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EXPLORING THE THERAPEUTIC POTENTIAL OF GREEN SYNTHESIZED PLANT-BASED SILVER NANOPARTICLES FOR ANTICANCER TREATMENT

[1]Arun Giri Raj.V, [2]Shyam S Kumar, [3]Dr.N.L.Gowrishankar, [4]Shabna.S, [5]Anjitha.M

[1]M.Pharm Student, [2]Associate Professor, [3]Principal, [4]M.Pharm Student, [5]M.Pharm Student
[1]Department of Pharmaceutics,
[1]Prime College of Pharmacy, Palakkad, India

Abstract: Nanotechnology is a rapidly advancing field within medical science that has versatile applications across various domains. Phyto-constituents are highly valuable and promising options for the creation of green synthesised silver nanoparticles (AgNPs), which show significant potential in addressing cancer therapy. This review provides a summary of the environmentally friendly method used for synthesizing AgNPs and their characterization. The present review further explores the potentials of Phyto-based AgNPs toward anticancer activity including its probable mechanism of action. The utilization of plant extracts in the synthesis of silver nanoparticles offers a sustainable and eco-friendly approach to developing novel cancer treatment strategies. By exploring the unique properties and mechanisms of action of these plant-based silver nanoparticles, this research aims to uncover their efficacy in inhibiting cancer cells. Therefore, this article primarily focuses on the utilization of environmentally friendly Phyto-based AgNPs for potential cancer applications, covering their mechanism of action and future therapeutic prospects in a comprehensive manner.

Key words: Nanotechnology, Green Synthesis, Plant-based, Silver Nanoparticle, Anticancer

I. INTRODUCTION

The invention of nanotechnology has greatly advanced medical science by offering remarkable ways to treat life-threatening diseases. [1] The National Nanotechnology Initiative established the definition of nanotechnology as the manipulation of matter with at least one dimension sized between 1 and 100 nanometres. [2]They find a range of applications in the fields of medical, chemistry, environment, energy, agriculture, information and communication, heavy industry, and consumer products. [3]An outstanding platform for a wide range of biological applications has been offered by nanotechnology. More specialized therapies, such Nano particles, are available for hard-to-manage illnesses like cancer.

The primary obstacle in cancer treatment is to stop the destruction of non-cancerous cells while slowing the growth of malignant cells. Oral or injectable current therapy circulating throughout the body is harmful. Only the malignant cells that are actively spreading will be the target of cytotoxicity in targeted medication therapy employing Nano sized fragments. Nano sized formulations are a truly extraordinary gift that can be used to treat long-term conditions like cancer [4].

Metallic nanoparticles are gaining a lot of attention due to their special qualities and applications. Silver metal nanoparticles have been examined the most because of their outstanding broad-spectrum activity. In Nano science, research on AgNPs has advanced significantly, particularly in the areas of antimicrobial, antibacterial, antioxidant, antifungal, anti-inflammatory, anticancer[5], and anti-angiogenic properties . AgNPs are small particles with distinct physico-chemical properties (size, shape, optical activity, electric conductivity, high surface area). Plant-mediated AgNPs are essential as reducing, stabilizing, and capping agents and are safe, economical, and environmentally benign. They are also quickly produced. As such, the green approach to AgNP synthesis has many benefits over chemical and physical approaches.

Among the several metallic nanoparticles used in biomedical applications, silver nanoparticles are among the most significant and fascinating nanostructures [6, 7]. A greater variety of people are becoming interested in silver nanoparticles due to their numerous applications in biomedicine.

They are applied topically to prevent infection of wounds, as anticancer drugs, and as antibacterial agents in wound dressings [8]. Because of its uniqueness and ability to significantly alter physical, chemical, and biological properties due to their surface to volume ratio, metallic nanoparticles have been used for a multitude of purposes [9]. High yield, solubility, and stability are demonstrated by green synthesized

nanoparticles. Biological approaches appear to be the most straightforward, quick, safe, and environmentally friendly ways to produce AgNPs with well-defined size and morphology under ideal conditions for conventional research, out of a variety of synthetic methods [10].

