On the Anti-Cancer Activities of Silver Nanoparticles

Abstract
In the present mini-review silver nanoparticles (AgNPs) due to their superior physicochemical, and biological properties are intensively dealt with. The proper knowledge of these characteristics is essential to maximize their potential applications in many areas while minimizing their hazards to humans and the environment. This manuscript aims to critically review AgNPs synthesized via different approaches, its utilization in cancer treatment and future challenges.

Keywords: Anti-cancer activities; AgNPs; IC50; Plasmon; HepG2; MCF-7; MDAMB231; SKBR3; Rosa indica

Introduction
Silver nanoparticles (AgNPs) constitute a class of materials with sizes in the range 1-100 nm. The interest in the study of AgNPs concerning their various behaviours has recently increased because of their unique and attractive physical, chemical, and biological properties [1-7]. AgNPs are also known to have particular functions regarding toxicity, surface plasmon resonance, and electrical resistance. Based on these, intensive research works have been conducted to investigate their properties and potential applications for several purposes such as antimicrobial agents in wound dressings, anticancer agents, electronic devices, and water treatment as well [8-15].

Cancer is a group of diseases, generating various pathological and metabolic changes in cellular environments. It is developed through diverse signaling mechanisms including cell proliferation, angiogenesis, and metastasis [16,17]. Cancer cells have abnormal metabolic activities in aerobic glycolysis, mitochondrial DNA depletion, and alterations in respiratory chains and genomic expressions. The physical and chemical treatments of cancer are limited at different stages. However, currently available therapies have an adverse effect and affect normal cell functions while giving excess drug and radiation exposures [18,19].

A marginal increase in cancer cases within the last few years ends up mostly, with death [20]. In several cancer types, we have to manipulate satisfactory medicine carriers similar to drug delivery to be applied as adequate chemotherapeutic agents [21,22]. Recently, AgNPs are reported to modulate the Pgp activity and therefore enhance the chemotherapeutic efficacy against multi-drug resistant cancer cells, thus, further emphasizing their excellent potential as combinational partners [23]. Moreover, the genotoxicity of AgNPs is supported by the generation of double-stranded DNA breaks along with chromosomal instability that drives the initiation of apoptotic execution [24,25]. This acting mechanism implies that AgNPs can be mutually associated with a great many DNA-targeting anticancer drugs (Figure 1).

![Figure 1: Mechanism of action of silver nanoparticles against cancer cells.](image)

There is several review papers published to address the issues associated with AgNPs regarding their toxicity properties during their use as antimicrobial agents for textiles, dental biomaterials, and bio-detectors, as well as during their syntheses [26-34]. For instance, toxicity properties including cytotoxicity and genotoxicity of capped or uncapped AgNPs have been reviewed in detail [35]. Their toxicity mechanisms after oral exposure were also thoroughly discussed [36]. Also, a recent review of AgNPs had focused on their synthesis using plant extracts for antimicrobial applications [37]. Most of the above studies concentrate chiefly on
the different synthesis methods and their bactericidal activities. The reviews on the anticancer activity are somewhat seldom. Therefore, this review aims to present the anticancer activities for silver nano-particles synthesized from different sources.

### Anticancer activity of silver nanoparticles

The Metallo-pharmaceuticals were included within the research field that was previously dominated by organic compounds and natural products. Many platinum and platinum-based compounds including carboplatin and oxaliplatin were approved as antitumor agents [30]. However, numerous drawbacks of platinum-based pharmaceuticals were reported proving, therefore, their curative effects.

Many cancer types are not susceptible to platinum drugs, and there are many toxic side effects, including gastrointestinal and haematological toxicity [39]. Moreover, several cancer cells have either intrinsic or acquired resistance to other platinating agents and cisplatin [40]. Consequently, current anticancer research has been devoted to the discovery of novel transition metal compounds. While silver was initially investigated because of its advantageous antimicrobial activity, there has been a recent interest in its anticancer functions (Table 1).

| AgNPs Synthesis Route | Tested Cancer Cell                                                                 | Reference |
|-----------------------|----------------------------------------------------------------------------------|-----------|
| plant dandelion- *Taraxacum officinale* | human liver cancer cells (HepG2)                                                  | [41]      |
| Plant Extract- *Commelina nudiflora* L | HCT-116 colon cancer cells                                                        | [42]      |
| Plant extracts of guava and clove | human colorectal adenocarcinoma, the human kidney, human chronic myelogenous, leukaemia, bone marrow, and human cervix | [43]      |
| Plant Extract- *Nostoc linckia* | MCF-7                                                                            | [31]      |
| Chemical synthesis | A549 (Human lung carcinoma), HeLa (Human cervical adenocarcinoma), MCF7 (Human breast adenocarcinoma), MDAMB231 (Human breast adenocarcinoma), and SKBR3 (Human breast adenocarcinoma) cells | [44]      |
| Plant Extract-ethanolic extract of rose (Rosa indica) petals | human colon adenocarcinoma cancer cell line HCT 15 | [42]      |

