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Research Article

Modified starch-based nanocarriers for stimuli-responsive anticancer drug delivery: A combined bibliometric and systematic analysis

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ABSTRACT

Starch-based nanocarriers have gained increasing attention as versatile platforms for controlled and stimuli-responsive anticancer drug delivery due to their biocompatibility, biodegradability, and structural adaptability. However, their comparative performance and translational potential remain inadequately understood. This study presents a hybrid bibliometric and systematic review to evaluate research trends, formulation strategies, and therapeutic applications of modified starch nanocarriers. Bibliometric analysis of publications indexed in Scopus (2000-2026) and Web of Science (1995-2026) revealed a rapidly expanding field, with an annual growth rate exceeding 10% and strong contributions from China, India, and Iran. A systematic review of 93 studies (2015-2025) demonstrated that chemical modifications, particularly hydroxyethyl starch-based systems, and hybrid polymer-nanomaterial formulations significantly enhance drug loading, stability, and controlled release. Stimuli-responsive mechanisms, including pH-, redox-, and reactive oxygen species (ROS)-triggered systems, were widely employed to improve tumor-targeted delivery efficiency. Most systems demonstrated high encapsulation efficiency and enhanced *in vitro* anticancer efficacy with acceptable cytocompatibility. Despite these advances, limited *in vivo* validation, insufficient pharmacokinetic data, and variability in tumor microenvironment responsiveness remain major barriers to clinical translation. Future research should prioritize scalable design, standardized evaluation, and regulatory alignment to facilitate clinical application.

Keywords:
Starch-based nanocarriers; Controlled release; Stimuli-responsive drug delivery; Anticancer therapy; Biodegradable nanocarriers

1. INTRODUCTION

Starch-based nanocarriers have garnered significant interest in pharmaceutical drug delivery due to their biocompatibility, biodegradability, and adaptability to established formulation processes [1]. These attributes enable the development of delivery systems with improved drug loading, controlled release, and reduced systemic toxicity, supporting their suitability for translational and clinical applications [1–6]. Modification of starch through physical or chemical approaches allows tuning of carrier performance, with each strategy differing in mechanism, safety considerations, and applicability to pharmaceutical manufacturing. Physical modification techniques, which alter starch structure through heat, pressure, or shear without introducing chemical reagents, are generally preferred for pharmaceutical use owing to their favorable safety and regulatory profiles [7]. Chemical modification, by contrast, introduces functional groups that expand formulation flexibility and enable the design of multifunctional delivery systems with tailored release characteristics [8].

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Among physical modification strategies, ultrasonication and double emulsion techniques are widely employed to enhance solubility, regulate particle size distribution, and improve drug encapsulation efficiency. Ultrasonication induces structural reorganization at the particle and molecular levels, leading to changes in crystallinity and rheological behavior that directly influence dissolution and drug release kinetics [7,9,10]. Such tunable rheological properties are particularly important for controlled release formulations, where modulation of matrix integrity governs release rates [11]. Double emulsion techniques (water-in-oil-in-water) enable efficient encapsulation of both hydrophobic and hydrophilic drugs, with encapsulation efficiency, particle morphology, and release profiles governed by formulation parameters such as emulsifier type, phase ratios, and homogenization conditions [12,13].

Hydroxyethyl starch (HES), a water-soluble chemically modified starch with FDA GRAS status for selected indications, is extensively used as a plasma expander and pharmaceutical excipient in sustained release formulations [14–16]. However, its use as a plasma volume substitute is restricted in critically ill and septic patients due to safety concerns, including renal impairment and coagulation disturbances [14,17]. In drug delivery applications, HES-based carriers form stable drug-polymer conjugates and micelles (self-assembled nanostructures) that enhance drug solubility, circulation stability, and therapeutic performance. Reports also suggest that HES-based systems may facilitate enhanced anticancer efficacy through intracellular stress mechanisms, including reactive oxygen species (ROS) generation [18]. While studies on HES-mitomycin C nanomedicines for hepatic malignancies remain limited, existing formulation-focused evidence indicates improved targeting and sustained exposure, indicating therapeutic relevance [18–21].

