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A review on silver nanoparticles-induced ecotoxicity and the underlying toxicity mechanisms

Jia Du*, Junhong Tang**, Shaodan Xu, Jingyuan Ge, Yuwei Dong, Huanxuan Li, Meiqing Jin

Institute of Environmental Science and Engineering, College of Materials and Environmental Engineering, Hangzhou Dianzi University, 1158, Baiyang Rd, Hangzhou, 310018, PR China

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A B S T R A C T

Silver nanoparticles (Ag-NPs) are increasingly being applied in many consumer products due to their unique properties. Widespread use of Ag-NPs leads to an increasing human exposure to Ag-NPs in many different pathways. This review summarized the toxicity mechanisms of Ag-NPs based on various environmentally relevant test species, such as bacteria, cells, plants, aquatic animals and mammals, in both *in vitro* and *in vivo* experiments. Nanoparticles were usually exposed to combination chemicals but to single chemicals in the environment and thereby exert combined toxicities to the organisms. Therefore, the joint effects of nanomaterials and their co-existing characteristics were also discussed. The current knowledge gaps and safe product designs of Ag-NPs have been discussed in detail. The limited and existing data implied that understanding the toxicity mechanisms is crucial to the future research development of nanomaterials.

1. Introduction

Nanomaterials are widely used in electronic devices, industrial fields, medical systems, biomedical fields, engineering, paints and cosmetics because of their unique designs and property combinations (Arvizo et al., 2012; Llevot and Astruc, 2012). Among these nanomaterials, silver (Ag) nanoparticles (NPs) are widely used in medicine, medicinal devices, pharmacology, biotechnology, electronics, engineering, energy, magnetic fields, and also in environmental remediation (Yu et al., 2013). Ag-NPs are considered one of the most important nanomaterials. Ag-NPs are rapidly growing in the areas of personal care, household, medical products, textiles and the food industry (Volker et al., 2013). The present production of Ag-NPs is estimated to be about 500 tons per year worldwide, and its production is foreseen to increase every year (Miao et al., 2010). Ag-NPs are the most preferred antimicrobial nanomaterials, owing to their inhibition of the growth of bacteria, fungi and algae (Ivask et al., 2012). Ag-NPs have been extensively utilized in surface-enhanced Raman scattering spectroscopy (SERS) for bacterial identification. Sensitive spectral alterations were observed on Ag-NPs with increasing NPs concentration or incubation time, accompanied by an obvious decrease in the number of viable bacteria (Cui et al., 2015b). NPs can be released into the environment through various processes such as their production, use and improper disposal (Gottschalk et al., 2009). Dumont et al. (2015) reported that Ag-NPs were broadly distributed in the European territory. They are found extensively in wastewater and are released into the environment. The widespread existence of nanomaterial led to human concerns regarding the fate of the environment and the biological potential for toxicity (Hendren et al., 2011). The excessive usage of NPs and their abundance in the environment would enter into plants and animals, which would become a threat to human health. According to Bondarenko et al. (2013), Ag-NPs are of especially high concern in the environment, and organisms are extremely sensitive to Ag-NPs.

However, the expanding production and widespread utilization of Ag-NPs may pose risks for organisms and ecosystem, and have a high degree of toxicity compared to other types of metal oxide NPs. The toxic effects of Ag-NPs towards bacteria, mammals, cells and plants have been demonstrated in many previous researches. Organisms are potentially exposed to Ag-NPs by oral, inhalation or the transdermal route. Researchers have usually studied the toxicity and bioaccumulation by the oral, inhalation or transdermal route. For example, short-term oral administration of high doses of Ag-NPs caused organ toxicity and oxidative stress in Sprague-Dawley rats (Patlolla et al., 2015). McTeer et al. (2014) investigated the bioaccumulation of Ag-NPs in the *Daphnia magna* using oral exposure. In addition, the synthesized Ag-NPs varies in size, shape, surface electric charge, and other physiological

* Corresponding author.
** Corresponding author.
E-mail addresses: djhd@hdu.edu.cn (J. Du), tangjunhong@hdu.edu.cn (J. Tang), xusd@hdu.edu.cn (S. Xu), gejingyuan@hdu.edu.cn (J. Ge), ywdong@hdu.edu.cn (Y. Dong), hxlee@hdu.edu.cn (H. Li), jmq@hdu.edu.cn (M. Jin).

