International Journal of Pharmacognosy and Life Science

E-ISSN: 2707-2835
P-ISSN: 2707-2827
www.pharmacognosyjournal.com
IJPLS 2022; 3(1): 01-06
Received: 17-11-2021
Accepted: 21-12-2021

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The medical applications of silver nanoparticles

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DOI: https://doi.org/10.33545/27072827.2021.v2.i2a.38

Abstract
Recent progresses in nano technology and nano science have developed the way we detect, treat, and prevent diseases. Silver nanoparticles (AgNPs) are one of the most important elements among the many metallic nanoparticles used in biomedical applications. Physical, chemical and photochemical procedures all have been used to synthesize AgNPs, as well as irradiation and biological approaches, electrochemical methods**.** The importance of AgNPs appears in antifungal, antibacterial, antiviral, anti-inflammatory, anti-cancer, and anti-angiogenic applications in biological and biomedical research. Furthermore, under some conditions, the free release of silver ions from AgNPs causes cell death in mammalian and microbial cells, indicating that AgNPs are broad-spectrum antibacterial agents. Reactive oxygen species (ROS) were shown to develop on AgNPs surface in prior studies. AgNPs, based on these properties, have a lot of promise in terms of minimizing wound inflammation and hence boosting wound healing when applied topically.

Keywords: Silver nanoparticles**,** biomedical applications, anti-cancer

Introduction

Nanoscience and nano technology have been introduced as interdisciplinary areas in biology, chemistry, physics and bioengineering. Silver (Ag) is a transition metal with anatomic weight of107.87, 961.78 °C for melting and 2162 °C for boiling. Silver is extremely malleable and ductile, and it also got the highest electrical and thermal conductivities among all metals in their pure state. When pure silver comes in to touch with chemicals containing Sulphur or chloride and don't react with water or air. Silver frequently found in ores including copper, lead, gold, and zinc, and is rarely found as a single metal. Instead, it is found in mixtures with sulphur, chlorine, arsenic, or antimony.

Depending on the application, nanoparticles can be made in a variety of shapes. Spherical Silver nanoparticles (AgNPs) are the most prevalent, but diamond, octagonal, and thin sheets are also often utilized [1]. Nano science is are latively recent inter disciplinary field that is based on the funda mental features of nanoscale objects [2]. Because of their large surface area to volume ratio, nanoparticles have more amazing optical, electrical, magnetic, and catalytic capabilities than bulk materials. Nanoparticles are particles with diameters ranging from 1 to 100 micrometers [3]. Because of their unique chemical, physical, and biological properties, they have a wide range of applications in spectral analysis, catalysis, electronics, sensors, and developing new drug manufacturing methods in the pharmaceutical industry [4].

Dueto their unique features, AgNPs have gotten alot of attention in nanobiotechnology research; so they have been widely used in food storage, house hold goods, health-care business, environmental and biological applications [1].

AgNPs chemical, physical and biological features' make them one-of-a-kind. As a result, nanoparticles have been used fora wide range of applications. Chemical, physical, photo chemical, and biological processes, such as chemical reduction, laser ablation, and green synthesis employing bioorganic plants, haveall been used in the synthesis of AgNPs [5]. Various biological and medicinal applications use AgNPs, including-cancer, anti-inflammatory, antibacterial, anti-fungal, antiviral and anti-angiogenic. Furthermore, under some conditions, the free release of silver ions from AgNPs causes cell death in mammalian and microbial cells, indicating that AgNPs are broad-spectrum antimicrobials [6]. ROS were found to develop on the surface of AgNPs in prior studies [7]. AgNPs, based on these characteristics, have a lot of promise in terms of limiting wound in inflammation and hence boosting wound healing when applied topically [8].