Optimization of starch-based nanocarrier systems requires consideration of drug physicochemical properties, particularly solubility and permeability, which affect bioavailability. Formulation strategies such as amorphous solid dispersions and liposomal systems help improve solubility, stability, and scalability. Amorphous solid dispersions are able to increase the solubility of poorly soluble drugs by maintaining the drug in a high energy amorphous state, which dissolves more readily than its crystalline counterpart [22], whereas liposomal formulations enhance solubility and stability while facilitating targeted delivery and reduce toxicity [23,24]. Molecular attributes such as nanoparticle size, charge, and polarity significantly influence drug delivery efficacy. Smaller nanoparticles possess a larger surface area-to-volume ratio, which enhances drug dissolution and absorption, while cationic surface charge enhances cellular uptake but may introduce formulation-dependent toxicity concerns [25–28]. Drugs exhibiting moderate lipophilicity (logP 2-4) typically demonstrated improved solubility and absorption across biological barriers [22,25,26].

Starch-based nanocarriers are also adaptable platforms for polymeric and stimuli-responsive drug delivery systems aimed at controlled and site-specific release. Polymeric matrix-based formulations, including layered tablets, multiparticulate systems, mucoadhesive polymers, and in situ gelling systems, offer established pathways, scalability, and reproducible release performance [29–35]. Stimuli-responsive systems enable drug release in response to endogenous triggers such as pH or enzymatic activity, or exogenous stimuli including ultrasound and magnetic fields, thereby enhancing targeting precision and minimizing off-target exposure [36–38]. Despite these advances, translating such systems from laboratory-scale to clinical practice remains constrained by challenges related to formulation stability, large-scale manufacturing, and regulatory requirements.

A summary of the major physical and chemical starch modification approaches and their functional roles in nanocarrier engineering is presented in Table 1. These modification strategies differ substantially in their effects on physicochemical behavior, biodegradability, rheological properties, and stimuli-responsiveness. Physical modifications are generally favored for their regulatory simplicity and minimal chemical residue, whereas chemical modifications provide greater flexibility for engineering targeted and multifunctional delivery systems. The selection of modification strategy therefore depends on the intended therapeutic application, drug physicochemical properties, and translational considerations.

Accordingly, this review addresses three key formulation-oriented questions: (1) which starch modification strategies optimize scalability and drug release reproducibility; (2) how stimuli-responsive systems can be integrated into pharmaceutically viable dosage forms to overcome intracellular delivery barriers; and (3) which hybrid starch-based platforms offer sufficient physiological and formulation robustness for clinical translation.

2. METHODOLOGY

2.1. Bibliometric analysis

A bibliometric analysis was conducted to evaluate the research landscape of starch-based nanocarriers in anticancer drug delivery. The literature search was performed using the Boolean query: (starch OR modified starch) AND (nanoparticle OR nanocarrier* OR nanogel* OR nanoformulation*) AND (cancer OR tumor OR anticancer). The search was applied

Table 1. Classification of starch modification strategies used in nanocarrier development.

Modification category	Technique / example	Structural effect	Pharmaceutical relevance	References
Physical modification	Ultrasonication	Reduced particle size and crystallinity, increased surface area, and structural reorganization through amylopectin depolymerization and altered hydrogen bonding.	Improves dissolution, drug loading and encapsulation efficiency.	Vela et al. [9], Zhang et al. [39], Medha et al. [40]
	Heat-moisture treatment	Structural reorganization through enhanced starch chain interactions, altered crystalline architecture, and modified gelatinization behavior.	Enhances matrix stability and controlled release performance.	Yang et al. [41], Marboh et al. [42], Pepe et al. [43]
	Double emulsion	Formation of compartmentalized core-shell structures capable of encapsulating multiple drug types.	Enables simultaneous encapsulation of hydrophilic and hydrophobic drugs; allows for targeted and sustained drug delivery.	Wang et al. [44], Flaiz et al. [45]
Chemical modification	Hydroxyethyl starch (HES)	Introduction of hydroxyethyl groups, resulting in enhanced hydrophilicity and altered molecular architecture.	Improves water solubility and circulation stability; enabling controlled and sustained drug release.	Wang et al. [21], Besheer et al. [46]
	Carboxymethyl starch (CMS)	Introduction of carboxymethyl groups, resulting in structural deformation, improved thermal stability, reduced crystallinity, and increased porosity.	Enhances pH responsiveness, swelling behavior, and drug loading capacity	Mal et al. [47], Li et al. [48], Das et al. [49]
	Oxidation/Dialdehyde starch (DAS)	Introduction of aldehyde groups, resulting in reduced crystallinity and structural deformation of starch granules.	Facilitates crosslinked hydrogel formation, stimuli-responsive release, and sustained drug delivery with enhanced biocompatibility.	Qin et al. [50], Dilmaghani et al. [51], Sheng et al. [52], Yong et al. [53]
	Crosslinked starch	Formation of covalent crosslinks that enhance structural stability, reduce swelling power and solubility, improve thermal stability, and modify granule morphology.	Enhances mechanical strength and matrix stability while enabling controlled swelling capacity and sustained drug release.	Tomar et al. [54], Wattanachant et al. [55], Kumar et al. [56]
	Quaternized starch	Introduction of cationic functional groups, improving solubility and interactions.	Enhances binding with negatively charged drugs and nucleic acids.	Garcia et al. [16], Kassim et al. [57]

