Folia Biologica et Oecologica 17: 14–31 (2021)

Acta Universitatis Lodziensis

Silver nanoparticles – possible applications and threats

BIOOPEN 2021 – POST-CONFERENCE ARTICLE

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ABSTRACT

Silver is known for its biocidal properties. This metal has been used for decorations and food preservation since ancient times and has also been used in medicine. Silver foil has been used to cover wounds and burns. In addition, silver solutions were created to help fight the microorganisms responsible for causing infections, which helped the wound healing process. Currently, to increase and optimize the properties of silver, it is used on a nanometric scale. Nanosilver, due to its expanded spectrum of properties, is used in many economic sectors, including in the production of disinfectants and food films, as well as in animal farms. Nanoparticles are also the basis of nanomedicine action. Creating new drug complexes with nanosilver and modifying the medical materials used in implantology or dentistry allow the lives of many people to be saved every day. In addition, nanosilver particles are commonly used as a specific disinfectant in the production of hospital materials: dressings, bandages, surgical masks, hospital clothing and shoes, and equipment. With the growing use of nanosilver, there are concerns about its harmful effects on living organisms, because not all its mechanisms of action are known. As is well known, the dose determines the toxicity of a given substance; the case is similar for nanosilver. However, is the dose providing antibacterial and antifungal properties non-toxic to animals and humans? This review presents a summary of the scientific research showing the scope of nanosilver activity and the resulting threats.

KEYWORDS: nanoparticles, nanosilver, colloidal silver, nanomedicine, nanomaterials

Introduction

Medicine is one of the oldest and most extensive sciences, which has made enormous progress over the centuries. Development and modernization of all research and equipment as well as the progress of knowledge about all fields of medicine and methods and their practical use allow the lives of many people to be saved every day. A new multidisciplinary field of nanotechnology has found its application in medicine and pharmacy. It is a relatively new scientific discipline,

DOI: https://doi.org/10.18778/1730-2366.16.10

the intensive development of which is observed in the 21st century (Rzeszutek *et al*. 2014). The precise application of nanotechnology in medicine is dealt with by nanomedicine. Its achievements have potential applications in research areas such as understanding biological processes at the molecular and cellular level, drug delivery, medical imaging, *in vitro* diagnostics, *in vivo* diagnostics, tissue regeneration, structural implants, sensory aids and surgical aids (Eaton 2007). Its activity is based on nanoparticles and nanomaterials (Song *et al*. 2019).

General characteristics of nanoparticles and nanomaterials

Nanoparticles (NP) are defined as particles of matter with a size not greater than 100 nm in each plane. This is a size comparable to that of enzymes or receptors whose size is within 5 nm. On the other hand, nanomaterials are structures in which at least one dimension is not larger than 100 nm. These include zero-dimensional structures such as quantum dots, one-dimensional structures, e.g., carbon tubes or fullerenes, and more complex structures such as dendrimers (Espinoza *et al*. 2020). Due to their nanometric size, NP have specific chemical, physical and biological properties (Sahoo *et al*. 2007). In addition to the physico-chemical properties typical of macroparticles, they gain additional unique features. They are distinguished by a high correlation of the number of surface atoms to the number of atoms in the particle core and a different behaviour under the influence of external forces (Sahoo *et al*. 2007). The unique properties obtained thanks to nanometric dimensions include disturbance of the wave function of electrons, resulting in a change of thermodynamic stability; changes in electrical, thermal and magnetic conductivity; reorganization of optical properties; increased reactivity, adsorption properties and antimicrobial activity; and agglomeration and high specific surface area (Panigrahi 2004; Su and Kang 2020).

Silver nanoparticles – properties

Scientists in nanotechnology focus their research on, among other things, metal NP. Among them, silver (Ag) is very popular. As the data show, this metal has been used since the earliest history of humankind. Silver was first used to make ornaments, but over time the spectrum of its properties has been used in everyday life for food preservation as well as in medicine. Silver foil has been used to cover wounds and burns, and Ag solutions were created to help fight the microorganisms responsible for causing infections. Currently, silver nanoparticles (NPAg) are used in many fields of science (Chen *et al*. 2009). It is also possible to modify various materials and raw materials with NPAg. This may consist of depositing NPAg in carriers or coating other surfaces with them. Thanks to such modifications, the newly created materials will acquire antifungal, antibacterial, virucidal, anti-static and impregnating properties (Xu *et al*. 2006). NPAg are observed to have from 20–15,000 element atoms in their structure. Their biocidal effect is possible due to the influence of silver on the damage to cell membranes, protein denaturation, generation of reactive oxygen species, inhibition of DNA replication and disruption of the synthesis of certain proteins (Szymański *et al*. 2012; Yamanaka *et al*. 2005). The bactericidal activity of NPAg depends on the composition of the bacterial cell wall. The presence of peptidoglycan in the cell wall reduces the sensitivity of bacteria to silver, so Gram-negative bacteria are more susceptible to the toxic effects of NP than Gram-positive bacteria (Kim *et al*. 2007). Moreover, studies have been conducted which show that the formation of connections of NPAg with antibacterial drugs such as amoxicillin, penicillin G or clindamycin enhances their action (Shahverdi *et al*. 2007).

Applications of nanosilver

Disinfectants

Colloidal silver has a wide range of potential applications due to its antimicrobial properties. Despite the contemporary improvements in hygiene in biomedicine, education, the surrounding environment and industry, the problem of public health in the world is becoming important. In order to overcome various strategies, infections have been reduced by using various disinfectants (Jones *et al*. 2008). Disinfectants are chemicals that are applied to a surface to kill or inhibit microorganisms. They are useful in our daily life as they kill especially microorganisms without endangering human health. Moreover, they are abundant in quantity, efficient, cheap and non-toxic (Jones *et al*. 2008). Various chemical compounds such as alcohols, quaternary ammonium cations, aldehydes, oxidizing agents such as sodium hypochlorite, hydrogen peroxides, iodine, etc. have been successfully introduced as disinfectants; however, due to various limitations such as harmfulness, corrosivity and bacterial resistance these compounds are no longer widely used. Agents containing colloidal silver can be used for the sterilization and disinfection of both production rooms, e.g. poultry processing plants, and medical rooms. A number of tests were carried out to determine whether nanosilver can prevent the production of odorous pollutants during incubation, and thus reduce the emission of harmful gases in breeding and farm rooms. The results showed that the use of nanosilver preparations to disinfect eggs and brooders reduced microbial contamination. The bactericidal and fungicidal effectiveness of the preparation used was comparable to that of UV radiation, and its effectiveness increased during incubation. Positive results were obtained in terms of the level of organic gaseous pollutants, which decreased by 86% after the use of nanosilver preparations (Banach *et al*. 2016; Chmielowiec-Korzeniowska *et al*. 2007).

Medical rooms and hospital rooms are particularly exposed to the presence of bacteria; in order to prevent the infection of patients and staff, disinfection with nanosilver is used. One of the main routes of transmission is through contact with contaminated surfaces where nosocomial pathogens form settled communities known as biofilms. During the formation of biofilms, these pathogens are extremely resistant to antibiotics and standard cleaning procedures. Therefore, in order to eliminate the formation of biofilms on these surfaces, intense efforts have been made, especially in recent years, to develop new antimicrobial surfaces containing silver or nanosilver that can be used to prevent biofilm formation. Disinfectants in use today are less effective against certain strains of bacteria. Microorganisms such as *Staphylococcus aureus* and *Pseudomonas aeruginosa*, which are found in hospital rooms, cause chronic infections by becoming resistant to disinfectants (Khalid *et al*. 2020; McCarlie *et al*. 2020). Examples of the use of NPAg as disinfectants are shown in Table 1.

Medical equipment

Currently, colloidal silver is widely used as a disinfectant in the production of hospital materials: dressings, bandages, surgical masks, hospital clothes and shoes, and medical equipment (Leaper

Table 1. Examples of use of NPAg as disinfectants (Alonso *et al*. 2013; Close *et al*. 2016; Deshmukh *et al*. 2018; Ko *et al*. 2014; Vasile *et al*. 2017).

Material	Disinfecting activity
Ag/TiO_2	Antibacterial activity
NPAg/SiO_2	Fast and synergistic antimicrobial activity in air filters
Ag-co-NP	Water purification
NPAg/chitosan	Wound healing
PLA/ZnO/Cu/Ag bionanocomposites	Prolonged freshness of food products

2006). NPAg are effectively used in catheters for better antimicrobial activity and zero thrombogenicity. Cardiovascular stents and catheters require coating with antimicrobial agents such as NPAg to prevent thrombosis. NP have prolonged activity, greater bactericidal and bacteriostatic properties, and lower toxicity *in vivo* (Chaloupka *et al*. 2010).