Saratale et al. [41] developed AgNPs from common medicinal plant dandelion, *Taraxacum officinale* and showed their high cytotoxic effect against human liver cancer cells (HepG2) [41]. The AgNPs Synthesized by Kuppasamy et al. [42] Using *Commelina nudiflora* L [42] aqueous extract showed a reduced cell viability and increased cytotoxicity against HCT-116 colon cancer cells. Biofunctionalized silver nanoparticles synthesized within different plant extracts of guava and clove showed the satisfactory anti-cancer effect against four different cancer cell lines; human colorectal adenocarcinoma, the human kidney, human chronic myelogenous, leukaemia, bone marrow, and human cervix [43]. The developed silver nanoparticles using a proteinaceous pigment phycocyanin extracted from Nostoc linckia as reducing agent exhibited effective cytotoxic activity against MCF-7. The inhibitory concentration (IC50) was 27.79 ± 2.3μg/ml [31]. Moreover, the chemically synthesized AgNPs composites possessed promising anticancer activity against the A549 (Human lung carcinoma), HeLa (Human cervical adenocarcinoma), MCF7 (Human breast adenocarcinoma), MDAMB231 (Human breast adenocarcinoma), and SKBR3 (Human breast adenocarcinoma) cells [44]. Kuppasamy et al. [42] successfully bio-synthesized silver nanoparticles using the ethanolic extract of rose (Rosa indica) petals. The Ag functionalized extract proved potential anticancer activity against human colon adenocarcinoma cancer cell line HCT 15 [42].

### Effect of silver nanoparticles size on their anticancer activity

The biological effects of various metal nanoparticles in p53-deficient tumor cells as well as *in vitro* tumor stroma and *in vivo* metastasis models were investigated [45]. A higher cytotoxicity was recorded for the smaller, 5 nm sized silver nanoparticles compared to their larger counterparts. Additionally, it was concluded that silver nanoparticles could induce apoptosis-dependent programmed cell death in the absence of the tumor suppressor p53. Conventional cancer therapy often fails to cause cell death in p53-deficient cancer cells. The unique chemotherapeutic potential of such developed AgNPs was proved. Moreover, it was concluded that nanoparticles of size 5-35 nm primarily induced cell death through the mitochondrial structure and function targeting. Although the smaller Ag nanoparticles are more cytotoxic, the apoptotic action mechanism of both 5 and 35 nm was identical [46]. Interestingly, the cytotoxic features of silver and silver hybrid nanoparticles are cell-type dependent. In this domain, a higher cytotoxicity was recorded against cancer cells compared to non-cancerous fibroblasts. Conclusively, the stimulation of tumor-associated fibroblast cells with metal nanoparticles represents a typical therapeutic strategy. Since the treatment by Ag and Ag hybrids suppress the cancer cell promoting the activity of a tumor associated fibroblasts. Additionally, the *in vivo* results proved the ability of Ag/hybrids to inhibit the 4T1 tumor metastatic spreading in mice. Impressively, Ag hybrids can enhance the therapeutic efficacy of intravenous doxorubicin treatment [47].

### Conclusion

The silver nanoparticles proved unique anticancer activity against different types of cancer cells. The several syntheses approaches significantly affect the cytotoxic activity of the achieved Ag nanoparticles. Future challenges on AgNPs synthesis...
and their release into the environment other than scaling up production, assess several potential avenues for future works are to promote a safer and more efficient utilization of these nanoparticles.

Acknowledgement

None.

Conflict of Interest

None.

References

1. Mohammed Fayaz A, Balaji K, Girilal M, Yadav R, Kalichelman PT, et al. (2010) Biogenic synthesis of silver nanoparticles and their synergistic effect with antibiotics: a study against gram-positive and gram-negative bacteria. Nanomedicine: Nanotechnology, Biology and Medicine 6(1): 103-109.

2. Sharma VK, Yngard RA, Lin Y (2009) Silver nanoparticles: green synthesis and their antimicrobial activities. Adv Colloid Interface Sci 145(1-2): 83-96.

