LINK MEDICAL JOURNAL
of Health and Community Research | LMJHCR
Volume 4, Issue 1 | June 2026 | ISSN 3007-3448

Indexed in DOAJ | CC BY 4.0
DOI: 10.61919/ehqtjy35

Original Article

Plant-Based Gold Nanoparticles for Targeted Drug Delivery in Breast Cancer: Progress and Prospects in Pakistan

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"Cite this Article" | **Received**: 13 March 2026; **Accepted**: 14 June 2026; **Published**: 26 June 2026.

ABSTRACT

Background: Breast cancer remains a major cause of morbidity and mortality among women, particularly in low- and middle-income countries where delayed diagnosis, limited access to targeted therapies, and treatment-related toxicity continue to compromise outcomes. Plant-mediated gold nanoparticles have emerged as a promising area of green nanomedicine because they combine the physicochemical advantages of gold nanoparticles with the reducing, stabilizing, and bioactive properties of plant-derived phytochemicals. Objective: This narrative review aimed to critically synthesize the progress, methodological limitations, and translational prospects of plant-based gold nanoparticles for targeted drug delivery in breast cancer, with emphasis on evidence relevant to Pakistan. Methods: A structured narrative synthesis was conducted using literature related to gold nanoparticles, green synthesis, medicinal plant extracts, breast cancer models, targeted drug delivery, cytotoxicity, apoptosis, biocompatibility, and nanomedicine translation. Evidence was organized thematically according to synthesis methods, plant sources, nanoparticle characterization, anticancer mechanisms, drug-delivery potential, biosafety, methodological challenges, and translational readiness. Because of heterogeneity in plant extracts, nanoparticle preparation, experimental models, assays, and outcome reporting, pooled quantitative analysis was not performed. Results: The strongest evidence was concentrated in laboratory-scale green synthesis, physicochemical characterization, and in vitro cytotoxicity against breast cancer cell lines such as MCF-7 and MDA-MB-231. Plant-mediated gold nanoparticles were associated with enhanced cellular uptake, reactive oxygen species generation, mitochondrial dysfunction, apoptosis-related signaling, DNA fragmentation, and preliminary drug-delivery potential, including doxorubicin conjugation and sustained release. However, evidence for in vivo efficacy, pharmacokinetics, biodistribution, long-term toxicity, regulatory readiness, and clinical application remained limited. Conclusion: Plant-based gold nanoparticles represent a promising but preclinical platform for targeted breast cancer drug delivery. Their future translational value in Pakistan depends on standardized synthesis, reproducible characterization, mechanistic validation, long-term biosafety assessment, and rigorous preclinical-to-clinical development. Keywords: Breast Cancer; Gold Nanoparticles; Green Synthesis; Nanomedicine; Plant Extracts; Targeted Drug Delivery; Pakistan; Biocompatibility.

EDITORIAL INFORMATION

Author Contributions: Concept: MAS; Design: MFA; Data Collection: FBB, AS; Analysis: ZHS, MA; Drafting: AM.
Ethical Approval: Universitas Prima Indonesia
Informed Consent: Written informed consent was obtained from all participants
Conflict of Interest: The authors declare no conflict of interest; **Funding**: No external funding; **Data Availability**: Available from the corresponding author on reasonable request; **Acknowledgments**: N/A.

INTRODUCTION

Breast cancer remains the most frequently diagnosed malignancy among women and continues to impose a substantial clinical, social, and economic burden worldwide. Its impact is particularly pronounced in

low- and middle-income countries, where delayed diagnosis, limited screening coverage, financial barriers, and unequal access to advanced oncological care contribute to poorer outcomes and higher treatment-related vulnerability. In Pakistan, breast cancer represents a major public health concern, with many patients presenting at relatively advanced stages because of inadequate awareness, social stigma, insufficient screening infrastructure, and restricted access to specialized cancer services. These challenges intensify the need for therapeutic strategies that are not only biologically effective but also safer, more affordable, and adaptable to resource-constrained healthcare settings (1).

Conventional chemotherapy remains an important component of breast cancer management, but its clinical utility is limited by nonspecific biodistribution, systemic toxicity, poor tumor selectivity, multidrug resistance, and treatment-related complications that compromise adherence and quality of life. The need to improve therapeutic precision has accelerated interest in nanomedicine-based drug delivery systems capable of enhancing tumor localization, improving intracellular uptake, and reducing collateral damage to healthy tissues. Among the nanomaterials investigated for oncological applications, gold nanoparticles have received considerable attention because of their tunable size and morphology, high surface-area-to-volume ratio, surface plasmon resonance, chemical stability, biocompatibility, and capacity for surface functionalization. These properties make them suitable platforms for targeted drug delivery, molecular imaging, biosensing, photothermal therapy, and controlled release of anticancer agents (2).

In breast cancer therapy, gold nanoparticles offer several theoretical and experimental advantages. Their nanoscale dimensions may facilitate preferential accumulation within tumor tissue through passive targeting mechanisms, while surface modification with drugs, ligands, antibodies, peptides, or phytochemical capping agents may support active targeting of malignant cells. Gold nanoparticle-based systems have also been explored for improving the delivery of chemotherapeutic agents with poor solubility or narrow therapeutic indices. By increasing local drug concentration within malignant tissue and reducing exposure to normal cells, these systems may help address persistent limitations associated with conventional chemotherapy, including dose-limiting toxicity and treatment resistance (3).

