A REVIEW ON: THE POTENTIAL ROLE OF SILVER NANOPARTICLES IN CANCER DIAGNOSIS AND TREATMENT

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Abstract**:** *This review's main goal is to provide the results of studies on the anticancer properties of silver nanoparticles. Nano biotechnology, a new branch of Nano science, employs nano-based technologies for a variety of biological applications. The prospect of utilizing therapeutic nanoparticles in the detection and treatment of human cancer has emerged as a result of this fast emerging field of Nano science. Silver nanoparticles (AgNPs) are most widely used in various clinical applications because of their antibacterial properties. Apart from antibacterial capabilities, AgNPs have unique cytotoxic effects against mammalian cells, which may make silver-based nanoparticles useful for tumor treatment. Here in this review, due attention has been given to highlight the anticancer properties of silver nanoparticles along with their mechanistic pathway. AgNPs are effective anticancer agents that influence the cell cycle, prevent the growth of cancer cells, cause oxidative stress, and spread programmed cell death (apoptosis). Understanding the mechanistic action of AgNPs responsible for their therapeutic efficacy will help to design anti-cancer therapies and treatments as a potential therapeutic tool.*

Index Terms: *Nanoparticles, Silver Nanoparticles (AgNPs), Synthesis and mechanism of silver Nanoparticles*

I. INTRODUCTION

Nanoparticles provide a novel approach to tumor identification, prevention, and therapy. Cancer mortality, recognized as one of the most lethal diseases, has been dramatically reduced as a result of the rapid advancement of various diagnostic instruments and therapy tactics. In the fields of biomedicine, diagnostics, pharmaceuticals, the industrial sector, and scientific research probes, nanotechnology has been extremely significant. [1] There are various types of metal nanoparticles, which include nanoparticles of iron, gold, silver, titanium, cerium, platinum. Due to their distinctive physicochemical and biological characteristics, such as their high surface area to volume ratio, excellent surface Plasmon resonance, ease of functionalization or conjugation with various types of ligands to obtain desired tailored properties, toxicity against pathogens, effective cytotoxicity towards cancer cells, and catalytic applications, silver nanoparticles are one of the most studied metal nanoparticles for a variety of scientific applications. [2]

Silver was solely recognized as a metal until the advent of nanotechnology, when it was discovered that silver could be created on a Nano scale. Metallic silver has seen significant technical breakthroughs, resulting in ultrafine particles with different morphologies and characteristics measured in nanometers (nm). [3] AgNPs are synthesized using various physical, chemical, and biological methods. In contrast to environmentally friendly biological synthesis, which forms AgNPs through enzymatic reduction with better control over the shape and size of the nanoparticles, chemical methods use reducing agents such as citrate, borohydride, or other organic compounds that are toxic to living organisms despite involving a very simple process. [4] The potent antiangiogenic and ant permeability effects of AgNPs along with their ability to arrest tumor progression in Pliss lymph sarcoma cells has prompted investigation of the antitumor effects of AgNPs in ascitic tumors. Silver nanoparticles inhibit vascular endothelial growth factor (VEGF)-induced angiogenesis in endothelial cells Bovine retina. [5,6]

Cancer therapy has showed a lot of interest in chemotherapeutic drug and nanoparticle combinations. Drug resistance is suppressed and synergism is promoted by combined therapy using anticancer medicines and nanoparticles through different modes of action at low doses. Nanoparticlemediated combination therapy increases the efficacy of anticancer, reduces undesired side effects and improves pharmacokinetics [7]

The application of multiple nanoparticles for chemical and siRNA therapeutics, the sequential administration of a single anticancer agent and selective nanoparticles, and the sequential administration of multiple anticancer drugs with multiple nanoparticles are some of the different types of approaches used in nanoparticles-mediated combination therapy to induce cytotoxicity. [8]

II. Synthesis and Characterization of AgNPs

Physical, chemical, and biological processes are the ones most frequently used for synthesis. Physical synthesis often employs a top-down approach to produce Nano sized particles from bulk materials, such as by the use of evaporation-condensation or laser ablation. [9,10] The most important advantage of these production regimens is that high amounts of the product can be prepared without chemical contamination; however, the stabilization of the nanoparticles is often not satisfyingly assured. Nanomaterial's are synthesized chemically and biologically via bottom-up processes. The majority of nanoparticles produced for industrial or scientific purposes is prepared by chemical reduction. [9]

In this case, metal salts are dissolved in proper aqueous or organic solvents and the metal ions are reduced chemically in the presence of reducing and capping agents to yield a stable colloidal solution. However, the final colloid may contain toxic by-products which obviously limit the biological applicability of the nanomaterial's. [9] A rising number of studies show the value of employing biological synthesis techniques with "green" materials in addition to traditional synthesis techniques to create nanomaterial's and prevent the creation of harmful byproducts in the final colloid. The majority of plant extracts used in green synthesis processes come from various plant components, such as leaves, seeds, or roots. Moreover, microbes, primarily bacteria or fungus, can be used to create green nanoparticles, albeit these techniques require additional thought if the nanoparticles are intended for use as human therapeutics. [11]

Following AgNP synthesis: A thorough characterization is required regardless of the kind of fabrication procedure to guarantee the biological applicability of the nanomaterial's. The initial stage in nanoparticle characterization should be a description of the physical-chemical characteristics of the nanoparticles, such as size, shape, surface charge, and degree of dispersity, which can intrinsically determine their biological impacts. The most popular methods include transmission and scanning electron microscopy, UV-Visible spectroscopy, dynamic light scattering, and zeta potential measurements (ZP). These methods provide pertinent data regarding the size, morphology, stability, mono- or polydispersity, and surface characteristics of the particles. To learn more about the chemical composition, surface residues, and functional groups on the nanoparticle surface properties of the particles, researchers can use Fourier transformed infrared spectroscopy (FT-IR), inductively coupled plasma mass spectrometry (ICP-MS), Raman spectroscopy, and X-ray photoelectron spectroscopy (XPS). [11, 12]

