INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: https://www.ijpsjournal.com

Review Article

Biopolymer-Based Stimuli-Responsive Systems for Herbal Drug Delivery: A Comprehensive Review

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ARTICLE INFO

Published: 20 Apr 2026
Keywords:
biopolymers; stimuli-responsive drug delivery; herbal drugs; chitosan; pH-responsive; nanoparticles; curcumin; targeted delivery; cancer therapy; smart drug delivery systems
DOI:
10.5281/zenodo.19667578

ABSTRACT

Herbal drugs have been used for centuries in traditional medicine and continue to represent a significant portion of global therapeutic interventions. However, their clinical translation is often hampered by inherent limitations such as poor aqueous solubility, low bioavailability, rapid metabolism, chemical instability, and nonspecific biodistribution. Biopolymer-based stimuli-responsive drug delivery systems (SR-DDS) have emerged as a promising strategy to overcome these barriers by enabling precise spatiotemporal control of drug release in response to specific physiological or pathological cues. These systems exploit endogenous triggers—including altered pH gradients, elevated temperatures, enzymatic activity, and reactive oxygen species (ROS)—as well as exogenous stimuli such as light and magnetic fields to govern the release of herbal bioactive at target sites. Common biopolymers employed include chitosan, alginate, hyaluronic acid, gelatine, cellulose derivatives, pectin, guar gum, and starch, each offering distinct physicochemical attributes amenable to functionalization. This review comprehensively examines the current landscape of biopolymer-based SR-DDS for herbal drug delivery, discussing the underlying mechanisms of stimuli-responsiveness, the physicochemical properties of clinically relevant biopolymers, and the challenges unique to herbal bioactive. Special emphasis is placed on anticancer applications, brain-targeted delivery, and colon-specific systems. Formulation strategies, in vitro and in vivo evidence, regulatory considerations, and future directions are also critically discussed. This review is intended to serve as a consolidated reference for researchers working at the intersection of biopolymer science, nanotechnology, and phytopharmacology.

INTRODUCTION

Herbal medicines and plant-derived bioactive compounds occupy a central position in global healthcare, particularly in developing nations where they constitute the primary source of primary care for a majority of the population [1].

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Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The World Health Organization (WHO) estimates that approximately 80% of the world's population relies on traditional plant-based remedies for some aspect of their healthcare [2]. Moreover, a substantial proportion of approved modern pharmaceutical drugs have been derived or inspired by natural products, underscoring their enduring pharmacological relevance [3].

Despite their therapeutic promise, herbal bioactive face formidable challenges in clinical translation. Many phytoconstituents—including curcumin, quercetin, berberine, resveratrol, and silymarin—exhibit poor aqueous solubility, extensive first-pass metabolism, limited membrane permeability, and rapid systemic clearance, collectively resulting in low oral bioavailability [4]. Additionally, the chemical complexity of plant extracts, the presence of multiple bioactive constituents, variability in potency, and lack of standardized quality control further complicate their formulation [5]. These limitations underscore the urgent need for innovative delivery platforms capable of optimizing the pharmacokinetic and pharmacodynamic profiles of herbal drugs.

Drug delivery systems (DDS) have evolved tremendously over the past three decades, advancing from conventional dosage forms toward intelligent systems capable of responding to biological signals [6]. Among these, stimuli-responsive drug delivery systems (SR-DDS)—also referred to as "smart" or "triggered" DDS—are engineered to release therapeutic payloads in a controlled manner upon exposure to specific internal or external stimuli [7]. These systems can be designed to respond to pH changes, temperature variations, enzymatic activity, redox gradients, light, magnetic fields, or combinations thereof (dual/multi-responsive systems) [8].

Biopolymers—naturally derived macromolecules including polysaccharides and proteins—have gained immense traction as building blocks for SR-DDS owing to their inherent biocompatibility, biodegradability, low immunogenicity, and structural versatility [9]. Their abundant functional groups (amine, hydroxyl, carboxyl) facilitate chemical modification to impart stimuli-responsive behaviour, allowing for the design of nanoparticles, hydrogels, micelles, liposomes, and microspheres capable of delivering herbal actives with spatiotemporal precision [10].

This review aims to provide a comprehensive and critical appraisal of biopolymer-based SR-DDS specifically tailored for herbal drug delivery. The review covers the classification and properties of relevant biopolymers, mechanisms of various stimuli-responsive platforms, the specific challenges associated with herbal drugs, recent advances in combining these technologies, and their applications in disease management including cancer and neurodegenerative conditions. Challenges, limitations, and future research directions are also discussed to provide a roadmap for translational research in this rapidly evolving field.

2. BIOPOLYMERS IN DRUG DELIVERY

2.1 Definition and Classification

Biopolymers are macromolecules produced by living organisms through biosynthetic processes. In the context of drug delivery, they encompass a broad range of naturally occurring and semi-synthetic polymers derived from plant, animal, microbial, and marine sources [11]. Biopolymers are broadly classified into polysaccharides (chitosan, alginate, cellulose, pectin, starch, guar gum, xanthan gum, carrageenan, hyaluronic acid) and proteins (gelatine, collagen, albumin, silk fibroin, zein) [12]. Each class offers distinct physicochemical properties exploitable in drug delivery design.

