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NANOSILVER AND ITS TOXICITY

Nanogümüş ve Toksisitesi

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ABSTRACT

The term nano means one billionth of something; nanometer(nm) also represents a billion of meter. Nanomaterials are materials which have at least one diameter between 1 to 100 nm. The materials at the nano-scale have many new features different from the properties of the bulk material, for this reason nano-sized materials have found wide application area nowadays. Nanosilver is one of the most widespread usage areas of nanomaterials. Nano silver is used for water purification, wound care, reconstructive orthopedic and cardiovascular surgery equipments, sun cream, food packaging, cosmetics, textiles, household appliances, biological imaging, medical diagnosis and treatment. Exposure to nano-silver is rapidly increasing due to its wide range usage. Results of nanosilver studies have been revised in the present review to draw attention to these exposures.

Keywords: nanoparticle, nanosilver, toxicity, nanomaterial, silver

ÖZET

Nano terimi bir şeyin bir milyarda biri anlamına gelmektedir, nanometre de metrenin bir milyarda birini ifade etmektedir. Nano malzemeler en az bir çapı 1-100 nanometre arasında olan malzemelerdir. Nano ölçekteki malzemeler kütlesel malzemelerin özelliklerinden çok farklı olan yeni özelliklere sahiptir, buna bağlı olarak nano boyutlu malzemeler günümüzde geniş kullanım alanı bulmaktadır. Nanogümüş en geniş kullanım alanı olan nano malzemelerin başında gelmektedir. Nanogümüş su temizlemede, yara bakımında, rekonstrüktif ortopedik ameliyatlarda, kardiyak aletlerde, güneş kremlerinde, yiyeceklerin paketlerinde, kozmetikte, tekstilde, elektrikli ev aletlerinde, biyolojik görüntülemede, tıpta tanı ve tedavi amacıyla kullanılmaktadır. Bu geniş kullanım alanlarına bağlı olarak nanogümüş maruziyeti hızla artmaktadır. Bu maruziyete dikkat çekmek için bu derlemede nanogümüş ile yapılan çalışmalar ve sonuçları gözden geçirilmiştir.

Anahtar Kelimeler: nano parçacık, nanogümüş, toksisite, nano materyal, gümüş

INTRODUCTION

Silver has been widely used due to antibiotic characteristics in particular during the history. It has a wide area of usage such as water transportation, wound care, materials used for bone prosthesis and reconstructive orthopaedic materials as well as surgical materials including cardiovascular equipments and catheters (1).

Terms of colloidal silver, silver nanoparticles or nanosilver means silver materials with dimensions varying between 1 and 100 nm (2).

The Woodrow Inventory List which is related to nanosilver materials includes 440 materials like healthcare materials, air freshener, detergents, washing machine, materials for water purification, wall paints, personal care products, sun screens, materials used for food packaging, food additives, cosmetic and textile products (3). Furthermore, nanosilver has a wide medical use such as biological imaging, diagnosis (4, 5) and treatment (6).

Consequently, due to wide area of use, gradually increasing entrance of nanosilver into the human body through inhalation, skin, urogenital system, blood and digestive tract (7).

MEDICAL USE OF NANOSILVER

Antimicrobial efficacy of nanosilver has been defined during 19th century; however, after introduction of penicillin in 1940, antibiotics have been used as a standard treatment for bacterial infections and use of silver was discontinued. Silver has started to be used for treatment of burns during 1960s and silver sulfadiazine, a combined form of silver with sulfonamide has taken place as a broad spectrum antibiotic treatment for burn. However, due to current resistance of the bacteria against antibiotics, wound care materials including silver with varying ratios are preferred by clinicians (8).

Some silver ions enter into the cell whereas some of them interact with the cell wall. A trial conducted with Escherichia coli (E. coli) exposed to silver nanoparticles showed significant changes and a severe damage on interior surface of bacteria membrane, characterized with accumulation. Furthermore, trials performed by silver ions which have negative charge did not change the result; this indicates that interaction of silver with the membrane is not associated with negative charge of the membrane or positive charge of silver (9). Besides cell wall, silver ions inside the cell also affect the bacteria; the mechanism is DNA condensation and loss of replication capability as well as triggering inactivation of bacterial proteins through binding of the proteins to thiol groups (10). Bacteriostatic and bactericidal effect of silver ion on E.coli are closely associated with the dose (11).

Silver ion affects gram negative bacteria more than gram positive bacteria; the reason is that cell wall of gram positive bacteria is thicker than cell wall of gram negative bacteria (10).

