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The Future Perspective of Silver Nanoparticles

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ABSTRACT-
Recent advances in nanoscience and nanotechnology have radically altered how we identify, treat, and prevent numerous diseases in all aspects of human life. Silver nanoparticles are among the metallic nanop articles that are utilized in biomedical applications. (AgNPs) are among the most important and intriguing nanomaterials. AgNPs are significant in the fields of nanotechnology and nanoscience, especially in nanomedicine. AgNPs have received attention because to their possible uses in cancer treatment and diagnosis, despite the fact that other noble metals have been employed for a variety of reasons. We go over the synthesis of AgNPs using chemical, physical and biological techniques in this review.
More importantly, we extensively discuss the multifunctional bio-applications of AgNPs; for example, as antibacterial, antifungal, antiviral, and anti-cancer agents. In addition, we discuss challenges for cancer therapy using AgNPs. Finally, we conclude by discussing the future perspective of AgNPs.
Keywords – Silver Nanoparticles, Nanomedicine,, Nanomaterials, Bioapplication, Cancer therapy, Mechanism.

I. INTRODUCTION

Silver nanoparticles (AgNPs) are increasingly used in various fields, including medical, food, health care, consumer, and industrial purposes, due to their unique physical and chemical properties. These include optical, electrical, and thermal, high electrical conductivity, and biological properties(1,2,3). They have been used for a variety of purposes due to their unusual properties, such as antibacterial agents, consumer goods, medical device coatings, optical sensors, and cosmetics; pharmaceutical and food industries; diagnostics, orthopedics, drug delivery; and finally, they have improved the tumor-killing capabilities of anticancer drugs.(4) Because of their unusual surface-to-volume ratio and ability to significantly alter physical, chemical, and biological properties, nanosized metallic particles have been used for a variety of purposes.(7.8) Different approaches have been used for synthesis in order to meet the demand of AgNPs. In general, traditional physical and chemical techniques appear to be highly costly and risky.(1,9) Interestingly, biologically-prepared AgNPs show high yield, solubility, and high stability [(1). Among several synthetic methods for AgNPs, biological methods seem to be simple, rapid, non-toxic, dependable, and green approaches that can produce well-defined size and morphology under optimized conditions for translational research. In the end, a green chemistry approach for the synthesis of AgNPs shows much promise.

Precise characterisation of the particles is required after synthesis, as the physicochemical characteristics of a particle may greatly influence their biological characteristics. Characterizing the manufactured nanoparticles before to application is important in order to solve the safety concern and utilize any nanomaterial to its fullest potential for the benefit of human welfare, nanomedicines, the health care business, etc.(10,11) The characteristic feature of nanomaterials, such as size, shape, size distribution, surface area, shape, solubility, aggregation, etc. need to be evaluated before assessing toxicity or biocompatibility. (12) To evaluate the synthesized nanomaterials, many analytical techniques have been used, including ultraviolet visible spectroscopy (UV-vis spectroscopy), X-ray diffractometry (XRD), Fourier transform infrared spectroscopy (FTIR), X-ray photoelectron spectroscopy (XPS), dynamic light scattering (DLS), scanning electron microscopy (SEM), transmission electron microscopy (TEM), atomic force microscopy (AFM), and so on. (13,14)

