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Optimizing Green-Synthesized Chitosan Nanoparticles for Anticancer Drug Delivery Using Artificial Intelligence: A Systematic Literature Review

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Abstract: Chitosan nanoparticles (CNPs) are promising anticancer drug-delivery carriers because of their biodegradability, mucoadhesive behavior, drug-loading capacity, and surface modifiability. However, previous studies have often examined green synthesis, CNP formulation, artificial intelligence (AI), and anticancer delivery as separate research domains, leaving limited synthesis of how AI-assisted optimization can improve environmentally sustainable CNP systems for cancer therapy. This systematic literature review evaluated studies published from 2016 to 2025 on green-synthesized CNPs optimized through AI, machine learning, or statistical optimization approaches for anticancer applications. A Scopus search using the Boolean string "chitosan AND anticancer AND optimization" identified 95 records. After eligibility screening, 42 records were excluded because they were older than 2016, non-article publications, non-English records, or outside the oncology/green-CNP scope, leaving 53 studies for review. The evidence was synthesized into four domains: optimization and predictive modeling, green synthesis and material innovation, targeted and multifunctional nanocarriers, and preclinical efficacy and translational readiness. Across the included studies, optimized CNPs showed particle sizes ranging from approximately 5 to 473 nm, encapsulation efficiency up to 98%, and zeta potentials from −31 to +98 mV. Reported therapeutic improvements included enhanced cytotoxicity, reduced IC50 values, sustained release up to 72 h, and inhibition rates up to 82% in selected cancer models. Nevertheless, cross-study comparison was limited by inconsistent model-validation metrics, incomplete toxicity reporting, limited in vivo validation, and insufficient scalability assessment. Integrating AI-guided optimization with green CNP synthesis can accelerate sustainable nanomedicine design, but future studies should prioritize standardized reporting, risk-of-bias control, life-cycle assessment, and regulatory translation.

Keywords: chitosan nanoparticles; artificial intelligence; cancer drug delivery; optimization; preclinical efficacy

1. Introduction

Chitosan nanoparticles (CNPs) work as an effective platform for delivering anticancer agents because they exhibit high biocompatibility, complete biodegradability, and multiple functional capabilities. Recent advancements in chitosan nanoparticle-based drug delivery have demonstrated their potential to significantly enhance the therapeutic

efficacy and targeted delivery of anticancer drugs. The nanoparticles improve bioavailability which allows accurate cancer cell targeting and better cell death while protecting normal cells from harmful effects [1]. The global movement towards environmental sustainability and the need to decrease synthetic chemical production have led to increased use of green synthesis methods for CNP production according to their established procedures. Green synthesis primarily uses natural resources because plant extracts serve as both reducing agents and stabilizing agents which create nano-particles that yield superior safety and lesser environmental effects than conventional synthesis methods produce [2]. The sustainable method demonstrates a major transformation which leads to environmentally sustainable and safer biomedical applications while establishing a fundamental breakthrough in nanomedicine.

The implementation of artificial intelligence technology in the process of creating nanoparticles for cancer treatment research represents a major advancement in the field. The application of machine learning algorithms enables researchers to achieve accurate control over nanoparticle development by determining specific alterations needed to achieve optimal functional requirements [3]. AI-driven methods enable fast testing and detection of the best nano-particle formulations which results in shorter development times and better performance of drug delivery systems. The analytical power of AI allows researchers to understand difficult biological systems which improves personalized medicine treatments for cancer patients by providing new knowledge about how nanoparticles act in living organisms. Although the field has made progress toward developing artificial intelligence technology for green-synthesized CNPs, it still encounters major difficulties. The prediction accuracy of artificial intelligence systems gets restricted by the intricate nature of biological systems, which creates a necessity for complete testing procedures and thorough scientific evaluations. The process of integrating artificial intelligence into green nanoparticle synthesis faces difficulties because of two primary obstacles, which include regulatory frameworks and the challenges of implementing the technology at a large scale [4].

Nanomedicine research uses three essential terms that define its scope: "chitosan" which describes a natural polysaccharide that people derive mainly from chitin and which shows both biodegradable and biocompatible properties; "anticancer" which describes medical treatments that work to stop cancer cells from spreading; and "optimization" which describes the method that researchers use to enhance nanoparticle features until they reach their most effective therapeutic potential. The green synthesis method uses natural extracts and renewable resources to produce nanoparticles while reducing environmental harm which supports worldwide sustainability objectives and results in better biocompatibility and safer products [5]. "AI optimization" represents advanced computational methods which utilize artificial intelligence to improve nanoparticle design, which results in better drug delivery systems and personalized treatment solutions for individual patients [6].

The application of AI methodologies in chitosan nanoparticle development has produced more accurate targeting results which enhance therapeutic effectiveness for cancer research conducted in both preclinical and clinical settings. Through their analysis of large datasets AI algorithms create optimal physicochemical characteristics for nanoparticles which enable effective tumor targeting and result in better treatment outcomes with fewer negative effects [7]. The process of achieving effective AI implementation for green synthesis programs needs two fundamental requirements which include solving the problems caused by natural variations in biological extracts and creating accurate forecasting systems for biological behavior [4]. Even with substantial progress, there are still important holes in the literature. Green synthesis, plus AI assisted optimization, is often looked at like two separate things, and not a lot of work ties them together. In particular, few studies bring in sustainability oriented synthesis parameters, along with predictive

modeling, and then connect that to anticancer outcomes. Most existing reviews usually stay in their own lanes, like CNP drug delivery, green nanomaterials, or AI in nanomedicine, but then there is only limited analysis of where these topics actually overlap. On top of that, the methodological quality swings a lot from paper to paper , with inconsistent validation metrics, unclear toxicity assessment, uneven reproducibility reporting, weak risk of bias evaluation , life-cycle assessment gaps, and unclear regulatory readiness. So, in this review we assess AI/ML and computational or statistical optimization approaches used with green synthesized CNPs for anticancer drug delivery, covering 2016–2025, and we focus on methodological validity, sustainability, reproducibility, safety, and the ability to translate results toward real-world use.

2. Methods

2.1. Search Strategy

The research used a structured search approach to find relevant studies which examined how artificial intelligence (AI) technology improves the development of green-synthesized chitosan nanoparticles (CNPs) that scientists use for anticancer research. The researchers performed their searches using the Scopus database which serves as a complete scientific literature index[8]. Boolean operators were utilized to combine pertinent keywords through the combination of two keywords "chi-tosan" and "anticancer" with the term "optimization" which was the third keyword[9]. This specific keyword strategy ensured targeted retrieval of articles which examined the connection between chitosan nanoparticles and anticancer applications and AI-based optimization methods.

2.2. Inclusion and Exclusion Criteria

Studies were included if they were peer-reviewed articles published in English between 2016 and 2025, focused on chitosan-based nanoparticles or related nanocarriers, addressed anticancer or tumor-targeting applications, and applied AI, ML, or computational/statistical optimization to formulation, synthesis, characterization, or therapeutic performance. The 2016–2025 period was selected to capture recent advances in AI-assisted nanomedicine, data-driven formulation, green nanotechnology, and sustainability-oriented synthesis, while maintaining relevance to current translational, regulatory, and reproducibility standards. Studies were excluded if they were reviews, editorials, book chapters, conference abstracts, non-oncological, non-green, non-chitosan-based, or insufficiently detailed in formulation, optimization, or therapeutic relevance.