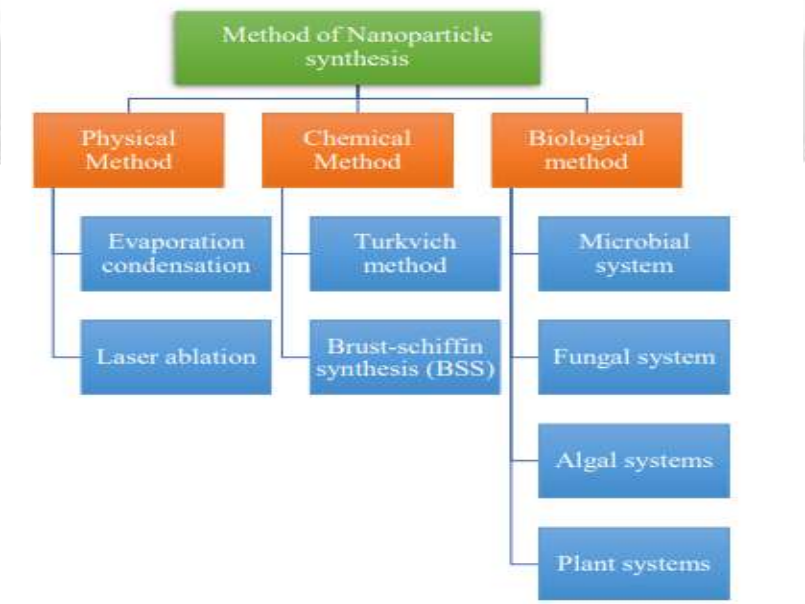

Figure 1: Methods of nanoparticle synthesis.[13]

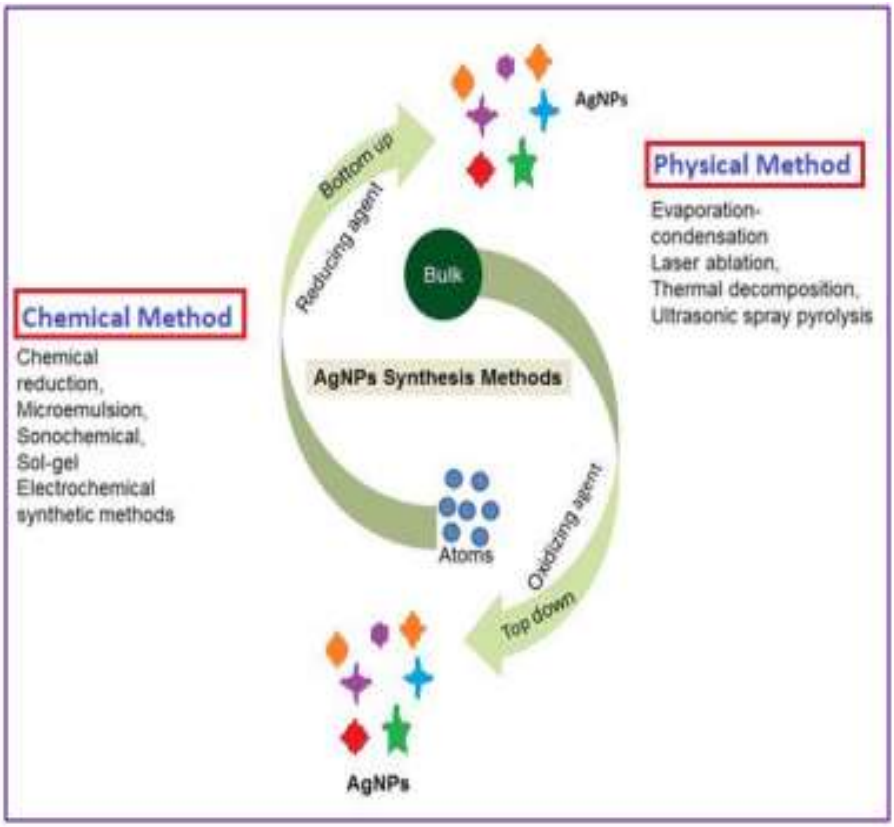

Figure 2: Physical and chemical methods for synthesis of AgNPs[14]

