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Review Article

THERAPEUTIC APPLICATIONS OF NANO-SILVER IN ONCOLOGY: INSIGHTS INTO MECHANISMS

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ABSTRACT

Cancer remains a major global health challenge, necessitating the continuous development of innovative and effective treatment strategies. Silver nanoparticles (AgNPs) have emerged as promising agents in anticancer drug therapy due to their unique physicochemical properties, including high surface area, biocompatibility, and ability to induce cytotoxic effects selectively in cancer cells. This review explores the synthesis methods, mechanisms of action, and therapeutic applications of AgNPs in cancer treatment. AgNPs exhibit potent anticancer effects through mechanisms such as reactive oxygen species (ROS) generation, mitochondrial dysfunction, DNA damage, and apoptosis induction. Moreover, their ability to enhance drug delivery, improve bioavailability, and overcome multidrug resistance has garnered significant attention in oncological research. The combination of AgNPs with conventional chemotherapeutic agents, such as Camptothecin, Methotrexate, Gemcitabine, and Cisplatin, has demonstrated synergistic effects, leading to enhanced cytotoxicity and reduced side effects. In addition, the green synthesis of AgNPs using plant extracts has opened new avenues for eco-friendly and sustainable nanomedicine approaches. Despite these promising findings, challenges related to toxicity, stability, and clinical translation remain areas of active investigation. Further studies are required to optimize nanoparticle formulations, evaluate long-term biocompatibility, and establish their efficacy through clinical trials. This review highlights the potential of AgNPs as a versatile and efficient tool in anticancer drug therapy, paving the way for future advancements in nanomedicine-based oncology treatments.

Keywords: Silver nanoparticles, Anticancer therapy, Preparation, Green synthesis, Reactive oxygen species(ROS).

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INTRODUCTION

The historical and contemporary use of silver in medicine

Silver has been utilized in medicine for over a century due to its potent antimicrobial properties. Historically, ancient civilizations such as the Greeks and Romans used silver vessels to store water and other liquids, reducing contamination risks. During the age of exploration, settlers placed silver coins in water and milk barrels to extend their shelf life. In the early 1800s, silver wires were used for wound closure, and during World War I, silver leaf was employed to treat soldiers' injuries by preventing infection and promoting healing. By the early 20th century, colloidal silver and silver nitrate became common disinfectants in hospitals, particularly for treating newborn eye infections. However, with the advent of antibiotics, the medical use of silver declined, only to regain interest in recent years due to its effectiveness against antibiotic-resistant bacteria.

Despite its historical significance, silver has been surrounded by misconceptions, particularly with the rise of alternative medicine and homemade colloidal silver preparations. Some sources claim colloidal silver can treat numerous diseases, including cancer and HIV, but scientific research does not support these assertions. Excessive silver consumption can result in argyria, a condition that causes irreversible bluish-gray skin discoloration. Although silver is not as toxic as mercury or lead, prolonged exposure may have adverse effects. Biologically, silver is not essential for human health, yet it is highly toxic to bacteria, fungi, and certain cancer cells. Silver ions (Ag^+) disrupt bacterial metabolic processes by binding to enzymes and DNA, damaging cell membranes, and ultimately causing cell death. Silver nanoparticles (AgNPs) enhance these effects by generating reactive oxygen species (ROS), which further impair microbial function. In addition, silver interferes with iron-sulfur clusters in bacterial cells, leading to metabolic breakdown. These mechanisms have led to a resurgence of interest in silver-based antimicrobial treatments. Today, silver-containing medical products remain widely used. Silver nitrate treats burns and removes warts, while silver sulfadiazine is a common topical treatment for burn injuries. Silver is also integrated into medical devices such as catheters, wound dressings, and surgical tools to prevent infections. Research into AgNPs has shown promise due to their increased surface area and prolonged antimicrobial properties, making them potential candidates for antibacterial, antifungal, and anticancer therapies. Despite its promising medical applications, further research is required to assess the long-term safety and efficacy of silver-based treatments. Ongoing studies aim to understand the mechanisms underlying silver's toxicity to bacteria and its potential use in cancer therapy. AgNPs have been shown to selectively target cancer cells by inducing oxidative stress, damaging mitochondrial function, and disrupting cellular communication pathways. These findings suggest silver could serve as an alternative to conventional chemotherapy. With advancements in nanotechnology-based silver therapies, silver's role in modern medicine is expanding. Its potential applications extend beyond treating infectious diseases to oncology, where its unique properties could play a significant role in cancer treatment. As research continues, silver-based medical innovations may provide valuable alternatives in the fight against drug-resistant infections and cancer (Fig. 1) [1-3].

Nanoparticles

Nanotechnology has garnered considerable interest owing to its extensive applications in medicine, electronics, environmental science, and energy storage. Nanoparticles at the heart of nanotechnology possess distinctive physical, chemical, and biological characteristics owing to a high surface area-to-volume proportion and dimensions on a nanoscale. Nanoparticles have revolutionized drug delivery systems, improving solubility, bioavailability, and the ability to deliver targeted treatment. This has led to a significant increase in the applications of pharmaceuticals, diagnostics, and regenerative medicine due to their capacity to enhance therapeutic efficacy while minimizing side effects. Advances in ongoing research are likely to have a substantial impact

on the development of precision medicine and innovative drug delivery techniques [4].

Nanoparticles are solid colloidal particles with sizes ranging from 10 nm to 1,000 nm. They can be formulated using synthetic, natural, and semi-synthetic polymers, which are often selected based on their biocompatibility and biodegradability. Two structural types exist within nanoparticle systems:

- Nanospheres (matrix-type systems where the drug is dispersed throughout the particle)
- Nano capsules (reservoir-type systems with a core containing the drug enclosed by a polymeric shell)

Advantages of nanoparticles

Nanoparticles offer several advantages over conventional drug delivery methods, including:

- Improved drug solubility and stability
- Increased bioavailability and prolonged drug retention in the body
- Site-specific drug delivery, reducing systemic side effects
- Protection of drugs from enzymatic degradation
- Potential to bypass biological barriers like the blood–brain barrier [5].

AgNP production techniques

AgNPs have garnered substantial interest because of their distinct physical, chemical, and biological characteristics, rendering them suitable for diverse applications across medicine, industry, and technology. AgNPs synthesis can be accomplished through various methods, which are generally classified into physical, chemical, and biological (green synthesis) techniques. These methods provide distinct benefits and drawbacks, which in turn affect the size, shape, and stability of the synthesized nanoparticles.

Preparation of AgNPs through physical and chemical synthesis:

Evaporation-condensation techniques are predominantly used in physical synthesis methods, typically implemented with tube furnaces operating under atmospheric pressure. Some conventional methods comprise spark discharge and pyrolysis, enabling the rapid synthesis process to be carried out without employing hazardous substances. These methods have drawbacks, including low yields, high energy usage, and inconsistent particle sizing.

The most widely used method for producing AgNPs is through chemical synthesis. This procedure involves the reduction of silver salts in water-based or organic solvents with the assistance of reducing and stabilizing agents. The chemical reduction process involves a two-step sequence of nucleation and subsequent growth. Sodium borohydride ($NaBH_4$), citrate, and ascorbate are frequently employed as reducing agents, often paired with stabilizing agents such as polyvinylpyrrolidone and thiols to inhibit aggregation. While chemical synthesis methods can produce high yields and operate efficiently, they usually necessitate the use of toxic substances, which detracts from their environmental sustainability.

Within the classification of chemical methods, there are two distinct approaches: "top-down" and "bottom-up." This top-down method involves decomposing large silver masses into nanoparticles through the use of mechanical processes, such as grinding and laser ablation. This approach assembles nanoparticles from atomic or molecular precursors through chemical reactions such as electrochemical reduction, sono-decomposition, and thermal decomposition. These methods result in high levels of nanoparticle production but may also generate hazardous byproducts and pose contamination risks.

Preparation of AgNPs through an environmentally friendly approach:

Chemical synthesis has several disadvantages, prompting the development of biological methods as a more environmentally sustainable and eco-friendly option. Microorganisms, including bacteria and fungi, as well as plant extracts and biomolecules such as proteins and amino acids, are used in green synthesis to convert silver ions (Ag^+) into AgNPs.

Bacteria such as *Pseudomonas stutzeri*, *Bacillus licheniformis*, and *Escherichia coli* have been utilized to synthesize AgNPs. These bacteria produce enzymes and metabolites that function as natural reducers and stabilizers, thereby facilitating the controlled development of nanoparticles. Fungal-mediated synthesis using species such as *Fusarium oxysporum* and Ganoderma neo-japonicum has been extensively studied due to the external release of stabilizing biomolecules.

The production of AgNPs can be efficiently and on a large scale achieved through plant-based synthesis using extracts from *Allophylus cobbe*, *Artemisia princeps*, and *Typha angustifolia*. Flavonoids, tannins, and terpenoids from plants are essential in reducing and stabilizing nanoparticles. Compared to chemical methods, green synthesis exhibits improved biocompatibility, enhanced stability, and controlled particle dimensions and structure.

