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Physiological Effects of Chitosan-Coated Magnetic Nanoparticles on Liver and Kidney Function: A Systematic Review of Oxidative Stress, Inflammation, and Cellular Responses

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التأثيرات الفيزيولوجية للجسيمات النانوية المغناطيسية المغلفة بالكيتوزان على وظائف الكبد والكلى: مراجعة منهجية للإجهاد التأكسدي والالتهاب والاستجابات الخلوية

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Abstract:
Background: Chitosan-coated magnetic nanoparticles (CMNPs) have emerged as a pivotal frontier in targeted oncology, offering enhanced biocompatibility and site-specific drug delivery. However a comprehensive physiological evaluation of their systemic safety profile remains essential for clinical translation.
Objective: This reference study aims to evaluate the therapeutic efficacy and biocompatibility of using nanoparticles on organs, with a particular focus on liver and kidney functions and blood parameters.
Methods: A rigorous synthesis of preclinical in vitro and in vivo studies was conducted. The analysis prioritized biochemical markers of liver and kidney function, histopathological outcomes, and the molecular pathways governing nanoparticle-organ interactions. Comparative assessments between coated and uncoated formulations were performed to elucidate the role of chitosan in mitigating systemic toxicity.
Results: Evidence indicates that chitosan functionalization significantly enhances nanoparticle stability and reduces off-target accumulation. Physiological data reveal that CMNPs generally maintain stable hepatic enzyme profiles and renal filtration markers exhibiting a protective or neutral effect on organ function. While transient fluctuations in certain hematological parameters were noted they remained within physiological reference ranges, suggesting minimal hemolytic potential.
Conclusion: CMNPs demonstrate a favorable safety profile with superior biocompatibility compared to conventional delivery systems. Despite these promising findings, the heterogeneity in existing longitudinal data necessitates standardized toxicological protocols. Future research should prioritize chronic exposure models to fully characterize the long-term physiological implications of CMNP-based therapies in nanomedicine.

Keywords: Chitosan-Coated Magnetic Nanoparticles, Targeted Cancer Therapy, Hepatic Function, Renal Physiology, Hematological Safety, Nanotoxicology.

الملخص
لخلفية: برزت الجسيمات النانوية المغناطيسية المغلفة بالكيتوزان (CMNPs) كأحدث التقنيات في مجال علاج الأورام الموجه، لما توفره من توافق حيوي مُحسّن وتوصيل دوائي دقيق إلى مواقع محددة. مع ذلك، يبقى التقييم الفيزيولوجي الشامل لسلامتها الجهازية ضروريًا لتطبيقها سريريًا.

الهدف: تهدف هذه الدراسة المرجعية إلى تقييم الفعالية العلاجية والتوافق الحيوي لاستخدام الجسيمات النانوية على الأعضاء، مع التركيز بشكل خاص على وظائف الكبد والكلى ومؤشرات الدم.
المنهجية: أُجري تحليل شامل للدراسات قبل السريرية، سواءً المخبرية أو الحيوية. ركز التحليل على المؤشرات الحيوية لوظائف الكبد والكلى، والنتائج النسيجية المرضية، والمسارات الجزيئية التي تحكم تفاعلات الجسيمات النانوية مع الأعضاء. كما أُجريت مقارنات بين التركيبات المغلفة وغير المغلفة لتوضيح دور الكيتوزان في الحد من السمية الجهازية.
النتائج: تشير الأدلة إلى أن إضافة الكيتوزان تُحسّن بشكل ملحوظ استقرار الجسيمات النانوية وتقلل من تراكمها في الأعضاء غير المستهدفة. تكشف البيانات الفيزيولوجية أن الجسيمات النانوية المغناطيسية المغلفة بالكيتوزان (CMNPs) تحافظ عمومًا على استقرار مستويات إنزيمات الكبد ومؤشرات الترشيح الكلوي، مما يدل على تأثير وقائي أو محايد على وظائف الأعضاء. وبينما لوحظت تقلبات عابرة في بعض المؤشرات الدموية، إلا أنها ظلت ضمن النطاقات المرجعية الفيزيولوجية، مما يشير إلى احتمال ضئيل لحدوث انحلال الدم.
الخلاصة: تُظهر الجسيمات النانوية المغناطيسية المغلفة بالكيتوزان (CMNPs) مستوى أمان جيدًا وتوافقًا حيويًا فائقًا مقارنةً بأنظمة التوصيل التقليدية. وعلى الرغم من هذه النتائج الواعدة، فإن التباين في البيانات الطولية الحالية يستلزم وضع بروتوكولات سمية موحدة. ينبغي أن تُعطي الأبحاث المستقبلية الأولوية لنماذج التعرض المزمن لتوصيف الآثار الفيزيولوجية طويلة الأمد للعلاجات القائمة على الجسيمات النانوية المغناطيسية المغلفة بالكيتوزان في مجال الطب النانوي توصيفًا كاملًا..

الكلمات المفتاحية: جسيمات نانوية مغناطيسية مغلفة بالكيتوزان، علاج السرطان الموجه، وظائف الكبد، فيزيولوجيا الكلى، السلامة الدموية، علم السموم النانوية.

Introduction

The investigation into chitosan-encapsulated magnetic nanoparticles (MNPs) for precision oncology has gained significant momentum, driven by their capacity to refine drug delivery protocols, mitigate systemic adverse effects and bolster therapeutic outcomes (Unsoy & Gündüz, 2017)(Rezaei et al., 2024). Recent breakthroughs in nanobiotechnology have facilitated the engineering of versatile nanoplatforms. By integrating superparamagnetic cores with biocompatible chitosan shells, these systems enable sophisticated applications in diagnostic imaging thermal ablation (hyperthermia), and kinetically controlled pharmacological release (Mistral et al., 2024)(Fernández-Álvarez et al., 2021).

Given that malignancies such as hepatocellular carcinoma (HCC) and breast cancer remain primary contributors to global mortality, there is a critical clinical imperative for novel intervention strategies (Badawy et al., 2022)(Taherian et al., 2021). Chitosan-coated MNPs present a robust framework for overcoming these challenges via active and passive targeting pathways, which enhance the bioavailability of chemotherapeutics while reducing off-target physiological toxicity (Hussein & Ruben, 2022)(Nair et al., 2024).

Despite these developmental milestones a comprehensive understanding of the physiological implications of these nanoparticles remains elusive. Specifically, their long-term impact on homeostatic mechanisms most notably hepatic and renal clearance functions and their interaction with hematological parameters require further rigorous empirical evaluation. Despite the documented anticancer efficacy of these nanocarriers under both in vitro and in vivo conditions (Agotegaray et al., 2017; Khedri et al., 2018), there remains a critical deficiency in comprehensive assessments regarding their systemic toxicity and biocompatibility profiles (Udupi et al., 2024; Ayyanaar et al., 2020; Fahmy et al., 2024). Current literature presents conflicting data concerning organ specific toxicities; while some findings suggest negligible adverse effects at therapeutic concentrations, others indicate significant pro-inflammatory responses or disruptions in enzymatic homeostasis (Lin et al., 2024; Mansour et al., 2020; Salehi et al., 2017). This lack of consensus underscores a profound knowledge gap regarding the physio-pathological safety and long-term biological impact of these nanomaterials factors essential for successful clinical translation (Lotfi et al., 2019; Paulino-Gonzalez et al., 2020). Addressing these gaps is imperative to ensure the development of physiologically safe and efficacious nanotherapeutics for oncological applications (Agotegaray et al., 2017).

From a physiological and bioengineering perspective magnetic nanoparticles functionalized with a chitosan coating synergistically combine the high-repressed magnetic targeting of iron oxide cores with the superior biocompatibility and functional adaptability of chitosan (Unsoy & Gündüz, 2017)(Rezaei et al., 2024). The chitosan encapsulation serves a dual physiological role: it enhances nanoparticle structural stability and promotes cellular internalization via electrostatic interactions with the cell membrane. Furthermore, this coating enables controlled pH-responsive drug delivery, while the paramagnetic core permits precise, externally guided localization and the application of therapeutic hyperthermia (Mistral et al., 2024)(Shen et al., 2014). A comprehensive understanding of the physiological interplay between these nanostructures and biological systems is paramount for maximizing therapeutic efficacy while mitigating systemic toxicity (Moghaddam et al., 2024). This conceptual framework is essential for the systematic assessment of their impact on hepatic and renal functions as well as hematological profiles within the context of oncological treatment (Udupi et al., 2024:Fahmy et al., 2024).

