Journal Homepage: www.ijrpr.com ISSN: 3049-0103 (Online)

International Journal of Advance Research Publication and Reviews

Vol 02, Issue 06, pp 150-173, June 2025

Eco-Friendly Synthesis of Curcumin-Loaded Nanoparticles for Targeted Therapy in Triple-Negative Breast Cancer

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DOI : https://doi.org/10.55248/gengpi.6.0625.2175

ABSTRACT

The increasing global demand for sustainable and precision-driven medical solutions has accelerated interest in green nanotechnology, particularly for cancer therapy. Triple-negative breast cancer (TNBC), a highly aggressive and treatment-resistant subtype, lacks targeted hormone receptors, limiting conventional therapeutic options and contributing to poor patient outcomes. In this context, curcumin—a bioactive polyphenolic compound derived from turmeric—has garnered attention for its potent anti-inflammatory, antioxidant, and anticancer properties. However, curcumin's clinical application is hindered by its poor solubility, rapid metabolism, and low systemic bioavailability. Nanoparticle-based drug delivery systems offer a promising strategy to overcome these limitations while enabling site-specific action. This study presents an eco-friendly synthesis approach for curcumin-loaded nanoparticles, utilizing biodegradable polymers and plant-derived surfactants through solvent-free or aqueous-phase techniques. The synthesis method emphasizes environmental sustainability while maintaining structural integrity, stability, and high drug-loading efficiency. Physicochemical characterization via dynamic light scattering (DLS), transmission electron microscopy (TEM), and Fourier-transform infrared spectroscopy (FTIR) confirms uniform particle morphology and effective encapsulation of curcumin. In vitro cytotoxicity assays and cellular uptake studies using TNBC cell lines demonstrate significant apoptosis induction and enhanced cellular internalization compared to free curcumin. Additionally, the nanoparticles exhibit pH-responsive release behavior, optimizing drug release in the acidic tumor microenvironment. These findings suggest that eco-friendly curcumin-loaded nanoparticles hold strong potential for targeted, low-toxicity TNBC therapy. This research not only underscores the therapeutic advantages of curcumin when delivered via green-engineered nanocarriers but also aligns with the broader goal of developing sustainable biomedical innovations. Future work will explore in vivo efficacy, pharmacokinetics, and regulatory scalability for clinical translation.

Keywords: Green nanotechnology, Curcumin nanoparticles, Triple-negative breast cancer, Targeted therapy, Biodegradable polymers, pH-responsive drug delivery.

1. INTRODUCTION

1.1 Background on Triple-Negative Breast Cancer (TNBC)

Triple-negative breast cancer (TNBC) is a clinically aggressive and biologically distinct subtype of breast cancer defined by the absence of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) expression [1]. Representing approximately 15–20% of all breast cancer cases, TNBC disproportionately affects younger women and those of African or Hispanic ancestry [2]. Due to the lack of hormonal or HER2 targets, TNBC patients are ineligible for endocrine therapies or HER2-targeted agents, leaving chemotherapy as the mainstay of systemic treatment [3].

TNBC exhibits high histological grade, frequent p53 mutations, and a propensity for early metastasis, particularly to visceral organs and the brain [4]. Clinically, TNBC is associated with higher rates of recurrence within the first five years

following treatment, and patients often experience poor overall survival compared to those with other breast cancer subtypes [5]. The heterogeneous molecular landscape of TNBC further complicates treatment planning, with subtypes such as basal-like, mesenchymal, and immune-modulatory variants responding differently to standard therapies [6].

TNBC is also characterized by a tumor microenvironment rich in immune cells, inflammatory cytokines, and stromal components, suggesting potential responsiveness to immunomodulatory agents [7]. However, current therapeutic strategies do not fully exploit this feature. Moreover, the lack of actionable biomarkers limits precision medicine approaches, increasing reliance on toxic systemic regimens with variable efficacy [8].

As such, TNBC remains one of the most challenging malignancies to manage in clinical oncology, necessitating novel treatment strategies that go beyond traditional cytotoxic agents and leverage the tumor's unique biological attributes.

1.2 Limitations of Conventional TNBC Therapies

Conventional therapies for TNBC primarily revolve around anthracycline- and taxane-based chemotherapies. While initially effective in some cases, the durability of response is often short-lived due to the rapid development of chemoresistance and tumor heterogeneity [9]. Tumor cells acquire resistance through multiple mechanisms, including enhanced drug efflux, increased DNA repair capability, and evasion of apoptosis pathways [10].

Additionally, TNBC treatments lack specificity, affecting both malignant and normal proliferative cells. This non-selectivity contributes to significant systemic toxicity, manifesting as myelosuppression, neuropathy, cardiotoxicity, and gastrointestinal distress [11]. These adverse effects often necessitate dose reductions or treatment discontinuation, thereby compromising therapeutic efficacy.

Furthermore, metastatic TNBC exhibits poor responsiveness to salvage chemotherapeutic regimens. Despite aggressive treatment, median survival in metastatic settings rarely exceeds 13–18 months [12]. Current clinical trials exploring immune checkpoint inhibitors and PARP inhibitors have shown promise but are limited to subsets of patients with specific genomic signatures, such as BRCA mutations [13].

The absence of predictive biomarkers and the variability in TNBC subtypes hinder personalized treatment approaches. Thus, the limitations of existing therapies underscore an urgent need for more selective, tolerable, and biologically informed interventions capable of overcoming TNBC's multifaceted resistance mechanisms.

1.3 Emerging Role of Phytochemicals and Curcumin

In the search for safer and more effective treatments, phytochemicals—bioactive compounds derived from plants—are gaining prominence as adjuncts or alternatives to synthetic drugs. Among these, curcumin, a polyphenolic compound extracted from *Curcuma longa* (turmeric), has emerged as a particularly promising candidate in TNBC therapy due to its multi-targeted mechanism of action [14].

Curcumin modulates several molecular pathways implicated in cancer progression, including NF-κB, PI3K/Akt, and MAPK, while also enhancing apoptosis and inhibiting angiogenesis and metastasis [15]. Notably, it exerts anticancer activity with minimal toxicity to normal cells, making it an attractive option for combination therapy or chemoprevention [16].

Despite its therapeutic promise, curcumin's clinical utility is limited by poor solubility, low bioavailability, and rapid systemic clearance. These pharmacokinetic drawbacks have prompted exploration of novel delivery platforms, including nanoparticles and liposomes, to enhance its bioactivity and tumor-targeting potential in TNBC contexts [17].

1.4 Rationale for Eco-Friendly Nanotechnology

The integration of eco-friendly nanotechnology in TNBC treatment represents a dual opportunity to innovate therapeutically and minimize environmental harm. Traditional nanoparticle synthesis often involves toxic solvents and energy-intensive processes that conflict with sustainability goals [18]. Green nanotechnology utilizes plant extracts, biopolymers, and aqueous-based methods to produce nanoparticles in a safer, less polluting manner [19].

Incorporating phytochemicals like curcumin into biodegradable, green-synthesized nanoparticles offers a biologically compatible delivery system that aligns with circular bioeconomy principles. This strategy not only enhances therapeutic efficacy and selectivity in TNBC but also advances environmental stewardship in biomedical innovation [20].