2.2 Key Biopolymers and Their Properties

2.2.1 Chitosan

Chitosan is a cationic, linear polysaccharide derived by partial deacetylation of chitin, the second most abundant natural polymer found in crustacean exoskeletons and fungal cell walls [13]. Its positive charge at physiological and mildly acidic pH facilitates strong electrostatic interactions with negatively charged cell membranes and mucus, conferring excellent mucoadhesive properties [14]. Chitosan-based nanoparticles have been extensively explored for oral, nasal, transdermal, and ocular drug delivery. Its primary amine groups (pKa ~6.5) render it inherently pH-responsive, with solubility increasing at acidic pH and gelling/precipitation occurring near neutral pH [15]. Furthermore, chitosan undergoes enzymatic degradation by lysozyme and chitinase in biological environments, offering additional control over drug release kinetics.

2.2.2 Alginate

Alginate is an anionic polysaccharide extracted from the cell walls of brown seaweeds (Phaeophyceae). Structurally, it is a copolymer of beta-D-mannuronic acid (M) and alpha-L-guluronic acid (G) residues [16]. Alginate rapidly forms hydrogels in the presence of divalent cations (Ca2+, Ba2+) through ionic crosslinking of G-blocks, a property exploited in the preparation of beads, microspheres, and scaffolds for controlled drug release [17]. Alginate exhibits pH-dependent swelling, dissolving at neutral-to-alkaline pH and collapsing in acidic environments, making it suitable for intestinal-targeted delivery systems. It has been used extensively to encapsulate herbal bioactive such as curcumin and resveratrol [18].

2.2.3 Hyaluronic Acid

Hyaluronic acid (HA) is a high-molecular-weight glycosaminoglycan composed of repeating disaccharide units of D-glucuronic acid and N-acetyl-D-glucosamine [19]. It is a natural component of the extracellular matrix (ECM) and plays critical roles in cell signalling, proliferation, and migration. HA binds with high affinity to the CD44 receptor, which is overexpressed on many tumour cells, making HA-functionalized nanocarriers attractive for active tumour targeting [20]. HA is also susceptible to enzymatic degradation by hyaluronidase (HAase), an enzyme overexpressed in the tumour microenvironment, enabling enzyme-triggered drug release [21]. These properties have been widely leveraged for anticancer herbal drug delivery.

2.2.4 Gelatine

Gelatine is a protein derived by partial hydrolysis of collagen from animal connective tissues. It exhibits thermoresponsive sol-gel transitions at physiologically relevant temperatures (around 30-35 degrees C) and is degradable by matrix metalloproteinases (MMPs), enzymes overexpressed in tumours and inflamed tissues [22]. Gelatine nanoparticles and hydrogels have been employed for loading hydrophobic herbal drugs, improving their aqueous dispersibility and enabling controlled release via both thermal and enzymatic mechanisms [23]. Chemical crosslinking with glutaraldehyde or genipin allows modulation of gelatine's mechanical properties and degradation rate.

2.2.5 Cellulose Derivatives

Cellulose, the most abundant natural polymer, forms the structural backbone of plant cell walls. Its derivatives—including hydroxypropyl methylcellulose (HPMC), carboxymethylcellulose (CMC), ethyl cellulose, and cellulose acetate phthalate (CAP)—are widely used as

pharmaceutical excipients [24]. HPMC exhibits thermally induced gelation and is used extensively in sustained-release matrix systems. CAP dissolves selectively at pH > 6.0, making it useful for enteric coating. CMC is anionic and swells extensively in aqueous media, providing sustained drug diffusion [25]. These derivatives have been used to formulate herbal extracts into pH-responsive and controlled-release tablets and capsules.

2.2.6 Pectin

Pectin is a complex anionic polysaccharide predominantly composed of galacturonic acid units and is extracted mainly from citrus peel and apple pomace [26]. It remains intact in the upper gastrointestinal tract but is specifically degraded by pectinolytic enzymes (pectinase, polygalacturonase) produced by colonic microflora, making it an ideal carrier for colon-targeted drug delivery [27]. Pectin hydrogels also exhibit pH-responsive swelling, being minimally soluble in the acidic stomach but dissolving progressively toward the colon. Herbal actives such as quercetin and resveratrol have been successfully encapsulated in pectin-based systems for colon-targeted delivery [28].

2.2.7 Other Biopolymers

Guar gum, a galactomannan from Cyamopsis tetragonoloba, and xanthan gum, a microbial exopolysaccharide, are both used as matrix-forming agents and thickeners in pharmaceutical formulations [29]. Both are degraded by colonic microflora and have been used in colon-targeted delivery. Carrageenan, derived from red algae, forms temperature-responsive gels and is used in controlled-release formulations. Starch and its derivatives (oxidized starch, starch phosphate) offer biodegradability and enzyme-responsiveness via amylase-mediated hydrolysis [30].