Types of silver Nano synthesis

There are sever always to make AgNPs, which can be classified in to chemical, physical, photochemical, irradiation, electrochemical, and biological processes. Chemical approaches, such as AgNO3reduction, could be deemed standard. UV lights frequently used in photochemical procedures to aid chemical reactions. Chemical procedures aided by irradiation are also frequently used. Physical approaches typically include condensation, evaporation or other high-energy processes, but these strategies are less widely used because of their high expense [9].

Chemical Methods

AgNPs are frequently synthesized by chemical reduction with organic and inorganic reducing agents, such as sodium citrate, sodium borohydride, as corbate, N, N-dimethylformamide, element alhydrogen, polyol process, Toll ensreagent, and poly (ethyleneglycol) - block copolymers [10]. These reducing agents lower Ag+, causing metallic silver to develop (Ag0), Silverions are reduced by nonionic surfactants in ethanol in the absence of light [10]. After that, the cells clump together into oligomeric clusters. As a result of these clusters, metallic colloidal silver particles are formed [11]. It is critical to apply protective agents to stabilize dispersive NPs and shield NPs that can absorb on or bind to nanoparticle surfaces, while preparing metal nanoparticles to prevent agglomeration [12].

Surfactants with functionality for particle surface interactions (e.g., thiols, amines, acids, and alcohols) can help to stabilize particle growth and prevent particles against sedimentation, agglomeration, and loss of surface characteristics. Ease of manufacture, low cost, and high yield are advantages of nanoparticles chemical synthesis; nevertheless, chemical reducing agents are toxic to living organisms [13].

Biological method

Three factors impact the biological production of nanoparticles: the solvent, the reducing agent, and the non-toxic material. As a result of the employment of ecologically benign and pollution-free biological molecules in the production of AgNPs (such as amino acids, proteins or secondary metabolites), biological approaches have several benefits over traditional chemical methods. Biological techniques appear to give regulated particle size and shape, which is crucial for a variety of biological applications [14].

Using reducing agents like bacterial proteins or plant extracts can enhance the adjustment of the form, size, and mono-dispersity of nanoparticles [15]. A wide variety of biological resources, reduced time requirements, high density and stability, and quick water solubility of produced nanoparticles are some of the advantages of biological approaches [16].

Physical methods

Nanoparticles are made via physical method at atmospheric pressure, by evaporation-condensation in a tube furnace [17]. Traditional physical processes such as sparkdis charge and pyrolysis were used to synthesize AgNPs [18].

Speed, the use of radiation as a reducing agent and the absence of dangerous chemicals are benefits of physical methods, while its weakness is attributed to the high energy consumption, low yield, solvent contamination and lack of uniform distribution [19].

Electrochemical Method

Another way to make AgNPs is to use an electrochemical approach. By adjusting electrolysis settings and modifying the composition of electrolytic solutions, it is possible to control particle size and promote AgNP homogeneity. Electrochemical reduction at the liquid/liquid interface was employed to create polyphenylpyrrole-coated silver nano-spheroids (3-20 nm). The silver metal ion was transferred from the aqueous to the organic phase, where it interacted with the pyrrole monomer to produce this nano-compound [20]. According to the silver exchange degree of compact zeolite film modified electrodes, electrochemical reduction within or outside zeolite crystals was employed to make monodisperse silver nanos pheroids (1-18nm).

Irradiation Methods

AgNPs may be made using a number of irradiation methods. Laser irradiation of an aqueous solution of silver salt and surfactant can create AgNPs with a well-defined for mand size distribution [22]. In addition, a photo-sensitization synthesis approach for producing AgNPs utilizing benzophenone was carried out using a laser. After brief irradiation times, low laser powers generated AgNPs of roughly 20 nm, whereas higher laser powers produced NPs of around 5 nm after extended erirradiation times. Light sources for the generation of AgNPs include a laser and a mercury lamp [23]. Photo-sensitized development ofsilver NPs with thiophene (sensitizing dye) and silver nanoparticle creation by illumination of $Ag(NH_3)^+$ inethanol have both been accomplished invisible ight irradiation investigations [24].