to the Scopus (2000 to 2026) and Web of Science (1995 to 2026) databases, yielding a total of 550 documents and 596 documents, respectively, without additional filtering. All retrieved records were exported and subjected to data cleaning and preprocessing using the RStudio package for analysis [58]. Following duplicate removal and dataset integration, the merged bibliometric dataset covered publications from 1995 to 2026. The cleaned dataset was subsequently used for bibliometric analysis, including evaluation of publication trends, authorship patterns, and keyword co-occurrence.

2.2. Systematic literature search and study selection

A systematic literature search was conducted to identify relevant studies on starch-based nanocarriers for anticancer drug delivery. The search was performed across Scopus and Web of Science databases, covering publications from January 2015 to December 2025.

The search strategy employed Boolean combinations of keywords related to starch-based nanocarriers and cancer drug delivery, as follows: (starch OR modified starch) AND (nanoparticle* OR nanocarrier*) AND (drug delivery OR delivery OR carrier) AND (cancer OR tumor OR anticancer)

As shown in Figure1, a total of 428 records were identified from Scopus (n = 171) and Web of Science (n = 257). After removing 128 duplicate records using Catchii software [59], 300 unique records were screened by title and abstract. Full-text assessment was performed on 213 articles, and 93 studies met the predefined inclusion criteria and were included in the final systematic review. Studies were included if they reported starch-based nanocarriers for anticancer drug delivery, provided quantitative formulation data (drug loading, encapsulation efficiency, or release profiles), and evaluated biological performance *in vitro* or *in vivo* cancer models. Studies were excluded if they were review articles, editorials, conference abstracts, non-starch-dominant nanocarriers, focused on non-cancer applications, lacked experimental drug delivery data, or were published before 2015 or in a non-English language.

2.2.1. Screening process

As shown in Figure 1, the study selection process followed the PRISMA 2020 guidelines. Titles and abstracts of all retrieved records were initially screened to assess relevance. Full-text articles of potentially eligible studies were subsequently evaluated against the predefined inclusion and exclusion criteria. The study selection process is illustrated in PRISMA flow diagram.