Table 1. Comparative Overview of Key Biopolymers Used in Stimuli-Responsive Drug Delivery Systems

Biopolymer	Source	Key Properties	Stimuli Responsiveness	Drug Release Mechanism	Reference
Chitosan	Crustacean shells	Cationic, biodegradable, mucoadhesive	pH, enzyme	Swelling, enzymatic degradation	[5,8,12]
Alginate	Brown seaweed	Anionic, hydrophilic, gel-forming	pH, ionic	Ion exchange, pH-swelling	[6,13,19]
Hyaluronic Acid	Microbial fermentation, animal tissue	High water retention, receptor targeting	Enzyme (hyaluronidase)	Enzymatic cleavage	[9,21,33]
Gelatine	Animal collagen	Thermoresponsive, biocompatible	Temperature, enzyme	Gel-sol transition, proteolysis	[7,14,25]
Cellulose derivatives (HPMC, CMC)	Plant cell walls	High viscosity, film-forming	pH, temperature	Matrix erosion, diffusion	[10,18,27]
Pectin	Plant cell walls (citrus)	Anionic, colon-specific	pH, enzyme (pectinase)	Enzymatic degradation in colon	[11,22,30]
Guar Gum	Cyamopsis tetragonoloba seeds	High swelling, thickening	Enzyme, pH	Swelling and enzymatic hydrolysis	[15,23,28]
Xanthan Gum	Xanthomonas fermentation	Stable, pseudoplastic, anionic	pH, ionic strength	Swelling, ion exchange	[16,24,31]

Carrageenan	Red algae	Thermo-gelling, anionic	Temperature, ionic	Gel-sol transition	[17,26,32]
Starch	Cereal grains, tubers	Biodegradable, abundant	pH, enzyme (amylase)	Enzymatic hydrolysis, swelling	[20,29,35]

HPMC = hydroxypropyl methylcellulose; CMC = carboxymethylcellulose; ROS = reactive oxygen species

3. STIMULI-RESPONSIVE DRUG DELIVERY SYSTEMS

3.1 Concept and Classification

Stimuli-responsive drug delivery systems are engineered to remain stable and retain their drug payload during circulation but release the drug in a triggered, controlled fashion upon encountering a specific stimulus at the target site [31]. Stimuli can be broadly categorized as endogenous (derived from pathophysiological alterations within the body) or exogenous (applied externally by a clinician or device). Endogenous stimuli include pH, temperature, enzymes, ROS, glucose concentration, and hypoxia. Exogenous stimuli include light (photodynamic), magnetic fields, ultrasound, and electric fields [32].

3.2 pH-Responsive Systems

The pH-responsive release mechanism exploits the distinct pH gradients that exist across various physiological compartments. The gastrointestinal tract exhibits a pH gradient from approximately 1.0-3.0 in the stomach to 5.5-6.5 in the small intestine and 6.4-7.0 in the colon [33]. Similarly, the tumour microenvironment is characteristically acidic (pH 6.5-6.8 extracellularly; pH 4.5-5.0 in endosomes and lysosomes) compared to normal tissue (pH 7.4) due to the Warburg effect and impaired lymphatic drainage [34]. pH-responsive biopolymers contain ionizable groups (e.g., carboxylic acids with pKa 4-6 or amines with pKa 6-8) that undergo protonation/deprotonation in response to pH changes, causing swelling, shrinking, or dissolution of the carrier and consequent drug release. Chitosan, alginate, pectin, CMC, and CAP are among the most widely used pH-responsive biopolymers for herbal drug delivery [35].

3.3 Thermoresponsive Systems

Thermoresponsive polymers undergo reversible phase transitions in response to temperature changes. Those exhibiting a lower critical solution temperature (LCST) are soluble below the LCST and precipitate or gel above it—a property exploited for triggered drug release at tumour sites or inflamed tissues [36]. Poly(N-isopropylacrylamide) (PNIPAM) is the most studied synthetic thermoresponsive polymer (LCST ~32 degrees C), often grafted onto biopolymer backbones to create biocompatible thermosensitive hybrids. Naturally thermoresponsive biopolymers such as gelatine and methylcellulose also exhibit sol-gel transitions near physiological temperatures. Thermosensitive chitosan-gelatine hydrogels, for example, have been used for the controlled delivery of quercetin and curcumin in cancer therapy [37].

3.4 Enzyme-Responsive Systems

Enzyme-responsive systems leverage the elevated expression or activity of specific enzymes in diseased tissues as a trigger for drug release [38]. Hyaluronidase overexpression in tumours enables Haase-mediated degradation of HA-coated nanoparticles, releasing the encapsulated herbal drug at the tumour site [39]. MMP-responsive gelatine nanoparticles exploit MMP-2 and MMP-9 overexpression in cancerous and inflamed

tissues for selective drug liberation. In the gastrointestinal tract, colonic enzymes (pectinase, dextranase, beta-glucuronidase) degrade polysaccharide carriers such as pectin and guar gum, enabling colon-specific drug delivery of herbal bioactive [40]. This enzyme-triggered approach offers high selectivity and reduced systemic toxicity compared to passive release systems.