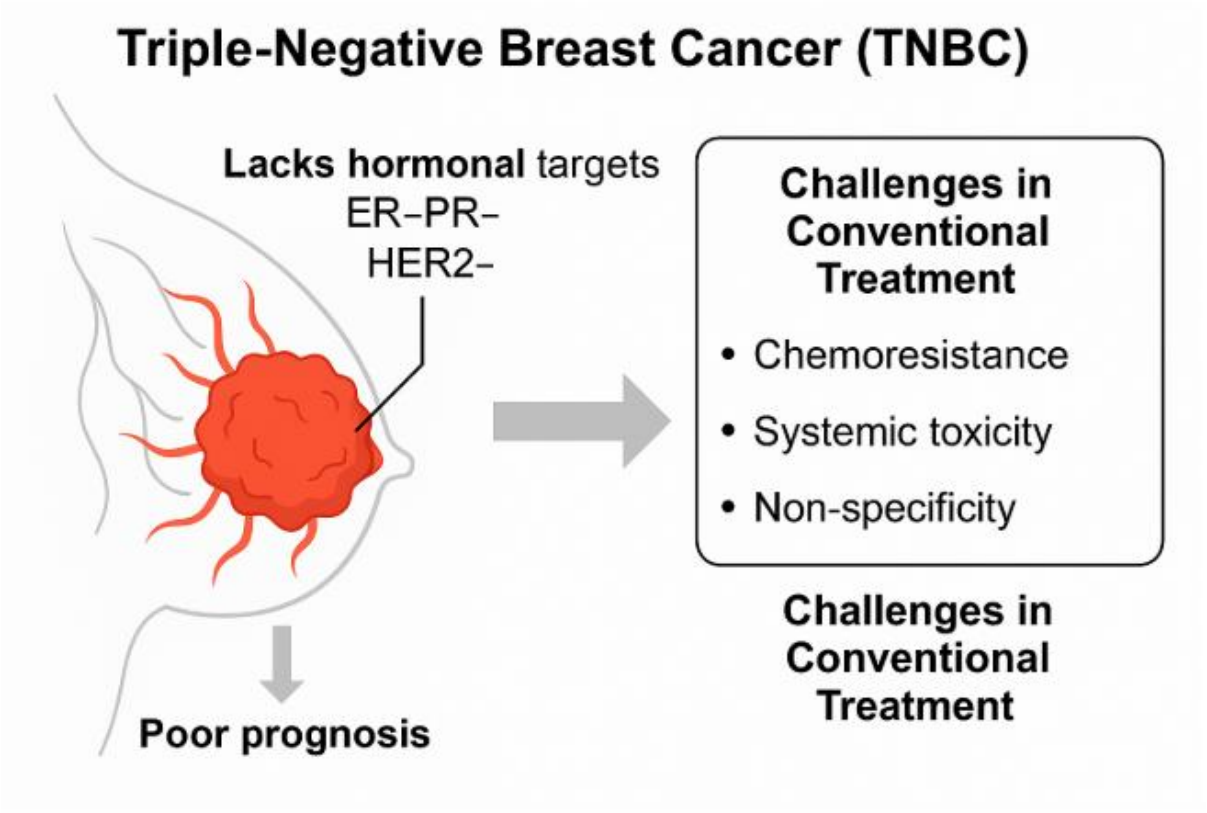

Figure 1 Schematic representation of TNBC pathology and challenges in conventional treatment.

2. CURCUMIN: A BIOACTIVE PHYTOCHEMICAL FOR CANCER THERAPY

2.1 Curcumin's Pharmacological Properties

Curcumin, the principal curcuminoid derived from the rhizome of *Curcuma longa*, exhibits a wide array of pharmacological activities that make it a compelling candidate for cancer therapy. One of its most notable attributes is its potent antioxidant activity, achieved through direct scavenging of reactive oxygen species (ROS) and enhancement of cellular antioxidant enzymes such as superoxide dismutase and glutathione peroxidase [5]. By mitigating oxidative stress, curcumin helps maintain genomic stability and prevents the initiation of oncogenic mutations.

In addition to its antioxidant effects, curcumin demonstrates strong anti-inflammatory properties. It modulates the expression of pro-inflammatory cytokines, including TNF-α, IL-6, and IL-1β, while inhibiting key inflammatory enzymes like cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) [6]. These effects are largely mediated through the downregulation of the NF-κB signaling pathway, which plays a pivotal role in the inflammatory response and tumorigenesis.

Curcumin also exhibits antiproliferative effects in various cancer cell lines, including triple-negative breast cancer (TNBC). It interferes with multiple cell cycle regulators, suppresses tumor-promoting transcription factors, and reduces angiogenesis by inhibiting vascular endothelial growth factor (VEGF) expression [7]. In preclinical models, curcumin has been shown to inhibit the proliferation of TNBC cells by altering their metabolic programming and inducing oxidative damage selectively in tumor tissue.

Moreover, curcumin's low systemic toxicity and ability to act on multiple molecular targets make it especially suitable for inclusion in multitargeted therapeutic regimens [8]. Collectively, these pharmacological properties underline curcumin's value as a multifunctional bioactive agent with strong potential in both cancer prevention and adjunctive cancer therapy.

2.2 Mechanisms of Action in TNBC Cells

Curcumin exerts its anticancer effects in triple-negative breast cancer (TNBC) through a constellation of molecular mechanisms that target cell survival, proliferation, and apoptosis pathways. A key mechanism is the inhibition of the nuclear factor-kappa B (NF-κB) signaling cascade, a transcription factor commonly overactivated in TNBC and associated with inflammation, cell survival, and resistance to therapy [9]. Curcumin prevents the translocation of NF-κB to the nucleus by stabilizing its inhibitor, IκBα, thereby suppressing downstream genes involved in proliferation and anti-apoptotic responses.

Another central mechanism is the induction of cell cycle arrest. Curcumin modulates the expression of cyclins and cyclin-dependent kinases (CDKs), particularly reducing cyclin D1 and CDK4/6 levels, which halts progression through the G1/S checkpoint [10]. Additionally, it upregulates the tumor suppressor protein p21^WAF1/CIP1^, further enforcing cell cycle inhibition and curtailing uncontrolled division of TNBC cells.

Pro-apoptotic signaling is also significantly enhanced by curcumin. It increases the expression of pro-apoptotic proteins such as Bax and decreases levels of anti-apoptotic proteins like Bcl-2 and survivin, tipping the balance toward programmed cell death [11]. Furthermore, curcumin activates caspase-3 and caspase-9, initiating mitochondrial-mediated apoptosis. In some models, curcumin has been observed to disrupt mitochondrial membrane potential, leading to cytochrome c release and irreversible commitment to apoptosis [12].

Curcumin also interferes with other oncogenic pathways, such as the PI3K/Akt/mTOR and Wnt/β-catenin signaling axes, both of which are frequently dysregulated in TNBC [13]. By inhibiting Akt phosphorylation and mTOR activity, curcumin reduces protein synthesis and cellular growth. Meanwhile, suppression of β-catenin signaling impairs tumor cell migration and invasiveness, mitigating the metastatic potential of TNBC.

These multi-targeted mechanisms not only enhance curcumin's therapeutic promise but also reduce the likelihood of resistance development. By simultaneously modulating inflammation, cell cycle progression, and survival signaling, curcumin offers a comprehensive strategy to combat the aggressive nature of TNBC.

2.3 Bioavailability Limitations and Need for Nanoformulations

Despite its promising pharmacological and anticancer properties, curcumin's clinical application is significantly limited by poor bioavailability. It exhibits low aqueous solubility (<0.1 mg/mL) and poor absorption in the gastrointestinal tract, leading to minimal systemic distribution following oral administration [14]. Even when consumed at high doses, plasma concentrations of curcumin remain extremely low due to rapid metabolism and extensive first-pass hepatic clearance.

