Chapter 7

Biological Activity of Silver Nanoparticles and Their Applications in Anticancer Therapy

Magdalena Skonieczna and Dorota Hudy

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.77075

Abstract

Nanotechnology delivers materials and nanoparticles (NPs) with high biological potential, useful in bioengineering, nanomedicine, and human health protection. Silver nanoparticles (NPs), because of their wide spectrum of activities and physical and chemical properties, are nowadays extensively researched. However, careful studies on living organism should be performed, with strong attention to biocompatibility. Multiple cellular effects, displayed after AgNP treatments, show interesting potential of metal-based NPs, not only in bio-nanotechnology but also in molecular medicine and anticancer therapy. AgNPs are promising anticancer agents, influencing the cell cycle, inhibiting cancer proliferation, and inducing oxidative stress and propagation of programmed cellular death (apoptosis). Additionally, they protect against bacterial, fungal, and viral infections. During chemo- and radio-therapies, such antimicrobial protection will be desirable because of the decreased immunological resistance of cancer patients. In conclusion, AgNPs often present in the human environment should be studied for novel findings and better characteristic. This article discusses advantages of AgNP's "eco-friendly" production, followed by green synthesis, with particular consideration of antimicrobial and anticancer properties. Cellular processes, induced after AgNP treatments, are focused on antiproliferative, pro-oxidative, and pro-apoptotic activities of NPs.

Keywords: silver nanoparticles (AgNPs), nanotechnology, anticancer therapies, microbiological activity, nanoparticles (NPs), cancer cell lines

1. Introduction

Nanotechnology has developed a wide spectrum of engineered materials, composites, and particles, which in size are defined as nanoscale (below 100 nm) [1]. Comprised of different

compounds, nanocomposites have opened possibilities for applications in fields of bioengineering for agriculture [2], green technology [3], antifungal plant protection [4], and different strategies for human and animal health care—from tissue remodeling and scaffold production in regenerative medicine [5] or antiviral [6], antimicrobial [6, 7], and anticancer therapies [7, 8], in conventional/unconventional medical and veterinary science (**Figure 1**) [10, 11].

Among engineered materials various compounds are used including metals: silver (Ag) [12, 13], gold (Au) [13, 14], copper (Cu) [14], zinc (Zn) [15, 16], gallium (Al) [17], metal oxides [16], and many others [1, 18, 19]. Based on the physical and chemical approaches of metal-based nanoparticles, numerous features can be used in their applications, including shape recognition, paramagnetic properties, biocompatibility, fluorescence, and optical density [19]. Some NPs are suitable in diagnostic techniques, because of their paramagnetic behavior, unique optical properties, and quantum size effect used in bio-imaging (**Figure 2**) [18]. NPs can be used separately, as spheres 10 nm [12] or 18 nm in diameter as reported by Zielinska et al. [20] diluted in aqueous citrate buffer. Colloidal solutions of AgNPs were for that reason applied at different concentrations of particles per ml of solvent. In combination with different active compounds such as antibiotics, AGNP complexes, with improved size of their active surfaces, improved cytotoxicity against bacteria [9]. Because of their antibacterial properties and biocompatibility with human cells, many of active commercially designed Ag-based compounds are used for nanomaterial production, including by the coaxial electrospinning process [5].

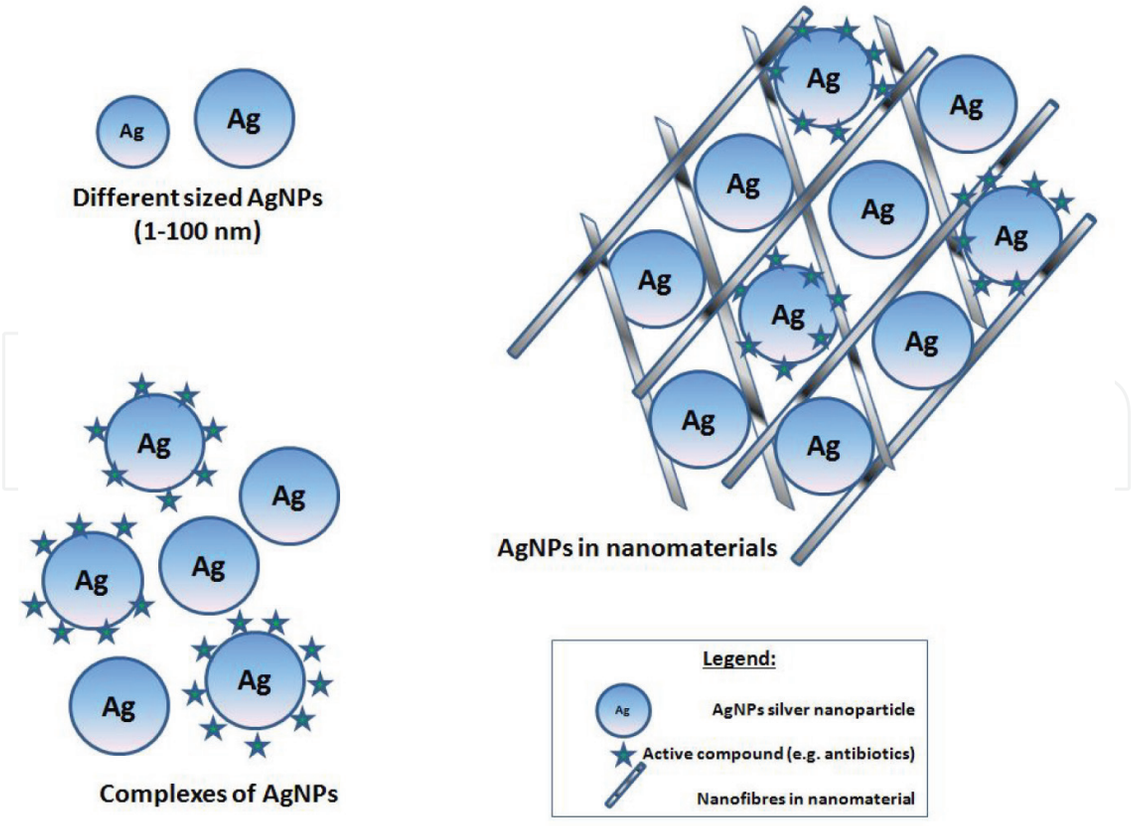

Figure 1. Types of applications for AgNPs as different-sized single particles in self-organized complexes with active compounds (e.g., antibiotics) or in nanofabricated materials (based on [5, 9]).

