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Review Article

Potential of Green-Synthesized Silver Nanoparticles from Herbal Plants as Anticancer Therapy: A Systematic Review of Anticancer Effectiveness

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ABSTRACT

Cancer is a leading cause of mortality worldwide due to uncontrolled proliferation, resistance to apoptosis, and metastasis. Chemotherapy and radiotherapy have improved survival, but the effectiveness is limited by toxicity and drug resistance. This condition has prompted the exploration of herbal medicines and nanotechnology-based alternatives. Green-synthesized silver nanoparticles (AgNPs), produced using phytochemical-rich plant extracts, are promising anticancer agents because of the eco-friendly synthesis, biocompatibility, and multitargeted effects. Therefore, this systematic review, following PRISMA 2020 guidelines, analyzed 26 in vitro studies published between 2015 and 2025 from PubMed, ScienceDirect, Taylor & Francis, Hindawi, and ProQuest. Evidence consistently showed selective cytotoxicity of green-synthesized AgNPs against cancer cells while sparing normal cells. Reported mechanisms included apoptosis induction through mitochondrial pathways, reactive oxygen species generation, cell cycle arrest, DNA damage, and inhibition of angiogenesis and metastasis. Smaller nanoparticles had higher potency, signifying the role of size and surface chemistry in therapeutic performance. In conclusion, green-synthesized AgNPs show considerable potential as novel anticancer nanomedicines. However, most evidence is limited to in vitro studies, with significant heterogeneity in synthesis methods. Standardized protocols, in vivo validation, and clinical examinations are required before clinical translation can be achieved.

Keywords: Anticancer, Green synthesis, In vitro studies, Phytochemicals, Silver nanoparticles

Introduction

Cancer is a broad group of diseases characterized by the unregulated proliferation of cells due to disruptions in intrinsic growth control mechanisms.[1] This unchecked growth leads to the formation of tumors that can develop in various organs or tissues. When left untreated, cancer cells may invade surrounding tissues and metastasize to distant sites through the circulatory and lymphatic systems. Additionally, tumor progression is supported by angiogenesis to meet the metabolic demands for growth.[2] Conventional cancer treatments include surgery, chemotherapy, radiotherapy, targeted therapies, and immunotherapy. Surgery removes the primary tumor, while chemotherapy and radiotherapy are used to eliminate residual malignant cells.[3] Targeted therapies and immunotherapies act on specific molecular pathways included in tumorigenesis.

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Despite major improvements in survival, these modalities are often followed by significant drawbacks, such as adverse side effects, drug resistance, and high therapy costs. Chemotherapy can induce nausea, fatigue, immunosuppression, and damage to healthy tissues. The formation of resistant cancer phenotypes poses persistent clinical challenges.[4,5] In response to the limitations, increasing attention has turned to herbal medicines as complementary or alternative therapeutic options. Historically rooted in traditional medicine systems, numerous plant-based compounds are scientifically evaluated for anticancer properties. Various herbs show efficacy by inducing apoptosis, inhibiting cancer cell proliferation, and suppressing metastasis. For example, *Ficus deltoidea* is rich in flavonoids, tannins, and phenolics that exhibit antiproliferative and cytotoxic effects. *Curcuma longa* contains curcumin, a compound known to inhibit tumor growth by modulating inflammatory pathways and oxidative stress.[6] More investigations of herbal therapies in combination with standard treatments are increasingly needed. Integrating plant-based compounds with conventional modalities may enhance therapeutic outcomes, reduce systemic toxicity, and mitigate the risk of drug resistance. To fully harness these benefits, comprehensive studies are needed to clarify the mechanisms of action of bioactive phytochemicals and to validate the safety and efficacy through robust preclinical and clinical investigations.[7] Rapid advancements in nanotechnology have simultaneously introduced innovative platforms for improving drug delivery and therapeutic targeting. Nanomedicine offers several advantages, such as enhanced drug solubility, prolonged circulation time, and site-specific delivery, thereby minimizing off-target effects

and improving efficacy. In oncology, nanoparticles show substantial promise as delivery systems capable of improving drug bioavailability and therapeutic index.[8] These nanosystems are engineered to stabilize therapeutic agents in the bloodstream and enable controlled release at tumor sites, optimizing clinical outcomes.[9]

Nanoparticles can be synthesized from a variety of materials, namely metals, lipids, polymers, and natural compounds, each imparting unique structural and functional properties. These include silver nanoparticles (AgNPs), which are considered promising in cancer therapy due to the ability to induce apoptosis, inhibit proliferation, and suppress metastasis.[10,11] The biological effects are mediated through various intracellular signaling pathways, signifying the potential as effective anticancer agents.[12] As metal-based nanomaterials, AgNPs possess additional antimicrobial and anti-inflammatory properties, further enhancing the biomedical applications. AgNPs are produced through physical, chemical, or biological methods, with green synthesis, using plant extracts as reducing and stabilizing agents, gaining preference for the eco-friendly and biocompatible advantages.[9,13] The small size and high surface-area-to-volume ratio promote better cellular uptake and tumor targeting. Furthermore, green-synthesized nanoparticles derived from herbal sources offer reduced toxicity and improved biocompatibility, leading to the positioning as attractive candidates for future cancer therapies.[14]

This review is novel in focusing specifically on anticancer potential of green-synthesized AgNPs derived from herbal plant extracts, showing the cytotoxic mechanisms, phytochemical contributions, and therapeutic potential. Compared to previous investigations that broadly discuss nanoparticles or herbal medicines, this review systematically evaluates recent in vitro studies (2015–2025) to provide an updated, targeted synthesis of evidence. The systematic review, conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines, ensures a transparent and reproducible method in identifying, selecting, and analyzing relevant studies. The primary objective is to assess cytotoxic effects, mechanisms of action, and the contribution of phytochemicals to the stability and efficacy of AgNPs. By synthesizing the results, this review aims to guide future study directions and facilitate potential clinical translation.