The first cardiovascular medical device to use silver in the clinic was a silver-coated silicone prosthetic heart valve that was designed to prevent bacterial infection on the silicone valve and reduce the inflammatory response (Grunkemeier *et al*. 2006). Metallic silver can cause hypersensitivity, inhibit the normal function of fibroblasts and lead to pericranial leakage in patients (Jamieson *et al*. 2009). NPAg are safe and non-toxic in medical devices, unlike metallic silver. Therefore, Andara *et al*. (2006) synthesized a new nanocomposite with NPAg and diamond-like carbon as the surface coating of heart valves and stents, and found that the surface of the nanocomposite exhibited antithrombotic and antibacterial properties. In addition, Ghanbari *et al*. (2009) and Fu *et al*. (2006) also constructed antimicrobial multilayer films containing NPAg and investigated their *in vitro* antibacterial, mechanical and haemodynamic properties for use in coating cardiovascular implants.

Much research has been done to investigate NPAg as antimicrobial materials for coating catheters, including central venous catheters and neurosurgical catheters. Silverline (Spiegelberg GmbH and Co. KG, Hamburg, Germany) and ON-Q Silver Soaker™ (I-Flow Corporation, California, USA) are two commercially available medical catheters containing NPAg to prevent infection (Chaloupka *et al*. 2010). Medical catheters are prone to bacterial infections that can spread rapidly into the wound and its surroundings and lead to serious complications. Andara *et al*. (2006) found that nanosilver-coated plastic catheter tubes can inhibit bacterial growth *in vitro* for at least 72 hours, without significant toxicity, in an animal model.

In addition, the bone cement used in surgery is doped with NPAg with poly(methyl methacrylate) (PMMA) to reduce the risk of bacterial infections. The rate of infection has been shown to be lower with Ag and shows no cytotoxicity in murine fibroblasts or human osteoblasts, indicating good biocompatibility (Jiranek *et al*. 2006). Alt *et al*. (2004) assessed the antibacterial activity of ordinary PMMA bone cement loaded with various concentrations of NPAg *in vitro* and found that bone cement loaded with 1% nanosilver completely inhibited the multiplication of *Staphylococcus epidermidis* and *S. aureus* without a significant difference between nanosilver bone cement and the non-toxic control group and qualitative cytotoxicity tests. NPAg was also added to ultra-high molecular weight polyethylene to produce inserts for total joint component replacement, and NPAg was found to drastically reduce polymer consumption (Morley *et al*. 2007). NPAg are also combined with materials such as mineral compounds or polymers, and used in implantology. This combination improves biocidal efficacy by counteracting particle aggregation, which is one of the more serious problems in the use of implants (Magalhães *et al*. 2012). In dental implantology, titanium plates are combined with nanosilver. Thanks to this application, bacteria such as *Porphyromonas gingivalis* and *Actinobacillus actinomycetemcomitans*, which cause periodontal disease, do not live on implants (Liao *et al*. 2010). In dentistry, preparations with the addition of nanosilver are increasingly used to eliminate bacterial biota. Currently, they are most often used in endodontics. There are also toothpastes on the market that contain NPAg in order to better combat oral microbiota (Pokrowiecki and Mielczarek 2012). NPAg are also used in dental appliances. It has been shown that a resin composite incorporated into materials containing NPAg exerts a long-lasting inhibitory effect against *Streptococcus mutans* (Faiyaz *et al*. 2019; Rabani *et al*. 2019; Yoshida *et al*. 1999). It has also been shown that a resin composite containing fillers implanted with silver ions releases antimicrobial silver ions on oral streptococci (Corrêa *et al*. 2015). Moreover, Magalhães *et al*. (2012) showed that the inclusion of NPAg in endodontic filling materials provides much better antibacterial activity against *Streptococcus milleri*, *Staphylococcus aureus* and *Enterococcus faecalis*. NPAg in dental adhesives is also very effective against streptococci without affecting the adhesives' mechanical properties, thus enabling their use in orthodontic procedures (Ahn *et al*. 2009; Gitipour *et al*. 2017).

Silver nanoparticle components with drugs and wound healing

The demand for drug delivery systems with a novel mode of action in order to improve the solubility and stability of potent drugs and to minimize their toxicity is a major impetus for research into drug delivery systems (Chirra *et al*. 2016; Ghosh *et al*. 2008; Mandal 2017). Features such as prolonged drug action or the release time of the active substance are also improved. Ligands can be attached to the surface of NP, allowing the distribution of drugs to precisely defined places in the biological system (Wojnicki *et al*. 2019).

The incorporation of NPAg into nucleic acid production is an ideal RNA-based therapy system. Lee *et al*. (2007) developed conjugates suitable for spherical nucleic acid colloids using NPAg functionalized with an oligonucleotide. These tricyclic disulphide groups in oligonucleotides improve particle stability and are effective in tolerating heat, ageing and oxidative degradation. The NP potential of the molecular entity to detect pathophysiological defects in malignant cells and tumours therapeutic gene load was significantly higher when it formed a drug (doxorubicin – DOX) conjugate with graphene oxide (GO). It was observed that the uptake of GO-Ag-DOX by tumour cells was 8.4 times higher than in normal cells. This GO-Ag-DOX combination not only selectively released the drug but also helped in photothermal ablation of the tumour after near-infrared stimulation (Shi *et al*. 2014). The creation of a composite of NPAg and drug resulted in increased affinity for malignant cells compared to normal cells, significantly reduced side effects and increased the chemophotothermal potential of the therapeutic agents.

Another study on the development of NPAg-drug complexes was carried out by Chen *et al*. (2013). They developed a hybrid nanocomposite Fe_3O_4-C-Ag, the combination of which with a cytostatic, after stimulation with infrared light, resulted in increased apoptosis of neoplastic cells. Wang *et al*. (2012) developed silver nanocarriers targeting a tumour bearing the folate receptor by functionalizing the surface of NPAg with folic acid. The presence of folic acid provided NPAg with an exceptionally high affinity for tumour receptors. Nanocarrier therapy resulted in a slow release of drug (DOX) into the tumour cytoplasm and induced apoptosis. They developed the biocompatible Ag-SiO_2-mTiO_2 triplex, an excellent example of using the NP endocytosis mechanism to increase cellular uptake and consistent delivery of anticancer drugs. Cytotoxicity studies with these nanocolloids against cellular breast adenocarcinoma have shown their biocompatibility. Thanks to the use of the Ag nanocarrier, the amount of mesoporous silica increased significantly, which made it possible to deliver more drug to cancer cells. Successful *in vitro* internalization and the potential to induce apoptosis of lung adenocarcinoma cells compared to normal cells demonstrated the biocompatibility of the nanocomposite, raising the prospect of using it as a vehicle for the treatment of lung cancer (Singh *et al*. 2013).

The combination of allicin and NPAg has been tested for skin infections due to methicillin-resistant *Staphylococcus aureus* (Sharifi-Rad *et al*.). The study showed that the minimum inhibitory concentration and minimum bacterial concentration for this drug combination are lower and therefore useful in treating the skin to avoid skin infections. Silver ions contained in dressings are present at a maximum equal concentration of 1 ppm. The Ag^+ ion concentration is related to the presence of chloride ions in the wound. Silver ions react with chloride ions to form an insoluble AgCl salt, which limits the access of Ag^+ ions to the deeper layers of the wound. *In vitro* studies show that a concentration of 1 ppm is sufficient to obtain a bactericidal effect (Ip *et al*. 2006).

The participation of nanosilver in the wound healing process is related to the mechanism of local production of hydrogen peroxide and other reactive oxygen species (ROS). They are mainly produced by active NADPH oxidase in inflammatory cells. Ag^+ ions inhibit the action of serine proteases, thanks to which they have anti-inflammatory properties. Further research has proved the anti-inflammatory properties of NPAg. In a porcine model of contaminated wounds, NPAg have been shown to inhibit the activity of matrix metalloproteinases, increasing the apoptosis of inflammatory cells, thereby reducing inflammation (Chambers *et al*. 2002). Laboratory studies in mice have also provided information about the anti-inflammatory properties of NPAg. Silver ions inhibit the expression of TNF-α and IL-12 cytokines, leading to the death of inflammatory cells. However, when used at an inappropriate concentration, NPAg show anti-proliferative activity (Bhol *et al*. 2004). Therefore, it is important to determine the appropriate dose of NPAg in various types of dressings or other medical materials applied directly to wounds. However, Ag^+ ions used in the nano form can unexpectedly interact with biological systems, showing high reactivity and toxicity. The distinguishing feature of the use of nano forms is the release of 100 times more Ag+ ions than when using macro-size NPAg (Asharani *et al*. 2009).