The objective of this systematic review is to critically evaluate the current evidence regarding chitosan-coated magnetic nanoparticles for targeted oncology, with a specific focus on their therapeutic efficacy and their physiological impact on hepatic and renal functions, as well as hematological profiles. By synthesizing data across various studies, this review aims to delineate safety profiles, identify existing gaps in knowledge, and provide insights into future research avenues to streamline clinical translation (Udupi et al., 2024: Agotegaray et al., 2017: Nair et al., 2024). This work contributes to the field by integrating efficacy outcomes with comprehensive toxicological assessments, thereby addressing a pivotal gap in the current literature.

A rigorous literature search was performed, encompassing in vitro and in vivo investigations that utilize chitosan-coated magnetic nanoparticles in cancer models. This review prioritized studies that report on therapeutic responses in conjunction with detailed analyses of liver and kidney biomarkers and homeostatic blood parameters. Data were analyzed qualitatively to identify physiological trends and discrepancies. The structure of this review first addresses therapeutic potential, followed by an in-depth evaluation of systemic physiological effects, concluding with the clinical implications and future investigative requirements (Udupi et al., 2024; Agotegaray et al., 2017; Fahmy et al., 2024).

Purpose and Scope of the Review

Statement of Purpose.

This report's goal is to summarize the current understanding of the biocompatibility, therapeutic potential, and safety profiles of physiological effects of chitons Zanco atùe düge magnetic nanoparticles on liver and kidney function and blood parameters. Chitosan-coated magnetic nanoparticles are a promising nanocarrier technology for targeted medication delivery and diagnostic applications, especially for hepatic and renal disorders, which makes this review crucial. Optimizing their design and practical translation requires an understanding of their physiological interactions and effects on hepatic and renal biomarkers as well as hematological. In order to provide a thorough basis for next studies and therapeutic development, the report attempts to clarify mechanisms of action biodistribution, toxicity and protective effects.

Specific Objectives:

1-To evaluate current knowledge on the synthesis, characterization, and targeting mechanisms of chitosan-coated magnetic nanoparticles in cancer therapy. Benchmarking of existing approaches to assess the impact of these nanoparticles on liver and kidney function biomarkers in preclinical models.
2-Identification and synthesis of data regarding hematological changes induced by chitosan-coated magnetic nanoparticles during cancer treatment.
3-To compare the therapeutic efficacy and toxicity profiles of chitosan-coated versus uncoated magnetic nanoparticles in targeted drug delivery.
4-To deconstruct the molecular and cellular pathways affected by nanoparticle administration that relate to organ function and systemic safety.

Methodology for Choosing Literature

1 .Transformation of Research Queries-

To ensure a comprehensive and systematic search the primary research question"Chitosan-coated magnetic nanoparticles for targeted cancer therapy and their impact on liver function, kidney function, and blood parameters"was expanded into multiple specific search statements. This approach guarantees that the literature search is both exhaustive and highly relevant. The transformed queries include:
1-Applications of chitosan-coated magnetic nanoparticles in targeted drug delivery for various cancer types and their effects on vital organ functions (liver and kidney).
2-Evaluation of organ-targeting efficacy and toxicity profiles of chitosan-coated magnetic nanoparticles with a focus on renal and hepatic biomarkers.
3-Systematic assessment of the biocompatibility of magnetic nanocarriers in hematological and physiological systems.

2 **.Database Search and Initial Screening**

We conducted an extensive search across major academic databases, including PubMed, Scopus, Google Scholar, Web of Science, and ScienceDirect. By applying strict Inclusion and Exclusion Criteria we identified an initial focused set of 85 papers from a global database of over 270 million research works.

3 .Citation Chaining (Identifying Additional Works)

To further enrich the study and ensure no foundational or emerging work was overlooked we employed two strategies:
1-Backward Citation Chaining: Reviewing the reference lists of core papers to identify foundational studies.
2-Forward Citation Chaining: Identifying recent studies that have cited the core papers to capture emerging debates and methodological advances.
Through this process, an additional 98 relevant papers were identified.

4 .Relevance Scoring and Final Selection

From the total pool of 183 candidate papers (85 from initial queries + 98 from citation chaining) we applied a relevance ranking system. This ensured that the most pertinent studies were prioritized. Out of these 178 papers were found to be directly relevant to the research topic of which 50 papers were of great importance.

Results

Descriptive Summary of Studies

This section delineates the research landscape of literature concerning chitosan-encapsulated magnetic nanoparticles for targeted cancer therapy, focusing on their effects on hepatic and renal functions, as well as hematological parameters. This includes synthesis, characterization, therapeutic efficacy, and safety assessments. The studies encompass various cancer models, particularly hepatocellular carcinoma (HCC) and breast cancer, utilizing different nanoparticle formulations and drug loading techniques.

Methodologies involve in vitro cytotoxicity assays, in vivo animal models, and detailed biochemical and histopathological analyses. This provides comprehensive insights into organ-specific toxicity and systemic hematological effects. Furthermore, this comparative analysis addresses critical research questions regarding the biodistribution of nanoparticles and biological indicators of organ function, hematological changes, and therapeutic outcomes, thereby guiding the future development of nanomedicine

Table (1) Comparative Analysis of Nanoparticle systems: characterizing, Efficacy and Toxicity

Study	Nanoparticle Characterization)	(Organ Function Biomarkers)	Hematological Parameters	Therapeutic Efficacy	Toxicity Profiles
(Udupi et al., 2024)	Superparamagnetic, 5-10 nm size, high uptake in HepG2 cells	No in vivo toxicity, improved liver antioxidant status	Not reported	Reduced tumor multiplicity and increased apoptosis in HCC mice	No toxicity observed in vivo; histopathology normal
(Lin et al., 2024)	Chitosan-MNP-rtPA conjugate, preserved thrombolytic activity	No liver or renal toxicity at therapeutic dose; portal edema at high dose	Not reported	Effective thrombolysis with magnetic guidance; reduced rtPA dose	Mild liver inflammation at high dose; no systemic toxicity
(Badawy et al., 2022)	Fe3O4/Cs nanocomposite, 11-20 nm, gamma radiation synthesis	Decreased ALT, AST, GGT; improved liver histology in DEN rats	Not reported	Ameliorated HCC biomarkers; induced apoptosis via caspase-3	Histopathology showed tumor necrosis; reduced inflammation
(Inhibitory of active dual cancer target..., 2022)	FA-CS-Bio/5-FU nanoparticles, enhanced targeting and sustained release	Alleviated liver function damage caused by 5-FU	Bone marrow suppression reduced	Increased 5-FU concentration in tumor; prolonged survival	Reduced systemic toxicity compared to free drug
(Medina-Moreno et al., 2024)	Magnetite/Chitosan core/shell, ~270 nm, pH-responsive release	Not reported	Excellent hemocompatibility	Enhanced antitumor activity; reduced IC50 in free drug	No cytotoxicity on normal cells; biocompatible ex vivo
(Alibrahimi et al., 2024)	Chitosan-coated Fe3O4 SPIONs, 11-20 nm, drug-loaded	Not reported	No cytotoxicity on fibroblasts; selective cancer cell toxicity	Papaverine-loaded MNPs inhibited breast cancer cell proliferation	Biocompatible; promoted ROS and apoptosis in cancer cells
(Dhar et al., 2024)	Chitosan-coated zinc cobalt ferrite NPs, pH-sensitive drug release	Not reported	Not reported	Sustained 5-FU delivery; enhanced OCT imaging contrast	Negligible cytotoxicity; potential theranostic platform
(Mistrat et al., 2024)	CS-coated SPIONs, 5-10 nm, varied acetylation;	Cytocompatible; no toxicity	Not reported	Suitable for MRI, hyperthermia,	Enhanced biocompatibilit

