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APPLICATIONS OF SILVER BASED PREPARATIONS: FROM CONVENTIONAL TO NOVEL DRUG DELIVERY – A REVIEW

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ABSTRACT

Silver-based treatments have been used in wound healing, wound care, and infection management since ancient times to provide adequate healing. These treatments have specific limitations, such as poisonousness, skin discoloration, and bacterial resistance, which have limited their use. As a result, new and inventive wound treatments, as well as techniques to improve on existing treatments, are being pursued. Silver nanoparticles (AgNPs) have demonstrated the ability to overcome the limitations associated with traditional silver-based therapies. AgNPs are effective against a wide variety of microorganisms while being less harmful, effective at lower concentrations, and causing no skin discoloration. This review examines the history and impact of silver-based treatments prior to the development of AgNPs and AgNP-based nanoformulations. It also has the properties of AgNPs that aid in wound healing and make it superior to traditional silver-based wound treatment therapies.

KEYWORDS: Nanotechnology, silver-based therapy, silver nanoparticles, antibacterial, anticancer.

INTRODUCTION

For thousands of years silver and its compounds have been utilized as antimicrobial and antibacterial agent. Silver preparations are also used to in burn care, wound management, treatment of ulcers and instrument disinfection. Topical silver based agents have been used for a very long time to treat infections related to burns and to speed up the healing process of burnt skin.[1] Over the past 40 years, silver sulfadiazine (SSD) has become a very popular antimicrobial silver delivery system. Different kinds of mixtures of sulfa drugs with silver were tested *in vitro*, but SSD seemed to be the most successful and therefore used as a conventional dressing agent in burn wounds.[2] Silver shows antibacterial activity, even at very low concentrations, against various organisms like *E. coli*, *P. aeruginosa*, *S. aureus*, *Providencia*, *Serratia* etc. The antibacterial activity of silver is mainly due to silver ions, which are released from a silver-containing substance and interact with the thiol groups of enzymes and proteins that support bacterial life, thus affecting cell respiration and killing the cells.[3] However, growth of bacterial resistance, weakened reepithelialization, etc. has been reported with silver-based formulation.[4, 5] This is because of the halide ions present in the environment, which binds with silver ion and leads to precipitation of silver, decreasing water solubility and ultimately losses the antibacterial activity of silver. Therefore, the antibacterial activity of free silver ions is very short when they are used alone. Other side effects include argyria, hepatic, bone marrow toxicity and renal toxicity.[4] These side effects demand new therapy options for greater wound therapy. One of such approach is silver nanoparticles (Ag NPs), from which silver ions are gradually released, thereby causing antimicrobial activity.[3] Nanosilver particles have no local or systemic toxicity and do not impair healing. Smaller the particle size of silver, greater contact with wound surface area, thus increasing bioactivity and silver solubility.

"Nanoparticles" depicts molecules with size in the range of 1nm-100nm, have increasing need of uses in various fields including food packaging materials, personal care products, and delivery systems of therapeutic agents to improve medical treatments.[6] Nowadays it has been used in the design and development of many novel formulations for prevention, treatment and diagnosis of many diseases. Nanoparticles can be made of materials of different chemical nature, the most well-known being metals, metal oxides, silicates, non-oxide ceramics, polymers, organics, carbon and biomolecules. Nanoparticles exist in a few unique morphologies like circles, chambers, platelets, tubes etc. Silver nanoparticles have unique electric, optical, catalytic and particularly antimicrobial properties which makes them even more interesting in their practical applications and are well investigated mainly in colloidal systems.[7] Recently silver nanoparticles have been extensively used due to their superior physical, chemical, and biological characteristics.[8] Furthermore, despite some possible risk to human health, they have been outlined to be used for several applications like antibacterial agents, as anticancer agents, in diagnostics, orthopaedics, wound dressings and biomedical devices. Various methods have been used for synthesis to fulfill the needs of silver nanoparticles.[9, 10] Controlling the size, shape and less of aggregation is the most systematic method for the preparation of silver nanoparticles.

The current review details the application of conventional as well as novel silver silver-based formulations leading up to Silver nanoparticles (AgNPs). Current review also deals with different methods for synthesis of AgNPs and various medical applications of AgNPs with special emphasis on antimicrobial and anticancer properties with that make them better than conventional silver-based treatment therapies.