Numerous *in vivo* studies have proven the greater antimicrobial efficacy of dressings using NPAg and not bulk silver. The penetration of xenobiotics and NP through broken skin is much easier than through non-traumatized skin. Therefore, new dressing formulas containing silver preparations began to be developed. Studies have shown that the Ag^+ ions released are not absorbed systemically. In the case of skin burn treatment with 0.5% silver nitrate, Ag^+ ions were localized in urine and blood at a maximum concentration of 120 μg/L. It was then found that silver was deposited in the tissues, leading to argyria. Similar data were provided by a report on the condition of a patient with extensive burns to the body treated with nanosilver dressings – the boy had symptoms of argyria and the plasma silver concentration was 107 μg/kg body weight (Trop *et al*. 2006).

Food films

In recent years, there has been a growing need in the food industry to develop antimicrobial films for food packaging, bottles and containers to avoid microbial spoilage of food and to extend or preserve the shelf life of food products. Food packaging is used to protect food, vegetables and fruit against environmental pollution or bacteria, to ensure product quality and consumer safety. Oxidation and microbial invasion are the main factors causing the deterioration of product quality during production, transport and storage (Han *et al*. 2018). Currently, NPAg, silver nitrate and nanoclay are widely used in the food packaging industry to counter microbial contamination and improve barrier properties, thus extending the shelf life and freshness of packaged food and beverages (Bumbudsanpharoke *et al*. 2015; Huang *et al*. 2018; Mousavi *et al*. 2015; Tavakoli *et al*. 2017).

Colloidal silver and silver nitrate have been used in the United States for over 100 years (Nowack *et al*. 2011). Martınez-Abad *et al*. (2012) incorporated silver nitrate (0.1–10%) into ethylene-vinyl alcohol (EVOH) films and tested their antimicrobial properties against *Listeria monocytogenes* and *Salmonella* spp. They used a bacterial challenge test (Russel 2003) to evaluate the antimicrobial resistance of EVOH composite films to low-protein food samples (lettuce, apple peel and eggshell) and high-protein food samples (chicken, marinated pork and cheese) contaminated with bacterial strains. The results showed a representative number of viable *L. monocytogenes* bacteria on apple skins treated with EVOH composite membranes containing 0.1, 1 and 10 wt% $AgNO_3$ (Ag^+ ions) but in the samples coated with the composite film containing 10% $AgNO_3$ or the control ($AgNO_3$ aqueous solution), a reduction in bacterial populations was demonstrated.

In general, NPAg show a beneficial effect on the silver nitrate salt in food packaging films, since NPAg allows sustained release of Ag^+ ions due to the size-dependent Ag^+/Ag^0 ratio on their surface (Chaloupka *et al*. 2010). In this regard, low NPAg charges are added to the polymer films to release enough Ag^+ ions to ensure effective bactericidal activity (Lopez-Carballo *et al*. 2013).

Tavakoli *et al*. (2017) produced polyethylene (PE) films with 1%, 2% and 3% NPAg using an extrusion process. They proved that PE/NPAg packaging films reduce mould and *E. coli* attack on walnuts, hazelnuts, almonds and pistachios for longer periods, thus increasing shelf life and preserving nut quality. The widespread use of polymer/NPAg packaging films in the food industry has raised concerns about the migration of NPAg from films or food containers. In this context, Huang *et al*. (2011) used commercial PE/nanosilver film bags for four kinds of food-simulating solutions, representing water, acid, alcohol and fatty foods, at 25–50 °C for 3 to 15 days, respectively. Based on spectroscopic measurements of atomic absorption, they observed the migration of Ag^0 from commercial PE/nanosilver films to food simulants. They believe that Ag^+ ions are also released from nano-composite films when exposed to food-simulating solutions. Moreover, Ag^+ ions are readily reduced to Ag^0 in the presence of acid environments. Echegoyen and Nerin (2013) have also reported the presence of both elemental Ag^0 and Ag^+ ions in commercial polyolefin foil packages and nanosilver containers.

The European Food Safety Authority (EFSA) has recommended upper limits for silver migration from packaging, which should not exceed 0.05 mg/L in water and 0.05 mg/kg in food. It shows that determination of the silver migration level is essential to ensure strong antimicrobial activity (EFSA Scientific Committee 2011).

Food packaging falls into two categories; first, improved packaging in which nanomaterials are embedded in gas barrier plastics, and second, active packaging in which nanomaterials interact directly with food and prevent its microbial contamination. In the film-making process, NPAg are coated, absorbed or incorporated directly by a simple chemical route (Duncan 2011; Vasile *et al*. 2017). Although NPAg increase the shelf life of food, there is a need to assess the hazards and risks of their migration from the packaging to the food for consumer safety. Improved food quality and shelf life are achieved through active packaging, which reduces microbial contamination from the field, and cold storage and consumption areas (Singh and Sahareen 2017).

Cozmuta *et al*. (2015) described Ag/TiO_2 nanocomposites in packaging made of high-density polyethylene (HDP-P) film, which increase the durability and microbiological safety of bread in comparison with commonly used packaging. Orange juice kept in PE-based packaging with an $Ag\text{-}TiO_2\text{-}Fe$ composite retained the same colour, texture and taste as freshly prepared juice, even after 10 days of storage. Silver and iron have been found to have better antimicrobial properties against yeasts and moulds than TiO_2 alone (Peter *et al*. 2014).

Ramos *et al*. (2016) reported that a study of NPAg migration from a plastic baby's bottle and food container revealed less agglomeration and oxidation of NPAg. This depends on the nature of the polymer and its storage conditions. SP-ICPMS techniques were used to determine the ionic silver and NPAg in extremely diluted samples. Therefore, this method is better for obtaining accurate information on the size and concentration of NP in complex extracts in a smaller amount in a short time, avoiding agglomeration and oxidation of NPAg.

Silver and copper NP were impregnated with guar gum nanocomposites and the effects on thermo-mechanical, optical, spectral, oxygen barrier and antimicrobial properties of the film were investigated. This material showed good film properties for active food packaging applications, although the commercialization of such materials requires additional research on the effects of NP on food and further impact on human health (Arfat *et al*. 2017).

Textiles

There is also now a growing interest in the use of silver-based nanomaterials as antimicrobials in the textile sector. As sterile textiles are one of the common goals identified by scientists, bacteria-free fabrics would be subject to different uses. In order to functionalize textiles, NP can play a major role due to their specification. Various textiles properties such as repulsion stimulation, non-creasing, anti-static, enhanced strength, hydrophobicity and antimicrobial activity are very important for increasing the durability, quality and elasticity of the textiles. The textile industry is changing and introducing new technologies not only in the processing of textiles, but also in the use of antimicrobials to avoid bacterial contamination. Nowadays, human awareness of bacterial infections caused by textile products has increased. The transfer of microorganisms from the surface of textiles to human skin is a serious health problem. Therefore, textiles can be 'treated' to avoid infection (Ahmad *et al*. 2020).

Modern methods used in the textile industry are largely based on nanotechnology. Choosing the right antimicrobial agent is a difficult task. The use of NP is more beneficial than that of traditional antimicrobial agents such as alkali metals, quaternary ammonium compounds and triclosan because they are more stable and cheaper to produce (Kim 2019; Wagener *et al*. 2016).

There are various methods of applying silver in textiles. These can involve colloidal solutions and dispersed NP as well as silver salts insoluble in water. One method is based on the reduction of the water-soluble silver salt that occurs directly on the surface and inside the pores of cellulose fibres (e.g. cotton). The product of this reaction is metallic silver at nano size. NPAg located inside the pores of cellulose fibres have the ability to aggregate, thanks to which they are fixed there, making it difficult to rinse them out of the material. This means that the enriched textile retains its bactericidal effect after repeated washing. Materials with NPAg inside and on the surface can be used for the production of medical devices used in the treatment of patients with skin infection caused by burns, wounds or postoperative infection. They can also be used to make socks, shoe inserts, underwear, duvet covers and bedding, towels, laboratory coats and medical clothing (Ilic *et al*. 2010; López *et al*. 2013).