Nanosilver has size-dependent interaction with Human Immunodeficiency Virus-1 (HIV-1); only nanosilver particles with a size of 1 to 10 nm bind to the virus. Given the fact that regular spatial location of binding nanosilver particles, distance between centers of nanosilver particles and disulphide bonding are primary binding regions for a nanoparticle, nanosilver preferably interacts with glycoprotein 120 (Gp120) of HIV-1. Due to aforesaid interactions, nanosilver inhibits adsorption of HIV-1 to host cells (12).

Silver coating of artificial silicon heart valves was considered to prevent bacterial infection and to reduce inflammatory response (13); however, the metal silver prepared for this purpose was detected as a cause of hypersensitivity reactions in patients as well as paravalvular leakage associated with inhibition of fibroblast function (14). Multilayer film application including nanosilver presents antibacterial as well as anticoagulant efficiency and does not have a cytotoxic effect (15).

A study investigating effect of nanosilver-coated urinary catheter on coagulase-negative staphylococci such as Staphylococcus epidermidis

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showed that nanosilver coating prevents bacterial adsorption and colony formation (16).

Nanocrystal silver particles reduce infection frequency after use of postoperative prosthetic patch and are useful as coating for prosthetic materials (17).

Bone cement including nanosilver with different concentrations was used; the cement including 1% of nanosilver inhibited staph. epidermidis, methicillin resistant staph. epidermidis and methicillin resistant staph. aureus proliferation; furthermore, no toxic finding was detected by cytotoxicity tests (18).

Silver ion release of the silver ion implanted filling material was shown as an antibacterial effect against oral streptococci (19). It was determined that a resin mixture combined with a material including nanosilver has a long term inhibitor effect against streptococcus mutans (20). A harder surface than conventional mixtures, less bacterial adhesion and slower bacterial colony formation were detected with nanosilver (21).

First topical application of silver nitrate was possibly for chronic wound treatment. Since no alive epithelial component on the wound surface in dermal burns, healing is dependent to epithelization and contraction on the wound edges. Therefore, wide wounds with less blood circulation heal slowly. Microorganism colony formation also cause a delay on healing process (22).

Pomades containing silver sulfadiazine are used topically for antibacterial efficiency in treatment of burns; as a result, significant advantages may be achieved through prevention of resistance development in bacteria (23).

Treatment with nanosilver material dressing was found less painful when compared with silver sulfadiazine and the cause of pain decrease was suggested easy change and long use of nanosilver material dressing (24). Wound dressing with nanosilver coating reduced healing process by 3.35 days than silver sulfadiazine and facilitated bacterial decontamination from infected wounds (25). Wound dressing with nanosilver coating was shown to increase healing in superficial burn wound dressing than silver sulfadiazine; however, no change was detected for deep burns (26). This indicates that nanosilver increases epithelial tissue formation but does not affect angiogenesis.

DISTRIBUTION OF NANOSILVER

Nanosilver was administrated to the rats subcutaneously to search distribution and accumulation of nanosilver; it was observed that nanosilver entered to blood circulation and diffused in the body mainly in kidneys, liver, spleen, brain and lungs. However, the aforesaid trial expressed that nanosilver damaged blood-brain barrier and caused neuronal degeneration together with increase in astrocyte cell volume (27).

Oral nanosilver administration to rats for 3 days to investigate possible hepatotoxic effects of nanosilver revealed hepatic lymphocyte infiltration and increase in gene expression related to apoptosis. Such increase also appears with silver microparticle, but, dominant with nanosilver (28).

After intraperitoneal administration of nanosilver, nanosilver was reported as a cause of apoptosis and neurotoxicity by modifying oxidative stress and gene expression due to toxic effects in the brain (29).

Gender-dependent difference of nanosilver accumulation was determined in the rat kidney; nanosilver accumulates more in female kidney than male kidney (30). This difference was shown to appear for all parts of the kidney including the cortex, internal and external medulla. Nanosilver preferably accumulate in basal membrane of renal tubules, medial and terminal parts of the internal medulla and in external medulla (31). It was stated that a 23 nm nanosilver which entered into the cell in renal tissue has not settled inside the nucleus and tended to aggregate in the cytoplasm without any different vesicle formation (32).

Diabetes mellitus is probably the widest metabolic disease worldwide (33) and individuals suffering from this disease incrementally increase (34). Systemic complications are most important mortality and morbidity causes for diabetes (35). Such complications lead significant problems in patients (36).

Diabetic foot ulcer is one of important complications associated with this disease. Since healing is very slow in these ulcers, contribution of multiple microbial infections to the progress may occur. Therefore, cases progressing to amputation of the extremities because of severe exudate formation on the foot may appear (37).

