# Silver NanoParticles

Summary:
1. smaller sizes desirable due to greater surface area, and cell penetration ( enhanced permeability and retention (EPR) effect)
2. - two main types: AgNP and silver ions
3. Dose example 80kg person: 1.12-2mg/day, which can be calculated based on ppm and volumne taken (see below)
target < 10ppm and 120mL per day (30ppm and 1L per day caused argyria 30mg/day ) (Case Report: 9-15 ppm@120mL, i.e. 1.1mg/L to 1.8mg/L per day)
likely 10ppm --> 10mg/L, hence if take 100mL, then 1mg/day? (for Cancer)
The current Rfd for oral silver exposure is 5 ug/kg/d with a critical dose estimated at 14 ug/kg/d for the average person
seems like the Cancer target range is 14ug/kg/day to 25ug/kg/day. 80Kg example: 1.12mg to 2mg
" 1.4µg/kg body weight. If I would have 70kg, I would want to use 100µg/day. However, for fighting active disease, I would tend to explore higher daily dose, as I think this may be too low."

4. AntiOxidants/NAC can counter act the effect of Silver NanoParticles from producing reactive oxygen species (ROS) and mitochondrial damage .
**NAC** is a supplement form of **cysteine**, an amino acid that helps make glutathione, a powerful antioxidant.

https://en.wikipedia.org/wiki/Silver_nanoparticle

There have been several studies that describe the *in vitro* toxicity of silver nanoparticles to a variety of different organs, including the lung, liver, skin, brain, and reproductive organs.[107] The mechanism of the toxicity of silver nanoparticles to human cells appears to be derived from oxidative stress and inflammation that is caused by the generation of reactive oxygen species (ROS) stimulated by either the Ag NPs, Ag ions, or both.[108][109][110][111][112] For example, Park *et al.* showed that exposure of a mouse peritoneal macrophage cell line (RAW267.7) to silver nanoparticles decreased the cell viability in a concentration- and time-dependent manner.[111] They further showed that the intracellular reduced glutathionine (GSH), which is a ROS scavenger, decreased to 81.4% of the control group of silver nanoparticles at 1.6 ppm.[111]

**Citrate reduction**
An early, and very common, method for synthesizing silver nanoparticles is citrate reduction. This method was first recorded by M. C. Lea, who successfully produced a citrate-stabilized silver colloid in 1889.[18] Citrate reduction involves the reduction of a silver source particle, usually $AgNO_3$ or $AgClO_4$, to colloidal silver using trisodium citrate, $Na_3C_6H_5O_7$.[19] The synthesis is usually performed at an elevated temperature (~100 °C) to maximize the monodispersity (uniformity in both size and shape) of the particle. In this method, the citrate ion traditionally acts as both the reducing agent and the capping ligand,[19] making it a useful process for AgNP production due to its relative ease and short reaction time. However, the silver particles formed may exhibit broad size distributions and form several different particle geometries simultaneously.[18] The addition of stronger reducing agents to the reaction is often used to synthesize particles of a more uniform size and shape.[19]

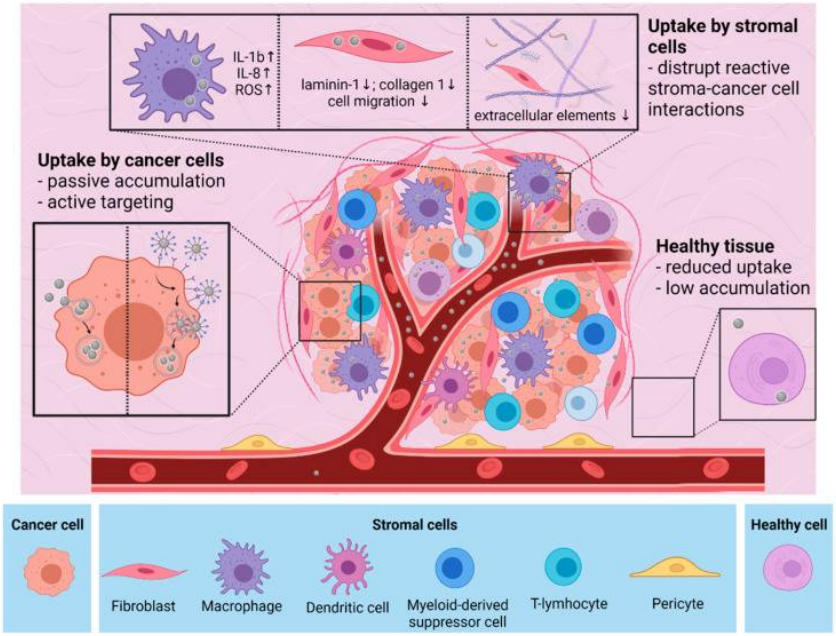
https://prairiedoghall.com/wp-content/uploads/2020/05/Cancer-cured-with-nano-silver-1.pdf
**Activity and pharmacology of homemade silver nanoparticles in refractory metastatic head and neck squamous cell cancer 2018**
**Background**: Silver nanoparticles (AgNP) show efficacy in cancer cell lines. We present the first in-human outcome of AgNP in a cancer patient.
**Methods**: Homemade AgNP solution is manufactured using online instructions by a 78-year old male. He started consuming AgNP while on hospice after he developed nasal cavity squamous cell cancer metastatic to liver and lung.
**Results**: Electron microscopy of AgNP solution revealed bimodal nanoparticle size distribution: 3 and 12 nm. Inductively coupled plasma mass spectrometry showed basal silver ion concentrations of 32 ng/g, rising to 46 ng/g 1 hour after ingesting 60 mL of AgNP solution. Urine showed no AgNP. No toxicities were observed and he had complete radiographic resolution of his cancer. He remains without evidence of cancer 18 months later.
**Conclusions**: AgNP ingestion was associated with sustained radiographic resolution of cancer. Further testing of AgNP should be done to confirm its efficacy in head and neck cancer.

After the time of diagnosis of metastatic disease, the patient began to manufacture and consume an AgNP solution, with the following method of production. Twelve ounces of distilled water is placed in a glass container containing two bars of 99.99% pure silver. Three 9-V radio batteries are hooked in series, producing a positive lead at one end and a negative lead at the other, resulting in a total output of 27 V of electricity. A current is applied until the metal content of the water measures **0.09-0.15 ppm** using a water tester, and this process averages 1 hour in duration. The resulting solution is strained with a mesh cloth to filter out remaining silver precipitate and the product is subsequently stored in a dark glass bottle.
He ingested 120 mL of the solution daily for 3 months during which time he had significant clinical improvement. The patient was seen at our facility with a completely normal functional status and feeling much better than when he had started hospice.

https://www.cancertreatmentsresearch.com/a-silver-bullet-to-kill-cancer/
Note: I actually have doubts that the patient discussed above measured 0.09 to 0.15 ppm. The accuracy of the water testers available online is such that it can measure minimum 1 ppm and not o.o1 ppm. These devices, usually have a display that shows 3 digits (Ref.). So I suspect that the man in the case report above reported to his doctors that he was measuring 009 to 015 ppm as it was displayed, but the MDs noted 0.09 to 0.15 ppm while that was actually 9 to 15ppm. This also makes sense to me given that the time used to create the solution was about an hour. If that is the case, he may have used a dose of up to 25ug/kg/day. If this is true, this dose is above what is considered to be a critical dose estimated at 14 ug/kg/d for the average person (Ref.). Yet, this is inline with doses suggested online, e.g. 3 to 6 ounce/day of 8ppm solution (Ref.) or even more (Ref.). This is my guess and I would like to verify this as soon as possible with the authors, but it would mean that the patient used a dose 100x higher compared to what is stated in the article. Actually, the fact that the patient was using mash cloth to filter out the remaining precipitated silver also indicated that the concentration he was getting was in the range of 10 to 20ppm (see this video to understand what I mean).

https://pmc.ncbi.nlm.nih.gov/articles/PMC8777983/
**Cancer Therapy by Silver Nanoparticles: Fiction or Reality? 2022**
In addition to anti-microbial activities, AgNPs possess unique cytotoxic features against mammalian cells as well, which properties render silver-based nanoparticles potentially applicable in tumor therapy. While a rapidly growing number of scientific data support their possible application as anti-cancer agents, to

develop silver nanoparticle-based therapeutic modalities with high efficacy and reliable safety, numerous issues should be elucidated in advance.
AgNPs also own this beneficial “nano” property, and all the advantages of a nano-system, e.g., the size-surface ratio or tunable surface, as well as intrinsic cytotoxic features, through reactive Ag ions (“silver” property). Therefore, AgNPs can be considered a two-in-one therapeutic system. Despite these favorable features, AgNPs appear to be somewhat toxic to healthy tissues [6,7]; therefore, it is important to assure that the applied nanoparticles accumulate preferentially only or mainly in the cancerous tissue, leaving other non-target organs unaffected.
Several research groups demonstrated the exceptional potential of AgNPs as anti-cancer agents; however, they have also emphasized that the toxic behavior of these nanomaterials renders them somewhat similar to conventional chemotherapy drugs.
Nevertheless, the main difference between AgNPs and conventional small molecular drugs lies within the “nano” nature of AgNPs, which ultimately helps to reduce the severity of undesired side effects. As a result of this nano-feature, AgNPs can be targeted either passively or actively to the tumor tissues, where they can, thus, accumulate in high concentrations (Figure 2). Passive accumulation is based on the unique architecture of the tumor tissue, where neo-angiogenesis leads to an atypical endothelial layer and to fenestrated vasculature, which together with the impaired lymphatic drainage guides the penetration and accumulation of nano-sized materials within the cancerous tissues [26]. This phenomenon is called the enhanced permeability and retention (EPR) effect, which has been exploited for drug design in the nanomedicine field [27]. It has also been proposed that shape, size, and capping materials applied on the surface of the nanoparticles can help to optimize their passive accumulation.




In fact, AgNP-triggered effects in tumor-associated macrophages have not been published so far, although it was shown that AgNPs of various sizes increase IL-1b and IL-8 mRNA levels and induce reactive oxygen species (ROS) production in macrophages [53].
Nanoparticle size has also been recognized as an important factor determining cellular uptake. A total of 5, 20, 50, and 100 nm AgNPs were added to methyl-beta-cyclodextrin- (caveolin-mediated endocytosis inhibitor)- and 5-(N-ethyl-N-isopropyl)-Amiloride (macro- and pinocytosis inhibitor)-treated cells, and it has been found that the uptake of smaller nanoparticles was suppressed by the caveolin-mediated endocytosis inhibitor treatments, while the macro- and pinocytosis inhibitors decreased predominantly the uptake of larger AgNPs, 50 and 100 nm [66]. We found that 5 nm and 35 nm AgNPs trigger identical apoptotic pathways in osteosarcoma cells, showing that once the smaller or larger AgNPs are internalized, their size does not affect the way of action [67].
As ROS are potent inducers of autophagy, it seems feasible that the mediator of AgNP-induced autophagy would be oxidative stress [113].

https://pmc.ncbi.nlm.nih.gov/articles/PMC7915205/
**Green Silver and Gold Nanoparticles: Biological Synthesis Approaches and Potentials for Biomedical Applications 2021**
The present review provides a comprehensive collection of the most recent green methodologies, surveys the major nanoparticle characterization techniques and screens the effects triggered by the obtained nanomaterials in various living systems to give an impression on the biomedical potential of green synthesized silver and gold nanoparticles.
Plants contain complex structures that can be used in the reduction and stabilization of the nanoparticles [57]. Plant materials generate nanoparticles by taking up, utilizing, accumulating and using different nutrients [58]. The general protocol for a typical plant-mediated metal nanoparticle synthesis requires first the collection and the purification of the plant part of interest [59]. The plant piece is then dried and powdered. For the plant extract preparation, usually, deionized distilled water is added to the plant powder according to the desired concentration. This solution is boiled and finally filtered. A certain volume of the extract is mixed with the appropriate amount of metal salt solution and the mixture is heated to the necessary temperature for the prescribed time under efficient mixing. To achieve the desired nanoparticles, optimization of every protocol is mandatory using different temperatures, solvents, pH conditions, extract concentrations and incubation times [60,61]. The reduction of metal ions to metal nanoparticles results in a color change of the solution, which can then be monitored by assessing UV-visible spectra.