Animal husbandry

Livestock farming is the only agricultural sector associated with animals as a source of meat, skin, milk, eggs or other foodstuffs. During the routine activity of animals, there is a possibility of infection with various pathogenic microorganisms. There is therefore a need to extend disinfection to animals. NPAg disinfectants are used to disinfect the surface of an animal's body and as a disinfectant for water. Various diseases caused by bacteria, viruses, fungi and other unicellular microorganisms have been successfully controlled with NPAg. They inhibit the reproduction and growth of bacteria and fungi responsible for infection, unpleasant odours, itching and impaired wound healing. NPAg have been found to be highly effective, fast acting, deodorizing, non-toxic, non-sensitizing, hydrophilic and therefore very effective in terms of bacterial res-istance. Therefore, NP are used as a disinfectant in animal husbandry for disinfection and disease prevention (Kovalenko *et al*. 2020; Nia 2009).

There are many potential sources of infection on poultry farms. Various microorganisms and their endotoxins are responsible for infectious diseases and spread in the environment through bioaerosols called organic dust. This organic dust reaches about 3 kilometres from its place of origin and causes serious respiratory infections (Hegarty *et al*. 2007; Tymczyna *et al*. 2007). Many attempts and studies have been made to defeat the infection in a way that does not endanger the environment and does not have a negative impact on human health. Many chemical compounds have been used, such as organic acids, hydrogen peroxide, sodium bicarbonate, sodium orthophosphate, etc. However, none of them meets all the requirements, being variously less soluble, expensive, toxic or not able to be applied directly to the product (Hegarty *et al*. 2007). One of the potential organic compounds used for disinfection is formaldehyde due to its low cost and high biocidal activity. However, it is too toxic and carcinogenic. Data in the literature show that NP with strong biocidal properties can be an outstanding alternative (Konopka *et al*. 2009; Metak and Ajaal 2013).

NPAg are effective against a wide range of Gram-negative and Gram-positive bacteria. Gram-negative bacteria include *Acinetobacter*, *Escherichia*, *Pseudomonas*, *Salmonella* and *Vibrio*, while Gram-positive bacteria include *Bacillus*, *Clostridium*, *Enterococcus*, *Listeria*, *Staphylococcus* and *Streptococcus* (Banach *et al*. 2016). Studies have shown that NP with a diameter of 22.5 nm enhance the antimicrobial activity of some antibiotics such as penicillin G, amoxicillin, erythromycin, clindamycin and vancomycin (Anjali *et al*. 2020; Kaur *et al*. 2019; Shahverdi *et al*. 2007). Sun *et al*. (2005) found that NPAg are effective against many viruses and also inhibit HIV-1 replication. NPAg have also been found to inhibit the reproduction of a large number of fungi: *Aspergillus*, *Candida* and *Saccharomyces* (Tsai *et al*. 2019).

As a disinfectant, nanosilver plays a very important role in animal husbandry where the sanitary conditions of transport chambers or the space used for storing animals are important (Gond *et al*. 2019). Some workers have reported that diets enriched with nanomaterials reduce the toxic activity of aflatoxin-contaminated feeds (Hassan *et al*. 2019).

Sawosz *et al*. (2012) assessed the levels of NPAg residues in egg shells and tissues. This study revealed that nanosilver stimulates oxidative stress in chickens obtained from eggs disinfected with nanosilver. Disinfection turned out to be very effective in the development of embryos and makes them sensitive to even very small amounts of toxic substances.

NPAg have been tested as feed additives to stimulate the growth of birds and weaning pigs. The study found that NPAg up to 100 nm in size exhibit higher antimicrobial activity than silver salts. Silver salts are inactivated by stomach acids and easily absorbed into the body through the intestinal mucosa. At the same time, NP cannot be digested by gastric juice in the intestines and have a less toxic effect compared to silver salts (Abad-Álvaro *et al*. 2019). NPAg used as a potential dietary supplement have a positive effect on the growth of piglets, which can be achieved thanks to the antimicrobial properties of the feed. The NPAg kill bacterial groups or reduce the microbial load of the small intestine of pigs (Deshmukh *et al*. 2019). In the future, there are many opportunities to expand innovative industrial pathways using nanosilver.

Toxicity of nanosilver

The toxicity of nanosilver is closely related to the release of Ag^+ ions. The oxidation rate of these ions depends on the surface coating of nanosilver, coexisting molecules, especially thiolcontaining compounds, lighting conditions and the interaction of nanosilver with nucleic acids, lipid molecules and proteins in the biological system. It has been shown that nanosilver penetrates cells and is internalized. One of the main mechanisms of toxicity is causing oxidative stress through the production of ROS, which causes DNA damage, activation of antioxidant enzymes, depletion of antioxidant molecules (e.g. glutathione), protein binding and inactivation, as well as damage to the cell membrane (Rezvani *et al*. 2019).

Nanosilver can penetrate the cell by diffusion and endocytosis, leading to mitochondrial dysfunction. An important mechanism of the toxicity of nanosilver is its interaction with sulphur-containing macromolecules such as proteins, due to the high affinity of silver for sulphur (Guo *et al*. 2019). Arora *et al*. (2009) studied the toxicity of nanosilver in primary fibroblasts and liver cells and found that nanosilver is present in mitochondria and triggers antioxidant mechanisms. Braydich-Strolle *et al*. (2010) used mouse stem cells and found that smaller nanosilver particles were more involved in the production of ROS and the induction of apoptosis.

Trickler *et al*. (2010) found that the cytotoxicity of polyvinylpyrrolidone (PVP)-coated nanosilver in rat brain cells depends on the size and shape of the NP and causes pro-inflammatory effects. Hussain *et al*. (2005) assessed the *in vitro* toxicity of several types of NP, including nanosilver (15 and 100 nm), against a liver-derived rat cell line (BRL 3A). After 24 hours of exposure, mitochondrial function and membrane integrity (measured as leakage of lactate dehydrogenase) were significantly reduced at the 5 and 10 mg/mL doses. The leakage of lactate dehydrogenase was dose-dependent and greater for 100 nm NP than for 15 nm nanosilver.

The results of many studies indicate that there are several routes of exposure to the toxic effects of nanosilver (Figure 1). Exposure to nanosilver can lead to genotoxicity and DNA damage (Ivask *et al*. 2015; Lebedová *et al*. 2017; Li *et al*. 2017b), an inflammatory response in the liver and kidneys, and lung, heart, intestinal and spleen dysfunction (Lankveld *et al*. 2010; Rosas-Hernández *et al*. 2009). Numerous in vivo studies on mammalian cells suggest that the liver is particularly vulnerable to nanosilver exposure, which, due to its detoxifying role in the body, accumulates relatively

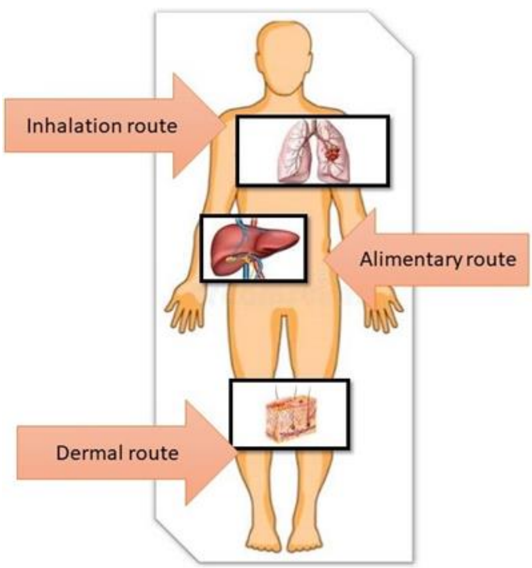

Figure 1. Potential routes of exposure to the toxic effects of nanosilver

large amounts of NP (Ema *et al*. 2017; Jia *et al*. 2017). Recent proteomic research has proven the adverse health effects caused by exposure to Ag^{+} and NPAg, where both forms of silver induced similar forms of signalling and metabolic changes (Juling *et al*. 2018). Subsequent work on the toxicological effects of NPAg and Au reports increased liver enzyme function, indicating liver toxicity and damage. Hepatitis is manifested by an increase in the amount of t he inflammatory cytokines interleu-kin-6 (IL-6) and tumour necrosis factor alpha (TNFα) (Al-Bishri 2018).

