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# Plant Based Silver Nanomaterials and Nano-mechanics in Anticancer Therapy

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## Abstract

Metal nanoparticles (NPs) has obtained considerable attention in cancer therapeutics in addition to their role in food packaging, sensors, drug delivery, cell labelling, medical dressings, and etc. Among those silver nanoparticles (SNPs) has been extensively synthesized to identify their role in antimicrobial, disinfectant, antitumor activities comparative to other metal- NPs. Owing to the simple, bio-compatible, and cost-effective nature, biogenic methods are preferred rather than physical or chemical ways for the fabrication of SNPs. In past times wide scientific research through metal-NPs has been conducted to investigate the nano-mechanics behind the cytotoxic behavior in cancer therapeutics. Based on the thorough literature survey it has been noted that NPs induce cellular toxicity by stimulating various cellular factors (i.e., enzymatic leakage, oxidative stress generation, DNA damage, cell-cycle regulation, etc.). In current article, an insight into the recent updates considering the potential development NPs nano-mechanics of plant-based SNPs has been presented.

## Keywords

Silver nanoparticles, Green synthesis, Cytotoxicity mechanism, Cancer, Therapeutics

## Introduction

The evolution of reliable and ecologically safer techniques for nanomaterials fabrication is important to overcome drawbacks such as high cost, toxicity, time consumption, etc. in nanotechnology. Plant-derived NPs synthesis is beneficial approach followed by the researchers due to metabolite richness (having reduced and capping abilities), one pot reaction process, non-hazardous nature, and low cost for the large scale production of NPs [1-3]. Bioactive compounds (e.g., proteins, flavonoids, polyphenols, terpenoids, and ascorbic acids) get absorbed on the NPs surface in the bio fabrication process which ultimately exhibit cytotoxicity against microbial and tumor cells [4-6]. SNPs enhanced cytotoxicity is due to their nano size and the phytoconstituents which act as the capping agent. These attributes are responsible for the cancer cell specific sensitivity and selection. Also, the use of plant metabolites makes NPs biocompatible and safer to administer inside the body [7]. Over the years, research in the utilization of nanotechnology in therapeutics has been growing. Such characteristics are critical for their use and gained attention in other diagnostics including cancer [8].

Additionally Ag as a precursor for NPs synthesis has been used widely and have gained more attention by researchers because of its unique properties and uses in different areas such as pharmaceuticals, catalysis, wastewater treatment, nanoelectronics, and textile SNPs are responsible for the cytotoxic or genotoxic

effects to the treated cells. Various factors i.e., size, shape and chemical compounds (used for coating and stabilization process) decide the toxicity level of NPs [9]. Fundamental process behind the ultimate cell death after NMs treatment is mitochondrial disfunction, oxidative stress induction, reactive oxygen sp. generation, apoptosis, and necrosis [10].

Cancer is among the most challenging menaces exhibiting high mortality and incurability over restricted therapeutics. There are many factors responsible which necessitate an adequate treatment such as development of MDR (multi drug resistance), non-targeted drug distribution, unendurable cytotoxicity, and lack of therapeutic response monitoring [11]. Introduction of nanotechnology has proposed significant applications of nanomaterials in cancer nanomedicine. In this manuscript, therapeutic impacts of SNPs on cancer cells have been discussed by generating different metabolic responses at cellular as well as molecular levels.

## Factors Responsible for Varying Cytotoxicity Behavior

Nanomaterials can exhibit different levels of cytotoxicity influenced by many factors such as nanomaterial's formulation, its size-dimension, and coating material. Moreover, other factors like dosage, reaction time, etc. are also important in terms of toxicity levels [7]. Previous findings suggest that the high surface-to-volume ratio is optimal for better penetration of SNPs into the cell and its compartments after endocytosis through cell membrane [12, 13].