3.5 ROS-Responsive Systems

Reactive oxygen species (ROS)—including hydrogen peroxide (H2O2), superoxide, and hydroxyl radicals—are overproduced in tumour microenvironments, inflammatory lesions, and ischemic tissues [41]. ROS-responsive carriers incorporate oxidation-sensitive linkers or groups such as boronic esters, thioethers, or selenium-containing moieties that are cleaved or oxidized upon ROS exposure, triggering drug release. Biopolymers modified with thioether or polysulfide groups have been used to formulate ROS-responsive nanoparticles for anticancer herbal drug delivery [42]. The integration of ROS-responsiveness with biopolymers is an active area of research offering promise for targeted oxidative-disease therapy.

3.6 Dual and Multi-Responsive Systems

Dual or multi-responsive systems are designed to respond to two or more stimuli simultaneously or sequentially, providing enhanced selectivity and control over drug release [43]. For instance, chitosan-coated magnetic nanoparticles loaded with curcumin can respond to both pH changes and magnetic fields, enabling magnetically guided targeting followed by pH-triggered release in the acidic tumour microenvironment [44]. Similarly, thermoresponsive/ pH-responsive hybrid hydrogels have been developed for the dual-triggered release of herbal actives. These systems are particularly valuable in complex disease microenvironments where a single stimulus may be insufficient for precise control [45].

4. HERBAL DRUGS AND THEIR CHALLENGES IN DELIVERY

4.1 Significance of Herbal Drugs

Herbal drugs and their derived bioactive compounds encompass a chemically diverse array of secondary metabolites including alkaloids, flavonoids, terpenoids, polyphenols, glycosides, and essential oils [46]. Many of these compounds exert potent biological activities including anticancer, anti-inflammatory, antioxidant, antimicrobial, antidiabetic, and neuroprotective effects [47]. Notable examples include curcumin (anticancer, anti-inflammatory), quercetin (antioxidant, anticancer), berberine (antidiabetic, antimicrobial), resveratrol (cardioprotective), silymarin (hepatoprotective), and paclitaxel (anticancer, derived from Taxus brevifolia) [48].

4.2 Physicochemical Challenges

A major limitation of most herbal bioactive is their poor aqueous solubility. Curcumin, for instance, has a water solubility of less than 1 microgram/mL, severely limiting its oral absorption [49]. Quercetin is categorized as a Biopharmaceutics Classification System (BCS) Class II compound (low solubility, high permeability), while berberine and resveratrol also demonstrate poor solubility profiles. The hydrophobic nature of many phytoconstituents leads to poor dissolution in gastrointestinal fluids, reduced intestinal absorption, and consequently low systemic bioavailability [50]. Furthermore, chemical instability under conditions of light, oxygen exposure, heat, and extreme pH leads to rapid degradation of active constituents prior to

absorption—a significant challenge for curcumin, which degrades rapidly at neutral-to-alkaline ph.

4.3 Biological and Pharmacokinetic Challenges

Beyond physicochemical limitations, herbal bioactive face significant pharmacokinetic challenges. Many are substrates of intestinal efflux transporters (P-glycoprotein), which actively pump them back into the intestinal lumen, reducing effective absorption [51]. Extensive phase I (CYP450-mediated) and phase II (glucuronidation, sulfation) metabolism in the intestinal wall and liver leads to rapid first-pass inactivation. For example, oral curcumin undergoes rapid glucuronidation and sulfation, with less than 1% reaching the systemic circulation in free form [52]. Short plasma half-lives, rapid tissue clearance, and non-specific biodistribution further limit target-site drug concentrations. These challenges necessitate delivery strategies that protect the bioactive from premature degradation, enhance membrane permeation, evade efflux transporters, and achieve site-specific accumulation.

4.4 Formulation Challenges

Formulating herbal extracts is inherently more complex than formulating single chemical entities due to the presence of multiple bioactive constituents with varying physicochemical properties [53]. Standardization of herbal extracts, ensuring batch-to-batch consistency in bioactive content, and developing scalable, commercially viable nano formulations remain challenging. The interaction of biopolymer excipients with multiple herbal constituents may alter the release profiles of individual components in unpredictable ways. Regulatory pathways for complex herbal nano formulations are also less well-defined compared to conventional pharmaceuticals, presenting additional barriers to clinical translation [54].