	tunable magnetism	regardless of coating amount		and drug delivery	y with chitosan coating
(Joshi et al., 2023)	Ultrasmall chitosan-magnetic nanohybrids, ~15 nm, DOX loaded	Not reported	Not reported	60% tumor volume reduction; MRI contrast enhancement	No reported toxicity; effective in vivo tumor suppression
(Akkaya & Akkaya, 2023)	Magnetic chitosan oligomer-sulfonate-stearic acid, cisplatin loaded	Not reported	Biocompatible in MCF-7 cells	pH and magnetic field-responsive cisplatin release; antiproliferativ e	Biocompatible; potential for thermotherapy
(Mngadi et al., 2020)	Chitosan-functionalized Mg0.5Co0.5Fe2O 4 NPs, ~20 nm, 5-FU loaded	Not reported	Targeted tumor-specific cytotoxicity; no toxicity on normal cells	Enhanced delivery and cytotoxicity in cancer cell lines	Promising therapeutic delivery system
(Ayyana ar- et al., 2020)	ROS-responsive chitosan-coated Fe3O4 NPs; 5-FLU loaded	Not reported	Not reported	Cytotoxic to A549 and HeLa cells; ROS and pH triggered release	Safe for anticancer applications; effective drug release
(Taheria n et al., 2021)	Black pomegranate peel extract loaded CCMNPs; ~30 nm size	Not reported	No toxicity on normal cells; selective cancer cytotoxicity	Improved drug efficiency; enhanced cancer cell uptake	Biocompatibl e; stable in serum-containing media
(Dincer et al., 2019)	Fe3O4 coated with glycol chitosan; carboplatin loaded	Not reported	Not reported	Higher cytotoxicity than free carboplatin on MCF-7 cells	Cytotoxic to cancer cells; biocompatibl e coating
(Unsoy & Gündüz, 2017)	Polymer-coated magnetic NPs; multifunctional targeting	Not reported	Not reported	Enhanced drug half-life and targeting; reduced side effects	Improved biocompatibil ity and multifunction ality
(Unsoy & Gündüz, 2017)	Polymer-coated magnetic NPs; multifunctional targeting	Not reported	Not reported	Enhanced drug half-life and targeting; reduced side effects	Improved biocompatibil ity and multifunction ality
(Lutfi et al., 2019)	Core-shell chitosan-coated Fe3O4; 10-15 nm size	Less cytotoxicity than bare Fe3O4; highest biocompatibility	Reduced hemolysis compared to other coatings	Not reported	Highest biocompatibil ity among tested coatings
(Agotega ray et al., 2017)	Magnetite core with chitosan coating; diclofenac loaded	No hematological or liver toxicity at tested doses	No erythrocyte or platelet damage; mild spleen changes	Not reported	No neurobehavio ral toxicity; mild nephritis at high dose
(Khedri et al., 2018)	Chitosan-coated Fe3O4 NPs; 5-10 nm size	Increased GPX enzyme activity; reduced toxicity vs uncoated	Not reported	Not reported	Dose-dependent toxicity mitigated by chitosan coating

(Fahmy et al., 2024)	Fe3O4 and Fe3O4-CS NPs; enhanced cytotoxicity on HepG2 cells	Altered oxidative stress markers; induced DNA damage	Not reported	Enhanced apoptosis and oxidative stress in HCC cells	Superior anticancer effect with chitosan coating
(Fernandez-Alvarez et al., 2021)	Maghemite/PLGA/chitosan core/shell/shell; ~325 nm size	Hemocompatible; no cytotoxicity on fibroblasts	Not reported	Effective hyperthermia; reduced colon cancer cell viability	Long-circulating; safe in vivo with histology confirmation
(Bai et al., 2018)	N-palmitoyl chitosan microparticles with SPIO and DOX	Improved liver enzyme profiles in HepG2 cells	Not reported	pH-sensitive drug release; better antitumor efficacy than free DOX	No reported toxicity; potential chemoembolization agent
(Garcia-Garcia et al., 2024)	Citrate-Fe3O4/chitosan cluster/shell NPs; ~187 nm size	Negligible cytotoxicity; suitable for parenteral use	Hemocompatible	Enhanced magnetic and photothermal hyperthermia	Safe with superior heating efficiency
(Sun et al., 2024)	CS-C60-Fe3O4 metallofullerene, ~194 nm size	Not reported	Not reported	Enhanced thermal ablation and ferroptosis in HCC	Stable in vivo; improved tumor targeting
(严文祥 et al., n.d.)	Fe@C nanocage-loaded chitosan NPs, heat generation in liver cancer	Not reported	Not reported	Effective tumor hyperthermia; significant tumor necrosis	Targeted heating; good therapeutic effect in rats
(Fu-rong et al., n.d.)	Carboplatin-Fe@C-loaded chitosan NPs, hepatic artery injection	Targeted drug accumulation in tumor; prolonged drug levels	Not reported	Enhanced tumor drug concentration; magnetic targeting	Accumulated in tumor; no off-target deposition
Salehi, et al., 2017)	Fe3O4 NPs coated with chitosan, blood parameter effects in mice	Not reported	Altered WBC and RBC counts; dose-dependent effects	Not reported	Dose-dependent hematological changes observed
(Javid et al., 2013)	Doxorubicin-loaded chitosan-coated SPIO NPs, ~82 nm size	Not reported	Not reported	High drug loading; significant ovarian cancer cell inhibition	Enhanced uptake and cytotoxicity in cancer cells
(Lin et al., 2015)	PEG-chitosan-iron oxide nanocomposites; MTX loaded	Not reported	Not reported	Synergistic targeting and imaging; dual model imaging	Effective tumor targeting; combined therapy potential
(Hazarika et al., 2024)	Gd-doped Fe3O4 NPs coated with chitosan; dipolar interaction	Not reported	Not reported	Enhanced magnetic hyperthermia via dipolar interactions	Improved heating efficiency for cancer therapy
(Badry et al., 2017)	Fe3O4 and NiFe2O4 NPs coated with	Dose-dependent cancer cell inhibition	Not reported	Cytotoxic to multiple cancer cell lines	Biocompatible; effective anticancer activity

	chitosan; 7-20 nm size				
(Hussein & Ruben, 2022)	Nanocarriers for liver cancer drug delivery; review	Not applicable	Not applicable	High drug accumulation; reduced toxicity	Focus on therapeutic advantages; no toxicity data
(Mohammadi-Samani et al., 2013)	Chitosan-coated Fe3O4 NPs, methotrexate loaded; ~152 nm	Slow drug release; paramagnetic behavior retained	Not reported	Controlled MTX delivery; cytotoxic to SK-BR-3 cells	Suitable for controlled drug delivery
(Nasrin et al., 2024)	Mn-Zn ferrite NPs coated with chitosan; <10 nm size	Non-toxic to HeLa cells; MRI contrast agent	Not reported	Suitable for hyperthermia and imaging	Biocompatible; effective heating properties
(Rezaei et al., 2024)	Review on chitosan-coated NPs in cancer biomedicine	Not applicable	Not applicable	Enhanced drug bioavailability and targeting	Emphasizes biocompatibility and reduced cytotoxicity
(Nassar et al., 2022)	Fe3O4/SiO2/chitosan nanocomposites; DOX loaded	pH-sensitive drug release; high loading efficiency	Not reported	High cytotoxicity against Hep-G2 and MCF-7 cells	Promising drug delivery carrier with low toxicity
(Mansour et al., 2020)	DOX and verapamil co-loaded chitosan NPs in HCC mice	Renal tissues showed negligible toxic effects	The underlying molecular pathways were not specifically investigated	Enhanced anticancer activity; apoptosis induction	Reduced systemic toxicity compared to free drugs
(Moghaddam et al., 2024)	Review on chitosan nanosystems for cancer therapy	Not applicable	Stimuli-responsive drug delivery; immunomodulation	Highlights clinical challenges and prospects	Highlights clinical challenges and prospects
(Zhou et al., 2014)	FA-PEG-CS-coated Fe3O4 NPs; folate targeting	Excellent biocompatibility; enhanced cell uptake	Not reported	Specific targeting to cancer cells; magnetic properties	Promising for targeted drug delivery and hyperthermia
(Nair et al., 2024)	Review on chitosan-based hybrid nanoplatforms	Not applicable	Not applicable	Improved drug targetability and cell uptake	Discusses toxicity concerns and clinical translation
(Taghizadeh et al., 2023)	Chitosan-coated magnetic nanorods and nanospheres	Low toxicity; porous nanorods, size 5-108 nm	Not reported	Efficient drug release; suitable for anticancer delivery	Nanorods show potential over spheres for delivery
(Ajalli et al., 2022)	Chitosan/gamma-alumina/Fe3O4/5-FU nanocarriers	pH-sensitive release; stable nanoparticles	Not reported	Increased apoptosis in breast cancer cells	Effective alternative to conventional treatments
(Paulino-Gonzalez et al., 2020)	Biological properties of chitosan magnetic NPs	Biologically inert; high cell affinity	No apoptosis or cytotoxicity induced	No synergism with anticancer drugs or X-ray	Safe scaffold for drug delivery;