Biological applications of AgNPs

AgNPs are widely employed in a variety of applications, including health-care, home products, food storage, environmental, and biological applications, due to their distinct properties. In addition to their antifungal, antibacterial, antiviral, anti-inflammatory, anti-cancer, and anti-angiogenic properties in biological and medicinal applications which we are particularly interested in. We focused on seminal studies that have previously been published and ended with some recent update sin our research. Figure [1] shows a schematic design of several AgNPs applications.

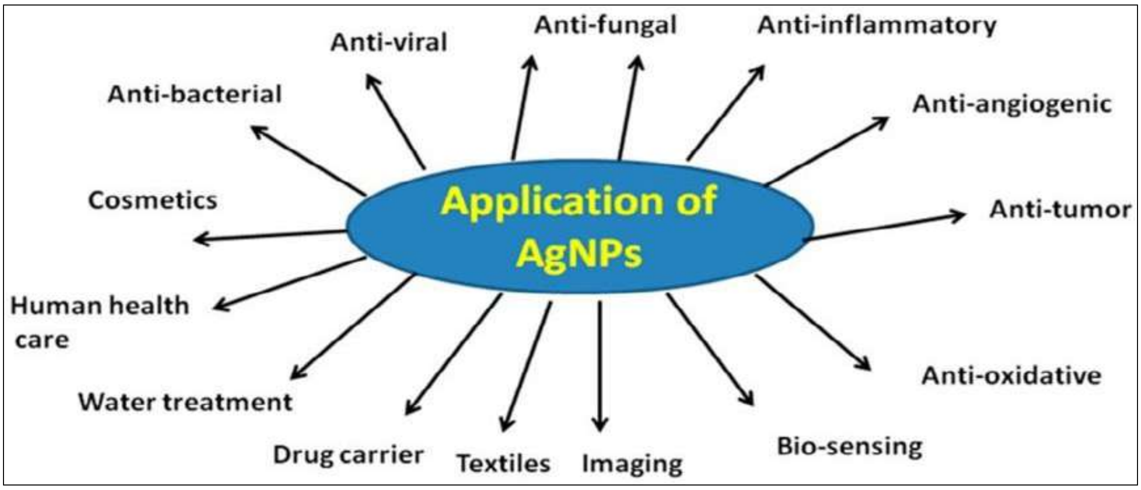

Fig 1: Representing various applications of AgNPs

Anti-bacterial activity of AgNPs

With an average particle size of 25 nm, four different types of saccharides were used to manufacture AgNPs, which proved to be effective against Gram-positive and Gram-negative bacteria in addition to multi-resistant diseases. AgNPs shape and size is critical for determining efficiency because they interact with the Gram-negative bacteria E. coli in a form-dependent manner [28].

In terms of antibacterial activity and the ability to overcome antibiotic resistance in bacteria, AgNPs appear to be a viable alternative to antibiotics. As a result, antibacterial agents based on AgNPs must be created. In addition to other promising nanomaterials, the high surface-to-volume ratios and the crystalline surface structure of AgNPs make them a potential antibacterial agent [25].

The findings imply that at low doses of AgNPs, yeast and E. coli growth is completely inhibited, whereas S. aureus growth is only somewhat inhibited [26]. Silver nanoparticles may release silver ions indefinitely, which could be a way for killing bacteria [27]. The exact process is unknown, but it is similar to how silver (Ag) ions Acton bacterium strains like trypanosomes and yeasts, where AgNPs accumulate inthe aqueous solution and eventually cause enzyme and protein saturation in the cell [27]. The authors hypothesized a mechanism in a published paper, stating that alterations generated by AgNPs in the cell Wallan nucleus, as well as DNA and RNA, are the primary cause of bacterial cell growth retardation. Meanwhile, Li *et al*. identified three probable mechanisms for AgNPs particle-induced bacterial cell death [28]. The first hypothesized mechanism is that the adherence of AgNPs to the bacterial cell wall (because to the tiny particle size) inhibits bacterial cell development and proliferation, creating alterations in the cell wall such that the membrane is unable to protect the internal part of the cell [29]. According to the authors, the diffusion of AgNPs into the bacterial cell causes alterations in the DNA, which slows down the cell' snormal activity and eventually leads to death. Silver nanoparticles enter the cell wall of bacteria, causing DNA damage. According to the third hypothesized mechanism, in the bacterial cell wall the Ag^+ ions interact with sulphur-containing proteins causing the cell wall to fail. This is thought to be the primary mechanism of anti-bacterial action [29].