Despite these advantages, conventional chemical and physical methods of gold nanoparticle synthesis often require hazardous reducing agents, stabilizing chemicals, high energy input, and complex processing conditions. These limitations have encouraged the development of green synthesis approaches using biological materials such as plant extracts, microorganisms, and biomolecules. Plant-mediated synthesis has emerged as a particularly attractive strategy because plant extracts contain phytochemicals, including flavonoids, phenolics, terpenoids, alkaloids, proteins, and sugars, that can reduce gold ions and stabilize the resulting nanoparticles. This approach is comparatively simple, cost-effective, environmentally sustainable, and potentially more biocompatible than many chemically mediated synthesis methods (4).

The relevance of plant-mediated gold nanoparticles is especially important in Pakistan because of the country's botanical diversity, traditional medicinal plant use, and growing academic interest in nanotechnology, biotechnology, pharmacy, and cancer research. Indigenous and locally available medicinal plants provide a rich source of bioactive compounds that may influence nanoparticle size, morphology, surface chemistry, stability, and biological activity. Plant extracts such as Moringa oleifera, Azadirachta indica, Aloe vera, Camellia sinensis, and other phytochemical-rich sources have been investigated for nanoparticle synthesis and anticancer applications. Their integration into gold nanoparticle platforms provides a scientific bridge between traditional phytomedicine and modern targeted drug delivery research (5).

Current experimental evidence suggests that plant-mediated gold nanoparticles may exert anticancer effects through multiple mechanisms, including enhanced cellular uptake, reactive oxygen species-mediated apoptosis, mitochondrial dysfunction, DNA fragmentation, caspase activation, and improved delivery of chemotherapeutic agents. Some studies have reported selective cytotoxicity against breast cancer cell lines with comparatively lower toxicity toward normal cells, while others have explored drug loading, controlled release, and nanoparticle-assisted enhancement of chemotherapeutic efficacy. However, most available evidence remains preclinical, with a predominance of in vitro studies and limited

in vivo validation. As a result, the therapeutic promise of these systems must be interpreted within the context of important methodological and translational limitations (6).

A major challenge in this field is the heterogeneity of green synthesis methods. Differences in plant species, extraction solvent, phytochemical composition, reaction temperature, pH, gold precursor concentration, incubation time, purification method, and storage conditions can substantially alter nanoparticle characteristics and biological performance. Similarly, variation in characterization techniques, cytotoxicity assays, cell lines, exposure durations, and outcome measures limits comparability across studies. Without standardized synthesis and reporting practices, reproducibility remains difficult, and translation from laboratory-scale experiments to clinically acceptable formulations remains uncertain (7).

Another important limitation is the gap between experimental promise and clinical readiness. Although plant-mediated gold nanoparticles have demonstrated potential in breast cancer models, evidence regarding pharmacokinetics, biodistribution, immune interaction, long-term toxicity, metabolism, elimination, and organ-specific accumulation remains insufficient. Clinical application also requires scalable manufacturing, quality-control standards, regulatory pathways, batch-to-batch reproducibility, and interdisciplinary collaboration among nanotechnologists, pharmacologists, oncologists, toxicologists, and industry partners. These requirements are particularly relevant in Pakistan, where research infrastructure and translational pathways for nanomedicine are still developing (8).

Existing reviews have discussed nanotechnology, gold nanoparticles, or green synthesis in broad biomedical contexts, but limited attention has been given to the specific intersection of plant-mediated gold nanoparticles, breast cancer drug delivery, and Pakistan's translational research environment. A focused synthesis is needed to clarify the current state of evidence, identify methodological weaknesses, distinguish experimental findings from clinical implications, and outline practical directions for future research. This narrative review therefore aims to critically synthesize the progress, limitations, and translational prospects of plant-based gold nanoparticles for targeted drug delivery in breast cancer, with particular emphasis on evidence relevant to Pakistan's biomedical research and healthcare context (9).

MATERIAL AND METHODS

This article was designed as a critical narrative review to examine the development, biological relevance, methodological limitations, and translational prospects of plant-mediated gold nanoparticles for targeted drug delivery in breast cancer, with emphasis on evidence relevant to Pakistan. A narrative review approach was selected because the available literature is heterogeneous in design, experimental model, plant source, nanoparticle synthesis method, characterization technique, and biological endpoint. The purpose was not to generate pooled quantitative estimates, but to provide a structured conceptual synthesis of experimental findings, methodological patterns, safety concerns, and future translational priorities.

The scope of the review was defined around four linked concepts: breast cancer therapeutics, plant-mediated or green synthesis of gold nanoparticles, targeted drug delivery or anticancer activity, and relevance to Pakistan. Pakistani relevance was defined as studies conducted in Pakistan, studies using medicinal plants commonly available or traditionally used in Pakistan, studies authored by Pakistan-based research groups, or studies addressing translational barriers applicable to Pakistan's biomedical and oncology research environment. The review focused on gold nanoparticles synthesized using plant extracts or plant-derived bioactive compounds and their application in breast cancer-related experimental models, drug delivery systems, cytotoxicity assessment, apoptotic mechanisms, biocompatibility evaluation, and translational development.

A structured literature search was conducted across PubMed/MEDLINE, Scopus, Web of Science, Google Scholar, ScienceDirect, SpringerLink, and relevant regional or institutional research sources. Searches were performed using combinations of terms related to the nanoparticle material, synthesis method, disease model, therapeutic application, and geographic context. Core search terms included "gold nanoparticles," "AuNPs," "green synthesis," "plant-mediated synthesis," "biosynthesized nanoparticles," "phytofabricated nanoparticles," "medicinal plants," "breast cancer," "MCF-7," "MDA-MB-231," "targeted

drug delivery," "doxorubicin delivery," "cytotoxicity," "apoptosis," "nanomedicine," "Pakistan," "Moringa oleifera," "Azadirachta indica," "Aloe vera," and "Camellia sinensis." Boolean combinations were used to broaden and refine the search, including "gold nanoparticles AND breast cancer," "green synthesis AND gold nanoparticles AND breast cancer," "plant-mediated gold nanoparticles AND drug delivery," and "Pakistan AND nanomedicine AND breast cancer."

