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Review Article

GREEN-SYNTHESIZED NANOPARTICLES FOR CANCER THERAPY

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Abstract

Green synthesis of nanoparticles has emerged as a transformative approach in cancer nanomedicine, offering a sustainable, biocompatible, and highly efficient alternative to conventional chemical and physical methods. Utilizing plant extracts, microorganisms, and natural polymers as reducing and stabilizing agents, this eco-friendly synthesis route eliminates toxic byproducts and enhances the biomedical potential of nanoparticles. These biogenic nanoparticles exhibit unique physicochemical properties such as high surface area, stability, and tunable morphology, which contribute to their superior anticancer efficacy. They demonstrate targeted cytotoxicity through mechanisms including reactive oxygen species (ROS) generation, mitochondrial disruption, DNA fragmentation, and induction of apoptosis in cancer cells while sparing normal tissues. Additionally, green-synthesized nanoparticles can be conjugated with chemotherapeutic drugs, antibodies, or phytochemicals to achieve site-specific delivery via enhanced permeability and retention (EPR) effect and ligand-receptor interactions. Their application extends to advanced therapeutic modalities including photothermal therapy, photodynamic therapy, and gene delivery systems, significantly improving treatment outcomes in various cancer models. The integration of diagnostic and therapeutic functions in a single nanoplatform further enables real-time monitoring and personalized treatment strategies. However, despite their promising therapeutic potential, challenges such as variability in biological sources, lack of standardized synthesis protocols, and limited clinical translation remain key obstacles. Future research focusing on mechanistic understanding, large-scale production, and regulatory validation is critical to harness the full potential of green-synthesized nanoparticles. Overall, this review highlights the emerging role of green nanotechnology in oncology, emphasizing its potential to revolutionize cancer treatment through safe, cost-effective, and sustainable innovations.

Keywords: Green synthesis, Nanoparticles, Cancer therapy, Biogenic nanotechnology, Targeted drug delivery

1. Introduction

Cancer remains one of the leading causes of morbidity and mortality worldwide, posing a major challenge to modern healthcare systems despite significant advances in diagnosis and therapy. Conventional cancer treatments—such as chemotherapy, radiotherapy, and surgery—are often limited by systemic toxicity, multidrug resistance, and lack of tumor selectivity[1]. In recent years, nanotechnology has emerged as a transformative

field in cancer management, offering innovative strategies for targeted drug delivery, early diagnosis, and image-guided therapy. Nanoparticles (NPs), owing to their tunable size, high surface area-to-volume ratio, and modifiable surface chemistry, can improve pharmacokinetics, enhance therapeutic index, and minimize off-target effects[2]. However, the traditional physical and chemical methods used to produce nanoparticles involve harsh reducing agents, high energy consumption, and toxic solvents, raising concerns about environmental impact and biocompatibility. This has driven researchers to explore eco-friendly synthesis routes that align with the principles of green chemistry[2].

The concept of green synthesis refers to the fabrication of nanoparticles using biological entities such as plant extracts, bacteria, fungi, algae, and biomolecules as reducing, stabilizing, or capping agents. This approach leverages the natural phytochemicals—such as flavonoids, terpenoids, polyphenols, alkaloids, and proteins—that possess inherent reducing and antioxidant properties capable of converting metal ions into stable nanoparticles under mild conditions[3,4]. Unlike conventional routes that depend on toxic chemicals such as sodium borohydride or hydrazine, green synthesis uses water-based solvents and ambient temperature, thereby minimizing hazardous by-products. It represents a sustainable and scalable approach that integrates nanoscience with principles of biotechnology and environmental chemistry. The biologically synthesized nanoparticles produced by this method often exhibit enhanced stability, improved dispersibility in aqueous media, and greater biocompatibility—key attributes for their biomedical applications[4].

In cancer therapy, green-synthesized nanoparticles offer multiple advantages over their chemically produced counterparts. The biological molecules capping these nanoparticles not only provide colloidal stability but can also impart intrinsic anticancer or antioxidant properties, augmenting therapeutic efficacy. For instance, plant-mediated silver and gold nanoparticles have demonstrated selective cytotoxicity toward cancer cells through mechanisms involving reactive oxygen species (ROS) generation, mitochondrial dysfunction, and apoptosis induction. Moreover, the surface functionalities of these green-synthesized nanoparticles enable conjugation with anticancer drugs, antibodies, or ligands for active tumor targeting. The eco-friendly preparation process ensures minimal residual toxicity, which is particularly important for formulations intended for clinical translation. Collectively, these characteristics make green nanoparticles promising candidates for the next generation of theranostic agents—materials that combine therapeutic and diagnostic functions within a single platform[5].