A comprehensive examination of influential parameters in the synthesis of AgNPs.

1. The characteristics of AgNPs, such as size, shape, and stability, are influenced by numerous factors, including:
2. Using higher concentrations of silver precursors can result in the formation of larger particles.
3. Chemical or biological reducing agents can significantly impact the rate of the reaction and the resulting nanoparticle properties.
4. Conditions of higher pH and temperature levels facilitate faster reduction processes, resulting in the formation of smaller nanoparticles.
5. AgNPs require stabilizing agents to prevent particle aggregation and ensure they remain dispersed uniformly.

The synthesis of AgNPs has undergone significant development, transitioning from traditional physical and chemical methods to environmentally friendly approaches inspired by biological processes. Chemical synthesis typically results in a high yield, but it frequently comes with environmental concerns. Compared to other methods, biological synthesis is a cost-efficient, environmentally friendly approach that allows for the production of nanoparticles with controlled properties and improved biocompatibility. Research into the synthesis of AgNPs is expected to concentrate on increasing scalability, lowering toxicity, and making modifications tailored to specific applications, thereby facilitating their ongoing utilization in nanomedicine, antimicrobial coatings, and sophisticated drug delivery systems [6-8].

Cancer is a complex and ungovernable disease characterized by the uncontrolled proliferation of abnormal cells (Fig. 2). It ranks as the second leading cause of death globally, surpassed only by cardiovascular diseases. In 2018 alone, there were approximately 18.1 million new cancer cases and 9.6 million cancer-related deaths worldwide. The most commonly diagnosed cancers across both genders include lung cancer, breast cancer (in females), colorectal cancer, stomach cancer, and liver cancer [9,10].

The unchecked growth of cancer cells makes it a significant global health challenge. In 2007, cancer was responsible for approximately 7.9 million deaths worldwide, accounting for about 13% of all deaths. In the United States, cancer remains the second leading cause of mortality, following cardiovascular diseases. Despite remarkable advancements in cancer treatment over the past five decades, it continues to pose a major public health burden. Consequently, extensive research efforts are being directed toward discovering innovative therapeutic strategies to combat this disease [11,12].

Nanotechnology has emerged as a promising frontier in the fight against cancer, offering novel approaches for tumor detection, prevention, and treatment. The rapid development of advanced diagnostic tools and therapeutic methods has significantly reduced cancer mortality rates in recent years. However, the inability to precisely identify and target cancer cells remains a critical challenge. Nanoparticles have emerged as a groundbreaking solution to this problem. Their unique physicochemical properties make them highly suitable for biomedical applications, and they hold the potential to revolutionize cancer diagnosis and treatment. By enabling targeted delivery and enhanced imaging, nanoparticles are paving the way for more effective and personalized cancer therapies [13,14].

MATERIALS AND METHODS

Camptothecin anticancer drug

Yuan *et al*. investigated the synergistic combinatorial effect of camptothecin (CPT) and AgNPs in human cervical cancer cells (HeLa). The objective was to determine whether the combination of these agents enhances cytotoxicity, induces apoptosis, and affects oxidative stress markers more effectively than monotherapy. CPT, with the abbreviation CPT, is a natural compound that can be extracted from *Camptotheca acuminata* tree. This compound has potent anti-cancer properties. It acts by inhibiting topoisomerase I, an enzyme crucial for DNA replication, leading to DNA damage, cell cycle arrest, and apoptosis in cancer cells. Due to its strong anticancer activity, CPT derivatives such as irinotecan and topotecan have been developed and approved for treating colorectal, ovarian, and lung cancers. However, its clinical use is limited by poor solubility and severe side effects, including myelosuppression and gastrointestinal toxicity. To overcome these challenges, recent research is exploring nanoparticle-based drug delivery systems and combination therapies to enhance efficacy and reduce adverse effects [15]. Yuan *et al*. investigated the strong anticancer properties that result from combining CPT with AgNPs in HeLa cells, which serve as a model for cervical cancer. The results showed a striking decrease in cell survival and reproduction, indicating a toxic effect that increased with dosage. The synergistic effect was attributed to the increased intracellular uptake of CPT that was facilitated by AgNPs, resulting in intensified toxicity toward cancer cells. As treatment advanced, oxidative stress became a vital element influencing cytotoxicity. The combined therapy resulted in a substantial increase in intracellular ROS levels, which in turn led to oxidative damage. This is apparent from a rise in lipid peroxidation indicators such as malondialdehyde (MDA) and protein oxidation levels, characterized by increased protein carbonyl content. At the same time, cellular antioxidant defenses such as glutathione (GSH), superoxide dismutase (SOD), catalase (CAT), and GSH peroxidase (GPx) were significantly depleted, further supporting the notion that oxidative stress is a key factor in causing cell death. Further analysis of the molecular processes revealed a substantial change in gene expression toward programmed cell death. This combined treatment activated certain genes that promote cell death, including Bax, p53, and Cyt C, while suppressing genes that prevent cell death, such as Bcl-2 and Bcl-xL, indicating a robust apoptotic reaction. Mitochondrial dysfunction was a crucial factor in this process, as the loss of mitochondrial membrane integrity led to depolarization and the activation of intrinsic apoptotic pathways. Western blot analysis also provided validation, indicating a rise in the expression of cleaved caspase-9, caspase-6, and caspase-3, which are crucial markers of programmed cell death. The biochemical changes were accompanied by striking morphological changes in HeLa cells. Using phase-contrast and fluorescence microscopy, the treated cells showed distinct evidence of apoptosis, such as cell shrinkage, chromatin condensation, nuclear fragmentation, membrane blebbing, and the creation of apoptotic bodies. This research showed that combining CPT with AgNPs leads to the killing of cancer cells through a complex process that includes oxidative stress, damage to the mitochondria, and the activation of apoptosis. The research outcomes demonstrate the benefits of combining treatments for cervical cancer, indicating this approach could be a more effective option than using a single therapy, due to its potential to decrease the development of drug resistance and enhance the overall effectiveness of treatment. These findings provide a foundation for future studies into the use of nanoparticles in cancer treatment as a pioneering method of drug delivery [16-18].

Methotrexate (MTX) anticancer drug

This research "Silver Nanoparticles for Targeted MTX Therapy in Colon and Lung Cancer" aims to combine MTX with AgNPs, characterize the resulting particles, and investigate their drug capacity, release patterns, and cancer-fighting effectiveness against HTC-116 and A-549 cells, as well as their suitability for human use through tests involving zebrafish, for the purpose of developing more effective chemotherapy treatments. Methotrexate, or MTX, functions by blocking dihydrofolate reductase, a vital enzyme required for DNA creation, as a folic acid antagonist. This compound is commonly employed as an anticancer, anti-inflammatory, and immunosuppressive medication [19]. Rozalen *et al*. explored the potential of MTX conjugated with AgNPs to improve chemotherapy delivery while reducing toxicity. MTX, commonly used for cancers such as leukemia, osteosarcoma, and breast cancer, is limited by a short half-life, rapid clearance, drug resistance, and severe side effects. To overcome these challenges, scientists developed polyethylene glycol-coated AgNPs (PEG-AgNPs) and graphene oxide as nanocarriers, enhancing drug retention and reducing ROS-induced damage. Studies on MCF-7 and HepG2 cancer cells confirmed improved anticancer effects with MTX-loaded nanoparticles compared to free MTX. *In vivo* zebrafish embryo assays further evaluated the safety of this approach. High doses of free MTX (91–681 mg/mL) caused severe developmental abnormalities, while even lower doses (10–30 mg/mL) led to increased mortality and reduced hatching rates. In contrast, AgNPs alone exhibited minimal toxicity, with mild, reversible defects. Notably, MTX conjugated to AgNPs significantly reduced toxicity, with only 16% mortality at high concentrations, nearly 100% hatching by 72 h, and no impact on heart rates. This indicated that AgNPs effectively reduced systemic toxicity while preserving MTX's therapeutic efficacy. These findings highlight AgNPs as promising carriers for MTX, offering improved drug stability, prolonged circulation, and reduced side effects. By lowering the required MTX dose while maintaining its potency, this nanoparticle-based approach could enhance chemotherapy outcomes and pave the way for safer, more effective cancer treatments [20,21].