Antifungal activity of AgNPs

Fungal infections represent more common in immune-compromised people, and conquering fungi-mediated disorders is a time-consuming process due to the restricted number of antifungal medications now accessible [30]. Consequently, there is an unavoidable and pressing need to produce biocompatible, non-toxic, and environmentally acceptable antifungal agents. AgNPs are now being employed as antifungal medicines to combat a variety of fungal illnesses. Antifungal activity of biologically produced AgNPs against a variety of phytopathogenic fungi was discovered. A thorough investigation into the efficacy of AgNPs' antibacterial actions against yeast, E. coli, and S.aureus was also carried out [31]. *In vitro* experiments revealed a possible molecular mode of action for AgNPs, in which released Ag^+ ions into the cytoplasmic compartment of fungal cells disturb the respiratory system and affect the DNA replication process as well as the expression of replication-related genes [31].

Antiviral activity of AgNPs

Viral-mediated diseases refer to ubiquitous and increasingly prevalent around the world, so antiviral drugs are critical. Antiviral therapy heavily depends on understanding the mechanisms of AgNPs' antiviral activity. Because of their size ranges and forms, AgNPs interact with bacteria and viruses in a unique way [32]. It was shown that nano-Ag integrated into polysulfone ultrafiltration membranes (nAg-PSf) had a significant antiviral activity against the MS2 bacteriophage, and this was due to increased membrane hydrophilicity [33]. Anti-human immunodeficiency virus (Anti-HIV) activity was discovered in the first mechanistic investigation in anearly stage of viral replication. Once AgNPs were coated with polyvinylpyrrolid one (PVP), cell-free HIV-1and cell-associated HIV-1 isolates were not transmitted.

AgNPs have been found to be potent HIV and hepatitis B virus (HBV) inhibitors [35]. AgNPs have antiviral capabilities and have been shown to suppress the transmission of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [10], which is still spreading due to a lack of effective antiviral therapies. Due to the 2019 coronavirus illness (COVID-19), medical research, particularly AgNP-related research, has intensified, with daily total global cases increasing. The inhibition activity of AgNPs was demonstrated in a Gram-positive bacterium, S. aureus, study by inhibiting the respiratory chain dehydrogenase into dihydroxyacetone through the metamorphosis of a number of enzymes, including glycerol

3-phosphated ehydrogenase, resulting in the bacteria's normal growth and metabolic activity being obstructed [35].

AgNPs favorably attack the viral surface proteins with sulfhydryl groups resulting in disulfide bonds cleavage and causing the protein destabilization and thus impact viral infectivity [36].

AgNPs attach to disulfide bonds in close proximity to the CD4 binding region of the gp120 surface protein, according to HIV studies [37]. Disulfide bonds are important in the binding of SARS-CoV-2 spike protein to the angiotensin converting enzyme-2 (ACE2) receptor, according to Hati and Bhattacharyya, and their destruction impairs viral attachment to the receptor. According to other authors' findings, AgNPs break disulfide links on the spike protein and ACE2 receptors, resulting in antiviral activity against SARS-CoV-2.Additional research is being carried out to determine AgNPs antiviral mechanism on SARS-CoV-2andto elucidate it in full later [37].