Secondary infections develop in retarded diabetic sores; therefore, materials containing silver nanoparticles and silver ions were reported to be useful. Such nanoparticles were specified to be helpful for diabetic patients for early wound healing with minimum scar. Silver nitrate remains to be a common antimicrobial agent used for treatment of chronic wounds (38).

A significant and relative decrease was observed in blood glucose levels of the diabetic patients whom nanosilver was applied. Furthermore, a hepatic glucokinase activity increase was determined after nanosilver application when compared with other diabetic patients (39). Nanosilver prevents final product of glycolysis and acts as an antidiabetic agent (40).

TOXICITY OF NANOSILVER

Some questions still remain enlightened while searching side effects of nanomaterials in nanotoxicology. These are: how much of the ions released from a nanomaterial is responsible from toxic effects, how much of physical characteristics of nanomaterials cause toxic effects, what is the level of oxidative stress on toxicity, do nanomaterials accumulate within the body, if do, in which cell types and subcellular formations do they tend to aggregate (41).

A previous research conducted on human epithelial colorectal adenocancer (Caco-2) cells exposed to nanosilver within the range of 0 to 200µg/ml for 24 hours determined that radical oxygen species (ROS) and superoxide dismutase were not significantly induced and a significant increase in intracellular glutathione level was observed (42).

Toxicity of nanosilver was shown to be dependent to the dose and particle size. It was found that nanosilver over 20 nm may enter into the cell less and cause less ROS production, increase proinflammatory interleukin-8 (IL-8) production less at high doses, affect cellular viability less and thereby cause less toxicity in the cell (7).

Nanosilver in different doses was applied to human skin carcinoma cells and human fibrosarcoma cells and nanosilver was found toxic as dose dependent and effective dose of nanosilver was found different according to the cell type (43). A study comparing fibroblast and liver cells showed that liver cells are naturally resistant against nanosilver when compared with fibroblasts; furthermore primary cells were shown to be more resistant against toxic effect of nanosilver than secondary cell series (44). This finding indicates that toxic effect of nanosilver on a cell depends on the cell type.

A previous study searching toxicity of nanosilver on fibroblast cell found that ROS formation, release of cytrochrome c to cytosole and translocation of Bax protein to the mitochondria were induced by nanosilver. This indicates mitochondria dependency of apoptosis in the fibroblast cells mediated by nanosilver (45).

A study carried out on root cell series of male rat spermatogonium showed a dose-dependent toxicity of nanosilver on the germinal cell (46).

Two different effects of nanosilver on coronary endothelial cell were found. Low dose nanosilver acts as an anti-proliferative/vasoconstructive factor disrupting nitric oxide (NO) production; however, high doses of nanosilver stimulates proliferation/vasorelaxation through NO (47). Such finding indicates that dose is very important for nanosilver toxicity.

When intracellular distribution of nanosilver was investigated, distribution both in nucleus and mitochondria was found. This finding raises the thought that nanosilver directly causes a DNA damage. Since nanosilver is inside the mitochondria, deterioration of mitochondrial respiration chain and thereby causing ROS-mediated damage are considered. Furthermore, nanosilver application is stated to stop cell cycle at G2/M phase (48).

It was detected in application of nanosilver on a rat macrophage cell series that dose-dependent nanosilver suppressed G1 and S phases of the cell cycle and induced apoptosis. There are different consider-

ations whether nanosilver toxicity is caused by the nanoparticle itself or the silver ion. Some investigators support the idea that nanosilver passes typical barrier by acting like a “trojan horse” and then release silver ion which is harmful for cellular mechanisms (49). Others argue about biological effects of nanosilver similar to silver ion (50). However, the argument that silver ions cannot explain toxicity alone and therefore nanosilver contributes to toxic effect (51) has become important. Nanosilver causes cellular and DNA damage while creating a carcinogenic, oxidative stress; genes regulating metal detoxification/metabolism as well as genes related to radical scavenging were induced. On the other hand, silver ion causes an inflammatory response and metallic detoxification process, but less stress response in total when compared with nanosilver (52).

CONCLUSION

A general view on size- and dose-dependent effect of nanosilver on cellular formations exists; however, there is not any sufficient information about safe dose and size range as yet. No consensus about cellular structures affected by nanosilver and its mechanism of action on these structures could be reached. It is still controversial whether the modifications appeared on these structures are caused by nanosilver itself or ion form of nanosilver. Different views indicate necessity of clearer scientific approaches about nanosilver and its toxicity as well as further studies.

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Conflict of Interest

The author declares that he has no conflict of interest