http://dx.doi.org/10.5772/intechopen.77075

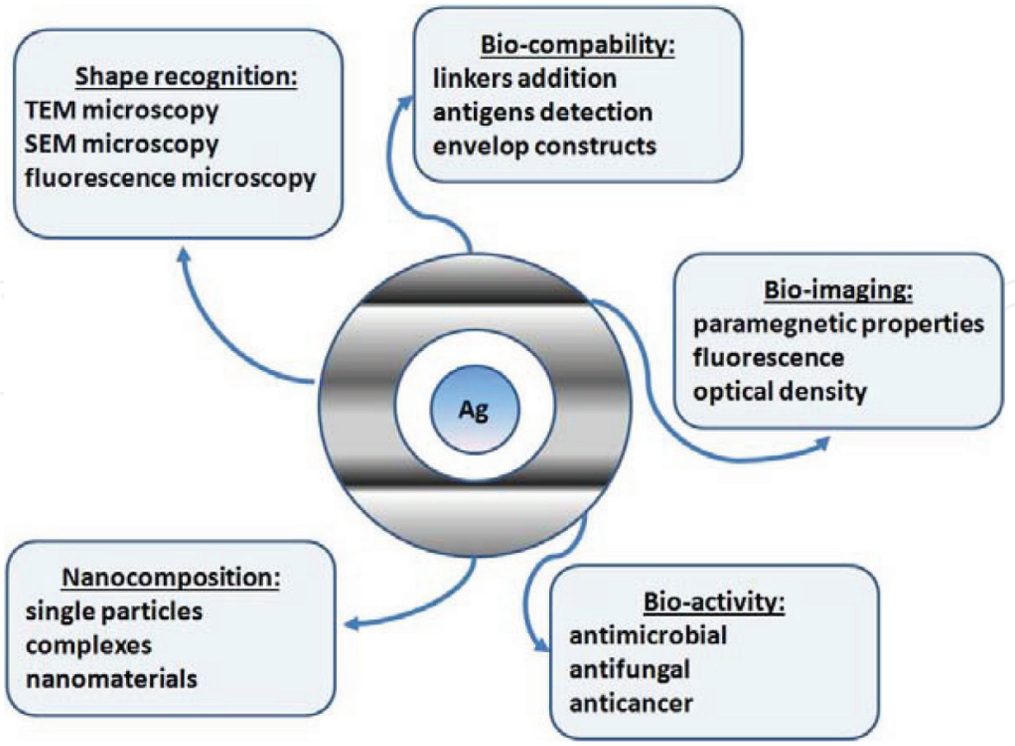

Figure 2. Physical and chemical properties of AgNPs implicated in their applications (based on [18]).

2. Characteristics of silver nanoparticles

Silver nanoparticles (AgNPs) are well known because of their wide spectrum of applications in diverse fields of research; this review will focus on their biological activities. For such reason size-dependent physical and chemical properties of AgNPs are discussed [18]. Living organisms are one-cell or multicellular structures with typically 10 μm across for a single cell, so the much smaller nanoparticles (NPs) (1–100 nm) can interact with cell surfaces (plasma membranes, plant cellulose walls, bacterial and fungal cell walls, and membranes). NPs or their active nano-complexes can penetrate and pass through the organism's external envelopes. The plasma membrane's permeability for small-sized AgNPs allows for accumulation of them in internal compartments of cells. Physical properties of Ag are used for tracking and visualization of NPs in living organisms and cells using, for example, TEM micrography or X-ray absorption spectroscopy [21]. The uptake mechanisms of NPs in eukaryotic cells were observed to be phagocytosis, endocytosis, or micropinocytosis [22] and were rather dose-dependent with diverse protection or cytotoxicity effects [21]. NPs must be well characterized before addition to cells and their physical and chemical properties well defined. These properties result mainly from different protocols of AgNP synthesis, and only nontoxic ones should be preferred in bioassays using living organisms.

2.1. Synthesis of AgNPs

Different strategies of AgNP synthesis should be focused on novel methods for ecological fabrication, allowing toxic chemical discrimination. Some so-called eco-friendly methods were

developed using ethanol extracts from many plant species, for example, ethanolic extract of *Rosa indica* petals [7]. Other procedures followed by encapsulation, microemulsions, or dispersion in polymeric solutions, based generally on plants or algae, also bacteria [23], and fungi organism. Intra- or externalization of NPs into one-cell organisms resulted with protein tagging, for example, AgNPs covered with proteins from the fungus *Coriolus versicolor* [24]. Protein-conjugated NPs could play a role of mimetic envelopes constructed from cellular proteins during inter- or externalization processes in living one-cell organisms. Bio-AgNP coverings stabilize NPs and extend the possibilities of their application in living tissues [24]. During simple aqueous synthesis, temperature elevation of a starch solution for 20 h above room temperature, with addition of silver nitrate and glucose is sufficient to produce eco-starched AgNPs [23]. It was reported also that virus particles also seem to be useful in NP production (**Figure 3**) [23].

2.2. Antimicrobial activity

2.2.1. Antibacterial properties

Among the biological activities of AgNPs, an antimicrobial action is already well characterized [7–9, 25]. The most effective is an antiproliferative impact where in a minimum inhibition concentration (MIC) assay, inhibition of bacterial growth on plate cultures is observed. Typically, the tests are made both Gram-negative and Gram-positive bacteria, with plate agar, liquid LB medium (lysogeny broth, named also Luria-Bertani medium), or a migration assay. It was reported, in MIC assays against different bacterial strains and human pathogenic bacteria such as *Streptococcus* mutants (MTCC-896), *Enterococcus faecalis* (MTCC-439) (Gram-positive), *E. coli*