HISTORY OF SILVER

For thousands of years silver has been utilized as a healing agent by developments from one side of the planet to the other. Silver and its subordinates have been for quite some time utilized as antimicrobial agents. For instance, silver has been used to prevent disease in its strong essential structure (eg silver wire put in injuries), as solutions of silver salts used to cleanse injuries (eg. silver nitrate arrangement), and also as creams or ointments containing a silver–anti-infection compound (silver sulfadiazine (SSD) cream).[11, 12] As regards to its medicinal properties silver is known for over 1000 years BC. Silver has been utilized in the treatment of different problems including ulcers.[13] Silver foil applied to surgical injuries was known to work on wound healing and reduce postoperative infections, and silver pencils were utilized to remove swelling and to operate ulcers.[14] Bone marrow toxicity spotted with SSDs primarily due to the propylene glycol component.

Why Silver?

Silver is one of the essential components that makes up our planet. Pure silver has the highest electrical and thermal conductivity, and has the least contact resistance. Metallic silver itself is insoluble in water, however metallic salts, for example, $AgNO_3$ and Silver chloride are dispersible in water (WHO, 2002). Metallic silver is utilized for the surgical prosthesis and splints, fungicides and coinage. Dissolvable silver mixtures like silver slats, have been utilized in treating dysfunctional behavior, epilepsy, nicotine expansion, gastroenteritis and irresistible illnesses including syphilis and gonorrhea.[15] Metallic silver seems to present minimal danger to wellbeing, though solvent silver mixtures are readily absorbed and can possibly deliver adverse effects.[16] The wide variety of employment of silver permits exposure through different routes of section into the body. Ingestion is the essential route for entry for silver mixtures and colloidal silver proteins. Dietary intake of silver is assessed at 70-90 µg/day. Since silver in any structure isn't believed to be poisonous to the immune, cardiovascular, nervous or reproductive system and it isn't viewed as cancer-causing, along these lines silver is moderately non-harmful.[17] Silver interest will rise as silver finds new uses, especially in materials, plastics and clinical businesses, changing the example of silver emission as these advancements and items diffuse through the worldwide economy.

APPLICATIONS OF VARIOUS FORMS OF SILVER

Silver Sulfadiazine

Silver sulfadiazine is a silver and sulfadiazine mixture in which the silver ion binds with the entity's DNA, releasing the sulfonamide that interferes with the microbe's intermediary metabolic pathway. It is most effective against *P. aeruginosa* and the enteric, and it is equally effective against *C. albicans* and *S. aureus* as any antifungal drug. It can be used in either closed or open methods with equal effectiveness. Silver sulfadiazine can be used alone or in combination with other antibacterial. It can be combined with any statin, which increases its antifungal activity. The use of silver sulfadiazine alone has been shown to slow wound healing.[18]

Muangman et al. compared the efficacy of 1% silver sulfadiazine versus Aquacel® Ag dressing in the treatment of second-degree burns. Aquacel Ag promoted time-to-wound healing, reduced pain symptoms associated with dressing changes, and tended to lower total treatment costs, according to this study. The obtained results indicate that Aquacel Ag is an effective burn dressing in superficial second-degree burns. Opasanon et al. found Askina Calgitrol Ag® to be more effective than 1% AgSD in the treatment of partial-thickness burn wounds. It has antibacterial properties, and increasing the moistness of the wound environment promotes rapid granulation and reepithelialization of damaged tissue. According to the findings, burns heal significantly faster in the Askina Calgitrol Ag group (7 days) than in the 1% AgSD-treated group (14 days).[19]

Silver Zinc Allantoinate

Also known as AZAC cream, this is a combination of an antibacterial (silver), a wound healing factor (zinc), and allantoin, which stimulates debridement and tissue growth. In a clinical trial of 400 patients with chronic wounds, 339 (85%) wounds healed with AZAC 1% treatment. Despite this promising preliminary data, no additional trials have been published, and no AZAC-containing product has entered routine clinical use.[20]

