant FBS decrease; modest plasma insulin elevation.	(52)
Wistar albino rats, male	150μg/kg	30 days Orally	Improved lipid profile; reduction in liver enzymes.	(53)
Wistar albino rats, male	86μg/kg	28 days Oral/Intraperitoneal	Consistent hypoglycemic effects; histological evidence of pancreatic protection.	(54)

3.5.2. Biodistribution, pharmacokinetics, and safety in diabetes management

Critical factors for AgNPs efficacy in diabetes mellitus include:

a. Particle characteristics: Size and surface chemistry determine absorption and target the liver and pancreas (55-57).
b. Toxicity concerns: Short-term studies show minimal histopathological changes, but the risk of long-term accumulation in non-target tissues (liver, kidneys, brain) needs careful evaluation (58, 59).
c. Optimization needs: Future work must refine dosing and develop biocompatible carriers to maximize efficacy and minimize toxicity.

3.6. In the osteomyelitis field

Osteomyelitis, an infectious infection affecting the bone or bone marrow, represents a significant and formidable complication in orthopedic surgery. Several factors that can negatively impact osteomyelitis include suboptimal surgical conditions commonly encountered in trauma cases, patient behaviors such as smoking and substance abuse, and health issues such as malnutrition and other immunodeficiency disorders (60). Diagnosis is challenging due to heterogeneous clinical presentations (localized pain,

Doi: 10.21608/odr.2025.379922.1049

fever, elevated C - C-reactive protein (CRP) /erythrocyte sedimentation rate (ESR)). Conventional imaging (X-rays) often fails to detect early changes; magnetic resonance imaging (MRI) and bone biopsy are crucial for definitive diagnosis. Standard treatments include prolonged intravenous antibiotics (4–6 weeks) and surgical debridement. Limitations include poor drug penetration and the persistence of intracellular pathogens (61). Research conducted over the years has demonstrated that silver, both directly and indirectly through various technologies, prevents bacterial adherence and highlights its antibacterial characteristics. Our group has already conducted studies demonstrating the effects of silver in various forms by directly applying it to surfaces as a robust antibacterial coating. A study utilized electrolytically deposited, firmly adhering silver nanoparticles on stainless-steel implants for in situ osteomyelitis therapy. Samples underwent heat treatment to improve the adherence of silver on 316 L stainless steel. Ex vivo tests were conducted to assess silver-release patterns from 316 L stainless steel screws implanted in equine cadaveric bones. No alterations in the release patterns of silver ions were seen in vitro between the implanted screws and the control group. *In Vivo* investigations were conducted utilizing an osteomyelitis rabbit model with 3 mm diameter silver-coated 316 L stainless steel pins at two distinct silver dosages: high and low. The infection control efficacy of pins for osteomyelitis treatment in a rabbit model was assessed using bacteriological, radiographic, histological, and scanning electron microscopic analyses. High-dose silver-coated pins have shown potential efficacy in treating infections in an animal model of osteomyelitis without causing damage to major organs (60).

3.7. In vector control (Malaria)

Silver nanoparticles (AgNPs) were evaluated as larvicides, pesticides, and adulticides against the malaria vector Anopheles Stephensi and the filariasis vector Culex quinquefasciatus. The data were acquired utilizing a UV-visible spectrophotometer, and the images were captured with a transmission electron microscope (TEM). The efficacy tests were subsequently conducted at various concentrations over an extended duration using probit analysis. The produced AgNPs exhibited a spherical morphology with varying dimensions, measuring 10.47 nm for the leaf and 19.22 nm for the bark. The larvae, pupae, and adults of the filariasis vector C. quinquefasciatus exhibited greater susceptibility to our AgNPs compared to the malaria vector (62).