From a broader perspective, the significance of green nanotechnology extends beyond therapeutic performance. It addresses the sustainability and ethical dimensions of modern nanomedicine by reducing the ecological footprint associated with nanoparticle production. The alignment of green synthesis with the "12 Principles of Green Chemistry" emphasizes atom economy, safer solvents, energy efficiency, and waste reduction values increasingly prioritized by the scientific community and regulatory agencies. Furthermore, green synthesis is often cost-effective and amenable to large-scale production, particularly when plant-based extracts are used as biofactories. This aspect is highly relevant for developing countries, where the burden of cancer is increasing and affordable therapeutic options are urgently needed[6,7].

Despite these advantages, several challenges hinder the widespread application of green-synthesized nanoparticles in cancer therapy. The composition of biological extracts varies with species, season, and extraction methods, leading to batch-to-batch variability in nanoparticle characteristics such as size, shape, and surface charge. Moreover, understanding the precise molecular mechanisms governing nanoparticle formation remains limited, which complicates reproducibility and standardization. Toxicological assessment is another critical issue;

while green synthesis reduces chemical hazards, the long-term biosafety and pharmacokinetic behavior of biogenic nanoparticles must be comprehensively evaluated before clinical use. Addressing these challenges requires interdisciplinary collaboration among chemists, biologists, toxicologists, and pharmaceutical scientists to develop reproducible, standardized, and regulatory-compliant production processes[8,9].

The objective for this review of recent progress in the green synthesis of nanoparticles and their applications in cancer therapy. It explains the various biological sources and mechanistic pathways involved in nanoparticle formation, explores the anticancer activities and underlying cellular mechanisms, and discusses preclinical evidence demonstrating therapeutic efficacy. This review also evaluates safety considerations, functionalization strategies, and formulation aspects that influence clinical translation.

2. Methodology

To build a coherent understanding of how green-synthesized nanoparticles contribute to cancer therapy, the field was mapped by scanning recent reviews and citation networks to identify the most influential papers published during the past decade. This preliminary mapping guided a deeper retrieval of primary research articles for focusing on the period 2015–2025, when green nanotechnology witnessed major scientific growth.

3. Green synthesis: sources, chemistries & mechanisms

Green synthesis of inorganic nanoparticles uses biological materials (plants, microbes, algal biomass or isolated metabolites) to reduce metal ions and stabilize the resulting particles, offering an eco-friendlier alternative to conventional chemical/physical routes. Below I summarise the common biological sources, the chemical roles of biomolecules (polyphenols, flavonoids, proteins, sugars), typical reaction conditions and how they determine nanoparticle size/shape, and a concise comparison with conventional methods — with focused references on plant-mediated synthesis and mechanisms[10-13].

A. Biological Sources: Biological feedstocks for green synthesis are chosen for their richness in reducing and capping molecules:

- **Plants:** leaf, fruit, peel, bark, root and flower extracts are most widely used. Aqueous or hydroalcoholic extracts supply a complex mixture of polyphenols, flavonoids, terpenoids, sugars and proteins that reduce metal salts (Ag^{+}, Au^{3+}, Fe^{3+}, etc.) to zerovalent metal or metal oxide nanoparticles and simultaneously cap them. Leaf extracts are especially common because of easy availability and high phytochemical content[11].
- **Algae:** Macro- and microalgae contain pigments, polysaccharides and polyphenols that reduce and stabilize metal/metal-oxide NPs; algal biomass is attractive for scale because of fast growth[12].
- **Fungi & Bacteria:** Living cells (or cell-free extracts) can produce NPs either intracellularly (reduction inside cells) or extracellularly (secreted enzymes/metabolites mediate reduction), often yielding different morphologies and potential for bioprocess control[14].
- **Microbial metabolites:** Isolated biomolecules (enzymes, peptides, exopolysaccharides) provide more defined chemistries and sometimes better reproducibility than crude extracts.

B. Chemical Role of Biomolecules (how reduction and capping happen): The reducing and stabilizing actions come from specific functional groups in biomolecules:

- **Polyphenols & Flavonoids:** These contain multiple phenolic OH groups and conjugated systems that readily donate electrons to metal ions, reducing $Ag^{+} \rightarrow Ag^{0}$ or $Au^{3+} \rightarrow Au^{0}$. The oxidized polyphenol residues remain adsorbed on particle surfaces and act as capping agents via hydrogen bonding and π interactions, limiting agglomeration. Tannins and gallic-type phenolics are often singled out as especially effective reducers[15].
- **Reducing Sugars (Glucose, Fructose,**

Polysaccharides): Aldehyde and ketone functionalities can reduce metal ions; polysaccharides or oligosaccharides also form a steric barrier on NP surfaces that stabilizes colloids.