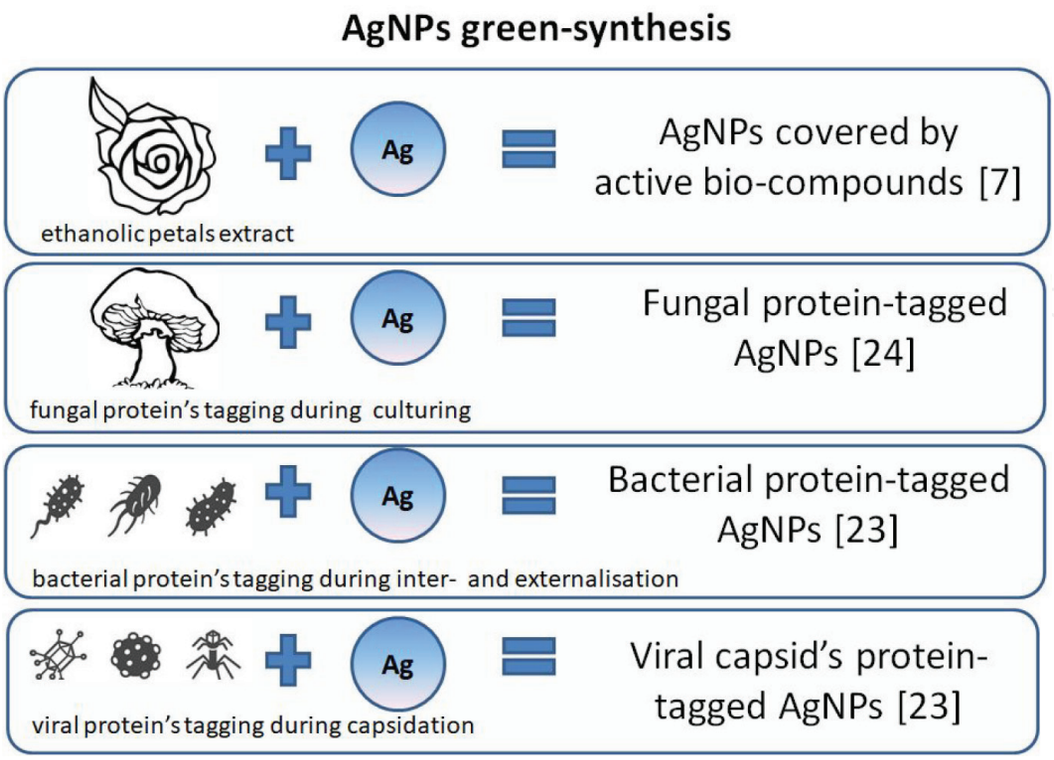

Figure 3. Scheme of green-synthesized "eco-friendly" AgNPs (based on [7, 23, 24]).

(MTCC-40), and *Klebsiella pneumonia* (MTCC-740) (Gram-negative), it was reported that addition of ethanolic petal extract of *Rosa indica* or $AgNO_3$ solutions (each 30 μl) reduced significant microbial proliferation significantly [7]. The mechanism of action that resulted in proliferative potential reduction during MIC assays was explained by the good permeability of AgNPs through the bacterial wall and plasma membranes [7]. The cytotoxic effect was improved when biologically synthesized nanoparticles were used together with $AgNO_3$ solutions [7]. On the other hand, addition of Ag^+ ions to the culture media resulted in reduction of biofilm formation by bacteria during growth. Anti-biofilm formation effects of AgNPs were observed against Gram-positive (*Enterococcus faecalis* and *Staphylococcus aureus*) and Gram-negative (*Shigella sonnei* and *Pseudomonas aeruginosa*) bacteria in biological assays [6]. Other pathogens, strains of *Escherichia coli*, *Staphylococcus aurous*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, and *Haemophilus influenzae*, were inhibited by AgNPs synthesized with leaf extract of *Artemisia vulgaris* [3]. The inhibitory effect was discussed there in terms of plasma membrane interaction of AgNPs and release of Ag^+ ions into the cytoplasm that eventually resulted in disruption of respiratory mechanisms located in in the bacterial membrane and mesosomes, and also of ion exchange processes, and blockade of synthesis of sulfur-containing proteins on ribosomes [3]. All of those schemes of action demonstrate the antimicrobial properties of AgNPs and implicate their usage as anti-pathogenic agents reducing the proliferative potential of microbes.

2.2.2. Antifungal properties

The unicellular *fungi*, and mostly multicellular *fungi*, are responsible within plant agricultures for plant diseases. They are cost-risky and noneconomic for vegetables and fruit farms, also during long-term production, storage, and transportation procedures. AgNP addition during plant growth could play a role of environmentally safe anti-fungicides [4, 26, 27]. AgNPs, added at different concentrations to agar plates, were very effective against plant phytopathogenic fungi in studies of 18 different fungal species [4]. In vitro studies showed a hypothetical molecular mechanism of action for AgNPs, where released Ag^+ ions into the cytoplasmic compartment of fungal cells disrupt respiratory system and have an impact on DNA replication process and on expression of genes implicated in replication [4, 28, 29]. Multifunctional bio-applications of AgNPs 20 nm in size were studied for protection against pathogenically species of fungi, strains of *Trichophyton mentagrophytes* and *Candida* species, in immunosuppressed patients [30]. Similar effects, with reduction of proliferation, were observed on agar plate assays against species potentially pathogenic for plants and humans: *Penicillium brevicompactum*, *Chaetomium globosum*, *Cladosporium cladosporioides*, *Mortierella alpina*, *Stachybotrys chartarum*, and *Aspergillus fumigatus* [30].

2.2.3. Antiviral properties

Anti-pathogenic activity of AgNPs is wide, and the spectrum of their action has been reported against viral infections in plants, animals, and humans [6, 31]. The most effective prevention against diseases caused by different viruses is an antiviral vaccine. Although effective vaccines have not been discovered against every viral infection, antiviral agents are still being developed, and AgNPs are also in this potential group [31]. Human viral diseases such as influenza, human immunodeficiency virus, hepatitis, chickenpox, infectious mononucleo-