Materials and Methods

Study eligibility

This systematic review was conducted in accordance with PRISMA 2020 guidelines to ensure transparency and methodological rigor. The written article adheres to the recommended structure for systematic reviews, consisting of a clearly defined title, rationale, objectives, methods, results, and discussion. The study selection process is shown in PRISMA flow diagram (Figure 1). Due to substantial heterogeneity in study designs, cancer models, and reported outcomes, only a qualitative synthesis was performed, without meta-analysis. The review protocol was developed following PRISMA standards and submitted for registration in International Prospective Register of Systematic Reviews (PROSPERO) with registration number: CRD420251075567. This protocol can be accessed at: https://www.crd.york.ac.uk/PROSPERO/view/CRD420251075567

Inclusion criteria

Inclusion criteria for this review were established based on the PECOS framework, which included: (1) Population: Cancer cell lines; (2) Exposure: Treatment with green-synthesized AgNPs derived from herbal plant extracts; (3) Comparison: Control and/or standard chemotherapeutic agents; (4) Outcome: Mechanistic insights into anticancer effects, including apoptosis induction, inhibition of cell proliferation, suppression of metastasis, and selective cell cytotoxicity toward cancer cells; and (5) Study design: Original in vitro experimental studies published in English between 2015 and 2025.

Exclusion criteria

Studies were excluded if they met any of the following conditions: (1) non-in vitro studies; (2) non-English publications; (3) review articles, book chapters, editorials, conference abstracts, or other non-original research; (4) studies utilizing AgNPs synthesized by chemical, microbial, or non-herbal green methods; (5) studies evaluating nanoparticles other than silver; (6) studies with outcomes irrelevant to anticancer activity; and (7) studies with inaccessible full-text.

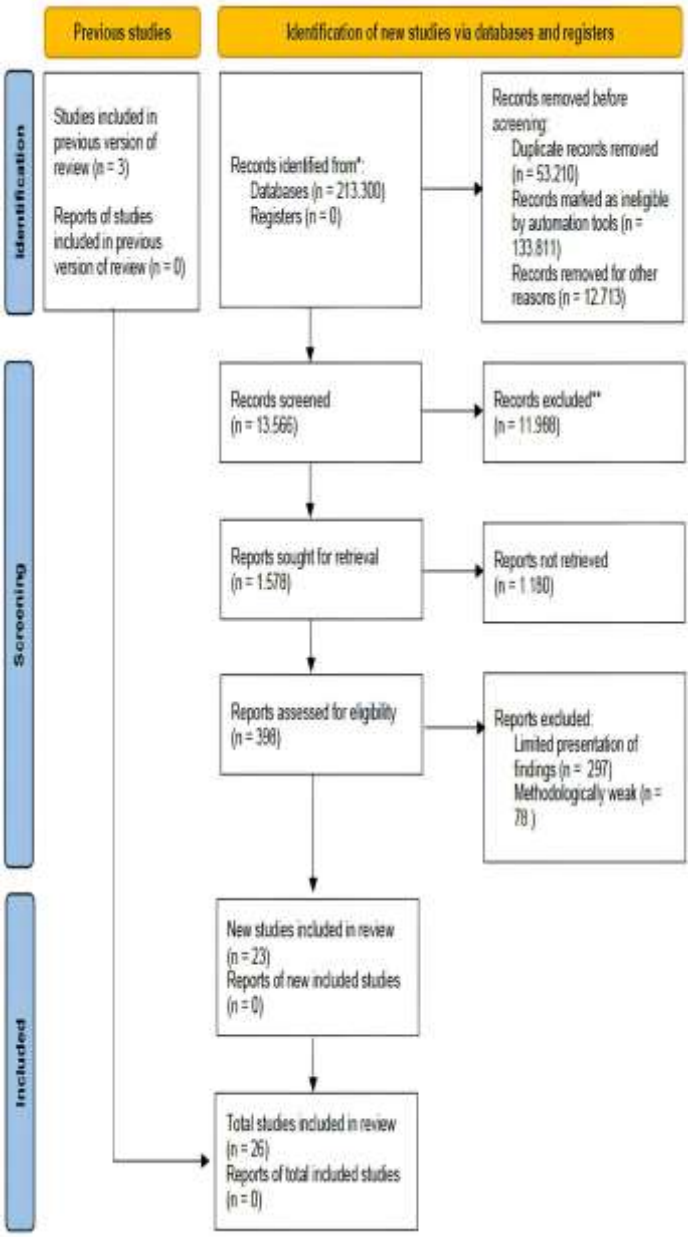

Figure 1: Flowchart of study selection process based on PRISMA 2020 guidelines.[15]

Data sources

A comprehensive electronic literature search was conducted across the databases, including PubMed, ScienceDirect, Taylor & Francis, Hindawi, and ProQuest, covering publications from 2015 to 2025. The search was performed between February 5th and March 6th 2025. The search strategy was based on Boolean operators using the terms: ("NANOPARTICLE" OR "SILVER NANOPARTICLE" OR "AgNP") AND ("GREEN SYNTHESIS") AND ("CANCER" OR "TUMOR"). Wildcard terms were applied where applicable to enhance sensitivity, and each database search and article screening was conducted independently by the authors. Reference management was facilitated using Mendeley Desktop, version 2.93 (Elsevier, Amsterdam, Netherlands, 2025). Discrepancies in study selection were resolved through discussion and consensus.