The biological activity of AgNPs depends on factors including surface chemistry, size, size distribution, shape, particle morphology, particle composition, coating/capping, agglomeration, and dissolution rate, particle reactivity in solution, efficiency of ion release, and cell type, and the type of reducing agents used for the synthesis of AgNPs are a crucial factor for the determination of cytotoxicity (15). The physicochemical properties of nanoparticles enhance the bioavailability of therapeutic agents after both systemic and local administration (16,17) and other hand it can affect cellular uptake, biological distribution, penetration into biological barriers, and resultant therapeutic effects (18,19). Therefore, the development of AgNPs with controlled structures that are uniform in size, morphology, and functionality are essential for various biomedical applications (20,21,22,23,24). Cancer is a complex, multifactorial disease which has the characteristic feature of the uncontrolled growth and spread of abnormal cells caused by several factors, including a combination of genetic, external, internal, and environmental factors and it is treated by various treatments including chemotherapy, hormone therapy, surgery, radiation, immune therapy, and targeted therapy(25). So, the task at hand is to find lead compounds with cell-targeted specificity that are sensitive, efficient, and affordable while also boosting sensitivity. Because of their therapeutic uses as anticancer drugs, diagnostic tools, and probing agents, AgNPs have garnered a lot of attention recently. Taking the literature into account, we concentrated on the most recent advancements in the synthesis, characterization and bio-applications of AgNPs in this review, primarily focusing on their antibacterial, antifungal, antiviral, anti-inflammatory, anti-cancer, and anti-angiogenic qualities as a whole. Furthermore highlighted in this study are the therapeutic techniques, the mechanism of action, and the difficulties and constraints associated with using nanoparticles in cancer treatment. Lastly, a conclusion and the future outlook for AgNPs round out this review.

II. SYNTHEIS OF SILVER NANOPARTICLES

Silver nanoparticles are produced via a variety of processes, including as physical, chemical, and biological synthesis. It is important to remember that every approach has benefits and drawbacks. The organism functions as a capping, reducing, or stabilizing agent during the biological manufacture of silver nanoparticles, reducing Ag+ to create Ag0 (26). Recent years have seen a rise in the use of biological technologies based on natural products derived from plant and microbe sources because of their low cost, high yields, and minimal toxicity to humans and the environment (27). Different methods for synthesis of silver nanoparticles are described in the following sections.

2.1 Chemical Methods-

Silver nanoparticles can be produced using a variety of techniques. Chemical procedures are advantageous because they require less complicated and handy equipment than biological approaches do. According to prior reports, silver ions take up electrons from the reducing agent and transform into a metallic form before aggregating to produce silver nanoparticles. AgNO3 is one of the most often utilized silver salts in the chemical production of silver nanoparticles because of its affordable price.(28,29)

In 2002, Sun and Xia reported the synthesis of monodispersed silver nanocubes through reducing nitrate (30). Mukherji and Agnihotri synthesised silver nanoparticles using $AgNO_3$ as a precursor, and sodium borohydride and trisodium citrate as stabilising agents. It has been reported that sodium borohydride is a good reducing agent for the synthesis of silver nanoparticles having a size range of 5–20 nm. In comparison, trisodium citrate is the most effective reducing agent for the synthesis of silver nanoparticles of the size range 60–100 nm (31). Polyvinylpyrrolidone (PVP) as a size controller and a capping agent, with ethylene glycol as a solvent and a reducing agent, is reported to give rise to silver nanoparticles with an average size less than 10 nm (32). Patil et al. confirmed the synthesis of silver nanoparticles using hydrazine hydrate as the reducing agent and polyvinyl alcohol as the stabilising agent. Their results revealed that the resultant nanoparticles had a spherical morphology and these particles showed significant applications in biotechnology and biomedical science (33). According to another important study, the synthesised silver nanoparticles were found to be spherical with different sizes (34).

The $AgNO_3$ solution is heated to the reaction temperature in the precursor heating method and the nanoparticle size is observed to be most affected by the ramping rate, whereas in the precursor injection method, a silver nitrate aqueous solution is injected, and the reaction temperature is a key factor for the reduction of particle size and for achieving monodispersity(35). High yield is the main advantage of chemical methods, compared to physical methods. Chemical methods are highly expensive, and chemicals and compounds used for silver nanoparticle synthesis such as borohydride, 2-mercaptoethanol, citrate and thio-glycerol are hazardous and toxic. It is extremely difficult to produce silver nanoparticles with a definite size and it requires an additional step to prevent particle aggregation(36). Numerous hazardous and toxic by-products are produced during synthesis.

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Moreover, the reducing agents used in these methods are toxic (37).

2.2 Physical Methods-

Physical methods for the preparation of silver nanoparticles include evaporation–condensation and laser ablation. The main drawbacks of these methods are the huge amount of energy required, plus long duration for completion of the whole process.