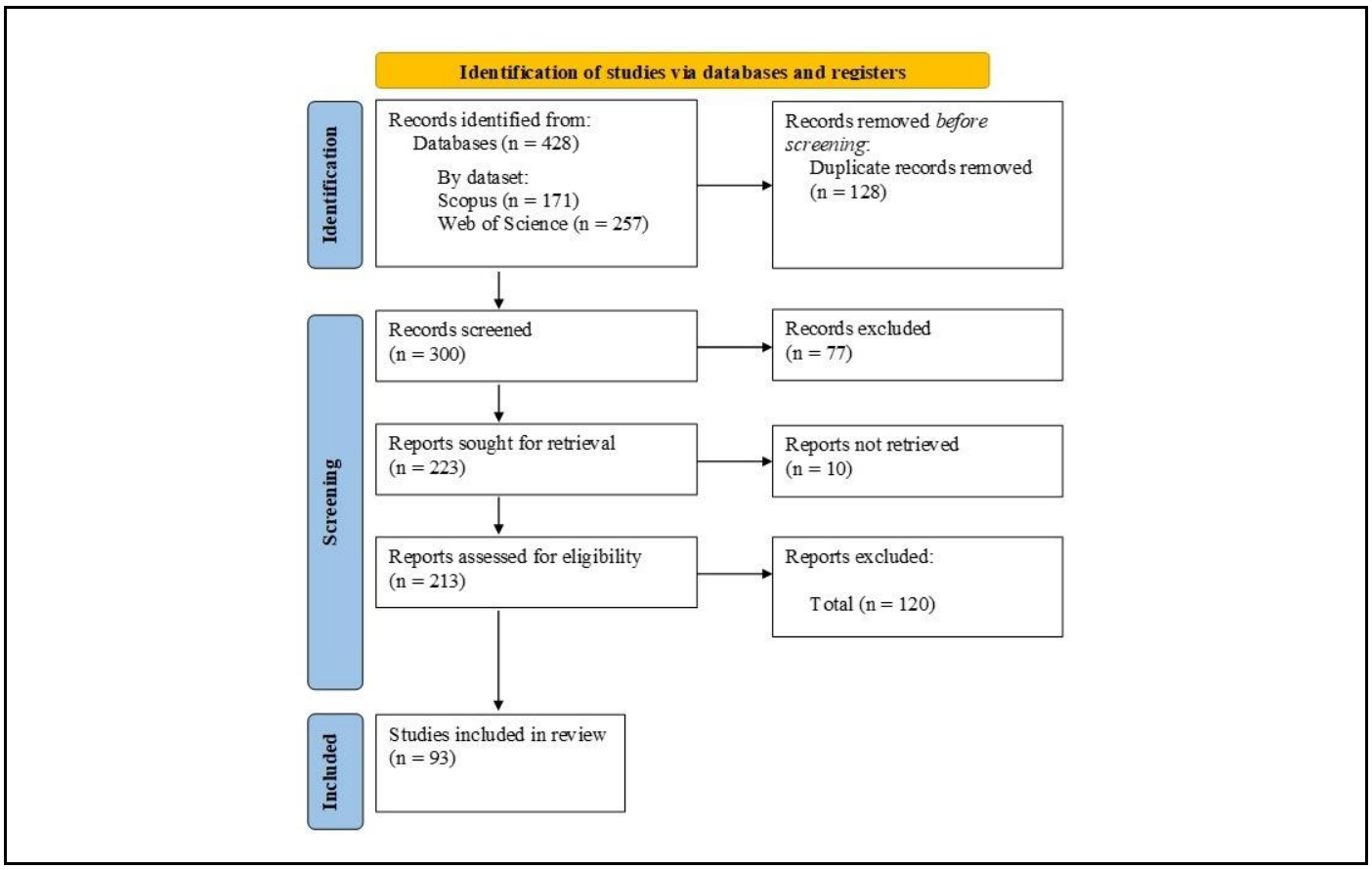

Figure 1. PRISMA flow diagram illustrating the study selection process for the systematic review of starch-based nanocarriers in anticancer drug delivery between 1995 and 2026.

2.2.2. Data extraction

A broader search strategy was employed for the bibliometric analysis (Scopus: 2000 to 2026; Web of Science: 1995 to 2026) to capture the overall research landscape, whereas a more focused search strategy was applied in the systematic review (2015 to 2025) to identify studies specifically addressing starch-based nanocarriers for anticancer drug delivery. This dual approach ensured comprehensive coverage while maintaining relevance for detailed qualitative synthesis. Data from the included studies were systematically extracted and tabulated.

2.2.3. Quality assessment

The methodological quality of included studies was evaluated using a structured critical appraisal approach, focusing on experimental design, reproducibility, and completeness of reporting. Particular attention was given to the presence of quantitative formulation data, biological validation, and clarity of experimental procedures.

3. RESULT

3.1. Bibliometric analysis of research trends

A total of 772 publications indexed in Scopus and Web of Science were included in the bibliometric analysis, spanning 367 sources and involving 2,891 authors. The field demonstrates a sustained and accelerating growth trajectory, with an annual growth rate of 10.64%.

The annual scientific production reveals a marked increase in research activity after 2015, with publications rising from fewer than 30 articles per year before 2015 to over 90 articles annually in 2024-2025. This sharp increase reflects the growing scientific and clinical interest in starch-based nanocarriers as adaptable platforms for advanced drug delivery applications.

Analysis of corresponding author affiliations reveals a strong geographical concentration of research output. China dominates the field, contributing nearly one-third of total publications, followed by India and Iran (Table 2). Despite lower overall output, countries such as the United States and South Korea exhibit higher multiple-country publication (MCP) ratios, indicating stronger international collaboration networks. This contrast suggests that while research productivity is concentrated in emerging economies, collaborative and cross-border research activities are more prominent in technologically advanced regions.

Keyword analysis further demonstrates that the field is strongly centered on nanoparticle-based drug delivery systems, with drug delivery, starch, and nanoparticles emerging as dominant terms. The frequent association with chemotherapeutic agents such as doxorubicin and curcumin indicates a sustained emphasis on anticancer applications. The prominence of HES further reflects the increasing focus on chemically modified starch derivatives to enhance solubility, stability, and stimuli-responsive drug release.

These thematic relationships are further illustrated in the keyword co-occurrence network (Figure 2), which reveals two major clusters corresponding to therapeutic applications and nanocarrier design. The spatial separation yet strong interconnection between these clusters highlights a dual research focus on formulation engineering and therapeutic performance, emphasising the necessity of integrated approaches in developing clinically translatable nanocarrier systems.