Study selection and data extraction

Three investigators independently screened the titles, abstracts, and full texts of all retrieved articles based on the predefined inclusion and exclusion criteria. The study selection process adhered to PRISMA guidelines, and any disagreements during the selection phase were resolved through discussion to reach a consensus. Data extraction was conducted using a structured form created in Google Sheets (Google LLC, Mountain View, CA, USA, 2025). Two distinct data extraction tables were developed. The first table recorded detailed study characteristics, including author name and year of publication, plant name, extracted plant part, extraction method, nanoparticles shape and size, and reported anticancer mechanisms of activity (Table 1). The second table focused solely on the half maximal inhibitory concentration (IC_{50}) values and reported outcomes, specifically the anticancer effects of the green-synthesized AgNPs against various cancer cell lines (Table 2). All data were cross-verified among authors to and consistency.

Risk of bias assessment

The quality of the included studies was assessed using Quality Assessment Tool for In Vitro Studies (QUIN), independently conducted by three reviewers. QUIN tool evaluates twelve domains, including clearly stated aims/objectives, explanation of sample size, sampling method, presence of a comparison group, detailed methodology, operator details, randomization, outcome measurement methods, outcome assessor information, blinding, statistical analysis, and result presentation. Each criterion was scored as 0 (not reported), 1 (unclear), or 2 (clearly reported), with a maximum total score of 24. The final quality score was calculated using the formula: (total score / 24) × 100%. Based on this percentage, studies were categorized with low (≥67%), moderate (34–66%), or high (≤33%) risk of bias. Any discrepancies in scoring were resolved through discussion to ensure consensus among the reviewers.

Outcome of interest

The primary outcomes of interest in this systematic review were anticancer effects shown by green-synthesized AgNPs derived from herbal plant extracts. Specifically, the review focused on mechanistic outcomes such as apoptosis induction, inhibition of cell proliferation, cell cycle arrest, generation of reactive oxygen species (ROS), suppression of metastasis, and selective cytotoxicity toward cancer cells. The outcomes were assessed based on quantitative and qualitative data reported in the included in vitro studies. Secondary outcomes associated with phytochemical contributions to nanoparticle stability and activity were considered. Only studies that reported clear cytotoxic evidence against cancer cell lines following exposure to green-synthesized AgNPs were included in the outcome evaluation.

Table 1: Characteristics and anticancer activity of AgNPs derived from various plant extracts

Ref.	Plant Name	Plant Part	Solvent	Size and Shape	Anticancer Effects
[19]	*Prunus spinosa*	Fruit	Acetonitrile	Spherical; 25 nm	Disrupted membranes, increased ROS, protein damage, mitochondrial dysfunction
[20]	*Pyrostegia venusta*	Leaves	Distilled water	Spherical; 12-20 nm	Induced ROS, DNA damage, disrupted mitochondria and cell signaling, inhibited proliferation
[21]	*Persicaria perfoliata*	Aerial parts	Distilled water	Quasi-spherical; 44.2 nm	Induced ROS, autophagy, disrupted cell membranes, fragmentation, and lysosomal damage
[22]	*Curcuma longa*	Leaves	Distilled water	Spherical; 25-45 nm	Induced ROS and mitochondrial apoptosis, genotoxicity leading to apoptosis-related gene upregulation
[23]	*Azadirachta indica*	Fruits	Distilled water	Spherical; 27 nm	Induced ROS and apoptosis, decreased metabolic activity
[24]	*Nepeta deflersiana*	Leaves	Distilled water	Spherical; 33 nm	ROS-mediated mitochondrial membrane disruption led to cell death
[25]	*Abelmoschus esculentus*	Pulp	Distilled water	Spherical; 21.29 nm	Increased ROS and mitochondrial membrane potential loss suggest apoptosis via mitochondrial damage
[26]	*Ginkgo biloba*	Leaves	Distilled water	Spherical; 39.1 nm	Induced ROS and Ag^+ release; disrupted cell membranes and triggered cell death
[27]	*Centratherum anthelminticum*	Seeds	Distilled water	Spherical; 58 nm	Induced apoptosis through saponins, avoided necrosis, promising for low-side-effect cancer therapy
[28]	*Leucas aspera*	Leaves	Distilled water	Spherical; 34.2 nm	Modulated >1,000 genes, including metallothionein, chaperone, and histone genes, altered gene expression profiles in cancer cells
[29]	*Dimocarpus longan*	Leaves	Distilled water	Spherical; 8–22 nm	Suppressed tumor growth, inhibited NF-κB, downregulated Bcl-2, and upregulated caspase-3 and survivin in cancer cells
[30]	*Hypericum perforatum*	Aerial parts	Distilled water	Spherical; 25 nm	High surface charge and organic coating enhanced cytotoxicity, caused cell membrane disruption and ROS-related damage
[31]	Not specified	Cellulose	Distilled water	Spherical; 150–159 nm	Induced ROS and mitochondrial damage, downregulated TNF-α expression