https://www.researchgate.net/publication/236066545_Silver-based_nanoparticles_induce_apoptosis_in_human_colon_cancer_cells_mediated_through_p53
**Silver-Based Nanoparticles Induce Apoptosis in Human Colon Cancer Cells Mediated Through P53 2013**
The authors have systematically investigated the anticancer potentiality of silver-based nanoparticles (AgNPs) and the mechanism underlying their biological activity in human colon cancer cells. Materials & methods: Starch-capped AgNPs were synthesized, characterized and their biological activity evaluated through multiple biochemical assays. Results: AgNPs decreased the growth and viability of HCT116 colon cancer cells. AgNP exposure increased apoptosis, as demonstrated by an increase in 4′,6-diamidino-2-phenylindole-stained apoptotic nuclei, BAX/BCL-XL ratio, cleaved poly(ADP-ribose) polymerase, p53, p21 and caspases 3, 8 and 9, and by a decrease in the levels of AKT and NF-κB.
Several lines of evidence suggest that AgNPs have a wide variety of applications in diverse fields, including cancer chemotherapy. Recently, investigators reported that AgNPs are capable of reducing tumor-cell growth in vivo and in vitro [11,12]. However, there is a lack of literature regarding the use of AgNPs as anticancer agents against colon cancer cells. Moreover the detailed biochemical mechanisms of the anticancer activity of AgNPs were not known. In the present report, we have shown for the first time that AgNPs exhibit anticancer activity in colon cancer cells and determined the mechanism of action. This study has systematically established the anticancer activity of AgNP colon cancer cells

**Executive summary**

③ Starch-embedded stable silver-based nanoparticles (AgNPs; 20-nm diameter) were synthesized, characterized and investigated for potential anticancer activity.
③ The AgNPs inhibited the proliferation of colon cancer cells in a dose-dependent manner.
③ AgNPs induced DNA damage and an S-phase arrest of the cell cycle.
③ Cell death induced by the AgNPs occurred through p53-dependent apoptosis.
③ Proapoptotic markers (BAX/BCL-XL, cleaved poly(ADP-ribose) polymerase, p53, p21, and caspases 3, 8 and 9) increased.
③ The antiapoptotic markers, AKT and NF-kB, decreased in AgNP-treated cells.
③ The transcription factor activity of NF-kB decreased after AgNP treatment.
③ The expression profile of BAX, BCL-XL, p21 and NF-kB proteins remained unchanged after AgNP treatment in HCT116 p53-/- cell lines, confirming their p53 dependence.

https://pmc.ncbi.nlm.nih.gov/articles/PMC10417642/

**Biogenic Silver Nanoparticles for Targeted Cancer Therapy and Enhancing Photodynamic Therapy 2023**

Biogenic (green) metallic silver nanoparticles (AgNPs) obtained using plant-mediated protocols are attractive to researchers exploring cancer treatment. Biogenic AgNPs present advantages, since they are cost-effective, easy to obtain, energy efficient, and less toxic compared to chemically and physically obtained AgNPs. Also, they present excellent anticancer abilities thanks to their unique sizes, shapes, and optical properties. This review provides recent advancements in exploring biogenic AgNPs as a drug or agent for cancer treatment. Thus, great attention was paid to the anticancer efficacy of biogenic AgNPs, their anticancer mechanisms, their efficacy in cancer photodynamic therapy (PDT), their efficacy in targeted cancer therapy, and their toxicity.

Innovative therapeutic intervention for cancer via nanotechnology suggests metallic silver nanoparticles (AgNPs) as promising nanoproducts for cancer treatment. They are confirmed to have anticancer properties, including the selective obstruction of the respiratory chain in the mitochondria, resulting in reactive oxygen species (ROS) and impairment of DNA [11]. AgNPs are obtained via the transformation of silver ions using nanotechnology into ultra-small materials that are quantified in nanometers (nanoscale) [12].

Moreover, great antitumor effects of AgNPs have been reported [1], and biogenic AgNPs can ameliorate the anticancer ability of photodynamic therapy (PDT) [16]. Moreover, carryover phytochemicals in biogenic AgNPs can be liberated in cancerous cells due to their acidic microenvironment, and they can aid in augmenting the anticancer efficacy of AgNPs.

For instance, metallic nanoparticles including AgNPs are known to strongly react when in contact with light, and this is known to be a surface plasmon resonance (SPR) phenomenon [81,82].

For instance, silver is known to have the strongest resonance, and its spectrum covers a broad range (from 300 to 1200 nm).

For instance, the absorption spectrum of AgNPs can be tunable to the region of near-infrared absorption by carefully optimizing the conditions (such as pH, temperature, salt concentration, and time) for AgNPs synthesis. This can help eliminate tissue autofluorescence interference, resulting in nanomaterials that are promising for deep-tissue imaging and for targeting tumors [85].

The cytotoxicity effects of AgNPs on mammalian cells are reported to be triggered via different types of mechanisms, such as the production of reactive oxygen species (ROS) and free radicals, damage to the cell membrane, which is attributed to direct contact with AgNPs, DNA replication impairment, disruption of cellular-dependent energy processes due to free silver ion uptake [87] and stimulation of apoptosis [12]

Also, a major damaging effect of AgNPs was linked to an increase in 8-oxoguanine levels [88,89].

Similar levels of ROS were induced in the cells by both AgNPs and $Ag^+$ within the first period of exposure, whereas an increase in ROS was noticed after 24 h for Jurkat T cells treated with AgNPs only. This could be due to the slow liberation of silver ions by AgNPs into the cell, leading to oxidative stress [90].

Kalishwaralal et al. [95] indicated that AgNPs can alter the proper functioning of vascular endothelial growth factor (VEGF). VEGF is also referred to as the vascular permeability factor and is a mitogen in endothelial cells. VEGF upregulation is stimulated by hypoxia in diseased cells and holds a fundamental role in the angiogenesis of tumors [95].

A study by Jia et al. [108] on the effect of AgNPs on human colon cancerous cells (HCT116) and normal colon cells (NCM-460) conveyed that as the AgNPs' concentrations increased, the cellular activities in both colon cell lines were reduced, while the intracellular ROS was increased.

The entry of AgNPs into cells has led to NF-κB and tumor necrosis factor-alpha (TNF-α) stimulation and a reduction in levels of glutathione (GSH).

However, the release of $Ag^0$ in cancerous and normal cells is greatly determined by the pH of the medium and the electrostatic differences in these cells [36]. For instance, excessive silver ions released from biogenic AgNPs at low pH (acidic pH) were affirmed to cause the selective killing of targeted cancer cells [36].

The skin is well known to be semipermeable and may not allow nanoparticles to simply penetrate through. For instance, a study by Kokura et al. [160] confirmed that treating the skin with AgNPs led to significant preservation effects against various fungi and bacteria, while no AgNPs were noted to penetrate into the skin.

However, clinical therapeutic applications of biogenic silver seem to be lacking. Yet, it is maintained that AgNPs may be toxic to different systems, including the skin, respiratory system, kidneys, eyes, immunological system, and hepatobiliary system [177]. The toxic effects of AgNPs in the development of target therapeutic procedures to overcome cancer, antibiotic-resistance infections, and other diseases are desirable. Nonetheless, the destruction of healthy normal cells should be avoided in targeted therapy [35].

https://www.dovepress.com/article/download/17874

**Photodynamic ability of silver nanoparticles in inducing cytotoxic effects in breast and lung cancer cell lines 2014**

The results showed that AgNPs used during the present study were found to be of spherical shape, with -0.0261 mV surface net charges, with an average size of 27 nm, and they were positively identified in both cell lines. Irradiated AgNPs promoted decreased viability and proliferation, increased cytotoxicity, and induced programmed cell death through apoptosis. AgNPs exhibited photodynamic activity in both cancer cell lines, but MCF-7 cells showed enhanced cytotoxic effects over the A549 cells. The novelty related to the study presented is twofold: while the maximum absorbance of most AgNPs lies in the wavelength region of 370–450 nm, the AgNPs produced and used in this research have a peak absorption at 631 nm that is of great significance, since this wavelength lies within the biological therapeutic window. This work clearly demonstrates that our AgNPs activated at 635 nm contribute significantly to the cytotoxicity induced in cancer cells, but more so in breast cancer cells (MCF-7) than in lung cancer cells (A549).

All laser irradiation was performed using a 635 nm (red) diode laser (supplied by the National Laser Centre of South Africa, Pretoria, South Africa) at a fluence rate of 10.288 mW · cm2, and samples were irradiated for 16 minutes and 11 seconds, 24 minutes and 17 seconds, and 32 minutes and 23 seconds to deliver light doses of 10 J/cm2, 15 J/cm2, and 20 J/cm2, respectively (Table 1).

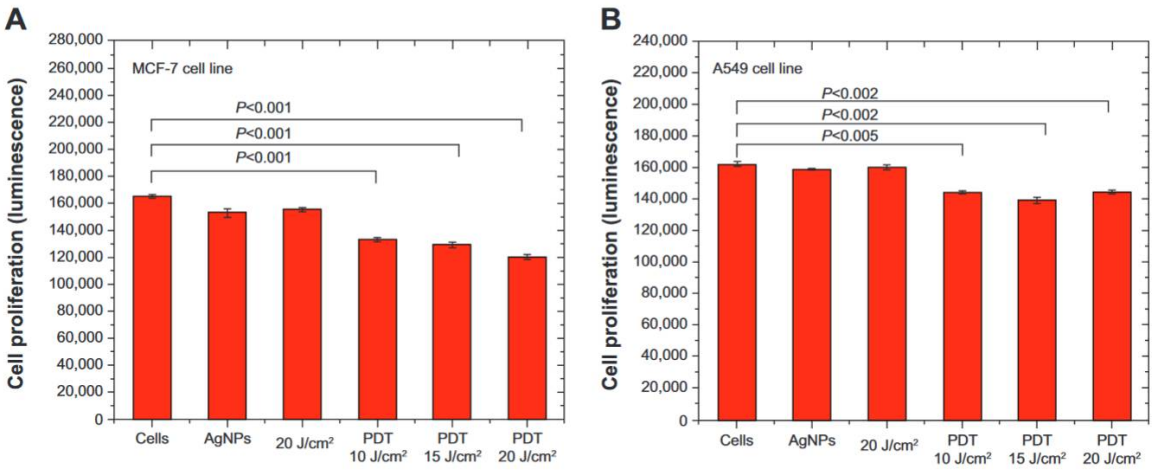



**Figure 4** Cellular proliferation of both MCF-7 and A549 cancer cells after treatment.
**Notes:** (**A**) Neither 3.23 mg/mL of AgNPs (AgNPs) nor 20 J/cm² laser irradiation (20 J/cm²) induced major changes in MCF-7 cell proliferation, but all PDT-treated cells showed significant decreased proliferation ($P<0.001$) when compared to untreated cells (cells). (**B**) In the same way, neither 3.23 mg/mL of AgNPs (AgNPs) nor 20 J/cm² laser irradiation (20 J/cm²) induced major changes in cell proliferation in A549 cells, but significant decreases were seen with PDT-treated cells with 10 J/cm² and 15 J/cm² ($P<0.002$) and 20 J/cm² ($P<0.005$).
**Abbreviations:** AgNPs, silver nanoparticles; PDT, photodynamic therapy.

https://www.researchgate.net/publication/385697470_Silver_nanoparticle_induced_immunogenic_cell_death_can_improve_immunotherapy
**Silver nanoparticle induced immunogenic cell death can improve immunotherapy 2024**
Cancer immunotherapy is often hindered by an immunosuppressive tumor microenvironment (TME). Various strategies are being evaluated to shift the TME from an immunologically 'cold' to 'hot' tumor and hereby improve current immune checkpoint blockades (ICB).
Our results suggest that Ag-citrate-5 nm is able to promote immune cell influx and increase tumor responsiveness to ICB therapies.
Tumors characterized by an immunosuppressive tumor microenvironment (TME) are known to exert mechanisms to "hide" from the immune system.
To overcome this immunosuppression, one of the most promising therapeutic approaches is immune checkpoint blockade (ICB), through so-called immune checkpoint inhibitors (e.g. anti-PD1, anti-CTLA-4 antibodies) [2].
Recent advancements in nanotechnology have paved the way for enhancing the effectiveness of immune checkpoint blockades (ICBs) by precisely targeting and regulating PD-L1 expression on tumor cells. Engineered nanoparticles can deliver therapeutic agents such as siRNA, CRISPR-Cas9, and chemotherapeutics directly to tumors, thereby, downregulating PD-L1 expression and improving immune system recognition and response.
In our explorations, we observed that among the different metallic NPs and with differently sized and coated AgNPs, Ag-citrate-5 nm showed the highest cytotoxicity to cancer cells while preserving the healthy cells at concentrations as low as 5 µg/ml, in vitro. This could be correlated to the ability of Ag NPs to induce ROSs.