4. Safety, toxicity, and nanomechanical interactions

4.1. Toxicity and safety considerations

The rising usage of nano-silver products is correlating with an increased risk of detrimental effects on human health and the environment. AgNPs exhibit distinct physiochemical characteristics, including size, surface area, solubility, aggregation propensity, chemical composition, and surface chemistry, compared to bulk silver. These physiochemical properties confer a larger surface area to nano-silver, resulting in heightened toxicity attributable to the activity of free silver released by the nanoparticles.

Generally, AgNPs exhibit lower toxicity than silver ions; nonetheless, some studies indicate that exposure to AgNPs might result in cytotoxicity, immunotoxicity, and genotoxicity in vertebrates, both in vitro and in vivo (Lingling Huo *et al*. 2001). Upon inhalation of AgNPs, they migrate to the olfactory bulb, where they localize in mitochondria, thereafter, translocating to the circulatory system, liver, kidneys, and heart (Oberdörster, G. *et al*.). AgNPs induce hematological disorders and colorectal carcinoma when detected in the blood and colon of patients, respectively Gatti 2004 *et al*. Gatti *et al*.). The antibacterial properties of AgNPs render them lethal to bacteria and exhibit toxic effects on human cells; similarly, concentrations of AgNPs that are lethal to bacteria are also detrimental to both keratinocytes and fibroblasts. Inhalation of AgNPs can lead to diseases such as asthma, bronchitis, emphysema, lung cancer, and neurological disorders. The gastrointestinal tract is associated with Crohn's disease and colon cancer. Silver nanoparticles that infiltrate the circulatory system are linked to the development of arteriosclerosis, thrombosis, arrhythmias, and cardiovascular diseases. They also contribute to autoimmune disorders such as systemic lupus erythematosus, scleroderma, and rheumatoid arthritis (Buzea *et al*., 2007). Upon oral administration, AgNPs were detected in significant organs such as the kidneys, liver, spleen, lungs, brain, and gastrointestinal (GI) tract. Certain nanoparticles traversed the gastrointestinal tract and were swiftly eliminated in feces and urine, suggesting their capacity for absorption beyond the gastrointestinal barrier and entry into the systemic circulation (Hagens *et al*., 2007). AgNPs must be considered a specific source of risk due to their possible toxicity to humans—exposure to AgNPs results in the development of bluish-colored skin. Numerous studies have extensively examined toxicities, including oxidative damage in biological systems (Danielle McShan *et al*. 2014) (63).

4.2. Nanomechanical interactions

Doi: 10.21608/odr.2025.379922.1049

AgNPs interact at the nano-bio interface, affecting cellular mechanics. AgNPs can induce mechanical stress on cell membranes, affecting fluidity and permeability. In addition, the absorption of biomolecules on nanoparticle surfaces alters their interaction with cells. Furthermore, quantitative studies suggest that AgNP-induced mechanical forces can reach the nano-Newton range, contributing to antimicrobial efficacy (25).

4.3. Preclinical Efficacy and Limitations

Preclinical studies have shown that AgNPs can reduce tumor burden effectively. However, challenges remain a burden:

a. Formulation complexity: Uniform particle size and stable surface modification are critical for reproducibility and efficacy.
b. Long-term safety: Localized application minimizes systemic toxicity, yet repeated exposure may have cumulative effects that require further study (64, 65).
c. Translational gap: More robust pharmacokinetic and toxicological data are needed to move from preclinical promise to clinical application.

5. Future perspectives and challenges

5.1. Convergence of mechanistic pathways

AgNPs exhibit therapeutic effects in both skin cancer and diabetes through shared pathways. In oncology, ROS-mediated apoptosis is central to tumor regression. In diabetic models, controlled oxidative modulation protects β-cells and improves insulin sensitivity. This overlap highlights the potential for a unified nanoparticle-based approach across diverse diseases.