sis, herpes keratitis, or viral encephalitis are still studied with novel therapeutics, because of their high mortality risk in the human population, together with increases of virus resistance against already used pharmaceuticals [31]. The interaction of AgNPs, synthesized by a biological method using fungi, was tested against herpes simplex virus types 1 and 2 (HSV-1 and HSV-2, respectively) and human parainfluenza virus type 3 (HPIV-3) [31]. In these reports the particular mechanism of prevention against viral infection in Vero cells *in vitro* was explained as a physical barrier, built by NPs [31]. Monolayer culture of Vero cells were preincubated with AgNPs for 1 h at 37°C and then infected with HSV-1, HSV-2, or HPIV-3 and in the next 2 days, the monolayers were fixed and stained with X-gal (HSV-1 and HSV-2) or crystal violet (HPIV-3), and plaque numbers were scored [31]. The final results showed a lower infectiveness of viruses for cells pretreated with AgNPs in comparison to untreated cells without NPs [31]. Size-dependent mechanical protection against Monkeypox virus infection was also previously reported in vitro, in tests with 10 nm AgNPs a, with significant inhibition of disease [32]. In human cells the addition of AgNPs could inhibit enzymes responsible for DNA replication, a crucial process for further viral infection [31]. Pure AgNPs, synthesized by the electrochemical method were tested against poliovirus by adding different concentrations of AgNPs were added to human rhabdomyosarcoma (RD) monolayer cells before viral infection [33]. The results confirm silver protection against poliovirus infection, with the cell viability up to 98% at 48 h postinfection [33]. For the food industry it is important to avoid viral infections within a big farm where the animals are cultured and are crowded. Food production in India could be endangered by infectious bursal disease (IBD) virus [34] and therefore alternative technology against IBD virus using AgNPs started to be developed. This strategy is based on two schemes, inoculation of viral particles first for 2 h with active AgNP solutions and then injection of such mixtures into embryonated chicken eggs, whereas the second method is first infection of embryonated chicken eggs with virus and then the AgNP injection. In both strategies the viral infection was reduced [34].

Antiviral activity of silver nanoparticles (AgNPs) is still unknown and needs to be studied, because of its usefulness for human applications. However, not only direct action on virus particles is important in developing novel strategies against viral infections. In many cases an intermediate carrier/host is required in the replication cycle of a virus, and a strategy was developed against such a vector using AgNPs fabricated with *Pedalium murex*, an ancient Indian medicinal plant's seed extract, for inducing mortality in mosquito's larvae stage [6]. Zika virus needs the vector *Aedes aegypti* for a complete replication cycle and spreading the disease. AgNPs fabricated with *P. murex* extract tested on fourth instar mosquito larvae reduced the viability of Zika vector after 24 h [6]. This promising finding showed a wide spectrum of applications of different fabricated AgNPs alone against different viral infections and diseases. The mode of action could be direct or indirect.

2.3. Anticancer activity

Combined cancer therapy allows limitation of the side effects of chemotherapy, decreasing effective doses or inducing cellular self-protection against damaging agents [35]. For many aspects of conventional therapies, combinations of novel drugs and NPs together with already well known compounds, is still tested. Searching for more effective protocols for drug

http://dx.doi.org/10.5772/intechopen.77075

administration leads to the modification of already existing procedures and combining pharmacological agents with natural, unconventional molecules. Metal-based AgNPs, known as pro-oxidative in different cancer cell lines [36] including breast MCF-7 and lung A549 cells [37] and squamous carcinoma SCC-25 cells [12], have shown novel applications in photodynamic therapy [37, 38]. The alkaloid berberine was tested on squamous carcinoma cells as an antiproliferative and pro-apoptotic agent alone [22, 39–41] or in combination with AgNPs that improved its anticancer properties [12]. The antimicrobial activity of AgNPs as aseptic or preservative agents has been known since decades, and they also serve for synthesis of novel nanomaterials with potential applications in regenerative medicine [5]. For many applications, compounds such as metal NPs should be carefully examined, especially when they are easily applied by living organisms.

2.3.1. Antiproliferative activity

Use of AgNPs in the food industry, as antimicrobial preservatives, has an impact on the human digestive tract. Interactions of AgNPs with healthy cells (epithelial cells, mucous membrane cells, etc.) and cancer cells (squamous, liver, or colon cells) through the gastrointestinal tract has implicated diverse actions of NPs as anti- or pro-oncogenic factors. Knowledge about processes of carcinogenesis are still unclear; however, applications of AgNPs as anticancer agents is nowadays strongly developed. The most widely used AgNPs disrupt the proliferative system and cell cycle of cancer cells, with finally inhibition of proliferation. Tested on squamous carcinoma SCC-25 cells, colloidal solutions of 10-nm-diameter NPs at a dose of 10 ng/ml arrested the cell cycle in the sub-G1 or G0/G1 phase after 24 and 48 h, respectively [12]. The cells responded with a failure of mitosis, and in the treated population there were not as many bi-nucleated and doublet cells as in controls. DNA synthesis was also stopped, probably because of DNA damage (single- and double-stranded breaks, sSBs and dSBs) and because of the presence of AgNP's inside the cell nuclei. This suggestion was confirmed by measuring production of reactive oxygen species (ROS) in parallel cytometric assays, which damage DN, influence the S-phase of the cell cycle, and inhibit replication [12]. Additionally, cell proliferation was monitored by colorimetric MTT assays, where absorbance measured at 570 nm is proportional to the amount of cells in each well on a plate. This simple assay showed that after AgNP treatment, viability and proliferation of SCC-25 cells decreased in dose-dependent manner with increased concentration of AgNPs [12]. Larger 20 nm diameter AgNPs also displayed antiproliferative effects at higher concentrations (up to 20 μg/ml) in two cancer cell lines, HepG2 (liver) and Caco-2 (colon) when cytotoxicity was estimated fluorometrically by the resazurin (Alamar Blue) reduction assay [42] in which nonfluorescent Alamar Blue is taken up by viable cells and reduced by mitochondria to the fluorescent product resorufin. Fluorescence is proportional to the viability of the cells and corresponds to the cell number [42]. After 24 h of incubation with AgNPs, viability and proliferation of HepG2 cells were more reduced than those of Caco-2 cells; however, in both cell lines they were significantly lower than untreated controls [42]. Tests on different human cell line models showed tissue-dependent sensitivity and the importance for applied doses potentially used in anticancer therapies of NPs. The same research group, working again with HepG2 and Caco-2 cells, discussed the genotoxic potential of AgNPs as a result of chromosome damage

during mitosis, where chromosomal abnormalities occurred as seen by micronucleus formation (Mn assay) [43]. The nanosilver genotoxicity resulted in viability reduction in a dose-dependent manner and was explained by cytokinesis blockade [43], which could be a result of abnormal formation of histone H2A, that disrupts cellular division and proper chromatin (chromosome) formation [44]. AgNPs act also as epigenetic factors and influence genetic profiles in treated cells [45]. It was reported that several genes could be impacted by AgNPs, especially those related to the cell cycle, where they could be upregulated or downregulated. The most important findings were connected with genes coding for cell cycle checkpoint proteins and also for DNA repair pathways during the S-phase [45–47]. All of these molecular disruptions resulted in the antiproliferative action of AgNPs in living cells, especially in cancer and cancer stem cells [44].