3. Kwak JL, An YJ (2016) Trophic transfer of silver nanoparticles from earthworms disrupts the locomotion of springtails (Collembola). J Hazard Mater 315: 110-116.

4. Huang Z, Chen G, Zeng G, Guo Z, He K, et al. (2017) Toxicity mechanisms and synergies of silver nanoparticles in 2,4-dichlorophenol degradation by Phanerochaete chrysosporium. J Hazard Mater 321: 37-46.

5. Sun X, Shi J, Zou X, Wang C, Yang Y, et al. (2016) Silver nanoparticles interact with the cell membrane and increase endothelial permeability by promoting VE-cadherin internalization. J Hazard Mater 317: 570-578.

6. Desireddy A, Conn BE, Guo J, Yoon B, Barnett RN, et al. (2013) Ultrasilvablesilver nanoparticles. Nature 501(7467): 399-402.

7. Kumar A, Praveen Kumar Vemula, Pulickel M Ajayan, George John (2008) Silver-nanoparticle-embedded antimicrobial paints based on vegetable oil. Nature Materials 7(3): 236-241.

8. Habiboollah G, Mahdi Z, Majid Z, Nasroollah S, Taghavi A, et al. (2014) Enhancement of Gingival Wound Healing by Local Application of Silver Nanoparticles Periodontal Dressing Following Surgery: A Histological Assessment in Animal Model. Modern Research in Inflammation 3(3): 128-138.

9. Kaur J, Tikoo K (2013) Evaluating cell specific cytotoxicity of differentially charged silver nanoparticles. Food Chem Toxicol 51: 1-14.

10. Chen D, Qiao X, Qiu X, Chen J (2009) Synthesis and electrical properties of uniform silver nanoparticles for electronic applications. Journal of Materials Science 44(4): 1076-1081.

11. Dankovich TA, Gray DG (2011) Bactericidal Paper Impregnated with Silver Nanoparticles for Point-of-Use Water Treatment. Environ Sci Technol 45(5): 1992-1988.

12. Mangala Praveena S, Suk Han L, Lung Than LT, Zaharin Aris A (2016) Preparation and characterization of silver nanoparticle coated on cellulose paper: evaluation of their potential as antibacterial water filter. Journal of Experimental Nanoscience 11(17): 1307-1319.

13. Mthombeni NH, Mpenya-Monyatisi L, Onyango MS, Momba MN (2012) Breakthrough analysis for water disinfection using silver nanoparticles coated resin beads in fixed-bed column. J Hazard Mater 217-218: 133-140.

14. Zhang H, Oyanedel-Craver V (2013) Comparison of the bacterial removal performance of silver nanoparticles and a polymer based quaternary amine functionalized silsesquioxane coated point-of-use ceramic water filters. J Hazard Mater 260: 272-277.

15. Sypafiddin A, Salmiati Salim MR, Beng Hong Kuek A, Hadibarata T, Nur H (2017) A Review of Silver Nanoparticles: Research Trends, Global Consumption, Synthesis, Properties, and Future Challenges. Journal of the Chinese Chemical Society 64(7): 732-756.

16. Jason R Mann, Raymond N DuBois (2004) Cancer chemoprevention: myth or reality? Drug Discovery Today: Therapeutic Strategies 1(4): 403-410.

17. Seigneuric R, Markey L, Nuyten DS, Dubernet C, Eevelo CT, et al. (2010) From nanotechnology to nanomedicine: applications to cancer research. Curr Mol Med 10(7): 640-652.

18. Rothwell PM, Wilson M, Elvin CE, Norrving B, Algra A, et al. (2010) Long-term effect of aspirin on colorectal cancer incidence and mortality: 20-year follow-up of five randomised trials. Lancet 376(9754): 1741-1750.

19. Wu X, Patterson S, Hawk E (2011) Chemoprevention–history and general principles. Best Pract Res Clin Gastroenterol 25(4-5): 445-459.

20. Raghunandan D, Ravishankar B, Sharanbasava G, Bedre Mahesh D, Harsoor V, et al. (2011) Anti-cancer studies of noble metal nanoparticles synthesized using different plant extracts. Nanotechnology 2(1-6): 57-65.

21. Wafa Abdel-Fattah, Abdel Sattar M'Sallam, Nagwa A Atwa, E Salama, Ahmed M Maghraby, et al. (2014) Functionality, antibacterial efficiency and biocompatibility of nanosilver/chitosan/silk/phosphate scaffolds 1. Synthesis and optimization of nanosilver/ chitosan matrices through gamma rays irradiation and their antibacterial activity. Mater Res Express 1(3): 035024.

