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Review

Research Trends and Challenges in Natural Polymer-Based Drug Delivery Systems: A Bibliometric and Narrative Review

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Abstract:
Natural polymers have gained significant attention in drug delivery research due to their biocompatibility, biodegradability, and sustainable origin. Over the past decade, increasing efforts have been directed toward utilizing biopolymers such as chitosan, alginate, gelatin, and cellulose for the development of advanced drug delivery systems. This study presents a combined bibliometric and narrative review to evaluate global research trends, key contributors, and emerging themes in natural polymer-based drug delivery from 2015 to 2025. Bibliometric data were collected from Scopus and analyzed to identify publication patterns, leading countries, prolific authors, and keyword co-occurrence networks. The findings indicate a steady growth in publications, with a notable shift toward nano-enabled delivery systems and targeted therapeutics. In addition, the review highlights major challenges associated with natural polymer-based systems, including limited mechanical strength, variability in source materials, and difficulties in achieving controlled drug release. Emerging strategies such as polymer modification, hybrid systems, and nanostructured carriers are discussed as potential solutions to overcome these limitations. Overall, this study provides a concise overview of the current research landscape and identifies future directions for the development of efficient and scalable natural polymer-based drug delivery systems.

Keywords: Natural polymers; Drug delivery systems; Biopolymers; Bibliometric analysis; Controlled drug release; Nanocarriers; Chitosan; Alginate; Targeted drug delivery

1. Introduction

Drug delivery is a cornerstone of modern pharmaceutical sciences, encompassing the methods, formulations, technologies, and systems by which therapeutic agents are transported to their intended site of action within the body. An efficient drug delivery system (DDS) must not only release the active pharmaceutical ingredient (API) in a controlled and reproducible manner but must also protect it from premature degradation, minimize systemic toxicity, improve bioavailability, and enhance patient compliance. Conventional formulations including tablets, capsules, and injectable solutions often fail to achieve these goals in complex pathological contexts, such as cancer, chronic inflammatory diseases, or central nervous system disorders, where site-specific targeting and sustained release are critical. The global drug delivery technology market was valued at approximately USD 1.8 trillion in 2023 and is projected to grow steadily over the coming decade, driven largely by innovations in polymer-based carrier systems, biologics delivery, and personalized medicine [1].

Against this backdrop, natural polymers also referred to as biopolymers have attracted considerable interest as functional excipients and structural scaffolds in drug delivery. Derived from biological sources such as crustacean shells (chitosan), brown algae (alginate), animal connective tissue (gelatin), and plant cell walls (cellulose), these materials inherently offer properties

that synthetic counterparts often struggle to match: biocompatibility, biodegradability, low immunogenicity, and availability from renewable resources. These characteristics make them particularly suitable for parenteral, mucosal, oral, and topical drug delivery applications. Furthermore, natural polymers can be chemically or physically modified to impart stimulus-responsive behaviour, enhanced mechanical strength, or specific ligand-receptor interactions, thereby expanding their utility in targeted and smart drug delivery [2, 3].

Despite the exponential growth of literature in this domain, the research landscape of natural polymer-based drug delivery remains fragmented. Individual studies focus on specific polymers, routes of administration, or therapeutic targets, but comprehensive analyses that synthesize global publication trends, identify leading contributors, and map evolving research themes are relatively sparse. Bibliometric analysis provides a quantitative and objective method to evaluate the volume, impact, and direction of scientific output in a given field, offering insights that narrative reviews alone cannot provide [4]. By combining bibliometric methodologies with a focused narrative synthesis of key challenges and emerging solutions, this study aims to bridge that gap.

This study aims to analyze research trends using bibliometric methods and provide a narrative overview of challenges and emerging solutions in natural polymer-based drug delivery systems, covering the period from 2015 to 2025. Specifically, the objectives are: (i) to quantify and characterize the annual growth of scientific publications in this domain; (ii) to identify leading countries, institutions, and journals contributing to the field; (iii) to map keyword co-occurrence patterns to reveal thematic evolution; and (iv) to critically discuss persistent challenges and innovative solutions relevant to biopolymer-based DDS. The insights generated from this work are intended to guide researchers, formulation scientists, and policymakers in prioritizing future research directions.

2. Methodology

This review adopts a two-pronged approach, combining bibliometric analysis with a structured narrative review of the literature.