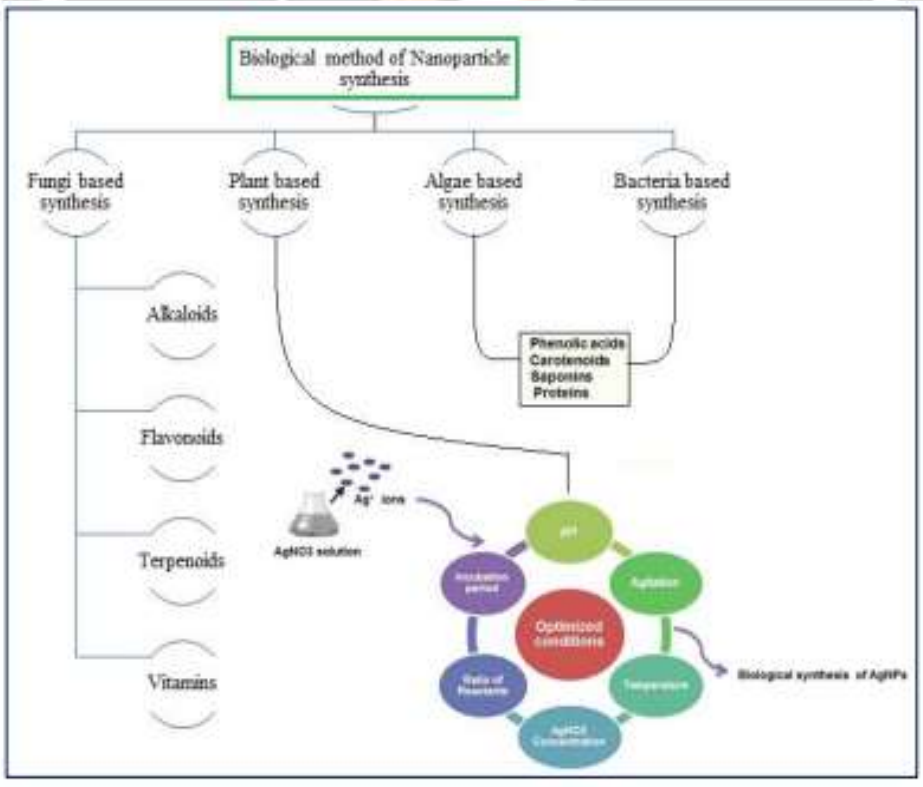

Figure 3. Biological method for the synthesis of AgNPs [15]

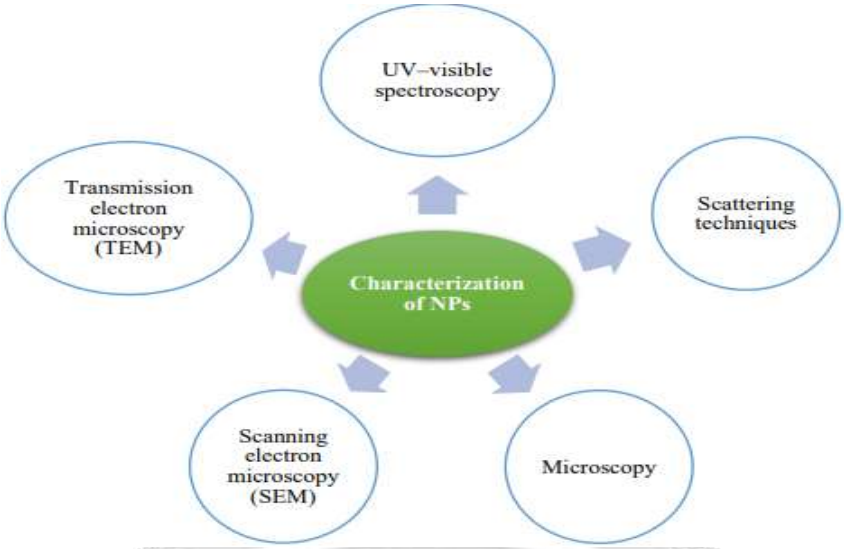

Figure 6: Characterization of NPs [16]

Turkevich method:

Turkevich's approach produced a polydisperse solution of NPs; an improved method was created in a paper published by Frens. The technique begins by heating the gold hydrochlorate solution to approximately 100 degrees Celsius and then adding 1% sodium citrate to the boiling solution. This technique of AuNPs synthesis using citrate solution is named after Turkevich even though the method was already devised in 1940 by Ernest and Lynn. After a few seconds of citrate addition, a faint blue colour develops, indicating the nucleation process. After a few more seconds of boiling, the solution turns from blue to a deep wine red, indicating the formation of spherical AuNPs. The citrate ion concentration is the most important factor influencing shape and size (36) and repeatability (37). Other noble metal NPs, such as silver, platinum, and palladium, may be manufactured using this approach in addition to gold. [17]

III. MECHANISM OF SILVER NANOPARTICLE (ANTITUMORAL ACTIVITY OF AgNPS)

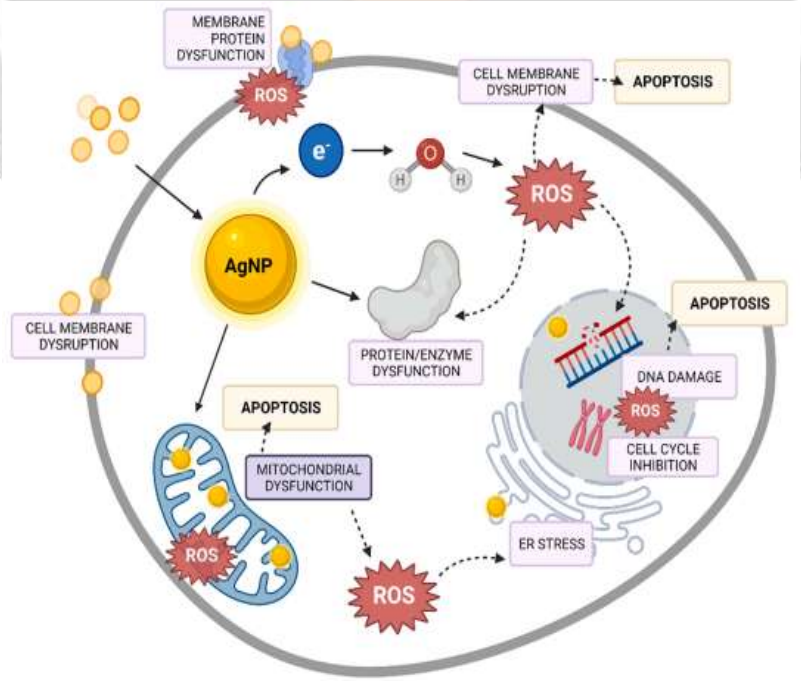

Figure 6: Mechanism of anticancer effect of silver nanoparticles [19]