Monodispersed silver nanocrystallites are produced through the thermal breakdown of Ag+-oleate complexes, according to Lee and Kang's research (38). In a work by Jung et al., metal nanoparticles were prepared by evaporation and condensation using a tiny ceramic heater. It was observed that polydispersed nanoparticles were produced over time by the heater surface maintaining a consistent temperature. These silver nanoparticles did not aggregate and were spherical (39). It has recently been shown that, when subjected to laser ablation, the polyol process yields spherical nanoparticles of varying diameters (40). Silver nanoparticles were synthesized by ablation using various lasers to investigate the effects of laser wavelength on particle size. It was observed that a drop in laser wavelength resulted in a reduction of the average particle diameter from 29 to 12 nm (41). Femtosecond pulse formation efficiency was much lower than nanosecond pulse formation efficiency. In addition, femtosecond laser pulses produced colloids with a smaller size dispersion than nanosecond laser pulses (42). Through the physical deposition of metal directly into glycerol, Seigal and associates investigated the creation of silver nanoparticles. For lengthy chemical processes, this method proved to be a good substitute. Additionally, the resulting nanoparticles had a restricted size range and were resistant to aggregation(43). The benefits of physical production methods include speed, the absence of hazardous reagents, and the use of radiation as a reducing agent. Physical approaches have non-uniform distribution, high energy consumption, low yield, and solvent contamination (44).

2.3 Biological Methods-

To overcome the shortcomings of chemical methods, biological methods have emerged as viable options. Recently, biologically-mediated synthesis of nanoparticles have been shown to be simple, cost effective, dependable, and environmentally friendly approaches and much attention has been given to the high yield production of AgNPs of defined size using various biological systems including bacteria, fungi, plant extracts, and small biomolecules like vitamins and amino acids as an alternative method to chemical methods—not only for AgNPs, but also for the synthesis of several other nanoparticles, such as gold and graphene (45,46,47,48,49). Bio-sorption of metals by Gram-negative and Gram-positive bacteria provided an indication for the synthesis of nanoparticles before the flourishing of this biological method; however, the synthesized nanomaterials were as aggregates not nanoparticles (50). Several studies reported the synthesis of AgNPs using green, cost effective, and biocompatible methods without the use of toxic chemicals in biological methods. In this green chemistry approach, several bacteria, including Pseudomonas stutzeri AG259 (51), Lactobacillus strains (52), Brevibacterium casei (53), fungi including Fusarium oxysporum (54), Ganoderma neo-japonicum Imazeki (55), plant extracts such as Allophylus cobbe (45), Artemisia princeps (56), and Typha angustifolia (57) were utilized. In addition to these, several biomolecules, such as biopolymers (58) starch (59), and Amino acids (60). Three elements are necessary for the biological synthesis of nanoparticles: (a) the solvent; (b) the reducing agent; and (c) the non-toxic substance. The availability of amino acids, proteins, or secondary metabolites involved in the synthesis process, the removal of the extra step necessary to prevent particle aggregation, and the use of biological molecules for the pollution-free and environmentally benign synthesis of AgNPs are the main benefits of biological methods. Controlled particle size and shape appears to be possible with biological approaches, which is crucial for a variety of biomedical applications.(61) Additional benefits of using biological processes include having access to a wide range of biological resources, requiring less time, producing nanoparticles with excellent density and stability, and having them readily soluble in water (62).AgNPs' morphology and structure, which are determined by the size and form of the particles, determine their biological activity (63,64). Smaller and truncated-triangular nanoparticles appear to be more effective and have better qualities in terms of size and form. Despite the fact that numerous research have produced AgNPs with a variety of shapes and sizes, they are still subject to some restrictions. For the synthesis of monodisperse and

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uniform-sized silver colloids, an excess of strong reducing agent, such as sodium borohydride ($NaBH_4$), was used to establish control over morphology and structure (65).