5.2. Challenges in formulation and delivery

The clinical performance of AgNPs depends critically on the following:

a. Optimization: achieving uniform particle size, effective surface modification, and stable ligand conjugation are necessary for reproducible results.
b. Delivery Methods: topical formulations are preferred for skin cancer to restrict systemic exposure, whereas in diabetes, enhancing gastrointestinal absorption and targeting metabolic organs is key.
c. Scale-Up and Standardization: addressing formulation complexity and ensuring scalable production remain essential hurdles for clinical translation.

5.3. Safety, Toxicity, and Long-Term Implications

While preclinical studies indicate favorable safety profiles, there are certain concerns:

a. Repeated Exposure: Localized AgNP applications in skin cancer may have cumulative effects that are not yet fully understood.
b. Biodistribution Concerns: In diabetes, chronic administration raises the risk of nanoparticle accumulation in non-target tissues such as the liver, kidneys, and brain.
c. Risk Mitigation: Future strategies should include biocompatible surface modifications (e.g., polymer coatings) to minimize off-target toxicity.

Future studies require linking the physiological properties of silver nanoparticles to their corresponding effect on the physiological environment upon application. Because silver nanomaterials are highly active compared to bulk silver, careful consideration of toxicity must be taken before their widespread use in wound care products (66, 67).

Conclusion

The unique physicochemical properties of silver nanoparticles have made them an important part of nanomedicine. This review focuses on both chemical and green synthesis of silver nanoparticles using eco-friendly biological methods, such as plant extracts, microbial processes, and biopolymer-assisted and enzyme-assisted synthesis. The green synthesis approaches offer sustainable alternatives to traditional chemical methods while ensuring biocompatibility and minimizing toxicity. The review also talks about the different biomedical uses of silver nanoparticles, especially their antibacterial, antibiofilm, anticancer, antifungal, and antiviral properties. Silver nanoparticles show potential in the treatment of diabetes, osteomyelitis, and vector control (malaria). Despite promising in vitro results, further research is needed to assess biocompatibility, toxicity, and clinical effectiveness. Challenges include optimizing synthesis for minimal side effects, targeting specific pathogens and cancer cells, and evaluating environmental interactions. Combining AgNPs with nanotechnology offers innovative solutions for medicine, particularly in cancer therapy and infectious disease management.

Ethical consideration

All the participants in this study gave their informed permission.

Conflicts of Interest

No conflicts of interest are disclosed.

The authors reported no potential conflict of interest.

Doi: 10.21608/odr.2025.379922.1049

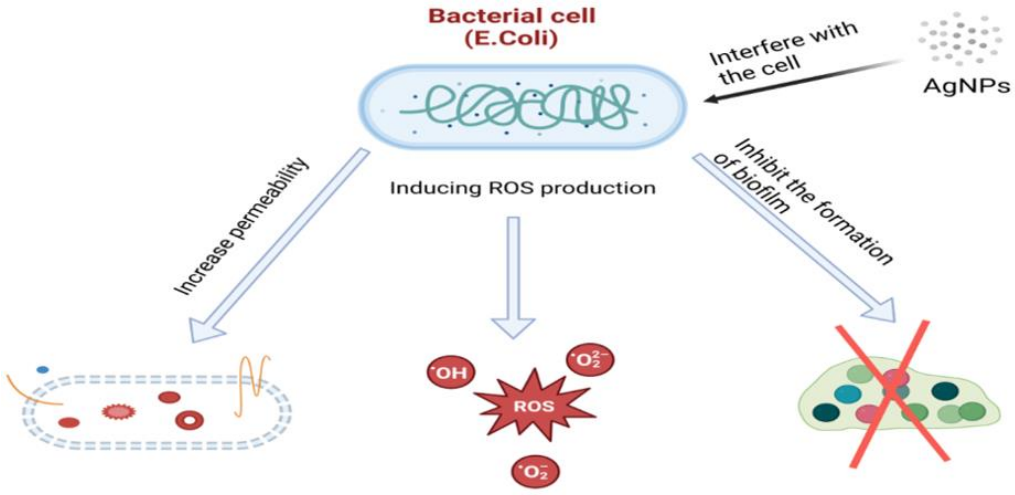

Figure 1. Antimicrobial Effects of Silver Nanoparticles (31)