Anti-inflammatory activity of AgNPs

An early immunological response by tissue to foreign particles is characterized by an increase in the creation of pro-inflammatory cytokines, immune system activation and the release of prostaglandins and chemotactic substances such as complement factors, interleukin-1 (IL-1), TNF- and TGF- [38]. AgNPs have recently played an important role in the anti-inflammatory field, among other anti-inflammatory drugs.

Although AgNPs have been shown to be antibacterial, their anti-inflammatory properties are still unknown. Anti-inflammatory effect in rats was reported by Bhol and Schechter [39], who found that it considerably reduced colonic inflammation. AgNPs treatment resulted in quick therapeutic and better cosmetic appearance in mice, which was dose-dependent. AgNP salso showed antibacterial activity, wound inflammation decrease, and cytokine regulation [40].

Anti-angiogenic activity of AgNPs

Pathological angiogenesis is a hallmark of cancer, as well as a variety of ischemia and inflammatory disorders [41]. A number of research groups are striving to develop novel anti- and pro-angiogenic chemicals for the treatment of angiogenic diseases. Although some synthetic medications with anti-angiogenic qualities have been discovered, a more physiological approach to treating angiogenesis-dependent diseases may be accessible in the near future [42]. Lately, AgNPs have been shown to exhibit anti-angiogenic and anti-cancer characteristics in various investigations employing both *in vivo* and *in vitro* models [43].

Anticancer activity of AgNPs

One in every three people will be diagnosed with cancer over their lifetime [43]. Despite the fact that many chemotherapy drugs are currently being utilized to treat several types of malignancies, the adverse effects are many and intravenous infusion administration of chemotherapeutic medicines is a time-consuming operation [43]. A study looked into AgNPs' chemical mechanism and discovered that programmed cell death was concentration-dependent under certain conditions. They also discovered that UPRT-expressing cells andnon-UPRT-expressing cell sin the presence of fluorouracil (5-FU) had a synergistic effect on apoptosis [44].

Toxicity of AgNPs

Due to their unique chemical and physical properties, AgNPs are ideal candidates foruse in several commercial products around the world. Furthermore, their anti-inflammatory anti-bacterial properties made them an outstanding candidate for usage in the medical field. Never the less, some research shave suggested that AgNPS could posea concern to the ecosystem and have harmful effects. Silver nanoparticles, like many other commonly known components, can cause oxidative stress, whether chemical, physical, or biological. The cytotoxic action of AgNPs via ROS production has been described in several investigations [30]. On the other hand, cells pre-treatment with NAC (N-acetylcysteine) as a systematic antioxidant can reduce the generation of ROS [31]. The mechanism of AgNPs' antioxidant function can be attributed to the fact that silver can exist in two oxidation states (Ag^{+} and Ag^{+2}) depending on reaction conditions, and the resultant AgNPs can quench free radicals by donating or absorbing electrons [46].

Another approach impacted by the inhibitory function of AgNPs is ROS, a kind of cellular oxidative stress in microorganisms [46]. Because of the nanoparticles' potential to generate ROS and free radicals, cell oxidative stress could be increased by AgNPs [47]. The ability of nanoparticles to cause lipid degradation, biomolecule perforation, and programmed cell death should be investigated, since evidence suggests that the existence and formation of intercellular ROS inside cells is one of the most important elements determining AgNPs toxicity [48].

Another study found that AgNPs antibacterial action is dependent on their size. So, 10 mg/L concentration of nanoparticles caused higher levels of ROS production in Azotobacter vinelandii and Nitro somonas europaea than 50 mg/L AgNPs concentration [49].

Conclusions

Silver ions are bioactive and have a broad variety of properties, including anti-bacterial, anti-fungal, anti-viral, anti-inflammatory, anti-angiogenic, and anti-cancer compounds.

Attributable to their distinctive physical and chemical properties, AgNP Sar progressively used in a range of industries like medicine, health care, food, consumer goods and industry. Nanoparticles, AgNPs particularly have a crucial role in nanotechnology and nanoscience, particularly in nanomedicine.

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