Colloidal Silver Gel

Colloidal Silver Gel is one of the few ointments on the market that can treat a variety of skin diseases caused by viruses, fungi, bacteria, and parasites. Colloidal Silver Gel is a colloidal silver ion-containing gel. Colloidal Silver is a potent antibiotic ointment. It has the ability to kill viruses, bacteria, fungi, parasites, and mites. Colloidal Silver also helps to speed up wound healing. In a mouse wound model, D. Mehta et al. investigated the effectiveness of a colloidal silver gel (Ag-gel) wound dressing in inhibiting bacterial growth. The Ag-gel prevented Gram-negative and Gram-positive bacterial biofilm infections.[21]

Silver-coated cloth

Wounds, whether minor or major, should be properly cared for, and wound dressing is part of this process. The dressing is designed to be in contact with the wound. Wet-to-dry dressings have historically been widely used for wound debridement. Introduction of modern wound dressing provide important characteristics such as moisture retention and fluid absorption (e.g. polyurethane foams, hydrocolloids, iodine-containing gels) which are designed to keep the wound moist and promote healing. A good wound dressing should keep the wound moist, allow for gaseous exchange, act as a barrier against microorganisms, and remove excess exudates. It must also be nontoxic and nonallergenic to the patient's tissue. In addition, the ideal dressing should be non-adherent and easily removed without causing trauma. It should be made of a readily available biomaterial with antimicrobial properties and wound healing properties.[22] Smith & Nephew Healthcare Acticoat is a high-density polyethylene dressing coated with nanocrystalline silver. It was tested in vitro and found to be effective against a wide range of clinical isolates. Acticoat was found to be more effective than silver nitrate and SSD in vitro and clinically superior to silver nitrate 0.5 percent solution in terms of wound sepsis and secondary bacteraemia in a study of burn patients. It is also claimed that the presence of proteins in wound exudates has no effect on its mode of action.[23]

Actisorb silver 220

Originally known as ActisorbPlusActisorb Silver 220 (manufactured by Johnson & Johnson Medical) is a combination of activated charcoal cloth impregnated with silver and enclosed within a porous nylon sleeve. The dressing attracts bacteria to the charcoal cloth, where they are exposed to the silver's antibacterial activity. Actisorb Silver 220 was found to be the most effective for odour control, reduced frequency of dressing changes, and overall improvement in ulcer condition in patients with leg ulcers when compared to a charcoal cloth dressing and a chlorhexidine dressing.[24]

Silvrstat wound dressing gel

SilvrSTAT is a water-based gel used to manage moist wounds. SilvrSTAT contains silver, which may aid in the inhibition of microorganism growth within the dressing. SilvrSTAT Antibacterial Wound Dressing Gel is a water-based gel wound dressing for over-the-counter use in the topical management of: first and second degree burns, lacerations, abrasions, minor cuts, skin irritations, and wounds such as stasis ulcers, pressure ulcers, diabetic ulcers, skin tears, surgical incision sites, device insertion site wounds, graft sites, and donor sites. SilvrSTAT Antibacterial Wound Dressing Gel contains silver, which has been shown in laboratory tests to inhibit the growth of microorganisms such as Staphylococcus aureus, Pseudomonas aeruginosa, Escherichia coli, antibiotic-resistant bacteria, MRSA, and VRE, as well as other pathogens.[25]

SILVER NANOPARTICLES

Progress in the field of nanotechnology helped us to come up with a new form of silver delivery system and have markedly improved the biologic value of silver. Silver nanoparticles have no local or systemic toxicity and do not impair healing.[26] Nano-silver particles are generally smaller than 100 nm and comprise around 20-15,000 silver molecules.[12] Smaller the particle size of silver, greater contact with wound surface area, thus increasing bioactivity and silver solubility. The recently developed nano based formulations seem to be as efficacious as conventional silver sulfadiazine or silver nitrate gels presently on the market, and in the absence of their major side effects. The newly developed gel is composed of nanoparticles, each with 1/50,000th the width of a human hair, and it contains 30 times less silver than silver sulfadiazine. It appears to be more effective than traditional silver sulfadiazine.[27]

To produce nanosilver, metallic silver has been designed into ultrafine particles by a few strategies; include sparkle releasing, electrochemical reduction, solution irradiation and cryo-chemical synthesis.[12] Moreover, nanostructures can be created as cylinders, wires, multifaceted or films. At the nano-scale, the silver particles exhibit deviating physico-chemical properties (like pH subordinate dividing to strong and disintegrated particulate matters) and biological activities compared with the normal metal.[28] This is because of the greater surface region per mass, permitting a bigger measure of molecules to connect with their environmental elements. Because of the properties of silver at the nanoscale, nanosilver in these days is utilized in an expanding number of consumer and clinical items. Since silver is a soft white lustrous component, a significant utilization of silver nanoparticles is to give an item a silver completion. In any case, the strong antimicrobial activity is the significant bearing for advancement of nano-silver items. Examples are food packaging materials and food supplements, odour resistant textiles, hardware, domestic devices, beauty care products and clinical advice, water sanitizers and room splashes.