Table 2. Selected Herbal Drugs and Their Biopolymer-Based Stimuli-Responsive Delivery Systems

Herbal Drug	Source Plant	Therapeutic Use	Biopolymer Used	Delivery System	References
Curcumin	Curcuma longa	Anticancer, anti-inflammatory	Chitosan, PLGA	pH-responsive nanoparticles	[37,42,48]
Quercetin	Allium cepa, various plants	Antioxidant, anticancer	Alginate, gelatine	Thermosensitive hydrogel	[38,43,49]
Berberine	Berberi's species	Antidiabetic, antimicrobial	Hyaluronic acid, chitosan	Targeted nanocarriers	[39,44,50]
Resveratrol	Vitis vinifera	Cardioprotective, neuroprotective	Pectin, alginate	Colon-targeted microbeads	[40,45,51]
Paclitaxel (semi-herbal)	Taxus brevifolia	Anticancer	Hyaluronic acid	CD44-targeted nanoparticles	[41,46,52]
Piperine	Piper nigrum	Bioavailability enhancer, anticancer	Cellulose, chitosan	Self-nanoemulsifying systems	[53,57]
Silymarin	Silybum marianum	Hepatoprotective	Guar gum, xanthan	Sustained-release matrix tablets	[54,58]
Andrographolide	Andrographis paniculata	Anti-inflammatory, anticancer	Chitosan, PLGA	pH-responsive nanoparticles	[55,59]
Baicalein	Scutellaria baicalensis	Neuroprotective, antitumor	Hyaluronic acid, gelatine	Brain-targeting nanoparticles	[56,60]

CD44 = cluster of differentiation 44; PLGA = poly(lactic-co-glycolic acid)

5. BIOPOLYMER-BASED STIMULI-RESPONSIVE SYSTEMS FOR HERBAL DRUG DELIVERY

5.1 pH-Responsive Biopolymer Systems

pH-responsive biopolymer-based nanocarriers represent the most extensively investigated class of SR-DDS for herbal drug delivery, capitalizing on the acidic microenvironments of tumours and the GI pH gradient. Chitosan-based pH-responsive nanoparticles have been widely developed for curcumin delivery. Saraf et al. demonstrated that chitosan-coated curcumin nanoparticles exhibited pH-dependent drug release, with minimal release at pH 7.4 (mimicking blood) and significantly enhanced release at pH 5.0 (mimicking end lysosomal conditions), resulting in superior antiproliferative activity against HeLa cells compared to free curcumin [55]. The protonation of chitosan's amine groups at acidic pH increases electrostatic repulsion within the nanoparticle matrix, causing swelling and accelerated drug diffusion.

Alginate-based systems have been extensively used for intestinal and colon-targeted delivery of herbal actives. Calcium alginate beads loaded with quercetin showed pH-dependent release profiles: negligible release in simulated gastric fluid (pH 1.2) but near-complete release in simulated intestinal fluid (pH 6.8 and 7.4) [56]. This behaviour arises from the protonation of alginate's carboxylate groups at low pH, collapsing the gel network, while deprotonation at higher pH causes bead swelling and drug release. Crosslinked alginate hydrogels incorporating pectin have been developed for dual pH and enzyme-responsive delivery of resveratrol to the colon, where both pH shift and pectinase activity contribute to drug release [57].

Cellulose acetate phthalate (CAP) and Eudragit-coated systems incorporating herbal extracts have been used for enteric protection, ensuring drug release only in the intestinal lumen [58]. HPMC-based matrix tablets loaded with silymarin showed controlled release governed by pH-dependent erosion and diffusion mechanisms, substantially improving oral bioavailability compared to the pure drug [59].

5.2 Thermoresponsive Biopolymer Systems

Thermoresponsive biopolymer hydrogels have been developed for localized delivery of herbal bioactive, particularly for injectable formulations and transdermal applications. PNIPAM-grafted chitosan hydrogels loaded with berberine demonstrated temperature-triggered release at 37-42 degrees C, suitable for hyperthermic cancer therapy or febrile inflammation [60]. The LCST of these hybrid systems can be tuned by varying the degree of PNIPAM grafting and chitosan concentration, allowing customization of the release temperature threshold.

Gelatine-based thermosensitive systems have been used for quercetin delivery. Gelatine meth acryloyl (GelMA) hydrogels loaded with quercetin exhibited a sol-gel transition near 35 degrees C, enabling sustained local delivery upon injection at body temperature [61]. The thermoresponsive behaviour was complemented by MMP-mediated enzymatic degradation, yielding a dual-responsive release profile suitable for tumour microenvironment-specific delivery. Methylcellulose-based thermosensitive gels have also been reported for nasal delivery of baicalein for brain targeting, exploiting the elevated nasal mucosa temperature to trigger gelation and sustain drug absorption across the nasal epithelium [62].

5.3 Enzyme-Responsive Biopolymer Systems

Enzyme-responsive biopolymer systems for herbal drug delivery have been designed to exploit the overexpression of specific enzymes at disease sites. Hyaluronic acid-conjugated chitosan nanoparticles loaded with curcumin were reported to exhibit HAase-triggered drug release in tumour tissues, with selective cytotoxicity against CD44-overexpressing cancer cells [63]. The HA shell provides stealth properties during circulation and active targeting via CD44 binding, while HAase-mediated shell degradation at the tumour site exposes the chitosan core and releases the encapsulated curcumin.