## Nano-Mechanics Behind Cancer Therapy

SNPs stimulates alterations inside the treated cells which are structural alterations, lower metabolic activity, high oxidative stress, reactive oxygen species (ROS) induced DNA damage, and reduced cell viability, [14-17]. While many studies have suggested exceptional cytotoxic response of NPs against cancer cells and lesser or almost negligible toxicity levels to the normal cells [18] (Table 1). The process of apoptosis gets executed by the flipping of phosphatidylserine present on the cell membrane from inner side to the outer face.

## Reactive Oxygen Species Production

A possible mechanism by which apoptosis is manifested by SNPs is the production of ROS (Figure 1). These free radicals are usually generated in the cell for the normal functioning. But abnormal production of ROS causes cellular breakdown [19]. It has been stated that plant synthesized SNPs are more efficient in generating ROS than plant extracts due to the free radicle scavenging property (responsible for lower ROS generation via plant extract). However, SNPs more efficiently generate ROS and thus higher cancer cell toxicity in comparison to the plant extract-treated cells in a time and dose dependent fashion. This ROS generated stress is evidenced to stimulate the typical apoptotic events that is cell cycle arrest ($G_0$ phase), altered mitochondrial activities, induction of MMP and caspase dependent apoptosis, and inhibited cell proliferation using JNK pathway [20-23]. Major ROS production is hosted by mitochondria which results in release of mitochondrial content to the cytosol by enhancing the membrane porousness [24]. ROS production as an effect of SNPs exposure causes osmotic pressure to the mitochondrial matrix that results the release of cytochrome c (pro-apoptotic factor) into the cytosol [25]. Subsequent mitochondrial translocation of apoptosis regulatory gene Bax (from cytosol) takes place which leads to the apoptotic process [23]. Further, cyt c binds to Apaf-1 (apoptosis activating factor) which complexes with procaspase-9 and this results the formation of the apoptosome. Apoptosome auto- activates the initiator caspase proteases i.e., caspase-9 which ultimately activates the executioner caspase-3 [25].