Gemcitabine (GEM) anticancer drug

Yuan *et al*. investigated whether "the combination of gemcitabine (GEM) and AgNPs can exert synergistic cytotoxic effects in the human ovarian cancer cell line A2780." GEM is commonly used in cancer treatment for conditions such as pancreatic cancer, non-small cell lung cancer, breast cancer, ovarian cancer, and bladder cancer. This medication is often given in conjunction with other chemotherapy drugs, such as cisplatin (CIS) or paclitaxel, to increase its effectiveness [23]. Yuan *et al*. investigated the anticancer effects of GEM and AgNPs on A2780 ovarian cancer cells, focusing on their ability to induce apoptosis. Using TUNEL assays, they observed significant morphological changes associated with programmed cell death. AgNPs-treated cells displayed early signs of apoptosis, including detachment from the surface and structural bulging, while GEM treatment resulted in cell rounding and reduced cell density. However, when GEM and AgNPs were combined, the apoptotic effects were amplified, leading to extensive cellular fragmentation and loss of adherence, indicating a strong synergistic interaction that intensified cell death. Further, cytotoxicity experiments demonstrated that both GEM and AgNPs reduced cell viability in a dose-dependent manner. A decrease in viability was evident at 25 nM for GEM, with AgNPs displaying an even stronger effect at the same concentration. Half-maximal inhibitory concentration (IC50) values were determined to be 10 nM for GEM and 90 nM for AgNPs, highlighting their potent anticancer activity. Comparisons with previous studies confirmed GEM's effectiveness across different cancers, including pancreatic and thyroid cancers, though its suppression varied by cell type and duration of exposure. The study also reinforced findings that AgNPs toxicity is highly dependent on particle size, with smaller nanoparticles (6 nm) exhibiting greater cytotoxicity due to their increased surface area

and enhanced cellular interactions. The combination of GEM with AgNPs further boosted their antiproliferative effects, with cell viability dropping by 30% and 35% with GEM and AgNPs alone, respectively, while their combination led to a striking 70% reduction, confirming a highly potent anticancer synergy. To understand the mechanism behind this enhanced cytotoxicity, researchers analyzed ROS production and mitochondrial dysfunction. The combination treatment significantly elevated ROS levels, with AgNPs generating more oxidative stress than GEM alone. Excessive ROS caused extensive cellular damage, while treatment with N-acetyl cysteine mitigated ROS production and reduced toxicity, confirming the role of oxidative stress in apoptosis. Mitochondrial membrane potential (MMP), a critical indicator of cell health, was also severely affected. While GEM alone caused a moderate decline in MMP and AgNPs, a more significant reduction, the combined treatment led to the most drastic drop, reinforcing the idea that mitochondrial dysfunction contributed to cell death. These findings suggest that GEM and AgNPs work together to induce apoptosis through oxidative stress and mitochondrial damage, offering a promising approach for ovarian cancer treatment. By enhancing cytotoxic effects while potentially reducing the required drug dosage, this combination therapy could provide a more effective and targeted strategy for combating ovarian cancer [23-25].

Salinomycin (Sal) anticancer drug

To evaluate the synergistic effect of Sal and AgNPs in promoting apoptosis and autophagy in human ovarian cancer cells, Zhang H *et al*. investigated their combined anticancer potential. Sal, a polyether antibiotic derived from *Streptomyces albus*, exhibits potent activity against cancer stem cells (CSCs) by disrupting ion homeostasis, inducing oxidative stress, and triggering apoptosis – especially in drug-resistant cancer cells, making it a promising alternative to conventional chemotherapy [26,27]. In their study, while Sal or AgNPs alone induced approximately 25% cell death, their combination significantly enhanced cytotoxicity, resulting in 81% cell mortality. Treated cells displayed clear signs of apoptosis, such as detachment and membrane damage, further supported by elevated lactate dehydrogenase release. Further analysis showed that the combination treatment triggered oxidative stress by increasing ROS levels and lipid peroxidation, while simultaneously depleting antioxidant defenses (GSH, SOD, and CAT). JC-1 staining confirmed mitochondrial dysfunction, leading to apoptosis-induced cell death. Gene expression analysis indicated upregulation of pro-apoptotic markers (Bax, Bak, p53) and activation of caspase-3 and caspase-9, while anti-apoptotic Bcl-2 expression decreased. In addition, the treatment induced autophagy, as evidenced by increased *Atg* gene expression and the presence of autophagic vesicles observed through transmission electron microscopy (TEM) imaging. These findings suggest that combining Sal with AgNPs enhances ovarian cancer cell death through ROS generation, mitochondrial disruption, apoptosis activation, and autophagy induction. This synergistic approach presents a promising strategy for targeting CSCs and improving ovarian cancer treatment [28-30].

Doxorubicin (DOX) anticancer drug

The main emphasis of the research is on finding a solution to the testicular damage that results from the chemotherapy medication DOX, which in turn can cause infertility or further testicular damage. This research aims to assess the effectiveness of a delivery system comprising AgNPs loaded with oleuropein (OLE) in reducing the adverse effects of DOX. DOX is a chemotherapy medication employed to treat diverse types of cancer, such as breast cancer, leukemia, lymphoma, and sarcomas. DOX exerts its effect by inserting itself between the DNA strands, thereby inhibiting the ability of cancer cells to reproduce. This process also blocks topoisomerase II, an enzyme crucial for DNA repair, resulting in cell death. This compound has significant anticancer properties, but its impact can extend to healthy cells as well, resulting in adverse effects [31].

Kciuk *et al*. conducted a controlled study to investigate the protective effects of AgNPs loaded with OLE-AgNP against DOX-induced testicular damage. Forty-eight male albino rats were divided into eight groups, including a control group, a DOX-treated group, and various treatment groups receiving OLE, AgNP, or their combinations with DOX. Over 11 days, researchers administered these treatments and analyzed testicular tissues to assess oxidative stress, inflammation, apoptosis, and sperm quality.

The results revealed that DOX exposure led to severe oxidative stress, indicated by increased MDA levels, while antioxidant markers such as SOD and GSH were significantly depleted. However, rats treated with OLE and OLE-AgNP showed a notable reduction in oxidative stress and improved antioxidant defenses. Histopathological analysis using the Johnsen scoring system further confirmed that OLE-AgNP provided superior protection compared to OLE alone. While the DOX-treated group exhibited severe damage with a Johnsen score of 3, those treated with OLE-AgNP + DOX achieved a score of 8, indicating well-preserved seminiferous tubules and better-organized germ cells. Moreover, the combination of OLE and AgNPs effectively reduced inflammation, apoptosis, and endoplasmic reticulum (ER) stress markers, preventing extensive testicular damage. The study highlighted that DOX-induced oxidative stress triggers ER stress, leading to altered protein expression and apoptosis through NF-κB activation. However, OLE-AgNPs treatment mitigated these harmful effects, preserving testicular function.

These findings suggest that OLE-AgNPs are a promising therapeutic strategy for reducing chemotherapy-induced reproductive toxicity. By leveraging nanotechnology-based drug delivery, OLE-AgNPs demonstrated superior protective effects compared to OLE alone, paving the way for new treatments aimed at minimizing the side effects of chemotherapy on male fertility [32-35].

Cyclophosphamide anticancer drug

Othman *et al*. aimed to evaluate the anticancer potential of AgNPs conjugated with berberine in Ehrlich solid carcinoma. Berberine, a natural alkaloid found in Berberis species, has antibacterial, anti-inflammatory, and antidiabetic properties. It inhibits bacterial DNA replication, making it effective against infections. Berberine also induces apoptosis in cancer cells, slowing tumor growth, and is being studied for its potential neuroprotective effects in Alzheimer's disease [36].

The conjugation of berberine with AgNPs has shown significant potential in enhancing its antitumor efficacy. *In vivo* studies demonstrate that AgNPs-BER effectively suppresses tumor proliferation by reducing tumor size and weight compared to the Ehrlich solid carcinoma control group. When combined with cyclophosphamide, a standard chemotherapeutic agent, AgNPs-BER exhibits a synergistic effect, leading to greater tumor suppression and an increase in mean survival time from 15 to 26 days. The significant improvement in the percentage increase in life span further supports its potential as an effective anticancer agent. Beyond tumor suppression, AgNPs-BER modulates oxidative stress by elevating MDA and nitric oxide levels, markers of oxidative damage, while simultaneously depleting key antioxidant enzymes such as GSH, GPx, GSH reductase, SOD, and CAT. This oxidative imbalance enhances apoptosis, as indicated by the upregulation of pro-apoptotic proteins Bax and Caspase-3, and the downregulation of the anti-apoptotic protein Bcl-2. These findings suggest that AgNPs-BER induces tumor cell death through intrinsic apoptotic pathways. In addition, AgNPs-BER inhibits angiogenesis, a key process in tumor growth and metastasis. It significantly reduces the expression of angiogenesis markers, with angiopoietin and vascular endothelial growth factor levels decreasing by 72.5% and 63.5%, respectively. Compared to cyclophosphamide treatment alone, which reduces angiopoietin and vascular endothelial growth factor by 52.5% and 41.7%, respectively, the combination therapy shows more pronounced suppression. These results highlight the effectiveness of AgNPs-BER in limiting tumor progression by inducing oxidative stress, promoting apoptosis, and disrupting angiogenesis. Its potential as a standalone or combination therapy offers promise for future clinical applications in cancer treatment [37,38].