Pectin and guar gum matrices have been extensively used for colon-targeted delivery of herbal bioactives by exploiting the colonic microflora-produced enzymes. Compressed matrix tablets of curcumin in a guar gum-pectin blend showed minimal drug release in the upper GI tract (< 10% at 6 hours) but rapid release (> 80% within 12-16 hours) in the presence of colonic enzymes, making them suitable for managing colorectal cancer and inflammatory bowel disease [64]. MMP-responsive gelatine nanoparticles loaded with andrographolide demonstrated selective drug release in MMP-2-rich tumour cell culture media, achieving higher intracellular drug concentrations than non-responsive controls [65].

5.4 ROS-Responsive and Redox-Responsive Systems

ROS-responsive biopolymer systems are particularly promising for anticancer herbal drug delivery given the characteristically elevated ROS levels in tumour microenvironments. Thioether-modified hyaluronic acid nanoparticles loaded with paclitaxel were developed to exploit H2O2 overproduction in tumour tissues [66]. Upon oxidation of the thioether linkages to hydrophilic sulfoxides by ROS, the nanoparticle hydrophobicity decreases dramatically, causing swelling and drug release selectively within tumour tissue. Similar strategies have been applied to curcumin-loaded ROS-responsive chitosan-based nanoparticles for targeted anticancer delivery [67].

Glutathione (GSH)-responsive disulfide-crosslinked biopolymer nanoparticles have been developed for intracellular herbal drug delivery. GSH concentrations in tumour cytoplasm (~10 mM) are orders of magnitude higher than in extracellular environments (~2 microM), providing a redox gradient for site-specific release [68]. Disulfide-crosslinked alginate nanoparticles loaded with berberine showed rapid GSH-triggered drug release in cancer cell cytoplasm, leading to enhanced apoptosis compared to free drug and non-responsive controls.

5.5 Dual and Multi-Responsive Systems

Dual-responsive biopolymer systems combining pH and temperature responsiveness have been developed for curcumin and quercetin delivery in cancer therapy. A chitosan-PNIPAM interpenetrating network hydrogel demonstrated pH-induced swelling at acidic pH combined with thermally induced phase transition, achieving highest drug release rates at tumour-mimicking conditions (pH 6.5, 40 degrees C) [69]. A similar approach using carboxymethyl chitosan and poly(N-vinyl caprolactam) enabled dual pH/thermo-responsive release of resveratrol with markedly improved cytotoxicity in MCF-7 breast cancer cells.

Magnetic field-responsive systems incorporating biopolymers have been used to achieve magnetically guided targeting combined with pH-triggered release. Iron oxide nanoparticles coated with pH-responsive chitosan and loaded with curcumin showed concentration at tumour sites under external magnetic guidance, with

subsequent acid-triggered drug release in the tumour microenvironment, leading to superior tumour reduction in murine breast cancer models compared to non-magnetic formulations [70]. These multi-responsive platforms represent the cutting edge of smart herbal drug delivery research.

6. APPLICATIONS OF BIOPOLYMER-BASED STIMULI-RESPONSIVE SYSTEMS

6.1 ANTICANCER APPLICATIONS

Cancer remains one of the leading causes of morbidity and mortality worldwide, with conventional therapies (chemotherapy, radiation) suffering from dose-limiting toxicity and non-specific biodistribution [71]. Herbal bioactive with demonstrated anticancer activity—including curcumin, quercetin, berberine, paclitaxel, and vincristine—are attractive candidates for cancer-targeted delivery using stimuli-responsive biopolymer nanocarriers. The enhanced permeability and retention (EPR) effect in solid tumours, combined with active targeting via biopolymer ligands (e.g., HA-CD44 interaction), enables preferential nanoparticle accumulation at tumour sites [72].

Curcumin-loaded HA-chitosan nanoparticles have demonstrated potent anticancer activity in a variety of tumour models including breast, colon, cervical, and hepatocellular carcinoma [73]. pH-responsive release of curcumin in the acidic tumour microenvironment results in intracellular ROS generation, mitochondrial membrane disruption, and activation of the intrinsic apoptotic pathway. Synergistic effects between herbal combinations (e.g., curcumin + piperine or quercetin + resveratrol) delivered via biopolymer nanoparticles have also been reported, with combination index analyses confirming synergistic cytotoxicity at lower individual drug doses [74].

Enzyme-responsive pectin and HA-based nanocarriers for colorectal cancer represent a growing area of research. Colon-targeted delivery of curcumin via pectin-coated nanoparticles achieved high intratumoral drug concentrations with minimal systemic exposure in rodent colorectal cancer models, demonstrating improved tumour regression and reduced hepatotoxicity compared to free drug administration [75]. Biopolymer-mediated co-delivery of herbal actives with conventional chemotherapeutics (e.g., curcumin + 5-fluorouracil) has shown promise in overcoming multidrug resistance (MDR) through inhibition of P-glycoprotein efflux [76].

6.2 Brain-Targeted Drug Delivery

The blood-brain barrier (BBB) represents the most formidable obstacle to central nervous system (CNS) drug delivery, restricting the passage of over 98% of small-molecule drugs and virtually all macromolecules [77]. Neuroprotective herbal bioactive such as baicalein, curcumin, resveratrol, and huperzine A hold significant promise for treating Alzheimer's disease, Parkinson's disease, stroke, and brain tumours, but their clinical utility is limited by poor BBB penetration [78].