1) Mechanisms of Antitumor Effects of AgNPs In Vitro:

The modes of action of silver nanoparticles and their conjugates with anticancer drugs include the generation of reactive oxygen species (ROS) and oxidative stress, DNA damage, cell cycle arrest, and the promotion of tumour cell death by apoptosis as well as nonapoptotic cell death. [19]

2) Effect of AgNPs on Cell Cycle Regulation:

Cell cycle progression is a necessary mechanism for DNA replication, cell growth and division, and organism renewal. Yet, excess of growth factors or mutations in genes/lack of tumor suppressor proteins cause cells to be unable to exit the cell cycle, resulting in uncontrolled cell proliferation. For this reason, modulation and targeting of cell cycle control mechanisms represent a suitable therapeutic target for antitumor therapy. [20] Many proteins, including cyclins, cyclin-dependent kinases (CdK), and CdK-activating kinases (CdK-AK), tightly control the cell cycle in healthy cells (CAKs). Topoisomerases, tubulins, different enzymes, and proteins from the cyclin-dependent kinase inhibitor family all play a role in cell cycle progression. Damage to DNA can cause irreversible cell cycle arrest at various stages of the cycle, which is directly connected to the activation of a complex mechanism that results in cell death. [21] Their ability to cause DNA double-strand breaks and increase the population of AgNPs-treated cells with subG0/G1 DNA content, which are considered apoptotic. [22] The most well-known proapoptotic transcription factor is p53, which is involved in intracellular processes such as the response to DNA damage and repair, control of cell metabolism and autophagy, ageing, and cell death. [23]

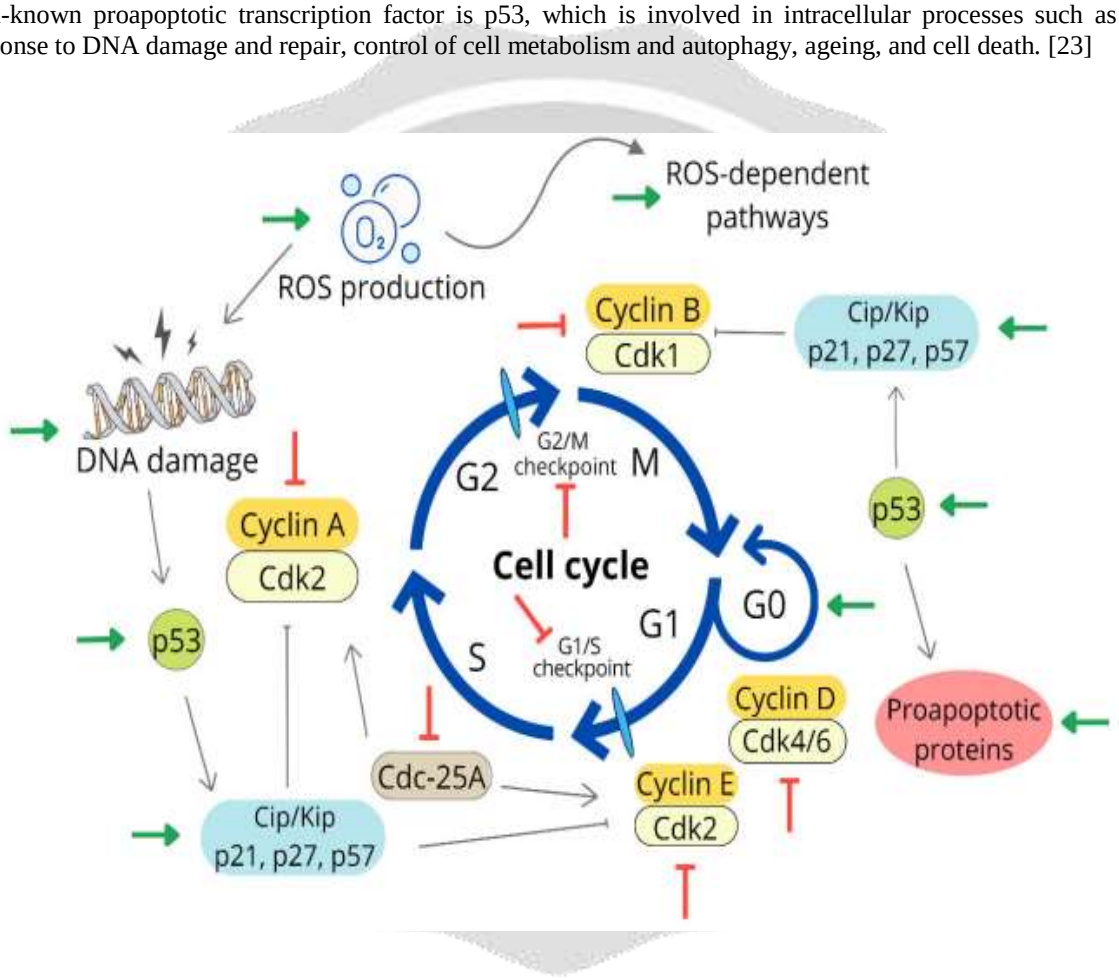

Figure 7: Cell cycle regulation modified by AgNPs. Green arrow—activation by AgNPs; red arrow inhibition by AgNPs [24]

3) AgNPs as Cell Death Inducers:

In healthy cells as well as throughout the body, cell death is a complex process that controls homeostasis and biochemical alterations. The goal of traditional anticancer treatment is to kill tumor cells by specifically impairing their intracellular pathways. Apoptosis and autophagy are now being researched extensively in relation to the production of cell death; their combined control may help to boost the efficiency of anticancer therapy. [25]

4) The synergic combination of AgNPs and chemotherapy drugs:

Combination chemotherapy refers to the administration of two or more drugs that target different cancer hallmarks to generate a synergic toxicity. This strategy can potentially enhance therapeutic efficacy, minimize drug resistance and side effects. The use of nanotechnology could make it possible to get around these problems. Clinically authorised anticancer medications are transported via nanocarrier systems, which also improve

circulation times and enable regulated drug release. Moreover, NCs can facilitate medication accumulation at the tumour location via passive (EPR impact) or active anticancer treatment targetintiveness. [26] AgNPs have the potential to cause synergic toxicity when used with a number of anti-cancer medications, according to research. The ability of 28 nm, citrate-coated, AgNPs to boost the toxicity brought on by anticancer medications (such verapamil, cisplatin, carmustine, and methotrexate) and demonstrated a synergic toxicity for all tested combinations against MDR colon adenocarcinoma cancer cell. [27] Silver NCs may also be used to deliver and act synergically with cancer small molecule inhibitors. For example histone deacetylase inhibitors (HDACis), for example, are a potential family of medicines for cancer treatment. HDACis activity can cause a variety of biological effects in cancer cells, including apoptosis and cell proliferation suppression. Moreover, the use of HDAC produces chromatin hyperacetylation, which results in an open chromatin shape, making the DNA more accessible to harmful chemicals. [28]

5) AgNPs and radiotherapy:

Several in vivo and in vitro investigations have demonstrated AgNPs' capacity to increase cell/tissue sensitivity to radiation (RT). To kill tumour cells, this oncotherapy technique uses the interaction of ionising radiation (such as -ray, X-ray photons, or charged particles) with biomolecules. RT is a routine adjuvant therapy for various malignancies and is presently used in around half of all cancer patients. However, its main drawbacks rely on tumor-acquired resistance, lack of selectivity, and dose escalation, which is limited due to severe side effects associated with ionizing radiation. [29,30] AgNPs' high atomic number is one of the primary characteristics that makes them more attractive as radio sensitizers (Z). As the core atom of high-Z elements is surrounded by a large density of electrons, ionising radiation may cause enhanced ionisation and cross-section with biomolecules. Similar to other high Z-number atoms. the interaction of AgNPs with X-ray photons results in the release of secondary electrons. These electrons either interact directly with the DNA, causing DNA double-strand breaks. [31,32] One of the early studies looking into AgNPs as potential radiosensitizers revealed a size-dependent improvement in the cytotoxicity of radiation doses in various glioma cell lines. The radiosensitizing effect of AgNPs decreases as particle size increases, with 20 nm AgNPs outperforming 50 and 100 nm nanoparticles. Given that smaller AgNPs typically release more Ag+ ions, the authors explained that this result was caused by the release of silver ions from the particles. [33]

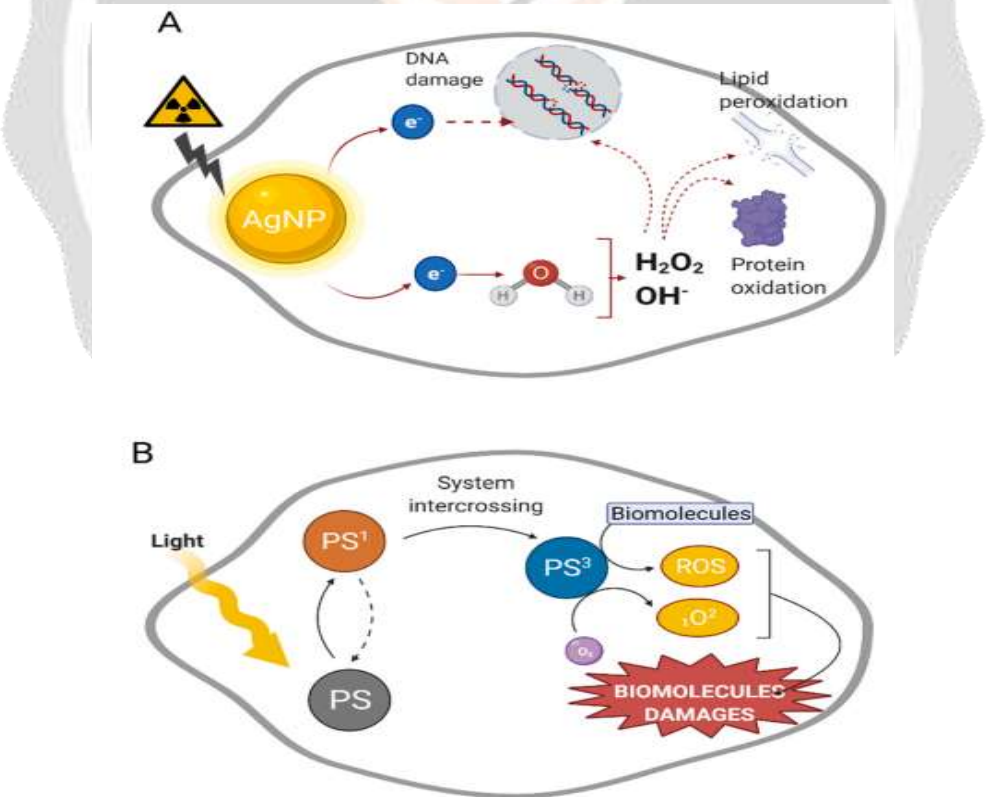

Figure. 8. (A) Schematic illustration of the proposed mechanism for radiotherapy in cells using AgNPs. Under ionizing radiation, high Z-elements such as AgNPs, releases secondary electrons that interact with cellular components, leading to biomolecules damages and cell death. (B) Schematic illustration of the proposed mechanism of PDT reaction in cells. Upon light irradiation, the PS undergoes physical changes, generating ROS in the presence of oxygen. [34,35,36]

