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# Silver Nanoparticles; A New Hope In Cancer Therapy?

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**ABSTRACT**

Nowadays, with the rapid developments in nanotechnology, there has been a significant increase in the usage of nanoparticles within the biomedical field. Nanoparticles are known as particles ranging in size between 1 and 100 nm. Especially, silver nanoparticles (AgNPs) have been extensively carried out biomedical areas because of their physicochemical, and biological therapeutic properties. Recent studies have shown that there are anti-fungal, anti-viral, anti-inflammatory, anti-angiogenic biological activities, especially anti-bacterial and anti-cancer features of silver nanoparticles. Also, the appropriate knowledge of these characteristics is crucial since this knowledge enhances their potential usage in many areas while decreasing their possible dangers for human and environment. Recent researches demonstrate that multifunctional cytotoxic biological activities of biosynthesized silver nanoparticles can be used as an anti-cancer agent. In this work, it is aimed to give a literature review of the studies on silver nanoparticles, synthesis techniques and their possible usages especially in cancer therapy.

**Key Words:** Silver nanoparticles, Anticancer, Nanotechnology

## Introduction

Nanotechnology, developing area, has several interdisciplinary fields, like electronics, medicine and biomaterials. Nanomedicine, in the long run aims to improve the health care system by dealing with mortal diseases more efficiently. Nanotechnology, ranging in size from 10 nm to 1000 nm, involves the design, synthesis and manipulation of structures in particles.

For creation of nanoscale value properties, microbial origins and plants are used because of their physical and chemical properties. Currently, nanobiotechnology is seen as means of producing the synthesis of nanoparticles an economical option for chemical and physical methods (1,2). Nanoparticles have unique chemical, physical and biological properties, and they are used in a lot of fields like therapeutics, cosmetics and drug delivery (3).

Nanoparticles present a new perspective for detection, protection and treatment of tumors. Because of, the speed improvement of varied diagnostic devices and therapeutic strategies, the mortality of cancer, known as one of the most deadly disease, has been significantly inhibited. Unfortunately, there is no method to select and bind cancer cells in order to prevent toxicity and side effects in all current cancer treatments. To overcome this situation, the synthesis of nanoparticles emerges as a new additive. To over come this problem, nanoparticles synthesis are emerged as a new contribution (4). Also, nanoparticles have been currently widely used in biomedical area due to its physicochemical properties and they are expected hopefully to reform the cancer diagnosis and therapy (5).

Nowadays, physical, chemical and biological techniques are used in the preparation nanoparticles. Although physical methods are used initially in the synthesis of nanoparticles, low yield is the biggest disadvantage. Chemical methods use various chemicals to synthesis of silver nanoparticles and to reduce metallic ions. But, chemical methods include some drawbacks related to the use of toxic chemicals and hazardous production according to the products. (6). Among these methods, biological method is a good way to fabricate nanoparticles. And also, this method is less toxic and eco friendly. Coating agents are used in the synthesis of nanoparticles. Nanoparticles absorb these coating agents which are usually organic molecules, and used to help stabilization of nanoparticles. From a medical point of view, biosynthesis of nanoparticles has been shown to greatly increase their clinical application.

The natural resources for green biosynthesis of nanoparticles are plants, bacteria, yeast, algae, fungi and viruses (7). Although creating a large platform of green biosynthesis in production of nanoparticles, the most commonly bacterial

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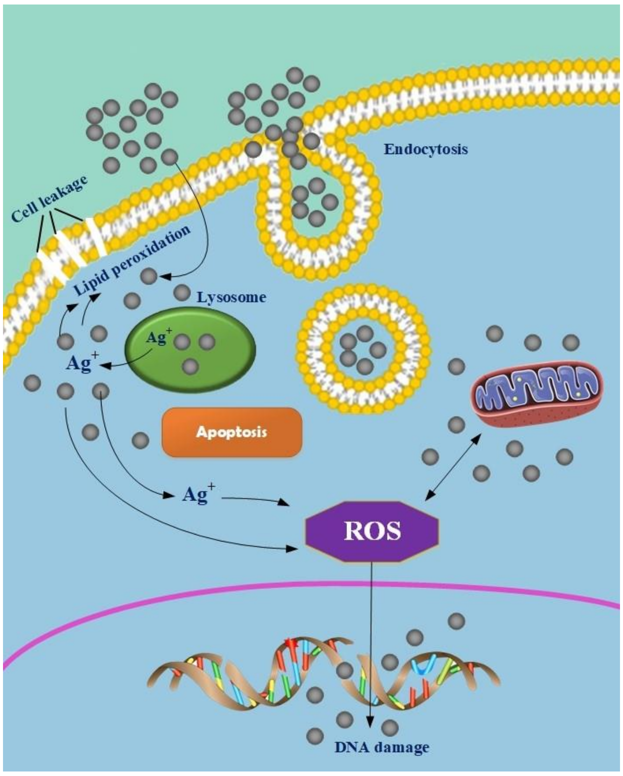