II. GREEN SYNTHESIS

The conventional techniques for creating NPs are expensive, toxic, and environmentally unfriendly. Scientists have identified the precise green paths—that is, naturally occurring sources and the components they contain—that may be utilized to create NPs in order to address these problems. Three categories can be used to identify the source of green synthesis: (a) utilizing microorganisms, such as bacteria, actinomycetes, fungi, and yeasts (eukaryotes); (b) using plants and plant extracts; and (c) using membranes, virus DNA, and diatoms. The green production of AgNPs utilizing plant extract was the main topic of this review [11].

This method requires no sophisticated equipment or chemicals, is simple, and is environmentally friendly. Since the stabilizing and reducing agents are derived from plants, no hazardous chemicals are used [12]. In addition to providing free lowering, stabilizing, and capping agents, plants significantly lower the cost of culture media and microorganisms. Decreasing the formulation's total cost in the end [13, 14]. This technique is a good substitute for traditional methods for synthesizing nanoparticles. This approach yields a more stable product with the proper size and shape.

III. SYNTHESIS OF AGNPS WITH PLANT EXTRACTS

Green synthesis, which uses plants and plant extracts, has become more and more popular because of its simple, fast development process, low cost, non-pathogenic nature, and environmental friendliness. Green synthesis based on plants usually happens more quickly than that of other microbes like bacteria and fungi. Consequently, the application of plant extract in green synthesis has prompted numerous investigations and research projects thus far. It was found that, depending on the type of plant extract, it was possible to produce metal NPs with plant extract in the metal salt solution quickly and at room temperature. Once the plant extract has been selected, the main impacting factors are pH, temperature, metal salt, and extract concentration [15].

Numerous primary and secondary metabolites, including proteins, amino acids, vitamins, nucleic acids, and alkaloids, terpenoids, flavonoids, saponins, and phenols, are found in naturally occurring phytoconstituents [16]. These plant extract's primary and secondary metabolites become oxidized and coat the newly formed particles, acting as reducing agents for silver ions. When exposed to oxygen, as that found in silver nitrate (AgNO3), these compounds undergo electron loss and oxidation through regular cellular processes, acting as reducing agents [17].

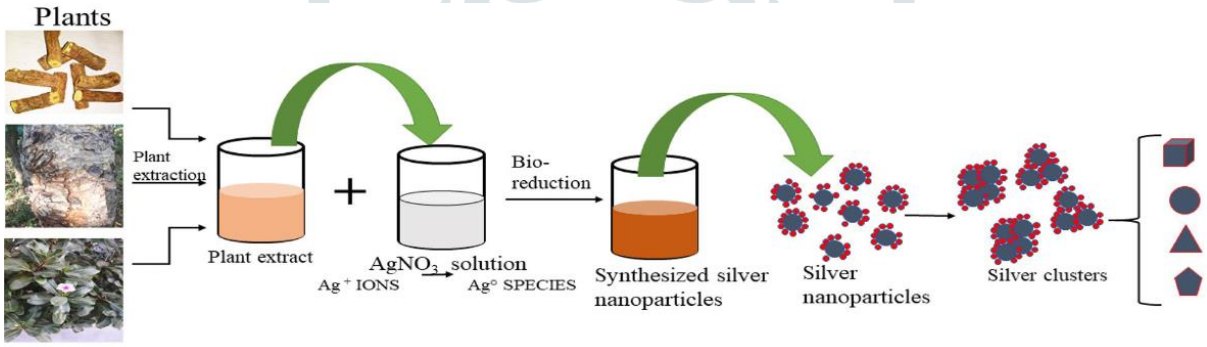

Fig.1 synthesis of plant based agnps through green synthesis method

When the plant extract is mixed with silver nitrate solution, green synthesis begin. The changes in color over a specific period of time denotes the synthesis of nanoparticles. When plant extract or active ingredients from plants are added to a solution of silver nitrate, which contains positive ions (Ag +), it transforms into a zero-valent state (Ag° species), acting as a reducing agent. After that, the nucleation process starts, and the immediate growth phase comes next. This results in the formation of larger, thermodynamically more stable nanoparticles by joining smaller ones. Ultimately, various shaped nanoparticles such as spheres, cubes, triangles, hexagons, pentagons, rods, and wires develop. Factors that affect the synthesis and formation of nanoparticles are pH, temperature, the concentration of plant extract, reaction time, the concentration of silver nitrate, pressure, and others [18, 19].