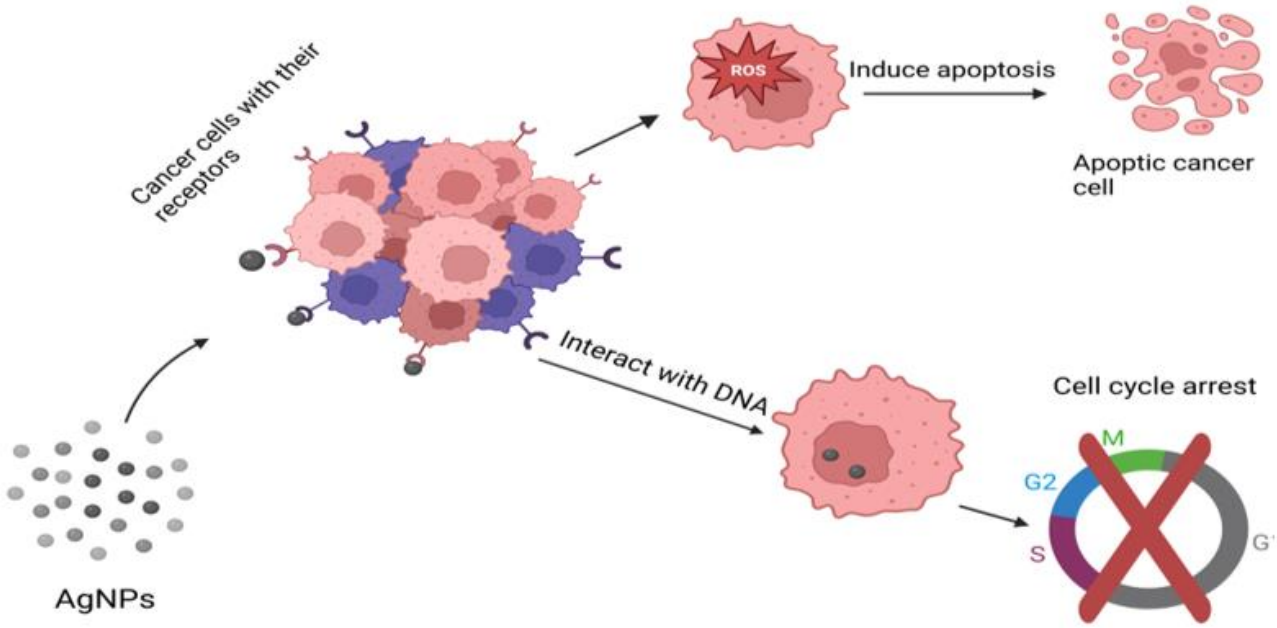

Figure 2. Mechanisms and effects of silver nanoparticles (AgNPs) in cancer therapy (36)

References

1. Huq MA, Ashrafudoulla M, Rahman MM, Balusamy SR, Akter S. Green synthesis and potential antibacterial applications of bioactive silver nanoparticles: A review. Polymers. 2022;14(4):742.
2. Zhang X-F, Liu Z-G, Shen W, Gurunathan S. Silver nanoparticles: synthesis, characterization, properties, applications, and therapeutic approaches. International journal of molecular sciences. 2016;17(9):1534.
3. Srikar SK, Giri DD, Pal DB, Mishra PK, Upadhyay SN. Green synthesis of silver nanoparticles: a review. Green and Sustainable Chemistry. 2016;6(01):34.
4. Spuch C, Saida O, Navarro C. Advances in the treatment of neurodegenerative disorders employing nanoparticles. Recent patents on drug delivery & formulation. 2012;6(1):2-18.