METHODS FOR SYNTHESIS OF SILVER NANOPARTICLES

Physical approaches:

Most significant actual methodologies incorporate evaporation condensation and laser ablation. Different metal nanoparticles like silver, gold, lead sulfide, cadmium sulfide, and fullerene have recently been incorporated utilizing the evaporation condensation strategy. It was shown that silver nanoparticles could be synthesized through a little earthenware radiator with a nearby warming source.[29] The evaporated vapor can cool at an appropriate quick rate, in light of the fact that the temperature angle near the warmer surface is extremely steep in examination with that of a cylinder heater. This makes possible the arrangement of small nanoparticles in high concentration. This physical method can be valuable as a nanoparticle generator for long term tests for inhalation toxicity studies, and as a calibration device for nanoparticle estimation hardware. Silver nanoparticles could be synthesized by laser ablation of metallic bulk materials in solution.[30] One significant benefit of laser ablation procedure contrasted with different strategies for creation of metal colloids is the absence of compound reagents in solution. Subsequently, unadulterated and uncontaminated metal colloids for additional applications can be prepared by this method.[31]

Chemical approaches

The most widely recognized methodology for synthesis of silver nanoparticles is chemical reduction by natural and inorganic reducing agents. As a rule, various reducing agents, for example, sodium citrate, ascorbate, sodium borohydride (NaBH4), basic hydrogen, polyol process, Tollens reagent, N, N-dimethylformamide (DMF), and poly (ethylene glycol)- block copolymers are utilized for reduction of silver particles (Ag+) in aqueous or nonaqueous solutions. The previously mentioned reducing agents reduce silver particles (Ag+) and lead to the development of metallic silver (Ag0), which is followed by agglomeration into oligomeric groups. These groups at last lead to development of metallic colloidal silver particles.[32,33] Utilize protective agents to settle dispersive nanoparticles throughout metal nanoparticle preparation, and secure the nanoparticles that can be retained on or bind onto nanoparticle surfaces, avoiding their agglomeration.[34]

Biological approaches

Lately, the development of effective green science techniques utilizing natural reducing, capping, and stabilizing agents to prepare silver nanoparticles with desired morphology and size have turned into a significant focus point of researchers. Biological methods can be utilized to synthesize silver nanoparticles without the utilization of any harsh, poisonous and costly synthetic substances.[35,36] The bioreduction of metal particles by mixing of biomolecules found in the concentrates of specific life forms (e.g., catalysts/proteins, amino acids, polysaccharides, and nutrients) is naturally harmless, yet chemically complicated. Many investigations have reported successful synthesis of silver nanoparticles utilizing life forms (microorganisms and biological systems).[37,38]

MEDICAL APPLICATIONS OF SILVER NANOPARTICLES

Antimicrobial

Till date many researchers have proved the effectiveness of AgNPs inhibiting against various pathogenic bacteria, fungi and viruses, including *E. coli*, *S. aureus*, *P. aeruginosa*, *Providencia*, *Serratia*, dermatophyte, HIV-1, etc.[39] The mechanism behind the antimicrobial activity of silver particles is firmly identified with their interaction with thiol (Sulfahydryl) bunch.[3,24] Amino acids and different mixtures containing thiol groups, for example, cysteine and sodium thioglycolate neutralized the action of silver against microscopic organisms.[40] Conversely, Amino acids containing disulphide bonds, non – sulfur containing amino acids, and sulfur containing mixtures, for example, cystathione, cysteic acid, L-methionine, taurine, sodium bisulfate, were all incapable to neutralize.[24] Silver particles cause the release of potassium ions from the microbes; in this way bacterial plasma or their cytoplasmic layer which is related with numerous enzymes is a significant objective for silver particles.[41]