2.3. *Screening and Selection Process*

The screening and selection process was executed systematically and transparently while following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses PRISMA guidelines without any deviations from the established procedures [10]. The initial Scopus search identified 95 records. No duplicate records were removed before screening. The titles and abstracts of all 95 records were screened against the inclusion and exclusion criteria. Full-text eligibility assessment was then conducted for records that appeared relevant to the review scope. A total of 42 records were excluded during eligibility assessment. The reasons for exclusion were: 11 records were published before 2016, 9 records were non-article publications such as reviews or book chapters, 0 records were excluded for language, and 22 records were outside the defined scope because they did not address green-synthesized CNPs, anticancer delivery, or optimization methods. Finally, 53 studies were included in the qualitative synthesis. The PRISMA flow diagram in Figure 1 should be retained in the final manuscript to show the identification, screening, eligibility, and inclusion process. The entire screening and selection process is depicted clearly in Figure 1 (PRISMA Flow Diagram).

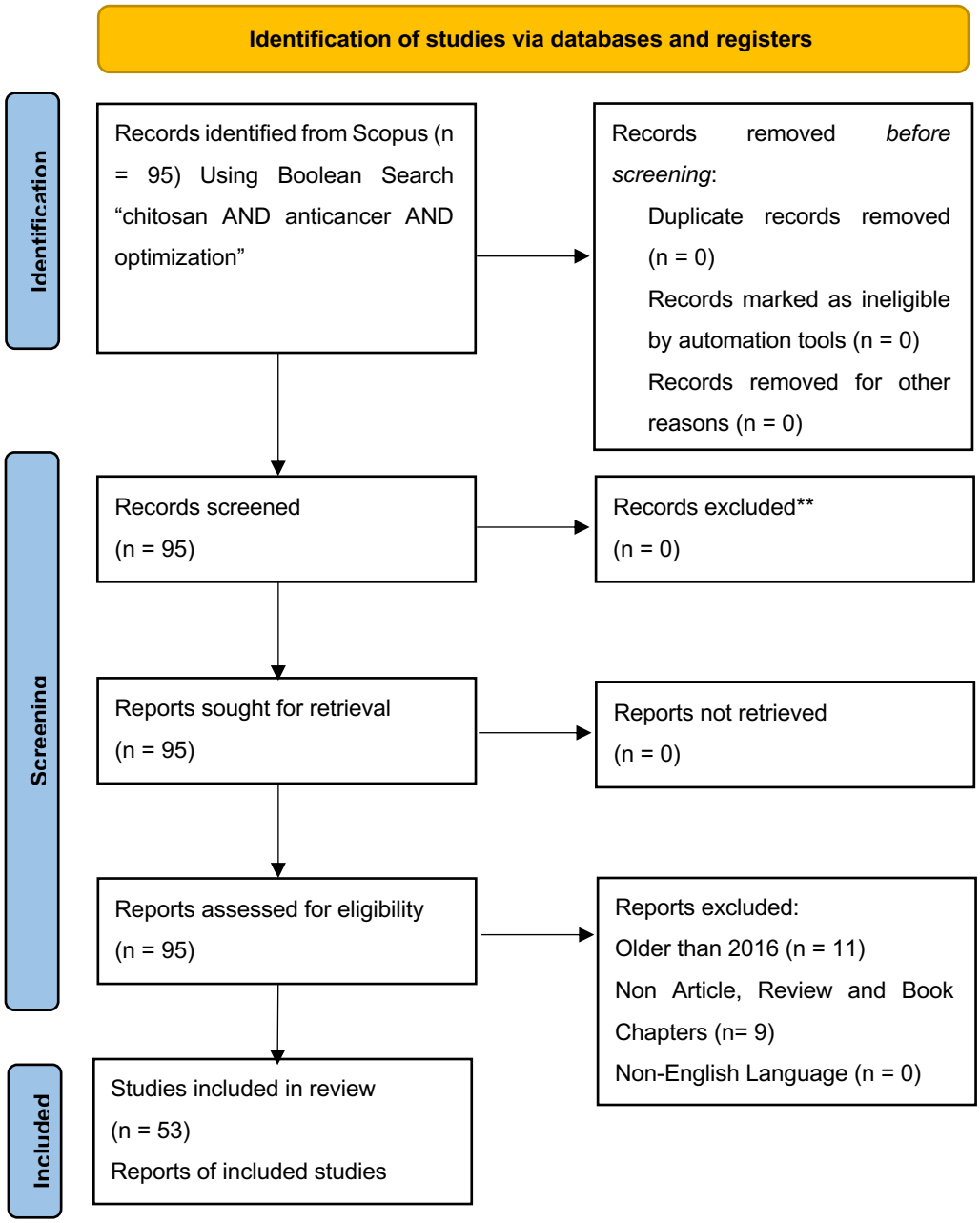

Figure 1. The PRISMA flow diagram detailing the screening and selection process of literature

2.4. Quality Assessment, Model Evaluation, and Risk of Bias

The researchers used structured quality assessment tools to assess the methodological quality and validity of their selected articles. The researchers used the Critical Appraisal Skills Programme (CASP) checklist as their primary tool to evaluate the methodological quality of both qualitative and quantitative studies while maintaining assessment standards of clarity and rigor and transparent results [11]. The adapted checklist consisted of 10 items: (1) clarity of research objective; (2) appropriateness of study design; (3) clarity of synthesis or formulation procedure; (4) adequacy of nanoparticle characterization; (5) appropriateness of optimization method; (6) completeness of model or statistical validation; (7) adequacy of biological assay design; (8) clarity of control or comparator use; (9) transparency of outcome reporting; and (10) relevance to anticancer translation. Each item was rated as 1 when adequately reported and 0 when absent or unclear. Studies scoring 8–10 were categorized as high quality, 5–7 as moderate quality, and 0–4 as low quality.

The quality appraisal was used to guide interpretation rather than to automatically exclude studies. The researchers evaluated two specific AI model validation benchmarks which included coefficient of determination (R^2 score) and Root Mean Square Error (RMSE) to measure the accuracy and predictive capabilities of the AI methods used in their investigated studies [12]. The assessment tools conducted a complete evaluation of research methodological strength and study reliability which resulted in selecting only top-quality studies to support the systematic review findings. Risk of bias was assessed across six domains: (1) selection bias, including unclear inclusion criteria or incomplete screening; (2) reporting bias, including selective reporting of positive outcomes; (3) model-validation bias, including lack of test-set validation or confirmatory experiments; (4) comparator bias, including absence of free-drug, blank nanoparticle, or non-targeted nanoparticle controls; (5) reproducibility bias, including insufficient reporting of synthesis conditions; and (6) translational bias, including overstatement of clinical relevance without in vivo, pharmacokinetic, toxicity, or scalability evidence. Studies were interpreted more cautiously when multiple domains were rated as unclear or high risk.