Sorafenib anticancer drug

The primary goal of study conducted by Khafaga *et al*. was to enhance the anticancer efficacy of sorafenib, a medication used to treat hepatocellular carcinoma, by combining it with a new zinc oxide-superparamagnetic iron oxide-silver (ZnO-SPION-Ag) nanocomposite. A nanocomposite was synthesized using a sustainable method that involved the *Fusarium oxysporum* fungus. The main aim of the investigation was to improve sorafenib's effectiveness as a treatment while reducing its negative side effects.

Sorafenib is an oral multikinase inhibitor used in cancer treatment, particularly for liver, kidney, and thyroid cancers. It works by blocking signaling pathways involved in tumor cell growth and angiogenesis, primarily targeting RAF kinases and VEGF receptors. Developed by Bayer and approved by the Food and Drug Administration (FDA), sorafenib is known for its efficacy but can cause side effects such as hypertension, diarrhea, and hand-foot skin reactions [39]. Khafaga *et al*. created a unique nanocomposite composed of zinc oxide, silver, and superparamagnetic iron oxide (ZnO-SPION-Ag). What distinguished this nanocomposite was its green synthesis, which utilized the *Fusarium oxysporum* fungus to develop an environmentally friendlier and biocompatible material. The concept was that by loading sorafenib onto this nanocomposite, it could be more accurately targeted to cancer cells, enhancing its effectiveness and decreasing side effects.

They carried out a comprehensive experiment on male albino rats to test their hypothesis. Initially, the researchers caused liver cancer in the rats by administering chemicals that replicated the disease's progression seen in humans. They were then grouped according to their treatment: One group received only sorafenib, a second group received only the nanocomposite, and the third group was treated with sorafenib combined with the nanocomposite. The findings were distinctly noticeable. The rats treated with nanocomposite-loaded sorafenib had the most favorable outcomes, characterized by enhanced tumor reduction, improved liver function, and decreased toxicity. At a genetic level, certain cancer-causing genes like DTL were inhibited, whereas genes that combat tumors, namely DUSP1, NFKBIA, and SOCS2, were stimulated. Indications were that the newly formulated treatment was not merely slowing the progression of cancer but was instead actively reversing some of the damage it caused. Test results from blood samples confirmed these results. The group that underwent the nanocomposite therapy experienced a notable drop in liver enzymes that typically rise during cancer advancement – ALT, AST, and ALP – suggesting reduced liver harm. Meanwhile, antioxidant levels increased, indicating the body's enhanced ability to counter oxidative stress, a key contributor to cancer development. Examination under a microscope revealed that untreated cancerous livers exhibited significant destruction, whereas those treated with the nanocomposite-sorafenib combination displayed a near-normal structure, indicating the possibility of regeneration. This study underscores the potential of nanotechnology to enhance cancer treatment by targeting specific cancer cells with medication, thereby increasing its efficacy and diminishing the associated toxicity. This could lead to significant advancements in liver cancer therapy for humans, resulting in improved outcomes and reduced side effects [40,41].

Epigallocatechin gallate (EGCG) anticancer drug

Granja *et al*. sought to create and assess the anticancer capabilities of AgNPs linked with EGCG, a naturally occurring polyphenolic compound with established antioxidant and anticancer properties. The objective was to find if EGCG-AgNPs could increase the cytotoxic effect against colon cancer cells compared to using EGCG or AgNPs separately. EGCG is a powerful polyphenol found in green tea, known for its strong antioxidant, anti-inflammatory, and anticancer properties. It helps protect cells from oxidative stress, supports cardiovascular health, and may inhibit tumor growth. EGCG is also being studied for its neuroprotective effects and potential role in preventing neurodegenerative diseases [42]. Initially, Granja *et al*. synthesized EGCG-conjugated AgNPs through a green synthesis method, which allowed the nanoparticles to remain stable and biologically effective. Once the nanoparticles were prepared, the researchers examined their impact on colon cancer cells in a laboratory setting. The experiment was separated into distinct treatment groups: Cells exposed to EGCG on its own, cells exposed to AgNPs on their own, and cells exposed to the new EGCG-AgNPs combination. The outcomes were highly persuasive. The EGCG-AgNPs exhibited a substantial decrease in cell viability, demonstrating enhanced cytotoxic properties compared to each individual component. This proposed a cooperative effect, whereby EGCG improved the delivery and penetration of AgNPs into cancer cells, thereby increasing their efficacy at triggering cell death. The researchers further investigated how these nanoparticles were exerting their lethal effect on cancer cells. Research revealed that EGCG-AgNPs led to apoptosis, a type of programmed cell death, which was confirmed by the elevated levels of caspase-3 activation. Oxidative stress was also a crucial factor in this process. The nanoparticles stimulated an excessive generation of ROS, which overpowered the cancer cells' antioxidant defenses and resulted in their destruction. Furthermore, the research demonstrated that EGCG-AgNPs interfered with mitochondrial function, which is another vital component contributing to their anticancer properties. The cell's energy-producing component, commonly referred to as the powerhouse of the cell, suffered significant damage, resulting in a halt to energy production and ultimately, cell demise. The nanoparticles also triggered DNA fragmentation, which ultimately sealed the fate of the cancer cells. The researchers found that the EGCG-AgNPs exhibited selective behavior in their action. They demonstrated significant anticancer activity against colon cancer cells, while displaying low levels of toxicity toward healthy cells. The key factor in this selectivity is that one of the primary obstacles in cancer treatment is preventing harm to normal tissues. By the conclusion of the research, the scientists had clear proof that the combination of EGCG and AgNPs was a prospective approach for colon cancer therapy. Multiple mechanisms not only contributed to enhanced cancer cell death but also lowered the danger of harming healthy cells, thereby making it a possibly safer replacement for conventional chemotherapy methods [43-45].

***Taxus baccata* anticancer drug**

Kajani *et al*. had the objective of developing a green and eco-friendly process to synthesize anisotropic AgNPs utilizing *T. baccata* extract. The purpose of this evaluation was to assess the potential anticancer effects of these nanoparticles, especially against MCF-7 breast cancer cells. *T. baccata* extract is derived from the yew tree and contains bioactive compounds like paclitaxel, a potent anticancer agent. It works by stabilizing microtubules, preventing cell division, and inducing apoptosis in cancer cells. While effective in chemotherapy, particularly for breast, ovarian, and lung cancers, it can cause side effects such as neuropathy, myelosuppression, and allergic reactions [46]. Kajani *et al*. looked to *T. baccata*, a plant well-known for its production of taxanes – potent compounds utilized in cancer treatment through chemotherapy – to generate AgNPs using an eco-friendly synthesis method. In a pioneering yet straightforward approach, the team utilized plant extracts as organic reducing and stabilizing agents to synthesize highly stable and distinctive AgNPs in the absence of hazardous chemicals. As the team progressed with their experiments, they found that the type of extract used had a significant impact on the formation of the final nanoparticles. The water-based extract resulted in the creation of spherical AgNPs, whereas the extract made from ethanol produced anisotropic (hexagonal and triangular) nanoparticles. The contrast in morphology was intriguing, as past research indicated that the shape of nanoparticles could have a substantial impact on their biological activity. To validate their theory, the researchers subjected MCF-7 breast cancer cells to these nanoparticles for testing. The outcome was quite notable. AgNPs prepared with an aqueous extract demonstrated the strongest anticancer properties, with an IC50 value of 0.25 μg/mL after 48 h, indicating they were highly effective at destroying cancer cells even at a low dose. The nanoparticles synthesized with the ethanolic extract showed a slightly less potent effect, with an IC50 of 5 μg/mL the mechanism by which these nanoparticles targeted cancer cells. The researchers' discovery revealed that the nanoparticles interfered with mitochondrial function, resulting in higher levels of oxidative

stress and cell apoptosis, a process also known as programmed cell death. Exposure to AgNPs resulted in DNA damage, which halted cellular replication and ultimately led to cell destruction. This study highlighted the nanoparticles' selectivity in targeting cancer cells while sparing healthy ones, reducing side effects compared to conventional chemotherapy. They remained stable in solution for over 6 months, making them promising for further nanomedicine development. Their optical properties suggest potential for imaging and drug delivery, enabling multifunctional cancer treatments [47,48].