- **Proteins & Enzymes:** Amino groups, thiols (—SH in cysteine), and carboxylates coordinate to metal surfaces. Enzymes (e.g., reductases) can catalyse ion reduction; proteins provide strong capping via multiple anchoring points, which can yield stable NPs with distinctive surface coronas [16].
- **Terpenoids, Alkaloids, Organic Acids:** Additional reducing/capping contribution and sometimes shape-directing influences through specific adsorption on crystal facets.

C. Mechanistically, Plant extracts function as multicomponent reaction media: one or more components reduce ions, others adsorb to particle surfaces to limit growth and coalescence, and minor molecules (e.g., organic acids) adjust local pH and ionic strength, all together determining nucleation and growth kinetics.

D. Typical reaction conditions and their effects on size & shape: Three kinetic regimes control final nanoparticle morphology: nucleation rate, growth rate and secondary aggregation/capping. Reaction parameters commonly varied are:

- **pH:** Strongly influences both reduction potential of biomolecules and their ionization state (e.g., phenolic OH deprotonation enhances reducing power). Typically, alkaline conditions accelerate reduction and favour many small particles (fast nucleation), whereas acidic conditions slow nucleation and may yield fewer, larger, or more anisotropic particles. pH also affects capping molecule binding and thus shape control[16-17].
- **Temperature:** Higher temperatures increase reduction kinetics and diffusion, generally producing smaller particles when nucleation is rapid, but can also promote Ostwald ripening (growth of larger particles) if growth dominates. Temperature can change the conformations of capping biomolecules and thus facet-specific adsorption (shape control)[17].
- **Metal salt concentration & extract ratio:** High metal ion concentration with insufficient capping/reducing biomolecules often produces larger, polydisperse NPs or aggregates. Increasing the extract: metal ratio usually increases the availability of reducers and stabilisers, promoting rapid nucleation and smaller, more uniform particles. Careful optimization of extract preparation (solvent, plant part, extraction time) is critical.
- **Reaction Time & Mixing:** longer times may permit growth and aggregation unless stabilizers strongly bind. Vigorous mixing improves homogeneity and reproducibility.

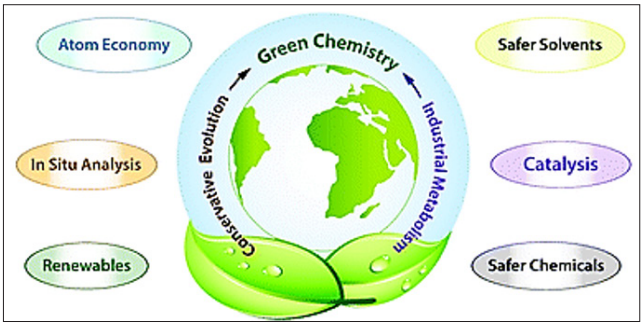

Figure 1: Industrial metabolism in green chemistry

Facet-selective adsorption by certain biomolecules can produce rods, triangles, plates or cubes rather than spheres; however, controlled anisotropic growth remains more reliably achieved with purified shape-directing agents than with crude extracts.

E. Green vs Conventional Methods are Toxicity and Reproducibility

- **Toxicity / Environmental Impact:** Green routes replace hazardous reductants (hydrazine, sodium borohydride) and toxic surfactants with benign, renewable biomolecules, reducing the environmental and occupational hazards of synthesis and often improving biocompatibility of end-products for biomedical use. Life-cycle and energy analyses in recent reviews show lower energy use and reduced chemical waste for many green protocols[17,18].
- **Reproducibility/ Scalability:** This is the main

limitation of many green approaches. Crude plant extracts are complex and variable (species, harvest season, plant part, geographic origin, extraction solvent), which causes batch-to-batch variability in phytochemical composition and hence NP nucleation/growth behaviour. Strategies to improve reproducibility include standardizing extract preparation, characterizing active phytochemical profiles, using purified metabolites, and applying multivariate optimization (DOE) for process parameters. When well-standardized, plant-mediated methods can produce application-grade NPs, but currently conventional chemical methods remain superior for tight size/shape control and industrial reproducibility[17-18].

4. Types of Green-Synthesised Nanoparticles Used in Cancer Therapy

Green nanotechnology has revolutionized biomedical research, particularly in the development of nanoparticles (NPs) for cancer diagnosis and therapy. Unlike conventional chemical synthesis, green synthesis employs biological entities such as plants, algae, fungi, and microbes as reducing and capping agents. This approach minimizes toxic residues and enhances the biocompatibility of the nanoparticles, making them suitable for anticancer applications[1]. This section discusses major types of green-synthesized nanoparticles used in cancer therapy, metallic, metal oxide/magnetic, and bimetallic or hybrid NPs—highlighting their mechanisms, characteristics, and therapeutic potential.