Sondi and Salopek-Sondi investigated the antimicrobial properties of AgNP in relation to *E. coli* (strain B) growth on Luria-Bertani (LB) agar plates. The results show that inhibition was affected by AgNP concentration and the number of cells used in the tests at the start. Bacterial growth was completely inhibited by silver nanoparticles at concentrations of 50–60 g cm3. However, bacterial growth was completely inhibited at a concentration of 20 g cm3.[42] Kim et al. investigated the antimicrobial activities of AgNP against yeast, *E. coli*, and *S. aureus* in 2007. These microorganisms were cultured on Mueller Hinton agar (MHA) plates with varying concentrations of AgNP (0.2 to 33 nM). They discovered that the minimal inhibitory concentration (MIC) of AgNP for *E. coli* was 3.3nM, while yeast had a MIC of 6.6nM. Surprisingly, AgNP's growth-inhibitory effects on *S. aureus* were observed at high concentrations (MIC > 33 nM).[43]

The mechanism of antimicrobial activity of AgNPs is it can accumulate in the cell wall of bacteria, releasing the free radicals from AgNPs which forms “pits” in the bacterial cell, leading to cell death.[44] Other antimicrobial mechanism of AgNPs are destruction of the bacterial membrane and leaking cellular contents; generation of ROS and disabling the respiratory chains, destruction of the DNA structure and blockage of DNA replication, inactivation and denaturation of enzymes and proteins.[39] Due to these various mechanisms, AgNPs show broad-spectrum and effective antibacterial properties.

Antifungal

Long-term, repeated administration of standard antifungal drugs increases fungal resistance, particularly in Candida species. As a result, new antifungal agents are constantly being researched. AgNPs have demonstrated numerous antifungal properties against common fungi, implying that they have the potential to be an effective antifungal agent. A recent study discovered that an AgNP-coated reverse osmosis membrane, which is used in water purification systems, has good antifungal activity against *Candida tropicalis, Candida krusei, Candida glabrata*, and *Candida albicans.* Esteban-Tejeda et al. created a soda-lime glass with an inert matrix containing AgNPs with an average size of 20 nm that exhibits enhanced biocidal activity. Monodisperse Nano-Ag sepiolitefibres inhibited Issatchenkiaorientalis growth significantly. AgNPs were found to have good antifungal activity against *Aspergillus niger* and a MIC of 25 g/mL against *Candida albicans*. Biologically synthesized AgNPs outperformed fluconazole in antifungal activity against *Phomaglomerata, Phomaherbarum, Fusarium semitectum, Trichoderma sp.,* and *Candida albicans*. When compared to conventional antifungal agents, AgNPs stabilized by sodium dodecyl sulphate demonstrated enhanced antifungal activity against *Candida albicans.*[44]

Anti-Inflammatory Properties

Despite billions of dollars spent on immunological research, few effective anti-inflammatory drugs have been developed. As a result, there is an urgent need for new drugs, as many inflammatory diseases are not sufficiently responsive to current medications. AgNPs have recently been shown to be effective anti-inflammatory agents, according to growing evidence. The anti-inflammatory properties of AgNPs were first investigated in a porcine model of contact dermatitis using AgNP-coated, 0.5 percent silver nitrate ($AgNO_3$), or saline wound dressings. Erythema, edema, and histological data showed that AgNP-treated pigs had near-normal skin after 72 hours, whereas other treatment groups remained inflamed. Anti-inflammatory activity in rats was reported by Bhol and Schechter. The colonic inflammation in rats treated intra-colonally with 4 mg/kg or orally with 40 mg/kg nanocrystalline silver (NPI 32101) was significantly reduced. Mice given AgNPs experienced rapid healing and improved cosmetic appearance in a dose-dependent manner. Furthermore, AgNPs demonstrated significant antimicrobial properties, wound inflammation reduction, and modulation of fibrogenic cytokines.[45,46]