Tamoxifen anticancer drug

Ostad *et al*. investigated whether combining AgNPs with tamoxifen or adding silver ions could increase the efficacy of tamoxifen against drug-resistant breast cancer cells. Tamoxifen is a selective estrogen receptor modulator used primarily to treat and prevent hormone receptor-positive breast cancer. It works by blocking estrogen receptors in breast tissue, slowing or stopping cancer cell growth. While effective, it can cause side effects such as hot flashes, blood clots, and an increased risk of endometrial cancer with long-term use [49]. In this, Ostad *et al*. investigation explored the potential of AgNPs and silver ions, which have well-documented cytotoxic effects, as a possible solution. The team produced AgNPs through a chemical reduction process, then examined them using various spectroscopic methods. Subsequent testing of the nanoparticles was conducted on two distinct cell lines derived from breast cancer: the parent T47D cells, which exhibit sensitivity to tamoxifen, and tamoxifen-resistant T47D cells that have developed a diminished response to the drug. The outcome was both remarkable and unforeseen. The AgNPs displayed significant toxicity toward the parent T47D cells, featuring an IC50 value of 6.31 μg/mL; in this case, a relatively low concentration was sufficient to be lethal to 50% of the cells. Tamoxifen-resistant cells displayed reduced sensitivity to AgNPs, necessitating a significantly larger concentration (IC50 of 37.06 μg/mL) to attain a comparable level of cell mortality. Silver ions, in the form Ag+, showed a contrasting effect – although they were less toxic to the parent T47D cells at a concentration with an IC50 of 33.06 μg/mL, they proved significantly more effective against tamoxifen-resistant cells, with an IC50 of 10.10 μg/m. The disparity in sensitivity implies that silver ions could potentially circumvent certain resistance mechanisms employed by cancer cells to avoid chemotherapy effects. Scientists hypothesized that tamoxifen-resistant cells, which possess more efficient drug-transporting systems, could potentially remove AgNPs more effectively than silver ions, thereby accounting for the greater toxicity of Ag+ to these cells. The most promising outcome was observed when researchers incorporated AgNPs or silver ions in conjunction with tamoxifen. At low concentrations that are not hazardous on their own, both AgNPs and silver ions increased the toxicity of tamoxifen against resistant cells. Even when used at reduced dosages, tamoxifen was still capable of delivering cancer-fighting results in conjunction with silver-based nanomaterials [50,51].

5-fluorouracil (5FU) anticancer drug

Breast cancer remains a leading cause of cancer-related deaths among women, driving the need for more effective treatments. Nanotechnology presents a promising solution by utilizing nanocarriers to minimize the adverse effects of cancer drugs. This study aimed to enhance the cytotoxicity of 5FU by conjugating it with AgNPs, forming AgNPs-5FU. Characterization using dynamic light scattering (DLS), scanning electron microscopy (SEM), ultraviolet-visible spectroscopy (UV-Vis), and Fourier-transform infrared spectroscopy (FTIR) confirmed the nanoparticles' properties, with sizes ranging from 18 to 28 nm and a PDI of 0.598. The controlled release of 5FU from AgNPs-5FU reached approximately 70%, demonstrating sustained drug delivery. Cytotoxicity analysis revealed that AgNPs-5FU exhibited IC50 values of 23.006 in MCF-7 cells and 10.41 in 4T1 cells, making it 2.14 and 4.64 times more effective than free 5FU, respectively, while showing minimal toxicity to HUVEC cells. This suggests that AgNPs-5FU could serve as a potent therapeutic agent against breast cancer. 5 FU – an antimetabolite medication called 5-FU, a fluoropyrimidine, is frequently used to treat cancer, especially colorectal cancer. 5-FU inhibits thymidylate synthase and incorporates its metabolites into DNA and RNA to produce its anticancer effects [52].

Breast cancer treatment is challenging due to its heterogeneous nature, which significantly influences therapeutic responses.

Danışman-Kalındemirtaş *et al*. employed DLS to analyze the size distribution of AgNPs-5FU, revealing a uniform distribution with sizes between 13 and 78 nm. The PDI increased from 0.412 to 0.535 upon drug binding, while the surface charge shifted from −18.6 mV to −46.2 mV, improving nanoparticle stability and interaction with cancer cells. FTIR analysis confirmed chemical interactions between 5FU and AgNPs, while UV-Vis spectroscopy showed shifts in absorption bands due to quantum dot effects and electronic transitions. Drug release studies demonstrated a sustained release pattern, with approximately 52% of 5FU released in 30 h and 70% after 60 h, stabilizing after 50 h. The chemosensitivity analysis revealed that AgNPs-5FU was more effective against MCF-7 and 4T1 cells than MDA-MB-231, which are highly aggressive and resistant to conventional treatments. These findings confirm that AgNPs-5FU enhances the anticancer effects of 5FU while reducing its toxicity, making it a promising candidate for breast cancer treatment [53-55].

CIS anticancer drug

Chitosan (CS)-modified AgNPs boost CIS efficacy in breast cancer cells AgNPs, known for their excellent conductivity, chemical stability, and therapeutic potential, were synthesized, functionalized with CS, and loaded with the anti-cancer drug CIS in this study. The successful conjugation, size distribution, and morphology of the nanocomplex were confirmed through UV-vis and FTIR spectroscopy, nanoparticle tracking analysis (NTA), and TEM. The encapsulated CIS (>80%) demonstrated efficient, pH-responsive release, favoring delivery in the tumor microenvironment. Cytotoxicity assays revealed that CS-AgNP-CIS nanocomplexes exhibited significant anti-cancer activity against MCF-7 and SKBR-3 breast cancer cell lines, surpassing the effectiveness of free CIS and inducing over 50% cell death. These findings suggest a promising nanoparticle-based drug delivery system with selectivity for breast cancer cells. One of the most promising and commonly used medications for the treatment of a variety of solid tumors, including testicular, ovarian, head and neck, bladder, lung, cervical cancer, melanoma, lymphomas, and several others, is CIS, also known as (SP-4-2)-diamminedichloridoplatinum II. Although CIS has anticancer properties through a variety of pathways, the most widely accepted mechanism is the creation of DNA lesions through interactions with purine bases on DNA, which are followed by the activation of various signal transduction pathways and ultimately apoptosis [56].

Characterization studies confirmed the successful synthesis and functionalization of AgNPs with CS, followed by effective CIS loading. UV-vis and FTIR spectroscopy demonstrated characteristic shifts confirming drug conjugation, while NTA and TEM analysis revealed well-dispersed nanoparticles with an optimal size range (<122 nm) for drug delivery. The nanocomplex exhibited high encapsulation efficiency (84.5%) and pH-responsive drug release, with faster CIS release in acidic conditions, mimicking the tumor microenvironment. Cytotoxicity assays indicated that the CS-AgNP-CIS nanocomplex significantly reduced cell viability in MCF-7 and SKBR-3 breast cancer cells, outperforming free CIS while demonstrating lower toxicity in normal HEK293 cells. Apoptosis assays confirmed that the nanocomplex effectively induced programmed cell death in breast cancer cells. The highly positive zeta potential further supported enhanced cellular uptake and stability. This approach shows potential for selective breast cancer treatment with minimal side effects on healthy cells. Future studies, including *in vivo* investigations, are necessary to further explore its therapeutic potential and mechanisms of action for improved cancer treatment strategies [57,58].

Vincristine and vinblastine anticancer drug

Cervical cancer is a major global health concern, especially in low- and middle-income countries. A study has synthesized AgNPs using

Catharanthus roseus leaves' extract. The extract reduced silver ions rapidly, displaying antiproliferative and cytotoxic effects against HeLa229 cervical cancer cells. AgNPs inhibited cancer cell migration and induced apoptosis and cell cycle arrest. These findings suggest AgNPs as an alternative to conventional chemotherapy with enhanced efficacy and potentially reduced side effects. Vinblastine and vincristine, two Catharanthus alkaloids that are plentiful in the plant's leaves, prevented cancer growth. Vinblastine and vincristine can impede the cell mitotic process and are extensively utilized in medicine to treat various types of cancers, including breast cancer, Hodgkin's lymphoma, and leukemia. Vinblastine and vincristine attach to tubulin, which is a structural protein located in the cytoplasm, thus preventing the formation of microtubule structures [59].

Hussein *et al*. did phytochemical screening confirming the presence of key bioactive compounds in *C. roseus* extract, including flavonoids, tannins, terpenoids, alkaloids, saponins, and phenols, which contributed to the reduction of Ag+ ions to Ag0. The synthesis of AgNPs was visually evident as the reaction mixture changed from pale yellow to reddish-brown within 12 h. UV-Vis spectroscopy displayed a well-defined surface plasmon resonance (SPR) band at 429 nm, confirming nanoparticle formation. FT-IR analysis further validated the presence of functional groups responsible for nanoparticle stabilization and capping, with shifts in characteristic peaks corresponding to hydroxyl, carboxyl, alkene, and amine groups. TEM/energy dispersive spectroscopy (EDX) and FE-SEM analysis showed spherical nanoparticles ranging from 6 to 33 nm, with X-ray diffraction (XRD) confirming their crystalline nature and an average size of 22 nm. The cytotoxicity assessment demonstrated that AgNPs effectively reduced the viability of HeLa229 cells, with IC50 values indicating significant antiproliferative activity compared to the crude *C. roseus* extract. Wound healing assays revealed a dose-dependent inhibition of cancer cell migration over 24, 48, and 72 h, suggesting strong antimetastatic potential. In addition, gene expression analysis indicated that AgNPs upregulated apoptosis-related genes (p53, Caspase-9) while downregulating survival-promoting genes (*BCL-2*, *CDK1*), leading to cell cycle arrest and programmed cell death. These findings underscore the promising therapeutic potential of AgNPs synthesized from *C. roseus* in cervical cancer treatment. However, further, *in vivo* studies are necessary to understand their mechanisms of action, safety, and clinical applicability. This study provides a foundation for the future development of nanoparticle-based targeted therapies with enhanced anticancer efficacy and minimal side effects [60-62].