Studies and review articles were considered eligible when they addressed plant-mediated synthesis of gold nanoparticles, physicochemical characterization of biosynthesized gold nanoparticles, breast cancer-related cytotoxicity or mechanistic testing, nanoparticle-assisted drug delivery, biosafety evaluation, or translational challenges in green nanomedicine. Experimental in vitro studies, preclinical studies, mechanistic studies, drug-delivery investigations, and relevant narrative or systematic reviews were considered where they contributed directly to the conceptual framework of the review. Articles were excluded when they focused exclusively on non-gold nanoparticles, non-plant-based synthesis, unrelated cancer types without relevance to breast cancer, purely chemical synthesis without biological or translational comparison, or nanotechnology applications unrelated to drug delivery, anticancer activity, or biosafety.

The retrieved literature was screened for relevance by title, abstract, and full text. Priority was given to studies that reported plant source, synthesis method, nanoparticle characterization, breast cancer model, biological assay, drug-delivery application, cytotoxic or apoptotic outcome, and safety-related findings. Particular attention was paid to whether studies reported key physicochemical characteristics such as nanoparticle size, morphology, surface charge, stability, functional groups, crystallinity, and drug-loading or release behavior. Evidence was then organized thematically rather than statistically because the included literature varied substantially in design, assay conditions, nanoparticle concentration, exposure duration, plant extract preparation, and outcome reporting.

The synthesis followed a conceptual and thematic framework. First, studies were examined according to the emergence of green nanotechnology for breast cancer applications in Pakistan. Second, plant sources and their influence on nanoparticle characteristics were evaluated, including the role of phytochemical composition in reduction, stabilization, morphology, and biological activity. Third, evidence related to targeted drug delivery was assessed, including passive tumor accumulation, surface functionalization, drug loading, controlled release, cellular internalization, and enhancement of chemotherapeutic efficacy. Fourth, anticancer mechanisms were synthesized with attention to cytotoxicity, oxidative stress, apoptosis, mitochondrial injury, DNA damage, and inhibition of cellular proliferation. Fifth, biosafety and biocompatibility evidence was reviewed, including selective toxicity, normal-cell response, concentration-dependent effects, and gaps in in vivo safety evaluation. Finally, methodological limitations, standardization issues, regulatory requirements, scalability concerns, and future translational pathways were critically interpreted within the Pakistani research and healthcare context.

Because this review was narrative in design, formal meta-analysis and pooled effect estimation were not performed. Quantitative synthesis was not appropriate because available studies differed substantially in plant extract composition, nanoparticle preparation, experimental concentration, exposure duration, cell line, assay method, and reporting format. Instead, the review emphasized direction of evidence, recurring mechanistic patterns, methodological consistency, strength of experimental support, and translational readiness. The interpretation distinguished between laboratory-based findings, preclinical potential, and requirements for clinical application, with particular emphasis on the need for reproducible synthesis protocols, standardized characterization, long-term toxicological assessment, pharmacokinetic studies, and phase-based clinical evaluation before therapeutic implementation.

Results and Synthesis

The reviewed literature indicates that plant-mediated gold nanoparticles have emerged as a promising experimental platform for breast cancer drug delivery, particularly within the context of green nanotechnology and resource-conscious biomedical innovation in Pakistan. Across the included evidence, the dominant research focus was laboratory-scale synthesis of gold nanoparticles using

medicinal plant extracts, followed by physicochemical characterization and assessment of anticancer activity in breast cancer cell models. The strongest evidence was concentrated in nanoparticle synthesis, characterization, in vitro cytotoxicity, apoptotic response, and preliminary drug-delivery potential, whereas weaker evidence was observed for in vivo efficacy, pharmacokinetic behavior, long-term biosafety, regulatory readiness, and clinical translation. The synthesis was therefore organized around plant sources, nanoparticle characteristics, anticancer mechanisms, drug-delivery potential, biosafety, methodological limitations, and translational prospects.

Table 1. Summary of Evidence Domains in Plant-Mediated Gold Nanoparticles for Breast Cancer Applications

Evidence Domain	Main Focus of Available Literature	Commonly Reported Elements	Overall Evidence Direction	Main Limitation
Green synthesis	Use of plant extracts as reducing and stabilizing agents for gold nanoparticle synthesis	Medicinal plant extract, gold precursor, visual color change, UV-visible confirmation	Supports feasibility of eco-friendly synthesis	Variation in extraction and reaction conditions limits reproducibility
Nanoparticle characterization	Confirmation of nanoparticle formation, morphology, size, surface chemistry, and stability	UV-visible spectroscopy, TEM, SEM, FTIR, zeta potential analysis	Supports formation of stable nanoscale particles	Characterization depth varies across studies
Plant-source influence	Effect of phytochemical profile on nanoparticle size, shape, stability, and activity	Moringa oleifera, Azadirachta indica, Aloe vera, Camellia sinensis, other medicinal plants	Plant phytochemicals appear to influence biological behavior	Extract composition is rarely standardized
Breast cancer cytotoxicity	Antiproliferative effects against breast cancer cell lines	MCF-7, MDA-MB-231, cell viability assays, dose-dependent response	Indicates selective anticancer potential in vitro	Limited representation of breast cancer molecular heterogeneity
Apoptotic and mechanistic effects	Cellular pathways involved in anticancer activity	ROS generation, mitochondrial dysfunction, chromatin condensation, DNA fragmentation, caspase activation	Suggests apoptosis-mediated anticancer action	Mechanistic assays are not uniformly performed
Drug-delivery potential	Use of gold nanoparticles as carriers for chemotherapeutic agents	Doxorubicin conjugation, drug loading, sustained release, enhanced intracellular uptake	Supports potential for improved therapeutic delivery	Limited comparative and in vivo drug-delivery data
Biocompatibility and safety	Toxicity toward malignant versus normal cells	Selective cytotoxicity, concentration-dependent toxicity, normal-cell response	Suggests improved compatibility at controlled concentrations	Long-term systemic toxicity remains insufficiently evaluated
Translational readiness	Progress toward clinical or scalable application	Standardization, regulatory requirements, scalability, interdisciplinary development	Highlights national research opportunity	Clinical trials and regulatory pathways are absent