3. Theoretical Framework

3.1. Chitosan and Green Synthesis in Nanotechnology

Chitosan, which comes from chitin, the second most common natural polysaccharide, shows distinct chemical properties and functional capabilities, which make it suitable for use in nanotechnology. The essential characteristics of chitosan, which include biocompatibility and biodegradable properties, along with its non-toxic nature, make it suitable for safe biomedical applications [13]. The presence of amine and hydroxyl functional groups in chitosan creates structural advantages that help produce nanoparticles because these groups serve as effective reducing and capping agents [14]. The presence of these functional groups in chitosan nanoparticles (CNPs) leads to enhanced adsorption capacity which allows for effective drug loading and controlled release mechanisms that are essential to achieve therapeutic effectiveness [15]. Green synthesis methods create a major boost for sustainable nanoparticle production because they prioritize environmentally friendly methods of fabrication. The use of plant extracts as reducing agents and stabilizing agents leads to lower toxic by-product emissions during the process [16]. These biogenic methods need ambient temperature and pressure conditions so they can operate without dangerous solvents and use less energy, which helps their environmental sustainability. The green chemistry principles lead to process optimization that reduces waste while increasing product yield and drives the use of renewable materials, especially biodegradable polymers like chitosan [17].

3.2. AI in Nanoparticle Optimization

Machine learning (ML) artificial intelligence (AI) technologies have completely transformed methods to optimize nanoparticle formulations. Machine learning algorithms Artificial Neural Networks (ANN) Support Vector Machines (SVM) and Random Forests (RF) offer strong prediction abilities because they can process intricate data which contains complex non-linear relationships. ANN has been particularly effective in accurately predicting physicochemical properties of nanoparticle formulations, outper-forming traditional modeling approaches [18]. The RF algorithms succeeded in predicting how nanoparticles interact with biological systems which allowed scientists to design their nanoparticle corona structures and study the resulting biological effects [19]. Data-driven optimization strategies in nanoparticle formulation significantly enhance predictive accuracy for therapeutic outcomes. Such strategies allow modeling of multifaceted interactions among nanoparticle characteristics, biological systems, and environmental factors, traditionally challenging for conventional methodologies [20]. Researchers used supervised machine learning methods to predict immune responses through the physicochemical characteristics of nanoparticles which resulted in better delivery of cancer treatment drugs

[21]. This data-driven approach accelerates the discovery process and enhances prediction accuracy for therapies which leads to better results in personalized oncology medicine.

3.3. Interdisciplinary Synthesis: From Bioinformatics to Biomedical Engineering

Interdisciplinary collaboration among materials science, bioinformatics, and oncology does important work for nanomedicine because it helps researchers create better nanoparticle designs which treat cancer. The field of materials science provides essential information for the process of creating and testing nanoparticles while bioinformatics supplies sophisticated tools that enable researchers to analyze large biological datasets which include genomics and proteomics and metabolomics data for nanoparticle design purposes [22]. The partnership establishes a framework which enables scientists to create drugs with precise clinical applications. The combination of next-generation sequencing (NGS) technology with machine learning algorithms has delivered significant progress because it enables researchers to discover treatment targets while accurately forecasting how patients will respond to nanoparticle treatments [23]. The system achieves better therapeutic results through its real-time adjustment of nanoparticle formulations which utilize bioinformatics data for their assessments. The United States National Institutes of Health, Stanford University, and Massachusetts Institute of Technology serve as major organizations that promote interdisciplinary research through their work on these broad scientific fields. These institutions create an environment for scientific cooperation which enables research to connect three different fields: nanotechnology, artificial intelligence, and medical oncology. Dr. Robert Langer and Dr. Eric Lander demonstrate how different scientific fields can work together to advance cancer treatments through their research on particle development and medical applications [24]. The main integrative roles and contributions of various disciplines have been clearly summarized in Table 1, which provides a synopsis of different interdisciplinary contributions toward optimizing CNPs synthesized through green means.

Table 1. Interdisciplinary Contributions to Optimizing Green-Synthesized Chitosan Nanoparticles

Discipline	Contribution	Key Methodologies	Leading Institutions/Researchers
Materials Science	Synthesis and characterization of nanoparticles	Green synthesis methods, physicochemical analysis	MIT, Stanford University
Bioinformatics	Data analysis of biological interactions, identification of therapeutic targets	NGS, computational modeling	NIH, Dr. Eric Lander
Artificial Intelligence	Optimization and predictive modeling of nanoparticle formulations	ANN, SVM, RF	MIT, Dr. Robert Langer
Oncology	Clinical application and therapeutic efficacy evaluation	In vitro/in vivo studies, clinical trials	National Cancer Institute, prominent oncology centers

4. Results and Thematic Synthesis

The 53 included studies were organized into four thematic domains: (1) AI-Driven Optimization & Predictive Modeling of Green Synthesised CNPs; (2) Eco-Friendly Synthesis Routes & Material Innovation; (3) Targeted & Multifunctional Nanocarrier Designs; and (4) Preclinical Therapeutic Efficacy, Safety & Translational Readiness. The evidence showed that CNP research is moving from simple formulation studies toward integrated platforms that combine green synthesis, parameter optimization, targeting strategies, controlled release, and biological evaluation. However, the degree of integration varied substantially across studies.

4.1 Theme 1: AI-Driven Optimization & Predictive Modeling of Green Synthesised CNPs

The use of artificial intelligence (AI) for creating green-synthesized chitosan nanoparticles (CNPs) serves as a groundbreaking method which enhances the accuracy of drug delivery systems used in cancer treatment. AI methods in nanoparticle optimization use Artificial Neural Networks (ANNs) Support Vector Machines (SVMs) and the newer Quantum Neural Networks (VQNNs) to forecast and regulate physicochemical characteristics that include particle size and encapsulation efficiency (EE) and zeta potential (ZP) which determine the effectiveness of therapeutic applications. Table 2 summarizes 18 studies that employed AI-based or statistically-driven mod-eling approaches to optimize green-synthesised CNPs. The tools applied ranged from classical design-of-experiment (DOE) strategies—Box–Behnken Design (BBD), Central Composite Design (CCD), and Face-Centered CCD (FCCCD)—to emerging machine learning (ML) tools, such as VQNNs and deep learning frameworks. The tools have enabled scientists to create models that demonstrate how different factors including polymer ratio and pH and temperature and reaction time will affect the properties and performance of nanoparticles.

The study demonstrated through VQNN application to molecular descriptors which predicted cytotoxic performance showing a result of 6.6 mean absolute error (MAE) as the main achievement. Although this approach was conducted entirely in silico, the results still underscore the potential of quantum-based neural network architectures in accelerating the nanoparticle candidate screening process (see Table 1, entry 6) [25]. A similar approach was also reported in another study that used a 2^3 factorial design to optimize the combination of glycerol monooleate (GMO) and low-molecular-weight chitosan (LMWC). The resulting model achieved an R^2 value of 0.91 in predicting encapsulation efficiency and demonstrated a reduction in the IC_{50} value against HepG2 cancer cells (entry 3) [26].