[32]	*Rubus glaucus*	Leaves	Distilled water	Quasi-spherical; 31 nm	Demonstrated no cytotoxicity against cancer cells, highlighted safety and antioxidant potential
[33]	*Alternanthera tenella*	Leaves	Distilled water	Spherical; 48 nm	Induced ROS production via mitochondrial respiratory chain disruption, caused ATP depletion and nucleic acid damage
[34]	*Podocarpus macrophyllus*	Leaves and stems	Distilled water	Spherical; 13–20 nm	Induced ROS and DNA damage, cell cycle arrest, modulated NOTCH2 expression involved in brain cancer
[35]	*Lantana camara*	Leaves	Distilled water	Spherical; 30 nm	Upregulated caspase-3 via p53/Bax-cytochrome-C cascade, induced apoptosis, nuclear fragmentation, and ATP disruption
[36]	*Cymodocea serrulata*	Leaves	Distilled water	Spherical; 22 nm	Interacted with sulfur-containing proteins, inhibited enzymatic function leading to cell death
[37]	*Quercus infectoria*	Fruit	Distilled water	Spherical; 40 nm	Exhibited long-term nanoparticles stability, potential breast cancer therapeutic agent
[38]	*Artocarpus heterophyllus*	Leaves	Distilled water	Spherical; 12.75 nm	Downregulated the expression of several oncogenes, such as cyclin D1, HER2, miR622, and COX-2, induced mitotic catastrophe, leading to apoptotic cell death
[39]	Not specified	Cellulose	Graded ethanol (30–100%)	Spherical; <20 nm	Higher cytotoxicity in cancer cells than normal, AgNPs selectively induced cancer cell death
[40]	*Tabebuia pallida*	Leaves	Hydroethanolic (60:40 ethanol)	Spherical; 10–60 nm	Exhibited antiproliferative and apoptosis-inducing activity
[41]	*Viburnum grandiflorum*	Leaves	Methanol	Spherical; 17.77 nm	High cellular uptake and stability, unaffected by p-glycoprotein efflux
[42]	*Olea europaea*	Leaves	Distilled water	Spherical; 28 nm	Triggered mitochondrial dysfunction, ROS generation, and DNA damage
[43]	*Sida acuta*	Leaves	Distilled water	Spherical; 5–25 nm	Induced apoptosis, phytochemical capping enhanced cytotoxicity
[44]	*Ocimum gratissimum*, *tenuiflorum*, *americanum*	Leaves	Distilled water	Spherical; 47–69 nm	Triggered apoptosis in cancer cells via chromatin condensation, cell shrinkage, and apoptotic body formation

Table 2: Outcomes and doses of AgNPs derived from various plant extracts.

Ref.	Cell Line	Dose	Outcome
[19]	L929 (normal fibroblast); A549 (lung cancer)	IC_{50}: 16 µg/mL	AgNPs-loaded nanocomposites were selectively cytotoxic to A549 lung cancer cells, while remaining biocompatible with healthy L929 cells. The particles induced apoptosis via ROS generation and mitochondrial dysfunction, showing potential for use in safe cancer-targeted treatments, food packaging, and healthcare materials.
[20]	COS-7 (african green monkey kidney)	IC_{50}: 50.48 µg/mL	AgNPs from *Pyrostegia venusta* showed cytotoxic activity against COS-7 cells, confirming ROS-mediated apoptosis, DNA damage, and mitochondrial disruption. The study supports their potential as antibiotic alternatives and anticancer agents by inducing cancer cell death and impeding cellular respiration through oxidative stress pathways.
[21]	HeLa (cervical cancer)	IC_{50}: 251.86 ± 58.90 µg/mL	AgNPs synthesized from *Persicaria perfoliata* showed weak cytotoxicity against HeLa but triggered ROS-mediated apoptosis, autophagy, and necrosis. They exhibited antimicrobial, antioxidant, and anticancer properties. The study supports their use in multifunctional biomedical applications, despite relatively high IC_{50} values.
[22]	HT-29 (colorectal cancer)	-	AgNPs synthesized using *Curcuma longa* demonstrated significant inhibitory effects on HT-29 colon cancer cell proliferation in a dose- and time-dependent manner. The underlying mechanisms involved increased production of ROS, disruption of mitochondrial membrane potential, and induction of both apoptosis and necrosis. Furthermore, the synthesis process is eco-friendly, highlighting the promise of nanoparticles as a sustainable and effective therapeutic candidate for colon cancer treatment.