The dominant pattern across the literature was the use of plant extracts as both reducing and capping agents during gold nanoparticle synthesis. Plant-derived phytochemicals, including phenolics, flavonoids, alkaloids, terpenoids, proteins, and other reducing biomolecules, were repeatedly described as contributors to nanoparticle formation and stabilization. This dual function is central to the appeal of green synthesis because it reduces reliance on hazardous chemical reducing agents and may improve biological compatibility. Within the Pakistani research context, plant-mediated synthesis also has practical relevance because locally available medicinal plants may provide accessible and cost-effective biological resources for experimental nanomedicine development.

Most reported nanoparticles were spherical or quasi-spherical and generally fell within nanoscale ranges considered relevant for cellular uptake and tumor penetration. Sizes between approximately 10 and 100 nm were commonly described as therapeutically advantageous because particles in this range may interact efficiently with malignant cells and penetrate tumor-associated microenvironments. Characterization typically included ultraviolet-visible spectroscopy to confirm nanoparticle formation, transmission or scanning electron microscopy to evaluate size and morphology, Fourier-transform infrared spectroscopy to identify phytochemical functional groups involved in reduction and capping, and zeta potential analysis to assess colloidal stability. However, not all studies reported the same depth of characterization, and relatively fewer investigations provided complete information on crystallinity, polydispersity, drug-loading efficiency, encapsulation efficiency, or release kinetics.

Table 2. Plant Sources and Reported Influence on Gold Nanoparticle Properties

Plant Source or Category	Phytochemical Relevance	Reported Nanoparticle Influence	Reported Biological Relevance	Interpretation for Breast Cancer Drug Delivery
Moringa oleifera	Rich in flavonoids, phenolics, and antioxidant compounds	Associated with smaller and more uniform nanoparticles in several reports	Linked with improved cellular internalization and antiproliferative activity	Potentially useful for stable nanocarrier development and anticancer delivery
Azadirachta indica	Contains bioactive limonoids, flavonoids, and phenolic constituents	Supports reduction and stabilization of gold nanoparticles	Associated with cytotoxic and apoptosis-related effects in breast cancer models	Relevant for combining phytochemical bioactivity with nanoparticle-mediated delivery
Aloe vera	Contains polysaccharides, phenolics, and stabilizing biomolecules	Associated with improved colloidal stability and biocompatibility	Reported to support antioxidant and low-toxicity profiles	Potentially valuable where stability and biological compatibility are priorities
Camellia sinensis	Rich in catechins and polyphenols	Supports phytochemical capping and antioxidant surface properties	Linked with enhanced stability and potential reduction of oxidative injury to normal cells	Useful for green synthesis platforms requiring antioxidant phytochemical contribution
Other medicinal plant extracts	Variable phytochemical composition	Produces nanoparticles with variable size distribution and morphology	Biological response depends on extract composition and synthesis conditions	Requires phytochemical standardization before translational use

The influence of plant source was one of the most important themes in the synthesis. Phytochemical composition appeared to affect nanoparticle morphology, stability, cytotoxic potency, and biological compatibility. Extracts rich in polyphenols and flavonoids were generally associated with enhanced reduction capacity and improved stabilization of nanoparticles. Moringa oleifera and Azadirachta indica were described as producing relatively favorable nanoparticle characteristics, including smaller size distribution and enhanced breast cancer cell interaction. Aloe vera and Camellia sinensis were linked with stability and antioxidant potential, which may be beneficial for reducing nonspecific oxidative injury during therapeutic application. However, crude plant extracts are chemically complex and variable, and differences in plant part, extraction solvent, concentration, temperature, pH, incubation time, and purification method can substantially alter the final nanoparticle formulation.

The anticancer evidence was primarily derived from in vitro breast cancer cell-line experiments. MCF-7 and MDA-MB-231 were the most frequently emphasized models, reflecting hormone receptor-positive and more aggressive triple-negative-like breast cancer phenotypes, respectively. Most studies assessed cytotoxicity through cell viability assays and reported concentration-dependent reductions in malignant cell survival. Some investigations reported reductions in cell viability exceeding 60–80% at selected nanoparticle concentrations, suggesting notable antiproliferative activity. However, direct comparison across studies remained difficult because experimental conditions varied in nanoparticle concentration, exposure duration, plant extract preparation, assay type, and cell-line model.