A. Metallic Nanoparticles in Cancer Therapy: Metallic nanoparticles, such as silver, gold, and iron oxide, are emerging as powerful tools in cancer therapy due to their unique physicochemical properties, biocompatibility and tunable surface chemistry. They enable targeted drug delivery, enhance therapeutic efficacy through reactive oxygen species generation, and induce apoptosis selectively in cancer cells while sparing healthy tissues. Additionally, their ability to be functionalized with ligands or antibodies makes them suitable for both therapy and diagnostics (theranostics)[1].

a) Silver Nanoparticles (AgNPs): Green-synthesized silver nanoparticles (AgNPs) are among the most extensively studied nanomaterials for cancer therapy. Plant extracts rich in phenolics and flavonoids (e.g., Azadirachta indica, Camellia sinensis, Curcuma longa) act as both reducing and stabilizing agents. The typical particle sizes range between 10–80 nm, depending on synthesis conditions and extract composition.

Anticancer Mechanism: AgNPs induce cytotoxicity via reactive oxygen species (ROS) generation, DNA fragmentation, and mitochondrial dysfunction in cancer cells. They disrupt cellular redox balance and trigger apoptosis by upregulating pro-apoptotic proteins (Bax, caspase-3) and downregulating anti-apoptotic proteins (Bcl-2). Studies have demonstrated selective cytotoxicity against breast (MCF-7), lung (A549), and cervical (HeLa) cancer cells while sparing normal fibroblasts[2,19-21].

Surface Chemistry: Capping biomolecules such as tannins, terpenoids, and proteins provide functional groups (–OH, –COOH, –NH_2) that improve water dispersibility and enable surface modification for targeted drug delivery or photothermal therapy.

Advantages:

- Low synthesis toxicity
- Enhanced oxidative stress-mediated killing
- Broad-spectrum anticancer activity

b) Gold Nanoparticles (AuNPs): Green-synthesized gold nanoparticles (AuNPs) have emerged as powerful tools for cancer diagnosis, photothermal ablation, and targeted delivery. They are typically synthesized using leaf or fruit extracts (e.g., Terminalia arjuna, Ocimum sanctum, Punica granatum). The particle sizes usually range from 5–50 nm with spherical or hexagonal morphology[1,2].

Anticancer Mechanism: AuNPs exhibit photothermal conversion under near-infrared (NIR) light, causing localized heating and tumor cell apoptosis. They also enhance drug delivery

of chemotherapeutics like doxorubicin by surface conjugation through thiol or amine linkers. Functionalization with biomolecules from the green synthesis process provides stealth and targeting ability, facilitating receptor-mediated uptake by tumor cells[21].

Surface Chemistry: AuNPs capped with polyphenols and proteins offer high stability, strong surface plasmon resonance (SPR) properties, and minimal immunogenicity. Surface modification with folic acid or antibodies enhances selective accumulation in cancer tissues[22].

Advantages:

- Non-toxic, inert core
- Excellent optical properties for imaging and therapy
- Tunable surface functionality

c) Copper Nanoparticles (CuNPs): Copper nanoparticles synthesized using plant or microbial extracts are emerging as cost-effective alternatives to noble metals. The particle size generally ranges from 20–70 nm.

Anticancer Mechanism: CuNPs exert cytotoxicity via ROS-mediated DNA damage, lipid peroxidation, and apoptosis. They also catalyze Fenton-like reactions generating hydroxyl radicals that destroy tumor cells. Some green-synthesized CuNPs exhibit dual functionality—anticancer and antibacterial activity—useful for post-surgical infection control[22].

Surface Chemistry: Phytochemicals such as flavonoids and terpenoids act as capping agents, forming a thin organic shell that improves stability and modulates cellular uptake.

Advantages:

- Inexpensive precursor metals
- Potent redox-active mechanism
- Potential synergism with conventional chemotherapy

d) Platinum Nanoparticles (PtNPs): Green-synthesized platinum nanoparticles display strong cytotoxic effects and act as next-generation anticancer agents. Typical sizes are 2–30 nm. They are synthesized from extracts of Coriandrum sativum, Piper betle, or microbial enzymes.

Anticancer Mechanism: PtNPs induce apoptosis by increasing ROS levels and causing DNA interstrand cross-linking, like cisplatin but with lower systemic toxicity. Their ability to overcome multidrug resistance (MDR) is being actively investigated[2,19].