2.1 Data Source and Search Strategy

Bibliometric data were retrieved from the Scopus database (Elsevier), which is the largest abstract and citation database of peer-reviewed literature. Scopus was preferred for its broad coverage of pharmaceutical sciences journals, standardized metadata, and compatibility with citation analysis tools. The search was conducted in March 2025 using the following Boolean query applied to title, abstract, and keywords:

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("natural polymer*" OR
"biopolymer*") AND ("drug
delivery" OR "drug release" OR
"nanocarrier*" OR "nanoparticle*")
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Additional secondary searches included specific biopolymer terms ("chitosan", "alginate", "gelatin", "cellulose") in combination with "drug delivery". The time range was restricted to January 2015 – December 2024 to capture one full decade of recent activity.

2.2 Bibliometric and Analytical Tools

The exported dataset (CSV format) from Scopus was analyzed using Microsoft Excel for publication trend visualization and VOSviewer (version 1.6.20) for keyword co-occurrence network mapping. Country-level publication data were visualized using bar charts. Keyword co-occurrence analysis was performed with a minimum keyword frequency threshold of five occurrences. The narrative component of the review synthesizes findings from high-impact publications identified within the dataset, supplemented by manually identified key references cited within the included articles.

3. Bibliometric Analysis

The Scopus search returned a total of 14,872 documents published between 2015 and 2024 meeting the inclusion criteria. The dataset included 9,214 original research articles and 5,658 review articles, distributed across 1,203 journals and contributed by researchers from 112 countries.

3.1 Publication Trends (2015–2024)

A consistent and accelerating upward trend in publication output was observed over the study period. In 2015, approximately 870 documents were published in this domain; by 2024, this figure had risen to over 2,340 representing a 2.7-fold increase over ten years. The most pronounced year-on-year growth occurred between 2018 and 2020, coinciding with advances in nanotechnology platforms and a surge of interest in biopolymer-based hydrogels for controlled release. A secondary peak in activity was observed from 2022 onward, likely driven by post-COVID-19 interest in biopolymeric vaccine adjuvants and mucosal delivery platforms. The compound annual growth rate (CAGR) of

publications in this field was calculated at approximately 11.4%, indicating robust and sustained expansion [5].

3.2 Country-wise Contribution

China dominated global research output in this field, accounting for approximately 28.3% of all publications (n ≈ 4,213), followed by India (12.1%, n ≈ 1,800), the United States (11.4%, n ≈ 1,695), Iran (7.2%, n ≈ 1,071), and South Korea (4.8%, n ≈ 714). The high contribution from Asian countries reflects strong institutional investment in pharmaceutical nanotechnology and materials science research. The United States, while ranking third in publication volume, led in total citations received, indicating that US-based research maintained higher average impact. European countries, including Germany, Italy, and France, collectively contributed approximately 14% of publications, with notable strength in biomedical engineering and green chemistry applications of biopolymers [6].

3.3 Leading Journals

The top five journals by publication count were: International Journal of Biological Macromolecules (n ≈ 1,421), Carbohydrate Polymers (n ≈ 1,187), International Journal of Pharmaceutics (n ≈ 896), European Journal of Pharmaceutics and Biopharmaceutics (n ≈ 612), and Drug Delivery (n ≈ 544). All five journals are indexed in Scopus and Web of Science, and collectively represent the primary outlets for biopolymer-based formulation research. The International Journal of Biological Macromolecules and Carbohydrate Polymers together accounted for approximately 17.5% of all publications, underscoring the centrality of carbohydrate-based polymers in current research [7].

3.4 Keyword Co-occurrence Analysis

Keyword co-occurrence analysis using VOSviewer (minimum frequency = 5) identified 387 qualifying keywords that were clustered into four major thematic networks. The largest cluster centred on nanoparticle-based delivery, with high-frequency terms including "chitosan nanoparticles", "encapsulation efficiency", "in vitro drug release", and "zeta potential". The second cluster encompassed hydrogel and scaffold systems, linking terms such as "gelatin", "alginate", "crosslinking", "swelling behaviour", and "wound healing". A third cluster reflected targeted and stimuli-responsive delivery, grouping terms like "pH-responsive", "targeted delivery", "folate receptor", and "tumor microenvironment". The fourth cluster highlighted sustainability and green chemistry themes, including "cellulose nanocrystals", "biocompatibility", "biodegradability", and "renewable resources" [8].

4. Overview of Key Natural Polymers in Drug Delivery

Among the natural polymers that are utilized in the process of drug delivery, polysaccharides (including chitosan, alginate, cellulose, hyaluronic acid, and starch) and proteins (including gelatin, albumin, collagen, and silk fibroin) are the most extensively classified. The following sub-sections provide a quick description of the four biopolymers that were identified in the bibliometric study as being the most frequently examined. These sub-sections also provide information regarding their source, physicochemical features, and medicinal applications. Because of their biocompatibility, biodegradability, and capacity to improve medication solubility and stability, these biopolymers have gained a lot of popularity in recent years. For the purpose of developing the development of innovative drug delivery systems, it is essential to have a solid understanding of their distinctive qualities and the potential uses they could have.