https://www.researchgate.net/publication/297700731_Enhanced_Antibacterial_Anticancer_Activity_from_Terminalia_chebula_Medicinal_Plant_Rapid_Extract_by_Phytosynthesis_of_Silver_Nanoparticles_Core-shell_Structures
**Enhanced Antibacterial, Anticancer Activity from Terminalia chebula Medicinal Plant Rapid Extract by Phytosynthesis of Silver Nanoparticles Core-shell Structures 2016**
The anticancer activity of Ag NPs was attained at 10 µg concentration.Conclusions: The present studies propose that the silver nanoparticles from T. chebula methanolic extract exhibit significant antibacterial and anticancer activity. This study insights the T. chebula synthesized silver NP's could be an effective applicability drug candidate for colon cancer and applied externally for the MDR bacteria wound infections.

https://pmc.ncbi.nlm.nih.gov/articles/PMC7700255/
**An Updated Review on Silver Nanoparticles in Biomedicine 2020**
They also evidenced that negatively charged spherical nanoparticles, with 13–40 nm physical size, induced cell cycle arrest [242]. Besides oxidative stress, the treatment of lung cancer cells with AgNPs synthesized with *Anemarrhena asphodeloides* medicinal plant extract also resulted in decreased cellular migration [243]. The latest nanoparticles also proved anticancer efficiency against human colon and breast cancer cell lines. In addition, pulmonary cancer cells treated with biosynthesized AgNPs overexpressed the pro-apoptotic caspase-3 gene [244,245].
Well-dispersed AgNPs (20–30 nm size), obtained with tamarind fruit shell extract, induced apoptotic death in human breast cancer cells. A dose-dependent anticancer effect was reported, as the local increase of ROS led to mitochondrial impairment and DNA damage [250].
In another study, biogenic AgNPs prepared by using honey from distinctive floral sources manifested antiproliferative activity against liver tumor cells [259]. Quasispherical silver nanoparticles biosynthesized with lotus extract showed significant cytotoxic effects against human prostate, liver and gastric cancer cells [260]. Gastric adenocarcinoma cells were also impaired after treatment with AgNPs biosynthesized with medicinal extracts from leaves of felty germander [261] and from fruits of *Crataegus microphylla* shrub [262]. Other recent data on the toxic effects of silver nanoparticles against cancer cells are included in Table 3.

Cytotoxicity of AgNPs against various cancers.

| Malignant Cells | Proposed Systems | Effects | Refs. |
|---|---|---|---|
| Bladder carcinoma | AgNPs bioreduced by Fusarium oxysporum strain | Apoptosis induced by DNA damage, reduced cellular migration and proliferation, tumor regression | [263] |
| Breast adenocarcinoma | AgNPs bioreduced by Penicillium citrinum strain | Apoptosis induced by DNA damage | [264,265] |
| AgNPs biosynthesized with fineleaf fumitory (Fumaria parviflora), rhododendron (Rhododendron ponticum), rhubarb (Rheum ribes) and cumin (Cuminum cyminum) extracts | | Cell death evidenced on distinctive tumor cell lines | [266,267,268,269] |
| Colorectal cancer | AgNPs biosynthesized with creeping woodsorrel (Oxalis corniculata) leaf extract | Cell death induced by apoptotic and necrotic mechanisms | [270] |
| AgNPs biosynthesized with peacock (Caesalpinia pulcherrima) flower extract | | Cell death induced by apoptosis and membrane damage | [271] |
| Hepatocellular carcinoma | AgNPs bioreduced by Bacillus safensis strain | Cell death induced by apoptotic and necrotic mechanisms | [272] |
| PVP-stabilized AgNPs | Cell death induced by damage of cellular organelles (especially mitochondria) and oxidative stress, upregulation of mitochondrial proapoptotic proteins | | [273] |
| Laryngeal carcinoma | AgNPs bioreduced by Penicillium italicum strain | Cell death induced by ROS-mediated membrane damage and essential enzymes impairment | [274] |
| Lung adenocarcinoma | AgNPs bioreduced by Bacillus amyloliquefaciens strain | Cell death induced by ROS generation and damage of cellular organelles | [275] |
| AgNPs biosynthesized with soursop (Annona muricate) and mangrove (Avicennia marina) leaf extracts | | Apoptosis induced by ROS generation, downregulation of antiapoptotic genes and upregulation of proapoptotic genes | [276,277] |

| | | | |
|---|---|---|---|
| Osteosarcoma | AgNPs biosynthesized with cempedak (Artocarpus integer) and mangrove (Rhizophora apiculata) leaf extracts and noni (Morinda citrifolia) bark extract | Cell death evidenced on distinctive tumor cell lines, cell death induced by membrane damage and oxidative stress | [278,279,280] |
| Rhabdomyosarcoma | AgNPs bioreduced by Bacillus sp. strain | Cell death induced by ROS generation | [281] |

https://www.researchgate.net/publication/328111631_On_the_anti-cancer_activities_of_silver_nanoparticles

**On the anti-cancer activities of silver nanoparticles 2018**

Table 1: Silver nanoparticles from different sources against several cancer cells.

| 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 Egtract-ethanolic extract of rose (Rosa indica) petals | human colon adenocarcinoma cancer cell line HCT 15 | [42 |

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.

https://www.researchgate.net/publication/330437318_Silver_nanoparticles_a_new_hope_in_cancer_therapy

**Silver nanoparticles; a new hope in cancer therapy? 2019**

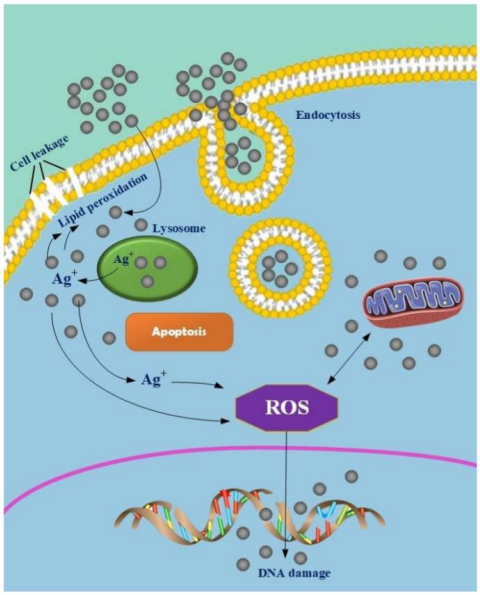



**Fig.1.** Schematic representation of the mechanism of anticancer effect of silver nanoparticles

Besides, silver nanoparticles can enter the mitochondria and produce reactive oxygen species (ROS) by affecting the respiration of cells. In summary, the mechanisms of AgNPs as toxic can lead to DNA damage, oxidative stress, induction of apoptosis, and mitochondrial damage to cancer cells. (21-26). The mechanism of action of silver nanoparticles on cancer cells is schematized in (figure 1).

Furthermore, there are studies that AgNPs affect the function of the vascular endothelial growth factor (VEGF).

https://www.researchgate.net/publication/269776438_Continuous_synthesis_of_size-tunable_silver_nanoparticles_by_green_electrolysis_method_and_multi-electrode_design_for_high_yield

**Continuous synthesis of size-tunable silver nanoparticles by green electrolysis method and multi-electrode design for high yield 2014**

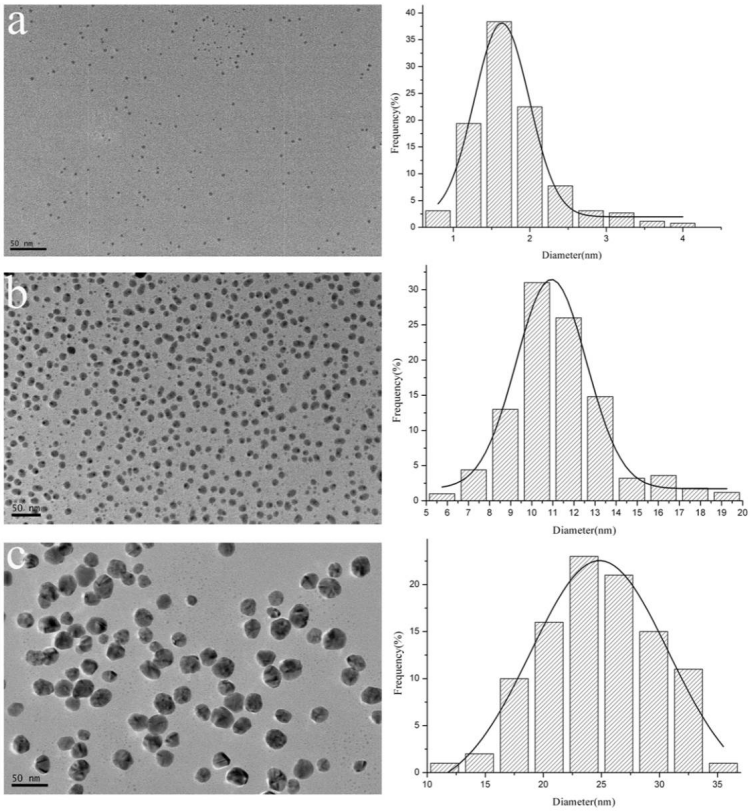



Fig. S6 TEM images and size distributions of AgNPs that synthesized by multi-electrode electrolytic reactor with different flow velocity: (a) 540mL/h, (b) 380mL/h, (c) 220mL/h

Firstly, two groups of silver electrodes were polished, washed, and fitted on the cover of the reactor, and 5mg/ml PVP aqueous solution was prepared. Secondly, the multi-electrode electrolytic reactor was laid in 70°C water bath, and two tubules were connected with the inlet and outlet of the reactor, respectively. A DC power source was connected with the two groups of parallel electrodes through the control device "Alternating Polarity Controller", and the alternating time of anodes and cathodes was set at one minute. When preparing colloidal AgNPs, the voltage of 7V was applied to silver electrodes under a magnetic stirring condition, and simultaneously the PVP solution was continuously pumped into the reactor with a peristaltic pump at the flow rate of 540mL/h, 380mL/h and 220mL/h, respectively. Finally, the AgNPs solution flowed out of the tube and was collected.

https://pmc.ncbi.nlm.nih.gov/articles/PMC5797005/

**Silver nanoparticles of different sizes induce a mixed type of programmed cell death in human pancreatic ductal adenocarcinoma 2017**

Our results indicated that AgNPs with size of 2.6 and 18 nm decreased viability, proliferation and caused death of pancreatic cancer cells in a size- and concentration-dependent manner.

In addition, we found that PANC-1 cells were more vulnerable to AgNPs-induced cytotoxicity compared to pancreatic non-tumor cells.

First, we evaluated the effects of 2.6 and 18 nm AgNPs on PANC-1 and hTERT-HPNE cells viability using MTT assay. We found that both 2.6 and 18 nm AgNPs decreased cell viability in a size- and concentration-dependent manner (Figure 2). AgNPs with size 2.6 nm exhibited stronger cytotoxicity against PANC-1 cells resulted in an $IC_{50}$ of 1.67 μg/mL than 18 nm AgNPs with $IC_{50}$ of 26.81 μg/mL after 24 h exposure. It has to be noted that non-tumor cells were more resistance to cytotoxic effect of 2.6 and 18 nm AgNPs with more than 2-fold higher IC value equaling 3.74 μg/mL and 58.46 μg/mL, respectively.

https://pubmed.ncbi.nlm.nih.gov/27536105/

**Combination of salinomycin and silver nanoparticles enhances apoptosis and autophagy in human ovarian cancer cells: an effective anticancer therapy 2016**

Our data show a strong synergistic interaction between Sal and AgNPs in tested cancer cells. The combination treatment increased the therapeutic potential and demonstrated the relevant targeted therapy for the treatment of ovarian cancer.