					aggregation limits uptake
(Yadav et al., 2024)	Review on chitosan nanoformulations in diverse diseases	Not applicable	Not applicable	Optimized drug delivery; improved therapeutic outcomes	Addresses regulatory challenges and clinical prospects
(Shen et al., 2014)	Mesostructured chitosan-coated Fe3O4 NPs with folic acid	Superparamagnetic; 28.5 emu/g saturation magnetization	Not reported	pH-dependent DOX release; high drug loading	Potential targeted drug delivery carrier
(Alsulays et al., 2024)	Ivosidenib-loaded chitosan-coated PLGA NPs	Increased particle size and positive charge	Not reported	Enhanced cytotoxicity in HepG2 cells; apoptosis	Improved delivery and efficacy over free drug
(Rahman & Ochiai, 2018)	Carboxy-chitosan stabilized magnetite NPs	Superparamagnetic; dispersible in physiological conditions	Low hemolytic activity; hemocompatible	Not reported	Suitable for biomedical applications
(Synthesis and Characterization Studies o..., 2022)	Chitosan-coated Fe3O4 NPs conjugated with folic acid	Characterized by XRD, SEM, FTIR; stable	Not reported	Not reported	Thermal stability confirmed
(Thorat et al., 2014)	Chitosan functionalized superparamagnetic NPs	Good colloidal stability; ~80% cell	Not reported	Reduced MCF7 viability by 40%	Biocompatible; potential for cancer

Nanoparticle Characterization:
Over 40 studies reported detailed nanoparticle size ranging from ultrasmall (5 nm) to larger (300 nm) with chitosan coatings enhancing stability and targeting capabilities (Udupi et al., 2024; Mistral et al., 2024; Taghizadeh et al., 2023).
Surface charge and coating efficiency were frequently measured, showing positive zeta potentials due to chitosan, which improved cellular uptake and colloidal stability (Medina-Moreno et al., 2024) (Zhou et al., 2014; Alsulays et al., 2024).
Various synthesis methods including co-precipitation, solvothermal, and gamma radiation were employed to optimize nanoparticle morphology and magnetic properties (Badawy et al., 2022) (Shen et al., 2014) (Lotfi et al., 2019).
Organ Function Biomarkers:
Approximately 10 studies assessed liver enzymes (ALT, AST, GGT), generally reporting mitigation of liver damage or no significant toxicity after treatment with chitosan-coated nanoparticles (Udupi et al., 2024) (Badawy et al., 2022) ("Inhibitory of active dual cancer targeti...", 2022).
Kidney function markers were less frequently reported but no significant renal toxicity was observed in studies that included such assessments (Lin et al., 2024).
Some studies demonstrated improved antioxidant enzyme activities and reduced inflammatory markers, indicating protective effects on liver function (Khedri et al., 2018; Fahmy et al., 2024).
Hematological Parameters:
Few studies explicitly evaluated hematological parameters; those that did reported minimal or no adverse effects on blood cell counts and indices, suggesting good systemic compatibility (Agotegaray et al., 2017).
Some dose-dependent hematological changes were noted but were generally mitigated by chitosan coating.
Hemocompatibility assays confirmed low hemolytic activity and preserved erythrocyte integrity in several studies (Lotfi et al., 2019; Rahman & Ochiai, 2018).

Therapeutic Efficacy:
Over 30 studies demonstrated enhanced tumor targeting, cellular uptake, and significant tumor volume reduction or apoptosis induction with chitosan-coated magnetic nanoparticles (Udupi et al., 2024; Joshi et al., 2023) (Mansour et al., 2020).
Drug-loaded nanoparticles showed improved cytotoxicity compared to free drugs, with sustained and pH-responsive release profiles enhancing therapeutic outcomes (Medina-Moreno et al., 2024; Ayyanaar et al., 2020; Nassar et al., 2022).
Multifunctional platforms combining imaging and therapy were reported, enabling theranostic applications (Joshi et al., 2023) (García-García et al., 2024; Lin et al., 2015).
Toxicity Profiles:

- Most studies reported low or no systemic toxicity, with histopathological analyses confirming organ safety and absence of significant inflammation or necrosis outside tumor sites (Udupi et al., 2024) (Agotegaray et al., 2017; Fernández-Álvarez et al., 2021).
- Some mild liver inflammation or portal edema was observed at high nanoparticle doses but without functional impairment (Lin et al., 2024).
- Aggregation of chitosan-coated nanoparticles in vitro may limit cellular uptake but does not translate into in vivo toxicity (Paulino-Gonzalez et al., 2020).
- •Reviews emphasized the biocompatibility and biodegradability of chitosan coatings as key factors reducing cytotoxicity and improving safety profiles (Rezaei et al., 2024) (Moghaddam et al., 2024).

Critical Analysis and Synthesis
The reviewed literature on chitosan-coated magnetic nanoparticles (MNPs) for targeted cancer therapy reveals significant advancements in synthesis, functionalization, and therapeutic efficacy, particularly in liver cancer models. Many studies demonstrate enhanced targeting capabilities, improved biocompatibility, and promising anticancer effects with reduced systemic toxicity. However, there remain notable gaps in comprehensive toxicity profiling, especially regarding long-term effects on liver and kidney functions and hematological parameters. Methodological heterogeneity and limited in vivo safety data also challenge the generalizability of findings. Overall, while chitosan coatings improve nanoparticle stability and targeting, further rigorous preclinical evaluations are necessary to fully establish their safety and therapeutic potential.

Table 2: Analysis of Literature Aspects

Aspect	Strengths	Weaknesses
Synthesis and Characterization of Chitosan-Coated MNPs	Studies consistently report successful synthesis of chitosan-coated MNPs with controlled size, morphology, and magnetic properties, using diverse methods such as co-precipitation, solvothermal, and ultrasonic atomization techniques. Characterization by TEM, XRD, FTIR, and VSM confirms superparamagnetic behavior and stable chitosan coatings that enhance colloidal stability and biocompatibility (Udupi et al., 2024; Khmara et al., 2024; Shen et al., 2016). Functionalization with targeting ligands like folic acid and galactosylated chitosan further improves specificity (Udupi et al., 2024; Zhou et al., 2014; Shen et al., 2014).	Despite robust physicochemical characterization, variability in nanoparticle size distribution and coating thickness across studies complicates direct comparisons. Some reports lack detailed analysis of coating uniformity and stability under physiological conditions, which are critical for reproducibility and clinical translation (Lotfi et al., 2019; Shen et al., 2014). Additionally, magnetic saturation values vary widely, potentially affecting therapeutic efficacy (Khmara., 2024; Taghizadeh et al., 2023).
Targeting Mechanisms and Therapeutic Efficacy	Chitosan coatings facilitate active targeting via receptor-mediated endocytosis (e.g., folate, asialoglycoprotein receptors), enhancing cellular uptake and tumor accumulation, as demonstrated in hepatocellular carcinoma and breast cancer models (Udupi et al., 2024). MNPs show improved cytotoxicity and tumor volume reduction compared to free drugs, with sustained and pH-responsive release profiles supporting controlled delivery (Medina-Moreno et al., 2024; Yun&Dong., 2020; David et al., 2015; Nassar et al., 2022). Multifunctional	Most efficacy studies are limited to short-term in vitro or small animal models, with insufficient data on long-term therapeutic outcomes and resistance mechanisms. Comparative analyses between chitosan-coated and uncoated MNPs are sparse, limiting understanding of the coating's incremental benefits (Badawy et al., 2022; Mousy & Gunalaz, 2017). Furthermore, heterogeneity in drug loading methods and dosing regimens hinders standardization of efficacy assessments (Mohammadi-Samani et al., 2012; Mansour et al., 2020).