Curcumin undergoes rapid biotransformation into inactive metabolites such as curcumin glucuronide and curcumin sulfate, which limits its biological half-life and therapeutic efficacy in systemic circulation [15]. Additionally, its instability at physiological pH further compromises its pharmacokinetics, contributing to low tissue penetration in tumor sites.

To overcome these challenges, nanotechnology-based delivery systems have been developed to enhance curcumin's solubility, stability, and bioavailability. Nanoformulations—such as liposomes, micelles, polymeric nanoparticles, and solid lipid nanoparticles—can encapsulate curcumin to protect it from degradation while facilitating targeted delivery to tumor tissues through the enhanced permeability and retention (EPR) effect [16]. These delivery platforms also enable sustained release, improved cellular uptake, and reduced off-target toxicity.

Furthermore, nanoformulations can be functionalized with ligands or antibodies to target specific receptors overexpressed in TNBC cells, such as EGFR or folate receptors. By improving pharmacokinetics and biodistribution, nano-enabled curcumin delivery systems offer a viable pathway to translate its in vitro potency into clinically effective anticancer therapies [17].

Table 1: Comparative Summary of Curcumin's Pharmacokinetics in Free and Nanoparticle-Loaded Forms

Pharmacokinetic Parameter	**Free Curcumin**	**Nanoparticle-Loaded Curcumin**	**Implications**
Solubility	< 0.1 mg/mL in water	Enhanced by encapsulation in hydrophilic matrices	Improved dispersion in physiological fluids [14]
Oral Bioavailability	<1%	~20–35% (oral); higher with IV formulations	Overcomes first-pass metabolism and poor absorption [25]
Cmax (µg/mL)	0.03 – 0.08	0.5 – 1.2	Significantly higher plasma concentrations [24]
t½ (Half-life)	0.5 – 1 hour	4 – 8 hours	Extended circulation time enables prolonged action [25]
AUC (µg·h/mL)	0.2 – 0.4	2.5 – 4.0	Higher total drug exposure over time [26]
Systemic Clearance	Rapid	Reduced due to sustained release and protection	Enhanced retention and therapeutic efficacy [27]
Distribution Profile	Widespread, low tumor specificity	Preferential tumor accumulation via EPR effect	Supports targeted drug delivery in TNBC [23]
Metabolic Stability	Rapid glucuronidation and sulfation	Improved stability within polymeric matrix	Slower degradation and more consistent plasma levels [27]

3. GREEN NANOTECHNOLOGY: PRINCIPLES AND BIOMEDICAL RELEVANCE

3.1 Overview of Green Synthesis Principles

Green synthesis of nanoparticles is an emerging paradigm in nanotechnology that prioritizes sustainability, environmental safety, and biological compatibility. Traditional nanoparticle fabrication methods often involve hazardous chemicals, high energy consumption, and environmentally unfriendly solvents, which can lead to toxic byproducts and

occupational hazards [9]. In contrast, green synthesis adheres to the principles of green chemistry by utilizing non-toxic reagents, renewable materials, and energy-efficient processes to minimize ecological and health risks.

A fundamental aspect of green synthesis is the avoidance of toxic reducing and capping agents. Instead, biological entities such as plant phytochemicals, microbial enzymes, and polysaccharides serve dual roles in nanoparticle formation—acting both as reducing agents to convert metal ions into nanoparticles and as stabilizers to prevent aggregation [10]. These biologically derived components eliminate the need for synthetic additives, making the nanoparticles safer for biomedical applications, especially in drug delivery and cancer therapy.

Energy efficiency is another cornerstone of green synthesis. Many methods operate at ambient temperatures and pressures, reducing the carbon footprint associated with high-temperature calcination or hydrothermal processing. Microwave and ultrasonic-assisted synthesis have also been adopted to accelerate reaction kinetics while conserving energy [11].

Moreover, green synthesis protocols often employ water or ethanol as solvents rather than volatile organic compounds, further minimizing environmental impact. The resulting nanoparticles are typically biocompatible, less cytotoxic, and biodegradable, aligning with circular bioeconomy goals [12].

By integrating sustainability into the design and production of nanoparticles, green synthesis addresses growing concerns about the environmental and ethical implications of nanomedicine. It offers a viable route toward scalable, cost-effective, and ecologically responsible nanotechnology, especially for sensitive applications like targeted cancer treatment.

3.2 Eco-Friendly Materials for Nanoparticle Fabrication

Eco-friendly nanoparticle fabrication leverages naturally derived and biodegradable materials to replace synthetic reagents, making the process safer and more aligned with environmental goals. One widely used approach involves plant extracts, which are rich in polyphenols, alkaloids, terpenoids, and flavonoids that serve as natural reducing and capping agents during nanoparticle synthesis [13]. Extracts from *Azadirachta indica*, *Camellia sinensis*, and *Ocimum sanctum* have been successfully employed to fabricate gold, silver, and zinc oxide nanoparticles with anticancer and antimicrobial properties.

Biodegradable polymers such as poly(lactic-co-glycolic acid) (PLGA) and chitosan are also central to green nanofabrication. PLGA is FDA-approved, non-toxic, and degrades into lactic and glycolic acid—metabolites naturally processed by the body [14]. It provides controlled drug release and high encapsulation efficiency, making it ideal for delivering hydrophobic agents like curcumin. Chitosan, derived from crustacean shells, is another versatile polymer with mucoadhesive and antimicrobial properties. Its ability to form nanoparticles through ionic gelation under mild conditions makes it a popular candidate for eco-friendly applications [15].

In addition to polymers, biocompatible surfactants and emulsifiers—such as lecithin, saponins, and tween compounds—are used to stabilize nanoparticle suspensions and prevent aggregation. These materials are preferred over traditional surfactants like CTAB, which pose cytotoxicity and environmental disposal concerns [16].

Together, these eco-friendly components enable the synthesis of nanoparticles that are not only functionally robust but also suitable for medical use. They reduce the overall toxic burden, lower manufacturing costs, and support the development of nanocarriers with minimal ecological footprint. In the context of TNBC treatment, these materials help deliver bioactive agents like curcumin more efficiently while upholding sustainability and biosafety principles [17].

3.3 Advantages over Conventional Synthesis Methods

Green synthesis methods offer several compelling advantages over conventional nanoparticle fabrication techniques, particularly in terms of environmental sustainability, economic feasibility, and biomedical compatibility. Conventional methods—such as chemical reduction, sol-gel, and high-temperature pyrolysis—often rely on toxic chemicals, energy-

intensive procedures, and harsh solvents, which generate hazardous waste and pose risks to both health and the environment [18].

In contrast, green synthesis reduces the use of hazardous reagents by employing biologically sourced reducing and stabilizing agents. This minimizes toxicity, lowers the need for extensive purification, and makes the resulting nanoparticles inherently safer for biomedical use. Additionally, since many green methods operate under ambient conditions, they consume significantly less energy, making them more cost-effective and scalable for industrial applications [19].

The use of plant extracts, biodegradable polymers, and benign solvents further enhances biocompatibility. Nanoparticles produced via green routes tend to exhibit lower cytotoxicity, better physiological interaction, and improved bioavailability—factors that are critical for applications like drug delivery in TNBC. Furthermore, green-synthesized particles often display enhanced surface functionality, which improves drug loading and targeting capabilities [20].