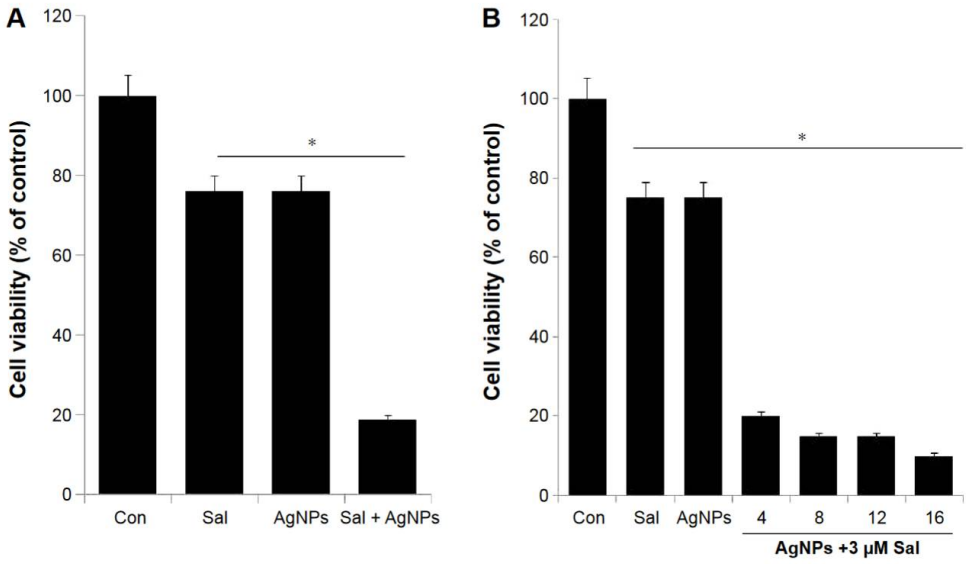



**Figure 3** Combination effect of Sal and AgNPs on cell viability of human ovarian cancer cells.
**Notes:** (**A**) The human ovarian cancer cells were incubated with Sal (3 μM), AgNPs (4 μg/mL), or a (**B**) combination of Sal (3 μM) and different doses of AgNPs (4–16 μg/mL) for 24 hours. The results are expressed as mean ± standard deviation of three independent experiments. The treated groups showed statistically significant differences from the control group by the Student's *t*-test (*$P<0.05$).
**Abbreviations:** AgNPs, silver nanoparticles; Con, control; Sal, salinomycin.

Next, we investigated the levels of GSH, SOD, and CAT in the cells exposed to Sal and AgNPs (Figure 6B–D). GSH plays an important role in various cellular processes, such as cell differentiation, proliferation, and apoptosis.73 An imbalance in GSH homeostasis is responsible for the etiology and progression of many human diseases, including cancer.73 Antioxidant defense system controls the level of ROS including SOD, CAT, and GSH peroxidase. Therefore, in the cells, the balance between ROS generation and ROS scavenging is essential for cell proliferation or death.68 We analyzed the level of GSH, SOD, and CAT. As expected, GSH, SOD, and CAT levels were significantly lower in cells treated with Sal (3 μM), AgNPs (4 μg/mL), or the combination of Sal and AgNPs (3 μM plus 4 μg/mL) for 24 hours than in controls (Figure 6B–D). These results suggest that Sal and AgNPs lead to a condition of oxidative stress in cells, which may arise due to the imbalance of oxidant and antioxidant levels in cells.78 Overall, oxidative stress was induced by the treatment of Sal and AgNPs as confirmed by the significant decrease in GSH, SOD, and CAT levels in the treated groups.
Sal is widely used as an anticoccidial agent. AgNPs are known to induce cytotoxicity in several types of cancer cells by generation of ROS and mitochondrial dysfunction. Therefore, we hypothesized that Sal together with AgNPs may effectively inhibit cell viability.

https://analyticalsciencejournals.onlinelibrary.wiley.com/doi/abs/10.1002/jat.2957
**Cytotoxicity and ROS production of manufactured silver nanoparticles of different sizes in hepatoma and leukemia cells 2013**
The aim of this study was investigate how AgNPs of different sizes (4.7 and 42 nm) interact with two different tumoral human cell lines (hepatoma [HepG2] and leukemia [HL-60]). I
A difference in the cellular response to AgNPs was found. HepG2 cells showed a higher sensitivity to the AgNPs than HL-60. However, the cytotoxicity induced by AgNPs was efficiently prevented by NAC treatment, which suggests that oxidative stress is primarily responsible for the cytotoxicity of AgNPs. Furthermore, cellular antioxidant status was disturbed: AgNPs exposure caused ROS production, glutathione depletion and slight, but not statistically significant inactivation of SOD.

https://pubmed.ncbi.nlm.nih.gov/21042421/
**Antitumor activity of silver nanoparticles in Dalton's lymphoma ascites tumor model 2010**
AgNPs significantly increased the survival time in the tumor mouse model by about 50% in comparison with tumor controls. AgNPs also decreased the volume of ascitic fluid in tumor-bearing mice by 65%, thereby returning body weight to normal. Elevated white blood cell and platelet counts in ascitic fluid from the tumor-bearing mice were brought to near-normal range. Histopathologic analysis of ascitic fluid showed a reduction in DLA cell count in tumor-bearing mice treated with AgNPs. These findings confirm the antitumor properties of AgNPs, and suggest that they may be a cost-effective alternative in the treatment of cancer and angiogenesis-related disorders.
Prior to the study of the antitumor effect of AgNPs, characterization of synthesized AgNPs was performed. TEM showed that the purified nanoparticles were spherical with a mean diameter of 50 nm, and the LAL endotoxin assay revealed that the purified AgNPs were endotoxin-free.

http://mathsci.free.fr/toxic.pdf
**Silver Products for Medical Indications: Risk-Benefit Assessment 1996**
Some researchers have suggested that Vitamin E or selenium deficiency may increase susceptibility to systemic silver toxicity. Wagner et al. and Bunyan et al. have shown that hepatic necrosis can be induced by administering silver preparations to hypothesized that toxicity was due to a silver-induced selenium deficiency that inhibits the synthesis of the seleno-enzyme glutathione peroxidase. Further, Bunyan et al. showed that if rat diets were supplemented with selenium or Vitamin E, exposure to silver as high as 140 mg/kg/d was still well tolerated.
If the silver in drinking water sources meets EPA guidelines, an average person who drinks 2 L/d is exposed to less than 200 ug of silver. However, a regular daily diet may contain up to about 90 ug of silver as a background level of exposure. For example, wheat flour contains 0.3 ug/g , bran contains 0.9 ug/g , and mushrooms contain up to several hundred ug/g of silver. Milk which contains about 27-54 ug/L is also a major contributor to daily silver intake.13
The current Rfd for oral silver exposure is 5 ug/kg/d with a critical dose estimated at 14 ug/kg/d for the average person.

https://onlinelibrary.wiley.com/doi/abs/10.1002/ajim.20670
**A case of generalized argyria after ingestion of colloidal silver solution 2008**
The patient had strikingly diffuse blue-gray discoloration of the skin, most prominent in sun-exposed areas, especially her face and hands.
She had ingested 1 L of colloidal silver solution daily for approximately 16 months as a traditional remedy. Her serum silver concentration was 381 ng/ml which was a very high (reference level: <15 ng/ml).
"Silver concentrations in two samples (one was a recent sample and the other was prepared several months ago) of the colloidal silver solution which she had

taken were measured by ICP optical emission spectroscopy (ICP-OES), 38.26 and 29.12 ppm, respectively. **1L/day of such a high concentration is indeed huge.** " quote from https://www.cancertreatmentsresearch.com/a-silver-bullet-to-kill-cancer/

https://www.researchgate.net/publication/317952618_The_silver_lining_Towards_the_responsible_and_limited_usage_of_silver/link/5aac051b0f7e9b4897bc8ff2/download?_tp=eyJjb250ZXh0Ijp7ImZpcnN0UGFnZSI6InB1YmxpY2F0aW9uIiwicGFnZSI6InB1YmxpY2F0aW9uIn19

**The silver lining: towards the responsible and limited usage of silver 2017**

These beneficial properties of silver can be utilized by using silver at very low concentrations which are not harmful to the human body and environment. The following review discusses the diverse medical applications of silver and further recommends human clinical studies for its in vivo usage.

Silver can exist in different forms such as elemental/metallic, ionic, nanosilver (1– 100 nm) and colloidal (1–1000 nm) (Kulinowski 2008). The latter three forms are preferred over the metallic form due to their smaller size and higher surface area which facilitates higher antimicrobial efficiency.

The reported minimum inhibitory concentration and minimum bactericidal concentration of AgNPs in the size range of 7-20 nm against standard reference cultures are in the range of 0.78-6.25 and 12.5 ug/ml respectively (Jain et al. 2009).

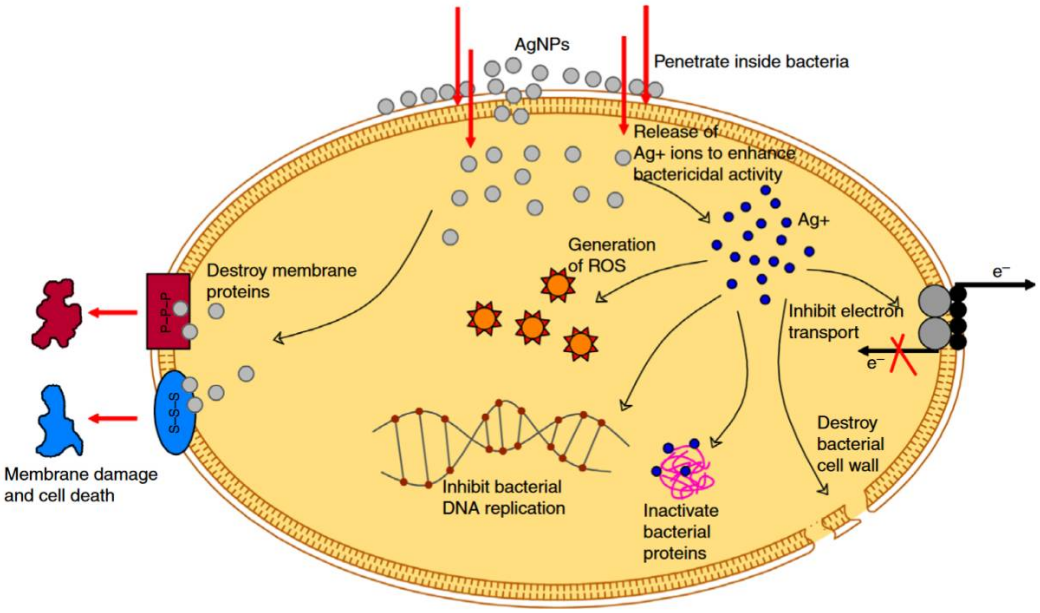



**Figure 1** Antibacterial mechanism of action of silver nanoparticles. [Colour figure can be viewed at wileyonlinelibrary.com]

Electrically generated silver ions at <2 ug/ml concentration were shown to exhibit more efficient fungicidal properties than silver compounds such as silver sulfadiazine and silver nitrate.

Recent research demonstrates that silver is so powerfully effective against viruses that it even stops the deadly HIV virus from infecting human cells. The vital requirement in order to exhibit such powerful antiviral activity is the size of the silver particles. Nanoparticles of size ranging from 1 to 100 nm are efficient as smaller size leads to more interaction and inhibition of viruses (Galdiero et al. 2011; Khandelwal et al. 2014). Silver nanoparticles undergo a size-dependent interaction with HIV-1 virus and nanoparticles in the size range of 1–10 nm were able to attach to the virus.

The primary mode of silver toxicity is its potential to release silver ions. Irrespective of the form of the silver used, a major characteristic that will affect the microbicidal effect of the silver is the concentration of silver ions released. The nano form with its large surface area to volume ratio has high potential for release of silver ions (Sotiriou and Pratsinis 2010).

Nanoparticles <10 nm in diameter can bind to bacterial cell wall and cause its perforation leading to rapid increase in cell permeability and ultimately cell death. In E. coli, nanosilver with average particle size of 12 nm is reported to result in formation of irregular shaped pits in the bacterial cell membrane. Silver ions can also cause the cell membrane to detach from the cell wall nevertheless, the mechanism of this process has still been unknown (Feng et al. 2000). Moreover, nanosilver binds with membrane proteins and sulphur-containing proteins through electrostatic interaction (Holt and Bard 2005; Wong and Liu 2010), and inhibits their function or damages their structure by generating free radicals (Choi and Hu 2008).

The creation of free radicals and induction of oxidative stress also contributes towards toxicity of AgNPs/ions (Kim et al. 2007; Cao and Liu 2010; Wong and Liu 2010). Production of ROS is dependent to some extent on the catalytic activity of nanoscale silver. ROS generation is initiated mainly as an outcome of the respiratory enzymes and respiratory chain dysfunction (Choi and Hu 2008). ROS are generated within or outside of the cell, as a consequence of cell damage/disruption (Liu et al. 2010).