**Fig.1.** Schematic representation of the mechanism of anticancer effect of silver nanoparticles

synthesis is preferred, because they are easy to process and genetic manipulation is also possible (8-10). Interestingly, recent studies demonstrated that using medical plants for production of nanoparticles could be cost effective and eco-friendly. For this reason, the green biosynthesis has become the most commonly used method for investigating therapeutic agents for cancer treatment (4).

Due to advances in nanotechnology, new therapeutic approaches have been developed for the use of nanoparticles in medicine. Among the commonly used nanoparticles, AgNPs have an impressive role due to their unique physical and chemical features. In addition, AgNPs have a stronger effect than the silver ions as disclosed in some research. Silver is a noble metal extensively used to make coin and jewelry over 200 years. Also, this element is resistant to bacteria and is a potential anti-bacterial agent with low toxicity (11). In ancient times, silver was used to protect water and its believed to be source the healing because of anti-disease properties by Hippocrates. Then, silver components were used in medical applications. These compounds have also been widely used against wound infections in World War I instead of antibiotics. Silver has been made to have extraordinarily novel morphological and characteristic properties with engineering and the development of new technologies. Due to nanotechnology, silver ions are processed and transformed into ultra-small particles measured in nanometers (nm) (12-16). Upon reaching nanoscale, silver particles have physicochemical properties and create exceptional biological activities. This distinctiveness of silver nanoparticles widen their application in anti-bacterial, anti-fungal, anti-viral, anti-inflammatory, anti-angiogenic and anti-cancer therapy. AgNPs are widely used in production of cosmetics, detergents and hygienic goods. Recent studies have indicated that AgNPs do not harm humans and kill viruses, bacteria and other eukaryotic microorganisms without any adverse effects in diluted concentrations. (17).

Many studies have shown that silver nanoparticles have made their way into therapeutic applications in cancer as anti-cancer agents (18). Several in vitro studies have indicated that silver nanoparticles can enter cells by endocytosis and their localization inside the cell can be determined as the perinuclear space of cytoplasm and endo-lysosomal compartment (19,20). 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). It is also known as vascular permeability factor and plays a major role in the angiogenesis within tumors (27). These results support AgNPs have anti-cancer properties that can be used as an alternative for cancer therapy and angiogenesis inhibitor therapy (28).

Theranostic applications of green-synthesized nanoparticles were investigated for biologically compatible and potential approaches in biomedical field (antimicrobial, anti-inflammatory, antinociceptive, anticancer and enzyme inhibition activities). Theranostic is defined a combination of diagnostics and therapy. The bio-synthesized AgNPs could be used in theranostic applications including anti-cancer therapeutic agent, drug delivery and bioimaging vehicle (29). Green AgNPs can be used as beneficial theranostic agents for further discovery of various biomedical applications (30-32). AgNPs, which were biosynthesized with various applications, were tested in different cancer cell lines. Table 1 summarizes the recent studies