[23]	A549 (lung cancer)	IC_{50}: 81.09 µg/mL	AgNPs from *Azadirachta indica* showed stronger cytotoxicity than cisplatin against A549 cells. AgNPs-cisplatin combination improved cytotoxicity. ROS generation and DNA damage induced apoptosis. A promising alternative or adjuvant in lung cancer chemotherapy.
[24]	HeLa (cervical cancer)	-	*Nepeta deflersiana*-derived AgNPs induced dose-dependent cytotoxicity in HeLa cells, causing up to 91% cell death at 100 µg/mL. This effect was linked to elevated ROS, increased lipid peroxidation, reduced GSH, mitochondrial dysfunction, subG1 cell cycle arrest, and apoptosis/necrosis (69.8% and 25.3%, respectively), highlighting their strong oxidative and apoptotic activity in cervical cancer cells.
[25]	Jurkat (leukemia)	IC_{50}: 16.15 µg/mL	AgNPs reduced Jurkat T cell viability significantly at 10, 25, and 50 µg/mL doses. Apoptosis induction was associated with increased ROS and mitochondrial membrane loss, confirming mitochondrial-mediated cytotoxicity.
[26]	MCF-7 (breast cancer)	-	AgNPs showed dose-dependent cytotoxicity against MCF-7 breast cancer cells, validated by MTT assay and Hoechst blue staining. The mechanism involved ROS generation and mitochondrial apoptosis, demonstrating their potential as effective candidates in nanoparticles-based breast cancer therapy.
[27]	MDA-MB-231 (breast cancer)	IC_{50}: 35.06 ± 1.2 µg/mL	AgNPs synthesized from *Centratherum anthelminticum* seed extract induced apoptosis in MDA-MB-231 breast cancer. Saponins played a critical role in mediating apoptosis without necrosis, which is beneficial for reducing treatment side effects. The study supports the therapeutic relevance of seed-based AgNPs in breast cancer management.
[28]	A549 (lung cancer)	IC_{50}: 328 µg/mL	AgNPs from *Leucas aspera* reduced viability in A549 cells by generating ROS, causing mitochondrial damage and DNA fragmentation. Over 1,000 genes were modulated, including those for metallothionein and chaperones. Despite mild cytotoxicity, the particles showed no toxicity in normal cells, supporting their role in alveolar cancer treatment with minimal side effects.
[29]	VcaP (prostate cancer), BxPC-3 (pancreatic cancer), H1299 (lung cancer)	IC_{50}: 5.33 ± 0.37 µg/mL	AgNPs induced dose-dependent apoptosis in various cancer cells. This cytotoxic effect was associated with inhibition of NF-κB activity, downregulation of the anti-apoptotic protein bcl-2, and upregulation of caspase-3 and survivin. Additionally, AgNPs significantly suppressed tumor growth in a mouse model, supporting their in vivo anticancer potential.
[30]	HeLa (cervical cancer), HepG2 (hepatocarcinoma), A549 (lung cancer)	IC_{50}: 6.72 µg/mL (HeLa), 6.88 µg/mL (HepG2), 6.08 µg/mL (A549)	AgNPs caused significant viability loss in HeLa, HepG2, and A549 cells, attributed to high surface charge and ROS generation, with rapid cytotoxic effect within 2 hours.
[31]	MCF-7 (breast cancer)	IC_{50}: 10 µg/mL	AgNPs synthesized using ethyl cellulose significantly downregulated TNF-α mRNA and protein levels in MCF-7 breast cancer cells, indicating anti-inflammatory and anticancer effects. They also showed minimal cytotoxicity to normal cells, suggesting their safety as a therapeutic agent. The results propose AgNPs as a potential TNF-α inhibitor in cancer treatment
[32]	HepG2 (hepatocarcinoma)	-	Surface-modified AgNPs showed no cytotoxicity on HepG2 cells but displayed >70% antioxidant activity via DPPH assay. Suggests use in oxidative stress–related disorders and as free radical scavengers, not direct cytotoxic agents.
[33]	MCF-7 (breast cancer)	IC_{50}: 42.5 µg/mL	AgNPs disrupted mitochondrial respiratory chain, leading to ROS generation and ATP synthesis inhibition, causing DNA/nucleic acid damage. This supports their use as mitochondrial-targeted anticancer agents.
[34]	GBM (glioblastoma), LGG (glioma)	-	AgNPs synthesized from *Podocarpus macrophyllus* leaves/stems exhibited cytotoxic effects against GBM and LGG cells via ROS production and DNA damage. Computational analysis showed AgNPs modulated NOTCH2 gene expression, and clinical data associated high NOTCH2 expression with poor prognosis, making this gene a potential therapeutic target.
[35]	A549 (lung cancer), MCF-7 (breast cancer)	IC_{50}: 49.52 µg/mL (A549), 46.67 µg/mL (MCF-7)	AgNPs synthesized using *Lantana camara* leaf extract exhibited cytotoxicity against MDA-MB-231. Mechanisms involved caspase-3 activation and cytochrome-C release, promoting apoptosis. The eco-friendly synthesis method and potent bioactivity suggest high potential in cancer nanotherapy and green nanotechnology.
[36]	HeLa (cervical cancer)	IC_{50}: 61.24 µg/mL	AgNPs synthesized from *Cymodocea serrulata* exhibited cytotoxic effects on HeLa cells. Mechanism involved replication arrest and enzyme inhibition via interaction with sulfur-rich proteins. *Cymodocea serrulata* components acted as reducers/stabilizers of AgNPs, supporting further therapeutic development.