***Euphorbia milii* (*E. milii*) anticancer drug**

Rauf *et al*. explored the green synthesis of AgNPs using *E. milii* leaf extract as a reducing agent. *E. milii*, also known as the crown-of-thorns plant, was selected due to its rich phytochemical composition. The leaves were extracted using six different solvents – hexane, chloroform, ethyl acetate, acetone, methanol, and distilled water – varying in polarity to isolate a diverse range of bioactive compounds. Each extract was mixed with a 1 mM$AgNO_3$ solution and incubated in the dark at room temperature for 24 h. The synthesized AgNPs were characterized using UV-Vis spectrophotometry, FTIR, and SEM. UV-Vis analysis confirmed nanoparticle formation with absorbance peaks between 415 nm and 485.5 nm, indicating surface plasmon resonance around ~450 nm. FTIR spectra identified functional groups such as OH, C-H stretching, C=O stretching, C=C stretching, and C-O stretching, which contributed to nanoparticle synthesis and stability. SEM analysis revealed variations in AgNP size, ranging from 67 nm to 843 nm, depending on the solvent extract used. *E. Milii* is known to have antitumor, antidiabetic, and antibacterial properties. These properties are attributed to different phytochemicals present in the plant. Phytochemical studies by *E. Miles* showed that flavonoids, triterpenes, saponins, phenols, and tannins are found in various parts of the plant [63].

The study successfully demonstrated the green synthesis of AgNPs using *E. milii* leaf extracts as reducing agents. A visible color change from colorless to brownish brown confirmed the formation of AgNPs. Six conjugated AgNPs were synthesized using different solvent extracts: Distilled water (SDW), hexane (SH), chloroform (SC), ethyl acetate (SE), acetone (SA), and methanol (SM). UV-Vis spectroscopy revealed SPR bands between 401 nm and 456 nm, with SH exhibiting the least stability, as its peak diminished within 3 days, while SC, SE, SA, SM, and SDW remained stable for extended durations. SEM analysis indicated that the size of AgNPs varied depending on the solvent used, with SE producing the smallest nanoparticles (67–441 nm) and SH yielding the largest (771–843 nm). FTIR analysis confirmed the presence of bioactive compounds, such as flavonoids, polyphenols, carboxylic acids, alkyl halides, and esters, which played a role in nanoparticle stabilization and capping. The study concluded that different solvent extractions influence AgNP size, stability, and synthesis efficiency. Among the extracts, ethyl acetate (SE) was the most effective in producing smaller, stable nanoparticles. This research highlights the potential of *E. milii* leaf extract as an eco-friendly alternative for AgNP synthesis, contributing to the development of sustainable nanotechnology [64].

***Nigella sativa* (*N. sativa*) and *piper nigrum* (*P. nigrum*) anticancer drug**

Mahfouz *et al*. explored the synthesis of AgNPs using *N. sativa* and *P. nigrum* seed extracts, focusing on their potential biomedical applications, including antibacterial, antiviral, and anticancer properties. Levels in *N. sativa* are mediated primarily by the signal pathways of NOS, p53, and caspase. Extracts from *N. sativa* can be used for effective and effective development of therapeutic anticancer agents [65]. *P. nigrum* is commonly utilized as a traditional remedy, including applications for alleviating pain, treating fevers, and serving as an anti-cancer substance. Nevertheless, the unrefined extract of piperine-free *P. nigrum*, which obstructs breast cancer, and its underlying mechanisms is still being concealed [66].

The study successfully synthesized spherical AgNPs (20–50 nm) using *N. sativa* and *P. nigrum* seed extracts, as confirmed by FTIR and TEM analysis. The AgNPs demonstrated strong antibacterial activity against both Gram-positive and Gram-negative bacteria, significant antiviral activity against HSV1 (83.23% and 94.54% inhibition for *P. nigrum* and *N. sativa*, respectively), and dose-dependent cytotoxicity against HepG2 cancer cells (IC50 values of 4.98 μg/mL and 7.12 μg/mL). In addition, the AgNPs enhanced seed germination and seedling growth in *Vicia faba* and *Zea mays*. These findings highlight the potential of green-synthesized AgNPs as effective, eco-friendly agents for biomedical and agricultural applications, offering a sustainable alternative to conventional methods [67].

Temozolomide (TMZ) anticancer drug

Liang *et al*. aimed to investigate the cytotoxic effects of AgNPs on human glioma U251 cells and their potential to enhance the therapeutic efficacy of TMZ, a standard chemotherapy drug, in treating glioblastoma multiforme (GBM). AgNPs, synthesized with a mean size of 26 nm, were evaluated for their ability to induce cell death, apoptosis, and cell cycle arrest, both alone and in combination with TMZ. TMZ is an approved oral anticancer drug agent for the treatment of newly diagnosed glioblastoma in combination with radiation therapy interacts with DNA that generates a broad spectrum of methyl adducts primarily represented by N-methylpurine. However, its antitumor activity was primarily due to O6-methylguanine, as tumor cell sensitivity was inversely correlated with the level of the alkylguanine alkyltransferase DNA O6-alkylguanine and requires an intact cohesion repair system [68].

The study demonstrated that AgNPs exhibited dose-dependent cytotoxicity against U251 glioma cells, inducing DNA damage, apoptosis, and G2/M cell cycle arrest. When combined with TMZ, AgNPs significantly enhanced the drug's efficacy, reducing cell survival and increasing apoptosis rates. TEM analysis revealed that AgNPs were internalized by cells, likely through endocytosis, and caused cellular damage. These findings suggest that AgNPs, at low concentrations (46 μmol/L), selectively target cancer cells while sparing normal cells, making them a promising therapeutic agent for GBM. The combination

of AgNPs and TMZ offers a potential strategy to improve chemotherapy outcomes for glioma patients [69].

Curcumin as an anticancer drug

Curcumin, a polyphenol derived from *Curcuma longa* (turmeric), has been extensively studied for its role in promoting health, preventing diseases, and offering therapeutic benefits, including anti-tumor, anti-inflammatory, and antioxidant properties. Curcumin lowers cell proliferation in a range of cancer cell lines, inhibits carcinogenesis, and shows cancer growth inhibition both *in vitro* and *in vivo* [70]. Curcumin's diverse actions on cancer cells are probably caused by a number of mechanisms of action: in addition to the mitotic block, G1/S arrest and apoptotic induction have been noted in many tumor cell lines [70].

Adahoun MA *et al*. focused on improving the solubility and bioavailability of curcumin nanoparticles using a wet-milling technique. The formulated nanocurcumin was then tested *in vitro* against the prostate cancer cell line (PC3), human embryonic kidney cells (HEK), human erythrocytes (RBCs), and four bacterial strains: two Gram-positive (*Micrococcus luteus* ATCC 9341, *Staphylococcus aureus* ATCC 29213) and two Gram-negative (E. coli ATCC 25922, Pseudomonas aeruginosa ATCC 27853) Adahoun MA *et al*. assessed cell viability, IC_{50}, and minimum bactericidal concentration (MBC). Nanocurcumin exhibited significantly higher cytotoxic activity against PC3 cancer cells while showing lower toxicity toward normal HEK cells compared to parent curcumin ($p<0.05$) . In addition, nanocurcumin demonstrated lower MBC values than parent curcumin across all tested bacterial strains, indicating enhanced antimicrobial effectiveness. Gram-positive bacteria showed greater sensitivity to both curcumin and nanocurcumin than Gram-negative strains . These findings suggest that nanocurcumin is a safe and potent compound with promising anti-cancer and antimicrobial properties. The reduction in particle size to the nanoscale significantly enhances its therapeutic potential, particularly for treating prostate cancer (PC3) and bacterial infections [71].

Imatinib anticancer drug

Emadi *et al*. aimed to develop and evaluate imatinib mesylate-loaded polybutylcyanoacrylate (PBCA) nanoparticles for targeted leukemia therapy using the K562 cell line. The nanoparticles were synthesized using the miniemulsion polymerization technique and characterized through DLS, UV-Vis spectrophotometry, FTIR, and SEM. Their drug-loading efficiency, release profile, cytotoxicity, and stability were also assessed. The nanoparticles exhibited a high encapsulation efficiency of 86% and demonstrated sustained drug release over 48 h, significantly reducing the burst effect commonly observed with free drug formulations. Cytotoxicity studies using the MTT assay revealed enhanced anticancer activity, with an IC50 value of 6μM for the nanodrug compared to 10 μM for free imatinib mesylate. The use of natural surfactants, including honey and olive oil, contributed to the improved biocompatibility and therapeutic efficacy of the nanoparticles. Stability evaluations confirmed that the formulation retained its physicochemical properties and cytotoxic potential even after 2 months. These findings suggest that PBCA nanoparticles serve as an efficient carrier for imatinib mesylate delivery, offering improved stability, controlled drug release, and enhanced therapeutic potential. Further *in vivo* studies are warranted to confirm their efficacy and safety for clinical applications in leukemia treatment. As a tyrosine kinase inhibitor, imatinib mesylate is used to treat gastrointestinal stromal tumor (GISTs) and chronic myelogenous leukemia (CML) by blocking the tyrosine kinase activity of BCR-Abl, Citation2 platelet-derived growth factor receptors, Citation3, and KITCitation4 proteins [72].