2.3.2. Pro-oxidative activity

Most of the findings about toxically effects of AgNPs in antimicrobial and anticancer defense, based on the mitochondrial activation and reactive oxygen species overproduction, are interpreted as pro-oxidative properties. AgNPs possess the ability to induce mitochondrial chain and complex disruption that leads to superoxide anion leakage [12, 22, 48]. After AgNP internalization, into cytoplasm compartments, typically Ag^+ ions are released which influence mitochondrial enzymes and also interact with –SH groups of proteins and glutathione (GSH). In such situation the ROS scavenging potential of GSH decreased and oxidative stress occurred [44]. DNA damage changed gene expression, and cellular death could be manifested as programmed death (apoptosis) [44]. In photodynamic therapy (PDT), AgNPs caused tumor cell sensitization via intracellular ROS overproduction [19, 37, 38]. Ag ions are captured by free electrons, which affect mitochondrial membrane potential (Ψ) and leads to an increase in mitochondrial membrane permeability [45]. The production of intracellular ROS is amplified by the next generation of oxidizing agents and lowered production of ATP by mitochondria in tumor cells [45]. The ROS production and damages resulting from oxidative stress are AgNP size-dependent; smaller NPs cause greater ROS overproduction [1]. Those observations result from the ability of AgNPs to interact with cellular components and to penetrate to organelles (mitochondria, nuclei, liposomes, endoplasmic reticulum, etc.) and to release free Ag^+ ions there (**Figure 4**) [1].

2.3.3. Pro-apoptotic activity

After AgNP internalization into cancer cells, a cascade of processes starts with loss of inner homeostasis and redox state destabilization. A series of free radical waves damages mitochondrial and nuclear membranes and propagates oxidative stress. Additionally, in S-phase (DNA replication) of the cell cycle, damaged DNA is not repaired effectively because repair enzymes are blocked by Ag+ ions and replication stops [12, 49]. Because of uncoupling in mitochondria and effects on mitochondrial membrane potential, the ROS level increases to propagate the canonical apoptotic pathway (**Figure 4**). The mitochondria-dependent apoptosis pathway was studied in SCC-25 cells at the transcriptional level, where expression of the genes Bax and Bcl-2 was assayed [12, 50]. The pro-apoptotic Bcl-2 gene was upregulated after 24 h of treatment with AgNPs [12]. ROS production in Caco-2 cells was manifested also by an inflammatory state that resulted in cellular death due to release of the pro-inflammatory

http://dx.doi.org/10.5772/intechopen.77075

cytokine interleukin(IL)-8 after 24 h of AgNP exposure [49]. This state was also propagated between cells by external pro-apoptotic signals. Use of AgNPs as good pro-apoptotic agents in cancer therapy seems to be reasonable. Toxicity of AgNPs is shown through the intrinsic ROS-mediated mitochondrial apoptotic pathway [49]. AgNPs could propagate a free radical wave, with further lysosomal rupture and free radical accumulation. Lysosomal damage leads to cathepsin release into the cytoplasm, which is a signal for lysosome-mediated apoptosis [1, 51]. Any of these disruptions have been described as cytotoxic effects of AgNPs of different origins; however, the most desirable one is the lethal apoptotic effect on cancer cells.

2.4. Applications of AgNPs

The numerous physical and chemical properties of AgNPs implicate possible applications in the human environment: in agriculture, food industry, cosmetology and finally in human health protection and medicine [1, 2, 13, 19]. Metal-based particles, because of their paramagnetic property and optical density (**Figure 2**), are widely used in bio-imaging as well as in electron microscopy, in magnetic resonance, in computed tomography for visualization, and in molecular diagnostics [19, 21, 50]. AgNPs, as cellular sensitizers with pro-oxidative and pro-apoptotic potential, also serve as therapeutic agents in photodynamic therapy against cancer cells [37, 38]. In future applications some possible controversies must be resolved: dosage for different tissues, because of tissue-specific biocompatibility and side effects during therapy or microbial resistance against NPs. Some effects of AgNPs appear to be dual

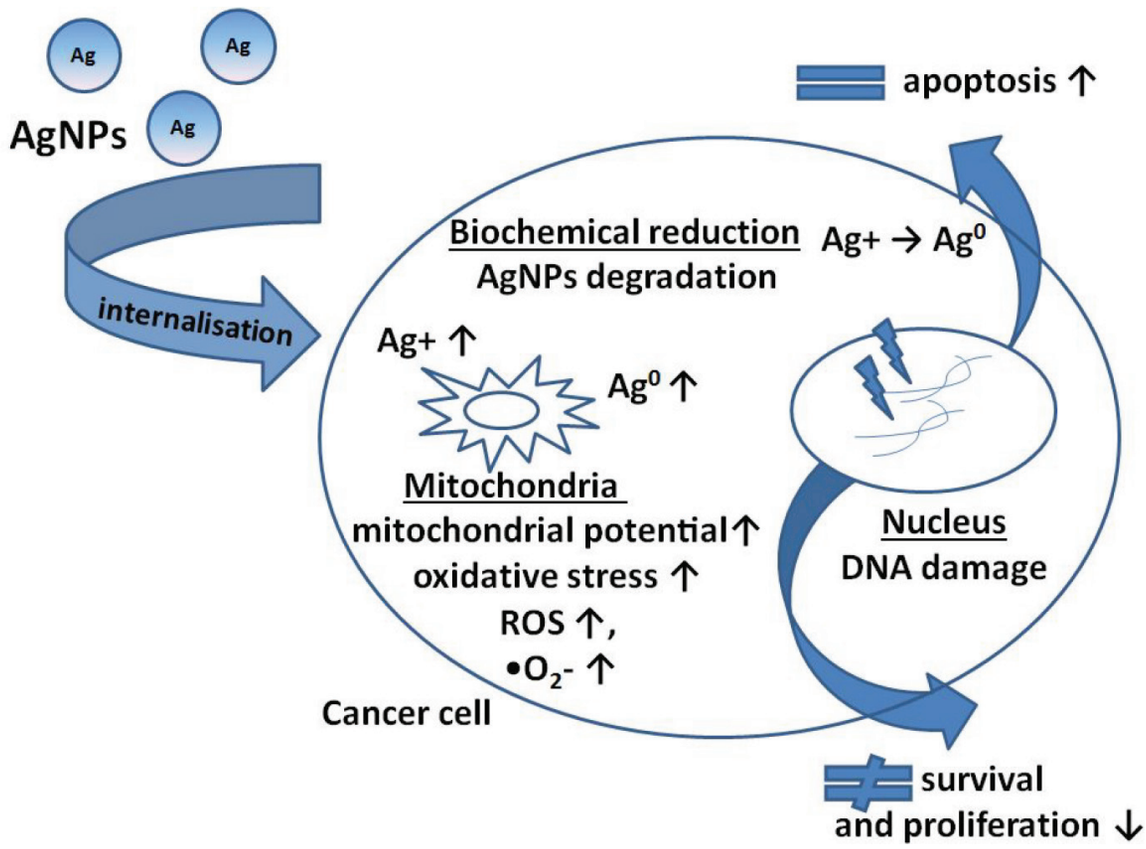

Figure 4. Pro-oxidative activities of AgNPs in cancer cells.