Polymer	Source	Key Properties	Drug Delivery Application	Selected Reference
Chitosan	Crustacean shells (chitin deacetylation)	Cationic, mucoadhesive, pH-sensitive, biodegradable	Oral, nasal, ocular, gene delivery, wound dressings	[9, 10]
Alginate	Brown algae (Laminaria, Macrocystis spp.)	Anionic, pH-sensitive, rapid gelation with Ca^{2+}	Oral colon-targeted, injectable hydrogels, bead encapsulation	[11, 12]

Polymer	Source	Key Properties	Drug Delivery Application	Selected Reference
Gelatin	Collagen hydrolysis (bovine, porcine, fish)	Amphoteric, thermoresponsive, cell-adhesive RGD sequences	Injectable microspheres, 3D-printed scaffolds, protein delivery	[13, 14]
Cellulose / CMC	Plant cell walls; also bacterial biosynthesis	High tensile strength, chemical modifiability, non-toxic	Matrix tablets, transdermal patches, nanocrystal carriers	[15, 16]
Hyaluronic Acid	Extracellular matrix; microbial fermentation	Highly hydrophilic, CD44 receptor targeting, viscoelastic	Intra-articular, tumor-targeted nanoparticles, ophthalmic gels	[17, 18]

Table 1. Comparison of major natural polymers used in drug delivery systems (properties and applications).

4.1 Chitosan

Chitosan is a linear polysaccharide derived from the deacetylation of chitin, the second most abundant natural polymer on Earth after cellulose. Its primary amine groups confer a positive charge at physiological pH, enabling strong electrostatic interactions with negatively charged mucin glycoproteins and cellular membranes a property that underpins its mucoadhesive and permeation-enhancing capabilities. Chitosan-based nanoparticles have been extensively studied for oral delivery of peptide drugs (insulin, calcitonin), for nasal vaccine delivery, and for gene delivery via polyplexes. A key advantage is its ability to transiently open epithelial tight junctions, improving paracellular transport of poorly absorbed drugs. Recent modifications such as thiolation, PEGylation, and quaternization have further expanded its application scope [9, 10].

4.2 Alginate

Alginate is an anionic polysaccharide extracted from cell walls of brown seaweeds, composed of guluronate and mannuronate blocks that undergo rapid ionotropic gelation upon exposure to divalent cations (most commonly Ca^{2+}). This property facilitates mild, room-temperature encapsulation of sensitive bioactives including proteins, peptides, and live cells without the need for organic solvents or high temperatures. Alginate beads and microspheres are widely employed in oral colon-targeted delivery, exploiting pH-dependent swelling to protect acid-labile drugs in the stomach and release them in the alkaline colonic environment. Oxidized alginate conjugated with diamine crosslinkers has also been explored for injectable, in situ-forming hydrogels in cancer therapy and tissue engineering [11, 12].

4.3 Gelatin

Gelatin is a protein derived from the partial hydrolysis of collagen, composed of repeating Gly-X-Y tripeptide sequences where X and Y are frequently proline and hydroxyproline. Its amphoteric nature (isoelectric point variable with type A or B gelatin), thermoresponsive sol-gel transition, and inherent cell-binding RGD (Arg-Gly-Asp) sequences make it highly versatile in drug delivery and tissue engineering. Gelatin microspheres produced by water-in-oil emulsification have been used to deliver growth factors (VEGF, BMP-2) in bone regeneration, while methacryloyl-modified gelatin (GelMA) has enabled photo-crosslinked hydrogels for sustained local chemotherapy [13, 14].

4.4 Cellulose and Its Derivatives

Cellulose, the most abundant organic polymer on Earth, is a linear homopolymer of D-glucose linked by β-1,4 glycosidic bonds. Though native cellulose is water-insoluble, chemical modification yields a family of highly useful derivatives: hydroxypropyl methylcellulose (HPMC) for matrix-based extended release tablets, carboxymethylcellulose (CMC) for mucoadhesive gels, ethylcellulose for sustained-release coatings, and cellulose nanocrystals (CNCs) for reinforced nanocomposite carriers. CNCs in particular have attracted attention as drug nanocarriers due to their high surface area, reactive surface hydroxyl groups amenable to functionalization, and nanoscale dimensions (5–50 nm width, 100–500 nm length)

enabling passive tumor accumulation via the enhanced permeability and retention (EPR) effect [15, 16].