IV. PHYTO-SYNTHESIZED SILVER NANOPARTICLES IN CANCER THERAPY

Plant-based silver nanoparticles harness the unique properties of silver at the nano scale, and when synthesized using phytochemicals present in plants, they offer an eco-friendly and potentially effective approach for cancer treatment. The methodology for creating plant-based silver nanoparticles involves mixing silver ions with plant extracts, which contain natural reducing agents that convert the ions into nanoparticles. This process not only provides a green synthesis method by avoiding harsh chemicals but also allows for the production of AgNPs with controlled sizes and shapes.

Cancer cells avoid apoptosis, or programmed cell death, and continue to proliferate. The above is a hallmark of cancer cells and the main focus of cancer treatment development. Plant-based nano-sized silvered becomes effective against cancer. Two signalling pathways, viz. an intrinsic pathway and an extrinsic pathway, exist to activate programmed cell death or apoptosis. DNA damage or severe cellular stress triggers apoptosis, which kills cancer cells [4]. Green AgNP synthesized using the bioactive fraction of *Pinus roxburgh* was reported to have cytotoxic activity against lung and prostate cancer cells. Apoptosis has been investigated through the inducible intrinsic pathway by mitochondrial depolarization and DNA damage. Increases in ROS, cell cycle arrest and activation of caspase-3also lead to cancer cell apoptosis [20]. AgNP-dipalmitoyl phosphatidyl choline composites forming liposomes (Lipo-AgNP) were found to be cytotoxic, causing ROS generation and DNA damage. Activation of the proapoptotic protein Bax and inhibition of the Bcl-2 protein leads to the release of cytochrome C and gradually activates caspase, causing apoptosis in macrophages [21].

AgNPs were also confirmed to have strong cytotoxicity by arresting the cell cycle at the G2/M phase. A study on A549 lung epithelial cells reported that AgNPs strongly upregulate protein kinase-C (PKCζ), leading to cell cycle capitulation in the G2/M phase. AgNPs are additionally associated with the formation of P-53 protein, Bax and Bid, caspase-3, ROS, and the regulation of anti-apoptotic protein-Bcl-2 and Bcl-w [22]. *Cynara scolymus*, also known as artichoke, was used to synthesize AgNPs, and further antitumor activity studiesphotodynamic therapy showed that AgNPs modulate mitochondrial apoptosis through ROS generation, regulate apoptotic proteins, and induce MCF7 breast cancer cell death [23].There are several related studies and research studies showing that AgNPs are effective candidates for cancer therapy, and plant-based silver nanoparticles are an exciting frontier, providing a novel way to approach targeted drug delivery for anticancer treatments.

V. MECHANISM OF ACTION

Plant-based silver nanoparticles exhibit several mechanisms of action that make them promising candidates for cancer therapy. The primary mechanisms include:

1) **Induction of Oxidative Stress:** AgNPs can generate reactive oxygen species when they come into contact with cancer cells. The influx of ROS can cause cellular damage by attacking vital cell components such as DNA, proteins, and lipids, leading to cancer cell apoptosis (programmed cell death) [4].
2) **Cell Membrane Disruption:** The small size of AgNPs allows them to interact with and penetrate the cell membranes of cancer cells. This can disrupt the membrane's integrity, leading to cell lysis or the triggering of apoptotic pathways.
3) **Interaction with Cellular Components:** Once inside the cell, AgNPs can bind to cellular components like mitochondria, ribosomes, and the nuclear contents. Interaction with mitochondria can induce apoptosis by disrupting the electron transport chain and ATP production. Binding to ribosomes may inhibit protein synthesis, which is crucial for cancer cell survival and proliferation.
4) **DNA Damage:** AgNPs can interact with the DNA within cancer cells, causing direct damage to the genetic material. This damage can induce cell cycle arrest and apoptosis, or it can hinder the ability of the cell to replicate and divide [4].
5) **Anti-angiogenesis:** Some studies suggest that AgNPs can inhibit angiogenesis, the formation of new blood vessels, which are necessary for tumour growth and metastasis. By preventing blood vessel growth, AgNPs can effectively starve the tumour of nutrients and oxygen, limiting its ability to grow and spread.
6) **Drug Delivery System:** AgNPs can be functionalized to carry anti-cancer drugs, proteins, or genes directly to the cancer cells, improving the specificity and efficacy of the treatment. The nanoparticle serves as a transport mechanism protecting the therapeutic agent until it reaches the tumor environment, where it can be released in a controlled manner.