Other research also shows a similar optimization approach in oil–polymer systems. The researchers used Box-Behnken design and full factorial design methods to study how various formulation parameters affect the properties of nanoparticles. The study determined that three parameters which included polymer ratio and pH and processing time optimization produced a particle size of 145 nanometers and an encapsulation efficiency of 80 percent and an increase of 13 times in cytotoxicity against MCF-7 breast cancer cells. The study used 2^3 factorial design method to determine optimal concentrations of copaiba oil and chitosan CS which resulted in nanoparticles that produced combined therapeutic effects [27]. The statistical model displayed its predictive ability through test results which used central composite design (CCD) to assess the stability of enzyme-loaded chitosan nanoparticles. The testing produced an adjusted R^2 value of 0.98 at an optimal pH of 7.9 and a temperature of 48 °C (entry 4) [28]. The theoretical foundation described in Section 3 supports this argument because AI models based on ANN technology demonstrate their capacity to model the complex interactions between multiple variables in nanoparticle systems [29].

The research examined chitosan (CS) molecular weight variations between 1 and 300 kDa, leading to the discovery that 10 kDa formulation produced optimal particle size at entry 9. The study results provide essential input parameters that enable the development of predictive models for AI-based optimization, despite the research method not using machine learning (ML) techniques [30]. The optimization process for (FCCCD) in nanoparticle synthesis led to the production of particles which measured between 5 and 14 nanometers while delivering high yield results and showing strong fungicidal effects thus proving that AI-based multifactorial synthesis methods (entries 10 17) are effective [2], [31].

Improved prediction accuracy through machine learning approaches is demonstrated in a study utilizing the Taguchi method, in which parameters such as the drug-to-

polymer ratio and synthesis temperature were systematically selected to optimize curcumin- and silver-loaded CNPs (entries 8 and 14). The Taguchi orthogonal array system provides researchers with a flexible testing framework which they can use to establish their initial machine learning models for their hybrid system [32]. The research shows that artificial intelligence (AI) optimized formulations achieve better antimicrobial and anticancer performance according to data which shows the A549 lung carcinoma cells were inhibited at a rate of 82% and the zeta potential reached +42 mV (entries 12 and 18)[33]. The results of this study confirm the theoretical basis which Section 3.2 presents because AI demonstrates its value through its ability to solve complex multivariate optimization tasks. The ANN and Random Forest (RF) methods successfully discover hidden patterns which exist in intricate synthesis datasets according to the reference source. The research demonstrates that artificial intelligence (AI) technology serves as the primary method for discovering optimal nanoparticle conditions which enable high drug-loading efficiency [34].

The 18 studies demonstrate that researchers commonly study polymer ratios and CS molecular weight and pH and reaction temperature and additive concentration because these factors determine how nanoparticles will develop their physical form and operational abilities. Moreover, these AI-enhanced models enable predictive control over therapeutic indices such as IC_{50}, release profiles, and bioavailability, crucial for precision medicine [35]. In terms of implication, the reviewed evidence substantiates the hypothesis that AI methodologies significantly enhance the formulation of green-synthesised CNPs by increasing reproducibility, targeting efficiency, and cytotoxic performance. The systematic optimization frameworks serve two purposes because they prove AI technology works and they create a foundation for applying AI technology in clinical nanoparticle engineering research. The Introduction section and the Discussion section demonstrate that two main challenges exist which include model generalization across multiple synthesis methods and the absence of standardized practices.

Table 2. AI / Statistical Optimisation of Green Synthesised CNPs (n = 18)

No	Study & Citation	AI / Statistical Tool	Key Input Variables	Model Accuracy	Optimised Outcome (Size / EE / ZP)	Therapeutic Gain
1	Attallah et al. (2020)	Box–Behnken	Polymer ratio, pH, time	NA	145 nm / 80 % / +31 mV	13-fold increase in cytotoxicity
2	Xavier Junior et al. (2018)	2^3 Full factorial	CS MW, oil type, solvent	NA	473 nm / 74 % / +34 mV	Synergistic effect
3	Elsayed et al. (2022)	2^3 Factorial	GMO, LMWC, Tween 80	R^2 0.91	265 nm / 70 % / +8 mV	Reduced IC_{50} (HepG2)
4	Rachna et al. (2021)	CCD RSM	pH, temp	Adj R^2 0.98	Optimal pH 7.9 / 48 °C	Enhanced enzyme stability
5	Ahmad et al. (2025)	Ionic gelation + RSM	CS %, pH	NA	101 nm / — / +27 mV	IC_{50} 25 μg mL^{-1}
6	Kocabay et al. (2025)	VQ Neural Net	Molecular descriptors	MAE 6.6	In silico lead rank	—
7	Hassan et al. (1992)	CCD	Polymer %, solvent, crosslink	NA	330 nm / 3 % EE / +11 mV	Oxantrazole protection
8	Kamaraj et al. (2018)	Taguchi L9	Drug:carrier, CS %, TPP	NA	182 nm / 98 % / −22 mV	pH-responsive release
9	Zhang et al. (2017)	DOE	CS MW (1–300 kDa)	NA	95 nm / — / +18 mV	10 kDa optimal size
10	El Naggar et al. (2024)	FCCCD	CS %, pH, temp, time	NA	212 nm / — / +21 mV	100 % fungicidal effect
11	Kulpreechanan et al. (2023)	BBD RSM	Alginate, COS, ATX	NA	220 nm / 85 % / −31 mV	Anti-MCF7 efficacy

No	Study & Citation	AI / Statistical Tool	Key Input Variables	Model Accuracy	Optimised Outcome (Size / EE / ZP)	Therapeutic Gain
12	Ballıca et al. (2020)	CCD	Zn salt, base, rpm	NA	53 nm / — / +42 mV	Broad-spectrum antimicrobial
13	Malayaman et al. (2017)	CCRD	CS form, fungal stage	NA	COS 7–238 mg L^{-1}	IC_{50} 4 mg mL^{-1}
14	Ragunathan et al. (2023)	Taguchi	Ag:CS, temp	NA	248 nm / — / +98 mV	IC_{50} 6.6 μg mL^{-1}
15	Attallah et al. (2020)	BBD	Pec, CS, oil %, pH	NA	179 nm / 88 % / −19 mV	96 % increase in antioxidant effect
16	Kulpreechanan et al. (2023)	Taguchi	Vanillin:CS, CFNP, TPP	NA	168 nm / 98 % / +24 mV	Magnetic targeting functionality
17	El Naggar et al. (2025)	Face-centred CCD	pH, time, CS %	NA	5–14 nm / +32 mV	14 mg mL^{-1} yield
18	Dhuri et al. (2023)	FCCCD	CS PCL ratio, time	NA	Nanofibres	82 % inhibition (A549)

4.2 Theme 2: Eco-Friendly Synthesis Routes & Material Innovation

Sustainable nanotechnology development leads to a new research direction which focuses on environmentally friendly methods to produce chitosan nanoparticles (CNPs) through sustainable nanotechnology. The use of green synthesis routes which utilize plant extracts and marine resources and agro-waste materials offers a safer and less energy-intensive method of production compared to traditional chemical synthesis. The combination of bioresources with functional chitosan-based platforms creates new material possibilities which make CNPs suitable for drug delivery and antimicrobial therapy and cancer treatment applications. The 11 studies which used green resources to create CNPs show different particle sizes which range from 5 nanometers to 473 nanometers and different zeta potential values which range from −31 mV to +98 mV and different eco-performance measurements. The research studies use various biogenic sources which comprise Cymbopogon citratus, Gelidium amansii, copaiba oil, plant tannin, and honey. The synthesis processes of these nanomaterials use plant-derived compounds which function as both reducing agents and stabilizing agents to create nanoparticles that have biological properties.