6) AgNPs and phototherapies:

Due to its low toxicity, limited invasiveness, and enhanced patient life quality, photodynamic therapy (PTD), a kind of phototherapy, has been effectively used in the treatment of cancer. Fig. 8.B shows a schematic illustration of a typical PDT reaction. Briefly, this strategy is based on the accumulation of a photosensitizer (PS) in the tumor tissue. Upon local exposure to light at an appropriate wavelength, the PS achieves an excited singlet state (PS1), which decays to the ground state or undergoes system intercrossing, forming a triplet state (PS3). This molecule has the ability to cause irreversible cell damage either indirectly (by transferring a proton or electron to biomolecules to create a radical, which then combines with O2 to produce ROS) or directly (by transferring PS3 energy to O2 to create singlet oxygen), resulting in cell death. [36,37] The application of nanoparticles in PDT has been a major evolution in overcoming some of the challenges associated with conventional photosensitizers. Metal nanoparticles, for instance, can be designed as a PS delivery system, improving their bio distribution in physiological media or even acting as a PS. [38] AgNPs have a significant optical feature known as surface plasmon resonance (SPR), which is the collective oscillation of electrons in the conduction band following the incidence of a photon with a resonance frequency. Because plasmonic nanoparticles may be transported to tumours and exposed to light at the resonant frequency, causing the collective oscillation to result in heat generation, this property is particularly intriguing for photothermal treatment (PTT). [39]

7) The safe use of AgNPs in oncotherapy:

It is crucial to comprehend the molecular processes underpinning potential interactions of AgNPs with biomolecules and cells as well as pharmacokinetic factors such absorption pathways, tissue biodistribution, bioaccumulation, long-term impacts, metabolism, and nanoparticle excretion. Regardless of the AgNPs' toxicity, optimising therapies and effective clinic translation depend on reducing nonspecific interactions and systemic biodistribution as well as improving particle tumour absorption. AgNPs may benefit from the EPR effect, but there is still room to improve their tumor target ability. Nanomedicines provide a number of benefits, one of which is the ability to modify the surface of nanoparticles to enable active target delivery. Higher selectivity and delivery effectiveness are achieved by functionalizing the surface of the NP with ligands that interact with certain receptors and biomarkers that are often overexpressed in tumor cells. [40,41]

8) The use of AgNPs in biosensing:

Because of their high conductivity, catalytic activity, and plasmonic features that may be used to increase the performance of biosensors, AgNPs are particularly appealing materials for use in diagnostics. The sensitivity of the biosensors is critical for detecting analytes at low concentrations. AgNPs were used to improve the electroactive area of the electrodes and, as a result, the electron transfer rate, so increasing the biosensor's sensitivity in terms of greater specificity and delivery efficacy. For electrochemical biosensors, AgNPs are especially interesting to be used as redox mediators, since they exhibit a well-defined oxidation peak in buffer solution. [42] AgNPs are especially appealing for use in colorimetric biosensors because they can cause a shift in the SPR band, resulting in colour changes in suspensions. Dewangan et al. developed colorimetric probes for cholesterol detection using AgNPs modified with cholesterol oxidase (ChOx). The method was based on the oxidation of free cholesterol by ChOx, which produced hydrogen peroxide (H2O2). The produced H2O2 oxidises the AgNPs (Ag0) to Ag+, causing the solution to change colour from yellow to colorless. [43]

9) AgNPs as ROS Inducers:

It is well known that silver nanoparticles may trigger reactive oxygen species (ROS) production in mammalian cells. The quantity of produced ROS is greatly dependent on the kind of cell, its metabolic activity (i.e., the number of mitochondria), the redox state of the surrounding environment, and a host of other factors. ROS consist of the superoxide anion (O2-), hydrogen peroxide (H2O2), and the hydroxyl radical (HO•). Under physiological settings, the reservoir of antioxidants in the cell keeps these signaling molecules at low concentrations. [44] Excessive ROS generation, on the other hand, is related to oxidative stress. The increase in ROS levels caused by AgNP exposure causes cytotoxicity, reducing cell proliferation rates, causing macromolecule and organelle damage, and ultimately leading to cell mortality. As a result, the majority of study indicates that nanosilver treatment raises ROS and oxidative stress. However, this has been challenged by research that found no increase in ROS. This might be the result of various experimental circumstances or difficulties in identifying the real amounts of ROS using H2DCFDA, the primary dye used to detect ROS. [45]

III) ANTIPROLIFERATIVE ACTIVITY OF AgNPs:

The use of AgNPs as antimicrobial preservatives in the food business has an effect on the human digestive system. Interactions of AgNPs with healthy cells (epithelial cells, mucous membrane cells, etc.) and cancer cells (squamous, liver, or colon cells) via the GI system have involved NPs in a variety of anti- and pro-oncogenic activities. Although the mechanisms of carcinogenesis remain unknown, uses of AgNPs as anticancer drugs are now well established. The most commonly used AgNPs interfere with the proliferation system cells' cell cycle, with eventual suppression of growth. Colloidal solutions of 10-nm-diameter NPs at a dosage of 10 ng/ml were tested on squamous carcinoma SCC-25 cells and found to halt the cell cycle in the subG1 or G0/G1 phase after 24 and 48 hours, respectively. The cells responded with a failure of mitosis, and in the treated population there were

not as many bi-nucleated and doublet cells as in controls. DNA synthesis was also stopped, probably because of DNA damage (single- and double-stranded breaks, sSBs and dSBs) and because of the presence of AgNP's inside the cell nuclei. This suggestion was confirmed by measuring production of reactive oxygen species (ROS) in parallel cytometric assays, which damage DN, influence the S-phase of the cell cycle, and inhibit replication. Additionally, colorimetric MTT tests were used to track cell proliferation. With these assays, the number of cells in each well of a plate is proportionate to the absorbance at 570 nm. This straightforward test demonstrated that after exposure to AgNPs, SCC-25 cells' viability and proliferation declined in a dose-dependent way as AgNP concentration .