Table 2. Top 10 contributing countries in starch-based nanocarrier research between 1995 and 2026.

Rank	Country	Articles	Percentage (%)	MCP* Ratio
1	China	218	29.78	0.096
2	India	129	17.62	0.233
3	Iran	86	11.75	0.140
4	USA	39	5.33	0.385
5	Korea	34	4.64	0.353
6	Egypt	24	3.28	0.458
7	Germany	22	3.01	0.136
8	Canada	16	2.19	0.313
9	Brazil	14	1.91	0.143
10	Pakistan	12	1.64	0.500

* MCP = multiple-country publication

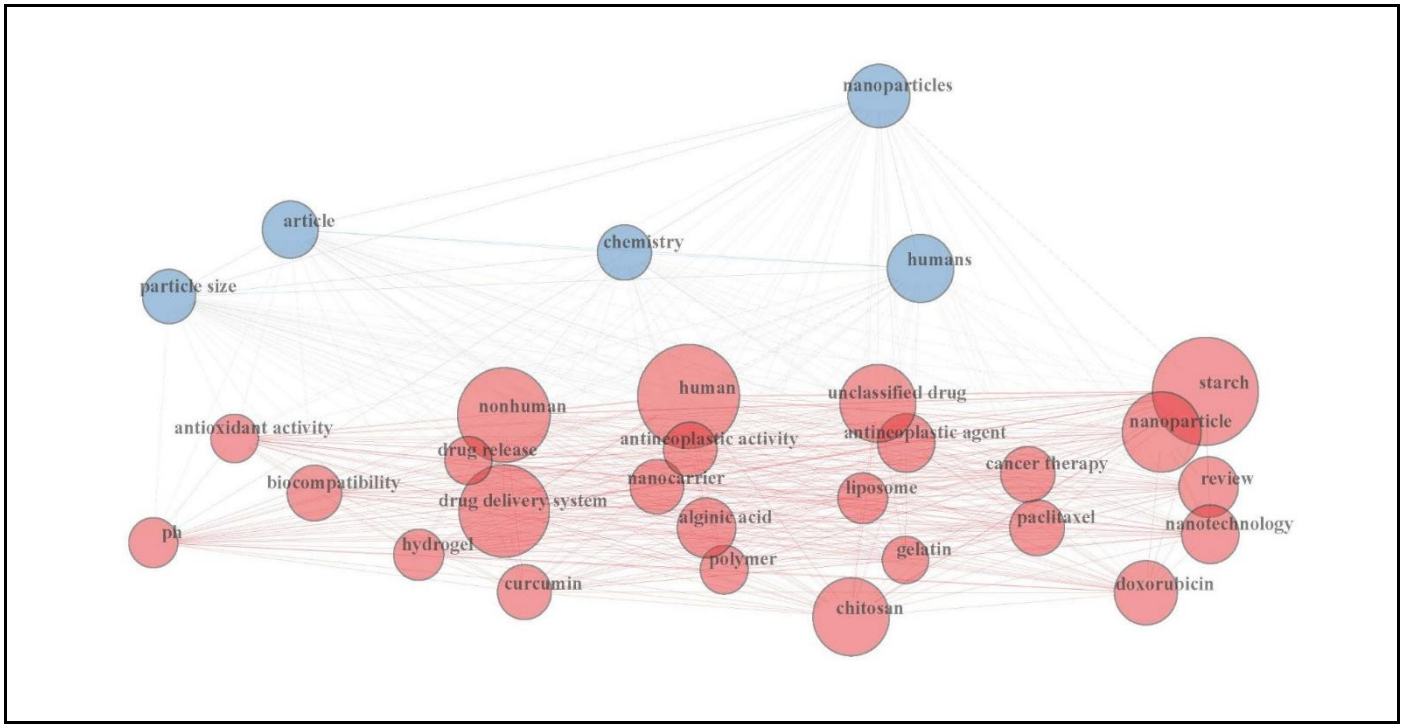

Figure 2. Keyword co-occurrence network of starch-based nanocarrier research for anticancer drug delivery between 1995 and 2026. Node size represents keyword frequency, and links indicate co-occurrence strength between keywords. Distinct clusters reflect the main thematic structure of the field.

Collectively, these bibliometric insights indicate a rapidly expanding and interdisciplinary research domain, with increasing emphasis on functionalized nanocarriers for targeted and controlled drug delivery. These trends provide a critical contextual framework for the subsequent systematic review, which focuses on formulation performance and translational challenges.