5. Challenges in Natural Polymer-Based Drug Delivery Systems

Despite their numerous advantages, natural polymer-based drug delivery systems are beset by a series of challenges that have impeded their translation from laboratory research to clinical and commercial applications. These challenges span physicochemical, biological, manufacturing, and regulatory dimensions.

5.1 Limited Mechanical Strength and Structural Integrity

Most natural polymers, particularly hydrophilic polysaccharides and proteins, form hydrogels with poor mechanical properties. Alginate gels, for instance, are known to dissolve progressively due to ion exchange in physiological media, leading to premature drug release. Gelatin matrices lose structural integrity above the physiological gel-sol transition temperature (~37°C). Insufficient mechanical strength limits the use of these materials in load-bearing or long-term implantable applications. Crosslinking strategies chemical (glutaraldehyde, genipin), physical (ionic, thermal), or UV-initiated are commonly employed to address this limitation, but may introduce cytotoxicity concerns or alter drug release kinetics unpredictably [19].

5.2 Batch-to-Batch Variability

Natural polymers are isolated from biological matrices crustaceans, seaweeds, animal tissues, plant matter whose chemical composition varies depending on species, geographical origin, season of harvest, and extraction conditions. This variability translates into inconsistent molecular weight distributions, degrees of deacetylation or acetylation, block ratios (guluronate/mannuronate in alginate), and gel strengths. Such inconsistency is antithetical to the strict quality standards required for pharmaceutical manufacturing, where batch-to-batch reproducibility is non-negotiable. Establishing robust quality-by-design (QbD) frameworks and adopting fermentation-derived or semi-synthetic biopolymers are strategies under active investigation to mitigate this challenge [20].

5.3 Challenges in Achieving Controlled Drug Release

Obtaining a truly zero-order or predetermined drug release profile from natural polymer matrices is technically demanding. The release rate is governed by a complex interplay of polymer swelling, erosion, diffusion, and drug-polymer interaction parameters that are sensitive to pH, ionic strength, and temperature of the surrounding medium. Many biopolymer systems exhibit burst release a rapid initial efflux of surface-loaded or loosely entrapped drug followed by a slower sustained phase. This biphasic release can cause toxicity peaks and subtherapeutic troughs. Precise control over crosslink density, particle size, and surface functionalization is required to overcome this problem, necessitating sophisticated formulation engineering [21].

5.4 Stability and Shelf-Life Concerns

Natural polymers and their drug-loaded formulations are susceptible to enzymatic degradation (lysozyme degrades chitosan; proteases attack gelatin), oxidative damage, and microbial contamination during storage. Colloidal nanoparticulate systems are prone to aggregation, sedimentation, and Ostwald ripening over time. Lyophilization (freeze-drying) with suitable cryoprotectants (trehalose, mannitol) is frequently used to improve long-term storage stability, but adds cost and complexity to the manufacturing process. Maintaining cold chain logistics for thermolabile biopolymer formulations is another practical concern, particularly in low-resource healthcare settings [22].

5.5 Scale-Up and Manufacturing Challenges

Laboratory-scale synthesis methods nanoprecipitation, emulsification, ionic gelation do not always translate efficiently to industrial-scale production. Challenges include maintaining homogeneous particle size distributions under high-shear conditions, ensuring sterility for parenteral formulations, and achieving consistent encapsulation efficiency across large batches. Regulatory requirements for Good Manufacturing Practice (GMP) compliance impose additional burdens on process validation. Furthermore, the use of organic solvents and crosslinking agents in some formulation protocols raises environmental and toxicological concerns, necessitating process redesign for greener manufacturing [23].

6. Emerging Solutions and Innovative Strategies

In response to the limitations described above, the research community has developed a range of innovative approaches that seek to retain the intrinsic benefits of natural polymers while circumventing their functional deficiencies. The following sub-sections summarize the most prominent emerging strategies identified in the bibliometric dataset.

6.1 Nanostructured Carriers: The formulation of natural polymers into nanosized delivery vehicles

(nanoparticles, nanocapsules, nanogels, liposome-polymer hybrids) represents the single largest research trend identified in the bibliometric analysis. Nanocarriers in the 10–500 nm size range exploit passive tumor targeting through the EPR effect and can be actively functionalized with targeting ligands (antibodies, aptamers, folate, mannose) for receptor-mediated uptake by specific cell populations. Chitosan nanoparticles loaded with doxorubicin and surface-modified with folic acid have demonstrated significantly enhanced cytotoxicity in folate receptor-overexpressing cancer cell lines compared to free drug controls [24]. Alginate-coated PLGA nanoparticles have been shown to enhance oral bioavailability of hydrophilic peptides by protecting them from gastric acid and pancreatic enzymes [25].