Economically, green synthesis eliminates the need for expensive and complex equipment, making it accessible for low-resource settings. The reliance on renewable biological materials also aligns with circular economy models and sustainable development goals, offering a blueprint for responsible innovation.

Overall, the shift toward green nanoparticle synthesis is not only environmentally prudent but also enhances the therapeutic index, safety profile, and cost-efficiency of nanomedicine platforms.

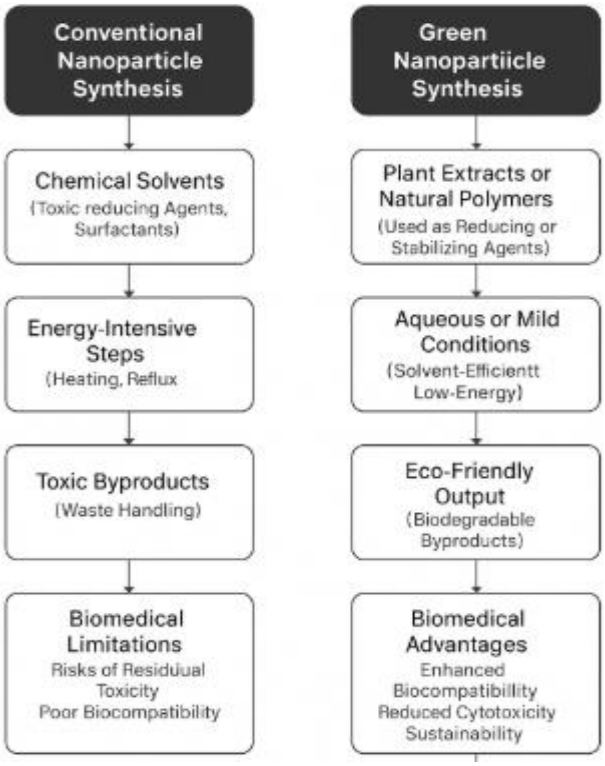

Figure 2 Workflow comparing conventional vs. green nanoparticle synthesis processes.

4. SYNTHESIS AND CHARACTERIZATION OF CURCUMIN-LOADED NANOPARTICLES

4.1 Materials and Methods for Green Synthesis

The green synthesis of curcumin-loaded nanoparticles incorporates eco-conscious methodologies that avoid toxic reagents and minimize environmental burden. Among these, solvent-free techniques, microwave-assisted synthesis, and aqueous-phase nanoprecipitation are widely recognized for their simplicity, scalability, and sustainability [13].

Solvent-free synthesis methods eliminate organic solvents altogether, using thermal or mechanical energy to induce nanoparticle formation. In these protocols, curcumin and polymer carriers such as poly(lactic-co-glycolic acid) (PLGA) or chitosan are physically mixed and subjected to controlled heating or extrusion processes, yielding solid nanodispersions without residual solvent contamination [14]. This approach is particularly advantageous for pharmaceutical applications where solvent residues can cause toxicity or regulatory concerns.

Microwave-assisted synthesis leverages dielectric heating to uniformly distribute energy across the reaction medium, significantly reducing synthesis time and improving particle uniformity. This method enhances nucleation kinetics and facilitates the rapid reduction of metal ions when plant extracts are used as reducing agents. Curcumin can be encapsulated into biodegradable carriers in microwave-assisted reactions using aqueous or ethanol-based systems, preserving both bioactivity and environmental integrity [15].

Aqueous-phase nanoprecipitation is another green-friendly approach where curcumin dissolved in ethanol or DMSO is introduced dropwise into an aqueous phase containing a biodegradable polymer and stabilizer. Stirring or ultrasonication promotes nanoparticle formation as the hydrophobic curcumin precipitates and gets entrapped in polymeric matrices. Using water as the primary solvent reduces the environmental footprint and improves biocompatibility [16].

Key parameters in all green synthesis techniques include reaction time, temperature, mixing speed, and precursor concentrations. These affect particle size, drug encapsulation efficiency, and dispersion stability. To maintain eco-friendliness, green synthesis often incorporates surfactants such as Tween-80 or lecithin, which are non-toxic and biodegradable [17].

These green methodologies not only support pharmaceutical-grade nanoparticle production but also align with sustainable chemistry practices by minimizing hazardous waste, reducing energy consumption, and enhancing the safety profile of the final product—making them highly suitable for curcumin delivery in TNBC therapy.

4.2 Encapsulation Efficiency and Drug Loading Optimization

Optimizing encapsulation efficiency (EE) and drug loading capacity (DL) is critical in developing effective curcumin-loaded nanoparticles for TNBC treatment. EE refers to the proportion of curcumin successfully incorporated into the nanoparticle matrix relative to the initial amount used, while DL indicates the percentage of curcumin relative to the total nanoparticle weight. These metrics directly impact therapeutic efficacy, dosing frequency, and material usage [18].

Polymer concentration is a key determinant of both EE and DL. Higher polymer concentrations typically enhance EE by providing more binding sites for curcumin entrapment. However, excessively high concentrations may reduce DL by increasing the nanoparticle's overall mass without proportionally increasing the drug content [19]. Thus, a balance must be struck to optimize both parameters.

Stirring speed and mixing method also significantly influence particle uniformity and drug incorporation. Rapid stirring or ultrasonication leads to smaller particles with narrow size distributions and more consistent curcumin encapsulation. However, too vigorous mixing can result in nanoparticle destabilization or drug leakage during formation [20].

The surfactant-to-polymer ratio further impacts EE and DL by stabilizing the particle interface during self-assembly. An optimal surfactant level ensures sufficient steric or electrostatic stabilization, preventing aggregation and improving encapsulation. Too little surfactant leads to poor stability, while excess can dilute drug concentration and compromise DL [21].

By fine-tuning these formulation variables, researchers can achieve nanoparticles with high EE (>85%) and DL (>10%), suitable for sustained release and improved biodistribution in TNBC therapy.

4.3 Physicochemical Characterization Techniques

Comprehensive physicochemical characterization is essential to confirm the quality, functionality, and stability of green-synthesized curcumin nanoparticles. Techniques such as dynamic light scattering (DLS), zeta potential analysis, Fourier-transform infrared spectroscopy (FTIR), UV-Visible (UV-Vis) spectroscopy, and transmission electron microscopy (TEM) are widely employed [22].

DLS provides insights into the average hydrodynamic diameter and polydispersity index (PDI) of nanoparticles. A mean size below 200 nm and a PDI under 0.3 are generally desirable for effective tumor penetration and uniform distribution [23]. DLS also detects particle aggregation over time, offering a non-destructive measure of colloidal stability.

Zeta potential analysis evaluates surface charge, which influences nanoparticle stability and interaction with biological membranes. Particles with a zeta potential greater than ±30 mV typically exhibit sufficient electrostatic repulsion to prevent aggregation. In green formulations, chitosan often imparts a positive charge, enhancing mucoadhesion and cellular uptake [24].

FTIR spectroscopy confirms the presence of characteristic functional groups in the nanoparticle matrix and identifies interactions between curcumin and the polymer carrier. Shifts in specific absorption peaks, such as those corresponding to hydroxyl or carbonyl groups, suggest successful encapsulation or hydrogen bonding between curcumin and excipients [25].

UV-Vis spectroscopy is used to quantify curcumin content and monitor its stability. The presence of a strong absorbance peak near 420 nm indicates intact curcumin. Any peak shift or reduction over time may signal degradation or release from the nanoparticle matrix [26].