Combination of curcumin nanoparticles and AgNPs inhibited biofilm formation more effectively as compared to when used alone (Loo et al. 2016).

This hepatocurative effect of damaged mice livers was attributed to the strong antioxidant effect of silver (Suriyakalaa et al. 2013).

Electrically generated silver ions were reported to kill numerous forms of infectious micro-organisms.

**Anticancer activity**

The idea that silver could be effective against cancer has been around since a long time. In 1970s, Dr. Becker proposed that silver can revert cancerous cells back to healthy cells when electrochemical treatment was used to generate silver ions directly into a cancer cell culture (Becker and Selden 1985). However, there are no further studies confirming such a mechanism.

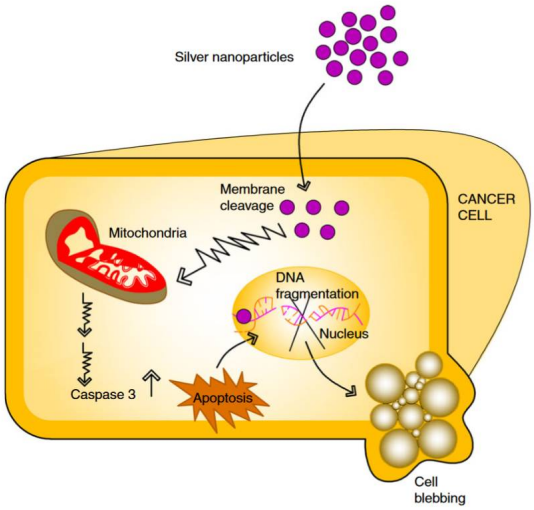



**Figure 5** Caspase-mediated cancer cell apoptosis by silver nanoparticles. [Colour figure can be viewed at wileyonlinelibrary.com]

https://pubs.acs.org/doi/abs/10.1021/nl301934w

**Negligible Particle-Specific Antibacterial Activity of Silver Nanoparticles 2012**

The most elusive question has been whether the AgNPs exert direct "particle-specific" effects beyond the known antimicrobial activity of released silver ions ($Ag^+$). Here, we infer that $Ag^+$ is the definitive molecular toxicant.

Furthermore, AgNPs may serve as a vehicle to deliver Ag + more effectively (being less susceptible to binding and reduced bioavailability by common natural ligands 14 ) to the bacteria cytoplasm and membrane (Figure 6), whose proton motive force would decrease the local pH (as low as pH 3.0) 37,38 and enhance Ag + release.

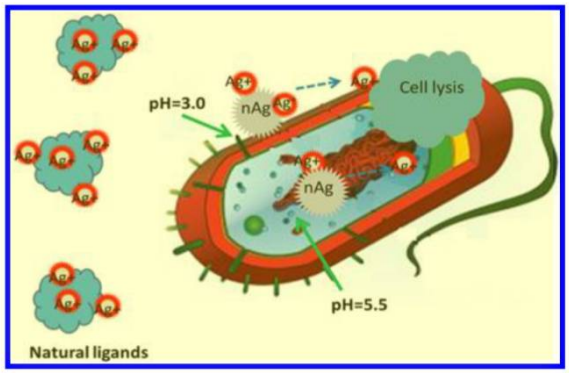



**Figure 6.** Schematic of AgNPs, $Ag^+$, and cell interactions. AgNPs may serve as a vehicle to deliver $Ag^+$ more effectively (being less susceptible to binding and reduced bioavailability by common natural ligands) to the bacteria cytoplasm and membrane, whose proton motive force would decrease the local pH (as low as pH 3.0) and enhance $Ag^+$ release.

https://pubmed.ncbi.nlm.nih.gov/23408729/

**Cytotoxic Activities of Silver Nanoparticles and Silver Ions in Parent and Tamoxifen-Resistant T47D Human Breast Cancer Cells and Their Combination Effects with Tamoxifen against Resistant Cells 2010**

In the present study, we investigated the potential cytotoxic effect of silver nanoparticles (Ag NPs) and silver ions (Ag(+)) in both parent and tamoxifen-resistant T47D cells in presence and absence of tamoxifen. Ag NPs were synthesized (< 28 nm) and MTT assay was carried out. The associated IC(50) values were found to be:
6.31 µg/ml for Ag NPs/parent cells,
37.06 µg/ml for Ag NPs/tamoxifen-resistant cells,
33.06 µg/ml for Ag(+)/parent cells and
10.10 µg/ml for Ag(+)/resistant cells. As a separate experiment, the effect of subinhibitory concentrations of Ag NPs and Ag(+) on the proliferation of tamoxifen-resistant cells was evaluated at non-toxic concentrations of tamoxifen. Our results suggested that in non-cytotoxic concentrations of silver nanomaterials and tamoxifen, the combinations of Ag(+)-tamoxifen and Ag NPs-tamoxifen are still cytotoxic. This finding may be of great potential benefit in chemotherapy of breast cancer; since much lower doses of tamoxifen may be needed to produce the same cytotoxic effect and side effects will be reduced.

https://pubmed.ncbi.nlm.nih.gov/36549400/

**Investigating silver nanoparticles and resiquimod as a local melanoma treatment 2023**

Over the last decade, the potential for silver nanoparticles (AgNP) to be used as an anti-melanoma agent has been supported by both in vitro and in vivo evidence. However, an undesirably high concentration of AgNP is often required to achieve an antitumor effect. Therefore a combination treatment that can maintain or improve antitumor efficacy (with lower amounts of AgNP) while also reducing off-target effects is sought. In this study, the combination of AgNP and resiquimod (RSQ: a Toll-like receptor agonist) was investigated and shown to significantly prolong the survival of melanoma-challenged mice when added sequentially. Results from toxicity studies showed that the treatment was non-toxic in mice. Immune cell depletion studies suggested the possible involvement of $CD8^+$ T cells in the antitumor response observed in the AgNP + RSQ (sequential) treatment. NanoString was also employed to further understand the mechanism underlying the increase in the treatment efficacy of AgNP + RSQ (sequential); showing significant changes, compared to the naive group, in gene expression in pathways involved in apoptosis and immune stimulation. In conclusion, the combination of AgNP and RSQ is a new combination worthy of further investigation in the context of melanoma treatment.

https://pmc.ncbi.nlm.nih.gov/articles/PMC9965924/

**The Role of Silver Nanoparticles in the Diagnosis and Treatment of Cancer: Are There Any Perspectives for the Future? 2023**

Silver is a noble metal having desirable biological characteristics, such as antibacterial and antifungal properties. Recent research has shown that several silver compounds have multiple impacts on cancer cells [15]. Due to the excellent physiological system of detoxifying in the human body, silver demonstrates low toxicity but poor absorption. Therefore, AgNPs are an effective means of avoiding this issue. Indeed, cells may internalize AgNPs by endocytosis and other uptake processes, releasing silver's reactive species, Ag+ ions, at the target locations [16].

The first way is that AgNPs are tailored to target the tumor site, specifically at the leaky blood vessels of the tumor, as well as the decreased rate of clearance owing to the absence of functioning lymphatic vessels, and the AgNPs will be retained. At the location of the tumor, AgNPs are conjugated with antibodies and bind to the antigens present. By localizing the AgNPs to the location of the tumor, it offers photoacoustic contrast with normal tissues, making it effective for the in vivo assessment of tumors.

Similar mechanisms were also described on human breast adenocarcinoma (MCF-7) cells after exposure to AgNPs prepared using *Bergenia ligulata* aqueous extract (at a concentration of 5 and 10 µg/mL). Increased activation, i.e., upregulation of p53 phosphorylation led to the arrest of the cell cycle in the G2/M phase and, together with oxidative stress mediated by ROS generation, probably participated in the induction of apoptosis.

Despite the promising findings of AgNPs as a novel treatment technique, they have not yet been put into clinical practice, mostly owing to a lack of information on their behavior and toxicity in people. Prior to its practical use, a comprehensive knowledge of the AgNP-induced effects on single cells, cancer tissues, and organs is required.

https://pubmed.ncbi.nlm.nih.gov/23278213/

**In vitro evaluation of silver nanoparticles on human tumoral and normal cells 2013**

Silver nanoparticles (AgNPs), which have well-known antimicrobial properties, are extensively used in various medical and general applications. Despite the widespread use of AgNPs, relatively few studies have been undertaken to determine the toxicity effects of AgNPs exposure. The aim of the present work was to study how AgNPs interact with four different human cell lines (hepatoma, leukemia, dermal and pulmonary fibroblast) in order to understand the impact of such nanomaterials on cellular biological functions. For toxicity evaluations, mitochondrial function (MTT assay) and membrane leakage of lactate dehydrogenase (LDH assay) were assessed under control and exposed conditions (24, 48 and 72 h of exposure). Furthermore, we evaluated the protective effect of N-acetyl-l-cysteine (NAC) against AgNP-induced cytotoxicity. Results showed that mitochondrial function decreased in all cell lines exposed to AgNPs at 6.72-13.45 µg/ml. LDH leakage also increased in all cell lines exposed to AgNPs (6.72-13.45 µg/ml). However, the cytotoxic effect of AgNPs (13.45 µg/ml) was prevented by pretreatment of different concentrations of NAC (1-20 mM). Our findings indicate that AgNPs are cytotoxic on human tumor and normal cells, the tumor cells being more sensitive to the cytotoxic effect of AgNPs. In addition, NAC protects human cells from cytotoxicity of AgNPs, suggesting that oxidative stress is in part responsible of this effect.

https://pubmed.ncbi.nlm.nih.gov/21182908/

**Silver nanoparticles induce oxidative cell damage in human liver cells through inhibition of reduced glutathione and induction of mitochondria-involved apoptosis 2011**

AgNPs induced reactive oxygen species (ROS) generation and suppression of reduced glutathione (GSH) in human Chang liver cells. ROS generated by AgNPs resulted in damage to various cellular components, DNA breaks, lipid membrane peroxidation, and protein carbonylation. Upon AgNPs exposure, cell viability decreased due to apoptosis, as demonstrated by the formation of apoptotic bodies, sub-G(1) hypodiploid cells, and DNA fragmentation. AgNPs induced a mitochondria-dependent apoptotic pathway via modulation of Bax and Bcl-2 expressions, resulting in the disruption of mitochondrial membrane potential ($\Delta\psi(m)$). Loss of $\Delta\psi(m)$ was followed by cytochrome c release from the mitochondria, resulting in the activation of caspases 9 and 3. The apoptotic effect of AgNPs was exerted via the activation of c-Jun NH(2)-terminal kinase (JNK) and was abrogated by the JNK-specific inhibitor, SP600125 and siRNA targeting JNK. In summary, the results suggest that AgNPs cause cytotoxicity by oxidative stress-induced apoptosis and damage to cellular components.

https://pubmed.ncbi.nlm.nih.gov/27180073/

**Differential genotoxicity mechanisms of silver nanoparticles and silver ions 2016**

In spite of many reports on the toxicity of silver nanoparticles (AgNPs), the mechanisms underlying the toxicity are far from clear. A key question is whether the observed toxicity comes from the silver ions ($Ag^+$) released from the AgNPs or from the nanoparticles themselves. In this study, we explored the genotoxicity and the genotoxicity mechanisms of $Ag^+$ and AgNPs. Human TK6 cells were treated with 5 nM AgNPs or silver nitrate ($AgNO_3$) to evaluate their genotoxicity and induction of oxidative stress. AgNPs and $AgNO_3$ induced cytotoxicity and genotoxicity in a similar range of concentrations (1.00-1.75 µg/ml) when evaluated using the micronucleus assay, and both induced oxidative stress by measuring the gene expression and reactive oxygen species in the treated cells. Addition of N-acetylcysteine (NAC, an $Ag^+$ chelator) to the treatments significantly decreased genotoxicity of $Ag^+$, but not AgNPs, while addition of Trolox (a free radical scavenger) to the treatment efficiently decreased the genotoxicity of both agents. In addition, the $Ag^+$ released from the highest concentration of AgNPs used for the treatment was measured. Only 0.5 % of the AgNPs were ionized in the culture medium and the released silver ions were neither cytotoxic nor genotoxic at this concentration. Further analysis using electron spin resonance demonstrated that AgNPs produced hydroxyl radicals directly, while $AgNO_3$ did not. These results indicated that although both AgNPs and $Ag^+$ can cause genotoxicity via oxidative stress, the mechanisms are different, and the nanoparticles, but not the released ions, mainly contribute to the genotoxicity of AgNPs.