The increasing possibilities of using nanosilver contribute to the increase in the number of people working in exposure to this substance; therefore, it is important to understand the mechanism of toxicity of NP to human cells. In studies on the toxic effects of NPAg on human cells, it was shown that, like in mice, the liver is the organ most susceptible to NPAg accumulation. The effect of NPAg on the HepG2 cell line was checked using the micronucleus test, viability test and DNA array analysis. Research shows that many major biological processes are altered, ultimately leading to cell apoptosis (Cavallin *et al*. 2018; Sahu *et al*. 2015). Genotoxicity is based on the evolution of the major DNA damage response pathway. The GADD45a gene was tested after exposure to NPAg in HepG2 liver and A549 lung epithelial cells. The results showed that NPAg produces a strong dose-dependent transcriptional increase and activation of the GADD45a promoter. This is indicated by luciferase activity along with a significant decrease in cell viability. Additionally, compared to A549 luciferase cells, HepG2 luciferase cells are more susceptible to NPAg because a higher level of genotoxicity is induced (Wang *et al*. 2017).

Inhalation is one of the potential ways of being exposed to nanosilver, particularly through consumer products such as disinfectants in the form of sprays. Inhaled NP can accumulate deep in the lungs and interact with pulmonary surfactant (PS). It has been found that upon contact with PS, NPAg are immediately surrounded by a crown of biomolecules that contains both lipids and proteins. While lipids remain unchanged, proteins undergo significant changes (Hu *et al*. 2017). Toxicity studies of starch-coated NPAg against IMR-90 human lung fibroblasts showed a dose-dependent reduction in ATP con-tent and DNA damage due to Ag deposition and interaction with DNA followed by G2/M cell cycle arrest (Asharani *et al*. 2009). Studies by Gliga *et al*. (2018) on the BEAS-2B cell line involved exposing the cells to 1 mg/mL NPAg (10 nm) for 6 weeks. RNA sequencing, as well as genome-wide DNA methylation analysis, showed that repeated, long-term human exposure to low doses of nanosilver is pro-fibrotic and induces epithelial-mesenchymal transition (EMT) and cell transformation.

Subsequent studies on the cytotoxicity of modified PEI-NPAg (polyethylene-imine-silver nanoparticles) and PEG-NPAg (polyethylene glycol-silver nanoparticles) were carried out on HTB182 lung cancer cells and normal human bronchial epithelial (hBE) cells. NPAg toxicity to HTB182 and hBE was shown to be dose-dependent and more noticeable in cancer cells. The surface modification of NPAg significantly influenced their anticancer/anti-proli-ferative properties (Su *et al*. 2017).

NPAg can now easily come into contact with the human reproductive system through the use of contraceptives and hygiene products. Given that NPAg can cross the placenta and that pregnant women and the early fetus are more susceptible to harmful external factors, it is important to understand the effects of nanosilver on the reproductive system and fetal development. The studies of (Kang and Park 2018) found that the effect of the minimum amount of Ag^+ ions on human prostate cancer cells reduces the transactivation of dihydrotestosterone, an essential male reproducetive hormone (Ema *et al*. 2017). Another relatively new study on sperm functionnality showed that NPAg adversely affect genes involved in spermatogenesis and sperm functionality, at both low and high doses. This study showed that NPAg interfere with the chemical activity of the reproductive endocrine system in prepuberty and adolescence (Cavallin *et al*. 2018).

Nanosilver is present in many consumer products, the production, use and disposal of which can lead to environmental hazards. Disinfecting and washing products are one of the many ways that NPAg can enter the ecosystem. They undergo many transformations in the environment, including aggregation and agglomeration, the most significant of which are dissolution and the resulting formation of various chemical compounds, mainly sulphides and chlorides. Silver sulphide (Ag_2S) is important because it is insoluble in all solvents, making it a persistent compound in the environment (Li *et al*. 2017a). Ag_2S can be found in wastewater treatment plants and sometimes even in freshwater. The biotoxicity of silver depends directly on the type of silver compound present in the environment. While the movement of Ag^+ in soil and sediments is extremely limited, silver may behave differently on a nanometric scale (Levard *et al*. 2012).

Summary

This article provides a comprehensive and up-to-date overview of the synthesis and properties of NPAg and their antibacterial and cytotoxic effects in mammalian cells. The bactericidal activity of NPAg has led to their widespread use in cosmetics, medical products, anti-microbial dressings, etc. However, the extensive use of NPAg has raised serious public concerns regarding the safety and environmental impact of these products. In this regard, it is considered necessary to study the interaction between NPAg and biological cells in order to better understand the health risks of using NP. Many studies have shown that nanosilver damages membranes and is responsible for mitochondrial disorders, the generation of ROS, oxidative stress and DNA damage.

References

Abad-Álvaro, I., Trujillo, C., Bolea, E., Laborda, F., Fondevila, M., Latorre, M.A., Castillo J.R. 2019. Silver nanoparticles-clays nanocomposites as feed additives: Characterization of silver species released during in vitro digestions. Effects on silver retention in pigs. Microchemical Journal, 149: 57–68.

Ahmad, S., Subhani, K., Rasheed, A., Ashraf, M., Afzal, A., Ramzan, K., Sarwar, Z. 2020. Development of conductive fabrics by using silver nanoparticles for electronic applications. Journal of Electronic Materials, 49: 1330 –1337.

Ahn, S.J., Lee, S.J., Kook, J.K., Lim, B.S. 2009. Experimental antimicrobial orthodontic adhesives using nanofillers and silver nanoparticles. Dental Materials, 25(2): 206–213.

Al-Bishri, W.M. 2018. Toxicity study of gold and silver nanoparticles on experimental animals. Pharmacophore, 1: 48–55.

Alonso, A., Muñoz-Berbel, X., Vigués, N., Rodríguez-Rodríguez, R., Macanás, J., Muñoz, M., Mas, J., Muraviev, D.N. 2013. Superparamagnetic Ag-co-nanocomposites on granulated cation exchange polymeric matrices with enhanced antibacterial activity for the environmentally safe purification of water. Advanced Functional Materials, 23(19): 2450–2458.

Alt, V., Bechert, T., Steinrücke, P. 2004. An in vitro assessment of the antibacterial properties and cytotoxicity of nanoparticulate silver bone cement. Biomaterials, 25(18): 4383–4391.

Andara, M., Agarwal, A., Scholvin, D. 2006. Hemocompatibility of diamondlike carbon-metal composite thin films. Diamond and Related Materials, 15(11–12): 1941–1948.

Anjali, C.G., Kumar, V.G., Stalin, D.T., Vkarthic, V., Govindaraju, K., Joselin, J.M., Baalamurugan, J. 2020. Antibacterial activity of silver nanoparticles (biosynthesis): A short review on recent advances. Biocatalysis and Agricultural Biotechnology, 1: 20–25.

Arfat, Y.A., Ejaz, M., Jacob, H., Ahmed, J. 2017. Deciphering the potential of guar gum/Ag-Cu nanocomposite films as an active food packaging material. Carbohydrate Polymers, 157: 65–71.

Arora, S., Jain, J., Rajwade, J.M. 2009. Interactions of silver nanoparticles with primary mouse fibroblasts and liver cells. Toxicology and Applied Pharmacology, 236: 310–318.

Asharani, P.V., Hande, M.P., Valiyaveettil, S. 2009. Anti-proliferative activity of silver nanoparticles. BMC Molecular and Cell Biology, 10: 65.

Banach, M., Tymczyna, L., Chmielowiec-Korzeniowska, A., Pulit-Prociak, J. 2016. Nanosilver biocidal properties and their application in disinfection of hatchers in poultry processing plants. Bioinorganic Chemistry and Applications, 2016: 5214783.

Bhol, K.C., Alroy, J., Schechter, P.J. 2004. Anti-inflammatory effect of topical nanocrystalline silver cream on allergic contact dermatitis in a guinea pig model. Clinical and Experimental Dermatology, 29(3): 282–287.

Braydich-Stolle, L., Lucas, B., Schrand, A.M. 2010. Silver nanoparticles disrupt GDNF/Fyn kinase signaling in spermatogonial stem cells. Toxicological Sciences, 116: 577–589.

Bumbudsanpharoke, N., Choi, J., Ko, S. 2015. Applications of nanomaterials in food packaging. Journal of Nanosciences and Nanotechnology, 15: 6357–6372.

Cavallin, M.D., Wilk, R., Oliveira, I.M., Cardoso, N.C.S., Khalil, N.M., Oliveira, C.A., Romano, M.A., Romano, R.M. 2018. The hypothalamic-pituitary-testicular axis and the testicular function are modulated after silver nanoparticle exposure. Toxicological Research, 7(1): 102 –116.