22. Abdel-Fattah WI, Eid MM, Ab El-Moaz SI, Mohamed E, Ali GW (2017) Synthesis of biogenic Ag@Pd Core-shell nanoparticles having anti-cancer/anti-microbial functions. Life Sci 183: 28-36.

23. Ignar K, Kovác D, Rázy Z, Kónya Z, Borosi IM, et al. (2016) Modulating chromatin structure and DNA accessibility by deacetylation inhibition enhances the anti-cancer activity of silver nanoparticles. Colloids Surf B Biointerfaces 146: 670-677.

24. Jiang X, Foldbjerg R, Micaus T, Wang L, Singh R, et al. (2013) Multi-platform genotoxicity analysis of silver nanoparticles in the model cell line CHO-K1. Toxicol Lett 222(1): 55-63.

25. Souza TA, Franchi LP, Rosa LR, Da Veiga MA, Takahashi CS (2016) Cytotoxicity and genotoxicity of silver nanoparticles of different sizes in CHO-K1 and CHO-XRS5 cell lines. Mutat Res Genet Toxicol Environ Mutagen 795: 70-83.

26. Riaz Ahmed KB, Nagy AM, Brown RP, Zhang Q, Malgham SG, et al. (2017) Silver nanoparticles: Significance of physicochemical properties and assay interference on the interpretation of in vitro cytotoxicity studies. Toxicol In Vitro 38: 179-192.

27. Maurer LL, Meyer JN (2016) A systematic review of evidence for silver nanoparticle-induced mitochondrial toxicity. Environ Sci Nano 3: 311-322.

28. Benjamin Le Ouay, Francesco Stellacci (2015) Antibacterial activity of silver nanoparticles: A surface science insight. Nano Today 10(3): 339-354.

29. Singh R, Shedalkar UU, Wadhwani SA, Chopade RA (2015) Bacteriogenic silver nanoparticles: synthesis, mechanism, and applications. Appl Microbiol Biotechnol 99(11): 4579-4593.
30. Barbara Simončič, Danijela Klemenčič (2016) Preparation and performance of silver as an antimicrobial agent for textiles: A review. Textile Research Journal 86(2): 210-223.

31. Rajeshkumar S (2016) Green Synthesis of Different Sized Antimicrobial Silver Nanoparticles using Different Parts of Plants- A Review. International Journal of ChemTech Research 9(4): 197-208.

32. Mashwani ZI, Khan T, Khan MA, Nadhman A (2015) Synthesis in plants and plant extracts of silver nanoparticles with potent antimicrobial properties: current status and future prospects. Appl Microbiol Biotechnol 99(23): 9923-9934.

33. Nidhiya Roy, Archana Gaur, Aditi Jain, Susinjan Bhattacharyya, Vibha Rani (2013) Green synthesis of silver nanoparticles: An approach to overcome toxicity. Environmental Toxicology and Pharmacology 36(3): 807-812.

34. Tarun Kumar Sharma, Aradhana Chopra, Mahak Sapra, Dinesh Kumawat, Supriya Deepak Patil, et al. (2012) Green Synthesis and Antimicrobial Potential of Silver Nanoparticles. International Journal of Green Nanotechnology 4(1): 1-16.

35. De Lima R, Seabra AB, Durán N (2012) Silver nanoparticles: a brief review of cytotoxicity and genotoxicity of chemically and biogenically synthesized nanoparticles. J Appl Toxicol 32(11): 867-879.

36. Galluzzi L, Senovilla L, Vitale I, Michels J, Martins I, et al. (2012) Molecular mechanisms of cisplatin resistance. Oncogene 31(15): 1869-1883.

37. El-Naggar NE, Hussein MH, El-Sawah AA (2017) Bio-fabrication of silver nanoparticles by phycocyanin, characterization, in vitro anticancer activity against breast cancer cell line and in vivo cytotoxicity. Sci Rep 7(1): 10844.

38. Melaiye A, Sun Z, Hindi K, Milsted A, Ely D, et al. (2005) Silver(I)-imidazole cyclophane gem-diol complexes encapsulated by electrospun teopholic nanofibers: Formation of nanosilver particles and antimicrobial activity. J Am Chem Soc 127(7): 2285-2291.

39. Kascatan-Nebioglu A, Melaiye A, Hindi K, Durmus S, Panzer MJ, et al. (2006) Synthesis from caffeine of a mixed N-heterocyclic carbene-silver acetate complex active against resistant respiratory pathogens. J Med Chem 49(23): 6811-6818.