Surface Chemistry: Capped with biomolecules rich in carbonyl, amine, and hydroxyl groups, PtNPs are stable under physiological conditions. The surface can be conjugated with drugs, peptides, or targeting ligands for enhanced tumor specificity[2 20].

Advantages:

- High catalytic activity
- Lower nephrotoxicity than cisplatin
- Potential in combined chemo-photothermal therapy

B. Metal Oxide and Magnetic Nanoparticles: Metal oxide and magnetic nanoparticles, such as ZnO, TiO_2, and Fe_3O_4, exhibit anticancer activity through ROS generation and controlled drug release mechanisms. Their magnetic properties allow targeted delivery and hyperthermia-based cancer therapy with minimal damage to surrounding healthy tissues.

a) Iron Oxide Nanoparticles (Fe_3O_4 NPs): Green-synthesized magnetite nanoparticles (Fe_3O_4) are valuable in magnetic hyperthermia, MRI imaging, and targeted drug delivery. They are produced using plant extracts like Moringa oleifera or Camellia sinensis, with particle sizes around 10–30 nm.

Therapeutic Mechanism: Under an alternating magnetic field, Fe_3O_4 NPs generate localized heat (43–45°C) that selectively destroys tumor cells. They can also serve as carriers for anticancer drugs guided magnetically to tumor sites. Furthermore, Fe_3O_4 exhibits radiosensitizing properties, enhancing radiation-induced DNA damage[2,22].

Surface Chemistry: The phytochemical capping

provides hydrophilic surfaces, minimizes aggregation, and allows drug or ligand conjugation.

Advantages:

- Biocompatible and biodegradable
- Dual diagnostic and therapeutic (theranostic) use
- Controllable by external magnetic field

b) Titanium Dioxide Nanoparticles (TiO_2 NPs): Green-synthesized TiO_2 NPs are widely studied for photodynamic and radiosensitization therapy. Plant-mediated synthesis (using Aloe vera, Eucalyptus globulus, etc.) produces anatase-phase nanoparticles(~20–50 nm)[1,2,22].

Mechanism: Under UV or visible light, TiO_2 generates electron-hole pairs, producing ROS (•OH, $O_2•^-$) that induce apoptosis in cancer cells. TiO_2 NPs can also enhance radiation therapy efficacy by amplifying oxidative damage.

Advantages:

- Photocatalytic ROS generation
- Stability and low cost
- Effective as imaging and drug delivery adjuncts

Limitation: Limited penetration of UV/visible light into deep tissues; ongoing work explores doping or hybridization for improved photothermal properties.

C. Bimetallic, Trimetallic, and Hybrid Nanoparticles: Bimetallic, trimetallic, and hybrid nanoparticles combine multiple metals or materials to enhance stability, surface functionality, and synergistic anticancer effects. Their multifunctional nature allows improved drug loading, targeted delivery, and superior therapeutic efficiency compared to single-metal nanoparticles[19,22].

a) Bimetallic Nanoparticless: Bimetallic NPs (e.g., Ag–Au, Au–Pt, Ag–Cu) combine the unique physicochemical properties of two metals, leading to enhanced catalytic, optical, and therapeutic efficiency. Green synthesis using plant extracts allows simultaneous reduction of both metal ions, leading to alloy or core–shell structures.

Mechanism and advantages:

- Synergistic cytotoxicity: ROS generation and enhanced electron transfer result in stronger anticancer effects.
- Tunable optical properties: Useful for photothermal and imaging-guided therapy.
- Improved stability: Dual capping and alloy formation enhance resistance to oxidation.

Examples include Ag–Au nanoparticles synthesized using Mangifera indica leaf extract, which showed superior cytotoxicity against MCF-7 and HeLa cells compared to monometallic analogs[1,2,21].

b) Trimetallic and Hybrid Nanoparticles: Trimetallic (e.g., Au–Ag–Pt) and hybrid (metal–polymer or metal–lipid) nanoparticles are new frontiers in green nanomedicine. The rationale is to combine multiple functionalities—magnetic, optical, and catalytic—within one nanosystem.

Mechanistic Benefits:

- Multimodal therapy: Enables chemo-, photo-, and magnetothermal synergism.
- Enhanced drug loading: Hybrid NPs with biopolymers (chitosan, alginate) provide improved drug encapsulation and release control.
- Reduced toxicity: Phytochemical capping enhances biodegradability and minimizes immune response [22].

Recent Results: Green-synthesized Au–Ag–Fe_3O_4 nanoparticles demonstrated triple-mode therapeutic efficiency (hyperthermia, photothermal, and chemotherapy synergy) in breast and liver cancer models.