It's worth noting that the anti-cancer properties of plant-based silver nanoparticles are influenced by their shape, size, surface coating, and the type of plant extract used for their synthesis. Phytochemicals present in the plant extract not only act as reducing and capping agents but might also contribute to the therapeutic efficacy and enhance biocompatibility.

The green synthesis approach of using plants to produce AgNPs is considered to provide added advantages in terms of biocompatibility and reduced toxicity. However, the precise mechanisms of action are complex and still under investigation to fully harness their potential.

VI. ANALYSIS OF PHYTO-SYNTHESIZED SILVER NANOPARTICLES

Various factors modulate the properties of AgNPs, such as shape, size, crystallinity, surface charge, surface coverage, and biological activity. Several techniques such as ultraviolet spectroscopy (UV-vis), X-ray diffraction (XRD), Fourier transform infrared spectroscopy (FTIR) and scanning are available to study the properties and characteristics of nanoparticles. Scanning electron microscopy (SEM), transmission electron microscopy (TEM), dynamic light scattering (DLS), and atomic force microscopy (AFM) [4].

1. Ultraviolet spectroscopy (UV-vis)

UV-visible spectrometric analysis is often used as a primary quantitative analysis to confirm nanoparticle formation and is also used to monitor stability. UV-visible spectroscopy is a very simple technique, sensitive and fast. Most importantly, it is selective for different nanoparticles. The synthesis was monitored by the color change of AgNO3 from colourless to brownish yellow, and its absorption spectra appeared at 410–430 nm. This determines the amount of UV or visible radiation detected by the sample in solution. The free moving electron in the nanoparticles produces surface plasmon resonance (SPR) spectra due to the combined vibration of the AgNP electrons with the incident light. Nanoparticle morphology, chemical composition, size and dielectric medium determine its absorption spectrum [24].

2. X-Ray diffraction (XRD)

XRD is widely used to study the crystal structure lines of nanoparticles, various biomolecules, polymers, etc. through the degree of crystallinity. It measures the solvent power of different chemical compounds, gives a rough idea of different chemical groups and particle sizes. The working principle of this analysis is that when a monochromatic X-ray beam is directed towards the crystal, it produces different diffraction patterns. These bent X-rays produce an interference pattern, which is then analysed using the Bragg equation to determine the properties of the crystalline or polycrystalline material. The XRD technique can be used on various other biomolecules such as polymers, superconductors, etc. Quantification of this method is in angstroms (Å) (1 Å = 0.1 nm). XRD is the primary determinant of typical crystal size and its unit size. For silver nanoparticles, XRD spectra determine the crystalline nature based on the overall oxidation state of the particles as a function of time [24].

3. Fourier transform infrared (FTIR) spectroscopy

Fourier transform infrared spectroscopy (FTIR) is used to evaluate surface chemistry, such as chemical bonds and functional atoms. It can also characterize the physical properties of synthesized nanoparticles to identify the biomolecules involved in nanoparticle formation. Researchers have used it to recognize a chemical compound in the leaves or other plant extract involved in nanoparticle synthesis. The principle behind this technique is that when infrared radiation passes through a sample, it absorbs some of the radiation and the unabsorbed radiation moves away from the sample. The spectrum determines the identity of the sample based on its absorbance and transmittance values. One publication reports that terpenoids or flavonoids, whatever are present in Prosopis juliflora leaf extracts, may be an important factor in the degradation of AgNP synthesis. In another report, AgNPs synthesized using Capsicum annuum extracts, FTIR analysis showed that the formation of nanoparticles depends on amine groups or secondary structure of proteins. In addition, FTIR is a non-invasive, convenient, important and very simple technique to study the role of plant extract in silver reduction [24].