3.2. Systematic review of starch-based nanocarriers

A total of 93 studies were included in the systematic review. Analysis of the extracted data revealed several key trends regarding formulation strategies, drug delivery performance, stimuli-responsive behavior, and biological evaluation.

3.2.1. Formulation and starch modification

The literature reveals diverse formulation strategies to overcome the inherent limitations of native starch, such as rapid degradation and high hydrophilicity [16,26]. Researchers frequently utilize chemical modifications, including HES, DAS, and quaternized starch, to enhance stability, self-assembly, and targeting capabilities [20,21,60]. Amphiphilic modifications, such as linking HES with cholesterol or fatty acids, enable the formation of stable core-shell micelles capable of encapsulating hydrophobic drugs, as demonstrated in HES-based nanocarrier systems for curcumin and camptothecin delivery [60,61].

Another dominant strategy involves blending starch with complementary polymers such as chitosan, polyvinyl alcohol, and carboxymethyl cellulose, forming robust nanocomposite hydrogels and microcapsules with improved mechanical and drug delivery properties [1,62–64]. These polymeric systems are increasingly integrated with inorganic or carbon-based nanomaterials, including graphene quantum dots (GQDs), mesoporous silica (SiO_2), and metal-organic frameworks, to enhance surface area, stability, and multifunctionality [65–68]. Nanoprecipitation remains the most widely employed synthesis technique due to its reproducibility, scalability, and compatibility with aqueous systems [12,13].

3.2.2. Encapsulated drugs and drug loading

Starch-based nanocarriers demonstrate strong potential for encapsulating poorly water-soluble chemotherapeutics, particularly doxorubicin, curcumin, quercetin, and 5-fluorouracil [20,60,61]. The incorporation of porous materials such as metal-organic frameworks and high-surface-area nanostructures like GQDs and SiO_2 significantly enhances drug loading and encapsulation efficiency, with reported encapsulation efficiencies exceeding 80% in several studies [62–66].

Drug release profiles are typically engineered to minimize premature leakage during systemic circulation while enabling sustained release at the tumor site [22,23]. Release kinetics frequently follow

Higuchi or Korsmeyer–Peppas models, indicating diffusion-controlled mechanisms governed by matrix swelling and degradation [29,35]. These findings highlight the importance of matrix composition and structural design in regulating drug release behavior.

3.2.3. Stimuli-responsive behavior

To enhance targeting precision and minimize off-target toxicity, recent starch-based nanocarriers increasingly incorporate stimuli-responsive mechanisms [36–38]. The acidic tumor microenvironment (pH 5.0–6.5) is the most widely exploited trigger, where pH-sensitive systems undergo protonation-induced structural changes, accelerating drug release [1,62,67].

Reduction-responsive systems are also widely investigated, utilizing elevated intracellular glutathione (GSH) levels to cleave disulfide linkages in starch-based prodrug systems [60]. Additionally, ROS-responsive nanocarriers, responsive nanocarriers, incorporating thioether or diselenide bonds, have been developed to exploit oxidative tumor environments. Dual-responsive systems combining pH and redox triggers further improve spatiotemporal control of drug release and therapeutic efficacy [61].

3.2.4. Biological evaluation

Biological evaluation consistently demonstrates that starch-based nanocarriers reduce the systemic toxicity of free drugs while maintaining or enhancing anticancer efficacy [5,25]. *In vitro* studies confirm excellent cytocompatibility of blank carriers in normal cell lines, such as L929 fibroblasts and MCF-10A cells, while drug-loaded systems exhibit dose-dependent cytotoxicity in cancer cell lines, including MCF-7, HT-29, and U87-MG [1,62,68].

In vivo studies, although limited, demonstrate improved pharmacokinetic behavior, enhanced tumor accumulation via the enhanced permeability and retention (EPR) effect, and reduced systemic toxicity in murine tumor models [20,60,61]. These findings support the therapeutic potential of starch-based nanocarriers but also highlight the need for more comprehensive *in vivo* validation.

3.2.5. Summary of trends

Overall, the systematic review demonstrates a consistent focus on optimizing formulation design while maintaining therapeutic efficacy. The HES-based nanocarriers and nanoparticle-based systems dominate the field, with doxorubicin and curcumin as the most commonly encapsulated drugs [20,21,60]. Stimuli-responsive designs are increasingly incorporated to enhance targeted delivery; however, gaps remain within *in vivo* validation and mechanistic understanding, emphasizing the need for further translational research [4,5].