5. Anticancer mechanisms of green NPs

Green-synthesized nanoparticles (green NPs), derived from plant extracts, microorganisms, and natural biomolecules, offer a multifaceted anticancer approach due to their biocompatibility, eco-friendly synthesis, and inherent therapeutic potential. One of the primary anticancer mechanisms is direct

cytotoxicity, where green NPs generate elevated levels of reactive oxygen species (ROS) within cancer cells. These ROS overwhelm the cellular antioxidant defense systems, resulting in oxidative stress, mitochondrial dysfunction, lipid peroxidation, and irreversible DNA damage. This oxidative damage disrupts membrane integrity through protein oxidation and pore formation, ultimately leading to cell lysis and death[23].

1. The selective toxicity of green NPs toward cancer cells is attributed to the higher metabolic activity and weaker antioxidant defenses in malignant cells compared to normal cells, making cancer cells particularly susceptible to ROS-mediated damage. Moreover, green NPs induce apoptosis and necrosis via intrinsic and extrinsic molecular pathways. In the intrinsic pathway, ROS triggers mitochondrial membrane depolarization, resulting in the release of cytochrome c into the cytosol. This activates caspase-9 followed by caspase-3, leading to programmed cell death characterized by DNA fragmentation, chromatin condensation, and membrane blebbing[23,24].
2. In the extrinsic pathway, green NPs activate death receptors such as Fas and TRAIL on the cell surface, triggering caspase-8 activation, which further amplifies the apoptotic cascade. Additionally, these nanoparticles modulate tumor suppressor proteins like p53 and downregulate anti-apoptotic proteins such as Bcl-2, tipping the balance toward cell death. In cases of excessive ROS production or ATP depletion, necrosis may occur, resulting in rapid cell swelling and plasma membrane rupture. Nature-inspired NPs also demonstrate efficacy in photothermal therapy (PTT) and photodynamic therapy (PDT)[24].
3. In PTT, green NPs absorb near-infrared (NIR) light and convert it into localized heat, causing thermal ablation of tumor tissues without harming surrounding normal tissues. In PDT, green NPs act as photosensitizers; upon light activation, they generate singlet oxygen, a highly reactive ROS, leading to oxidative destruction of cancer cells. These methods provide spatial and temporal control over therapy, minimizing systemic toxicity. Furthermore, green NPs play a crucial role in drug delivery and targeted therapy, enhancing therapeutic efficacy while reducing side effects. Due to their nanoscale size (typically 10–200 nm), green NPs passively accumulate in tumor tissues via the enhanced permeability and retention (EPR) effect, where leaky tumor vasculature allows nanoparticles to infiltrate and remain localized in the tumor microenvironment. In addition to passive targeting, green NPs can be functionalized with ligands such as antibodies, peptides, folic acid, or aptamers, enabling active targeting by binding to overexpressed receptors on cancer cells[25].

- This ligand conjugation facilitates receptor-mediated endocytosis, resulting in higher intracellular drug concentrations precisely at the tumor site. Moreover, these nanoparticles provide controlled and sustained release of chemotherapeutic agents, improving bioavailability and overcoming multidrug resistance by enabling drug accumulation in cancer cells. Green NPs also enhance cellular uptake through endosomal pathways and disrupt efflux pumps, thus bypassing one of the major challenges in conventional cancer therapy. In addition, their natural phytochemical capping agents often possess intrinsic anticancer properties that synergize with the loaded drug, producing a combined therapeutic effect[24,25].

Overall, green nanoparticles represent a highly promising platform in oncology due to their ability to induce oxidative stress, trigger programmed cell death pathways, facilitate advanced phototherapies, and deliver drugs with precision targeting, thereby offering an effective and sustainable alternative for cancer treatment aligned with modern precision medicine and nature-inspired nanotechnology.

6. In Vitro and in Vivo Evidences

Green synthesized nanoparticles (NPs) have been extensively evaluated using in vitro cancer cell line

models to establish their anticancer efficacy, cellular uptake mechanisms, and potential therapeutic advantages.