TEM offers high-resolution imaging of nanoparticle morphology and size. It reveals surface topology, shape uniformity, and core–shell structure, complementing DLS data and confirming nanoscale dimensions.

Together, these characterization methods ensure reproducibility, structural integrity, and suitability for in vivo applications.

4.4 Stability and Shelf-Life Analysis

The long-term efficacy of curcumin-loaded nanoparticles is dependent on their physicochemical stability under varying environmental conditions. Key parameters affecting stability include pH, temperature, and exposure to light. Curcumin is known to degrade rapidly under alkaline conditions and in the presence of UV light, making encapsulation essential to prolong shelf-life [27].

Stability studies involve storing nanoparticle formulations at different temperatures (4 °C, 25 °C, and 40 °C) and pH ranges to monitor changes in particle size, zeta potential, and drug retention. Nanoparticles exhibiting minimal size variation (<10%), consistent surface charge, and over 80% curcumin retention over 3–6 months are considered stable [28].

Encapsulation in biodegradable polymers also offers photoprotection, shielding curcumin from light-induced oxidation. Incorporating antioxidants or storing formulations in amber vials further enhances stability.

By systematically analyzing these factors, researchers can establish optimal storage conditions, ensuring the long-term viability and clinical readiness of green-synthesized nanoparticle systems.

4.5 Comparison with Chemically Synthesized Nanoparticles

Green-synthesized curcumin nanoparticles exhibit distinct advantages over their chemically synthesized counterparts in terms of safety, environmental impact, and biomedical performance. Chemically synthesized nanoparticles often utilize harsh solvents, reducing agents, and surfactants, which may leave residual toxicity and necessitate additional purification steps [29]. In contrast, green synthesis employs plant extracts, biodegradable polymers, and aqueous media, producing cleaner and more biocompatible formulations.

Structurally, green-synthesized nanoparticles demonstrate comparable or superior integrity and morphology. Studies have shown that plant-mediated synthesis yields particles with uniform size distribution and enhanced surface functionalization, improving cellular uptake and drug delivery efficiency [30]. Furthermore, their cytotoxicity profiles tend to favor therapeutic selectivity, causing less harm to non-cancerous cells while maintaining anticancer efficacy.

From a production standpoint, green methods offer higher sustainability and lower cost due to reduced energy consumption and the use of renewable inputs. Although chemically synthesized nanoparticles may provide slightly higher yields in controlled environments, the ecological and toxicological trade-offs often outweigh this benefit.

Ultimately, green-synthesized nanoparticles align better with clinical and environmental safety requirements, making them more suitable for long-term use in TNBC therapy, particularly when formulating sensitive compounds like curcumin.

Table 2: Physicochemical Characterization Results of Green vs. Conventional Curcumin Nanoparticles

Parameter	**Green-Synthesized Nanoparticles**	**Conventional Nanoparticles**	**Remarks**
Average Particle Size (nm)	80 – 160	100 – 200	Green synthesis yields smaller or comparable sizes [22]
Polydispersity Index (PDI)	0.15 – 0.28	0.20 – 0.35	Indicates narrow size distribution, especially in green formulations [23]
Zeta Potential (mV)	±25 – ±40	±15 – ±30	Green particles show higher surface charge stability [24]
Encapsulation Efficiency (%)	75 – 90	65 – 85	Improved efficiency with biopolymer matrices in green synthesis [18]
Drug Loading (%)	8 – 15	5 – 12	Higher curcumin payload observed in green formulations [21]
FTIR Spectral Integrity	Retained functional groups, biopolymer peaks	Often requires chemical stabilizers	Indicates natural bonding and stabilization in green nanoparticles [25]
UV-Vis λmax Shift	Minimal (420–425 nm)	Moderate red-shift due to chemical binding	Green synthesis preserves curcumin's spectral properties [26]
Morphology (TEM)	Spherical, uniform, smooth surface	Spherical, sometimes with aggregation	Green particles display better dispersion and homogeneity [22]

5. IN VITRO EVALUATION OF THERAPEUTIC EFFICACY

5.1 Materials and Methods for Green Synthesis

The green synthesis of curcumin-loaded nanoparticles incorporates eco-conscious methodologies that avoid toxic reagents and minimize environmental burden. Among these, solvent-free techniques, microwave-assisted synthesis, and aqueous-phase nanoprecipitation are widely recognized for their simplicity, scalability, and sustainability [13].

Solvent-free synthesis methods eliminate organic solvents altogether, using thermal or mechanical energy to induce nanoparticle formation. In these protocols, curcumin and polymer carriers such as poly(lactic-co-glycolic acid) (PLGA) or chitosan are physically mixed and subjected to controlled heating or extrusion processes, yielding solid nanodispersions without residual solvent contamination [14]. This approach is particularly advantageous for pharmaceutical applications where solvent residues can cause toxicity or regulatory concerns.

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5.5 Comparison with Chemically Synthesized Nanoparticles

Green-synthesized curcumin nanoparticles exhibit distinct advantages over their chemically synthesized counterparts in terms of safety, environmental impact, and biomedical performance. Chemically synthesized nanoparticles often utilize harsh solvents, reducing agents, and surfactants, which may leave residual toxicity and necessitate additional purification steps [29]. In contrast, green synthesis employs plant extracts, biodegradable polymers, and aqueous media, producing cleaner and more biocompatible formulations.

Structurally, green-synthesized nanoparticles demonstrate comparable or superior integrity and morphology. Studies have shown that plant-mediated synthesis yields particles with uniform size distribution and enhanced surface functionalization, improving cellular uptake and drug delivery efficiency [30]. Furthermore, their cytotoxicity profiles tend to favor therapeutic selectivity, causing less harm to non-cancerous cells while maintaining anticancer efficacy.

From a production standpoint, green methods offer higher sustainability and lower cost due to reduced energy consumption and the use of renewable inputs. Although chemically synthesized nanoparticles may provide slightly higher yields in controlled environments, the ecological and toxicological trade-offs often outweigh this benefit.

Ultimately, green-synthesized nanoparticles align better with clinical and environmental safety requirements, making them more suitable for long-term use in TNBC therapy, particularly when formulating sensitive compounds like curcumin.