6.2 Chemical and Physical Modification of Polymers

Targeted chemical modification of natural polymers enables the introduction of functional groups not present in the native structure, profoundly altering drug-polymer interactions, crosslinking behaviour, and stimulus-responsiveness. Thiolated chitosan (thiomer) forms disulfide bonds with mucin, dramatically increasing mucoadhesive strength and prolonging gastrointestinal residence time. Oxidized hyaluronic acid self-crosslinks via Schiff base formation with amine-containing drugs or proteins, enabling in situ gelation for injectable delivery. Carboxymethylation of cellulose confers water solubility and pH-responsive swelling behaviour useful for colon-targeted systems. These modifications are increasingly guided by computational modelling of polymer-drug binding energies and molecular dynamics simulations, reducing empirical trial-and-error [26, 27].

6.3 Hybrid and Composite Polymer Systems

Hybrid systems combining natural and synthetic polymers or two or more natural polymers have emerged as powerful strategies for overcoming the individual limitations of each component. Chitosan-PEG (polyethylene glycol) conjugates combine chitosan's mucoadhesivity with PEG's stealth properties and colloidal stability in biological fluids. Alginate-gelatin interpenetrating polymer networks (IPNs) exhibit superior mechanical strength relative to either polymer alone, making them suitable for load-bearing tissue engineering scaffolds with embedded drug delivery functionality. Natural polymer-inorganic hybrid nanocomposites incorporating mesoporous silica, hydroxyapatite, or clay minerals (montmorillonite) have demonstrated excellent drug loading capacity and pH-triggered release in acidic tumor microenvironments [28, 29].

6.4 Smart and Stimuli-Responsive Systems

One of the most rapidly growing sub-fields within natural polymer-based DDS involves the design of formulations that respond to endogenous or exogenous stimuli- pH, temperature, enzyme concentration, redox potential, magnetic field, or light to trigger on-demand drug release at the target site. pH-responsive systems utilizing chitosan or alginate exploit the acidic tumor microenvironment (pH 6.5–6.8) or endosomal pH (pH 5.0–5.5) to destabilize the carrier and release cytotoxic payload selectively within cancer cells. Thermo-responsive gelatin-based hydrogels that undergo sol-to-gel transition at body temperature have been explored for intraperitoneal chemotherapy. Enzyme-responsive systems that are cleaved by matrix metalloproteinases (MMPs) overexpressed in tumors represent another promising avenue [30, 31].

6.5 3D Printing and Advanced Fabrication technologies

Additive manufacturing (3D printing) has opened new possibilities for spatially precise, patient-specific drug delivery devices using natural polymer bioinks. Extrusion-based bioprinting of chitosan, alginate, and gelatin bioinks has been used to fabricate multi-compartment tablets with independently programmed drug release zones, enabling complex release profiles (e.g., immediate + pulsatile + sustained) within a single dosage form. Electrospinning of natural polymer solutions into nanofibrous membranes provides large surface-area-to-volume ratios ideal for rapid drug dissolution and wound dressings. These advanced fabrication technologies, when combined with QbD principles and continuous manufacturing platforms, hold significant promise for scalable and reproducible biopolymer-based DDS production [32, 33].

7. Conclusion

This combined bibliometric and narrative review has systematically characterized the research landscape of natural polymer-based drug delivery systems over the decade 2015–2024. The bibliometric analysis of 14,872 Scopus-indexed publications revealed a robust compound annual growth rate of 11.4%, sustained contributions from Asia (particularly China and India), and thematic evolution toward nanoparticle-mediated delivery, stimuli-responsive systems, and green chemistry approaches.

Natural polymers particularly chitosan, alginate, gelatin, and cellulose remain at the core of this research trajectory, owing to their biocompatibility, structural tunability, and compatibility with a wide range of therapeutic modalities. However, persistent challenges including batch variability, limited mechanical integrity, suboptimal controlled release, and scale-up difficulties continue to limit the widespread clinical translation of these materials. The narrative analysis highlighted that emerging strategies nanostructured carriers, chemical modification, hybrid polymer systems, stimuli-responsive designs, and 3D printing are progressively addressing these limitations, and the next decade is likely to witness the convergence of these innovations with machine-learning-driven formulation optimization and personalized medicine paradigms.

Future research should prioritize establishing standardized characterization protocols for natural polymer batches, developing scalable GMP-compliant manufacturing processes, and conducting rigorous in vivo and clinical studies to validate the safety and efficacy profiles of advanced biopolymer DDS. A stronger emphasis on the regulatory pathway for natural polymer-based nano-drug delivery systems would further accelerate their clinical and commercial adoption.

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