[37]	MCF-7 (breast cancer)	IC_{50}: 50 µg/mL	AgNPs showed enhanced anticancer efficacy and long-term nanoparticles stability up to one month, indicating its potential as a breast cancer therapeutic.
[38]	MCF-7 (breast cancer)	IC_{50}: 124.62 µg/mL	Treatment with *Artocarpus heterophyllus*-AgNPs led to an increased number of cells in the G2/M phase, suggesting that it induces mitotic abnormalities, ultimately resulting in cell death. Additionally, AgNPs suppressed the expression of several oncogenes linked to cancer cell growth and survival. It demonstrated strong potential as an innovative anticancer agent, offering both biocompatibility and the advantages of eco-friendly, cost-efficient, plant-based nanoparticles production.
[39]	HCT-116 (colorectal cancer), MCF-7 (breast cancer), MG-63 (osteosarcoma), L929 (normal fibroblast)	IC_{50}: 60 µg/mL (HCT-116), 80 µg/mL (MCF-7, MG-63), 140 µg/mL (normal fibroblast)	AgNPs induced apoptosis in HCT-116 cells through chromatin condensation and apoptotic body formation. Additionally, they exhibited antibacterial activity. The mechanism involved ROS generation and membrane disruption, highlighting their dual potential as anticancer and antimicrobial agents.
[40]	Primary blood and lung cancer	-	AgNPs were encapsulated into liposomes with high efficiency (82.25%), exhibiting sustained and pH-dependent release (73.32% at pH 5.5, simulating tumor environment). The formulation demonstrated significant antiproliferative and apoptosis-inducing properties in blood and lung cancer cells, supporting its application in targeted cancer drug delivery systems.
[41]	RD (rhabdomyosarcoma)	IC_{50}: 21.49 µg/mL	Methanol-extract AgNPs demonstrated notable cytotoxicity against RD cells, along with antibacterial and antioxidant activities, indicating their potential for broad-spectrum biomedical applications.
[42]	MCF-7 (breast cancer), HeLa (cervical cancer), HT-29 (colorectal cancer)	IC_{50}: 10 µg/mL	*Olea europaea*-AgNPs exhibited high anticancer activity, inhibiting 79–82% of cancer cell growth, higher than both olive extract (55–67%) and doxorubicin (75–79%). They also showed antimicrobial activity. These results highlight AgNPs as multifunctional agents with anticancer, antibacterial, and antifungal potential for biomedical use.
[43]	MCF-7 (breast cancer)	IC_{50}: 100 µg/mL	*Sida acuta*–mediated AgNPs demonstrated significant cytotoxicity against MCF-7 cancer cells, along with potent anti-inflammatory (99.18%), antidiabetic (96.09%), and antioxidant (75.68%) activities. Their high thermal stability and enhanced cytotoxicity due to phytochemical capping suggest promising application in cancer therapy and chronic disease management.
[44]	MCF-7 (breast cancer)	IC_{50}: 14.78–18.04 µg/mL	AgNPs synthesized from *Ocimum tenuiflorum*, *O. gratissimum*, and *O. americanum* leaves showed strong cytotoxicity against MCF-7 cells. Among them, am-AgNPs were the most effective, inducing apoptosis through chromatin condensation and apoptotic body formation. The study confirms *Ocimum*-based AgNPs as potent plant-derived anticancer agents.

Results and Discussion

Study selection and identification

The process of study selection was conducted in accordance with PRISMA 2020 guidelines. A total of 213,300 records were identified through database searches from PubMed, ScienceDirect, Taylor & Francis, Hindawi, and ProQuest using the keywords: ("NANOPARTICLE" OR "SILVER NANOPARTICLE" OR "AgNP") AND ("GREEN SYNTHESIS") AND ("CANCER" OR "TUMOR"). Following the removal of 53,210 duplicate records, 133,811 entries were excluded through automation tools, and 12,713 records were removed for other reasons, leading to the subjection of 13,566 articles to title and abstract screening. Among the articles, 1,578 full-text reports were searched for retrieval, and 1,180 could not be accessed. A total of 398 full-text articles were assessed for eligibility, from which 375 studies were excluded due to limited presentation of results or weak methodological quality. Approximately 23 new studies met the inclusion criteria and were incorporated into the review. Additionally, 3 relevant studies identified from previous reviews were included, increasing the total number of eligible in vitro studies to 26. The identification and screening process is presented in PRISMA 2020 flow diagram (Figure 1).

Summaries of the included studies

The entire 26 in vitro studies included in this review are summarized in Tables 1-2. The studies investigated anticancer effects of green-synthesized AgNPs derived from various herbal plant extracts rich in phytochemicals such as flavonoids, phenolics, terpenoids, and saponins. The nanoparticles were tested against multiple cancer cell lines, including MCF-7, A549, HeLa, HepG2, and PC-3. The primary outcomes reported were dose-dependent cytotoxicity, ROS generation, mitochondrial dysfunction, and apoptosis induction through intrinsic pathways. Some AgNPs provided anti-inflammatory effects by downregulating tumor necrosis factor-α (TNF-α) and inhibiting metastatic pathways. Studies showed that smaller nanoparticles had higher ROS-generating capacity and greater cytotoxicity. Additionally, innovative delivery systems, such as liposomal AgNPs, helped to enhance targeted release and bioavailability. IC_{50} values varied across studies, with several being close to the efficacy of standard chemotherapeutics such as doxorubicin.

Risk of bias assessment

The risk of bias for all included in vitro studies was assessed using QUIN tool, a validated instrument specifically designed to evaluate methodological quality. This tool consists of 12 items addressing key domains, such as study design, experimental clarity, intervention protocols, statistical methods, and result reporting. Each item was scored on a scale of 0 to 2, with 0 signifying that the item was not reported, 1 denoting unclear report, and 2 representing clearly reported information. Based on Table 3, the maximum total score for each study was 24, and was classified into three categories, namely low (≥67%), moderate (34-66%), and high (≤33%) risk of bias. All the 26 included studies fell into the category of moderate risk of bias, with none meeting criteria for low or high risk. This suggested that while many

methodological components were adequately addressed, there were consistent gaps in complete and transparent reporting. The risk of bias assessment was conducted independently by three reviewers, and discrepancies were resolved through discussion to ensure consistency and accuracy.