3.3. Translational challenges of starch-based nanocarriers

3.3.1. Reproducibility and scalability

Although advanced starch-based nanocarriers demonstrate promising *in vitro* performance, their structural complexity presents major obstacles to large-scale production. Multi-step synthesis processes, precise functionalization requirements, and strict control over particle size and distribution hinder reproducibility and scalability [4,5]. These limitations restrict industrial translation despite strong laboratory performance.

3.3.2. Stimuli-responsive design limitations

Stimuli-responsive starch nanocarriers heavily depend on specific tumor microenvironment cues, particularly acidic pH gradients and elevated intracellular GSH or ROS levels. However, these biological triggers are highly heterogeneous *in vivo*. Variability in tumor microenvironments may lead to premature drug release or insufficient activation at target sites, reducing therapeutic efficiency [36–38].

3.3.3. Gaps in biological evaluation

Despite encouraging *in vitro* results, comprehensive biological evaluation remains limited. Most studies do not extend beyond small animal models, and long-term pharmacokinetics, biodistribution, and immunogenicity are rarely investigated [5,25]. Furthermore, the interaction of hybrid nanocomposites with biological systems remains insufficiently understood. Moreover, the long-term biodistribution, immunogenicity, and chronic toxicity data for modified starch-based nanocarriers remain limited, particularly for repeated-dose administration. In nanomedicine, HES has emerged as a promising alternative to polyethylene glycol (PEG) for nanoparticle surface engineering, offering enhanced biocompatibility while mitigating the limitations associated with the 'PEG dilemma' [69–71]. While PEG is non-biodegradable, prone to tissue accumulation, and known to stimulate the production of anti-PEG antibodies that accelerate the clearance of subsequent doses, HES degrades safely via endogenous α-amylase and exhibits remarkably low intrinsic immunogenicity due to its structural similarity to glycogen [69,71,72]. Despite these advantages, the clinical safety of HES has faced intense scrutiny in specific medical contexts. In critically ill patients, particularly those suffering from severe sepsis or requiring intensive care fluid resuscitation, the administration of

high molecular weight HES has been correlated with an increased risk of acute kidney injury and mortality. Mechanistic investigations suggest that the hyperbranched, colloidal architecture of HES can become physically entrapped within the renal glomeruli, exacerbating kidney damage under compromised physiological conditions [72]. Nevertheless, when finely tuned as a nanoscale drug carrier rather than a bulk volume expander, HES significantly attenuates the severe cardiotoxicity and nephrotoxicity associated with free chemotherapeutics like doxorubicin, underscoring its protective potential when administered in controlled therapeutic regimens [60].

3.3.4. Pharmacopoeial and regulatory considerations of modified starch-based nanocarriers

While native starch is biocompatible and widely regarded as safe, chemical modifications and incorporation of inorganic materials alter its safety profile [16]. These modifications introduce regulatory challenges, requiring extensive toxicity, stability, and quality control validation before clinical application [4,5]. Modified starch-based nanocarriers serve as a highly promising platform for targeted cancer therapy due to their natural biocompatibility, biodegradability, and cost-effectiveness [67,73,74]. To overcome the rapid enzymatic degradation and high hydrophilicity of native starch, researchers utilize chemical modifications of starch such as HES, CMS and DAS [64,66,75]. These modifications allow for the engineering of stable micelles, hydrogels, and nanoparticles capable of efficiently encapsulating and co-delivering poorly water-soluble chemotherapeutics (like doxorubicin, 5-fluorouracil, and curcumin) as well as gene therapies like siRNA [67,76,77].

From a pharmacopoeial perspective, native starch is recognized in major compendia, including the United States Pharmacopeia, European Pharmacopoeia, and British Pharmacopoeia, where it is widely used as a pharmaceutical excipient [8,16]. HES has also been incorporated into pharmaceutical practice for specific parenteral applications [14,20,21]. In contrast, other modified starch derivatives such as CMS, DAS and advanced stimuli-responsive starch conjugates remain primarily at the research stage and have not yet achieved widespread pharmaceutical adoption or pharmacopoeial recognition for nanomedicine applications. Consequently, additional quality, safety, and regulatory evaluations are required before broader pharmaceutical implementation [16,53,61].

To maximize therapeutic efficacy and mitigate off-target toxicity, these formulations heavily rely on stimuli-responsive mechanisms. They are engineered to exploit the specific conditions of the tumor microenvironment, triggering localized drug release in response to acidic pH levels, elevated glutathione (redox), or ROS [61,73,78,79]. Both *in vitro* and *in vivo* evaluations demonstrate that these targeted systems enhance cellular uptake, overcome multidrug resistance, and effectively eradicate malignant cells and cancer stem cells, all while sparing healthy bystander tissues [18,80,81].