https://pubmed.ncbi.nlm.nih.gov/27441588/

**Size- and coating-dependent cytotoxicity and genotoxicity of silver nanoparticles evaluated using in vitro standard assays 2016**

The coatings had less effect on the relative genotoxicity of AgNPs than the particle size. Loss of heterozygosity analysis of the induced Tk mutants indicated that the types of mutations induced by AgNPs were different from those of ionic silver. These results suggest that AgNPs induce cytotoxicity and genotoxicity in a size- and coating-dependent manner.

https://pubmed.ncbi.nlm.nih.gov/25964273/

**Silver nanoparticles: correlating nanoparticle size and cellular uptake with genotoxicity 2015**

AgNPs of all sizes tested (10, 20, 50 and 100nm), along with silver nitrate (AgNO3), were negative for mutagenicity in bacteria. No AgNPs could be identified within the bacteria cells using transmission electron microscopy (TEM), indicating these bacteria lack the ability to actively uptake AgNPs 10nm or larger. Clastogenicity (flow cytometry-based micronucleus assay) and intermediate DNA damage (DNA strand breaks as measured in the Comet assay) were assessed in two mammalian white blood cell lines: Jurkat Clone E6-1 and THP-1. It was observed that micronucleus and Comet assay end points were inversely correlated with AgNP size, with smaller NPs inducing a more genotoxic response.

https://pubmed.ncbi.nlm.nih.gov/20428844/

**Cytotoxicity and genotoxicity of silver nanoparticles in the human lung cancer cell line, A549 2011**

The cytotoxicity of both silver compounds was greatly decreased by pretreatment with the antioxidant, N-acetyl-cysteine, and a strong correlation between the levels of reactive oxygen species (ROS) and mitochondrial damage (r(s) = -0.8810; p = 0.0039) or early apoptosis (r(s) = 0.8857; p = 0.0188) was observed. DNA damage induced by ROS was detected as an increase in bulky DNA adducts by (32)P postlabeling after Ag NP exposure. The level of bulky DNA adducts was strongly correlated with the cellular ROS levels (r(s) = 0.8810, p = 0.0039) and could be inhibited by antioxidant pretreatment, suggesting Ag NPs as a mediator of ROS-induced genotoxicity.

https://pubmed.ncbi.nlm.nih.gov/23872425/

**Investigating oxidative stress and inflammatory responses elicited by silver nanoparticles using high-throughput reporter genes in HepG2 cells: effect of size, surface coating, and intracellular uptake 2013**

Silver nanoparticles (Ag NP) have been shown to generate reactive oxygen species; however, the association between physicochemical characteristics of nanoparticles and cellular stress responses elicited by exposure has not been elucidated. Here, we examined three key stress-responsive pathways activated by Nrf-2/ARE, NFκB, and AP1 during exposure to Ag NP of two distinct sizes (10 and 75 nm) and coatings (citrate and polyvinylpyrrolidone), as well as silver nitrate (AgNO3), and CeO2 nanoparticles. The in vitro assays assessed the cellular response in a battery of stable luciferase-reporter HepG2 cell lines. We further assessed the impact of Ag NP and AgNO3 exposure on cellular redox status by measuring glutathione depletion. Lastly, we determined intracellular Ag concentration by inductively coupled plasma mass spectroscopy (ICP-MS) and re-analyzed reporter-gene data using these values to estimate the relative potencies of the Ag NPs and AgNO3. Our results show activation of all three stress response pathways, with Nrf-2/ARE displaying the strongest response elicited by each Ag NP and AgNO3 evaluated here. The smaller (10-nm) Ag NPs were more potent than the larger (75-nm) Ag NPs in each stress-response pathway, and citrate-coated Ag NPs had higher intracellular silver concentrations compared with both PVP-coated Ag NP and AgNO3. The cellular stress response profiles after Ag NP exposure were similar to that of AgNO3, suggesting that the oxidative stress and inflammatory effects of Ag NP are likely due to the cytotoxicity of **silver ions**.

https://pubmed.ncbi.nlm.nih.gov/18831567/

**Unique cellular interaction of silver nanoparticles: size-dependent generation of reactive oxygen species 2008**

The present study was designed to evaluate size-dependent cellular interactions of known biologically active silver nanoparticles (NPs, Ag-15 nm, Ag-30 nm, and Ag-55 nm).

A more than 10-fold increase of ROS levels in cells exposed to 50 microg/mL Ag-15 nm suggests that the cytotoxicity of Ag-15 nm is likely to be mediated through oxidative stress.

n summary, a size-dependent toxicity was produced by silver nanoparticles, and one predominant mechanism of toxicity was found to be largely mediated through oxidative stress.

https://pubmed.ncbi.nlm.nih.gov/19236062/

**Cytotoxicity and genotoxicity of silver nanoparticles in human cells 2009**

. Ag-np reduced ATP content of the cell caused damage to mitochondria and increased production of reactive oxygen species (ROS) in a dose-dependent manner. DNA damage, as measured by single cell gel electrophoresis (SCGE) and cytokinesis blocked micronucleus assay (CBMN), was also dose-dependent and more prominent in the cancer cells. The nanoparticle treatment caused cell cycle arrest in G(2)/M phase possibly due to repair of damaged DNA. Annexin-V propidium iodide (PI) staining showed no massive apoptosis or necrosis. The transmission electron microscopic (TEM) analysis indicated the presence of Ag-np inside the mitochondria and nucleus, implicating their direct involvement in the mitochondrial toxicity and DNA damage. A possible mechanism of toxicity is proposed which involves disruption of the mitochondrial respiratory chain by Ag-np leading to production of ROS and interruption of ATP synthesis, which in turn cause DNA damage. It is anticipated that DNA damage is augmented by deposition, followed by interactions of Ag-np to the DNA leading to cell cycle arrest in the G(2)/M phase. The higher sensitivity of U251 cells and their arrest in G(2)/M phase could be explored further for evaluating the potential use of Ag-np in cancer therapy.

https://pubmed.ncbi.nlm.nih.gov/21945414/

**Genotoxic effects of silver nanoparticles stimulated by oxidative stress in human normal bronchial epithelial (BEAS-2B) cells 2011**

The Ag-NPs dispersed in medium were 43-260nm in size. We observed distinct uptake of Ag-NPs into BEAS-2B cells. The Ag-NPs aggregates were wrapped with an endocytic vesicle within the cytoplasm and nucleus of BEAS-2B cells. In the comet assay and micronucleus (MN) assay for BEAS-2B cells, Ag-NPs stimulated DNA breakage and MN formation in a dose-dependent manner. The genotoxic effect of Ag-NPs was partially blocked by scavengers. In particular, of the scavengers tested, superoxide dismutase most significantly blocked the genotoxic effects in both the cytokinesis-block MN assay and the comet assay. In the modified comet assay, Ag-NPs induced a significant increase in oxidative DNA damage. Furthermore, in the oxidative stress assay, Ag-NPs significantly increased the reactive oxygen radicals. These results suggest that Ag-NPs have genotoxic effects in BEAS-2B cells and that oxidative stress stimulated by Ag-NPs may be an important factor in their genotoxic effects.

https://pubmed.ncbi.nlm.nih.gov/39452955/

**Silver Nanoparticles in Therapeutics and Beyond: A Review of Mechanism Insights and Applications 2024**

The unique characteristics of silver NPs, such as their higher surface-area-to-volume ratio, make them ideal for a variety of biological applications. They are easily processed thanks to their large surface area, strong surface plasmon resonance (SPR), stable nature, and multifunctionality. With an emphasis on the mechanisms of action, efficacy, and prospective advantages of silver NPs, this review attempts to give a thorough overview of the numerous biological applications of these particles. The utilization of silver NPs in diagnostics, such as bioimaging and biosensing, as well as their functions in therapeutic interventions such as antimicrobial therapies, cancer therapy, diabetes treatment, bone repair, and wound healing, are investigated. The underlying processes by which silver NPs exercise their effects, such as oxidative stress induction, apoptosis, and microbial cell membrane rupture, are explored. Furthermore, toxicological concerns and regulatory issues are discussed, as well as the present difficulties and restrictions related to the application of silver NPs in medicine.

https://www.mdpi.com/1422-0067/19/8/2269

**Cytotoxic Potential and Molecular Pathway Analysis of Silver Nanoparticles in Human Colon Cancer Cells HCT116 2018**

The viability and proliferation of colon cancer cells treated with 5 µg/mL biogenic AgNPs were reduced by 50%. Increased lactate dehydrogenase leakage (LDH), reactive oxygen species (ROS) generation, malondialdehyde (MDA), and decreased dead-cell protease activity and ATP generation were observed

The average particle size obtained based on the XRD pattern using the Scherrer equation was approximately 6 nm for AgNPs synthesized using NAR.

The potential toxicity of AgNPs depends on ROS generation and depletion of the antioxidant defense systems, as well as the loss of mitochondrial membrane potential [44].

https://pubmed.ncbi.nlm.nih.gov/30111752/

**Combination Effect of Silver Nanoparticles and Histone Deacetylases Inhibitor in Human Alveolar Basal Epithelial Cells 2018**

. Interestingly, the combination of AgNPs and MS-275 significantly induces apoptosis, which was accompanied by an increased level of reactive oxygen species (ROS); leakage of lactate dehydrogenase (LDH); secretion of TNFα; dysfunction of mitochondria; accumulation autophagosomes; caspase 9/3 activation; up and down regulation of pro-apoptotic genes and anti-apoptotic genes, respectively; and eventually, induced DNA-fragmentation. Our findings suggest that AgNPs and MS-275 induce cell death in A549 lung cells via the mitochondrial-mediated intrinsic apoptotic pathway. Finally, our data show that the combination of AgNPs and MS-275 is a promising new approach for the treatment of lung cancer and our findings contribute to understanding the potential roles of AgNPs and MS-275 in pulmonary disease.

https://pmc.ncbi.nlm.nih.gov/articles/PMC3877176/

**In Vivo Human Time-Exposure Study of Orally Dosed Commercial Silver Nanoparticles 2015**

We prospectively studied commercial 10- and 32-ppm nanoscale silver particle solutions in a single-blind, controlled, cross-over, intent-to-treat, design. Healthy subjects (n=60) underwent metabolic, blood counts, urinalysis, sputum induction, and chest and abdomen magnetic resonance imaging. Silver serum and urine content was determined.

Results

No clinically important changes in metabolic, hematologic, or urinalysis measures were identified. No morphological changes were detected in the lungs, heart or abdominal organs. No significant changes were noted in pulmonary reactive oxygen species or pro-inflammatory cytokine generation.

Conclusion

In vivo oral exposure to these commercial nanoscale silver particle solutions does not prompt clinically important changes in human metabolic, hematologic, urine, physical findings or imaging morphology. Further study of increasing time exposure and dosing of silver nanoparticulate silver, and observation of additional organ systems is warranted to assert human toxicity thresholds.

The average daily ingestion of this elemental silver colloid formulation is estimated to be 100 µg/day for 10 ppm, and 480 µg/day for 32 ppm silver.

https://pubmed.ncbi.nlm.nih.gov/30670028/

**Endoplasmic reticulum stress: major player in size-dependent inhibition of P-glycoprotein by silver nanoparticles in multidrug-resistant breast cancer cells 2019**

Although both sized AgNPs induced significant ROS production and mitochondrial damage, 5 nm AgNPs were more potent than 75 nm AgNPs in this respect, therefore, these effects can not to be accounted for the reduced transport activity of ATP-driven pumps observed after 75 nm AgNP treatments. Instead we found that 75 nm AgNPs depleted endoplasmic reticulum (ER) calcium stores, caused notable ER stress and decreased plasma membrane positioning of Pgp.

**Conclusion:** Our study suggests that AgNPs are potent inhibitors of Pgp function and are promising agents for sensitizing multidrug resistant breast cancers to anticancer drugs. This potency is determined by their size, since 75 nm AgNPs are more efficient than smaller counterparts. This is a highly relevant finding as it renders AgNPs attractive candidates in rational design of therapeutically useful agents for tumor targeting. In the present study we provide evidence that exploitation of ER stress can be a propitious target in defeating multidrug resistance in cancers.

https://pmc.ncbi.nlm.nih.gov/articles/PMC5977333/

**Silver Nanoparticles: Synthetic Routes, In Vitro Toxicity and Theranostic Applications for Cancer Disease 2018**

With this in mind, Ag NPs are a promising tool as anticancer agents in diagnostics and probing [9], with strong effects against different cancer cell lines offering many advantages [10]. Their better penetration, and the possibility to track Ag NPs in the body make them a more efficient tool in cancer treatment with less risk compared to standard therapeutic procedures [11]. The unique Ag NP properties, such as easy surface functionalization, optical properties, reproducible synthetic routes and high surface: volume ratio, makes them suitable for cancer treatment [12].