III. BIOMEDICAL APPLICATION OF SILVER NANOPARTICLES-

3.1 Antibacterial and Antifungal activity-

These days, a major medical issue that needs to be treated as quickly as possible is the resistance of bacteria belonging to the genera Streptococcus, Salmonella, Escherichia, Pseudomonas, etc. to several well-known antibiotics. AgNPs have been identified as a particularly promising area in the fight against pathogens in the hunt for novel bio medicines. The great majority of studies believe that silver nanoparticles have the capacity to stop the growth and kill harmful germs that cause a variety of common human diseases. As was already established, the AgNPs' enduring antibacterial activity is derived from their ability to connect with a variety of biomolecules found in microbial cells. Plant extracts are a limitless source of AgNP synthesis nowadays. Plants, which frequently have their unique medicinal qualities and create AgNPs in a particular manner, Thus, an inhibitory effect has been shown against Str. aureus, E. coli (66), K. pneumoniae, Acinetobacter baumannii (67), Proteus vulgaris, Serratia marcescens, Ps. aeruginosa, B. subtilis (68), Enterococcus faecalis, C. albicans (69), S. typhimurium, S. enteritidis (70), A. niger, A. flavus (71), B. cereus (72), Fusarium sp., Rhizopus sp. (73), F. oxysporum, Alternaria brassicicola (74), C. kefyr (75), Vibrio parahaemolyticus (76), E. aerogenes, B. bronchiseptia (77), and Mycobacterium tuberculosis (78). It is interesting that more exotic objects are used for the synthesis of AgNPs. For example, algae Gracilaria parvispora was used by Hussein et al. to produce silver nanoparticles that inhibited the growth of Str. aureus and Ps. aeruginosa (79), and brown algae Sargassum longifolium was applied for the synthesis of AgNPs against A. fumigatus, C. albicans, and Fusarium sp. (80). Another peculiar source for nanoparticle production with antibacterial potential are lichens (81,82). They are extremely interesting in this case because lichen-specific metabolites such as, for example, antranorin, may play a significant role in the synthesis of AgNPs (83).

The bacteria themselves turn out to be "biofactories" for the creation of AgNPs, despite the fact that plant extracts are often used in the synthesis of AgNPs. Bacillus bacteria as well as other bacteria like E. coli, Brevibacterium casei, Str. albogriseolus, S. typhirium, Acinetobacter calcoaceticus, Sporosarcina koreensis, Aeromonas sp., Phenerochaete chrysosporium, Streptacidiphilus durhamensis, or Paracoccus sp., Ps. aeruginosa et al. serve as a bacterial "plant" for AgNPs that have an inhibitory effect on pathogenic microorganisms themselves. (84-102).

Microscopicfungi Aspergillus, Penicillium , Fusarium, Trichoderma, C.albicans, yeasts Schizosaccharomyces (103-109) and cyanobacteria such as Oscillatoria limnetica, Synechococcus sp., Nostoc sp., Scytonema sp., and Phormidium sp. (110,111,112) are also used for the synthesis of AgNPs. Currently, the combined use of AgNPs as antibacterial agents and some antibiotics is practiced in experimental medicine. However, this synergistic effect is not achieved for all antibiotics (113).

3.2 Antiviral activity

Nanoparticles provide an alternative to drugs for treating and controlling the growth of viral pathogens. Biosynthesis of silver nanoparticles could result in potent antiviral agents to restrict virus functions. Suriyakalaa et al. studied bio-silver nanoparticles with convincing anti-HIV actions at an early stage of the reverse transcription mechanism (114). Biosynthesised metallic nanoparticles have multiple binding sites for gp120 of the viral membrane to control the function of the virus. While another study reported that bio-based nanoparticles act as effective virucidal agents against free HIV or cell-associated virus (115). Silver nanoparticles have been demonstrated to exert antiviral activity against HIV-1 at non-cytotoxic concentrations. These silver nanoparticles were evaluated to elucidate their mode of antiviral action against HIV-1 using a panel of different in vitro assays (116). Another study reported the antiviral activity of silver nanoparticles with or without a polysaccharide coating against monkeypox virus. This study found that silver nanoparticles meaningfully inhibit monkeypox virus infection in vitro (117).