Chaloupka, K., Malam, Y., Seifalian, A.M. 2010. Nanosilver as a new generation of nanoproduct in biomedical applications. Trends in Biotechnology, 28(11): 580–588.

Chambers, J.L., Christoph, G.G., Kreiger, M. 2002. Silver ion inhibition of serine proteases: Crystallographic study of silver-trypsin. Biochemical and Biophysical Research Communications, 59: 70–74.

Chen, D., Qiao, X., Qiu, X., Chen, J. 2009. Synthesis and electrical properties of uniform silver nanoparticles for electronic applications. Journal of Material Science, 44: 1076–1081.

Chen, J., Guo, Z., Wang, H.B., Gong, M., Kong, X.K., Xia, P., Chen, Q.W. 2013. Multifunctional Fe_3O_4-C-Ag hybrid nanoparticles as dual modal imaging probes and near-infrared light-responsive drug delivery platform. Biomaterials, 34(2): 571–581.

Chirra, H.D., Biswal, D., Hilt, Z. 2016. Gold nanoparticles and surfaces: Nanodevices for diagnostics and therapeutics. Drug Delivery Nanoparticles Formulation and Characterization, 191: 92.

Chmielowiec-Korzeniowska, A., Tymczyna, L., Drabik, A. 2007. Use of organic and mineral materials for biofiltration of air in hatcheries. Annals of Animal Science, 7(1): 153–162.

Close, D., Liang, Z., Lu, H., Yang, J., Chen, R. 2016. Novel asymmetric wettable AgNPs/chitosan wound dressing: In vitro and in vivo evaluation. ACS Applied Materials and Interfaces, 8(6): 3958–3968.

Corrêa, J.M., Mori, M., Sanches, H.L., Dibo da Cruz, A., Poiate, E., Venturini, I.A., Poiate, P. 2005. Silver nanoparticles in dental biomaterials. International Journal of Biomaterials, 1: 1–9.

Cozmuta, M.A., Peter, A., Mihaly-Cozmuta, L., Nicula, C., Crisan, L., Baia, L., Turila, A. 2015. Active packaging system based on Ag/TiO_2 nanocomposite used for extending the shelf life of bread. Chemical and microbiological investigations. Packaging Technology and Science, 28(4): 271–284.

Deshmukh, S.P., Mullani, S.B., Koli, V.B., Patil, S.M., Kasabe, P.J., Dandge, P.B., Pawar, S.A., Delekar, S.D. 2018. Ag nanoparticles connected to the surface of TiO_2 electrostatically for antibacterial photoinactivation studies. Photochemistry and Photobiology, 94(6): 1249–1262.

Deshmukh, S.P., Patil, S.M., Mullani, S.B., Delekar, S.D. 2019. Silver nanoparticles as an effective disinfectant: A review. Materials Science and Engineering: C, 97: 954–965.

Duncan, T.V. 2011. Applications of nanotechnology in food packaging and food safety: Barrier materials, antimicrobials and sensors. Journal of Colloid and Interface Science, 363(1): 1–24.

Eaton, M. 2007. Nanomedicine: Industry-wise research. Nature Materials, 6: 251–253.

Echegoyen, Y., Nerin, C. 2013. Nanoparticle release from nano-silver antimicrobial food containers. Journal of Food Technology and Food Chemistry, 62: 16–22.

Ema, M., Okuda, H., Gamo, M., Honda, K. 2017. A review of reproductive and developmental toxicity of silver nanoparticles in laboratory animals. Reproductive Toxicology, 67: 149 –164.

Espinoza, S.M., Patil, H.I., Martinez, S.M., Casañas, E., Pimentel, R., Ige, P.P. 2020. Poly-ε-caprolactone (PCL), a promising polymer for pharmaceutical and biomedical applications: Focus on nanomedicine in cancer. International Journal of Polymeric Materials and Polymeric Biomaterials, 69: 85–126.

Faiyaz, A., Prashanth, S.T., Sindhu, K., Nayak, A., Chaturvedi, S. 2019. Antimicrobial efficacy of nanosilver and chitosan against Streptococcus mutans, as an ingredient of toothpaste formulation: An in vitro study. Journal of Indian Society of Pedodontics and Preventive Dentistry, 37(1): 46–54.

Fu, J., Ji, J., Fan, D., Shen, J. 2006. Construction of antibacterial multilayer films containing nanosilver via layer-by-layer assembly of heparin and chitosan-silver ions complex. Journal of Biomedical Materials Research Part A, 79(3): 665–674.

Ghanbari, H., Viatge, H., Kidane, A.G., Burriesci, G., Tavakoli, M., Seifalian, A.M. 2009. Polymeric heart valves: New materials, emerging hopes. Trends in Biotechnology, 27(6): 359–367.

Ghosh, P., Han, G., De, M., Kim, C.K., Rotello, V.M. 2008. Gold nanoparticles in delivery applications. Advanced Drug and Delivery Reviews, 60(11): 1307–1315.

Gitipour, A., Al-Abed, S.R., Thiel, S.W., Scheckel, K.G., Tolaymat, T. 2017. Nanosilver as a disinfectant in dental unit waterlines: Assessment of the physicochemical transformations of the AgNPs. Chemosphere, 173: 245–252.

Gliga, A.R., Di Bucchianico, S., Lindvall, J., Fadeel, B., Karlsson, H.L. 2018. RNA sequencing reveals long-term effects of silver nanoparticles on human lung cells. Scientific Reports, 8: 14.

Gond, S.K., Mishra, A., Verma, S.K. 2019. Synthesis and characterization of antimicrobial silver nanoparticles by an endophytic fungus isolated from Nyctanthes arbor-tristis. Proceedings of the National Academy of Sciences, India Section B, 1: 15–23.

Grunkemeier, G.L., Jin, R.Y., Starr, A. 2006. Prosthetic heart valves: Objective performance criteria versus randomized clinical trial. The Annals of Thoracic Surgery, 82(3): 776–780.

Guo, Z., Zeng, G., Cui, K., Chen, A. 2019. Toxicity of environmental nanosilver: Mechanism and assessment. Environmental Chemistry Letters, 17: 319–333.

Han, J.W., Ruiz-Garcia, L., Qian, J.P., Yang, X.T. 2018. Food packaging: A comprehensive review and future trends. Comprehensive Reviews in Food Science and Food Safety, 17: 860–877.

Hassan, A.A., Hafsa, A.S.H., Elghandour, M.M.M.Y., Reddy, P.R.K., Monroy, J.C., Salem, A.Z.M. 2019. Dietary supplementation with sodium bentonite and coumarin alleviates the toxicity of aflatoxin B1 in rabbits. Toxicon, 171: 35–42.

Hegarty, R., Goopy, J., Herd, R., McCorkell, B. 2007. Cattle selected for lower residual feed intake have reduced daily methane production. Journal of Animal Science, 85(6): 1479–1486.

Hu, Q.L., Bai, X., Hu, G.Q., Zuo, Y.Y. 2017. Unveiling the molecular structure of pulmonary surfactant corona on nanoparticles. ACS Nano, 11(7): 6832–6842.

Huang, Y., Chen, S., Bing, X., Gao, C., Wang, T., Yuan, B. 2011. Nanosilver migrated into food-simulating solutions from commercially available food fresh containers. Packaging Technology and Science, 24: 291–297.

Huang, Y., Mei, L., Chen, X., Wang, Q. 2018. Recent developments in food packaging based on nanomaterials. Nanomaterials, 8: 830.

Hussain, S.M., Hess, K.L., Gearhart, J.M. 2005. In vitro toxicity of nanoparticles in BRL 3A rat liver cells. Toxicology In Vitro, 19: 975–983.

Ilic, V., Šaponjić, Z., Vodnik, V., Lazović, S.A., Dimitrijevic, S., Jovancic, P., Nedeljkovic, J.M., Radetic, M. 2010. Bactericidal efficiency of silver nanoparticles deposited onto radio frequency plasma pretreated polyester fabrics. Industrial and Engineering Chemistry Research, 49(16): 7287–7293.

Ip, M., Lui, S.L., Poon, V.K.M. 2006. Antimicrobial activity of silver dressings: An in vivo comparison. Journal of Medical Microbiology, 55: 59–63.