When the Ag NPs were endocitated, they undergo a degradation process that induce a release of $Ag^+$ causing Reactive Oxygen Species (ROS) generation and glutathione (SGH) level reduction.

Ag NPs exhibit unique physical and chemical features that make them suitable for cancer theranostic applications. As other metallic NPs, Ag NPs have a larger surface area and area:volume ratio, which in turn enhance their catalytic activity. Owing to their nanosize, they can be vehiculated to the tumor site either by passive targeting (exploiting the enhanced permeability and retention effect), or by active targeting (by means of proper ligand surface functionalization)

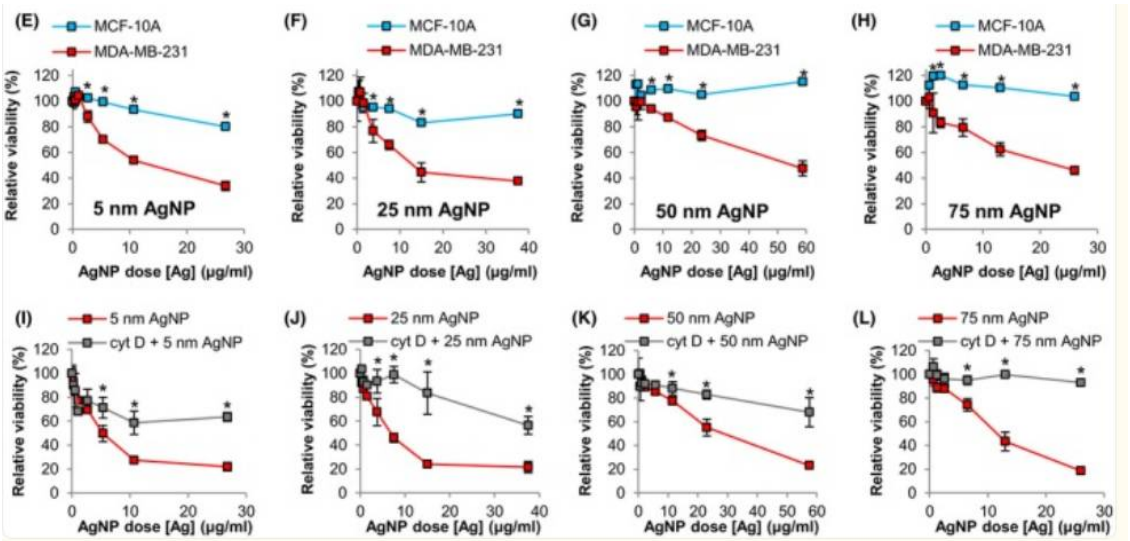
https://pmc.ncbi.nlm.nih.gov/articles/PMC6996381/

**Silver nanoparticles selectively treat triple-negative breast cancer cells without affecting non-malignant breast epithelial cells in vitro and in vivo 2019**

Silver nanoparticles (AgNPs) show promise for treatment of aggressive cancers including triple-negative breast cancer (TNBC) in preclinical cancer models. For clinical development of AgNP-based therapeutics, it will be necessary to clearly define the specific physicochemical features of the nanoparticles that will be used, and to tie these properties to biological outcomes. To fill this knowledge gap, we performed thorough structure/function, mechanistic, safety, and efficacy studies to assess the potential for AgNPs to treat TNBC. We establish that AgNPs, regardless of size, shape, or stabilizing agent, are highly cytotoxic to TNBC cells at doses that are not cytotoxic to non-malignant breast epithelial cells. In contrast, TNBC cells and non-malignant breast epithelial cells are similarly sensitive to exposure to silver cation ($Ag^+$), indicating that the nanoparticle formulation is essential for the TNBC-specific cytotoxicity. Mechanistically, AgNPs are internalized by both TNBC and non-malignant breast cells, but are rapidly degraded only in TNBC cells. Exposure to AgNPs depletes cellular antioxidants and causes endoplasmic reticulum stress in TNBC cells without causing similar damage in non-malignant breast epithelial cells. AgNPs also cause extensive DNA damage in 3D TNBC tumor nodules in vitro, but do not disrupt the normal architecture of breast acini in 3D cell culture, nor cause DNA damage or induce apoptosis in these structures. Lastly, we show that systemically administered AgNPs are effective at non-toxic doses for reducing the growth of TNBC tumor xenografts in mice. This work provides a rationale for development of AgNPs as a safe and specific TNBC treatment.

Initially, we used monodisperse AgNPs of increasing diameters (5, 25, 50, 75 nm) stabilized with a high (>74% by mass) percentage of PVP to determine if AgNP size influences the TNBC-selective cytotoxicity we previously observed.

Despite these limitations, we demonstrate effective treatment of a TNBC tumor in vivo at an AgNP dose that did not cause overt toxicity in mice (Figure 8). It is likely that the silver still found in the tumors 30 days after treatment cessation (Figure 8G) is in the form of **silver sulfides**, which are insoluble and can be retained in humans for long periods of time without toxicity.54 The main cause for concern from such compounds is argyria, a discoloration of the skin that can be treated with dermal lasers.55 However, no color change indicative of argyria was observed for the mice in our study. Our finding regarding the lack of overt in vivo toxicity of 25 nm, PVP-stabilized AgNPs at a repeated, 6 mg/kg IV dose is in agreement with comprehensive toxicity studies in rodents previously performed using PVP-stabilized AgNPs with similar characteristics to our AgNPs.




https://jnanobiotechnology.biomedcentral.com/articles/10.1186/s12951-015-0073-9

**Characterization of interaction of magnetic nanoparticles with breast cancer cells 2015**

All these findings indicate that dimercaptosuccinic acid-coated superparamagnetic iron oxide nanoparticles have excellent properties in terms of efficiency and biocompatibility for application to target breast cancer cells.

https://pmc.ncbi.nlm.nih.gov/articles/PMC8507678/

**Alpha-Lipoic Acid Prevents Side Effects of Therapeutic Nanosilver without Compromising Cytotoxicity in Experimental Pancreatic Cancer 2021**

We synthesized nanosilver and used it to treat several pancreatic cancer cells and normal cells in the presence or absence of α-lipoic acid. Silver selectively eliminated pancreatic cancer cells and α-lipoic acid supported the cytotoxicity, whereas benign cells largely resisted. α-Lipoic acid formed complexes with silver particles and reduced silver-induced formation of reactive oxygen species, mitochondrial damage and liver toxicity. Our data suggest that nanosilver application in the presence of α-lipoic acid is safe and effective in the treatment of pancreatic cancer.

https://jeccr.biomedcentral.com/articles/10.1186/1756-9966-29-148

**Antitumor activity of colloidal silver on MCF-7 human breast cancer cells 2010**

Background

Colloidal silver has been used as an antimicrobial and disinfectant agent. However, there is scarce information on its antitumor potential. The aim of this study was to determine if colloidal silver had cytotoxic effects on MCF-7 breast cancer cells and its mechanism of cell death.

Methods

MCF-7 breast cancer cells were treated with colloidal silver (ranged from 1.75 to 17.5 ng/mL) for 5 h at 37°C and 5% CO2 atmosphere. Cell Viability was evaluated by trypan blue exclusion method and the mechanism of cell death through detection of mono-oligonucleosomes using an ELISA kit and TUNEL assay. The production of NO, LDH, and Gpx, SOD, CAT, and Total antioxidant activities were evaluated by colorimetric assays.

Results

Colloidal silver had dose-dependent cytotoxic effect in MCF-7 breast cancer cells through induction of apoptosis, shown an LD50 (3.5 ng/mL) and LD100 (14 ng/mL) (*P < 0.05), significantly decreased LDH (*P < 0.05) and significantly increased SOD (*P < 0.05) activities. However, the NO production, and Gpx, CAT, and Total antioxidant activities were not affected in MCF-7 breast cancer cells. PBMC were not altered by colloidal silver.

Conclusions

The present results showed that colloidal silver might be a potential alternative agent for human breast cancer therapy.

https://faseb.onlinelibrary.wiley.com/doi/full/10.1096/fba.2019-00021

**Silver nanoparticles selectively treat triple-negative breast cancer cells without affecting non-malignant breast epithelial cells in vitro and in vivo 2019**

We establish that AgNPs, regardless of size, shape, or stabilizing agent, are highly cytotoxic to TNBC cells at doses that are not cytotoxic to non-malignant breast epithelial cells. In contrast, TNBC cells and non-malignant breast epithelial cells are similarly sensitive to exposure to silver cation ($Ag^+$), indicating that the nanoparticle formulation is essential for the TNBC-specific cytotoxicity. Mechanistically, AgNPs are internalized by both TNBC and non-malignant breast cells, but are rapidly degraded only in TNBC cells. Exposure to AgNPs depletes cellular antioxidants and causes endoplasmic reticulum stress in TNBC cells without causing similar damage in non-malignant breast epithelial cells. AgNPs also cause extensive DNA damage in 3D TNBC tumor nodules in vitro, but do not disrupt the normal architecture of breast acini in 3D cell culture, nor cause DNA damage or induce apoptosis in these structures. Lastly, we show that systemically administered AgNPs are effective at non-toxic doses for reducing the growth of TNBC tumor xenografts in mice.

All sizes of AgNPs inhibited growth of MDA-MB-231 cells without significantly affecting MCF-10A cells for all particle sizes at silver concentrations of 5 µg/mL or greater.

https://pubmed.ncbi.nlm.nih.gov/37895881/

**Current Overview of Metal Nanoparticles' Synthesis, Characterization, and Biomedical Applications, with a Focus on Silver and Gold Nanoparticles. 2023**

This article offers a comprehensive overview of the most recent advancements in the manufacturing, characterization, and biomedical utilization of metal NPs, with a primary focus on silver and gold NPs. Their potential as effective anticancer, anti-inflammatory, and antimicrobial agents, drug delivery systems, and imaging agents in the diagnosis and treatment of a variety of disorders is reviewed. Moreover, their translation to therapeutic settings, and the issue of their inclusion in clinical trials, are assessed in light of over 30 clinical investigations that concentrate on administering either silver or gold NPs in conditions ranging from nosocomial infections to different types of cancers. This paper aims not only to examine the biocompatibility of nanomaterials but also to emphasize potential challenges that may limit their safe integration into healthcare practices. More than 100 nanomedicines are currently on the market, which justifies ongoing study into the use of nanomaterials in medicine. Overall, the present review aims to highlight the potential of silver and gold NPs as innovative and effective therapeutics

in the field of biomedicine, citing some of their most relevant current applications.

https://pubmed.ncbi.nlm.nih.gov/39501968/
**Advanced Nanomaterials for Cancer Therapy: Gold, Silver, and Iron Oxide Nanoparticles in Oncological Applications. 2024**
Gold nanoparticles have garnered significant attention for their exceptional biocompatibility, tunable surface chemistry, and distinctive optical properties, rendering them ideal candidates for various cancer diagnostic and therapeutic strategies. Silver nanoparticles, renowned for their antimicrobial properties, exhibit remarkable potential in cancer therapy through multiple mechanisms, including apoptosis induction, angiogenesis inhibition, and drug delivery enhancement. With their magnetic properties and biocompatibility, iron oxide nanoparticles offer unique cancer diagnosis and targeted therapy opportunities. This review critically examines the recent advancements in the synthesis, functionalization, and biomedical applications of these nanoparticles in cancer therapy.

https://pubmed.ncbi.nlm.nih.gov/32432393/
**Going even smaller: Engineering sub-5 nm nanoparticles for improved delivery, biocompatibility, and functionality. 2020**
Driven by achieving the ultimate goal of clinical translation, sub-5 nm nano-constructs, in particular inorganic nanoparticles such as gold, silver, silica, and iron oxide nanoparticles, have been developed in recent years to improve the biocompatibility, delivery and pharmacokinetics of imaging probes and drug delivery systems, as well as in vivo theranostic applications.