	platforms combining imaging and therapy (theranostics) are also reported (Yun&Dong., 2020; Garcia-Garcia et al., 2024).	
Impact on Liver and Kidney Function	Several studies report minimal or no significant hepatotoxicity and nephrotoxicity at therapeutic doses, with some indicating protective antioxidant effects or amelioration of liver enzyme elevations in cancer models (Udupi et al., 2024; Lin et al., 2024; Badawy et al., 2022; Khedri et al., 2018). Histopathological evaluations often show no adverse changes in liver and kidney tissues following chitosan-MNP administration (Lin et al., 2024; Li et al., n.d.). Pharmacokinetic studies demonstrate enhanced drug accumulation in tumor tissue with limited off-target deposition (Fu-rong et al., n.d.).	Toxicity assessments are frequently limited to acute or subacute timeframes, lacking comprehensive chronic toxicity data. Some reports note mild liver inflammation or portal edema at high doses, raising concerns about dose-dependent toxicity (Lin et al., 2024; Agotejaray et al., 2017). Kidney function markers are underreported or inconsistently measured, and few studies evaluate functional biomarkers alongside histology (Agotejaray et al., 2017; Khedri et al., 2018). The influence of nanoparticle physicochemical properties on organ-specific toxicity remains inadequately explored (Mousy & Gunalaz, 2017; Taghizadeh et al., 2023).
Hematological and Blood Parameter Effects	Blood compatibility assays indicate that chitosan-coated MNPs generally do not induce hemolysis, platelet aggregation, or morphological alterations in blood cells, supporting their hemocompatibility (Agotejaray et al., 2017; Rahman & Ochiai, 2018). Some studies demonstrate stable hematological parameters post-administration, with no significant cytotoxicity to erythrocytes or leukocytes (Sallam et al., 2017; Paulino-Gonzalez et al., 2020).	Data on hematological changes are limited and often lack detailed quantitative analyses of blood cell counts, coagulation profiles, or immune responses. Few studies investigate potential immunomodulatory effects or inflammatory markers in blood, which are critical for systemic safety evaluation (Agotejaray et al., 2017; Sallam et al., 2017). The impact of repeated or high-dose exposure on hematological parameters remains unclear (Sallam et al., 2017).
Biocompatibility and Cytotoxicity Profiles	Chitosan coatings enhance nanoparticle biocompatibility by reducing cytotoxicity to normal cells while maintaining or improving anticancer activity (Mistral et al., 2024) (Lutfi et al., 2019) (Fahmy et al., 2024) (Paulino-Gonzalez et al., 2020). Multiple in vitro assays confirm low toxicity to fibroblasts and normal cell lines, with selective cytotoxicity toward cancer cells (Al-ebrahimi et al., 2024) (Tanerian et al., 2021) (Fahmy et al., 2024). The coatings also improve nanoparticle stability and reduce aggregation, facilitating safer systemic administration (Mistral et al., 2024) (Thoral et al., 2014).	Some studies report variability in cytotoxicity results depending on nanoparticle size, coating degree, and cell type, indicating a need for standardized testing protocols (Lutfi et al., 2019) (Fahmy et al., 2024). The mechanisms underlying differential toxicity are not fully elucidated, and genotoxicity assessments are limited (Fahmy et al., 2024). Moreover, in vivo biocompatibility data are often preliminary and lack long-term follow-up (Paulino-Gonzalez et al., 2020).
Methodological Robustness and Data Quality	The body of research employs a wide range of advanced analytical techniques and relevant cancer models, including chemically induced hepatocellular carcinoma and orthotopic tumor models, enhancing translational relevance (Udupi et al., 2024) (Badawy et al., 2022) (贾文君 et al., n.d.). Multimodal imaging and biodistribution studies provide valuable insights into nanoparticle behavior in vivo	There is considerable heterogeneity in experimental designs, dosing regimens, and endpoints measured, which complicates cross-study comparisons and meta-analyses (Unsoy & Gündüz, 2017) (Hussein & Ruben, 2022). Many studies have small sample sizes and lack appropriate controls or blinded assessments, potentially biasing results (Agotegaray et al., 2017) (Salehi, et al., 2017). Standardized protocols for toxicity

	(Lin et al., 2024) (Joshi et al., 2023) (Fernández-Álvarez et al., 2021).	and efficacy evaluation are often absent, limiting reproducibility and clinical extrapolation (Hussein & Ruben, 2022) (Moghaddam et al., 2024).
Influence of Physicochemical Properties on Biological Interactions	Research highlights that nanoparticle size, shape, surface charge, and degree of chitosan acetylation critically influence cellular uptake, biodistribution, and magnetic responsiveness (Mistral et al., 2024) (Hazarika et al., 2024) (Taghizadeh et al., 2023). Shape variations (e.g., nanorods vs. nanospheres) affect drug release and targeting efficiency (Taghizadeh et al., 2023). pH-responsive and ROS-sensitive coatings enable controlled drug release in tumor microenvironments (Medina-Moreno et al., 2024) (Ayyanar et al., 2020).	Despite recognition of these factors, systematic studies dissecting the precise relationships between physicochemical parameters and biological outcomes are limited. Many reports focus on single formulations without comparative analyses, hindering optimization efforts (Mistral et al., 2024) (Hazarika et al., 2024). The impact of coating heterogeneity and stability under physiological conditions on therapeutic performance and toxicity is underexplored (Lotfi et al., 2019) (Shen et al., 2014).

Thematic Review of Literature

The reviewed literature prominently explores the synthesis, characterization, and biomedical applications of chitosan-coated magnetic nanoparticles (MNPs) in targeted cancer therapy, emphasizing their enhanced targeting capabilities and biocompatibility. A major focus lies on evaluating their therapeutic efficacy and safety profiles, particularly their effects on liver and kidney function as well as hematological parameters. Studies frequently assess how chitosan coatings improve nanoparticle stability, drug loading, and controlled release, while minimizing systemic toxicity. Additionally, emerging research highlights the multifunctional theragnostic potential of these nanocarriers, incorporating imaging and hyperthermia alongside drug delivery for comprehensive

Table 3: Summary of Research Themes

Theme	Appears In	Theme Description
Synthesis, Characterization, and Targeting Mechanisms of Chitosan-Coated Magnetic Nanoparticles	35/50 Papers	Extensive research details various methods for synthesizing chitosan-coated magnetic nanoparticles (MNPs), including co-precipitation and solvothermal techniques. Thorough physicochemical characterization (TEM, XRD, FTIR, and magnetic property analyses) confirms successful coating, precise size control, and superparamagnetic behavior. These features are critical for targeted drug delivery, particularly when functionalized with ligands like folic acid or phosphorylated galactosylated chitosan to enhance tumor-specific uptake (Udupi et al., 2024; Badawy et al., 2022; Medina-Moreno et al., 2024; Mistral et al., 2024; Lotfi et al., 2019; Shen et al., 2014; Zhou et al., 2014).
Therapeutic Efficacy and Anticancer Activity of Chitosan-Coated Magnetic Nanoparticles	30/50 Papers	Chitosan-coated MNPs demonstrate significant antineoplastic activity in vitro and in vivo, often exhibiting superior cytotoxicity compared to free-form agents. Studies report effective tumor reduction in hepatocellular, breast, and colorectal models. Mechanistically, these platforms induce apoptosis via ROS generation and modulation of signaling pathways such as PI3K/Akt/mTOR and MAPK (Badawy et al., 2022; Aliebrahimy et al., 2024; Joshi et al., 2023; Taherian et al., 2021; Fahmy et al., 2024; Mansur et al., 2020). Drug-loaded variants (e.g., Doxorubicin, Methotrexate) provide sustained release, increasing therapeutic potency while sparing healthy tissues (Javid et al., 2013; Nassar et al., 2022).
Biocompatibility and Safety Profiles Including Effects on Liver, Kidney Function, and Blood Parameters	25/50 Papers	Multiple studies assess the biocompatibility and systemic safety of chitosan-coated MNPs, reporting minimal cytotoxicity and hemolysis. No significant adverse effects were observed on renal or hepatic biomarkers (ALT, AST, GGT). Hematological profiles, including complete blood counts, generally remain within physiological ranges, supporting their safety for systemic use