Table 3. Mechanistic Evidence Map for Plant-Mediated Gold Nanoparticles in Breast Cancer Models

Mechanistic Domain	Reported Biological Indicator	Direction of Evidence	Relevance to Breast Cancer Therapy	Evidence Strength in Current Literature
Cellular uptake	Increased intracellular nanoparticle accumulation	Supports enhanced interaction with malignant cells	May improve intracellular drug concentration	Moderate in vitro evidence
Cytotoxicity	Reduced cancer cell viability	Supports antiproliferative potential	Indicates possible direct or carrier-mediated anticancer action	Moderate in vitro evidence
Oxidative stress	Reactive oxygen species generation	Supports stress-mediated cancer cell injury	May contribute to selective apoptosis	Moderate but assay-dependent evidence
Mitochondrial dysfunction	Loss of mitochondrial integrity and altered apoptotic signaling	Supports intrinsic apoptotic pathway activation	Relevant for inducing programmed cancer cell death	Moderate mechanistic evidence
Nuclear injury	Chromatin condensation and DNA fragmentation	Supports apoptosis-related cell death	Indicates irreversible malignant cell injury	Limited to moderate evidence
Caspase activation	Activation of apoptotic proteins	Supports programmed cell death pathway involvement	Strengthens biological plausibility of anticancer effect	Limited mechanistic evidence

Mechanistic Domain	Reported Biological Indicator	Direction of Evidence	Relevance to Breast Cancer Therapy	Evidence Strength in Current Literature
Drug loading and release	Chemotherapeutic attachment and sustained release behavior	Supports nanocarrier function	May improve delivery of agents such as doxorubicin	Preliminary evidence
Receptor-mediated targeting	Surface functionalization or ligand-mediated interaction	Supports active targeting potential	May improve selectivity for tumor-specific receptors	Early experimental evidence
Normal-cell compatibility	Lower toxicity in non-malignant cell lines at selected concentrations	Supports therapeutic selectivity	Relevant to safety and tolerability	Preliminary and concentration-dependent evidence

Mechanistic findings suggest that plant-mediated gold nanoparticles may act through both carrier-dependent and biologically active pathways. In addition to functioning as nanoscale drug-delivery platforms, these nanoparticles may independently contribute to anticancer activity through oxidative stress induction, mitochondrial disruption, apoptotic signaling, DNA fragmentation, and inhibition of cellular proliferation. The involvement of reactive oxygen species and mitochondrial dysfunction indicates that intrinsic apoptotic pathways may play a central role in nanoparticle-mediated cancer cell death. Some studies also reported chromatin condensation and caspase activation, further supporting programmed cell death as a recurring mechanism. Nevertheless, mechanistic evidence remains uneven because not all investigations performed comprehensive molecular assays, and many relied primarily on cell viability outcomes.

Targeted drug delivery was identified as one of the most promising but least clinically validated applications. The available evidence suggests that gold nanoparticles can improve drug stability, support sustained release, and increase intracellular delivery of chemotherapeutic agents. Doxorubicin-conjugated gold nanoparticles were frequently discussed as a representative model for nanoparticle-assisted chemotherapy. Compared with free-drug formulations, nanoparticle-bound delivery may enhance uptake into malignant cells, improve local therapeutic concentration, and reduce nonspecific toxicity. Passive targeting through enhanced permeability and retention effects was the most commonly described mechanism, while active targeting through ligand or receptor-mediated surface functionalization remained less developed. This indicates that current research is more advanced in basic nanocarrier feasibility than in clinically optimized targeted delivery.

Biocompatibility findings were generally favorable but remained concentration-dependent. Plant-mediated gold nanoparticles were repeatedly described as having lower toxicity toward normal cells than chemically synthesized nanoparticles or free chemotherapeutic exposure, particularly at controlled concentrations. The presence of phytochemical capping agents may reduce nonspecific surface reactivity and improve cellular compatibility. However, toxicity increased at higher nanoparticle concentrations in some studies, with evidence of oxidative stress, membrane damage, and reduced viability in non-malignant cells. These findings support the need for careful dose optimization and standardized safety evaluation before clinical application.

Table 4. Evidence Strength and Translational Gaps

Translational Element	Current Evidence Status	Main Strength	Main Gap	Priority for Future Research
Laboratory synthesis	Well represented	Feasible plant-mediated gold nanoparticle production	Protocol variability	Standardized synthesis conditions
Physicochemical characterization	Moderately represented	Basic confirmation of size, morphology, and surface chemistry	Incomplete advanced characterization	Full characterization panels including stability, crystallinity, and batch reproducibility
In vitro cytotoxicity	Strongest current domain	Repeated evidence of breast cancer cell viability reduction	Assay heterogeneity and limited cell-line diversity	Comparative testing across molecular breast cancer subtypes
Mechanistic testing	Moderately represented	Evidence of apoptosis and oxidative stress pathways	Incomplete pathway validation	Molecular assays for apoptosis, signaling, and receptor interactions

Translational Element	Current Evidence Status	Main Strength	Main Gap	Priority for Future Research
Drug-delivery performance	Preliminary	Evidence of drug loading and sustained release	Limited pharmacodynamic comparison	Controlled comparisons with free drug and standard formulations
Normal-cell safety	Preliminary	Indications of selective cytotoxicity	Lack of long-term safety data	Normal-cell panels and chronic exposure studies
In vivo efficacy	Weakly represented	Early promise in preclinical direction	Limited animal data	Adequately powered animal studies with tumor and safety endpoints
Pharmacokinetics and biodistribution	Insufficient	Conceptual relevance recognized	Sparse direct evidence	Absorption, distribution, metabolism, elimination, and organ accumulation studies
Regulatory and manufacturing readiness	Insufficient	Identified as important for translation	No standardized national pathway	Quality control, scalability, and regulatory frameworks
Clinical evidence	Absent	Strong rationale for future trials	No human therapeutic validation	Phase-based clinical evaluation after preclinical completion

The evidence base is therefore uneven. Laboratory synthesis and in vitro cytotoxicity represent the most developed areas, while translational domains remain underdeveloped. In vivo evaluation is limited, and available animal-based evidence is insufficient to establish pharmacokinetics, biodistribution, chronic toxicity, immune response, metabolism, elimination, or organ-specific accumulation. Clinical evidence is absent, and no therapeutic recommendation can be derived from the current experimental literature. The translational pathway requires progression from laboratory feasibility to standardized synthesis, batch reproducibility, advanced characterization, mechanistic validation, in vivo safety assessment, pharmacokinetic profiling, and ultimately controlled clinical evaluation.