and even opposite in different situations, such as anti- or pro-oxidative, anti- or pro-apoptotic, biosensing, or bioresisting-activity depending on the type of organism or cells [30]. Nanotechnology allows for technical applications of AgNPs, for example for fabrication in material technology [5]. Size-dependent activities and the ability to form different complexes with natural or pharmaceutical compounds have opened further applications for AgNPs, especially in biomaterials, health care, cancer therapy, environment protection, agriculture, and chemical synthesis [5, 9, 52]. Biomedical applications, particularly in nanomedicine, are nowadays the most desirable.

3. Conclusions

Silver nanoparticles, because of their wide spectrum of activities and physical and chemical properties, are nowadays studied extensively. However, careful studies on living organisms should be performed, with strong attention to biocompatibility. Multiple effects displayed after AgNP treatment show an interesting potential of metal-based NPs, not only in bionanotechnology but also in molecular medicine and anticancer therapy. AgNPs are promising anticancer agents: they influence the cell cycle, inhibit cancer cell proliferation, induce oxidative stress, and propagate programmed cellular death (apoptosis). Additionally, they protect against bacterial, fungal, and viral infections. During chemo- and radio-therapies, such antimicrobial protection is desirable, because of the decreased immunological resistance of cancer patients. In conclusion, more studies on AgNPs should be carried out for novel findings and better characteristic of silver NPs.

Acknowledgements

Magdalena Skonieczna received financial support from the Association for the Support of Cancer Research in Gliwice, Poland.

Conflict of interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Author contributions

Magdalena Skonieczna conceived the idea of this review, participated in writing of the manuscript, and performed all literature surveys. Dorota Hudy prepared the figures and reviewed the literature. Both authors were involved in revising the paper's important content, read, and approved the final manuscript.

Author details

Magdalena Skonieczna[1,2]* and Dorota Hudy[1,2]

*Address all correspondence to: magdalena.skonieczna@polsl.pl

1 Biosystems Group, Silesian University of Technology, Institute of Automatic Control, Gliwice, Poland

2 Biotechnology Centre, Silesian University of Technology, Gliwice, Poland

References

[1] Riaz Ahmed KB, Nagy AM, Brown RP, Zhang Q, Malghan SG, Goering PL. Silver nanoparticles: Significance of physicochemical properties and assay interference on the interpretation of in vitro cytotoxicity studies. Toxicology in Vitro. 2017;**38**:179-192. DOI: 10.1016/j.tiv.2016.10.012

[2] Bouwmeester H, Dekkers S, Noordam MY, et al. Review of health safety aspects of nanotechnologies in food production. Regulatory Toxicology and Pharmacology. 2009;**53**(1): 52-62. DOI: 10.1016/j.yrtph.2008.10.008

[3] Rasheed T, Bilal M, Iqbal HMN, Li C. Green biosynthesis of silver nanoparticles using leaves extract of Artemisia vulgaris and their potential biomedical applications. Colloids and Surfaces. B, Biointerfaces. 2017;**158**:408-415. DOI: 10.1016/j.colsurfb.2017.07.020

[4] Kim SW, Jung JH, Lamsal K, Kim YS, Min JS, Lee YS. Antifungal effects of silver nanoparticles (AgNPs) against various plant pathogenic fungi. Mycobiology. 2012;**40**(1):53-58. DOI: 10.5941/MYCO.2012.40.1.053

[5] Hudecki A, Gola J, Ghavami S, et al. Structure and properties of slow-resorbing nanofibers obtained by (co-axial) electrospinning as tissue scaffolds in regenerative medicine. PeerJ. 2017;**5**:e4125. DOI: 10.7717/peerj.4125

[6] Ishwarya R, Vaseeharan B, Anuradha R, et al. Eco-friendly fabrication of Ag nanostructures using the seed extract of Pedalium murex, an ancient Indian medicinal plant: Histopathological effects on the Zika virus vector Aedes aegypti and inhibition of biofilm-forming pathogenic bacteria. Journal of Photochemistry and Photobiology B: Biology. 2017;**174**(July):133-143. DOI: 10.1016/j.jphotobiol.2017.07.026

[7] Baghbani-Arani F, Movagharnia R, Sharifian A, et al. Biosynthesis of silver nanoparticles using ethanolic petals extract of Rosa indica and characterization of its antibacterial, anticancer and anti-inflammatory activities. Journal of Photochemistry and Photobiology B: Biology. 2017;**138**(July):640-649. DOI: 10.1016/j.jphotobiol.2017.07.026

[8] Baghbani-Arani F, Movagharnia R, Sharifian A, Salehi S, Shandiz SAS. Photo-catalytic, anti-bacterial, and anti-cancer properties of phyto-mediated synthesis of silver nanoparticles

from Artemisia tournefortiana Rchb extract. Journal of Photochemistry and Photobiology B: Biology. 2017;**173**(July):640-649. DOI: 10.1016/j.jphotobiol.2017.07.003

[9] Deng H, McShan D, Zhang Y, et al. Mechanistic study of the synergistic antibacterial activity of combined silver nanoparticles and common antibiotics. Environmental Science & Technology. 2016;**50**(16):8840-8848. DOI: 10.1021/acs.est.6b00998

[10] Hill EK, Li J. Current and future prospects for nanotechnology in animal production. Journal of Animal Science and Biotechnology. 2017;**8**(1):1-13. DOI: 10.1186/s40104-017-0157-5