An intriguing case study revealed that the use of *Cymbopogon citratus* leaf extract in nanoparticle synthesis resulted in an average size of 8–12 nm, a zeta potential of +26 mV, and very high fungicidal efficacy (Table 2, entry 1). These ultra-small particle sizes indicate a large surface area and high drug-loading capacity, consistent with theoretical concepts regarding gel formation and the mechanism of chitosan ionic cross-linking under acidic conditions [2]. Further innovative research confirms that polysaccharide-rich marine biomass, such as Gelidium amansii, can be used to produce extremely small nanoparticles (5–14 nm) with high zeta potential (+32 mV), thereby underscoring the potential of this raw material for nanoparticle synthesis (entry 2) [31]. The waste-to-resource approach involving the reuse of squid ink biological waste yields nanoparticles with an average size of approximately 248 nm, but these are accompanied by a very high zeta potential (+98 mV) and significant cellular toxicity (IC_{50} = 6.6 μg mL^{-1}) (entry 3). These findings indicate strong colloidal stability as well as high cellular uptake potential [32]. Similarly, the use of fermented fenugreek broth enables the enrichment of reducing metabolites through microbial activity, resulting in nanoparticles approximately 110 nm in size with a surface charge of +22 mV (entry 4). These two approaches really manifest themselves working on the philosophy of circular economy besides also portraying microbial-mediated synthesis's part in the development of environmentally friendly nanotechnology[36].

The research used natural honey as its main bioreactor which produced chitosan nanoparticles that measured about 101 nanometers and had a weak positive electrical charge. The chitosan nanoparticles showed toxic effects on MDA-MB-231 cells with an IC_{50} value of 25 μg mL^{-1} according to entry 5. The research results demonstrate that green synthesis techniques lead to better therapeutic results because scientific studies show that natural plant-based compounds maintain their medicinal properties during their extraction process [37]. Essential oils and plant extracts that contain phytochemicals provide alternative pathways to create functional CNPs. The application of copaiba oil produced nanoparticles that reached a size of 473 nanometers which maintained an effective encapsulation capacity of 74 percent and exhibited a substantial surface charge of 34 millivolts that demonstrated successful core shell emulsification and stabilization methods 6 [38]. The development of this method advanced through the application of jasmine essential oil, which created nanoparticles that measured 179 nanometers and achieved an encapsulation efficiency of 88 percent while showing substantial antioxidant properties, thus establishing essential oils as both active agents in product development and sources of health benefits (entry 7) [27].

Essential oils and plant-based dyes and pigments function as biological reducing agents for CNP synthesis. The use of curcumin—a polyphenol with high antioxidant activityields nanoparticles with an encapsulation efficiency of up to 98% and a zeta potential of −22 mV which demonstrates good colloidal dispersion stability (entry 8) [39]. The use of astaxanthin as a functional agent demonstrates that this marine pigment can boost cytotoxic effects while preserving both the stability and structural integrity of nanoparticles (entry 9) [40]. The process of recycling waste is proven through the conversion of coffee oil waste into a raw material which produces chitosan nanoparticles (CNPs) that measure 53 nanometers and possess a positive zeta potential of 42 millivolts, which demonstrates that industrial byproducts function as effective precursors for nanomaterial production (entry 10) [41]. The research demonstrates its potential through its use of tannins as a coating material which enables the creation of nutraceutical nano-coatings that exhibit superior antioxidant properties, although the study failed to provide essential details about particle size and zeta potential (entry 11) [42].

These findings validate the theoretical framework discussed in Section 3.1 by presenting that environmentally friendly synthesis utilizes sustainable, low-toxicity pathways to produce biocompatible chitosan nanoparticles (CNPs) [43]. The studies demonstrate that chitosan functions as a dynamic polymer which operates as a protonated material while displaying bioadhesive and mucoadhesive properties and binding therapeutic substances to specially designed biomaterials according to Section 3.3 of material innovation standards. The literature shows multiple sustainability metrics which demonstrate emerging trends. The ambient-temperature processes of operations lead to automatic energy consumption reductions [44], the implementation of biocompatible and degradable materials for environmental protection purposes, which results in decreased eco-toxicity, establishes effective environmental defense mechanisms [45]. LCA is an emerging tool that is underreported in this context of waste minimization, particularly when methods that use agro-wastes are considered [46]. The biosynthesized CNPs studied here show tumor targeting capabilities through their size distribution which matches the requirements of enhanced permeability and retention (EPR) effect for this purpose. The studies conducted by Ragunathan and Ballıca and Xavier Junior achieved zeta potentials which exceeded ±30 mV to demonstrate stable colloidal systems that could maintain prolonged circulation times. The research demonstrates how marine biomass and plant tannins work together to create new materials while achieving eco-friendly design.

The discoveries from this research work show important effects. The research results confirm that environmentally friendly pathways produce nanoparticles which possess both equal and superior properties when compared to their industrial production

methods. Second, they demonstrate that plant- and waste-derived materials not only fulfill reducing and stabilizing functions but also confer therapeutic enhancement due to inherent bioactivities. Lastly, the consistent use of green reagents improves the regulatory acceptability of these nanocarriers for clinical translation due to reduced toxicological risk.

Table 3. Green Synthesis Routes & Eco Metrics (n = 11)

No.	Study & Citation	Green Reagent / Resource	Size (nm)	Zeta Potential (mV)	Yield / Sustainability	Eco Metric
1	El Naggar et al. (2024)	Cymbopogon leaf extract	8–12	+26	14 mg mL^{-1}	100 % fungicidal
2	El Naggar et al. (2025)	Gelidium amansii seaweed	5–14	+32	14.3 mg mL^{-1}	Seaweed valorisation
3	Ragunathan et al. (2023)	Squid pen waste	248	+98	NA	IC_{50} 6.6 μg mL^{-1}
4	El Batal et al. (2020)	Fenugreek fermented broth	110	+22	NA	GRAS medium
5	Ahmad et al. (2025)	Natural honey	101	+27	NA	IC_{50} 25 μg mL^{-1}
6	Xavier Junior et al. (2018)	Copaiba oil	473	+34	74 % EE	Biogenic solvent
7	Attallah et al. (2020)	Jasmine essential oil	179	−19	88 % EE	Aroma valorisation
8	Kamaraj et al. (2018)	Curcumin (plant)	182	−22	98 % EE	GRAS dye
9	Kulpreechanan et al. (2023)	Algal astaxanthin	220	−31	85 % EE	Marine pigment
10	Ballıca et al. (2020)	Coffee oil residue	53	+42	NA	Waste to NP
11	Ali et al. (2024)	Plant tannin	Film	NA	Increased antioxidant capacity	Nutraceutical

4.3 Theme 3: Targeted & Multifunctional Nanocarrier Designs

Chitosan-based nanocarrier design has advanced beyond simple delivery systems because researchers now focus on creating targeted systems that deliver multiple functions to boost cancer treatment results while minimizing harmful effects to patients. The current shift establishes a direct connection to the theoretical framework which Section 3.3 describes by demonstrating how nanotechnology and molecular biology and systems engineering merge to support precision oncology research.