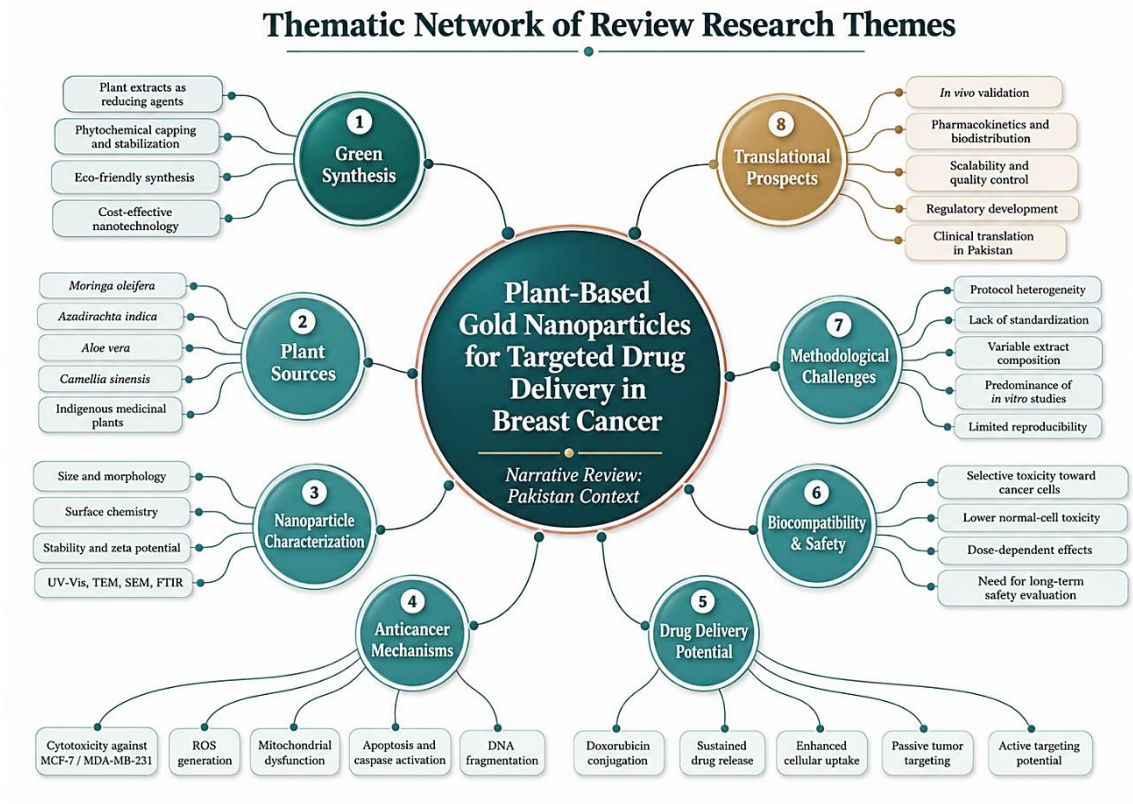

Figure 1 Thematic network of review research themes for plant-based gold nanoparticles in targeted breast cancer drug delivery. The conceptual framework illustrates the central review focus and its eight interconnected thematic domains: green synthesis, plant sources, nanoparticle characterization, anticancer mechanisms, drug delivery potential, biocompatibility and safety, methodological challenges, and translational prospects. Subtheme nodes summarize the major supporting concepts identified in the narrative synthesis, including phytochemical-mediated synthesis, breast cancer cell-line cytotoxicity, apoptosis-related mechanisms, doxorubicin conjugation, sustained release, standardization gaps, in vivo validation, pharmacokinetics, regulatory development, and clinical translation within the Pakistani context.

Methodological heterogeneity was a recurring limitation across the evidence. Plant extraction procedures, reaction conditions, gold salt concentrations, pH, temperature, incubation duration, purification methods, and storage conditions differed substantially across studies. Since nanoparticle behavior is highly sensitive to physicochemical properties, these variations affect size, shape, charge, stability, drug-loading capacity, cellular uptake, and biological response. Outcome assessment also varied, with different assays used for cytotoxicity, oxidative stress, apoptosis, and drug-release behavior. This heterogeneity prevents quantitative pooling and limits direct comparison across studies.

The synthesis also highlights the need to distinguish between experimental promise and translational readiness. Plant-mediated gold nanoparticles show credible potential as sustainable nanocarriers for breast cancer applications, especially where cost, biocompatibility, and local resource availability are important. However, the current evidence is strongest at the exploratory and preclinical laboratory level. Translation into oncological practice will require standardized phytochemical profiling, reproducible nanoparticle synthesis, validated drug-loading methods, comparative efficacy testing, long-term toxicological evaluation, regulatory quality standards, and collaboration between nanotechnology laboratories, oncology centers, pharmacology units, and industrial partners.

In the Pakistani context, the field offers both scientific opportunity and practical challenges. Pakistan's medicinal plant diversity provides a strong foundation for green nanotechnology research, while increasing institutional interest in biotechnology, pharmacy, and cancer therapeutics supports further development. At the same time, limited access to advanced characterization platforms, small-scale experimental designs, fragmented research collaboration, and underdeveloped regulatory pathways remain major barriers. The available evidence supports continued investigation of plant-mediated gold nanoparticles as an experimental breast cancer drug-delivery platform, with priority given to reproducibility, safety, mechanism-based validation, and translational infrastructure.