[11] Singla R, Guliani A, Kumari A, Yadav SK. Metallic nanoparticles, toxicity issues and applications in medicine. Chapter 3. In: Yadav SK, editor. Nanoscale Materials in Targeted Drug Delivery, Theragnosis and Tissue Regeneration. Singapore: © Springer Science+Business Media; 2016:41-80. DOI: 10.1007/978-981-10-0818-4

[12] Dziedzic A, Kubina R, Buldak RJ, et al. Silver nanoparticles exhibit the dose-dependent anti-proliferative effect against human squamous carcinoma cells attenuated in the presence of berberine. Molecules. 2016;**21**(3). DOI: 10.3390/molecules21030365

[13] Aueviriyavit S, Phummiratch D, Maniratanachote R. Mechanistic study on the biological effects of silver and gold nanoparticles in Caco-2 cells—Induction of the Nrf2/HO-1 pathway by high concentrations of silver nanoparticles. Toxicology Letters. 2014;**224**(1):73-83. DOI: 10.1016/j.toxlet.2013.09.020

[14] Czerwińska K, Golec M, Skonieczna M, et al. Cytotoxic gold(III) complexes incorporating a 2,2′:6′,2″-terpyridine ligand framework—The impact of the substituent in the 4′-position of a terpy ring. Dalton Transactions. 2017;**46**(10):3381-3392. DOI: 10.1039/C6DT04584G

[15] Maduray K, Karsten A, Odhav B, Nyokong T. In vitro toxicity testing of zinc tetrasulfophthalocyanines in fibroblast and keratinocyte cells for the treatment of melanoma cancer by photodynamic therapy. Journal of Photochemistry and Photobiology B: Biology. 2011;**103**(2):98-104. DOI: 10.1016/j.jphotobiol.2011.01.020

[16] Mishra PK, Mishra H, Ekielski A, Talegaonkar S, Vaidya B. Zinc oxide nanoparticles: A promising nanomaterial for biomedical applications. Drug Discovery Today. 2017; **22**(12):1825-1834. DOI: 10.1016/j.drudis.2017.08.006

[17] Maduray K, Odhav B, Nyokong T. In vitro photodynamic effect of aluminum tetrasulfophthalocyanines on melanoma skin cancer and healthy normal skin cells. Photodiagnosis and Photodynamic Therapy. 2012;**9**(1):32-39. DOI: 10.1016/j.pdpdt.2011.07.001

[18] Salata OV. Applications of nanoparticles in biology and medicine. Journal of Nanobiotechnology. 2004;**6**(3):1-6. DOI: 10.1186/1477-3155-2-12

[19] Rai M, Ingle AP, Birla S, Yadav A, Santos CA Dos. Strategic role of selected noble metal nanoparticles in medicine. Critical Reviews in Microbiology 2016;42(5):696-719. DOI: 10.3109/1040841X.2015.1018131

[20] Zielinska E, Zauszkiewicz-Pawlak A, Wojcik M, Inkielewicz-Stepniak I. Silver nanoparticles of different sizes induce a mixed type of programmed cell death in human pancreatic ductal adenocarcinoma. Oncotarget. 2017 Nov 20;**9**(4):4675-4697. DOI: 10.18632/oncotarget.22563

[21] Veronesi G, Deniaud A, Gallon T, et al. Visualization, quantification and coordination of Ag^{+} ions released from silver nanoparticles in hepatocytes. Nanoscale. 2016;**8**(38):17012-17021. DOI: 10.1039/C6NR04381J

[22] Foldbjerg R, Jiang X, Miclăuş T, Chen C, Autrup H, Beer C. Silver nanoparticles—Wolves in sheep's clothing? Toxicology Research. 2015;**4**:563-575. DOI: 10.1039/C4TX00110A

[23] Raveendran P, Fu J, Wallen SL, Am J. Completely "green" synthesis and stabilization of metal nanoparticles. Journal of the American Chemical Society. 2003;**125**(46):13940-13941. DOI: 10.1021/ja029267j

[24] Sanghi R, Verma P. Biomimetic synthesis and characterisation of protein capped silver nanoparticles. Bioresource Technology. 2009;**100**(1):501-504. DOI: 10.1016/j.biortech.2008.05.048

[25] Bello-Vieda N, Pastrana H, Garavito M, Ávila A, Celis A, Muñoz-Castro A, et al. Antibacterial activities of azole complexes combined with silver nanoparticles. Molecules. 2018;**23**(2):361. DOI: 10.3390/molecules23020361

[26] Jo YK, Kim BH, Jung G. Antifungal activity of silver ions and nanoparticles on phytopathogenic fungi. Plant Disease. 2009;**93**:1037-1043. DOI: 10.1094/PDIS-93-10-1037

[27] Park HJ, Kim SH, Kim HJ, Choi SH. A new composition of nanosized silica-silver for control of various plant diseases. Plant Pathology Journal. 2006;**22**:295-302. DOI: 10.5423/PPJ.2006.22.3.295

[28] Kim SW, Kim KS, Lamsal K, Kim YJ, Kim SB, Jung M, Sim SJ, Kim HS, Chang SJ, Kim JK, et al. An *in vitro* study of the antifungal effect of silver nanoparticles on oak wilt pathogen *Raffaelea sp*. Journal of Microbiology and Biotechnology. 2009;**19**:760-764. DOI: 10.4014/jmb.0812.649

[29] Min JS, Kim KS, Kim SW, Jung JH, Lamsal K, Kim SB, Jung M, Lee YS. Effects of colloidal silver nanoparticles on sclerotium-forming phytopathogenic fungi. Plant Pathology Journal. 2009;**25**:376-380. DOI: 10.5423/PPJ.2009.25.4.376

[30] Zhang X-F, Liu Z-G, Shen W, Gurunathan S. Silver nanoparticles: Synthesis, characterization, properties, applications, and therapeutic approaches. International Journal of Molecular Sciences. 2016;**17**(9):1534. DOI: 10.3390/ijms17091534

[31] Gaikwad S, Ingle A, Gade A, Rai M, Falanga A, Incoronato N, et al. Antiviral activity of mycosynthesized silver nanoparticles against herpes simplex virus and human parainfluenzavirus type 3. International Journal of Nanomedicine. 2013;**8**:4303-4314. DOI: 10.2147/IJN.S50070

[32] Speshock JL, Murdock RC, Braydich-Stolle LK, Schrand AM, Hussain SM. Interaction of silver nanoparticles with Tacaribe virus. Journal of Nanbiotechnology. 2010;**8**:19. DOI: 10.1186/1477-3155-8-19