		(Udupi et al., 2024; Lim et al., 2024; Badawy et al., 2022; Lotfi et al., 2019; Khedri et al., 2018; Salmani et al., 2017). However, elevated dosages may trigger localized inflammatory responses without systemic toxicity (Lin et al., 2024; Agotegaray et al., 2017).
Drug Loading, Controlled Release, and Delivery Efficiency	22/50 Papers	Chitosan coatings optimize drug encapsulation efficiency and enable stimuli-responsive release profiles (e.g., pH-sensitive or ROS-triggered). These platforms allow targeted delivery of chemotherapeutics like 5-fluorouracil and carboplatin, enhancing bioavailability while minimizing off-target effects. The efficacy of these systems has been validated through improved antitumor activity and reduced systemic side effects in various models (Udupi et al., 2024; Medina-Moreno et al., 2024; Ayyanaar et al., 2020; Mohammadi-Samani et al., 2013; Shen et al., 2014).
Multifunctional and Theranostic Applications Combining Imaging and Hyperthermia	15/50 Papers	Several reports highlight the integration of chitosan-coated MNPs as multifunctional "theranostic" platforms. These nanostructures exhibit superparamagnetic properties suitable for enhanced MRI contrast and heat generation under alternating magnetic fields (AMF), facilitating magnetic hyperthermia for tumor ablation. Novel composite formulations enhance circulation time and targeting precision (Mistral et al., 2024; Fernandez-Alvarez et al., 2021; Garcia-Garcia et al., 2024; Sun et al., 2024; Thorat et al., 2014).
Molecular and Cellular Mechanisms Underlying Therapeutic Effects and Toxicity	13/50 Papers	Research elucidates that chitosan-coated MNPs influence cellular signaling pathways, including apoptosis via caspase activation, inhibition of oncogenic PI3K/Akt/mTOR, and induction of ferroptosis in hepatocellular models. The coating influences cellular uptake, oxidative stress response, and cytokine production, contributing to therapeutic benefits and biocompatibility. These mechanisms support the potential of these MNPs to selectively eradicate malignant cells while minimizing systemic physiological toxicity (Badawy et al., 2022; Fahmy et al., 2024; Sun et al., 2024; Mansur et al., 2020).
Biocompatibility and Safety Profiles Including Effects on Liver, Kidney Function, and Blood Parameters	25/50 Papers	Multiple studies assess the biocompatibility and systemic safety of chitosan-coated MNPs, reporting minimal cytotoxicity and hemolysis. No significant adverse effects were observed on renal or hepatic biomarkers (ALT, AST, GGT). Hematological profiles, including complete blood counts, generally remain within physiological ranges, supporting their safety for systemic use (Udupi et al., 2024; Lim et al., 2024; Badawy et al., 2022; Lotfi et al., 2019; Khedri et al., 2018; Salmani et al., 2017). However, elevated dosages may trigger localized inflammatory responses without systemic toxicity (Lin et al., 2024; Agotegaray et al., 2017).
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Chronological Review of Literature

Research on chitosan-coated magnetic nanoparticles for targeted cancer therapy has evolved significantly from foundational synthesis and characterization studies to advanced applications integrating multifunctionality and targeted delivery. Early efforts focused on developing stable, biocompatible magnetic nanoparticles with chitosan coatings, aiming to improve drug loading and controlled release. Subsequent studies expanded to include specific targeting ligands, enhanced therapeutic efficacy, and assessment of toxicity and organ-specific impacts, with increasing attention to liver and kidney functions and hematological parameters. Recent advancements emphasize multifunctional theranostic platforms, stimuli-responsive systems, and clinical translational prospects that optimize cancer treatment outcomes while minimizing systemic toxicity.

Tables 4: Stages evolution of CS-MNPs in Cancer therapy

Year Range	Research Direction	Description
2013–2014	Foundational Synthesis and Characterization	Initial investigations focused on the fabrication of chitosan-coated superparamagnetic iron oxide nanoparticles (SPIONs), emphasizing their physicochemical properties and controlled-release kinetics. Studies validated that chitosan encapsulation enhances colloidal stability and magnetic responsiveness while mitigating cytotoxicity against malignant cell lines. Preliminary models utilized methotrexate and doxorubicin for breast and ovarian cancer, establishing the technical framework for targeted delivery.
2015–2017	Targeted Delivery and Biocompatibility	Research shifted toward surface functionalization using ligands such as folate and polyethylene glycol (PEG) to improve cellular uptake and systemic circulation time. Significant efforts were directed at utilizing polymer coatings to prevent nanoparticle agglomeration and enhance biocompatibility. This period also saw the emergence of multifunctional nanocarriers integrating therapeutic payloads with diagnostic imaging to minimize the systemic side effects of conventional chemotherapy.
2018–2020	Preclinical Toxicity and Therapeutic Efficacy Assessment	Studies increasingly prioritized in vivo toxicity, biodistribution, and organ-specific impacts. Investigations demonstrated that chitosan coatings reduce oxidative stress and improve antioxidant enzyme profiles in animal models. Advanced strategies involved co-treatment with chitosan-coated nanoparticles to enhance therapeutic synergy and reduce off-target toxicity. Synthesis protocols were further refined to optimize particle size and achieve stimuli-responsive release for hepatic carcinoma treatments.
2021–2022	Multifunctional Nanoplatforms and Theranostics	The field advanced toward multifunctional theranostic hybrids, integrating targeted chemotherapy with real-time imaging modalities like MRI and Optical Coherence Tomography (OCT). The development of pH-responsive and stimuli-triggered release mechanisms became paramount for improving delivery specificity. Extensive research on breast and liver cancer models highlighted nanoparticles designed for enhanced intracellular uptake, sustained release, and the reduction of hematological and bone marrow toxicity.
2023–2024	Advanced Targeting, Combination Therapies, and Clinical Translation	Contemporary research focuses on sophisticated nanoparticulate systems featuring enhanced targeting moieties and multimodal therapies (e.g., hyperthermia and photothermal effects). Current investigations explore the impact of nanoparticle morphology and optimized coating compositions on molecular pathways influencing systemic safety. There is a strategic emphasis on chitosan-based hybrid nanoplatforms for cancer theranostics and immune modulation, addressing translational challenges related to biodistribution and therapeutic efficacy.

Agreement and Divergence Across Studies

The reviewed literature consistently acknowledges the pivotal role of chitosan coatings in augmenting nanoparticle stability, biocompatibility, and targeted delivery efficiency in oncological applications. A broad consensus exists regarding the improvement of therapeutic efficacy, characterized by enhanced cellular internalization, potent tumor suppression, and minimized systemic toxicity—evidenced by the preservation of hepatic and renal functions.

However, scholarly divergences remain concerning the magnitude of biochemical impacts on organ function biomarkers and hematological parameters; while some studies report negligible toxicity, others observe mild physiological alterations at higher dosages or with specific formulations. These discrepancies are largely attributed to variations in nanoparticle composition, surface modifications, experimental models, dosing protocols, and the diverse evaluation methodologies employed across the studies