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characteristics. The physiological characteristics of Ag-NPs may be beneficial to provide good catalytic activity and high electronic conductivity. Moreover, the high surface area and nanometer size may affect the ability of Ag-NPs to attach to the negatively charged cell wall, or to interact with the cell membrane. Despite these evidences, the knowledge about the toxic effects of Ag-NPs interact with physiological characteristics is still limited. The toxic effects of Ag-NPs on mammals and other species have been the focus of both *in vitro* and *in vivo* toxicity assessments. Despite the important role of experimental methods in the ecosystem, the toxicity impact of Ag-NPs to organisms is not well studied. The comprehensive understanding the Ag-NPs-induced adverse effects and the mechanisms of their action are of great importance to assess the environmental risk of Ag-NPs. At present, the mechanisms of the toxicity of Ag-NPs and their short- or long-term exposure outcomes are still limited. Only thorough understanding of the mechanisms that drove the toxicity of Ag-NPs might address the goals of designing efficient antimicrobials or designing safe products. Previous studies have mostly referred to the toxicity of single Ag-NPs exposure. However, the complex physical and chemical transformations of other compounds affect NPs formation and toxicity potential to organisms in the environment. Therefore, an overview of the available co-exposure toxicity data of nanomaterials is also necessary to systematically summarize in this review.

This review aims to give a comprehensive literature overview of Ag-NPs on individual or composite organisms with a broad range of taxa (bacteria, cell, algae, plants, invertebrates and vertebrates) both *in vivo* and *in vitro* studies, and discuss the underlying toxicity mechanisms. The relationship between the physicochemical properties and Ag-NP-induced toxicity to organisms are studied for not only bacteria, yeast, aquatic organisms such as algae, protozoa, daphnids, fish, but also mammalian cells *in vitro*. Furthermore, the applications and potential hazards of nanomaterials in various fields are discussed in depth. Finally, the direction for future research development and perspectives are also presented.

The database Web of Science was searched on May 20, 2018, for papers that focused on Ag-NPs toxicity, and the search was limited to articles published between 2003 and 2018. There were 6193 matched articles. Most of the studies characterized the tested Ag-NPs, but with different methods and details. Although the publications might have differed in their details, we assembled studies that were deemed relevant and evaluated them for quality and consistency. Then, we collated the assembled information to write this review. We searched the selected 723 studies from Web of Science using "size, shape, charge, oxidative stress, mechanism, organ, *in vivo*, *in vitro*" as keywords to organize the discussion into specific sections. This method of evaluating the literature and considering the weight of evidence was adapted from Rajesh et al. (2015). After an initial assessment of content, 88 pertinent articles that focused on the toxic effect of Ag-NPs exposure, both in culture cells *in vitro* and in experimental organisms *in vivo*, were isolated. A summary of the search results is detailed in Fig. 1. This review will promote a better understanding of the risks of Ag-NPs particles when they enter the environment.

2. Physico-chemical properties, bioaccumulation and amplification of Ag-NPs

Ag-NPs are being developed and synthesized because of their special physicochemical characteristics size, shape, surface electric charge, coating layer, dose of NPs and agglomeration of Ag-NPs. The different physicochemical properties of Ag-NPs play a vital role in inducing toxicity in different organisms. Previous studies showed that size was one of the important factors that determined the toxic effect of Ag-NPs. Some researches found that the potency of Ag-NPs to induce cell damage compared to silver ions was cell type and size-dependent. For example, L929 mouse fibroblasts were shown to be more susceptible to the Ag-NPs size-dependent. The results showed that Ag-NPs with 20 nm induced more cytotoxic than the larger-size Ag-NPs (80 nm and 113 nm) (Park et al., 2011). Similarly, Ag-NPs induced cytotoxicity with size-dependent in human cell models and macrophage cells such as A549, SGC-7901, HepG2, MCF-7, macrophages, human lung cells and human lung fibroblasts (Liu et al., 2010; Gliga et al., 2014; Li et al., 2013; Carlson et al., 2008). However, Souza et al. (2016) indicated that the cytotoxicity and genotoxicity induced by the 100-nm Ag-NPs were greater than those induced by the 10-nm Ag-NPs for CHO-K1 and CHO-XRS5 cell lines (Souza et al., 2016). In addition, the size of Ag-NPs did not impact the viability of mammalian tumor cells (HeLa and U937 cells). Ag-NPs cytotoxic might be associate with the rate of intracellular Ag release-a 'Trojan horse' effect (Gliga et al., 2014). Besides the cells, Ag-NPs also showed size-dependent effects in the growth of seed planted (Yin et al., 2012). Indeed, the size of Ag-NPs might be affect the rate of dissolution and ionization of Ag ion released into solution, affect its active surface area, and affect the formation of aggregation, which related to the toxicity of Ag-NPs.