Induction of apoptosis through oxidative stress

Various herbal plants contain a wide range of bioactive compounds, including alkaloids, phenolics, anthraquinones, coumarins, flavonoids, saponins, tannins, and triterpenoids, which are distributed across different plant parts, such as leaves, stems, rhizomes, and aerial portions. Recent studies found slight variations in total phenolic content among these parts, with leaves generally showing higher concentrations. The extraction method significantly influences yield, with methanolic extracts primarily producing higher levels of phenolics and flavonoids compared to dichloromethane or water extracts.[16-18] Similarly, nanoparticles show multiple mechanisms contributing to anticancer activity, including the photothermal effect, where nanoparticles absorb and convert laser light into heat for thermal ablation of cancer cells. Nanoparticles generate free radicals during light exposure, which damage cancer cells and trigger apoptosis. These enhance targeted drug delivery, improving chemotherapy effectiveness while minimizing systemic side effects.[13]

The generation of ROS as oxidative stress is among the most extensively documented mechanisms through which AgNPs exert anticancer effects. Many of the reviewed studies, particularly those using green-synthesized AgNPs, reported high intracellular ROS levels following therapy, which initiated apoptotic pathways through mitochondrial damage and oxidative stress. ROS accumulation and subsequent death in A549 and COS-7 cells were observed post AgNPs exposure.[19-20] Similar ROS-mediated apoptotic responses were confirmed in HeLa and HT-29 cells, including nuclear fragmentation.[21-22]

Oxidative damage and DNA fragmentation were reported in A549 cells,[23] while enhanced ROS and lipid peroxidation, along with depleted glutathione levels, confirmed oxidative stress as a central cytotoxic mechanism.[24] Disruption of mitochondrial membrane potential was associated with ROS generation, reinforcing the role in AgNPs-induced cell death.[25-26] Additionally, saponin-mediated ROS production facilitated selective tumor cell apoptosis in MCF-7 cells.[27]

DNA damage, gene modulation, and cell cycle arrest

AgNPs modulate gene expression, damage DNA, and disturb the cell cycle in addition to inducing oxidative stress. *Leucas aspera*-mediated AgNPs altered the regulation of over 1,000 genes, including histone and metallothionein genes.[28] In H1299 cells, AgNPs suppressed NF-κB activity and shifted the balance of apoptotic regulators, decreasing bcl-2 and increasing caspase-3.[29] Dose-dependent reductions in cell viability were observed in HeLa, HepG2, and A549 cells, as signified by IC_{50} values.[30] SubG1 cell cycle arrest was shown in HeLa cells, connecting DNA fragmentation to genotoxic stress.[24] In MCF-7 cells, TNF-α expression was suppressed at both mRNA and protein levels, suggesting an anti-inflammatory regulatory mechanism.[31]

Mitochondrial dysfunction and intracellular damage

Mitochondrial disruption serves as a critical downstream effect of ROS overload. In Jurkat cells, AgNPs led to mitochondrial membrane potential dissipation and apoptosis.[25] In HepG2 and MCF-7 cells, mitochondrial respiratory chain inhibition and adenosine triphosphate (ATP) depletion were key cytotoxic mechanisms.[32-33] The combined effects of silver ion release and ROS generation destabilized redox homeostasis in mitochondria, enhancing apoptotic signals.[26] Further confirmation of mitochondrial impairment was found in the reduced membrane potential and increased cytochrome-C release.[24]

Modulation of apoptotic and inflammatory signaling pathways

AgNPs modulate molecular signaling pathways included in cell survival, apoptosis, and inflammation. Inhibition of NF-κB and upregulation of caspase-3 were identified in H1299 and HCT-116 cells, showing dual pathway regulation.[29,34] Increased expression of p53 and caspase-3 in MDA-MB-231 cells confirmed activation of intrinsic apoptosis.[35] Enzyme inhibition through AgNPs-protein interactions was another mechanism disrupting cell function in HeLa cells.[36] Enhanced inhibition of MCF-7 proliferation was observed with Jaft extract containing AgNPs, with minimal cytotoxicity.[37] Furthermore, saponin-coated AgNPs from *Centratherum anthelminticum* seeds induced DNA fragmentation and intrinsic apoptotic pathway activation, supporting antitumor efficacy.[27] Complementing the results, therapy with *Artocarpus heterophyllus*-mediated AgNPs initiated G2/M phase cell cycle arrest, suggesting mitotic abnormalities that led to cell death. These green-synthesized nanoparticles downregulated key oncogenes associated with cancer cell proliferation and survival, such as cyclin D1, HER2, miR-622, and COX-2, thereby inducing mitotic catastrophe and promoting apoptotic cell death.[38]

Selectivity and safety toward normal cells

Selective cytotoxicity toward cancer cells while sparing normal cells is a key advantage of AgNPs-based therapies. Silver nanocomposites selectively targeted A549 cells without harming L929 fibroblasts.[19] Minimal cytotoxicity was observed in normal HBL-100 and fibroblast cells at therapeutic doses.[25] Bovine serum albumin (BSA)-AgNPs had selective cytotoxicity toward HCT-116 and HeLa cells, while sparing HEK-293 cells.[39] Apoptotic cell death further supports the safety profile of the nanoparticles.[27] These results show the potential for AgNPs as safe anticancer agents with tumor-selective activity.