4. Electron microscopy

Electron microscopy is high-resolution microscopy and the most accepted method for determining the morphology of nanoparticles. This includes scanning electron microscopy (SEM) and transmission electron microscopy (TEM). Green synthesized AgNPscan be visualized when an electron beam hits the structured particles. Structural characterization of AgNPs by electron microscopy provides qualitative and quantitative information on size, shape, size distribution, and dry diameter distribution [25, 26].

5. Scanning electron microscopy (SEM)

The principle behind the scanning electron microscope (SEM) technique is that projected electron beams interact with atoms at different depths in the sample. The reflected secondary electrons are captured by detectors and converted into images. Currently, SEM is the most effective method of all microscopy techniques to distinguish different sizes and shapes of nanoparticles. It can also determine information about nanoparticle surface morphology at the nanoscale. SEM is coupled to energy dispersive X-ray spectroscopy (EDX). A histogram of the number of particles can be calculated manually from the image or using some special software. This can determine the chemical composition of the particle. As a limitation, SEM cannot determine the internal structure of nanoparticles. The advantage of using SEM is that it can resolve sizes smaller than 10 nm [24].

6. Transmission electron microscopy (TEM)

TEM is the most common and very effective method for characterizing silver nanoparticles. It is often used to obtain quantitative values of SNPs such as size and morphology. The principle of TEM is that it uses an electron beam that interacts with the sample and the image is displayed on a photographic plate. TEM has a very high resolution, so it can detect and quantify individual nanoparticles. The power of spatial resolution is an advantage of using TEM over SEM. The development of various high-resolution microscopy techniques forces researchers in this field of Nano science and technology to obtain information using high-energy electron beams [24].

7. Dynamic light scattering (DLS)

DLS gives the diameter of the particles in the compound dispersed in the liquid. This determines the size of the AgNP colloidal suspension. DLS is based on the principle of light scattering. DLS has been widely used to characterize AgNPs synthesized using phytocomponents [27, 28]. Dispersed particles in a colloidal suspension scatter light and as a result, an image of the particles is obtained and the size distribution can be determined between 0.3 and 10 μm. The average particle distribution of Pedalium murex leaf extracts-mediated AgNPs was 73.14 nm. Similarly, AgNPs synthesized by *Salvia miltiorhiza* extract showed a particle size of 128 nm [29].

8. Atomic force microscopy (AFM)

AFM is also used to analyse the size, surface morphology, mechanical structure and physical properties with a phosphorus-doped silicon probe [20]. For characterization, an AgNP sample is prepared by dissolving it in water or ethanol, and a drop is applied to a silicon substrate and allowed to dry. After drying, AFM analysis of the silicon substrate is performed with the probe consisting of the sample on it [26]. AFM studies of tamoxifen-loaded AgNPs showed an average size of 17.5 ± 2.5 nm [30].

VII. EXPLORING THE POTENTIAL OF PLANT-BASED SILVER NANOPARTICLES IN ANTICANCER THERAPY

AgNPs synthesized from *Mentha pulegium* leaf extract were found to be cytotoxic to Hela and MCF-7 cancer cells [31].The morphological characteristics of AgNPs treated with MCF-7 cell lineshow drastic changes. Membrane integrity was disrupted and cell growth stopped. In addition, cytoplasmic shrinkage and cell clustering were observed in contrast to AgNP-treated normal cells. Cells were treated with a concentration of20 lg/ml AgNPs and kept for 48 hours for further observation and cell apoptosis was observed [31].AgNPs synthesized with Coriandrum sativum and *Prosopis cin-eraria* extract as reductant. Anticancer activity against MCF-7 cancer cells [32, 33]. Angelica pubescensa roots Chinese herbal plant-mediated novel AgNPs with crystal size 12.48 with antioxidant activity against 2,2-diphenyl-1-picrylhydryl (DPPH) radicals; antimicrobial activity against human pathogens including *Escherichia coli, Staphylococcus aureus, Pseudomonas aeruginosa and Salmonella enterica*. Cytotoxicity of AgNPs was studied in RAW 264.7 cells and LPS-stimulated RAW 264.7 cells [34]. AgNPs synthesized by a one-step pot method using sea *mushroom extract (Haliclona exigua*) and AgNPs showed antibacterial and anticancer effects against oral biofilm bacteria and oral cancer cell lines (KB cells). The zone of inhibition was 9.1 mm for oral biofilm bacteria and an IC50 value of 0.6 lg/ml was found for oral cancer cell lines. Green AgNPs were synthesized using Andrographis echioides leaf extracts and characterized. Its antibacterial and toxicity were demonstrated by zone of inhibition and MTT assays, respectively. They used MCF-7 and a human keratinocyte cell line (HaCaT) for anticancer activity [17]. Caffeic acid, which is a natural extract, has been successfully used to prepare AgNPs, where caffeic acid acts as both a reducing agent and a stabilizing agent. In addition, its anticancer activity was evaluated against human hepatoma HepG2 cells [24].