Biopolymer-based nanocarriers functionalized with BBB-targeting ligands—including transferrin, lactoferrin, Angiopep-2, and glucose transporter (GLUT) substrates—have been investigated for herbal drug delivery to the CNS [79]. Lactoferrin-modified chitosan nanoparticles loaded with baicalein demonstrated significantly enhanced brain uptake via receptor-mediated transcytosis across the BBB, achieving approximately 3.5-fold higher brain drug concentrations compared to unmodified nanoparticles in intracranial glioma-bearing mice

[80]. Thermosensitive methylcellulose-based nasal gels for baicalein have also shown promise, utilizing the olfactory route to bypass the BBB and deliver drug directly to brain tissue [62].

ROS-responsive HA nanoparticles loaded with curcumin were reported to accumulate preferentially in glioma tissue, taking advantage of both CD44 receptor overexpression on glioma cells and the highly oxidative tumour microenvironment to achieve triggered drug release [81]. The neuroprotective and anti-neuroinflammatory effects of biopolymer-encapsulated curcumin have also been evaluated in Alzheimer's disease models, with results showing reduced amyloid-beta aggregation, improved cognitive function, and attenuated neuroinflammatory markers compared to free curcumin.

6.3 Colon-Targeted Delivery

The colon is a pharmacologically important target for both local disease (inflammatory bowel disease, colorectal cancer) and systemic absorption of drugs that are degraded in the upper GI tract [82]. Biopolymer-based stimuli-responsive systems for colon targeting exploit pH changes and colonic microflora-produced enzymes. Pectin, guar gum, xanthan gum, and inulin-based carriers are selectively degraded by colonic microbiota, releasing encapsulated herbal actives locally in the colon. Colon-targeted curcumin delivery via calcium pectinate beads demonstrated anti-inflammatory efficacy in a rat model of ulcerative colitis, with significant reductions in colonic myeloperoxidase activity, TNF-alpha, and IL-6 compared to controls [83].

6.4 Hepatoprotective and Other Applications

Silymarin, the active flavonolignan complex from Silybum marianum, is widely used for hepatoprotection but has poor oral bioavailability due to low aqueous solubility and limited intestinal absorption [84]. Guar gum and xanthan gum-based sustained-release matrix formulations of silymarin have demonstrated prolonged plasma drug concentrations in pharmacokinetic studies, improving AUC by approximately 2-3 fold compared to conventional tablets. Transdermal biopolymer gels incorporating herbal actives such as andrographolide and curcumin have been developed for anti-inflammatory therapy, with chitosan-based penetration-enhancing gels showing significantly improved skin permeation [85].

7. CHALLENGES AND LIMITATIONS

7.1 Physicochemical Stability

A major challenge confronting biopolymer-based SR-DDS for herbal drugs is the physicochemical stability of both the carrier and the encapsulated bioactive. Many herbal bioactive are chemically labile and prone to oxidation, photodegradation, and pH-dependent hydrolysis. Encapsulation within biopolymer matrices can provide protection, but the stability of the carrier itself—particularly under varying ionic strength, pH, and temperature conditions encountered during processing, storage, and physiological transit—must be rigorously characterized and optimized [86]. Aggregation of nanoparticles, polymer hydrolysis, and loss of stimuli-responsiveness upon storage are documented challenges that require careful formulation engineering and stabilizer selection.

7.2 Complexity of Herbal Drug Standardization

The intrinsic chemical complexity of herbal drugs presents significant formulation challenges. Plant extracts contain mixtures of active constituents

with varying polarity, molecular weight, and chemical reactivity, making standardized encapsulation and reproducible release profiles difficult to achieve [87]. Batch-to-batch variability in herbal raw materials further complicates quality control. Developing analytically validated methods for the simultaneous quantification of multiple bioactive in complex biopolymer formulations is technically demanding and resource-intensive.

7.3 Scale-Up and Manufacturing

The translation of biopolymer-based nano formulations from laboratory scale to industrial production faces significant challenges related to scale-up, process reproducibility, cost of goods, and the requirement for specialized equipment [88]. Many preparation methods (e.g., nanoprecipitation, ionic gelation, emulsification-crosslinking) that work well at milligram to gram scale encounter mixing, shear, and heat transfer issues at kilogram or ton scale. Ensuring batch-to-batch consistency in particle size, drug loading efficiency, encapsulation efficiency, and in vitro release profile is critical for regulatory approval.

7.4 In Vivo Translation and Regulatory Concerns

Despite promising in vitro results, many biopolymer-based SR-DDS for herbal drugs fail to demonstrate equivalent efficacy in in vivo models due to the complexity of biological environments—including protein corona formation, opsonization, macrophage clearance, and the heterogeneous nature of the tumour microenvironment [89]. Regulatory frameworks for complex herbal nano formulations are still evolving; current guidelines from agencies such as the FDA, EMA, and WHO do not fully address the unique characterization, safety, and quality requirements of stimuli-responsive herbal nano formulations. The interplay of biopolymer excipients with herbal constituents may also introduce novel toxicity concerns that require dedicated safety assessments.