Doi: 10.21608/odr.2025.379922.1049

5. Abbasi-Oshaghi E, Mirzaei F, Mirzaei A. Effects of ZnO nanoparticles on intestinal function and structure in normal/high fat diet-fed rats and Caco-2 cells. Nanomedicine. 2018;13(21):2791-816.
6. Caracciolo G, Vali H, Moore A, Mahmoudi M. Challenges in molecular diagnostic research in cancer nanotechnology. Nano Today. 2019;27:6-10.
7. Garg D, Sarkar A, Chand P, Bansal P, Gola D, Sharma S, *et al*. Synthesis of silver nanoparticles utilizing various biological systems: mechanisms and applications—a review. Progress in Biomaterials. 2020;9:81-95.
8. Horst JA, Ellenikiotis H, Milgrom PL. UCSF protocol for caries arrest using silver diamine fluoride: rationale, indications, and consent. Journal of the California Dental Association. 2016;44(1):17-28.
9. Rosenblatt A, Stamford T, Niederman R. Silver diamine fluoride: a caries "silver-fluoride bullet". Journal of dental research. 2009;88(2):116-25.
10. Nuñez-Anita RE, Acosta-Torres LS, Vilar-Pineda J, Martínez-Espinosa JC, de la Fuente-Hernández J, Castaño VM. Toxicology of antimicrobial nanoparticles for prosthetic devices. International Journal of Nanomedicine. 2014:3999-4006.
11. Zhang K, Melo MAS, Cheng L, Weir MD, Bai Y, Xu HH. Effect of quaternary ammonium and silver nanoparticle-containing adhesives on dentin bond strength and dental plaque microcosm biofilms. Dental Materials. 2012;28(8):842-52.
12. Melo MAS, Cheng L, Zhang K, Weir MD, Rodrigues LK, Xu HH. Novel dental adhesives containing nanoparticles of silver and amorphous calcium phosphate. Dental Materials. 2013;29(2):199-210.
13. Godoy-Gallardo M, Rodríguez-Hernández AG, Delgado LM, Manero JM, Javier Gil F, Rodríguez D. Silver deposition on titanium surface by electrochemical anodizing process reduces bacterial adhesion of Streptococcus sanguinis and Lactobacillus salivarius. Clinical oral implants research. 2015;26(10):1170-9.
14. Liu Y, Zheng Z, Zara JN, Hsu C, Soofer DE, Lee KS, *et al*. The antimicrobial and osteoinductive properties of silver nanoparticle/poly (DL-lactic-co-glycolic acid)-coated stainless steel. Biomaterials. 2012;33(34):8745-56.
15. dos Santos Jr VE, Vasconcelos Filho A, Targino AGR, Flores MAP, Galembeck A, Caldas Jr AF, *et al*. A new "silver-bullet" to treat caries in children–nano silver fluoride: a randomized clinical trial. Journal of dentistry. 2014;42(8):945-51.
16. Jia Z, Xiu P, Li M, Xu X, Shi Y, Cheng Y, *et al*. Bioinspired anchoring AgNPs onto micro-nanoporous TiO2 orthopedic coatings: Trap-killing of bacteria, surface-regulated osteoblast functions and host responses. Biomaterials. 2016;75:203-22.
17. Alkaladi A, Abdelazim AM, Afifi M. Antidiabetic activity of zinc oxide and silver nanoparticles on streptozotocin-induced diabetic rats. International journal of molecular sciences. 2014;15(2):2015-23.
18. Fathi-Achachelouei M, Knopf-Marques H, Ribeiro da Silva CE, Barthès J, Bat E, Tezcaner A, *et al*. Use of nanoparticles in tissue engineering and regenerative medicine. Frontiers in bioengineering and biotechnology. 2019;7:113.
19. Chowdhury S, Chakraborty P, Kar K. Kamalika Mazumder and Arijit Mondal 2 1Department of Pharmaceutical Chemistry, BCDA College of Pharmacy and Technology, Kolkata, West Bengal, India, 2Department of Pharmaceutical Chemistry, MR College of Pharmaceutical Sciences and Research, Balisha, West Bengal, India. Nanostructured Materials for Tissue Engineering. 2023:55.