[33] Huy TQ, Hien Thanh NT, Thuy NT, Chung PV, Hung PN, Le AT, Hong Hanh NT. Cytotoxicity and antiviral activity of electrochemical-synthesized silver nanoparticles against poliovirus. Journal of Virological Methods. 2017 Mar;**241**:52-57. DOI: 10.1016/j.jviromet.2016.12.015. Epub 2016 Dec 28

[34] Pangestika R, Ernawati R, Suwarno. Antiviral activity effect of silver nanoparticles (AgNPs) solution against the growth of infectious bursal disease virus on embryonated chicken eggs with ELISA test. KnE Life Sciences. 2017;**3**(6):536-548. DOI: 10.18502/kls.v3i6.1181

[35] Khuda-Bukhsh AR, Mondal J, Panigrahi AK. Conventional chemotherapy: Problems and scope for combined therapies with certain herbal products and dietary supplements. Austin Journal of Molecular and Cellular Biology. 2014;**1**(1):1-10

[36] Dayem AA, Hossain MK, Lee S, et al. The role of reactive oxygen species (ROS) in the biological activities of metallic nanoparticles. International Journal of Molecular Sciences. 2017;**18**(1):E120. DOI: 10.3390/ijms18010120

[37] Mfouo-Tynga I, El-Hussein A. Photodynamic ability of silver nanoparticles in inducing cytotoxic effects in breast and lung cancer cell lines. International Journal of Nanomedicine. 2014;**9**:3771-3780. DOI: 10.2147/IJN.S63371

[38] El-Hussein A, Hamblin MR. ROS generation and DNA damage with photo-inactivation mediated by silver nanoparticles in lung cancer cell line. IET Nanobiotechnology. 2017;**11**(2):173-178. DOI: 10.1049/iet-nbt.2015.0083

[39] Ho YT, Lu CC, Yang JS, et al. Berberine induced apoptosis via promoting the expression of caspase-8, −9 and −3, apoptosis-inducing factor and endonuclease G in SCC-4 human tongue squamous carcinoma cancer cells. Anticancer Research. 2009;**29**:4063-4070. DOI: 10.1002/mnfr.200900265

[40] Ho YT, Yang JS, Li TC, et al. Berberine suppresses *in vitro* migration and invasion of human SCC-4 tongue squamous cancer cells through the inhibitions of FAK, IKK, NF-kappaB, u-PA and MMP-2 and -9. Cancer Letters. 2009;**279**:155-162. DOI: 10.1016/j.canlet.2009.01.033 Epub 2009 Feb 28

[41] Seo YS, Yim MJ, Kim BH, et al. Berberine-induced anticancer activities in FaDu head and neck squamous cell carcinoma cells. Oncology Reports. 2015;**25**:3025-3034. DOI: 10.3892/or.2015.4312

[42] Sahu SC, Zheng J, Graham L, et al. Comparative cytotoxicity of nanosilver in human liver HepG2 and colon Caco2 cells in culture. Journal of Applied Toxicology. 2014;**34**(11):1155-1166. DOI: 10.1002/jat.2994

[43] Sahu SC, Roy S, Zheng J, Ihrie J. Contribution of ionic silver to genotoxic potential of nanosilver in human liver HepG2 and colon Caco2 cells evaluated by the cytokinesis-block micronucleus assay. Journal of Applied Toxicology. 2016;**36**(4):532-542. DOI: 10.1002/jat.3279

[44] Braydich-Stolle LK, Lucas B, Schrand A, Murdock RC, Lee T, Schlager JJ, et al. Silver nanoparticles disrupt GDNF/Fyn kinase signaling in spermatogonial stem cells. Toxicological Sciences. 2010;**116**:577. DOI: 10.1093/toxsci/kfq148. Epub 2010 May 20

[45] Dubey P, Matai I, Kumar SU, Sachdev A, Bhushan B, Gopinath P. Perturbation of cellular mechanistic system by silver nanoparticle toxicity: Cytotoxic, genotoxic and epigenetic potentials. Advances in Colloid and Interface Science. 2015;**221**:4-21. DOI: 10.1016/j.cis.2015.02.007

[46] Foldbjerg R, Irving ES, Hayashi Y, Sutherland DS, Thorsen K, Autrup H, et al. Global gene expression profiling of human lung epithelial cells after exposure to nanosilver. Toxicological Sciences. 2012;**130**:145. DOI: 10.1093/toxsci/kfs225. Epub 2012 Jul 24

[47] AshaRani PV, Mun LKG, Hande MP, Valiyaveettil S. Cytotoxicity and genotoxicity of silver nanoparticles in human cells. ACS Nano. 2009;**3**:279. DOI: 10.1021/nn800596w

[48] Skonieczna M, Cielar-Pobuda A, Saenko Y, et al. The impact of dids-induced inhibition of voltage-dependent anion channels (VDAC) on cellular response of lymphoblastoid cells to ionizing radiation. Medical Chemistry (Los Angeles). 2017;**13**(5):477-483. DOI: 10.2174/1573406413666170421102353

[49] Chen N, Song Z-M, Tang H, et al. Toxicological effects of Caco-2 cells following short-term and long-term exposure to Ag nanoparticles. International Journal of Molecular Sciences. 2016;**17**(6):974. DOI: 10.3390/ijms17060974

[50] Liu Y, Li X, Bao S, Lu Z, Li Q, Li CM. Plastic protein microarray to investigate the molecular pathways of magnetic nanoparticle-induced nanotoxicity. Nanotechnology. 2013;**24**:175501. DOI: 10.1088/0957-4484/24/17/175501. Epub 2013 Apr 4

[51] Haase A, Rott S, Mantion A, Graf P, Plendl J, Thünemann AF, Meier WP, Taubert A, Luch A, Reiser G. Effects of silver nanoparticles on primary mixed neural cell cultures: Uptake, oxidative stress and acute calcium responses. Toxicological Sciences. 2012;**126**:457-468. DOI: 10.1093/toxsci/kfs003

[52] Calderón-Jiménez B, Johnson ME, Montoro Bustos AR, Murphy KE, Winchester MR, Vega Baudrit JR. Silver nanoparticles: Technological advances, societal impacts, and metrological challenges. Frontiers in Chemistry. 2017;**5**(February):1-26. DOI: 10.3389/fchem.2017.00006

IntechOpen