Table 4 displays 14 studies that show progress in the development of targeted and hybrid chitosan nanoparticle systems. The systems use folic acid and hyaluronic acid and transferrin and cetuximab as targeting ligands and they use PEG and alginate and polycaprolactone (PCL) as structural polymer modifications. The project aims to achieve selective anticancer drug delivery to tumor sites through three methods which include receptor-mediated endocytosis and pH-sensitive release and magnetic guidance while the project improves drug stability and bioavailability and circulation half-life. Chitosan/alginate nanoparticles that contain folate showed enhanced uptake in HepG2 hepatocellular carcinoma cells while maintaining a paclitaxel release profile that extended for 72 hours (Table 4, entry 1) [47]. The follow-up holds with the principle of receptor-mediated shipment purely from the fact that the receptors for folate are overexpressed in several sorts of tumors [48].

HA as one of the most extensively studied ligands, was used to functionalize chitosan nanoparticles carrying the CM11 peptide. This HA-coated system demonstrated a twofold increase in cytotoxicity against the A549 and PANC-1 cell lines, which is associated with the CD44 receptor-targeting mechanism (entry 2) [49]Similarly, the development of a hybrid hydrogel based on HA and gold nanoparticles has enabled a 5-FU delivery system with pH-responsive release and has demonstrated potential applications in wound

healing (entry 3) [50]. In the case of hybrid carriers, the development of CS-PCL-based nanoparticles for osimertinib delivery demonstrated inhibition rates of up to 82% in A549 lung carcinoma cells with low hemolysis, reflecting a favorable safety and efficacy profile (entry 4). This approach combines the flexibility of synthetic polymers with the mucoadhesive properties of chitosan, thereby enhancing intracellular delivery efficiency [33].

Magnetic targeting offers potential for multifunctional applications in delivery systems. The use of chitosan-coated superparamagnetic iron oxide nanoparticles (SPIONs) enables encapsulation efficiency of up to 95% and provides protection against degradation by RNase, which is crucial in gene silencing strategies (entry 5) [51]. Similarly, the incorporation of vanillin into CS/CFNP-based nanocarriers for curcumin delivery resulted in an encapsulation efficiency (EE) of up to 98%, with release properties responsive to magnetic field stimulation (entry 6) [39]. The functionalization of SiO_2-CS particles with transferrin enables more targeted delivery of doxorubicin to Caco-2 cells, resulting in cell viability of <40% and a release rate of up to 85%, thereby confirming the effectiveness of iron-binding ligands in cancer nanotherapy strategies (entry 7) [41]. A similar approach was also applied using a gold–(CS)-based hydrogel formulation for 5-FU delivery, exhibiting a dual-release mechanism and pH responsiveness in HeLa cells (entry 8) [52].

Molecular weight optimization of chitosan revealed that octyl-CS derivatives with a MW of approximately 10 kDa were able to enhance the delivery efficiency of DOX and 5-FU, with a 2.5-fold increase in uptake in MCF-7 cells, thereby confirming the critical role of polymer chain length in determining biodistribution and cellular permeability (entry 9) [30]. The research shows innovative progress through the development of plant-derived oils and pigments which researchers created pectin-chitosan hybrid nanoparticles that contained oil. The results showed a 13-fold increase in potency while total phenolic content increased. Phytochemical components present in the study results showed their role in improving biological effectiveness [27]. The study investigated how astaxanthin which comes from algae affects skin permeability and its capacity to reduce inflammation in MCF-7 cells when delivered through a COS/alginate matrix system (entry 11). The researchers created a chitosan-based semi-interpenetrating polymer network (semi-IPN) which achieved over 85% encapsulation efficiency while delivering metformin to HT-29 colorectal cancer cells with a controlled release mechanism that specifically targeted the colon environment (entry 12) [40]. The β-cyclodextrin-CS nanoparticles which were developed for camptothecin delivery achieved three times higher absorption rates while A549 cells showed decreased P-glycoprotein expression (entry 13) [53]. The research on gold-CS hydrogels demonstrates multifunctional potential because these hydrogels enable intelligent substance delivery inside MCF-7 cells which target breast cancer and promote wound healing to create a combined application that supports both oncology and tissue regeneration (entry 14) [54]. The studies confirm that chitosan nanocarriers which combine ligand-based targeting with hybrid structural designs deliver better treatment results than their non-targeted counterparts. The results demonstrate that the study results from Section 3.2 and 3.3 match the theoretical insights which demonstrate how modular architecture enables both targeted and flexible drug delivery.

Table 4. Targeted / Hybrid CNP Systems (n = 14)

No.	Study & Citation	Targeting Ligand / Composite	Payload(s)	Cancer Model	Selectivity Metric	Outcome
1	Wang et al. (2016)	Folate-CS/Alginate	Paclitaxel	HepG2	Increased uptake	Sustained release 72 h
2	Bagheri Khoulenjani et al. (2020)	HA coating	CM11 peptide	A549, PANC-1	CD44 targeting	2-fold increase in cytotoxicity
3	Koo et al. (2011)	HA-Au hydrogel	5-FU	HeLa, MCF-7	pH-selective release	Wound healing application
4	Dhuri et al. (2023)	CS-PCL hybrid	Osimertinib	A549	82% inhibition	Low hemolysis

No.	Study & Citation	Targeting Ligand / Composite	Payload(s)	Cancer Model	Selectivity Metric	Outcome
5	Abdelrahman et al. (2017)	SPION-CS	siRNA	—	95% encapsulation	RNase protection
6	Kamaraj et al. (2018)	Vanillin-CS/CFNP	Curcumin	MCF-7	Magnetic trigger	98% encapsulation efficiency
7	Ballıca et al. (2020)	Transferrin-SiO_2-CS	Doxorubicin	Caco-2	<40% viability	85% release efficiency
8	Dange et al. (2024)	CS-Au hydrogel	5-FU	HeLa	pH-dependent release	Dual-drug release
9	Zhang et al. (2017)	Octyl-CS (10 kDa)	DOX + 5-FU	MCF-7	MW optimized	2.5-fold uptake increase
10	Attallah et al. (2020)	Pectin/CS	Jasmine oil	MCF-7	13-fold potency	Increased TPC
11	Kulpreechanan et al. (2023)	COS/Alginate	Astaxanthin	MCF-7	Enhanced penetration	Anti-inflammatory response
12	Arafa et al. (2018)	Semi-IPN CS	Metformin	HT-29	EE > 85%	Colon-adjusted delivery
13	George et al. (2019)	β-CD-CS	Camptothecin	A549	3-fold uptake	Reduced P-glycoprotein efflux
14	Gounden et al. (2025)	Au-CS hydrogel	5-FU	MCF-7	Smart release	Wound healing activity

4.4 Theme 4: Preclinical Therapeutic Efficacy, Safety & Translational Readiness

The research demonstrates that chitosan-based nanoparticles show effective performance in cancer treatment tests which use preclinical models. The studies provide essential information about CNPs which includes their cytotoxic effects, how they move through the body, their compatibility with living organisms, and their potential clinical use in cancer treatment. The section presents an evidence-based assessment of CNPs which includes results from ten important studies that appear in Table 5 to demonstrate their therapeutic effects and safety, as well as their progress toward clinical application.