The characterization of imatinib mesylate-loaded PBCA nanoparticles confirmed their suitability as a drug delivery system. The successful polymerization process was evident from the transition of the reaction medium from colorless to milky within 10 min. The nanoparticles exhibited a mean size of approximately 200 nm with a zeta potential of −9 mV, indicating good colloidal stability. The FTIR spectra confirmed the physical entrapment of the drug without structural modifications, as evidenced by the presence of characteristic functional groups. SEM imaging further verified the formation of spherical, homogenous nanoparticles. The drug-loading efficiency was found to be 4.5%, while the encapsulation efficiency reached 86%, demonstrating an effective drug incorporation within the nanoparticle matrix. The *in vitro* drug release study showed a biphasic pattern, with an initial burst release of 45% within the 1st h, followed by a sustained release, where only 10% of the encapsulated drug was released after 48 h. The controlled release profile can be attributed to the use of PEG, which enhanced stability and reduced premature drug leakage. Compared to similar studies, this formulation exhibited a faster release rate while maintaining effective drug retention. Cytotoxicity evaluations using the MTT assay revealed a significant enhancement in the anticancer efficacy of imatinib mesylate when encapsulated in PBCA nanoparticles. The nanodrug exhibited a lower IC50 value (6 μM) compared to the free drug (10 μM), indicating increased potency. This improvement is likely due to the enhanced cellular uptake of nanoparticles and the sustained drug release mechanism. In addition, stability studies confirmed that the nanoparticles retained their physicochemical properties and cytotoxic potential even after 2 months of storage, highlighting their robustness as a drug delivery system. Overall, the study demonstrated that PBCA nanoparticles are a promising carrier for imatinib mesylate delivery to leukemia cells, offering advantages such as enhanced encapsulation efficiency, controlled drug release, improved cytotoxicity, and stability. The use of honey and olive oil as natural surfactants further contributed to the formulation's biocompatibility and therapeutic potential. However, *in vivo* studies are required to evaluate the pharmacokinetics, biodistribution, and potential side effects before clinical translation. These findings pave the way for future advancements in nanoparticle-based leukemia therapy, providing a more effective and targeted approach for cancer treatment [73].

Busulfan anticancer drug

Thombre *et al*. synthesized AgNPs using a biophysical approach and characterized through UV-Vis (showing characteristic surface plasmon resonance at 418–420 nm), EDX, SEM, and XRD. The research evaluated the cytotoxic effects of AgNPs on THP-1 acute myeloid leukemia cells, with particular focus on their interaction with chemotherapeutic drugs cyclophosphamide, busulfan, and mercaptopurine. The inert prodrug cyclophosphamide needs to be activated chemically and enzymatically. The resulting nitrogen mustard creates the intrastrand and interstrand DNA cross-links that give it its cytotoxic effects. A DNA alkylating medication called busulfan is used to treat CML. The first active metabolite inhibitor that has been demonstrated to inhibit cancer cells is 6-mercaptopurine. Thombre *et al*. successfully synthesized spherical AgNPs of ~20 nm using a bio-physical method combining Bacillus

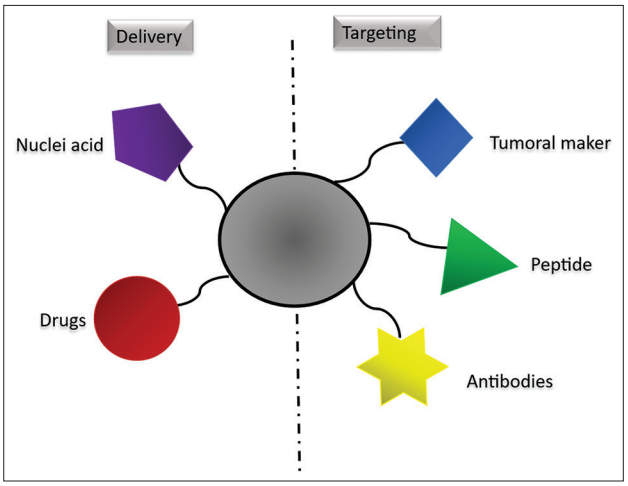

Fig. 1. Targeting moieties to silver nanoparticles

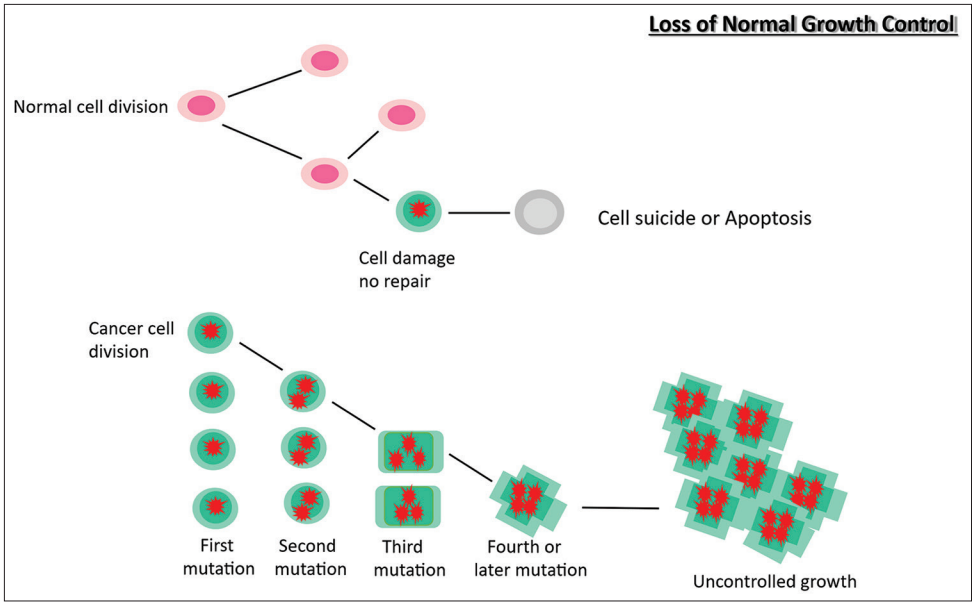

Fig. 2. Schematic representation of cancer cell division

Table 1: FDA Approval status and patent information of selected anticancer agent

Drug name	Inventor	FDA approval date	Patent no.	References
Camptothecin	Qin Dawei Wang Lizhen	Pending	CN112972429A	[81]
Methotrexate	Nancy Mohamed Elbaz Wael Mamdouh Sayed Sayed Ahmed Laila Ziko Rania SIAM	December 10, 2019	US10500164B2	[82]
Gemcitabine	Sentissi Abdelhabi Sentissi Abdelhabi Jacoby Douglas B. Jacoby Douglas	August 16, 2017	JP6181265B2	[83]
Salinomycin	Michelle S. Bradbury Ulrich Wiesner M. Orwell Holzer H. Schermacher	September 21, 2021	CN108377643B	[84]
Doxorubicin	Cho Myung Haing	July 12, 2017	KR101757273B1	[85]
Epigallocatechin	Guo Mingquan Ding Jun	Pending	CN105664168A	[86]
Tamoxifen	Sentissi Abdelhabi Sentissi Abdelhabi Jacoby Douglas B. Jacoby Douglas	August 16, 2017	JP6181265B2	[87]
Cisplatin	Yang Hong, Xu Tao, Chen Huabing, Zhang Mia, Chen Liang, Deng Yibin, Yao Jialu, Luo Jiali, Zhai Yanhua	November 04, 2022	CN111840549B	[88]

subtilis supernatant with microwave irradiation, as confirmed by UV-visible spectroscopy (410–415 nm plasmon resonance), SEM (spherical morphology), EDX (Ag-specific peaks at 1.3–3.2 keV), and XRD analysis. *In vitro* cytotoxicity testing against THP-1 leukemia cells revealed that AgNPs alone induced cell death through ROS generation and DNA damage, while combination studies showed enhanced efficacy when AgNPs were paired with cyclophosphamide (through increased DNA crosslinking) or busulfan (through alkylation and interstrand crosslinking) but reduced effectiveness with mercaptopurine which worked better alone. These results demonstrate that bio-physically synthesized AgNPs can potentiate specific chemotherapeutics (cyclophosphamide and busulfan) while maintaining their own anticancer properties, suggesting their potential as combination therapy agents to reduce required drug dosages, though drug-specific interactions require further investigation to optimize therapeutic protocols for leukemia treatment [74,75].