Antiviral Properties

AgNPs also show good antiviral activity against hepatitis B virus (HBV), human parainfluenza virus (HPIV), herpes simplex virus (HSV) and influenza A (H1N1) virus.[39] The exact mechanism of antiviral action of Ag NPs is still not clearly understood. One possibility is due to the lower particle size, Ag NPs may act on the surface of the virus inhibiting the replication of viral cells.[47] Silver nanoparticles (average diameter 10 nm, diameter 5-20 nm) inhibit HIV-1 virus replication. When compared to silver nanoparticles, gold nanoparticles (average diameter 10 nm) demonstrated relatively low anti-HIV-1 activity (6-20%) (98%). Silver nanoparticles have been shown to have size-dependent antiviral activity against the HIV-1 virus. The interaction of silver nanoparticles with HIV-1 was limited to a size range of 1-10 nm.[48] AgNPs can bind to the glycoprotein knobs and inhibit the reverse transcriptase (RT) of HIV-1 and interact with the virus in size- and dose-dependent manner.[39] Gaikwad et al. indicate that Ag NPs of size 7–20 nm has antiviral effects against types 1/2 herpes simplex virus (HSV) and type-3 human parainfluenza virus. The reason behind it may be the agglomeration of nanoparticle which may facilitate the interaction or internalization of virus particle within host cells, increasing the number of observed PFU. Therefore, particle size of Ag NPs seems very important for antiviral properties of Ag NPs.[47]

Anti Cancer

Cancer is a serious disease that affects people all over the world and is a leading cause of mortality. According to the WHO, this fatal disease claimed the lives of 9.6 million people worldwide in 2018.[49] The possibility of aberrant proliferation exists in any tissue or cell in the body, which is why cancer is so diverse. Radiation therapy, surgery, chemotherapy, hormone therapy, bone marrow transplantation, targeted therapy, cryoablation, and other treatment options are available for various types of malignancies. In the recent few decades, cancer treatment supported by nanomaterials has arisen with effective therapeutic advantages, catching the attention and enthusiasm of researchers to develop novel nanotechnology-based treatments for a variety of tumours.[50]

AgNPs have been observed to exhibit good anticancer activities in breast cancer, cervical cancer, colon cancer, ovarian cancer, pancreatic ductal adenocarcinoma, lung cancer, hepatocellular carcinoma, melanoma, osteosarcoma, etc. Various mechanisms can be used to explain the anticancer effects of silver nanoparticles. Because cancer cells exhibit the enhanced permeability and retention effect (EPR), which results in the entry and accumulation of more and more silver nanoparticles, cancer cells are killed or their uncontrolled division is hampered. AgNPs also work by downregulating and upregulating signalling physiological pathways, resulting in early apoptosis or slowing the rate at which tumour cells divide.[50] Silver nanoparticles serve as carriers for therapeutic anticancer payloads (drugs), resulting in higher anticancer drug efficiency and potency, as well as aiding targeted anticancer drug delivery to reduce the harmful effects of chemotherapy on normal healthy tissues.[51,52]

Shejawal et al. produced silver nanoparticles with 1 percent aqueous extract of the Carotenoid phytopigment "Lycopene" derived from tomato, extracted in benzene, and found their anticancer effect in a recently published study. The Lycopene AgNPs were evaluated on Hella, COLO320DM, and H29 cancer cell lines, and the percent inhibition was reported as 40.9 0.69, 41.41 0.41, and 35.43 0.67 against Hella, COLO320DM, and H29 cancer cell lines, respectively, using the MTT assay.[53]

Silver nanoparticles can be an innovative approach for cancer treatment as carriers of anticancer drugs, which act a transport system providing many advantages over free anticancer substances.[61] Rozalen et al 2020, synthesized AgNPs coupled with methotrexate (AgNPs-

MTX) through chemical synthesis method using sodium borohydride and citrate as reducing agents. From the release study it was observed that AgNPs-MTX showed delayed release of drug (75–80% release in 5 h) as compared to the free MTX (80% of release in 100 min). The anticancer activity of the free drug MTX, AgNPs, and AgNPs-MTX, was evaluated against colorectal cancer cell line (HTC-116) and lung carcinoma cell line (A-549). A synergistic effect between AgNPs and methotrexate (AgNPs-MTX 400) on the HTC-116 cell line (IC_{50} for free MTX = 70 µg/mL, IC_{50} for AgNPs = 63 µg/mL and IC_{50} for AgNPs-MTX 400= 23 µg/mL, at 48 h) was observed, which means that a lower dose of AgNPs-MTX was required compared to the free methotrexate for the same anticancer effect.[62]