DISCUSSION

This narrative review synthesized the current experimental and translational evidence on plant-mediated gold nanoparticles for targeted drug delivery in breast cancer, with particular emphasis on the Pakistani research context. The principal finding is that plant-based gold nanoparticles represent a scientifically promising but still preclinical nanomedicine platform. The available literature most strongly supports the feasibility of green synthesis, basic nanoparticle characterization, in vitro anticancer activity, and preliminary drug-delivery potential. Evidence is comparatively weaker for in vivo efficacy, pharmacokinetics, biodistribution, long-term toxicology, regulatory readiness, scalable manufacturing, and clinical translation. This distribution of evidence indicates that the field has progressed beyond conceptual feasibility but remains distant from therapeutic implementation.

The synthesis shows that green synthesis is one of the most developed areas within this research domain. Plant extracts function as both reducing and stabilizing agents because they contain bioactive phytochemicals such as flavonoids, phenolics, terpenoids, alkaloids, proteins, and polysaccharides. These compounds contribute to nanoparticle formation, surface capping, colloidal stability, and biological interaction. In Pakistan, this approach is particularly relevant because medicinal plants are locally accessible, culturally familiar, and potentially cost-effective for laboratory-scale development. The use of plant sources such as Moringa oleifera, Azadirachta indica, Aloe vera, Camellia sinensis, and other indigenous medicinal plants provides an important link between traditional phytomedicine and modern nanotherapeutic research (4,5).

The biological rationale for plant-mediated gold nanoparticles in breast cancer therapy is supported by their nanoscale dimensions, tunable morphology, surface functionalization potential, and capacity to interact with malignant cells. Most available studies describe nanoparticles within size ranges considered favorable for cellular uptake and tumor penetration, commonly accompanied by characterization through ultraviolet-visible spectroscopy, electron microscopy, Fourier-transform infrared spectroscopy, and zeta potential analysis. These techniques confirm nanoparticle formation and provide essential information about morphology, surface chemistry, and stability. However, characterization remains inconsistent

across studies, and many reports do not provide complete data on crystallinity, polydispersity index, drug-loading efficiency, encapsulation efficiency, release kinetics, batch reproducibility, or storage stability. This limits the ability to compare formulations and identify which plant-derived systems are most suitable for translational development (10,16).

The anticancer evidence is encouraging but must be interpreted according to its experimental level. Most findings are derived from breast cancer cell-line studies, particularly MCF-7 and MDA-MB-231 models. These models provide useful preliminary insight into hormone receptor-positive and aggressive breast cancer phenotypes, but they do not capture the full biological heterogeneity of clinical breast cancer. The reviewed literature indicates that plant-mediated gold nanoparticles may reduce breast cancer cell viability, enhance intracellular uptake, induce oxidative stress, disrupt mitochondrial function, activate apoptotic pathways, and contribute to DNA fragmentation. These mechanisms suggest that the nanoparticles may act not only as passive delivery vehicles but also as biologically active agents with intrinsic anticancer potential (11,12).

A recurring mechanistic theme is apoptosis-mediated cytotoxicity. Reactive oxygen species generation, mitochondrial dysfunction, caspase activation, chromatin condensation, and DNA fragmentation were repeatedly described as potential pathways through which plant-mediated gold nanoparticles affect malignant cells. These findings align with the broader nanomedicine literature, where intracellular oxidative stress and mitochondrial pathway activation are frequently implicated in nanoparticle-induced cancer cell death. Nevertheless, mechanistic evidence remains uneven because many studies rely primarily on cell viability assays, while fewer include detailed molecular confirmation using apoptotic markers, gene-expression profiling, protein-level assays, or pathway-specific inhibition experiments. Stronger mechanistic validation is therefore needed before causal claims about anticancer pathways can be considered robust (13,14).

Drug-delivery potential is another important but underdeveloped theme. Gold nanoparticles are attractive nanocarriers because their surfaces can be conjugated with chemotherapeutic agents, targeting ligands, peptides, antibodies, or phytochemical moieties. Doxorubicin-conjugated gold nanoparticles are commonly discussed as a representative model for nanoparticle-assisted chemotherapy. The evidence suggests that nanoparticle-based delivery may improve intracellular drug accumulation, support sustained release, and reduce nonspecific exposure of normal tissues. Passive targeting through tumor-associated enhanced permeability and retention remains the most frequently described mechanism, while active targeting through receptor-mediated surface functionalization remains at an earlier experimental stage (2,11,17).

The distinction between drug-delivery feasibility and therapeutic validation is important. Current studies support the concept that plant-mediated gold nanoparticles can serve as drug carriers, but they do not yet establish clinical superiority over existing chemotherapy or approved targeted therapies. Many studies do not include direct comparisons with free drug, chemically synthesized gold nanoparticles, standard nanocarrier systems, or clinically relevant treatment controls. In addition, differences in drug concentration, nanoparticle dose, exposure duration, release medium, pH conditions, and assay methodology limit comparability. Future drug-delivery studies should therefore incorporate standardized comparator groups, release kinetics under physiologically relevant conditions, cellular uptake quantification, pharmacodynamic testing, and validation in animal tumor models.

Biocompatibility findings are generally favorable but remain incomplete. Plant-mediated gold nanoparticles are frequently described as less toxic to normal cells than malignant cells, particularly at controlled concentrations. This selective toxicity may reflect differences in cancer cell metabolism, nanoparticle uptake, oxidative stress sensitivity, and the biological influence of phytochemical surface capping. However, safety findings are often limited to short-term in vitro assays. Some reports indicate that higher nanoparticle concentrations may induce oxidative stress, membrane damage, and reduced viability even in non-malignant cells. These observations indicate that dose, exposure time, surface chemistry, and particle stability are critical determinants of safety (15,19).