Ivask, A., Voelcker, N.H., Seabrook, S.A., Hor, M., Kirby, J.K., Fenech, M., Davis, T.P., Ke, P.C. 2015. DNA melting and genotoxicity induced by silver nanoparticles and graphene. Chemical Research in Toxicology, 28(5): 1023–1035.

Jamieson, W.R., Fradet, G.J., Abel, J.G. 2009. Seven-year results with the St Jude Medical Silzone mechanical prosthesis. The Journal of Thoracic and Cardiovascular Surgery, 137(5): 1109–1115.

Jia, J., Li, F., Zhou, H., Bai, Y., Liu, S., Jiang, Y., Jiang, G., Yan, B. 2017. Oral exposure to silver nanoparticles or silver ions may aggravate fatty liver disease in overweight mice. Environmental Science and Technology, 51(16): 9334–9343.

Jiranek, W.A., Hanssen, A.D., Greenwald, A.S. 2006. Antibiotic-loaded bone cement for infection prophylaxis in total joint replacement.

Journal of Bone and Joint Surgery, 88(11): 2487–2500.

Jones, K.E., Patel, N.G., Levy, M.A., Storeygard, A., Balk, D., Gittleman, J.L., Daszak, P. 2008. Global trends in emerging infectious diseases. Nature, 451(7181): 990.

Juling, S., Bohmert, L., Lichtenstein, D., Oberemm, A., Creutzenberg, O., Thunemann, A.F., Braeuning, A., Lampen, A. 2018. Comparative proteomic analysis of hepatic effects induced by nanosilver, silver ions and nanoparticle coating in rats. Food and Chemical Toxicology, 113: 255–266.

Kang, J.S., Park, J.-W. 2018. Insight on cytotoxic effects of silver nanoparticles: Alternative androgenic transactivation by adsorption with DHT. Science of the Total Environment, 618: 712–717.

Kaur, A., Preet, S., Kumar, V., Kumar, R., Kumar, R. 2019. Synergetic effect of vancomycin loaded silver nanoparticles for enhanced antibacterial activity. Colloids and Surfaces B: Biointerfaces, 176: 62–69.

Khalid, A., Hamza, A., Fasih, A.A., Alisha, A.A., Jehangir, A., Junaid, R., Uroosa, T., Syed, H.A. 2020. Analysis of anti-microbial and anti-biofilm activity of hand washes and sanitizers against S. aureus and P. aeruginosa. Journal of Pakistan Medical Association, 70(1): 100–104.

Kim, J.S., Kuk, E., Yu, K.N. 2007. Antimicrobial effects of silver nanoparticles. Nanomedicine, 3(1): 95–101.

Kim, Y.K. 2019. 8 – Nanotechnology-based advanced coatings and functional finishes for textiles. Smart Textile Coatings and Laminates, 2nd Edition: 189–203.

Ko, Y.S., Joe, Y.H., Seo, M., Lim, K., Hwang, J., Woo, K. 2014. Prompt and synergistic antibacterial activity of silver nanoparticle-decorated silica hybrid particles on air filtration. Journal of Materials Chemistry B, 2(39): 6714–6722.

Konopka, M., Kowalski, Z., Wzorek, Z. 2009. Disinfection of meat industry equipment and production rooms with the use of liquids containing silver nano-particles. Archives of Environmental Protection, 35(1): 107–115.

Kovalenko, A.M., Tkachev, A.V., Tkacheva, O.L., Gutyj, B.V., Prystupa, O.I., Kukhtyn, M.D., Dutka, V.R., Veres, Y.M., Dashkovskyy, O.O., Senechyn, V.V., Riy, M.B., Kotelevych, V.A. 2020. Analgesic effectiveness of new nanosilver drug. Ukrainian Journal of Ecology, 10(1): 300–306.

Lankveld, D.P., Oomen, A.G., Krystek, P., Neigh, A., Troost-de Jong, A., Noorlander, C., Van Eijkeren, J., Geertsma, R., De Jong, W. 2010. The kinetics of the tissue distribution of silver nanoparticles of different sizes. Biomaterials, 31(32): 8350–8361.

Leaper, D.J. 2006. Silver dressings: Their role in wound management. International Wound Journal, 3(4): 282–294.

Lebedová, J., Hedberg, Y.S., Odnevall-Wallinder, I., Karlsson, H.L. 2018. Size-dependent genotoxicity of silver, gold and platinum nanoparticles studied using the mini-gel comet assay and micronucleus scoring with flow cytometry. Mutagene, 33(1): 77–85.

Lee, J.S., Lytton-Jean, A.K., Hurst, S.J., Mirkin, C.A. 2007. Silver nanoparticle-oligonucleotide conjugates based on DNA with triple cyclic disulfide moieties. Nano Letters, 7(7): 2112 –2115.

Levard, C., Hotze, E.M., Lowry, G.V., Brown, G.E. 2012. Environmental transformations of silver nanoparticles: Impact on stability and toxicity. Environmental Science and Technology, 46(13): 6900–6914.

Li, L.X.Y., Xu, Z.L., Wimmer, A., Tian, Q.H., Wang, X.P. 2017a. New insights into the stability of silver sulfide nanoparticles in surface water: Dissolution through hypochlorite oxidation. Environmental Science and Technology, 51(14): 7920–7927.

Li, Y., Qin, T., Ingle, T., Yan, J., He, W., Yin, J.-J., Chen, T. 2017b. Differential genotoxicity mechanisms of silver nanoparticles and silver ions. Archives of Toxicology, 91(1): 509–519.

Liao, J., Anchun, M., Zhu, Z., Quan, Y. 2010. Antibacterial titanium plate deposited by silver nanoparticles exhibits cell compatibility. International Journal of Nanomedicine, 5: 337 –342.

López I.J., Vilchis, N.A.R., Sánchez Mendieta, V., Avalos Borja, M. 2013. Production and characterization of silver nanoparticles supported on cotton fibers. Superficies y Vacío, 3(26): 73–78.

Lopez-Carballo, G., Higueras, L., Gavara, R., Hernandez-Muñoz, P. 2013. Silver ions release from antibacterial chitosan films containing in situ generated silver nanoparticles. Journal of Agricultural and Food Chemistry, 61: 260–267.

Magalhães, A.P.R., Santos, L.B., Lopes, L.G. 2012. Nanosilver application in dental cements. ISRN Nanotechnology, 2012: 1–6.

Mandal, A.K. 2017. Silver nanoparticles as drug delivery vehicle against Infections. Global Journal of Nanomedicine, 3(2): 1–4.

Martınez-Abad, A., Lagaron, J.M., Ocio, M.J. 2012. Development and characterization of silver-based antimicrobial ethylene-vinyl alcohol copolymer (EVOH) films for food-packaging applications. Journal of Agricultural and Food Chemistry, 60: 5350–5359.

McCarlie, S., Boucher, C.E., Bragg, R.R. 2020. Molecular basis of bacterial disinfectant resistance. Drug Resistance Updates, 48: 1–4.

Metak, A., Ajaal, T. 2013. Investigation on polymer based nano-silver as food packaging materials. International Journal of Food, Agriculture and Veterinary Sciences, 7(12): 772–778.

Morley, K.S., Webb, P.B., Tokareva, N.V. 2007. Synthesis and characterisation of advanced UHMWPE/silver nanocomposites for biomedical applications. European Polymer Journal, 43(2): 307–314.

Mousavi, F.P., Pour, H.H., Nasab, A.H., Rajabalipour, A.A., Barouni, M. 2015. Investigation into shelf life of fresh dates and pistachios in a package modified with nanosilver. Global Journal of Health Science, 8: 134–144.

Nia, J.R. 2009. Using of Nanosilver in Poultry, Livestock and Aquatics Industry. Google Patents US20090028947A1.

Nowack, B., Krug, H.F., Height, M. 2011. 120 years of nanosilver history: Implications for policy makers. Environmental Science and Technology, 45: 1177–1183.

Panigrahi, S., Kundh, S., Ghosh, S.K., Nath, S., Pal, T. 2004. General method of synthesis for metal nanoparticles. Journal of Nanoparticle Research, 6: 411–414.

Peter, A., Mihaly-Cozmuta, L., Mihaly-Cozmuta, A., Nicula, C., Indrea, E., Barbu, T.L. 2014. Testing the preservation activity of Ag-TiO_2-Fe and TiO_2 composites included in the polyethylene during orange juice storage. Journal of Food Process Engineering, 37(6): 596–608.

Pokrowiecki, R., Mielczarek, A. 2012. Wybrane przykłady wykorzystania nanocząsteczek srebra w procedurach medycznych. Nowa Stomatologia, 3: 117–121.