Table 4: illustrates the agreement and disagreement across studies

Comparison Criterion	Studies in Agreement	Studies in Divergence	Potential Explanations
Nanoparticle Characterization	Several studies report successful synthesis of chitosan-coated magnetic nanoparticles with controlled size (generally 5–200 nm), uniform morphology, positive surface charge, and superparamagnetic properties facilitating targeting and stability (Udupi et al., 2024) (Badawy et al., 2022) (Mistral et al., 2024) (Taherian et al., 2021) (Zhou et al., 2014) (Taghizadeh et al., 2023). Coatings improve colloidal stability and prevent aggregation, enhancing biocompatibility (Mistral et al., 2024) (Lotfi et al., 2019) (Paulino-Gonzalez et al., 2020).	Studies vary in particle size ranges (from ultrasmall <10 nm to larger >300 nm) and magnetic saturation values depending on synthesis methods, coatings, and core materials (Medina-Moreno et al., 2024) (Hasanika et al., 2024) (Nasiri et al., 2024) (Shen et al., 2014). Some report differences in coating thickness and degree of acetylation influencing magnetic properties and stability (Mistral et al., 2024) (Lotfi et al., 2019).	Differences in synthesis techniques (co-precipitation, solvothermal, gamma radiation), coating methods, chitosan molecular weights or derivatives, and nanoparticle core types explain variability in size, charge, and magnetic saturation measurements.
Organ Function Biomarkers	Consensus exists that chitosan-coated magnetic nanoparticles exhibit minimal or no significant hepatotoxicity and nephrotoxicity at therapeutic doses, with stable liver enzymes (ALT, AST, GGT) and kidney markers (creatinine, BUN) post-treatment (Udupi et al., 2024) (Lin et al., 2024) (Badawy et al., 2022) (Khedri et al., 2018) (Salehi, et al., 2017) (Mansour et al., 2020). Some studies show amelioration of liver injury markers through anti-inflammatory and antioxidant effects (Badawy et al., 2022) (Fahmy et al., 2024) (Mansour et al., 2020).	A few studies note mild hepatic inflammation or changes in biomarkers at higher nanoparticle doses or prolonged exposure (Lin et al., 2024) (Khedri et al., 2018). Some report enhanced enzyme activity or oxidative stress markers but overall no overt toxicity (Fahmy et al., 2024) (Salehi, et al., 2017).	Variations in dosing regimes, animal models, nanoparticle formulation (e.g., additional functional groups), and duration of exposure may explain discrepancies in biochemical outcomes. Higher doses or long-term exposure might reveal subclinical toxicity not evident at lower doses.
Hematological Parameters	Studies generally agree that chitosan-coated magnetic nanoparticles do not induce significant hematotoxicity, with stable blood cell counts and morphology post-treatment (Agotegaray et al., 2017) (Salehi, et al., 2017) (Paulino-Gonzalez et al.,	Some reports highlight subtle hematological changes or immunomodulatory effects such as increased megakaryocytes or mild splenic changes in specific models (Agotegaray et al., 2017). Others observe no changes in parameters even at	Differences in nanoparticle size, coating chemistry, animal species, dose, and duration of treatment contribute to variable hematological findings. Immune system variability and

	2020). Blood compatibility assays indicate no adverse effects on erythrocytes, platelets, or leukocytes at evaluated doses (Agotegaray et al., 2017) (Paulino-Gonzalez et al., 2020). Inhibitory of active dual cancer targets..." (2022); (Zhou et al., 2014).	higher doses (Salehi et al., 2017).	the sensitivity of assays used may also play roles.
Therapeutic Efficacy	Multiple studies confirm enhanced anticancer activity of chitosan-coated magnetic nanoparticles via improved cellular uptake, controlled and pH-responsive drug release, increased apoptosis, and tumor growth inhibition compared to free drugs or uncoated nanoparticles (Udupi et al., 2024) (Badawy et al., 2022) (Alibrahimi et al., 2024) (Joshi et al., 2023) (Taherian et al., 2021) (Nassar et al., 2022) (Mansour et al., 2020). Enhanced tumor targeting is achieved through surface modifications like folate or galactosylation (Udupi et al., 2024).	Variability exists in the magnitude of therapeutic effects reported, with some formulations showing moderate efficacy or differential activity depending on cancer type and drug load (Alibrahimi et al., 2024) (Taherian et al., 2021) (Javid et al., 2013). Some studies focus on hyperthermia or combined therapies with differing outcomes (Garcia-Garcia et al., 2024) (Sun et al., 2024)	Differences in nanoparticle composition, drug payload, surface functionalization, cancer models, and therapeutic modalities (chemotherapy, hyperthermia, radiotherapy) explain variability in efficacy. Delivery method and treatment duration also influence outcomes.
Toxicity Profiles	There is broad agreement that chitosan coatings enhance biocompatibility, reducing cytotoxicity and systemic toxicity of magnetic nanoparticles; coated nanoparticles exhibit lower toxicity to normal cells than free drugs or uncoated particles (Mistral et al., 2024) (Lotfi et al., 2019) (Fahmy et al., 2024) (Paulino-Gonzalez et al., 2020) (Thorat et al., 2014). Histopathological analyses confirm minimal organ damage post-treatment (Badawy et al., 2022) (Agotegaray et al., 2017) (Khedri et al., 2018).	Some studies report dose-dependent toxicity manifestations at high nanoparticle concentrations or prolonged exposure, including mild inflammation or oxidative stress (Lin et al., 2024) (Khedri et al., 2018) (Salehi, et al., 2017). Aggregation-induced effects and variability in coating quality can lead to differing toxicity outcomes (Paulino-Gonzalez et al., 2020	Differences in experimental design (dose, administration route, exposure duration), nanoparticle aggregation states, coating quality, and sensitive biomarkers assessed account for divergent toxicity results. Some studies use more comprehensive toxicity panels than others

Theoretical and Practical Implications

Practical Implicatisions

Enhanced Therapeutic Precision: The demonstrated improvements in targeting efficiency and the reduction of systemic toxicity in chitosan-coated magnetic nanoparticles highlight their potential for clinical translation. These nanoparticles offer a safer and more efficacious alternative to traditional chemotherapy, particularly in the treatment of liver and breast malignancies (Udupi et al., 2024) (Taherian et al., 2021) (Mansour et al., 2020).

Controlled and Stimuli-Responsive Release: These nanoparticles enable controlled, sustained, and stimuli-responsive drug delivery, which significantly enhances therapeutic efficacy while minimizing adverse effects. Such attributes are pivotal for the advancement of sophisticated pharmaceutical formulations (Medina-Moreno et al., 2024) (Bai et al., 2018) (Mohammadi-Samani et al., 2013).

Integrated Theranostic Capabilities: The multi-functional nature of chitosan-coated magnetic nanoparticles—including their application in magnetic resonance imaging (MRI), hyperthermia, and drug delivery—provides significant opportunities for integrated diagnostic and therapeutic (theranostic) interventions. This facilitates the development of personalized medicine within oncology (Mistral et al., 2024) (Fernández-Alvarez et al., 2021) (Ajalli et al., 2022).

Optimization of Physicochemical Parameters: These findings underscore the necessity of optimizing nanoparticle characteristics, such as coating thickness, deacetylation degree, and morphology. Balancing magnetic responsiveness with biocompatibility is essential for establishing rigorous manufacturing and quality control standards in nanomedicine (Mistral et al., 2024) (Lotfi et al., 2019) (Taghizadeh et al., 2023).

Biocompatibility and Regulatory Feasibility: The observed biocompatibility and negligible hematological or immunological side effects support the feasibility of navigating regulatory pathways for chitosan-coated magnetic nanoparticle-based therapies. These results encourage further preclinical and clinical trials (Agotegaray et al., 2017) (Paulino-Gonzalez et al., 2020) (Yadav et al., 2024).

Clinical Potential in Liver Cancer: The successful implementation of magnetic targeting and hyperthermia in preclinical liver cancer models emphasizes the potential for non-invasive, site-specific treatments. Such innovations could potentially lower healthcare expenditures and enhance patient quality of life (严文辉 et al., n.d.) (Fu-rong et al., n.d.) (Garcia-Garcia et al., 2024).

Table 5: illustrates the limitations of the literature

Area of Limitation	Description of limitation	Papers which have limitation
Constraint of Small Sample Sizes	A significant portion of research utilizes restrictive animal models or in vitro cell lines, which may not accurately replicate complex human systemic physiology or homeostatic interactions. This limitation narrows the external validity and translational potential of the findings.	(Udupi et al., 2024) (Badawy et al., 2022) (Aliebrahimi et al., 2024) (Mansour et al., 2020)
Deficiency in Longitudinal Toxicity Data	Current literature predominantly examines acute biocompatibility, leaving a critical gap in understanding the long-term physiological impact, chronic cellular responses, and potential bioaccumulation-driven toxicity of these interventions.	(Lin et al., 2024) (Lotfi et al., 2019) (Khedri et al., 2018) (Paulino-Gonzalez et al., 2020)
Narrow Organ-Specific Toxicity Profiles	Comprehensive physiological assessments are often confined to renal and hepatic functions, neglecting the intricate toxicological effects on other vital systems, such as the hematological, neurological, or cardiovascular environments.	Agotegaray et al., 2017) (Lin et al., 2024) (Paulino-Gonzalez et al., 2020)
Heterogeneity in Nanoparticle Characterization	Non-standardized methodologies in defining physicochemical properties hinder the reproducibility of results. This variability complicates the assessment of how nanoparticle characteristics influence biological uptake and physiological safety.	(Mistral et al., 2024) (Lotfi et al., 2019) (Taghizadeh et al., 2023) (Shen et al., 2014
Paucity of Clinical Evidence	Research remains largely in the preclinical phase. The scarcity of human clinical trials restricts the empirical evidence required to establish therapeutic efficacy and safety within complex human biological systems.	(Hussein & Ruben, 2022) (Moghaddam et al., 2024) (Nair et al., 2024)
Incomplete Biodistribution Mapping	There is a lack of rigorous quantitative analysis regarding nanoparticle kinetics and clearance in non-target tissues. Understanding these pathways is essential for mitigating off-target physiological effects and optimizing delivery strategies.	(Udupi et al., 2024) (Lin et al., 2024) (Fu-rong et al., n.d.)
Specificity to Limited Oncological Models	Investigations are heavily skewed toward hepatocellular and mammary carcinomas. This narrow focus limits the broader physiological understanding of treatment responses across diverse pathological and tissue environments.	(Udupi et al., 2024) (Badawy et al., 2022) (Taherian et al., 2021 Mansour et al., 2020)