20. Hritcu L, Stefan M, Ursu L, Neagu A, Mihasan M, Tartau L, *et al*. Exposure to silver nanoparticles induces oxidative stress and memory deficits in laboratory rats. Open Life Sciences. 2011;6(4):497-509.
21. Sun J, Zhang Q, Wang Z, Yan B. Effects of nanotoxicity on female reproductivity and fetal development in animal models. International journal of molecular sciences. 2013;14(5):9319-37.
22. Yamashita K, Yoshioka Y, Higashisaka K, Mimura K, Morishita Y, Nozaki M, *et al*. Silica and titanium dioxide nanoparticles cause pregnancy complications in mice. Nature nanotechnology. 2011;6(5):321-8.
23. Liu Y, Guan W, Ren G, Yang Z. The possible mechanism of silver nanoparticle impact on hippocampal synaptic plasticity and spatial cognition in rats. Toxicology letters. 2012;209(3):227-31.
24. Vanlalveni C, Lallianrawna S, Biswas A, Selvaraj M, Changmai B, Rokhum SL. Green synthesis of silver nanoparticles using plant extracts and their antimicrobial activities: A review of recent literature. RSC advances. 2021;11(5):2804-37.
25. Shanmuganathan R, Karuppusamy I, Saravanan M, Muthukumar H, Ponnuchamy K, Ramkumar VS, *et al*. Synthesis of silver nanoparticles and their biomedical applications-a comprehensive review. Current pharmaceutical design. 2019;25(24):2650-60.
26. Naganthran A, Verasoundarapandian G, Khalid FE, Masarudin MJ, Zulkharnain A, Nawawi NM, *et al*. Synthesis, characterization, and biomedical application of silver nanoparticles. Materials. 2022;15(2):427.
27. Dhir R, Chauhan S, Subham P, Kumar S, Sharma P, Shidiki A, *et al*. Plant-mediated synthesis of silver nanoparticles: unlocking their pharmacological potential–a comprehensive review. Frontiers in Bioengineering and Biotechnology. 2024;11:1324805.
28. Abdullah HD, Kamal I, Sabry SA, Abd Elghany M, El hakim Ramadan A. Effective tailoring of cefepime into bilosomes: A promising nanoplatform for enhancing oral absorption, extending half-life, and evaluating biocompatibility, antibacterial, anti-biofilm, anti-breast cancer activity, ex-vivo, and in-vivo studies. International Journal of Pharmaceutics. 2025;668:125001.
29. Iravani S, Korbekandi H, Mirmohammadi SV, Zolfaghari B. Synthesis of silver nanoparticles: chemical, physical and biological methods. Research in pharmaceutical sciences. 2014;9(6):385-406.
30. Singh P, Kim YJ, Singh H, Wang C, Hwang KH, Farh ME-A, *et al*. Biosynthesis, characterization, and antimicrobial applications of silver nanoparticles. International journal of nanomedicine. 2015:2567-77.
31. Prabhu S, Poulose EK. Silver nanoparticles: mechanism of antimicrobial action, synthesis, medical applications, and toxicity effects. International nano letters. 2012;2:1-10.
32. Abdullah HD, Kamal I, Sabry SA, El hakim Ramadan A. Clarithromycin-tailored cubosome: A sustained release oral nano platform for evaluating antibacterial, anti-biofilm, anti-inflammatory, anti-liver cancer, biocompatibility, ex-vivo and in-vivo studies. International Journal of Pharmaceutics. 2024;667:124865.
33. Franci G, Falanga A, Galdiero S, Palomba L, Rai M, Morelli G, *et al*. Silver nanoparticles as potential antibacterial agents. Molecules. 2015;20(5):8856-74.
34. Galdiero S, Falanga A, Vitiello M, Cantisani M, Marra V, Galdiero M. Silver nanoparticles as potential antiviral agents. Molecules. 2011;16(10):8894-918.
35. Rozhin A, Batasheva S, Kruychkova M, Cherednichenko Y, Rozhina E, Fakhrullin R. Biogenic silver nanoparticles: Synthesis and application as antibacterial and antifungal agents. Micromachines. 2021;12(12):1480.