While basic modified starches often benefit from a GRAS status, their clinical translation into nanomedicine faces substantial hurdles. Modern nanocarrier designs are increasingly complex, frequently integrating inorganic materials such as carbon quantum dots or metal oxides and synthetic cross-linkers to achieve dual-responsiveness [76,82,83]. This structural complexity raises concerns regarding long-term systemic accumulation, potential immunogenicity, and batch-to-batch manufacturing scalability [82,84]. Consequently, advancing these nanocarriers to clinical trials requires a transition from basic *in vitro* testing to rigorous, long-term *in vivo* pharmacokinetic and toxicological profiling in advanced mammalian models.

4. DISCUSSION

The findings of this study demonstrate a strong alignment between bibliometric trends and experimental developments in starch-based nanocarriers. The increasing research output reflects growing interest in developing functionalized nanocarriers for targeted drug delivery [2,3]. Chemically modified starch derivatives, particularly HES, play a central role in enhancing solubility, stability, and therapeutic performance [20,21]. The incorporation of stimuli-responsive mechanisms further improves targeting precision; however, their effectiveness under physiological conditions remains insufficiently validated [36–38]. Despite promising preclinical outcomes, several translational barriers persist, including formulation variability, limited scalability, and insufficient *in vivo* validation [4,5]. Addressing these challenges requires interdisciplinary approaches combining material science, pharmacology, and regulatory science.

5. RECOMMENDATIONS FOR FUTURE RESEARCH

Future research should prioritize simplifying nanocarrier design to improve scalability, reproducibility, and regulatory compliance. Greater emphasis should also be placed on green synthesis strategies to support sustainable pharmaceutical manufacturing. Environmentally friendly fabrication approaches, including aqueous nanoprecipitation, solvent-free processing, microwave-assisted synthesis, and the use of biodegradable cross-linkers, may reduce dependence on toxic organic solvents and minimize hazardous chemical waste. These strategies could

improve process safety, lower manufacturing costs, and facilitate compliance with Good Manufacturing Practice (GMP) requirements. Future studies should also evaluate the environmental impact of nanocarrier production through life-cycle assessment and green chemistry metrics. The replacement of hazardous reagents with bio-based crosslinkers, utilization of renewable starch sources, and adoption of energy-efficient processing technologies may contribute to more sustainable and economically viable manufacturing pathways. Such approaches are increasingly aligned with regulatory expectations for environmentally responsible pharmaceutical production. In addition, standardized reporting of formulation parameters and characterization methods is essential to improve reproducibility across studies and reduce translational barriers. Comprehensive *in vivo*, pharmacokinetic, and long-term toxicological evaluations remain necessary to support the clinical translation of modified starch-based nanocarriers.

6. CONCLUSION

This systematic review and bibliometric analysis provide a comprehensive overview of starch-based nanocarriers for anticancer drug delivery. Bibliometric trends indicate a rapidly growing field, with notable contributions from China, India, and Iran, and an increasing focus on formulation engineering and therapeutic performance. The systematic review of 93 included studies highlights that HES-based nanoparticles are the most commonly studied, with doxorubicin and curcumin as the primary encapsulated drugs. Stimuli-responsive designs, particularly pH- and redox-sensitive systems, are increasingly utilized to enhance targeted drug release.

Despite promising preclinical outcomes, several translational challenges remain, including reproducibility, scalability, mechanistic validation of stimuli-responsive behavior, limited *in vivo* and pharmacokinetic evaluation, and regulatory considerations. Addressing these gaps through standardized protocols, comprehensive *in vivo* testing, mechanistic studies, and alignment with regulatory requirements is essential for advancing these nanocarriers toward clinical application.

In summary, starch-based nanocarriers hold significant promise for anticancer drug delivery, but future research must focus on bridging the gap between experimental innovation and clinical translation to realize their full therapeutic potential.

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Author contribution
The author solely contributed to the conceptualization, literature search, data analysis, and manuscript preparation.

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Conflict of interest
None to declare.

Ethics approval
None to declare.

Declaration of generative AI and AI-assisted technologies in the manuscript preparation process
During the preparation of this work, the author used OpenAI to assist with language refinement, clarity, and grammatical improvement. All generated content was carefully reviewed, revised, and validated by the author. The author takes full responsibility for the accuracy, integrity, and originality of the final manuscript.

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