3.3 Anticancer activity

Cancer cells have abnormal metabolic behaviors and genomic expressions by causing various pathological and metabolic alterations in cellular surroundings developed by cell signaling, rapid proliferation, angiogenesis and metastasis. Many studies reported depicts that the use of silver nanoparticles enhances the chemotherapeutic efficacy against multidrug resistant cancer cells emphasized with specifications and combinations. Nanoparticles coated with specific binders can recognize particular surface receptors and targets only the cancerous cells or the anomalous cells. Many platinum nanoparticles and platinum based compounds were approved as anticancer agents. Though many cancer types are susceptible to platinum based drugs accompanied with toxic side effects. Consequently other metal nanoparticles are explored in search of a better anticancer agents, while silver with advantageous antimicrobial activity arose into interest as an effective anticancer agent. Cancer cells such as HepG2 (human liver cancer cells) (118), HCT (Human colon cancer cells), HeLa (Human cervical adenocarcinoma cells), MCF 7 (Human breast adenocarcinoma cells) (118) and various other cancer cells were used to study the cytotoxicity effect of silver nanoparticles. Silver nanoparticles synthesized using different plant extracts showed potentially high cytotoxicity and less cell viability against various cancer cells. Moreover, nanoparticles of 5-35 nm sizes effectively induced cell death through mitochondrial structure targeting (119).

Challenges for Cancer Therapy Using AgNPs

Nanomedicine is as one of the fast developing and promising strategies to combat cancer using metallic nanoparticles. Current treatment for cancer, such as chemo- and radiation therapy, has limitations due to unexpected drug-associated side effects, lack of specificity of low drug concentrations at the tumor target site, and the development of chemoresistance (120,121). Nanoparticle-mediated therapy is the best, most suitable, and alternative therapeutic strategy in cancer therapy. Nanoparticles (NPs) have the ability to target through passive or active targeting of particular diseased cells or tumor tissues by the encapsulation of therapeutic agents with nanoparticles, and they have been used as drug delivery systems (122). Although many nanoparticle-mediated strategies have been developed, heterogeneity of the tumor and its stroma is a significant challenge for nanotechnologists and clinicians to come up with specific formulations to precisely target specific cancer cells. To achieve higher specificity, reduction in toxicity, biocompatibility, safety, better efficacy, and to overcome the limitations of conventional chemotherapy, using new nanoparticles in single platform-based strategies is another challenge in cancer therapy. However, there is a need to address the challenges and limitations of using nanoparticles for cancer therapy; these include physiological barriers, limited carrying capacity, enhanced permeability and retention effect (EPR), variability of nanoparticles, and regulatory and manufacturing issues (122).

IV. CONCLUSION-

This review comprehensively addressed synthesis, and bio-applications of silver nanoparticles, with special emphasis on anticancer activity and its challenges for cancer treatment using AgNPs. Recently, both academic and industrial research has explored the possibility of using AgNPs as a next-generation anticancer therapeutic agent, due to the conventional side effects of chemo- and radiation therapy. Although AgNPs play an important role in clinical research, several factors need to be considered, including the source of raw materials, the method of production, stability, bio-distribution, controlled release, accumulation, cell-specific targeting, and finally toxicological issues to human beings.

Moreover, AgNPs offer enormous promise for use in cancer diagnosis and treatment; numerous techniques have been developed to address this issue. The synergistic effects of AgNPs and antibiotics on antibacterial drugs or several therapeutic agents on anti-cancer activity/tumor reduction remain unclear despite the availability of various approaches. Consequently, additional research is needed to understand the combined effects of the two distinct cytotoxic drugs at one particular time. These studies have the potential to shed light on the processes and effectiveness of the synergistic effects of two or more drugs; as a result, they could aid in the development of a novel system with numerous components that work synergistically to treat different forms of cancer. Finally, the great concern is that the developing nanotechnology-based therapy should be better than available technologies, and it should overcome the limitations of existing treatment techniques.

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