In certain in vivo studies, the impact of metal nanoparticles on cell lines is greatly influenced by their capping agent. It has been noted that AgNPs with different capping agents can exhibit cytotoxic effects in certain instances. Thus, considering these challenges, plant-based AgNPs could serve as a valuable resource for researchers in addressing these diseases, given their unique physical-chemical properties and biological benefits.

VIII. FUTURE THERAPEUTIC PROSPECTIVE OF PLANT-BASED SILVER NANOPARTICLES

Green-synthesized silver nanoparticles (AgNPs) represent a promising area of research with significant potential. Utilizing plant-derived phytoconstituents for green synthesis offers a wide range of potent drugs that show promising activity against serious diseases like cancer and viral infections. The size, shape, and surface charge of AgNPs play a crucial role in their biological activity. Therefore, a comprehensive understanding of the pharmacodynamics and pharmacokinetics is essential to grasp the precise mechanisms, distribution, toxicity, and potential side effects. While some controlled studies have indicated the toxicity of AgNPs in macrophage immune cells, it is important to note the differences between in vitro and in vivo conditions [35].

After examining recent research on the use of silver nanoparticles (AgNPs) in cancer and viral infection treatment, several issues and limitations have been identified. These include: (a) Identifying specific targets that AgNPs can effectively target to kill cancer cells and create a targeted drug delivery system using AgNPs. (b) Determining which specific viruses AgNPs are most potent against. (c) Discovering specific combinations that maximize the potency of AgNPs for treating cancer and viral infections. (d) Conducting extensive in vivo studies to develop AgNPs as a clinically viable treatment option for chronic diseases like cancer. (e) Clarifying the exact mechanism involved in the synthesis of green AgNPs. (f) Conducting detailed studies on the toxicity of AgNPs in vivo to better understand their potential effects.

Additionally, various methods can be employed to enhance the effectiveness of silver nanoparticles, such as through combination or hybridization. For instance, the use of magnetic hybrid colloid coated on AgNPs has demonstrated promising outcomes in combating specific

viruses by inhibiting viral proteins. Nano-sized particles can effectively combat viral infections with complex mechanisms, while nano-scale silver offers potential for enhancing anticancer activity through several approaches.

IX. CONCLUSION

This review comprises the exploring the therapeutic potential of green synthesized plant-based silver nanoparticles for anticancer treatment. Here, we first gave an overview of the green synthesis of AgNPs with plant extract, then reviewed the phyto-synthesized silver nanoparticles in cancer therapy and their possible mechanism for cytotoxic activities. Further analysis of phyto-synthesized silver nanoparticles and exploring the potential of plant-based silver nanoparticles in anticancer therapy. Finally, some future therapeutic prospective of plant-based silver nanoparticles were summarized.

The exploration of the therapeutic potential of green-synthesized plant-based silver nanoparticles for anticancer treatment presents a promising avenue for innovative cancer therapy. The use of eco-friendly methods to synthesize silver nanoparticles from plant extracts not only offers a sustainable approach but also demonstrates significant potential in enhancing the effectiveness of cancer treatment. Further research and clinical trials are warranted to fully understand the mechanisms and optimize the use of these plant based silver nanoparticles in combating cancer, offering hope for improved outcomes in cancer therapy.

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