TOXICITY OF AgNPs

Silver nanoparticles' unique physical and chemical properties make them excellent candidates for a variety of day-to-day activities, and their antimicrobial and anti-inflammatory properties make them excellent candidates for a variety of medical applications. However, some studies and reports claim that AgNPs can have negative effects on both humans and the environment. Tons of silver are estimated to be released into the environment from industrial wastes, and it is thought that the toxicity of silver in the environment is primarily due to free silver ions in the aqueous phase. The negative effects of these free silver ions on humans and all living beings include permanent bluish-gray discoloration of the skin (argyria) or the eyes (argyrosis), and exposure to soluble silver compounds may result in toxic effects such as liver and kidney damage; eye, skin, respiratory, and intestinal tract irritations; and abnormal changes in blood cells.[54] AgNPs has grown in popularity since the beginning of the twenty-first century, and it is now used in almost every field, most notably medicine. However, there have been reports that AgNPs cannot distinguish between different strains of bacteria and thus destroys beneficial microbes to the environment.[55] AgNPs has also been linked to severe toxic effects on the male reproductive system. According to research, it can cross the blood-testis barrier and end up in the testes, where it can harm sperm cells. Even commercially available silver-based dressings have been shown to have cytotoxic effects on various experimental models.[56] Silver is also said to be released when nanoparticles are stored for a long period of time, according to research. As a result, AgNP is more toxic than new one. Silver ions can interact with the gills of fish and inhibit basolateral Na+-K+-ATPase activity, which can inhibit osmoregulation in the fish.[57] Though these studies tend to suggest that AgNPs can cause toxicity in living beings, it should be noted that the studies on AgNPs toxicity were conducted in *in vitro* conditions that are vastly different from *in vivo* conditions, and at extremely high concentrations of AgNP particles. As a result, more research is needed to assess the toxicity of AgNPs *in vivo* before reaching a conclusion on its toxicity.

CONCLUSION AND FUTURE PERSPECTIVES

From thousands of years silver and its formulations have been used in different forms and treatments traditionally. But due to these traditional formulations having a number of flaws, including toxicity and bacterial resistance, researchers have explored nanosilver (AgNP). Over decades AgNP have been studied extensively due to their broad prospects in medical applications like antimicrobial, antibacterial, antiviral, anti-inflammatory, wound-healing and anticancer properties. Because of their nanoscale size, AgNPs have unique chemical, physical, electronic, optical and catalytic properties, so now entered the fray to overcome the shortcomings of traditional silver-based therapies. AgNPs can also be used as a clinical potential in the field of biosensing and imaging due to their unique optical properties, an additive or adjuvant in bone scaffolds, vaccines, dental materials, antidiabetic agent.[39] Furthermore, AgNPs can be combined with a variety of other materials to create potent formulations such as nanocomposites, coatings, and scaffolds, resulting in synergistic effects that result in enhanced activity.

Beyond medicine, nanotechnology has opened up a plethora of new and exciting opportunities. Although AgNPs are well known for their antibacterial activity, research over the years has revealed that these nanomaterials have additional health-related benefits. They are used as diagnostic, drug delivery, sensitizing, and therapeutic agents in medical applications.[58] Although safer and greener methods of producing AgNPs with lower toxic effects have been reported, there may be a higher risk of exposure when AgNPs are produced in larger quantities. These products are non-biodegradable and are most likely to be ingested or absorbed through the skin. These elements raise numerous concerns about human health and the environment.[59] AgNPs, as previously stated, can travel through the body, accumulate in various organs, and cause serious harm. New fabrication methods are constantly being developed to help reduce the bystander effects of AgNPs.[60] Disposal strategies must be investigated in order to reduce their environmental impact. The exciting properties demonstrated by green-synthesized AgNP-based systems demonstrate that less expensive and more user-friendly treatments can be developed to address the current concern. The development of reproducible manufacturing protocols is a major challenge for green AgNP synthesis methods and, by extension, the formulation of AgNP-based wound treatments. Variations in phytochemicals found in plant extracts, for example, can have a significant impact on the consistency of nanomaterial synthesis. Another difficult task is identifying all of the phytochemicals in AgNPs. While these green synthesis methods ostensibly produce more bio-friendly nanomaterials, it is critical to investigate the environmental and potential toxic effects of AgNP-based systems. These issues must be resolved before these treatments can be approved by regulators.

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