36. Hembram KC, Kumar R, Kandha L, Parhi PK, Kundu CN, Bindhani BK. Therapeutic perspective of plant-induced silver nanoparticles: application as an antimicrobial and anticancer agent. Artificial cells, nanomedicine, and biotechnology. 2018;46(sup3):38-51.
37. Ratan ZA, Haidere MF, Nurunnabi M, Shahriar SM, Ahammad AS, Shim YY, *et al*. Green chemistry synthesis of silver nanoparticles and their potential anticancer effects. Cancers. 2020;12(4):855.
38. Jou PC, Tomecki KJ. Sunscreens in the United States: current status and future outlook. Advances in experimental medicine and biology. 2014;810:464-84.
39. Slominski A, Tobin DJ, Shibahara S, Wortsman J. Melanin pigmentation in mammalian skin and its hormonal regulation. Physiological reviews. 2004.
40. Miller AJ, Mihm Jr MC. Melanoma. New England Journal of Medicine. 2006;355(1):51-65.
41. Gray-Schopfer V, Wellbrock C, Marais R. Melanoma biology and new targeted therapy. Nature. 2007;445(7130):851-7.
42. Celebi ARC, Kiratli H, Soylemezoglu F. Evaluation of the 'Hedgehog'signaling pathways in squamous and basal cell carcinomas of the eyelids and conjunctiva. Oncology Letters. 2016;12(1):467-72.
43. Nindl I, Gottschling M, Stockfleth E. Human papillomaviruses and non-melanoma skin cancer: basic virology and clinical manifestations. Disease markers. 2007;23(4):247-59.
44. Wehner MR, Shive ML, Chren M-M, Han J, Qureshi AA, Linos E. Indoor tanning and non-melanoma skin cancer: systematic review and meta-analysis. Bmj. 2012;345.
45. Huang X, El-Sayed IH, Qian W, El-Sayed MA. Cancer cell imaging and photothermal therapy in the near-infrared region by using gold nanorods. Journal of the American Chemical Society. 2006;128(6):2115-20.
46. Sokolov K, Follen M, Aaron J, Pavlova I, Malpica A, Lotan R, *et al*. Real-time vital optical imaging of precancer using anti-epidermal growth factor receptor antibodies conjugated to gold nanoparticles. Cancer research. 2003;63(9):1999-2004.
47. Gupta S, Bansal R, Gupta S, Jindal N, Jindal A. Nanocarriers and nanoparticles for skin care and dermatological treatments. Indian Dermatology online journal. 2013;4(4):267-72.
48. Knorr F, Lademann J, Patzelt A, Sterry W, Blume-Peytavi U, Vogt A. Follicular transport route–research progress and future perspectives. European Journal of Pharmaceutics and Biopharmaceutics. 2009;71(2):173-80.
49. Paul S, Sarkar I, Sarkar N, Bose A, Chakraborty M, Chakraborty A, *et al*. Silver nanoparticles in diabetes mellitus: therapeutic potential and mechanistic insights. Bulletin of the National Research Centre. 2024;48(1):33.
50. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030 Diabetes Care 27: 1047–1053. Find this article online. 2004.
51. Sharma R, Juyal D, Negi A. Epidemiology of diabetes mellitus and its recent awareness with the use of advance medication. The Pharma Innovation Journal. 2018;7(6):87-8.
52. Virgen-Ortiz A, Limón-Miranda S, Soto-Covarrubias M, Apolinar-Iribe A, Rodríguez-León E, Iñiguez-Palomares R. Biocompatible silver nanoparticles synthesized using rumex hymenosepalus extract decreases fasting glucose levels in diabetic rats. Dig J Nanomater Biostruct. 2015;10(3):927-33.