https://pubmed.ncbi.nlm.nih.gov/39030546/
**Inorganic nanoparticle-based treatment approaches for colorectal cancer: recent advancements and challenges 2024**
Nanotechnology has emerged in cancer therapy by alleviating the drawbacks of current treatment approaches. In the past few decades, inorganic nanoparticles have shown promise in combating colorectal cancer, offering advantages over conventional chemotherapy. Compared to organic nanoparticles, inorganic nanoparticles exhibit properties like photosensitivity, conductivity, magnetic allure, and thermal proficiency, allowing them to function as both drug carriers and therapeutic agents. Derived primarily from carbon, silica, metals, and metal oxides, they offer superior drug-loading capacity, heightened quantum yield, and participation in advanced photothermal and photodynamic therapies. This review provides a brief overview of the pathophysiology of colorectal cancer and the pivotal role of inorganic nanoparticles in photothermal therapy photodynamic therapy, and drug delivery. Additionally, it discusses numerous inorganic nanoparticles in colorectal cancer therapy based on recent literature.

https://pubmed.ncbi.nlm.nih.gov/34770941/
**Metal Nanoparticles for Photodynamic Therapy: A Potential Treatment for Breast Cancer 2021**
In recent years, photodynamic therapy (PDT) has shown significant advantages in cancer treatment. PDT involves activating photosensitizers with appropriate wavelengths of light, producing transient levels of reactive oxygen species (ROS). Compared with free photosensitizers, the use of nanoparticles in PDT shows great advantages in terms of solubility, early degradation, and biodistribution, as well as more effective intercellular penetration and targeted cancer cell uptake. Under the current circumstances, researchers have made promising efforts to develop nanocarrier photosensitizers. Reasonably designed photosensitizer (PS) nanoparticles can be achieved through non-covalent (self-aggregation, interfacial deposition, interfacial polymerization or core-shell embedding and physical adsorption) or covalent (chemical immobilization or coupling) processes and accumulate in certain tumors through passive and/or active targeting. These PS loading methods provide chemical and physical stability to the PS payload. Among nanoparticles, metal nanoparticles have the advantages of high stability, adjustable size, optical properties, and easy surface functionalization, making them more biocompatible in biological applications. In this review, we summarize the current development and application status of photodynamic therapy for breast cancer, especially the latest developments in the application of metal nanocarriers in breast cancer PDT, and highlight some of the recent synergistic therapies, hopefully providing an accessible overview of the current knowledge that may act as a basis for new ideas or systematic evaluations of already promising results.

https://pubmed.ncbi.nlm.nih.gov/32294275/
**Rhodium Nanoparticles as a Novel Photosensitizing Agent in Photodynamic Therapy against Cancer. 2020**
Photodynamic therapy (PDT) is a promising alternative treatment for different types of cancer due to its high selectivity, which prevents healthy tissues from being damaged. The use of nanomaterials in PDT has several advantages over classical photosensitizing agents, due to their unique properties and their capacity for functionalization. Especially interesting is the use of metallic nanoparticles, which are capable of absorbing electromagnetic radiation and either transferring this energy to oxygen molecules for the generation of reactive oxygen species (ROS) or dissipating it as heat. Although previous reports have demonstrated the capacity of Rh derivatives to serve as anti-tumor drugs, to the best of our knowledge there have been no studies on the potential use of small-sized Rh nanoparticles as photosensitizers in PDT. In this study, 5 nm Rh nanoparticles have been synthesized and their potential in PDT has been evaluated. The results show that treatment with Rh nanoparticles followed by NIR irradiation induces apoptosis in cancer cells through a p53-independent mechanism.

https://pubmed.ncbi.nlm.nih.gov/32443890/
**Two Sides to the Same Coin-Cytotoxicity vs. Potential Metastatic Activity of AgNPs Relative to Triple-Negative Human Breast Cancer MDA-MB-436 Cells. 2020**
AgNPs were toxic to MDA-MB-436 cells and the probable mechanism of toxicity was the induction of oxidative stress. These promising effects, giving the opportunity to use AgNPs as an anti-cancer agent should, however, be treated with caution in the light of further results. Namely, the treatment of MDA-MB-436 cells with AgNPs was associated with the increased secretion of several cytokines and chemokines, which were important in breast cancer metastasis.

https://pubmed.ncbi.nlm.nih.gov/21104301/
**Inorganic nanoparticles in cancer therapy. 2011**
Herein, we will focus on gold, silver and platinum nanoparticles, discussing recent developments for therapeutic applications with regard to cancer in terms of nanoparticles being used as a delivery vehicle as well as therapeutic agents.

https://pubmed.ncbi.nlm.nih.gov/26089024/
**Strategic role of selected noble metal nanoparticles in medicine 2016**
Due to the small size, nanoparticles can easily interact with biomolecules both at surface and inside cells, yielding better signals and target specificity for diagnostics and therapeutics. Noble metal nanoparticles inspired the researchers due to their remarkable role in detection and treatment of dreadful diseases. In this review, we have attempted to focus on the biomedical applications of noble metal nanoparticles particularly, silver, gold, and platinum in diagnosis and treatment of dreaded diseases such as cancer, human immunodeficiency virus (HIV), tuberculosis (TB), and Parkinson disease.

https://pmc.ncbi.nlm.nih.gov/articles/PMC8078871/
**Therapeutic strategies and potential implications of silver nanoparticles in the management of skin cancer 2021**

**Anticancer effect of AgNPs**

Experimental studies have been conducted on the cytotoxicity of AgNPs in different cancers including cervical cancer, breast cancer, lung cancer, hepatocellular carcinoma, nasopharyngeal carcinoma, hepatocellular carcinoma, glioblastoma, colorectal adenocarcinoma, and prostate carcinoma [123]. Contributing factors for effective treatment include dose, time of exposure, and size and shape of the AgNP. Molecular mechanisms of AgNP-mediated apoptosis involve production of ROS, mitochondrial membrane disruption, DNA damage, and signaling pathways leading to programmed cell death [124].

AgNP and SC

With regard to AgNP and SC, their absorption through intact and damaged skin was very low but detectable. However, in case of damaged skin, increased permeation has been observed [142]. In contrast, another study has revealed that AgNPs were able to penetrate through the intact human skin in vivo and could be found beyond the stratum corneum at depths of the reticular dermis [143]. The penetration of AgNPs is linked to the size of AgNPs. Human epidermal keratinocytes' cytoplasmic vacuoles showed the presence of AgNPs (20, 50, and 80 nm) [144], while 100 nm diameter AgNPs were unable to penetrate into the human epithelial line [145] and 0.002–0.02 ppm AgNPs did not penetrate through intact human epidermal keratinocyte cell line (HaCaT) keratinocytes [146].

The uptake of AgNPs is mainly through endo-cytosis via lysosomes [159]. Exposure to the acidic environment of lysosomes leads to dissolution of AgNPs into Ag ions producing hydroxyl radicals [158]. The internalized AgNPs disrupt the integrity of the cell membrane, causing lysosomal swelling and even rupture lysosomal membranes [160]. The released Ag ions interact with reduced glutathione-S-transferase, superoxide dismutase in the cytoplasm, cell membrane, and inner membranes of a mitochondrion affecting membrane integrity. Furthermore, damage to mitochondria impairs electron transfer, inhibits adenosine triphosphate synthesis, and triggers oxidative stress through lipid peroxidation [161]. AgNPs induce apoptosis through mitochondrial, intrinsic, or p53-mediated pathway [162]. All these events inhibit of cell proliferation through cell-cycle arrest in the G2/M phase [163]. Downregulation of total protein kinase B (AKT) and high expression of p38 are documented along with increased expression of H2A histone family member X (H2AX), Caspase-3, p-p53, and total p53 [164]. AgNP-induced phosphorylation of histone protein leads to activation of c-Jun N-terminal kinase (JNK) pathway [165]. Images from transmission electron microscopy and elemental mapping of single cells have revealed that AgNPs can translocate to the nucleus and cause DNA damage inducing mutations [158] In addition, AgNP can activate a range of pathways such as MAPK and nuclear factor kappa-light-chain-enhancer of activated B (NFκB) pathways resulting in transcription of many genes involved in the proliferation and inflammatory response [166]. Differential regulation of intracellular factors mediating cell cycle, DNA repair, and inflammation have been associated with AgNP-induced cytotoxicity [167]. A schematic representation of AgNP-induced cytotoxicity is explained in Figure 4 for better understanding of the mechanism.

Green synthesis

Because of the toxic side effects of AgNPs to non-target organs, green synthesis of AgNP has been proposed as a promising technique for SC management. Similar to other synthesis methods, physical characteristics such as size and shape of the NPs are altered by controlling pH and temperature [192]. Green synthesis of AgNPs involves the utilization of bacteria, fungi, yeasts, algae, or plant extracts as reducing and/or stabilizing compounds [157].

https://pmc.ncbi.nlm.nih.gov/articles/PMC10896653/

**Anticancer Action of Silver Nanoparticles in SKBR3 Breast Cancer Cells through Promotion of Oxidative Stress and Apoptosis 2024**

One of the probable mechanisms by which AgNPs reveal their antitumoral action is through the generation of reactive oxygen species (ROS). These ROS molecules might cause oxidative stress within cancer cells, leading to DNA damage, protein denaturation, and ultimately cell death. Additionally, AgNPs have been shown to disrupt the mitochondrial function of cancer cells, further impairing their survival and proliferation [1, 3].

Angiogenesis is generally called the process of growth and creation of new vessels from existing vessels. Abnormal or increased angiogenesis is recognized as one of the characteristics of cancer [10]. Secretion of vascular permeability factor and vascular endothelial growth factor-A (VEGF-A) from tumoral cells is one of the main factors of angiogenesis. In addition, VEGF-A is a dimer glycoprotein and plays a central role in angiogenesis [11]. This glycoprotein together with a coreceptor called NRP1 (Neuropilin-1) forms a complex with VEGF receptors and causes angiogenesis in breast cancer [12]. Binding of VEGF to its receptor activates several downstream signaling pathways such as PI3K/Akt/mTOR pathways [13].

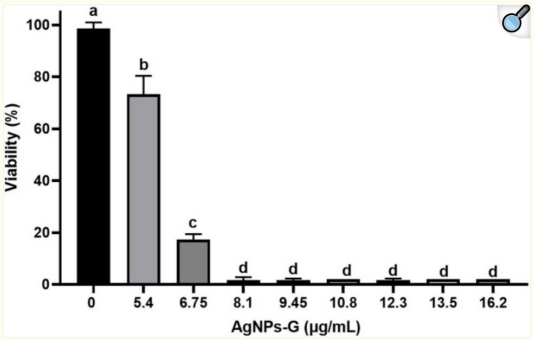
According to the results of present report, AgNPs have the ability to attenuate the activity of antioxidant enzymes and change the oxidant/antioxidant status, which is consistent with the former investigations [17, 26, 27]. Similarly, in A2780 ovarian cancer cells, AgNPs decreased the activity of CAT and SOD enzymes and the level of glutathione. Additionally, a considerable increase in MDA levels indicates the onset of oxidative stress by AgNPs [28]. In line with our data, Panax ginseng Meyer-mediated AgNPs showed considerable anticancer effects on A549, MCF-7, and HepG2 cancer cells as revealed by heightened level of oxidative stress [29]. In contrast, some previous reports emphasized the antioxidant properties of AgNPs in which an enhancement of antioxidant enzymes such as SOD and CAT is reported [30]. In essence, the characteristic of nanoparticles might affect their final biological activity within cells [31]. Moreover, some plant extracts have anticancer activity though they are known as antioxidant agents [32, 33]. Though promising, a balance has not yet been found between the killing properties of pro-oxidant agents in cancer cells and their oxidative damage on normal tissues [34].

Our results showed that AgNPs have the potential to induce oxidative stress and cell death as revealed by increased level of oxidative markers, reduced antioxidant capacity, and upregulated Bax/Bcl-2 gene expression. Simultaneously, AgNPs suppressed the expression of VEGF-A, PI3K, and AKT genes, dose dependently. Despite the promising results of the current study, more research is still needed to better discover the process of action as well as possible side effects of AgNPs on normal cells. Additionally, optimizing their synthesis methods and determining the appropriate dosage for effective treatment are important considerations for their clinical translation.

https://pmc.ncbi.nlm.nih.gov/articles/PMC10851876/

**Antitumor efficacy of silver nanoparticles reduced with β-D-glucose as neoadjuvant therapy to prevent tumor relapse in a mouse model of breast cancer. 2024**

The AgNPs-G treatment decreased the cellular viability of 4T1 breast cancer cell line in all doses tested (5.4–16.2 μg/mL), in a dose-dependent manner ($p < 0.05$) when compared with the control without treatment in a period of 24 h (Figure 1). Starting from the dose of 8.1 μg/mL, cellular viability reached values near to zero.

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Decrease in cell viability of the 4T1 line induced by AgNPs-G. The cells