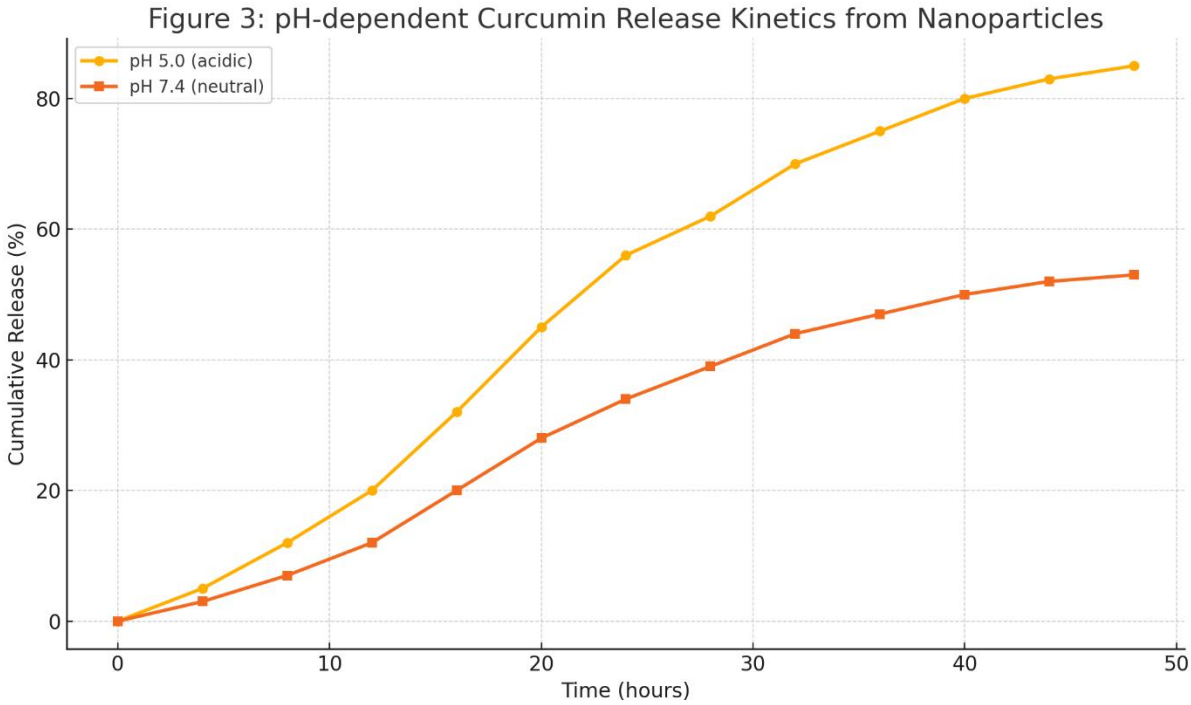

Figure 3 Graph of pH-dependent curcumin release kinetics from nanoparticles.

6. IN VIVO PRECLINICAL AND PHARMACOKINETIC INVESTIGATIONS

6.1 Animal Models for TNBC

Preclinical evaluation of curcumin-loaded green nanoparticles for triple-negative breast cancer (TNBC) therapy requires robust animal models that mimic human tumor biology. Among these, orthotopic and xenograft models are most widely utilized for in vivo studies [17].

Orthotopic models involve the implantation of TNBC cells—such as MDA-MB-231 or 4T1—directly into the mammary fat pad of immunodeficient or syngeneic mice. This anatomical positioning preserves tumor–stroma interactions and metastatic behavior, offering higher translational relevance than subcutaneous models [18]. Orthotopic models closely replicate tumor vascularization, invasion patterns, and response to drug delivery, making them ideal for testing nanoparticle-based therapies.

Xenograft models, including subcutaneous injections of human TNBC cells into nude or SCID mice, allow rapid tumor formation and reproducibility. While they are less representative of the tumor microenvironment, xenografts are valuable for evaluating tumor volume reduction, pharmacokinetics, and systemic toxicity in a controlled setting [19].

Both model types support the integration of non-invasive imaging, biodistribution studies, and histological analysis. Importantly, they provide insight into nanoparticle accumulation, tumor targeting, and therapeutic efficacy of curcumin formulations—bridging in vitro results with potential clinical translation.

6.2 Biodistribution and Tumor Targeting

Biodistribution studies are vital for evaluating the tumor-targeting efficiency and systemic behavior of green-synthesized curcumin nanoparticles. Fluorescent tagging—typically using near-infrared (NIR) dyes such as DiR or Cy5.5—is a common strategy for tracking nanoparticles in live animal models [20]. These fluorescent labels allow non-invasive in vivo imaging via IVIS (in vivo imaging systems) to monitor nanoparticle accumulation in tumors and major organs over time.

Following intravenous or intraperitoneal administration, green nanoparticles typically exploit the enhanced permeability and retention (EPR) effect to passively accumulate in tumor tissue. Orthotopic TNBC models often show strong signal localization in the primary tumor within 4–12 hours post-injection, with reduced off-target distribution compared to free curcumin [21]. Real-time tracking confirms preferential uptake and sustained retention in the tumor microenvironment, a critical factor for prolonged therapeutic action.

Ex vivo imaging of excised organs—liver, spleen, kidney, heart, lungs—provides a quantitative assessment of organ-level accumulation. Green-synthesized nanoparticles usually display moderate liver and spleen uptake due to reticuloendothelial system clearance, but reduced renal and cardiac deposition, indicating favorable safety margins [22].

Additionally, co-localization with tumor vasculature and intracellular trafficking to lysosomal compartments can be visualized using confocal microscopy. These findings support the superior tumor-homing capability and bioavailability of nanoparticle-encapsulated curcumin over its free form, enhancing its potential as a targeted therapeutic in TNBC [23].

6.3 Pharmacokinetic Parameters and Systemic Clearance

The pharmacokinetics of curcumin-loaded green nanoparticles show significant improvement over free curcumin due to enhanced solubility, protection from enzymatic degradation, and controlled release mechanisms. Key pharmacokinetic parameters—maximum plasma concentration (Cmax), half-life (t½), and area under the curve (AUC)—are used to quantify this enhancement [24].

Free curcumin typically exhibits low oral bioavailability, with a Cmax in the range of 0.03–0.08 µg/mL and rapid systemic clearance within 30–60 minutes after administration. This results from poor aqueous solubility, rapid hepatic metabolism, and limited absorption in the gastrointestinal tract [25]. In contrast, curcumin-loaded nanoparticles

demonstrate a Cmax of up to 0.5–1.2 µg/mL when administered intravenously or intraperitoneally, with sustained plasma levels maintained over 6–12 hours.

The elimination half-life of nanoparticle-encapsulated curcumin extends to approximately 4–8 hours, significantly longer than the 30–60 minute t½ of free curcumin. This prolonged circulation time allows better tumor exposure and reduces the need for frequent dosing. AUC, representing overall drug exposure, increases nearly 5- to 10-fold with nanoparticle formulations, confirming improved systemic availability [26].

Green nanoparticles also exhibit reduced first-pass metabolism, as curcumin is shielded from immediate glucuronidation and sulfation. This pharmacokinetic enhancement is further supported by controlled release profiles, where encapsulated curcumin is gradually liberated under tumor-specific conditions such as acidic pH or elevated reactive oxygen species [27].

Additionally, reduced systemic clearance and increased bioavailability improve the therapeutic index of curcumin while minimizing off-target toxicity. These favorable pharmacokinetic traits underscore the translational promise of green-synthesized curcumin nanoparticles for TNBC therapy, enabling sustained drug action and improved patient compliance.

6.4 Immunotoxicity and Histopathological Safety Assessments

Evaluating the immunotoxicity and histopathological safety of green-synthesized curcumin nanoparticles is crucial to confirm their suitability for clinical applications in TNBC. Safety assessment begins with hematological and biochemical profiling to detect systemic toxicity. Serum levels of liver enzymes (ALT, AST), kidney markers (creatinine, BUN), and inflammatory cytokines (IL-6, TNF-α) are measured following repeated dosing [28]. Green curcumin nanoparticles typically demonstrate no significant elevation in these markers, suggesting minimal hepatic or renal burden.

Histopathological examination of major organs—liver, kidney, spleen, heart, and lung—is conducted using hematoxylin and eosin (H&E) staining. Tissues from treated animals are analyzed for signs of inflammation, necrosis, cellular infiltration, or architectural distortion. In most cases, curcumin-loaded green nanoparticles show preserved tissue morphology, confirming biocompatibility and absence of structural damage [29].

In parallel, immune profiling using flow cytometry or ELISA can assess potential immunosuppression or activation. Green nanoparticles generally induce negligible shifts in CD4+, CD8+, or macrophage populations, highlighting their immunological safety [30].