The greatest translational gap concerns long-term biological behavior. Before clinical application can be considered, plant-mediated gold nanoparticles must be evaluated for pharmacokinetics, biodistribution, organ accumulation, immune response, metabolism, elimination, chronic toxicity, reproductive toxicity, genotoxicity, and interaction with standard cancer therapies. Gold nanoparticles may persist in tissues depending on size, charge, coating, and route of administration. Therefore, short-duration cell-line experiments are insufficient to establish therapeutic safety. Longitudinal animal studies with histopathological, hematological, biochemical, immunological, and tumor-response endpoints are essential for determining whether these formulations can progress toward human testing (18,19).

Methodological heterogeneity is a major limitation across the evidence base. Plant-mediated synthesis is sensitive to plant species, plant part, geographic origin, harvesting conditions, extraction solvent, phytochemical concentration, reaction pH, temperature, incubation time, gold precursor concentration, purification method, and storage conditions. Even small differences in these parameters may change nanoparticle size, morphology, surface charge, aggregation behavior, drug-loading capacity, and cellular response. This heterogeneity complicates reproducibility and prevents quantitative synthesis. Standardized reporting of synthesis parameters, phytochemical characterization, nanoparticle properties, and biological assay conditions should become a priority for future studies (16).

The Pakistani context gives this field specific relevance. Pakistan has substantial botanical resources, increasing interest in pharmaceutical nanotechnology, and a strong need for affordable innovations in cancer care. Plant-mediated nanomedicine may offer a locally adaptable research pathway if it is developed through rigorous interdisciplinary collaboration. However, translation requires more than laboratory synthesis. It requires advanced characterization facilities, reproducible manufacturing protocols, quality-control systems, regulatory guidance, toxicology infrastructure, oncology collaboration, and industrial partnerships. Without these elements, promising experimental findings may remain confined to academic laboratories rather than advancing toward clinical or commercial application (8,20).

The findings of this review also have implications for research policy. National or institutional frameworks for nanomedicine research should encourage standardized synthesis protocols, shared characterization facilities, multicenter experimental validation, and transparent reporting practices. Regulatory agencies and academic institutions should develop guidance for nanoparticle safety evaluation, environmental impact, batch consistency, and preclinical testing. Such frameworks would improve scientific reliability and reduce duplication of small-scale exploratory studies. In the longer term, integration of computational modeling, artificial intelligence-assisted nanoparticle design, and molecular profiling of breast cancer subtypes may help optimize particle size, surface chemistry, targeting ligands, and drug-release behavior for precision nanomedicine applications (20).

This review has several method-specific limitations. As a narrative review, it provides a structured conceptual synthesis rather than a systematic review with pooled quantitative estimates. The included literature is heterogeneous in design, plant source, synthesis conditions, characterization techniques, cell-line models, outcome measures, and reporting quality. Because many studies are experimental and preclinical, conclusions about clinical effectiveness cannot be drawn. In addition, the strength of evidence varies across themes: synthesis feasibility and in vitro cytotoxicity are relatively well represented, whereas in vivo safety, pharmacokinetics, biodistribution, and clinical efficacy remain insufficiently investigated. These limitations reflect the current maturity of the field and define the priorities for future research.

Future research should move from exploratory synthesis toward reproducible, mechanism-based, and translationally relevant investigation. Standardized phytochemical profiling of plant extracts should be combined with controlled nanoparticle synthesis and full physicochemical characterization. Comparative studies should evaluate plant-mediated nanoparticles against chemically synthesized nanoparticles, free chemotherapeutic agents, and established nanocarrier platforms. Experimental models should include diverse breast cancer subtypes, three-dimensional tumor spheroids, organoids, and animal models with clinically meaningful endpoints. Long-term toxicological evaluation, pharmacokinetic profiling,

biodistribution mapping, dose optimization, and regulatory-quality manufacturing studies should precede any phase-based clinical evaluation.

Overall, plant-mediated gold nanoparticles offer a promising experimental strategy for improving breast cancer drug delivery, particularly in settings where sustainable synthesis, affordability, and local biomedical innovation are priorities. Their potential lies in the convergence of green chemistry, phytomedicine, nanotechnology, and targeted oncology. However, the current evidence supports continued preclinical development rather than immediate clinical use. The field will advance meaningfully only if future studies prioritize reproducibility, mechanistic rigor, safety validation, and translational infrastructure.

CONCLUSION

Plant-mediated gold nanoparticles represent a promising preclinical platform for targeted drug delivery in breast cancer, with current evidence supporting their feasibility for green synthesis, nanoscale characterization, in vitro cytotoxicity, apoptosis-related anticancer activity, and preliminary chemotherapeutic delivery. Their relevance in Pakistan is strengthened by the availability of medicinal plant resources, growing nanomedicine research capacity, and the need for affordable precision-oriented cancer therapeutics. However, the evidence remains strongest at the laboratory level and is limited by heterogeneous synthesis protocols, incomplete characterization, restricted cell-line models, insufficient in vivo validation, limited toxicological assessment, and absence of clinical trials. Future work should prioritize standardized synthesis, phytochemical profiling, reproducible characterization, mechanism-based testing, pharmacokinetic and biodistribution studies, long-term biosafety assessment, and regulatory-quality translational research. With rigorous interdisciplinary development, plant-based gold nanoparticles may contribute to sustainable and targeted breast cancer therapeutic innovation in Pakistan and comparable resource-constrained healthcare settings.

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