1. The most investigated cell lines include breast cancer (MCF-7, MDA-MB-231 for triple-negative breast cancer or TNBC), lung cancer (A549), colon cancer (HT-29, HCT-116), prostate cancer (PC-3, DU145), liver cancer (HepG2), and cervical cancer (HeLa). These cell lines represent different genetic backgrounds and metastatic potential, enabling comprehensive evaluation of nanoparticle activity. In vitro experiments often rely on assays like MTT or MTS to assess cell viability and metabolic activity through mitochondrial dehydrogenase activity. Apoptosis assays, including Annexin V/PI staining and caspase-3/9 activation studies, provide insight into programmed cell death induced by green NPs. ROS generation assays using DCFH-DA fluorescent probes demonstrate oxidative stress induction as a key mechanism of cytotoxicity[16,18,19]. Additionally, cell migration and invasion assays, such as wound healing and Transwell assays, are used to assess the anti-metastatic properties of nanoparticles. Studies consistently report a dose-dependent inhibition of proliferation, increased ROS generation, mitochondrial depolarization, and DNA fragmentation[6,20,24]. For example, in TNBC cell lines like MDA-MB-231, green gold nanoparticles synthesized using plant extracts have demonstrated IC50 values as low as 10–20 µg/mL, significantly inhibiting migration and inducing apoptosis through caspase activation. These effects suggest that the combination of phytochemicals and metallic or polymeric nanostructures exerts synergistic anticancer effects, enhancing cellular uptake and cytotoxic efficiency compared to conventional drugs alone[5,6,20,24].
2. In in vivo studies, animal models provide essential insights into the biodistribution, pharmacokinetics, tumor regression capacity, and systemic toxicity of green nanoparticles. The most widely used models include xenograft models, where human cancer cells are implanted subcutaneously into immunocompromised mice, and orthotopic models, where cancer cells are implanted into the organ of origin (e.g., mammary fat pad for breast cancer, liver implantation for hepatic cancer). Orthotopic models more accurately mimic tumor microenvironments and metastatic patterns compared to xenografts. Green nanoparticles exhibit preferential accumulation in tumor tissues due to the enhanced permeability and retention (EPR) effect, slow clearance rates, and reduced uptake by healthy tissues[20,24].
3. Pharmacokinetic studies reveal that nanoparticles coated with natural biomolecules improve circulation half-life, reduce opsonization by macrophages, and facilitate cellular internalization via receptor-mediated endocytosis. Biodistribution studies using fluorescent tagging or radiolabeling techniques show significant accumulation in tumor tissues, liver, and spleen, indicating involvement of both passive targeting and reticuloendothelial system (RES) uptake. Representative studies in mouse models demonstrate tumor volume reduction ranging from 40% to 80% after treatment with green-synthesized silver, gold, or zinc oxide nanoparticles, sometimes outperforming standard chemotherapy agents[20,21,24].
4. In certain orthotopic breast cancer models, treatment with green silver nanoparticles led to complete suppression of lung metastasis and significant improvement in survival rates without major toxicity to kidneys or liver. These results highlight not only the anticancer potential but also the relative biosafety of green nanoparticles when compared with chemically synthesized counterparts[23].
5. However, despite these promising results, a major scientific concern is the reproducibility and standardization of green NP synthesis and

testing models. Differences in plant extract composition, nanoparticle size distribution, and surface chemistry often lead to variability in outcomes across laboratories. Many studies lack standardized reporting of nanoparticle characterization parameters such as zeta potential, polydispersity index, and crystallinity, making it difficult to correlate physicochemical properties with biological activity[2,3,24,25].

Additionally, inconsistent dosages, differences in animal species or strain, and variability in tumor implantation techniques lead to divergent therapeutic outcomes. Studies often show significant effect sizes in vitro with IC50 values below 50 µg/mL, but these results are not always reproducible in in vivo models due to differences in nanoparticle stability, protein corona formation, and immune system interactions. Furthermore, there is a lack of long-term toxicity studies and pharmacokinetic modeling to support clinical translation. Another limitation is that many studies use small sample sizes and do not perform proper statistical validation or comparative analysis with standard chemotherapeutic drugs[6,24,25].

7. Integrated Clinical Translation Outlook for Green Nanoparticles: Safety, Functionalization, Challenges and Future Roadmap

Green-synthesized nanoparticles (NPs) are emerging as promising agents in cancer therapy due to their eco-friendly production and inherent bioactivity derived from natural capping agents. However, their successful clinical translation demands a comprehensive understanding of safety, toxicity, formulation, and regulatory challenges.