Nanoparticles delivery systems and in vivo efficacy

Innovative delivery platforms and in vivo experiments support the translational potential of AgNPs. Liposomal AgNPs with high encapsulation efficiency showed an enhanced delivery and pH-responsive release in tumor environments.[40] In vivo tumor suppression was detected in severe combined immunodeficient (SCID) mouse xenografts following AgNPs therapy.[29] The combination of AgNPs with cisplatin enhanced anticancer efficacy.[23] Methanol and distilled water extract-based AgNPs showed potent cytotoxic, antibacterial, and antioxidant properties.[41-42] *Sida acuta*-mediated AgNPs had multifunctional bioactivity including anticancer and anti-inflammatory effects.[43] Strong cytotoxic and apoptotic effects were further confirmed in COS-7 and MCF-7 cells.[20,44] Stability and biocompatibility of nanoparticles were found in long-term formulations.[32,36]

Study limitations

This systematic review provides valuable insights into anticancer potential of green-synthesized AgNPs from herbal plants, but certain limitations persist. Specifically, all included studies were conducted in vitro, which might not fully reflect in vivo biological complexity. There was variability in synthesis protocols, plant synthesis, and cancer cell lines, which limited direct comparison and precluded meta-analysis. Despite the constraints, this review offers a strong foundation for future in vivo and clinical investigations and shows consistent anticancer effects across diverse AgNPs formulations.

Table 3: Risk of bias assessment using QUIN tool.

Ref.	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Score (%)
[19]	2	0	2	2	1	0	0	2	2	0	2	2	62,50% (MEDIUM)
[20]	2	0	2	1	1	0	0	1	2	0	2	2	54,10% (MEDIUM)
[21]	2	0	2	2	1	0	0	2	2	0	2	2	62,50% (MEDIUM)
[22]	2	0	1	2	2	0	0	2	0	0	2	2	54,10% (MEDIUM)
[23]	2	0	2	2	2	0	0	2	2	0	2	2	66,70% (MEDIUM)
[24]	2	0	0	2	2	0	0	2	0	0	2	2	50% (MEDIUM)
[25]	2	0	0	2	2	0	0	2	0	0	2	2	50% (MEDIUM)
[26]	2	0	1	2	2	0	0	2	0	0	2	2	54,10% (MEDIUM)
[27]	2	0	0	2	2	0	0	2	0	0	2	2	50% (MEDIUM)
[28]	2	0	0	2	2	0	0	2	2	0	1	2	54,10% (MEDIUM)
[29]	2	0	1	2	2	0	0	2	0	0	2	2	54,10% (MEDIUM)
[30]	2	0	2	2	2	0	0	2	1	0	2	2	62,50% (MEDIUM)
[31]	2	0	2	2	0	0	0	2	0	0	2	2	50% (MEDIUM)
[32]	2	0	2	2	1	0	0	2	1	0	2	2	58,30% (MEDIUM)
[33]	2	0	0	2	2	0	0	2	1	0	2	2	54,10% (MEDIUM)
[34]	2	0	1	2	1	0	0	2	2	0	2	2	58,30% (MEDIUM)
[35]	2	0	1	1	2	0	0	2	1	0	2	2	54,10% (MEDIUM)
[36]	2	0	2	2	2	0	0	2	1	0	2	2	62,50% (MEDIUM)
[37]	2	0	0	2	2	0	0	2	0	0	2	2	50% (MEDIUM)
[38]	2	0	0	2	2	0	0	2	0	0	2	2	50% (MEDIUM)
[39]	2	0	2	2	2	0	0	2	2	0	2	2	66,70% (MEDIUM)
[40]	2	0	2	2	1	0	0	2	2	0	2	2	62,50% (MEDIUM)
[41]	2	0	1	2	2	0	0	2	0	0	2	2	54,10% (MEDIUM)
[42]	2	0	2	2	1	0	0	2	2	0	2	2	62,50% (MEDIUM)
[43]	2	0	0	1	2	0	0	2	0	0	2	2	45,83% (MEDIUM)
[44]	2	0	1	2	2	0	0	2	0	0	1	2	50% (MEDIUM)

Q1 = clearly stated aims/objective; Q2 = thorough explanation of sample size calculation; Q3 = detailed description of the sampling technique; Q4 = comparison group details; Q5 = comprehensive methodology explanation; Q6 = operator details; Q7 = randomization; Q8 = outcome measurement method; Q9 = outcome assessor details; Q10 = blinding; Q11 = statistical analysis; Q12 = result presentation

Conclusion

In conclusion, green-synthesized AgNPs derived from various plant extracts have significant potential as anticancer agents. Studies show the cytotoxic effects against multiple cancer cell lines, including brain, breast, lung, prostate, cervical, and colon cancers, through mechanisms such as apoptosis induction, oxidative stress generation, mitochondrial dysfunction, and inhibition of cell proliferation. AgNPs have strong selectivity, targeting cancer cells while sparing normal cells, leading to consideration as promising therapy candidates with minimal side effects. The effectiveness is dose-dependent, with higher concentrations leading to greater cytotoxicity. Additionally, AgNPs show antimicrobial, antioxidant, and anti-inflammatory properties, enhancing the therapeutic value. Future studies should focus on clarifying the molecular mechanisms, optimizing synthesis methods, and validating the clinical efficacy for potential applications in nanomedicine-based cancer therapy.

Conflict of Interest

The author`s declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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