The most significant discoveries were related to genes that code for proteins involved in cell cycle checkpoints as well as mechanisms for DNA repair during the S-phase. [46]

IV) THERAPEUTIC STRATEGIES IMPLYING SILVER-BASED NANOPARTICLES:

AgNPs may be used in cancer treatment as active components of complicated nanosystems or as a combination with other therapeutic methods, according to a number of encouraging in vivo study data. However, their applicability as anticancer agents; thus, their clinical translation has still never been addressed. AgNPs are already commercialized to manage various clinical conditions, including the treatment of wounds and burns. The use of AgNPs for wound care has a long history, and basic study shows that in addition to their antimicrobial properties, AgNPs can promote tissue regeneration by activating fibroblasts, immune cells, and keratinocytes in the vicinity of the lesion. For these uses, AgNPs are mixed into fabrics, creams, or other delivery matrices; consequently, they could locally exercise their positive effects when applied topically. [47,48]

V) SIGNIFICANT CHALLENGES IN THE CLINICAL APPLICATION OF AGNPS:

The first stage is to grasp and define cancer because silver nanoparticle cancer treatment is complex. Receptor profiling and high-throughput personalized tumor analysis techniques, such as DNA sequencing and transcriptomic, proteomic, and metabolomics analyses, are necessary additions due to the heterogeneity of tumor in order to find mutations, signaling pathways, and cellular characteristics that have been compromised during tumor development and progression. These results should be used to create specialized, patient-specific multipurpose silver nanoparticles. The ideal size/shape and surface charges for efficient metabolism, including the buildup of tumor-specific AgNPs, are among these modifiable properties. Additionally, when designing customized nanoparticles, consideration should be given to surface alterations for active cancer cell targeting, such as conjugating AgNPs with receptor ligands, antibodies, and cell-penetrating peptides. Last but not least, the use of such complicated AgNPs must be supported by therapies like chemotherapy and radiation that complement one another. This nanoparticle-based medicine may soon become a reality. However, the dilemma of how to continue persists.[24]

VI) GREEN CHEMISTRY APPROACH FOR THE SYNTHESIS OF AgNPs:

Biological techniques have become practical alternatives to address the shortcomings of chemical techniques. Many studies have focused on the highly effective development of AgNPs of defined size using various biological systems, including bacteria, fungi, plant extracts, and small ones. Recently, biologically mediated synthesis of nanoparticles has been demonstrated to be straightforward, inexpensive, dependable, and environmentally friendly approaches.In addition to using chemical processes to create AgNPs, biomolecules like vitamins and amino acids may also be used to create other nanoparticles, such gold and graphene. Prior to the development of this biological process, the manufacture of nanoparticles was demonstrated by the bio absorption of metals by gram-negative and gram-positive bacteria; nevertheless, the generated nanomaterials were aggregates rather than nanoparticles. [49]

VII.THE INTERFACE OF PHYTO-NANOTECHNOLOGY AND CANCER:

The use of medicinal plants has expanded the prospects and treatment options for cancer. They aid in the development of cutting-edge cancer treatment strategies like the green production of AgNPs and serve as a source of new chemicals through phytochemical screening. These green synthesized nanoparticles may overthrow the obstacles and complications of conventional diagnosis and treatment therapies. The cancer cells differentiate from normal healthy cells in the context of blood vessels proliferation (angiogenesis), reduced permeability of capillaries and lymphatic drainage system. This altered microenvironment of cancerous cells provides a platform to nanotechnologists to device suitable nanodrug having selective advantage to precisely target cancer cells. [50] Nanoparticles possess site specific and targeted action which enhances the drug efficiency as nanoparticles move across impermeable membrane and could tackle the immune system response, so suitable for cancer treatment. [51]

VIII. PHYTONANOTECHNOLOGY AND CANCER TREATMENT: A MECHANISTIC APPROACH:

AgNPs are regarded as exceptional candidates for cancer treatment due to their tiny size and propensity to cause cell death via a variety of methods. Through rupturing double stranded DNA, oxidative stress, and chromosomal instability, AgNPs cause cell death. Although smaller AgNPs (10 nm) are more likely to cause cellular toxicity because of how easily they penetrate cells and locate inside the nuclei, bigger AgNPs (100 nm) are more efficient at producing these effects. According to reports, AgNPs cause cytotoxicity in mammalian cells through a number of different mechanisms, including (a) disruption of energy-dependent cellular processes and

impaired DNA replication brought on by the uptake of free silver ions (b) production of reactive oxygen species (ROS) and free radicals (c), and (d) cell membrane damage brought on by direct contact with AgNPs. [52]