**Table 1.** Application of AgNPs used in different cancer cell lines

| | | | | | |
|---|---|---|---|---|---|
| Green synthesis Ganoderma neo-japonicum Imazeki | Breast Cancer | MDAMB-231 | $IC_{50}$: 8,7 µg/mL | Dose-dependent inhibition of cell growth | 33 |
| Green synthesis Sucrose | Malignant skin melanoma and squamous cell lung carcinoma | HT144 and H157 | $ID_{50}$: 3.6 µM | Remarkable antitumor potency compared to the clinically used reference compounds vincristine and methotrexate | 34 |
| Chemical synthesis Polyvinylpyrrolidone(PVP) | Acute myeloid leukemia | AML | 0–10 mg/mL | AgNPs has been observed to have an inhibitory effect with low $IC_{50}$ (0.90-3.43 mg / mL) in six AML cells. | 35 |
| Green synthesis Taraxacum officinale | Liver hepatocellular carcinoma | HepG2 | 10 to 200 µg/mL dose-dependent | A high cytotoxic effect was observed in HepG2 | 36 |
| Green synthesis Commelina nudiflora L. | Colon Cancer | HCT-116 | $IC_{50}$:100 µg/mL | Diminished cell viability and increased cytotoxic effect in HCT-116 | 37 |
| Chemical biosynthesis Phycocyanin | Human breast adenocarcinoma | MCF-7 | $IC_{50}$:27.79±2.3µg/mL. | Inhibition of tumor growth in Ehrlich-ascites carcinoma-bearing mice | 38 |
| Green synthesis Melia dubia | Human breast cancer | MCF-7 | $IC_{50}$:31.2 µl/ml | AgNps showed remarkable cytotoxicity activity with evidence of high therapeutic index value against MCF-7 | 39 |
| Mycosynthesis Inonotus obliquus | Human lung cancer human breast cancer | A549 and MCF7 | $IC_{50}$:100 µl/ml | Significant cytotoxic effect in A549 and MCF-7 cell lines | 40 |
| Green synthesis Erythrina indica lam | Breast and lung cancer | MCF-7 and HEP G2 | 23.89 ± 0.39 µl/ml for MCF-7<br>13.86 ± 0.95 µl/ml for HEP G2 | Significant cytotoxic effect in MCF-7 and HEP G2 cell lines | 41 |
| Green Synthesis Acalypha indica Linn | Human breast cancer | MDA-MB-231 | $IC_{50}$:100 µg/ml | Important cytotoxic effects and apoptotic properties | 42 |
| Green Synthesis Dendrophthoe falcata (L.f) Ettingsh | Human breast cancer | MCF-7 | $IC_{50}$:5 µg/mL | Significant cytotoxic effect in MCF-7 cell line | 43 |
| Green Synthesis Datura inoxia | Human breast cancer | MCF7 | $IC_{50}$:20µg/ml | Antiproliferative effect, cell cycle arrest, decreased DNA synthesis and apoptosis | 44 |
| Green Synthesis Piper longum | Epidermoid Larynx Carcinoma | HEp-2 | $IC_{50}$:500 lg/mL | Exhibit a prominent cytotoxic effect (94.02 %) on HEp-2 cell lines | 45 |
| Green Synthesis Sargassum vulgare | Human myeloblastic leukemic and cervical cancer | HL60 and HeLa | EC50: 93.57 µg/ml | Preventing the irradiation-related carcinogenesis with DNA damage and apoptosis | 46 |
| Mycosynthesis Saccharomyces boulardii | Human breast cancer | MCF-7 | (10–100 µg/mL), | Very low concentration of AgNps showed very high activity in MCF-7 cells compared to silver ions | 47 |
| Green Synthesis Pimpinella anisum seeds | Human neonatal skin stromal and colon cancer | hSSCs and HT115 | >10 µg (20, 30, 40, 50 µg/mL) | AgNps doses showed few effects on cell proliferation below 10 µg, while doses above 10 µg resulted in increased cytotoxicity | 48 |
| Green Synthesis Indigofera tinctoria leaf extract | Lung cancer | A549 | $IC_{50}$:56.62 ± 0.86 µg/ml | Nanoparticles has higher antioxidant activities and more cytotoxic effect on cancer cell than the pure leaf extract | 49 |
| Green Synthesis Chaenomeles sinensis | Human breast cancer | MCF7 | $IC_{50}$:725.93 µg/mL | Cytotoxic against breast cancer cells | 50 |
| Green Synthesis Clinacanthus Nutans | Oral squamous cell carcinoma | HSC-4 | $IC_{50}$:1.61 µg/mL | Apoptotic effects observed at G1 phase and $IC_{50}$ was low compared to few studies | 51 |

comparing potential therapeutic approaches of AgNPs on different cancer types. Currently, the production of many toxicological data related to nanoparticles occasionally causes an adverse perception of their use. Nevertheless, toxicity may be helpful in cancer treatments because the cytotoxic effect is desirable for cancer cells. Many studies suggest that positive results have been obtained when incorporating silver nanoparticles into cancer therapies.

Today, silver nanoparticles, which are present in metallic nanoparticle groups and exhibit antibacterial properties, are frequently used in food shelf life extension, food packaging, medical, biomedical and cosmetic industries. Other biomedical nanomaterials have different biological, physical and chemical properties of silver particles. therefore, silver particles can serve as a therapeutic agent in many biomedical fields.

New properties of silver nanoparticles and rapidly changing new application fields are emerging along with the increase in the number of scientific studies. In particular, the development of different techniques for the synthesis of silver nanoparticles leads to enlarge the application fields in medicine. It is thought that silver nanoparticles produced by green biosynthesis using plant extracts or microorganisms may be more suited to clinical approaches than the physical or chemical methods. Additionally, green biosynthesis of AgNPs is a simple, safe, cost effective and eco friendly approach. Because of all these reasons, green silver nanoparticles seems to be a promising an anti-cancer agent in the field of medicine. But, further researches need to enhance its selectivity on cancer cells, and to determine biocompatibility and side effect in animal models.

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