7.5 Biocompatibility and Toxicity

While biopolymers are generally regarded as biocompatible and biodegradable, certain chemical modifications—such as crosslinking with glutaraldehyde, introduction of synthetic polymer grafts, or incorporation of metallic nanomaterials (iron oxide, gold)—may introduce cytotoxic elements that need to be carefully evaluated [90]. The immunogenicity of proteinaceous biopolymers such as gelatine and albumin in specific patient populations, as well as the potential for nanoparticle-induced inflammasome activation, must be assessed. Long-term biocompatibility, organ accumulation, and clearance kinetics of biopolymer-herbal nano formulations remain insufficiently characterized in most reported studies.

8. FUTURE PERSPECTIVES

The field of biopolymer-based stimuli-responsive delivery of herbal drugs is at a pivotal juncture, with significant opportunities for advancement across multiple dimensions. Several key future directions are highlighted below.

The development of multi-stimuli-responsive biopolymer systems that can integrate pH, enzyme, ROS, and/or temperature responsiveness within a single platform holds great promise for achieving highly precise spatiotemporal drug release in complex pathological microenvironments [91]. Progress in supramolecular chemistry, dynamic covalent chemistry, and stimuli-responsive polymer design will enable the creation of increasingly sophisticated smart carriers for herbal bioactive.

The application of artificial intelligence (AI) and machine learning (ML) to biopolymer formulation design represents an emerging frontier. Predictive ML models trained on large datasets of biopolymer-drug interactions, formulation parameters, and in vitro/in vivo release profiles could significantly accelerate the identification of optimal biopolymer-herbal drug combinations and stimulus-responsive designs, reducing the time and cost of formulation development [92].

Personalized medicine approaches integrating stimuli-responsive biopolymer DDS with companion diagnostics represent an exciting future direction. Nano formulations that can be activated by patient-specific biomarkers (e.g., tumour-specific enzymes, individualized pH profiles) could enable precision herbal medicine tailored to individual pathophysiology [93].

Advances in three-dimensional (3D) bioprinting of biopolymer-based controlled release systems open new avenues for patient-specific implantable drug delivery devices incorporating herbal actives with programmable release profiles [94]. The combination of biopolymer SR-DDS with immunotherapy approaches—using herbal immunomodulators (e.g., astragalus polysaccharides, With Ania somniferous adaptogens) encapsulated in targeted, enzyme-responsive nanocarriers—may synergize with immune checkpoint inhibitors for cancer treatment.

From a regulatory perspective, development of standardized characterization protocols, in vitro-in vivo correlation (IVIVC) models specifically validated for herbal nano formulations, and harmonized global regulatory guidelines will be critical to facilitate the clinical translation of biopolymer-based SR-DDS for herbal drugs [95]. Collaboration between academia, industry, and regulatory agencies is urgently needed to bridge the translational gap in this field.

CONCLUSION

Biopolymer-based stimuli-responsive drug delivery systems represent a powerful and versatile platform for overcoming the inherent limitations of herbal bioactive—including poor solubility, low bioavailability, chemical instability, and non-specific biodistribution—and for enabling their targeted, controlled delivery to specific disease sites. Biopolymers such as chitosan, alginate, hyaluronic acid, gelatine, pectin, and cellulose derivatives offer rich structural diversity and functional versatility that can be harnessed to design pH-, temperature-, enzyme-, ROS-, and multi-responsive nanocarriers tailored to specific therapeutic applications. The integration of active targeting ligands, combination drug loading, and diagnostic capabilities into these systems further enhances their clinical utility.

Significant progress has been made in the development of biopolymer-herbal nano formulations for anticancer therapy, brain-targeted delivery, colon-specific systems, and hepatoprotective applications, with promising in vitro and preclinical in vivo evidence. However, substantial challenges remain in the areas of physicochemical stability, herbal drug standardization, scalable manufacturing, in vivo translation, and regulatory approval. Addressing these challenges through interdisciplinary collaboration, advanced characterization methods, AI-assisted formulation design, and harmonized regulatory frameworks will be essential for realizing the clinical potential of these innovative delivery platforms.

The convergence of biopolymer science, nanotechnology, phytopharmacology, and

precision medicine positions biopolymer-based stimuli-responsive herbal drug delivery at the frontier of next-generation pharmaceutical development. Continued research investment and translational effort in this domain holds considerable promise for advancing evidence-based herbal medicine and expanding therapeutic options for patients worldwide.

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HOW TO CITE: Preeti Sah, Vishal Makwana, Dr. Pritesh Paliwal, Dr. Nimita Manocha, Biopolymer-Based Stimuli-Responsive Systems for Herbal Drug Delivery: A Comprehensive Review, Int. J. of Pharm. Sci., 2026, Vol 4, Issue 4, 3138-3156. https://doi.org/10.5281/zenodo.19667578