53. Patel D, Kumar R, Prasad S, Sairam K, Hemalatha S. Antidiabetic and in vitro antioxidant potential of Hybanthus enneaspermus (Linn) F. Muell in streptozotocin-induced diabetic rats. Asian Pacific journal of tropical biomedicine. 2011;1(4):316-22.
54. Modi P. Diabetes beyond insulin: review of new drugs for treatment of diabetes mellitus. Current drug discovery technologies. 2007;4(1):39-47.
55. Furchner J, Richmond C, Drake G. Comparative metabolism of radionuclides in mammals-IV. Retention of silver-110m in the mouse, rat, monkey, and dog. Health Physics. 1968;15(6):505-14.
56. Nefzger M, Kreuter J, Voges R, Liehl E, Czok R. Distribution and elimination of polymethyl methacrylate nanoparticles after peroral administration to rats. Journal of pharmaceutical sciences. 1984;73(9):1309-11.
57. Gaillet S, Rouanet J-M. Silver nanoparticles: their potential toxic effects after oral exposure and underlying mechanisms–a review. Food and Chemical Toxicology. 2015;77:58-63.
58. Loeschner K, Hadrup N, Qvortrup K, Larsen A, Gao X, Vogel U, *et al*. Distribution of silver in rats following 28 days of repeated oral exposure to silver nanoparticles or silver acetate. Particle and fiber toxicology. 2011;8:1-14.
59. Van der Zande M, Vandebriel RJ, Van Doren E, Kramer E, Herrera Rivera Z, Serrano-Rojero CS, *et al*. Distribution, elimination, and toxicity of silver nanoparticles and silver ions in rats after 28-day oral exposure. ACS Nano. 2012;6(8):7427-42.
60. Nandi SK, Shivaram A, Bose S, Bandyopadhyay A. Silver nanoparticle deposited implants to treat osteomyelitis. Journal of Biomedical Materials Research Part B: Applied Biomaterials. 2018;106(3):1073-83.
61. Taddio A, Ferrara G, Insalaco A, Pardeo M, Gregori M, Finetti M, *et al*. Dealing with chronic non-bacterial osteomyelitis: a practical approach. Pediatric Rheumatology. 2017;15:1-8.
62. Soni N, Prakash S. Silver nanoparticles: a possibility for malarial and filarial vector control technology. Parasitology research. 2014;113:4015-22.
63. Dos Santos CA, Seckler MM, Ingle AP, Gupta I, Galdiero S, Galdiero M, *et al*. Silver nanoparticles: therapeutical uses, toxicity, and safety issues. Journal of pharmaceutical sciences. 2014;103(7):1931-44.
64. Panáček A, Kvítek L, Smékalová M, Večeřová R, Kolář M, Röderová M, *et al*. Bacterial resistance to silver nanoparticles and how to overcome it. Nature nanotechnology. 2018;13(1):65-71.
65. Xu L, Wang Y-Y, Huang J, Chen C-Y, Wang Z-X, Xie H. Silver nanoparticles: Synthesis, medical applications, and biosafety. Theranostics. 2020;10(20):8996.
66. Torabian F, Akhavan Rezayat A, Ghasemi Nour M, Ghorbanzadeh A, Najafi S, Sahebkar A, *et al*. Administration of silver nanoparticles in diabetes mellitus: a systematic review and meta-analysis on animal studies. Biological Trace Element Research. 2022;200(4):1699-709.
67. Dasari S, Yedjou CG, Brodell RT, Cruse AR, Tchounwou PB. Therapeutic strategies and potential implications of silver nanoparticles in the management of skin cancer. Nanotechnology reviews. 2020;9(1):1500-21.