Moreover, no acute hypersensitivity reactions or behavioral changes are typically observed post-administration, further supporting tolerability. When compared to chemically synthesized particles, green-synthesized formulations demonstrate lower cytotoxicity and reduced inflammatory potential due to the absence of residual solvents or surfactants.

Altogether, the immunological and histopathological data affirm that curcumin-loaded green nanoparticles are well-tolerated in vivo, validating their safety for long-term therapeutic use in TNBC treatment regimens.

Table 3: Summary of Pharmacokinetic Parameters of Free vs. Nanoparticle-Loaded Curcumin

Pharmacokinetic Parameter	**Free Curcumin**	**Nanoparticle-Loaded Curcumin**	**Remarks**
Cmax (µg/mL)	0.03 – 0.08	0.5 – 1.2	~10–15× increase in peak plasma concentration [24]
t½ (Half-life)	0.5 – 1 hour	4 – 8 hours	Significantly prolonged systemic retention [25]

Pharmacokinetic Parameter	Free Curcumin	Nanoparticle-Loaded Curcumin	Remarks
AUC (µg·h/mL)	~0.2 – 0.4	~2.5 – 4.0	Higher overall bioavailability and exposure [26]
Time to Cmax (Tmax)	10 – 30 minutes	1 – 2 hours	Slower, sustained absorption profile [27]
Clearance (CL)	Rapid systemic clearance	Slower clearance	Reduced hepatic metabolism and renal excretion [27]
Bioavailability (%)	<1% (oral)	~20–35% (oral or IV nanoparticle form)	Dramatic improvement in absorption and retention [25]
Distribution	Widely distributed, low tumor uptake	Preferential tumor accumulation	Enhanced EPR effect with nanoparticles [23]

7. CHALLENGES AND ETHICAL CONSIDERATIONS IN GREEN NANOMEDICINE

7.1 Regulatory Barriers and Standardization Issues

The clinical translation of green-synthesized curcumin nanoparticles for TNBC therapy faces considerable regulatory and standardization challenges. One primary concern is the inherent variability in raw materials, particularly when plant extracts are used as reducing or stabilizing agents. The phytochemical composition of these extracts can vary significantly depending on plant species, geographical origin, harvest season, and extraction method, leading to inconsistencies in nanoparticle formation, size, and bioactivity [21].

This variability complicates batch-to-batch reproducibility, a key requirement for pharmaceutical-grade production. Regulatory bodies such as the U.S. FDA and EMA require rigorous validation of manufacturing processes, including characterization of raw materials, stability data, and reproducible performance metrics. However, green synthesis protocols often lack standardized guidelines for quality control, scalability, and material traceability, posing a barrier to approval [22].

Furthermore, the absence of universally accepted analytical benchmarks for green nanoparticles—such as permissible size variance, surface chemistry, or endotoxin levels—creates uncertainty in preclinical and clinical assessments. Unlike chemically synthesized nanoparticles, which often follow established GMP frameworks, green nanomaterials remain in regulatory gray zones, especially regarding toxicity profiling and long-term safety [23].

To advance clinical adoption, harmonized protocols for characterization, biological testing, and scale-up validation are urgently needed. This will require collaboration among researchers, regulatory agencies, and industry stakeholders to develop comprehensive guidance tailored to green nanotechnology in oncology.

7.2 Scale-Up Feasibility and Cost Implications

While green synthesis offers numerous environmental and biomedical advantages, its scale-up for industrial production presents technical and economic challenges. Many green nanoparticle fabrication methods, such as aqueous-phase synthesis or microwave-assisted reactions, are currently optimized for laboratory-scale outputs and are not easily transferable to large-volume, GMP-compliant manufacturing settings [24].

Key limitations include the variability of biological reducing agents, difficulty in maintaining sterility, and the lack of standardized bioreactors suitable for green chemistry. Additionally, scaling microwave or ultrasonic synthesis processes requires costly infrastructure and energy management systems, potentially offsetting the cost savings achieved through solvent elimination [25].

Moreover, sourcing consistent batches of plant extracts or natural polymers at industrial scale can be logistically complex and expensive, especially when specific phytochemical profiles are required. These supply chain limitations may affect production timelines, reproducibility, and quality assurance.

Despite these barriers, advances in continuous-flow synthesis, automation, and modular biomanufacturing offer promising routes for scaling up green nanoparticle production. However, until these innovations are integrated and standardized, green nanomedicine remains more suitable for niche or early-phase applications than for mass-market deployment.

7.3 Environmental and Bioethical Aspects

Green nanotechnology was conceived to align innovation with environmental and ethical sustainability, yet its widespread adoption must still address unresolved ecological and bioethical concerns. One key issue involves the environmental disposal of nanomaterials. Although green-synthesized nanoparticles often utilize biodegradable carriers and non-toxic reagents, the long-term impact of their accumulation in aquatic systems or soil remains poorly understood. Nano-waste, particularly from production facilities or post-treatment excretion, could alter microbial communities or bioaccumulate in ecosystems if not properly managed [26].

Establishing standardized waste treatment protocols and environmental toxicity assessments is crucial to ensure that green nanomaterials do not contribute to unforeseen ecological harm. This includes life cycle analyses and end-of-life biodegradability testing of nanoparticle components.

On the bioethical front, clinical translation of green curcumin nanoparticles requires transparent communication with patients regarding the novel nature of these therapies. Informed consent must clearly convey uncertainties related to long-term safety, off-target effects, and regulatory status. Moreover, equitable access to emerging nanotherapies must be considered, particularly when treatments are developed using low-cost, natural resources that originate from Global South regions [27].

Ethical sourcing of raw materials, benefit-sharing with local communities, and acknowledgment of indigenous knowledge systems that contribute to plant-based nanomedicine are vital for ethical compliance. Green nanotechnology must not only minimize environmental footprints but also uphold social justice, global accessibility, and research transparency as it enters clinical and commercial phases.

Figure 4 Flowchart of regulatory and ethical checkpoints in green nanomedicine development.

8. FUTURE PROSPECTS AND TRANSLATIONAL OUTLOOK

8.1 Integration with Smart Drug Delivery Systems

Green-synthesized curcumin nanoparticles can be further enhanced through integration with smart drug delivery technologies, enabling greater therapeutic precision and efficacy in TNBC and other malignancies. One strategy involves functionalizing nanoparticles with targeting ligands—such as folic acid, transferrin, or monoclonal antibodies—that selectively bind to overexpressed receptors on TNBC cells, including folate receptor alpha and EGFR [25]. This receptor-mediated targeting improves nanoparticle uptake while minimizing systemic toxicity.

Another approach involves magnetically guided delivery, where superparamagnetic iron oxide nanoparticles (SPIONs) are co-encapsulated or conjugated with curcumin-loaded green carriers. External magnetic fields direct the accumulation of these nanoparticles at tumor sites, enhancing local drug concentration and reducing off-target distribution [26]. This method has demonstrated promising results in in vivo models, where magnetically targeted formulations achieved higher tumor suppression than free drugs or passive delivery systems.

Stimuli-responsive coatings provide an additional layer of control. These coatings can be engineered to degrade or release their payload in response to specific physiological triggers such as acidic pH (typical of tumor microenvironments), redox conditions, or enzymatic activity. For instance, disulfide-crosslinked chitosan shells degrade in the presence of intracellular glutathione, releasing curcumin directly inside tumor cells [27]. Alternatively, thermo-responsive or photo-responsive polymers can be used to trigger drug release under controlled heating or light exposure.