Tannic acid modified as anticancer agent

Using tannic acid (0.01 M, pH 8) as a reducing and stabilizing agent, tannic acid-modified TA-AgNPs were created by a chemical reduction method. They were then added to a boiling solution of silver nitrate (25.5 mg in 150 mL) and stirred for 1 and ½ h to create a stable brown colloidal suspension. TEM, XRD, FTIR, UV-Vis spectroscopy, TGA, zeta potential analysis, fluorescence spectroscopy, and ICP-OES were used to characterize the resultant nanoparticles (17.3 mg). As demonstrated by MTT and Live/Dead staining assays, biocompatibility studies employing normal MRC-5 and Vero cells demonstrated that TA-AgNPs displayed negligible cytotoxicity at concentrations up to 500 µg/mL. To achieve effective drug loading verified by UV-Vis analysis, the chemotherapeutic agent epirubicin (EPI) was loaded onto TA-AgNPs for anticancer application by combining EPI (1.0 mg/mL) with TA-AgNPs (1.0 mg/mL) and stirring for 24 h in the dark. Fluorescence spectroscopy was used to measure the regulated, pH- and redox-responsive release of EPI in *in vitro* drug release experiments, which were carried out in PBS at pH 7.4, pH 5.0, and pH 7.4 with 10 mM GSH. Confocal microscopy revealed that cellular uptake experiments in Hep G2 liver cancer cells showed increased internalization of TA-AgNPs/EPI in comparison to free EPI. According to cytotoxicity tests, TA-AgNPs/EPI considerably decreased Hep G2 cell viability more efficiently than either free EPI or TA-AgNPs by itself. The therapeutic potential of TA-AgNPs as a nanocarrier for anticancer drug delivery was further confirmed by *in vivo* studies using Hep G2 tumor-bearing BALB/c nude mice. These studies demonstrated that intravenous administration of TA-AgNPs/

EPI (5 mg/kg EPI dose, QOD for 3 weeks) effectively suppressed tumor growth, as evidenced by reduced tumor volume, stable body weight, and no significant systemic toxicity [76].

Caffeic acid as anticancer agent

The study focuses on the manufacture of AgNPs at room temperature by employing the natural polyphenol caffeic acid as a stabilizing and reducing agent. The color shift from pale yellow to brown signified the creation of nanoparticles. UV–Vis, FTIR, Raman spectroscopy, DLS, zeta potential analysis, atomic force microscopy (AFM), and SEM were used to characterize the synthesized caffeic acid–AgNP conjugates. The effective synthesis was confirmed by UV-Vis, which revealed absorption peaks for AgNPs at 418 nm and caffeic acid–AgNPs at 445 nm. Functional groups including hydroxyl and carbonyl were detected by FTIR, suggesting that the surface of the nanoparticles contained oxidized polyphenols. The existence of caffeic acid functional groups bonded to AgNPs was validated by Raman analysis. DLS revealed good dispersity with average particle sizes of 29.3 nm for AgNPs and 127.6 nm for caffeine–AgNPs. A surface charge of −67.8 mV was revealed by zeta potential measurement, suggesting stable particles. The spherical shape and caffeic acid adsorption on the nanoparticle surface were verified by AFM and SEM. Using the MTT assay, cytotoxicity was assessed on A549 lung cancer cells. After 48 h, caffeic acid–AgNPs had notable cytotoxic effects, with an IC50 value of 78 μg/mL, as opposed to 141 μg/mL for plain AgNPs. Cell cycle study demonstrated G0/G1 phase arrest in 81.74% of cells after 24 h and 64.61% after another 24 h, compared to 55.18% in the control group. Morphological investigations also revealed changes in cells following treatment. According to the study's findings, the combination of AgNPs with caffeic acid produces stable, spherical nanostructures that have strong anticancer effects on lung cancer cells, suggesting that they could be used as both environmentally benign and efficient anticancer treatment agents [77-79].

Carboplatin anticancer drug

The study on the synthesis and characterization of AgNPs loaded with carboplatin highlights the promising role of AgNPs in cancer therapy. Incorporation of carboplatin into AgNPs enhanced tumor suppression, improved targeted delivery, and reduced systemic toxicity, demonstrating their potential as an efficient nanocarrier system for anticancer treatment. The synthesized carboplatin-loaded AgNPs (AgNPs-Car) were confirmed to be stable and well-formed, with particle sizes increasing from 2.32 nm to 28.85 nm upon drug loading.

Biological evaluation showed that AgNPs-Car exhibited strong antiproliferative and pro-apoptotic activity against MCF-7 (breast), A549 (lung), and C6 (glioma) cancer cell lines, with the highest selectivity and potency in C6 glioma cells (IC50=16.18 μg/mL), while sparing normal WI-38 cells. Compared to free carboplatin, AgNPs-Car achieved similar or higher efficacy at significantly lower doses. Flow cytometry confirmed apoptosis induction through DNA fragmentation, not necrosis.

Overall, the study concludes that AgNPs enhance the therapeutic performance of anticancer drugs, offering improved delivery, targeted cytotoxicity, and reduced side effects. The AgNPs-Car nanocomplex demonstrates strong promise for targeted cancer therapy, especially in treating aggressive tumors like glioblastoma [80].

APPLICATIONS OF AGNPS IN ANTICANCER ACTIVITY

- AgNPs exhibit selective toxicity toward cancer cells (e.g., U251 glioblastoma, MCF-7 breast cancer) over normal cells (e.g., IMR-90 lung fibroblasts, MCF10-A breast cells).
- AgNPs induce programmed cell death (apoptosis) in cancer cells through concentration-dependent mechanisms.
- AgNPs increase oxidative stress, leading to mitochondrial damage, DNA fragmentation, and cell death in cancer cells.
- In combination with chemotherapeutic drugs (e.g., 5FU), AgNPs sensitize cancer cells, enhancing the effectiveness of the drug.
- Treatment with AgNPs causes morphological changes in cancer cells, which are early indicators of apoptosis.
- AgNPs are internalized mainly through endocytosis, leading to various intracellular effects like upregulation of stress proteins and mitotic arrest.
- CS-based carriers enhance the delivery and efficacy of AgNPs at lower concentrations, improving cytotoxic efficiency.
- Magnetic and SERS-active AgNPs composites are used for cancer cell detection (e.g., SKBR3, SP2/O) and targeted therapy.
- AgNPs conjugated with molecules like chlorotoxin improve targeted delivery to specific cancer cells (e.g., glioblastoma).
- AgNPs synthesized from bacteria, fungi, and plants demonstrate strong anticancer properties with eco-friendly production methods.
- Smaller-sized and shaped AgNPs (e.g., nanotriangles) show greater anticancer efficacy due to enhanced cell penetration and surface interaction.
- Effective against multiple cancer types: Breast cancer (MCF-7, T47D, MDA-MB-231), lung cancer (A549), glioma (U251, C6), colon cancer (HT29), liver cancer (Bel-7402), and leukemia (AML, SP2/O).

FUTURE PROSPECTS

With advancements in nanotechnology, AgNPs are transitioning from theoretical promise to real-world medical applications. To fully harness their potential, future research should focus on:

- Optimized synthesis and functionalization: Green synthesis methods using plant extracts and biopolymers can improve AgNPs' biocompatibility, stability, and safety.
- Combination therapies: Integrating AgNPs with conventional chemotherapy and radiotherapy can enhance therapeutic efficacy while minimizing side effects.
- Targeted drug delivery: Functionalizing AgNPs with tumor-specific ligands, antibodies, and peptides can improve targeting precision and reduce systemic toxicity.
- Preclinical and clinical evaluations: Comprehensive *in vivo* and clinical trials are needed to assess AgNP pharmacokinetics, biodistribution, and long-term safety.
- Environmental and safety considerations: Investigating the environmental impact and toxicity of AgNPs is crucial for ensuring their responsible and sustainable medical use.
- Nano formulations for personalized medicine: Advances in nanotechnology can facilitate the development of patient-specific AgNPs-based therapeutics tailored to individual cancer profiles.
- Biosensor integration for early detection: AgNPs can be incorporated into biosensors to enable early cancer detection and real-time monitoring of treatment responses.

CONCLUSION

AgNPs represent a promising frontier in cancer therapy, offering multiple mechanisms of action against tumor cells while addressing the limitations of conventional treatments. However, further research is necessary to optimize their synthesis, improve biocompatibility, and establish their long-term safety profile. With continued advancements in targeted drug delivery, combination therapies, and nanomedicine, AgNPs hold immense potential as next-generation anticancer therapeutics. Addressing existing challenges through rigorous scientific research and clinical validation will accelerate their transition from laboratory studies to approved medical treatments, ultimately improving patient outcomes and revolutionizing cancer therapy. Moreover, researchers and innovators in this field should ensure exclusive rights to their inventions [Table 1] through appropriate intellectual property protection, fostering innovation and responsible commercialization of AgNP-based therapeutics.

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AUTHORS CONTRIBUTION

The first draft of the manuscript was written by Ruchi Pednekar and Dnyaneshwari Phalke. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

CONFLICTS OF INTEREST

The author declares that there are no conflicts of interest regarding the publication of this review article.

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