Rabani, M., Aref, P., Askarizadeh, N., Ashrafitamay, I. 2019. Comparison of the antibacterial effect of nanosilver and chlorhexidine mouthwash on Streptococcus mutans (invitro). Iranian Journal of Pediatric Dentistry, 15(1): 93–102.

Ramos, K., Gómez-Gómez, M., Cámara, C., Ramos, L. 2016. Silver speciation and characterization of nanoparticles released from plastic food containers by single particle ICPMS. Talanta, 151: 83–90.

Rezvani, E., Rafferty, A., McGuinness, C., Kennedy, J. 2019. Adverse effects of nanosilver on human health and the environment. Acta Biomaterialia, 94: 145–159.

Rosas-Hernández, H., Jiménez-Badillo, S., Martínez-Cuevas, P.P., Gracia-Espino, E., Terrones, H., Terrones, M., Hussain, S.M., Ali, S.F., González, C. 2009. Effects of 45-nm silver nanoparticles on coronary endothelial cells and isolated rat aortic rings. Toxicology Letters, 191: 305–313.

Russel, A.D. 2003. Challenge testing: Principles and practice. International Journal of Cosmetics Science, 25: 147–153.

Rzeszutek, J., Matysiak, M., Czajka, M. 2014. Zastosowanie nanocząstek i nanomateriałów w medycynie. Hygeia Public Health, 49(3): 449–457.

Sahoo, S.K., Parveen, S., Panda, J.J. 2007. The present and future of nanotechnology in human health care. Nanomedicine: Nanotechnology, Biology, and Medicine, 3: 20–31.

Sahu, S.C., Zheng, J., Yourick, J.J., Sprando, R.L., Gao, X. 2015. Toxicogenomic responses of human liver HepG2 cells to silver nanoparticles. Journal of Applied Toxicology, 35(10): 1160–1168.

Sawosz, F., Pineda, L.M., Hotowy, A.M., Hyttel, P., Sawosz, E., Szmidt, M., Niemiec, T., Chwalibog, A. 2012. Nano-nutrition of chicken embryos. The effect of silver nanoparticles and glutamine on molecular responses, and the morphology of pectoral muscle. Journal of Baltic Studies, 2: 29–45.

Shahverdi, A.R., Fakhimi, A., Shahverdi, H.R., Minaian, S. 2007. Synthesis and effect of silver nanoparticles on the antibacterial activity of different antibiotics against Staphylococcus aureus and Escherichia coli. Nanomedicine, 3(2): 168–171.

Sharifi Rad, J., Hoseini Alfatemi, S., Sharifi Rad, M., Iriti M. 2014. Antimicrobial Synergic Effect of Allicin and Silver Nanoparticles on Skin Infection Caused by Methicillin-Resistant Staphylococcus aureus spp. Annals of Medical Health Science Research, 4(6): 863–868.

Shi, J., Wang, L., Zhang, J., Ma, R., Gao, J., Liu, Y., Zhang, C., Zhang, Z. 2014. A tumor-targeting near-infrared laser-triggered drug delivery system based on GO-Ag nanoparticles for chemo-photothermal therapy and X-ray imaging. Biomaterials, 35(22): 5847–5861.

Singh, M., Movia, D., Mahfoud, O.K., Volkov, Y., Prina-Mello, A. 2013. Silver nanowires as prospective carriers for drug delivery in cancer treatment: An in vitro biocompatibility study on lung adenocarcinoma cells and fibroblasts. European Journal of Nanomedicine, 5(4): 195 –204.

Singh, M., Sahareen, T. 2017. Investigation of cellulosic packets impregnated with silver nanoparticles for enhancing shelf-life of vegetables. LWT Food Science and Technology, 86: 116–122.

Song, W., Anselmo, A.C., Huang, L. 2019. Nanotechnology intervention of the microbiome for cancer therapy. Nature Nanotechnology, 14: 1093–1103.

Su, S., Kang, P.M. 2020. Systemic review of biodegradable nanomaterials in nanomedicine. Nanomaterials, 10: 656.

Su, W., Ma, L., Wu, S.H., Li, W., Tang, J.X., Deng, J., Liu, J.X. 2017. Effect of surface modification of silver nanoparticles on the proliferation of human lung squamous cell carcinoma (HTB182) and bronchial epithelial (HBE) cells in vitro. Journal of Biomedicine and Nanotechnology, 13(10): 1281–1291.

Sun, R.W.-Y., Chen, R., Chung, N.P.-Y., Ho, C.-M., Lin, C.-L.S., Che, C.-M. 2005. Silver nanoparticles fabricated in Hepes buffer exhibit cytoprotective activities toward HIV-1 infected cells. Chemical Communications, 40: 5059 –5061.

Szymański, P., Markowicz, M., Mikiciuk-Olasik, E. 2012. Zastosowanie nanotechnologii w medycynie i farmacji. LAB, 17(1): 51–56.

Tavakoli, H., Rastegar, H., Taherian, M., Somadi, M., Rostami, H. 2017. The effect of nano-silver packaging in increasing the shelf life of nuts: An in vitro model. Italian Journal of Food Safety, 6: 6874.

Trickler, W.J., Lantz, S.M., Murdock, R.C. 2018. Silver nanoparticle induced blood–brain barrier inflammation and increased permeability in primary rat brain microvessel endothelial cells. Toxicological Sciences, 118: 160–170.

Trop, M., Novak, M., Rodl, S. 2006. Silver-coated dressings acticoat caused raised liver enzymes and argyria-like symptoms in burn patient. The Journal of Trauma and Acute Care Surgery, 60(1): 648–652.

Tsai, C-H., Whiteley, C.G., Lee, D-J. 2019. Interactions between HIV-1 protease, silver nanoparticles, and specific peptides. Journal of the Taiwan Institute of Chemical Engineers, 103: 20–32.

Tymczyna, L., Chmielowiec-Korzeniowska, A., Drabik, A. 2007. The effectiveness of various biofiltration substrates in removing bacteria, endotoxins, and dust from ventilation system exhaust from a chicken hatchery. Poultry Science, 86(10): 2095–2100.

Vasile, C., Râpă, M., Moujl, S., Stan, M., Macavei, S., Darie-Niţă, R., Barbu, T.L., Vodnar, D., Popa, E., Ştefan, R. 2017. New PLA/ZnO: Cu/Ag bionanocomposites for food packaging. Express Polymer Letters, 11(7): 531–544.

Wagener, S., Dommershausen, N., Jungnickel, H., Laux, P., Mitrano, D., Nowack, B., Schneider, G., Luch, A. 2016. Textile functionalization and its effects on the release of silver nanoparticles into artificial sweat. Environmental Science and Technology, 50(11): 5927–5934.

Wang, J., Che, B., Zhang, L.W., Dong, G., Luo, Q., Xin, L. 2017. Comparative genotoxicity of silver nanoparticles in human liver HepG2 and lung epithelial A549 cells. Journal of Applied Toxicology, 37(4): 495–501.

Wang, Y., Chen, L., Liu, P. 2012. Biocompatible Triplex Ag-SiO_2-mTiO2 Core-Shell Nanoparticles for Simultaneous Fluorescence-SERS Bimodal Imaging and Drug Delivery. Chemistry a European Journal, 18(19): 5935 –5943.

Wang, Y., Newell, B.B., Irudayaraj, J. 2012. Folic acid protected silver nanocarriers for targeted drug delivery. Journal of Biomedicine and Nanotechnology, 8(5): 751–759.

Wojnicki, M., Tokarski, T., Hessel, V., Fitznera, K., Luty-Błochoa, M. 2019. 2H and 4H silver colloidal suspension synthesis, as a new potential drug carrier. Chemical Engineering Journal, 382: 1–22.

Xu, J., Han, X., Liu, H., Hu, Y. 2006. Synthesis and optical properties of silver nanoparticles stabilized by gemini surfactant. Colloids and Surfaces A: Physicochemical and Engineering Aspects, 273: 179–183.

Yamanaka, M., Hara, K., Kudo, J. 2005. Bactericidal actions of a silver ion solution on Escherichia coli, studied by energy-filtering transmission electron microscopy and proteomic analysis. Applied and Environmental Microbiology, 71(11): 7589–7593.

Yoshida, K., Tanagawa, M., Matsumoto, S., Yamada, T., Atsuta, M. 1999. Antibacterial activity of resin composites with silver-containing materials. European Journal of Oral Science, 107(4): 290–296.