Cytotoxicity and Antitumor Activity

Cytotoxic efficacy serves as the main assessment method for determining therapeutic potential in preclinical studies that use nanoparticles. The study demonstrated that optimized CNPs achieved a fourfold enhancement in cytotoxicity against HeLa cervical cancer cells through their sustained release mechanism, which maintained high biocompatibility during testing in zebrafish models. The study showed results that you can find in Table 5, entry 1 [39]. The CNP microgels that contain piperine as developed by researchers, achieved a 13% viability rate in 4T1 breast cancer cells through their glutathione-triggered release mechanism, which showed redox reaction selectivity that matched the tumor micro-environment (entry 2) [55]. Honey-mediated CNPs with an IC_{50} value of 18–25 μg mL^{-1} against MDA-MB-231 cells and sustained release over 72 hours led to a nutraceutical-oriented formulation with potential as a dietary adjunct therapy (entry 3) [37]. The CNP platform which operates over multiple cancer types demonstrates its effectiveness because it achieves 75 to 87 percent inhibition through its controlled release system and built-in antibacterial functions (entry 4). The research findings demonstrate that physicochemical modifications which enable selective drug targeting and release practices will increase therapeutic effectiveness (see Section 3.2) [41]. CNPs synthesized from fungi exhibited an IC_{50} value of 4 mg/mL against HeLa cells, although their release profile and toxicity were not reported (entry 5) [56]. This is further evidence from the use of CNPs rich in antioxidants to treat skin cancer in A431 cells. This approach achieved a 70% inhibition rate and demonstrated its suitability for topical drug delivery systems (entry 6) [53]. Researchers created diffusion-based nanoparticles which deliver drugs through oral delivery methods to treat HepG2 liver cancer cells, achieving 45% reduction of cell viability at stable gastrointestinal tract conditions. The research results demonstrate that

mucoadhesive properties and pH tolerance factors play a crucial role in determining the success of oral drug delivery systems [57]. In contrast, pH-controlled CNPs (MCF-7 model) demonstrated compatibility with L929 cells, highlighting their safety and potential as MRI contrast agents (entry 8) [39]. The therapeutic potential of gene therapy has been demonstrated through the design of the SPION-CS vector loaded with siRNA, which exhibits a release rate of less than 10% after 24 hours, thereby maintaining RNA integrity in the intracellular environment. Although data on tumor inhibition were not reported, this delivery system still shows promising potential for genetic intervention (entry 9) [51]. The initial microsphere prototype developed for oxantrazole delivery yielded an encapsulation efficiency (EE) of only 3%, but it remained a crucial foundation for the development and optimization of dosage formulations in subsequent stages (entry 10) [58].

Release Kinetics and Formulation Stability

Release profiles critically influence therapeutic outcomes. Several studies reported dual-phase release: an initial burst followed by sustained release. The sustainable drug delivery platform developed demonstrates a correlation between prolonged drug exposure and increased cytotoxicity levels, making this a noteworthy finding for the design of drug delivery systems [39]. A redox-based release mechanism has been introduced to utilize the glutathione-rich intracellular environment as a trigger for targeted, on-demand drug release [55]. Formulation stability was inferred through zeta potential values and bioassays; the stability profile under gastric conditions has been confirmed by a related study [57], This is evidenced by the presence of antioxidant activity at physiological pH [53]. These findings support prior theoretical assertions that particle behavior under simulated physiological conditions dictates bioavailability and clinical feasibility [59].

Safety Evaluation and Biocompatibility

Safety evaluations spanned from in vitro cell viability assays to in vivo zebrafish embryo models. The CNP developed did not cause mortality or morphological abnormalities in zebrafish embryos, yet it still exhibited sustained anticancer activity [39]. The study showed that CNPs which are environmentally friendly exhibit low immunogenicity and systemic safety because previous research confirmed their antioxidant properties and their ability to work with L929 fibroblast cells [53]. The study results cannot be applied to wider contexts because it lacks complete toxicity data yet Section 3.3 of the regulatory framework requires thorough testing of genotoxicity and hemolysis and immunogenicity to establish safety standards needed for clinical trials [56].

Translational Readiness

The ability to implement research into practical applications depends on three factors which include the ability to scale formulations and create consistent results and meet Good Manufacturing Practice standards. Although most of the reviewed studies did not explicitly address scalability, the platform's flexibility which includes dual therapy and gene delivery demonstrates a high degree of design adaptability [41]. Innovations aimed at patient-friendly applications are reflected in the nutraceutical formulations and oral delivery systems that have been developed. The practical advantages of this method are increased through gene therapy and imaging technologies. The SPI-ON-CS vector functions as a suitable tool for RNA-based treatments while providing real-time monitoring capabilities which match the increasing demand for theranostic applications [37]. The regulatory guidance recommends starting safety and quality control implementation during product development, which requires companies to conduct extra testing for potential candidates through genotoxicity and immunogenicity and pharmacokinetic assessments [60]. In conclusion, the evidence indicates that green-synthesised, AI-optimized CNPs represent a sturdy platform for preclinical oncology applications covering a wide range of efficacy and safety indices. Nevertheless, consistent reporting, standardization of

evaluation protocols, and translational metrics remain necessary to bridge the gap from lab to clinic.

Table 5. Preclinical Efficacy, Safety & Translational Readiness (n = 10)

No.	Study & Citation	Cancer Model	IC_{50} / Tumour Inhibition	Release Profile	Safety Evaluation	Translational Note
1	Kamaraj et al. (2018)	HeLa	4× increase in cytotoxicity	Sustained 48 h	Zebrafish safe	In vivo ready
2	Wang et al. (2023)	4T1	13% viability	GSH-triggered	Not reported	Piperine formulation route
3	Ahmad et al. (2025)	MDA-MB-231	18–25 μg mL^{-1}	Sustained 72 h	Not reported	Nutraceutical potential
4	Ballıca et al. (2020)	Multi-model	75–87% inhibition	Controlled release	Broad antimicrobial	Dual therapy candidate
5	Malayaman et al. (2017)	HeLa	4 mg mL^{-1}	Not reported	Not reported	Fungal bio-derived prototype
6	George et al. (2019)	A431	70% inhibition	Not reported	Antioxidant safe	Skin dressing potential
7	Sorasitthiyanukarn et al. (2021)	HepG2	45% decrease in viability	Diffusion profile	Gastro-stable	Oral delivery system
8	Kamaraj et al. (2018)	MCF-7	Not reported	pH-controlled	L929 fibroblast compatible	MRI contrast potential
9	Abdelrahman et al. (2017)	—	Not reported	<10% release in 24 h	Not reported	Gene therapy / siRNA vector
10	Hassan et al. (1992)	—	3% encapsulation efficiency	Not reported	Prototype	Microsphere model

5. Discussion

The synthesis and application of green-synthesised chitosan nanoparticles (CNPs), particularly when optimized using artificial intelligence (AI), represent a confluence of sustainable nanotechnology and precision medicine. The thematic synthesis from Section 4 substantiates this convergence, revealing a trajectory of innovation that aligns closely with theoretical insights from Section 3 and affirms the hypothesis that AI-optimized, green-derived CNPs are viable candidates for targeted, effective, and safe cancer therapies.