1. Evaluating safety and biocompatibility is crucial, as nanoparticles can display distinct acute and chronic toxicity profiles. Short-term exposure may show minimal toxicity, but long-term studies reveal the potential for organ accumulation in the liver, spleen, and kidneys, as these are primary sites for nanoparticle clearance and uptake by the mononuclear phagocyte system. Issues of genotoxicity, oxidative stress, and immune activation have been reported, though green capping agents (such as flavonoids and polyphenols from plant extracts) often mitigate toxicity through antioxidant and anti-inflammatory effects. At the same time, these natural biomolecules introduce complexity due to variability in composition, which may influence pharmacokinetics and biological interactions[3,7,12]. Regulatory bodies emphasize the need for detailed toxicological profiling, including immunogenicity, genotoxicity, biodistribution, and degradation studies, to establish safety prior to human use.
2. To improve therapeutic performance and reduce systemic toxicity, green NPs are engineered with advanced functionalization strategies. Surface modification with polymers like PEG enhances biocompatibility and circulation time while reducing immune recognition. Conjugation with antibodies, peptides, or aptamers enables active targeting to tumor-specific receptors, significantly improving drug delivery efficiency[11,12,14]. Controlled release formulations are designed using stimuli-responsive mechanisms, where nanoparticles release their payload in response to pH changes in the tumor microenvironment, enzymatic activity, magnetic fields, or light exposure. These smart formulations maximize therapeutic efficacy while minimizing adverse effects. However, large-scale manufacturing under Good Manufacturing Practices (GMP) presents challenges, particularly for green nanoparticles due to biological variability in plant extracts or microbial sources. Achieving uniform particle size, reproducible surface chemistry, and long-term stability remains difficult, making scaling from laboratory to industrial production a critical translational hurdle[22,25].
3. Despite rapid advances, key challenges limit clinical progression. The biggest barrier is batch-to-batch variability in green synthesis, affecting reproducibility of biological activity. Lack of

standardized characterization techniques and incomplete understanding of the interaction between natural capping agents and biological systems impede regulatory approval. Long-term toxicity data and controlled clinical trials are scarce, and there is limited insight into chronic exposure risks. Regulatory frameworks for biologically synthesized nanoparticles are still evolving, requiring extensive preclinical data on pharmacokinetics, immune response, degradation pathways, and environmental safety. Moreover, stability and storage conditions for green NPs are not well-established, impacting their shelf-life and commercial viability[17,21,25].

4. Looking toward the future, a strategic roadmap is essential to accelerate the clinical translation of green nanoparticles. First, standardized synthesis and characterization protocols must be established globally to ensure reproducibility. Comparative studies with conventional nanoparticles should be conducted to clearly demonstrate the advantages of green formulations in terms of safety and efficacy[17,24]. Incorporation of multi-omics toxicity screening across genomics, proteomics, and metabolomics will enhance mechanistic understanding of biological interactions. Collaborative industrial partnerships will be necessary for scale-up, process validation, and GMP manufacturing. Furthermore, early phase clinical trials should be designed to evaluate not just therapeutic efficacy but also long-term safety, biodistribution, and immune modulation. With integrated regulatory frameworks, interdisciplinary collaboration, and technological innovation, green nanoparticles hold strong potential to transform cancer nanomedicine and progress from laboratory research to real-world clinical applications[25].

8. Conclusion

Green synthesis of nanoparticles represents a pivotal advancement in the future of cancer nanomedicine by integrating sustainability, biocompatibility, and therapeutic efficacy into a single technological platform.

- Unlike conventional nanoparticle fabrication that often relies on toxic chemicals and energy-intensive processes, green synthesis harnesses phytochemicals, microbial enzymes, and natural biomolecules as reducing and capping agents, resulting in environmentally benign nanoparticles with enhanced clinical potential. These biogenic nanoparticles not only demonstrate reduced toxicity and improved physiological stability, but also exhibit intrinsic anticancer activity through mechanisms such as reactive oxygen species generation, mitochondrial dysfunction, DNA fragmentation, apoptosis induction, and inhibition of metastasis. Their ability to be functionalized with targeting ligands or chemotherapeutic agents enables precise delivery to cancer cells via passive and active targeting mechanisms, thereby minimizing systemic side effects and overcoming the limitations of traditional therapies such as multidrug resistance and lack of selectivity.
- Furthermore, the incorporation of green-synthesized nanoparticles into photothermal therapy, photodynamic therapy, and magnetically guided drug delivery has demonstrated significant tumor regression in both in vitro and in vivo models, validating their potential as multifunctional theranostic agents. The eco-friendly nature of green synthesis aligns with global sustainability goals and offers a cost-effective and scalable approach suitable for both developed and resource-limited healthcare systems. However, despite these promising advantages, challenges such as variability in biological extracts, lack of mechanistic clarity, and difficulties in achieving large-scale reproducibility must be addressed through standardized extraction protocols, advanced characterization techniques, and interdisciplinary collaboration. Overall, green-synthesized nanoparticles embody the

convergence of nanotechnology, biotechnology, and environmental science, offering a transformative pathway toward safer, more targeted, and more effective cancer therapies. Their continued development holds immense promise for revolutionizing precision oncology and establishing a new paradigm in sustainable cancer treatment.

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