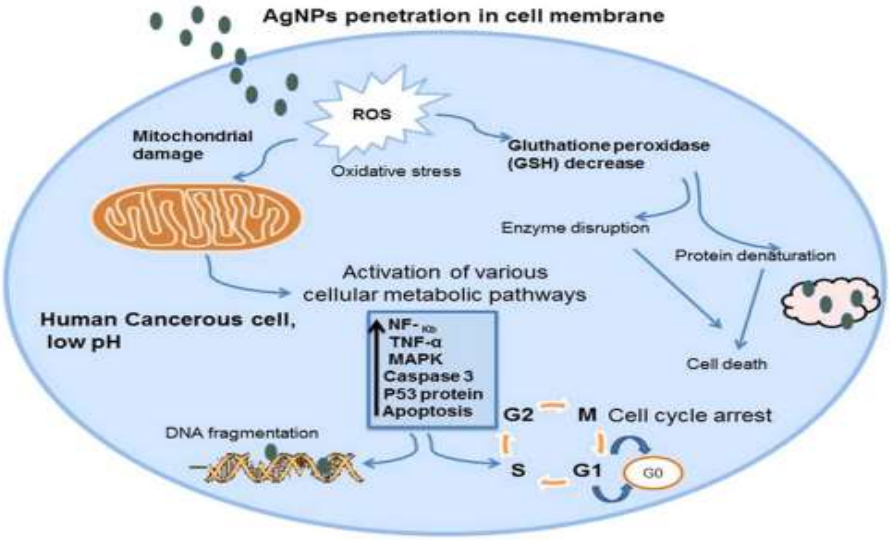

***Figure 9. Possible anticancer mechanism of green synthesized AgNPs and various pathways involved in cytotoxic effects of AgNP*[52]**

Reactive oxygen species (ROS), which are produced as a result of green generated AgNPS, cause cell death. The signal transduction pathways that lead to cell apoptosis are negatively impacted by ROS production. The production of hydrogen peroxide alters the membrane potential of mitochondria, which causes the respiration to become decoupled. Once within the cell, AgNPs cause the production of ROS, a decrease in glutathione (SGH) levels, activation of nuclear factor kB (NF- kB), and production of tumour necrosis factor-alpha (TNF-alpha). The increased levels of superoxide radicals change the potential of the mitochondrial transmembrane and disrupt the signalling pathway, which causes apoptosis and cell death. This is a direct interaction with AgNPs.[53] The increased ROS production and decreased GSH evokes cellular components damage such as DNA fragmentation, peroxidation of lipid membrane and protein carbonylation (protein harmful oxidation). Figure 5 shows the possible mechanism for anticancer potential of green synthesized AgNPs. Furthermore, altered mitochondrial membrane potential lead to activation of caspases 3 and 9 leading to cellular apoptosis. Subsequently, it activates c-Jun NH2 terminal kinase (JNK)which triggers formation of apoptotic bodies and DNA breaks results into cell cycle arrest. The proposed mechanism for the anticancer action of green synthesised AgNPs is apoptosis induced by caspase dependent and mitochondrial dependent pathways, cell cycle arrest in sub-G1 phase, generation of ROS and disturbance of cellular equilibrium, activation of p53 protein and upregulation of casepase 3, pH dependent release of silver ions and selective killing of cancerous cells, and inhibition of VEGF induced activities. [54]

Death of cancer cells is displayed by release of silver ions from green synthesized AgNPs. Hence, selective killing of cancerous cells is direct by concentration of silver ions released inside cells. Release of silver ions in normal cell lines differ from cancer cell lines in different pH. Electrostatic interaction between normal cells and cancer cells also determines the silver ions release. Selective killing of cancer cells also depends on wide ranging electrostatic interaction between normal and cancer cells. AgNPs produced by biosynthesis inhibited the cell proliferation brought on by vascular endothelial growth factor, demonstrating their antiangiogenic characteristics (VEGF). After entering the cell, AgNPs blocked the Src-dependent route that VEGF and 1L-1 used to increase vascular permeability [55].

IX) FUTURE RESEARCH DIRECTION:

The research area for the synthesis of AgNPs using green technology is growing, and their application potential is enormous. Plant-derived phytochemicals and the green synthesis of nanoparticles can enable the development of excellent techniques to treat various deadly diseases, such as cancer. The translation of the nanomedicine for preclinical trials needs to address several critical issues. Firstly, target specificity of the nanoparticles and drugs to the desired site of the tumor tissues is a difficult challenge. A survey reported that less than 1% of the nanoparticles being injected reach the desired site of a tumor. It is clear from multiple papers in recent years that treating different cancers using nanoparticles is seen to be an innovative, alluring way to enhance cancer therapy. These substances, like AgNPs, can build up in the tumour tissues, interact with the various cancerous and stromal cells present in this microenvironment, and then become internalised by the cells. Here, they activate a number of signalling pathways, leading to the dysfunction of the mitochondria, oxidative stress, autophagy, ER stress, and various forms of cell death.

In addition to having a direct anti-cancer effect, AgNPs may be used as platforms for the administration of other cytotoxic medications or to improve the anti-cancer effectiveness of combination partners during chemotherapy or radiation. Current science focuses on the biomedical properties of nanoparticles; however, there are concerns regarding their long-term toxicity. Recent trends in the production and surface manipulation of nanoparticles, such as the use of characteristic biogenic capping agents, have enabled the preparation of nontoxic, surface-functionalized, and monodispersed nanoparticles for medical applications. [56,57] .

CONCLUSION:

Silver nanoparticles have the potential to be highly effective in the delivery of anticancer medications, alleviating some of the challenges associated with current therapy. The biosynthesis of AgNPs is gaining popularity since it is a straightforward and ecologically friendly technique that does not require the use of chemical reagents. The present articles showed that silver nanoparticles can have a synergistic effect with anticancer drugs, allowing the use of lower doses. AgNPs are incredibly desirable building blocks for the development of innovative cancer detection and treatment systems. AgNPs have a variety of uses in diagnostics, including enhancing the functionality of biosensors, boosting the electro active area and electron transfer rate in electrochemical electrodes, and serving as redox mediators. AgNPs can also be used in SPR-based biosensors or as colorimetric probes for imaging. The production of AgNPs using plants is a developing and exciting area of nanotechnology that has the potential to have an impact on the field's advancement. This work summarizes recent progress in AgNP characterisation methods, mechanism, and optimization conditions.

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