Shape was one of the important factors that determined the toxic effect of Ag-NPs. For example, Stoehr et al. (2011) found that wires of Ag-NPs (100–160 nm) significantly reduced cell viability and increased LDH release from alveolar epithelial cells, whereas spherical Ag-NPs (30 nm) had no effect. Ag nanoplates induced more serious acute toxic than nanosize Ag spheres and nanosize Ag wires in zebrafish embryos at the dose of 0.39–25 μg/ml (George et al., 2012). Coating Ag-NPs could produce electrostatic and electrosteric repulsions between NPs, which further prevented the aggregation of Ag-NPs. The surface coating of Ag-NPs could affect the shape, aggregation, and dissolution ratio. For example, uncoated Ag-NPs exhibited a significant cytotoxicity at higher doses (> 1.0 mg/L), induced abnormal cellular morphology and caused much stronger damage to chromosomes than that in polystyrene-coated Ag-NPs (Kawata et al., 2009). Nguyen et al. (2013) found that uncoated Ag-NPs (20, 40, 60 and 80 nm) appeared to suppress inflammatory responses and enhance oxidative stress more so than polyvinylpyrrolidone (PVP)-coated Ag-NPs (10, 50, and 75 nm) in J774A.1 macrophage and HT29 epithelial cells at higher concentrations (25 μg/ml). However, no differences on growth or mortality were observed in earthworms after exposed to Ag-NPs with polyvinylpyrrolidone (773.3 mg/kg) or oleic acid coatings (727.6 mg/kg) (Shoults-Wilson et al., 2011).

As a result of Ag-NPs wide applications, Ag-NPs released into aquatic ecosystems by many process, such as washing, transport and discharge. 0.1 μg/L Ag-NPs had been detected in the contamination of sewage sludge and wastewater effluent (Mitrano et al., 2012). The interaction of Ag-NPs with complexing ligands affected Ag-NPs bioaccumulation and amplification in the water. McTeer et al. (2014) assessed the bioavailability, toxicity and transfer of Ag-NPs in two model food chain organisms: the alga *Chlamydomonas reinhardtii* and the grazing crustacean *Daphnia magna*. They found that phosphate affected the bioaccumulation and amplification of Ag-NPs in *Daphnia magna*. Zhou et al. (2016) investigated the interaction of exopolymeric substances (EPS) with citrate and polyvinyl pyrrolidone (PVP) coated Ag-NPs and its roles in bioaccumulation and toxicity of the Ag-NPs to *Chlorella pyrenoidosa*. They found that EPS inhibited of bioaccumulation of Ag-NPs and Ag-NPs-released toxic ions. 12 nm non-coated Ag-NPs resulted in Ag ions accumulation in the blood, liver, kidneys, spleen, stomach and small intestine after oral exposure to male rats. After 250 mg/kg of body weight daily doses exposure, the highest Ag contents were detected in the liver (0.87 ± 0.37 mg/g of organ) and kidney (0.24 ± 0.02 mg/g of organ) (Hendrickson et al., 2016). Ag-NPs firstly accumulated predominately in liver and spleen, and then dissolved and released Ag ions to accumulate in other organs of rats (Su et al., 2014). Bioaccumulation is an important process of Ag-NPs toxicity and migration in the aquatic ecosystem. Ag-NPs can be surface adsorbed and internalized by organisms and amplified though the food chain. The physicochemical properties of Ag-NPs are also relevant to bioaccumulation and amplification in the environment. The agglomeration process