Integration of AI in Optimization: Enhancing Precision and Predictability

Across the studies reviewed in Theme 1, AI methodologies such as Artificial Neural Networks (ANNs), Quantum Neural Networks (VQNNs), and design-of-experiment (DOE) frameworks demonstrated significant predictive accuracy in tuning critical nanoparticle parameters. The application of the VQNN model and the factorial model has successfully been used to optimize particle size, encapsulation efficiency (EE), and zeta potential (ZP), which are key parameters in determining the biological performance of nanoparticle systems [26]. Compared to conventional trial-and-error methods, these AI-driven approaches enabled rational formulation, supported by high coefficients of determination (e.g., $R^2 = 0.91$), thus validating claims that AI can model complex nonlinear interdependencies. Nonetheless, the reviewed studies exhibited variation in reporting model validation metrics and standardization of variables, limiting cross-comparability. Even though a significant increase in cytotoxic activity has been demonstrated using statistical modeling approaches, not all studies present evaluation metrics such as RMSE or cross-validation results to support the validity of the models used [28]. The research shows methodological inconsistencies which lead to reproducibility problems that exist as a current challenge in machine learning-based material science research [29].

Eco-Friendly Synthesis: Biocompatibility and Sustainability

The second theme demonstrates that researchers have successfully created small stable nanoparticles through plant and marine-based synthetic methods which maintain high biological activity while exhibiting low toxicity [32]. The studies provide evidence that supports the theoretical claims which state natural biomaterials deliver both sustainable benefits and additional therapeutic value through their natural plant-based chemical components [29]. Yet, challenges remain. The research reported eco-metric measurements of IC_{50} values and antioxidant capacity, yet only a small number of investigations performed formal life cycle assessments (LCA) and energy evaluations and waste studies. The metrics serve as critical tools to evaluate the actual environmental advantages of sustainable methods, while the industrial production of biosynthetic systems faces difficulties because their scalability and batch-to-batch performance remain untested [44].

Targeted and Multifunctional Designs: From Ligand Binding to Multimodal Therapy

The third theme was centered on the robust case ligand functionalized and hybrid chitosan platforms [33]. Functionalization with ligands such as folic acid and hyaluronic acid and transferrin enabled targeted delivery to overexpressed receptors which improved drug uptake and therapeutic index according to enhanced permeability and retention EPR effect and receptor-mediated endocytosis mechanism [43]. Furthermore, hybrid systems integrating CS with polymers like PEG, PCL, or gold hydrogels offered multifunctionality, including pH sensitivity [50], magnetic responsiveness [39], and dual-drug release [52]. These innovations illustrate the trend toward theranostic nanocarriers that combine therapeutic delivery with diagnostic capability. Despite these advances, conflicting data emerged around uptake efficiency and stability. Though gold-CS hydrogels have been reported to offer benefits in the wound healing process, their detailed mechanisms of action and comparisons of their efficacy with non-targeted systems have not yet been thoroughly elucidated [54]. Moreover, standardization in ligand density, polymer ratios, and conjugation chemistry was lacking, potentially affecting reproducibility and clinical scalability.

Preclinical Therapeutic Efficacy and Safety: Readiness for Translation

Theme 4 synthesizes preclinical data strongly supporting the therapeutic efficacy and safety of CNP synthesized via an environmentally friendly approach, such as sustained-release effects and selective cytotoxicity[37], safety aspects through antioxidant activity and improved oral bioavailability have also been validated in various studies [53]. Collectively, these studies support the proposed theoretical concept regarding the importance of dual-release kinetics and pH responsiveness in optimizing targeted drug delivery to tumor tissues while minimizing systemic exposure [61]. However, the translational readiness remains uneven. Few studies included complete in vivo pharmacokinetic data or engaged with regulatory frameworks. Safety evaluations such as hemolysis, immunogenicity, and genotoxicity were inconsistently reported. For instance, although zebrafish embryo models have been used in certain studies, most other research is still limited to in vitro testing. The statement shows how regulatory requirements which demand biocompatibility testing and stability assessment before clinical approval can establish the need for evaluation [39]. Industrial challenges which include GMP compliance and reproducibility during scale-up and the need to integrate systems with current drug delivery processes remain insufficiently investigated. These gaps align with earlier critiques, which have emphasized the need for early engagement with regulatory authorities and standards-setting bodies to ensure that development aligns with applicable requirements [60].

Research Gaps and Methodological Limitations

Several gaps emerged from this review. First, while AI tools were widely adopted, integration with green synthesis protocols remains conceptually and practically limited. Most studies optimized either formulation or synthesis separately, rather than co-optimizing them under a unified framework. Meta-analysis and benchmarking suffer because

studies do not use standardized reporting methods. The researchers failed to document three variables which included their ability to load drugs and their biodistribution in living organisms and their capacity to maintain stability over extended periods. The lack of longitudinal animal models together with conventional drug and synthetic nanoparticle (NP) comparison groups limits the ability to apply preclinical findings to real-world situations. Research shows that publication practices create biases because studies which find positive treatment results tend to receive more publication attention.

Implications for Theory, Practice, and Future Research

Second, the absence of standardized reporting methods in research studies creates obstacles for both meta-analysis and benchmarking activities. The research results validate the interdisciplinary synthesis model which was introduced in Section 3.3. The combined effect of AI's predictive capabilities with green synthesis methods which provide sustainable and biocompatible results and multifunctional designs which create targeted therapeutic solutions establishes the essential elements of this research. The researchers used an integrated strategy to create next-generation nanomedicines. The use of green reagents together with smart ligands provides practical benefits because it fulfills current international needs for environmentally friendly biomedical research. Natural resources like honey and Cymbopogon citratus provide therapeutic benefits while they decrease environmental damage and simplify the process of meeting regulatory standards [2].

For future research, a multi-pronged agenda is recommended:

- Standardization: Development of reporting frameworks for nanoparticle properties, validation metrics, and eco-indices.
- Integration: Simultaneous AI modeling of green synthesis and therapeutic optimization.
- In vivo validation: Expanded studies using animal models, pharmacokinetics, and histological analysis.
- Scalability: Pilot manufacturing and shelf-life stability testing under GMP conditions.
- Regulatory alignment: Early consultation with FDA/EMA on nanocarrier qualification criteria.

In conclusion, green-synthesized and AI-optimized CNPs provide substantial preclinical oncology potential, but their complete development needs scientific methods, future research planning, and interdisciplinary teamwork. The field stands ready to advance through ongoing scientific innovation that follows sustainable methods.

6. Conclusion

This systematic review demonstrates that AI/ML and computational/statistical optimization can improve the design of green-synthesized CNPs for anticancer drug delivery by supporting prediction and control of particle size, zeta potential, encapsulation efficiency, release behavior, and therapeutic response. The 53 included studies show promising outcomes, including high encapsulation efficiency, sustained release, enhanced cytotoxicity, and improved targeting in selected cancer models. The main contribution of this review is the integration of three previously fragmented domains: sustainable CNP synthesis, optimization-based formulation design, and anticancer nanocarrier performance. However, the evidence remains limited by inconsistent validation metrics, incomplete risk-of-bias reporting, insufficient sustainability assessment, and limited in vivo and translational evaluation. Scientifically, the integration of AI-guided optimization with green CNP synthesis provides a pathway toward more precise and environmentally responsible nanomedicine. To realize this potential, future research must adopt standardized reporting, model-specific validation, reproducibility testing, life-cycle assessment, and regulatory-oriented preclinical evaluation.

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