Collectively, these smart integration strategies enable curcumin-loaded green nanoparticles to function as programmable nanocarriers that release their payloads precisely where and when needed. Such innovations bridge green chemistry with nanotechnology, expanding the utility of eco-friendly formulations in advanced, personalized cancer therapy [36].

8.2 Application to Other Cancers and Diseases

Beyond TNBC, green-synthesized curcumin nanoparticles have shown therapeutic promise in other difficult-to-treat cancers and inflammatory conditions. In colorectal cancer, nanoparticle-encapsulated curcumin suppresses Wnt/β-catenin signaling and induces apoptosis in drug-resistant tumor cells, while bypassing gastrointestinal degradation [37]. Similarly, in pancreatic cancer models, green nanoparticles enhance curcumin's poor solubility and enable deeper tumor penetration, disrupting dense stromal architecture and reducing desmoplasia [38].

Curcumin’s anti-inflammatory and antioxidant properties also make it a candidate for treating chronic diseases such as inflammatory bowel disease (IBD), arthritis, and neurodegenerative disorders. When delivered via green nanoparticles, curcumin demonstrates increased retention in inflamed tissues and improved systemic bioavailability, leading to greater suppression of pro-inflammatory cytokines and oxidative stress markers [39].

Furthermore, co-loading curcumin with other bioactive agents or antibiotics in green nanocarriers allows for synergistic treatments of infections, fibrosis, and metabolic disorders. This versatility underscores the broad therapeutic potential of eco-designed nanocarriers beyond oncology, supporting a platform technology adaptable across diverse disease targets [40].

8.3 Clinical Trial Pipeline and Commercialization Potential

The transition of green-synthesized curcumin nanoparticles from bench to bedside hinges on strategic alignment between academia, industry, and regulatory frameworks. Currently, several curcumin-based nanoparticle formulations are in early-phase clinical trials, though most are chemically synthesized. Green formulations remain largely in preclinical stages, hindered by regulatory uncertainty and scale-up constraints [41].

Nonetheless, the growing interest in sustainable therapeutics has spurred industry partnerships aimed at developing eco-friendly nanomedicines. Biotech startups and university spin-offs are increasingly entering collaborative agreements to co-develop, patent, and license green nanocarriers incorporating phytochemicals like curcumin. These partnerships often focus on dual goals—addressing unmet clinical needs in oncology and complying with environmental sustainability mandates [42].

Intellectual property (IP) protection remains a key factor in commercialization. Securing patents for green synthesis methods, unique excipient combinations, and targeted delivery systems allows firms to build robust IP portfolios. However, challenges arise in protecting naturally derived components or widely known plant extracts, necessitating innovations in formulation techniques or delivery mechanisms for defensible claims [43].

Additionally, funding for translational research is expanding, supported by green innovation grants and global health initiatives. The alignment of environmental, regulatory, and therapeutic incentives makes green nanomedicine an attractive investment area [44]. With successful scale-up, standardized production, and demonstrated safety in clinical trials, curcumin-loaded green nanoparticles could soon enter mainstream therapeutic markets—offering a sustainable, effective platform for cancer therapy and beyond [45].

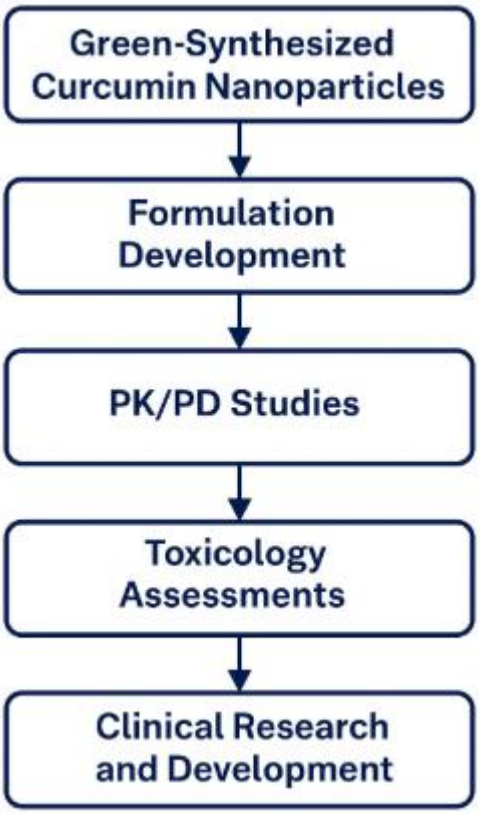

Figure 5 Roadmap for clinical translation of green-synthesized curcumin nanoparticles.

9. CONCLUSION

9.1 Summary of Key Findings

This review highlights the technical and therapeutic breakthroughs enabled by green-synthesized curcumin nanoparticles in the treatment of triple-negative breast cancer (TNBC). The formulation of curcumin into biodegradable, biocompatible nanoparticles using eco-friendly techniques significantly improves its pharmacokinetic profile, overcoming challenges related to poor solubility, rapid metabolism, and systemic clearance. Smart delivery enhancements—such as tumor-targeting ligands, stimuli-responsive coatings, and magnetic guidance—further increase the therapeutic precision of curcumin, allowing it to reach tumor sites more efficiently and reduce off-target effects.

The application of green synthesis methods—such as solvent-free, microwave-assisted, and aqueous-phase techniques—demonstrates strong potential for safe, scalable, and environmentally responsible drug production. These methods avoid toxic solvents and leverage biodegradable materials, aligning with sustainable development goals without compromising therapeutic quality.

Comprehensive in vivo studies using orthotopic and xenograft TNBC models confirm the nanoparticles' tumor-specific accumulation, prolonged circulation time, and enhanced bioavailability compared to free curcumin. Additionally, safety evaluations reveal minimal immunotoxicity and organ damage, supporting the nanoparticles' viability for clinical translation. Broad applicability to other cancers and inflammatory conditions, along with ongoing advances in smart nanocarrier integration, positions green curcumin nanoparticles as a versatile platform for next-generation oncology therapeutics.

In sum, green nanotechnology offers a compelling, dual-purpose strategy—enabling both clinical efficacy in aggressive cancers like TNBC and the advancement of environmentally conscious pharmaceutical development.

9.2 Final Reflections on Sustainability and Impact

The development of green-synthesized curcumin nanoparticles epitomizes the convergence of scientific innovation, environmental stewardship, and global health equity. By leveraging the principles of green chemistry, researchers are not only improving drug delivery for life-threatening diseases but also redefining how therapeutics can be sustainably produced and deployed. The replacement of hazardous reagents with plant-based, biodegradable materials contributes to safer production cycles and reduced ecological harm—benefits that extend well beyond the laboratory.

Importantly, the alignment of this technology with the needs of resource-constrained health systems cannot be overstated. Using accessible, plant-derived inputs and scalable fabrication processes, green nanomedicine holds promise for more affordable cancer treatments. This is particularly relevant for low- and middle-income countries, where TNBC prevalence is rising and access to advanced therapies remains limited.

Ethical sourcing of natural materials, fair licensing practices, and equitable access strategies are vital to ensure that green innovations do not replicate historical inequalities in pharmaceutical development. As researchers, industries, and policymakers collaborate to bring such therapies into mainstream use, these principles must remain central to decision-making.

In its essence, the journey of green curcumin nanomedicine reflects a larger movement toward systems-level thinking in science—one that integrates human health, environmental responsibility, and economic inclusivity. The model presented here may well serve as a blueprint for future drug development, demonstrating that sustainability and high-impact medicine can—and must—coexist.

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