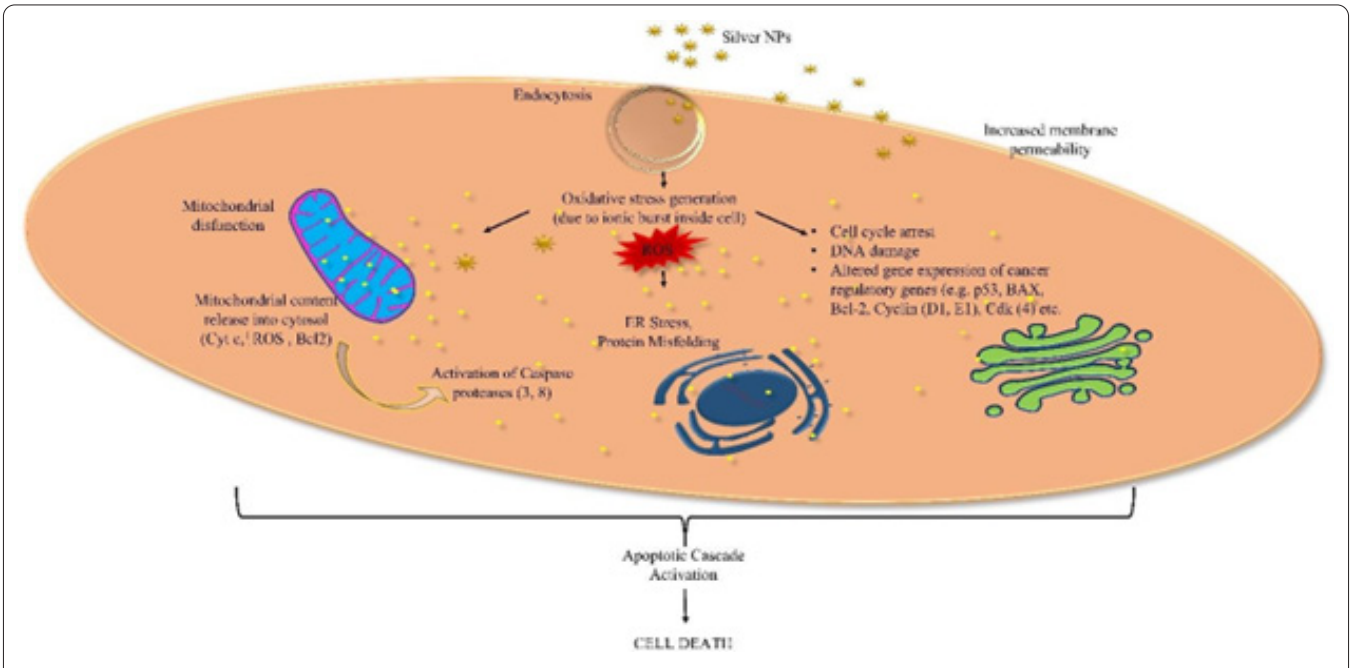


**Figure 1:** Schematic presentation of SNPs mediated cytotoxicity in cancer cell.

## Regulation of Caspase Proteases

Another important aspect which confirms the apoptotic induction is activation or regulation of caspase proteases. SNPs are reported to activate caspases 3, 8 and 9 which are responsible for regulating the inflammatory responses and activation of apoptotic (intrinsic and extrinsic) pathways [19, 26]. Caspase proteases are of two categories, the effector proteases (3, 6, and 7) and the initiators (2, 8, 9 and 10). Interaction of caspase proteases 3 with 8 and 9 leads to the apoptotic fate of cancer cells. Increase in the levels of 3 & 9 (referred as terminal phase inducer of apoptosis in cancer cells) are stated when cancer cells get exposure of SNPs (act as external stimuli) [19]. Apoptosis is also termed as the programmed cellular demise that causes intracellular component's breakdown while on the other hand prevents damage to the adjacent cells [27]. In addition, ROS also contribute to the cancer cell toxicity by causing DNA damage, protein misfolding, ER (endoplasmic reticulum) stress, and cell death. Enhanced caspase-3 results fractionation and translocation of caspase-activated DNAse which causes DNA degradation a crucial event of programmed cell death [19, 28].

Caspase-activated DNAse results the DNA degradation in response to the cleavage and translocation by caspases 3 activation. Other resultant changes in cancer cells have been described as cellular shrinking, membrane blebbing, lost membrane integrity, decreased cellular density, appearance of pyknotic body (chromatin condensation), cytoplasmic enlargement, non-adherence, and cellular death because of SNPs treatment [19, 29, 30]. The regulatory apoptotic factors Bcl-2 and Bax induces the mitochondrial integrity inhibition during the apoptotic cascade [31]. SNPs treatment to the cancer cell lines prevents the confluency over the injured cells and results no wound closure in a time-based process [19]. Additionally, the development of metastasis is one of the essential elements which lowers the success against cancer [32]. SNPs synthesized from plants prohibit the metastatic cascade by inhibiting the angiogenesis, nearby cells invasion, migration, and neoplastic cell colonization. These activities