Aggregation and Colloidal Stability Challenges	The tendency of nanoparticles to aggregate in physiological media can drastically alter cellular internalization and bioactivity, posing significant methodological challenges in interpreting both in vitro and in vivo outcomes.	(Paulino-Gonzalez et al., 2020) (Taherian et al., 2021)

Table 6: illustrates the Gaps and Future Research Directions

Gap Area	Description	Future Research Directions	Justification	Research Prioity
Long-term in vivo toxicity profiling	Most studies focus on acute or subacute toxicity; chronic effects of chitosan-coated MNPs on liver, kidney, and hematological parameters remain underexplored (Lin et al., 2024) (Badawy et al., 2022) (Agotegaray et al., 2017).	Conduct longitudinal in vivo studies assessing chronic toxicity, including repeated dosing regimens, with comprehensive biochemical, histopathological, and hematological monitoring over extended periods.	Chronic toxicity data are essential to ensure safety for clinical translation, as short-term studies may miss cumulative or delayed adverse effects (Lin et al., 2024) (Agotegaray et al., 2017).	High
Comprehensive kidney function assessment	Kidney toxicity markers are infrequently reported and often limited to histology without functional biomarker evaluation (Lin et al., 2024) (Agotegaray et al., 2017).	Integrate detailed renal function tests (e.g., serum creatinine, BUN, urine analysis) alongside histopathology in preclinical models to evaluate nephrotoxicity of chitosan-coated MNPs.	Kidney is a critical clearance organ; subtle functional impairments may not be detected by histology alone, risking overlooked nephrotoxicity (Lin et al., 2024).	High
Standardization of hematological toxicity evaluation	Hematological assessments are sparse and lack standardized parameters such as coagulation profiles, immune cell subsets, and inflammatory markers (Agotegaray et al., 2017) Salehi, et al., 2017)	Develop and apply standardized hematological panels including complete blood counts, coagulation assays, and cytokine profiling in nanoparticle toxicity studies.	Hematological safety is crucial for systemic administration; inconsistent data limit risk assessment and regulatory approval Salehi, et al., 2017)	High
Influence of nanoparticle physicochemical properties on organ-specific toxicity	Variability in size, coating thickness, surface charge, and shape affects biodistribution and toxicity but systematic studies dissecting these relationships are lacking (Mistral et al., 2024) (Lotfi et al., 2018) (Taghizadeh et al., 2023).	Perform controlled comparative studies varying single physicochemical parameters to elucidate their impact on liver and kidney accumulation, toxicity, and therapeutic efficacy.	Understanding these relationships enables rational design of safer, more effective nanocarriers tailored to minimize organ toxicity (Lotfi et al., 2018) (Taghizadeh et al., 2023).	High
Comparative efficacy and toxicity of chitosan-	Few studies directly compare therapeutic outcomes and safety profiles between coated	Design head-to-head in vivo studies comparing chitosan-coated and bare	Such comparisons clarify the incremental benefits of chitosan coatings, guiding	Medium

coated vs. uncoated MNPs	and uncoated nanoparticles (Badawy et al., 2022) (Ünsoy & Gündüz, 2017) (Fahmy et al., 2024).	MNPs for cancer therapy, assessing biodistribution, efficacy, and multi-organ toxicity.	clinical development decisions (Badawy et al., 2022) (Fahmy et al., 2024).	
Impact of nanoparticle aggregation on cellular uptake and toxicity	Aggregation of chitosan-coated MNPs reduces cellular uptake and may alter toxicity profiles, but in vivo relevance is unclear.(Paulion-gonzalez et al.,2020)	Investigate strategies to minimize aggregation (e.g., surface modification, dispersants) and evaluate effects on biodistribution.	Aggregation may compromise therapeutic efficacy and safety; addressing it is critical for clinical translation (Paulion-gonzalez et al.,2020)	Medium
Limited data on immunomodulatory and inflammatory responses	Few studies assess systemic immune responses or inflammatory cytokine changes following nanoparticle administration (Agotegaray et al., 2017) (Moghaddam et al., 2024).	Incorporate immunological assays including cytokine profiling, immune cell phenotyping, and inflammation markers in preclinical toxicity studies.	Immune activation or suppression can impact safety and therapeutic outcomes; understanding these effects is vital (Moghaddam et al., 2024).	Medium
Optimization of drug loading and release kinetics	Variability in drug loading efficiency and release profiles across studies limits reproducibility and efficacy comparisons (Medina-Moreno et al., 2024) (Mohammadi-Samani et al., 2013) (Nassar et al., 2022).	Standardize drug loading protocols and characterize release kinetics under physiological and tumor-mimicking conditions to optimize therapeutic windows.	Controlled and reproducible drug delivery enhances efficacy and reduces off-target toxicity (Medina-Moreno et al., 2024) (Nassar et al., 2022).	Medium
Insufficient exploration of shape effects on biodistribution and toxicity	Nanoparticle shape (e.g., nanorods vs. nanospheres) influences biological interactions but remains under-investigated (Taghizadeh et al., 2023).	Conduct systematic in vivo studies comparing different chitosan-coated MNP shapes to assess effects on targeting efficiency, organ accumulation, and toxicity.	Shape-dependent effects can be exploited to improve targeting and minimize adverse effects (Taghizadeh et al., 2023).	Low
Lack of standardized protocols for toxicity and efficacy evaluation	Heterogeneity in experimental designs, dosing, and endpoints complicates cross-study comparisons and meta-analyses (Unsoy & Gündüz, 2017) (Hussein & Ruben, 2022).	Develop consensus guidelines for preclinical evaluation of chitosan-coated MNPs, including standardized dosing, controls, and outcome measures.	Standardization improves reproducibility, facilitates regulatory approval, and accelerates clinical translation (Hussein & Ruben, 2022).	High

Overall Synthesis and Conclusion

chitosan-functionalized magnetic nanoparticles (MNPs) underscores their pivotal role in precision oncology. By integrating the biocompatible properties of chitosan with the superparamagnetic core, these constructs optimize pharmacokinetic profiles, thereby augmenting therapeutic index while mitigating off-target systemic toxicity. From a physiological perspective, the physicochemical attributes—specifically hydrodynamic diameter, surface topography, and the degree of N-acetylation—govern the nano-bio interface. The cationic surface charge (positive zeta potential) inherent to chitosan facilitates electrostatic interactions with the negatively charged sialic acid

residues on neoplastic plasma membranes. This interaction primes the complex for receptor-mediated endocytosis, ensuring efficient intracellular cargo delivery and enhanced intratumoral accumulation via the enhanced permeability and retention (EPR) effect. Toxicological and Histopathological Assessment: Quantitative assessments of renal and hepatic biomarkers demonstrate that chitosan-coated MNPs maintain cellular homeostasis at therapeutic concentrations. Evidence suggests a lack of significant hepatotoxicity and nephrotoxicity, with data indicating a cytoprotective antioxidant modulation that counteracts chemotherapy-induced oxidative stress and prevents the elevation of transaminases. Furthermore, histopathological analysis confirms the preservation of tissue architecture, with an absence of pathological inflammatory infiltration or necrotic foci, affirming the high biocompatibility of these nanostructures within complex physiological systems.

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