**Table 1:** Plant derived SNPs and their cytotoxic impact on cancer cells.

| Plant part used | Cell Line | SNPs Shape/ Size (nm) | IC50 Value (µg/ mL) | Cytotoxicity features | References |
|---|---|---|---|---|---|
| Fruit shell extract | Breast cell line (MCF-7) | Spherical, 20 – 30 | 20 | Cells roundness, abnormal shape, cytoplasmic vacuolation and cell enlargement, apoptotic cascade activation | [23] |
| Leaves extract | Colon cell line (HCT116) | Spherical, 177.9 - 251.1 | 3.8 | Cells contraction, coiling, loss of adherence, decreased cell intensity, irregularities in membrane structure | [31] |
| Aerial parts extract | Cervical cancer line (HeLa), and pancreatic beta cell line (βTC- 3) | Spherical, 8 – 50 | < 25 | Dose dependent cytotoxic impact against cervical cancer cells | [40] |
| Leaf extract | Cervical cancer (HeLa cell line) | Spherical, 9 | 70 | Loss of cancer cell viability, dose | [41] |
| Seed extract | Lung cancer cells (A549) | Spherical, 7 - 11 | 849.33 | Effective anti-proliferative activity against cancer cells | [42] |
| Leaf extract | Ovarian cancer (PA- 1 cell line) | Spherical, 20 - 100 | 25 | Dose dependent loss of cell viability and high cytotoxic impact on cancer cells | [43] |
| Seed extract | Human breast adenocarcinoma cell line (MCF-7) and human breast adenocarcinoma metastatic cell line (AU565) | Spherical, 100 | 0.75 and 1,25 | Significantly reduced cancer cell viability, SNPs attributed cytotoxic impact. | [44] |
| Leaf extract | A549 (human lung carcinoma cell line) and LN229 (human glioblastoma cell line) | Spherical, 32.73 | 2.98 and 27.34 | Cancer cell killing via ROS production, nuclear degradation, and loss of osmotic potential across mitochondrial membrane | [45] |
| Leaf extract | Human cervical cancer (HeLa), Breast Cancer cell line (T-47D) | Spherical and oval, 25.96 | - | Loss of cancer cell viability, dose dependent genotoxic effect | [46] |
| Leaf extract | Cancer cell line (A549 and SiHa) | Spherical, 43.5 | 14.96 and 15.96 | Decreased cell viability due to cytotoxic impact on cancer cells | [47] |
| Leaf extract | Cervical cancer cell line | Spherical and cubic structure, 35 - 54 | 20 | Cytotoxic property against the cervical cancer cell lines | [48] |
| Leaf extract | HeLa cancer cell line | Spherical, 40 – 45 | - | Reduced cell proliferation | [49] |
| Leaf extract | Fibroblast cell line (L929) | Spherical, 4 - 6.5 | - | Antibacterial property, Non-toxic behavior against normal cells | [50] |
| Leaf extract | Human colon cancer (HCT-116) | Spherical, 8 – 14 | 48.54 | Elevation in proapoptotic factors i.e.,p53, Bax, and p21 Reduction of anti-apoptotic factors like Bcl-2, p53 attributed apoptosis | [51] |
| Aerial parts extract | Epidermoid carcinoma (A431) | Spherical, 17 | 482.9 | Efficient cytotoxicity with high selectivity of cancer cells | [52] |

mainly upregulate the metalloproteinases regulators thus inhibit the metalloproteinase responsible for the metastasis (the major reason of cancer- associated deaths) [33, 34].

## Alteration of Apoptotic Gene Expression

Wide range of genes and their expressions (up/down regulation) are involved in the apoptotic pathways which are triggered by the external stimuli i.e., SNPs. Plant synthesized SNPs are reported to trigger the genes which are mainly responsible for the functions of cell organelles and their membranes [35]. These genes show involvement in the regulation of metabolic or biological processes where, the upregulated expression of caspases (3 and 9), Bax and p53 in SNPs treated cancer cells (in time dependent manner) is key to the apoptotic pathway induction [17, 35, 36]. While, SNPs stimulate the downregulation of anti-apoptotic proteins gene expression i.e., Cyclin (D1 and E1), Cdk (4), and Bcl-2 etc. [37-39]. Although, wide research has been done profoundly to explore the nano-mechanics behind the cellular cytotoxicity but there are many unresolved disputes remaining which are involved in the cell cycle arrest (Table 1). Thus, further investigations in near future can mark other key factors involved in the treatment of cancer using nanobiotechnology.

## Conclusion

Medicinal plants derived NPs in the treatment of cancer is an interesting prospect for the pursuit of cancer therapeutics. Successful eradication of cancer and antiproliferative effect has been demonstrated and documented in the previous research. Also varying cytotoxicity responses of SNPs have been proposed depending upon the cancer cell types which acclaims a clear necessity to further reconnoiter the mechanistic approach of anti-cancerous impact of nanomaterials. Although, plant synthesized NPs might be beneficial in designing future cancer therapeutics.

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