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Review Article

Hydrogel Microsphere Based Delivery of *Panax quinquefolius L*. for Targeted Gut Microbiome Modulation with Design Strategies, Mechanistic Insights, and Therapeutic Prospects

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Abstract

The gut microbiota is essential for modulating host metabolism, immune responses, intestinal barrier function, and overall health. Dysbiosis of the gut microbial ecosystem has been associated with various chronic diseases, such as inflammatory bowel disease, metabolic disorders, diabetes, cancer, and neuroinflammatory diseases. The biologically active constituents of Panax quinquefoliusL. (American ginseng), mainly ginsenosides and polysaccharides, may interact with the gut microbiota and may be biotransformed by microbes to potentially bioactive metabolites. However, poor stability, variable gastrointestinal metabolism, and inconsistent oral bioavailability may limit the therapeutic application of these phytoconstituents. Microspheres are a promising platform for drug delivery that can protect sensitive phytochemicals and enable controlled, site-specific, and stimuli-responsive release in the gastrointestinal tract. This review highlights the pharmacological relevance of Panax quinquefolius, interactions with the gut microbiome, and the potential of hydrogel microspheres for enhanced gastrointestinal and colon-targeted delivery. Emphasis is placed on the selection of polymers, encapsulation techniques, pH-, enzyme-, and microbiome-responsive systems, and the mechanisms of controlled release and hydrogel–microbiome–host interactions. Possible applications include inflammatory bowel disease, gut-brain axis related disorders, immune regulation, cancer, and neuroinflammatory disorders. Current challenges include variability of gut microbiota, standardization of herbal extracts, and scalability of formulation, long-term safety, and limited clinical evidence. To summarize, hydrogel-based delivery of Panax quinquefoliusis a promising research approach for microbiome-targeted therapy; further mechanistic, preclinical, and clinical studies are needed to establish its safety, reproducibility, and therapeutic relevance.

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1. Introduction

The human gut microbiome is a crucial regulator of host physiology and affects immunological responses, disease susceptibility, and metabolic homeostasis [1]. Increasing evidence indicates that dysbiosis, or alterations in the composition and function of the gut microbial community, is associated with a variety of chronic conditions, including cancer, diabetes, metabolic syndrome, inflammatory bowel disease, and neuroinflammation [2]. Simultaneously, herbal medicines have attracted renewed scientific attention because of their long-standing traditional use and diverse, multi-targeted pharmacological properties [3]. However, poor stability, low oral bioavailability, and non-specific gastrointestinal distribution continue to limit the therapeutic application of many phytochemicals [4]. To fully realize the therapeutic potential of herbal bioactives, advanced delivery systems capable of protecting bioactive compounds and facilitating controlled or site-specific release are therefore important [5]. Among emerging approaches, hydrogel-based delivery systems, including hydrogel microspheres, offer promising advantages for localized and controlled delivery to the gastrointestinal tract and may therefore have potential for targeted modulation of the gut microbiome [5].

1.1 The Gut Microbiome as a Therapeutic Target

The gut microbiome is a complex and dynamic ecosystem composed of trillions of microorganisms that actively interact with host signaling pathways, dietary components, and xenobiotics [6]**.** These microorganisms contribute to vital physiological functions, including the production of short-chain fatty acids (SCFAs), bile acid metabolism, immune maturation, maintenance of intestinal epithelial barrier integrity, and gut–brain and neuroendocrine signaling [7]**.** Rather than representing merely secondary consequences of disease, alterations in microbial composition and function have been implicated in the development and progression of several disorders, with increasing mechanistic evidence supporting causal roles in conditions such as inflammatory bowel disease, obesity, type 2 diabetes, and liver disease [8,9]**.** Consequently, microbiota-targeted therapeutic approaches, including probiotics, prebiotics, postbiotics, and phytochemicals, have gained considerable scientific interest as strategies for restoring or modulating microbial homeostasis [10,11]. The gut microbiome therefore represents a promising therapeutic target because microbiome-directed interventions can influence host physiology through microbial metabolites, immune pathways, barrier function, and gut–organ communication, providing opportunities for systemic effects beyond the direct modulation of a single biochemical pathway [12,13]

1.2 Limitations of Conventional Herbal Delivery Systems

In their oral form, many herbal formulations present significant delivery challenges despite their diverse pharmacological compositions. Many phytoconstituents exhibit poor aqueous solubility, limited gastrointestinal permeability, chemical instability, extensive presystemic metabolism, and low oral bioavailability, which restrict their therapeutic effectiveness [14,15]. Moreover, conventional dosage forms, such as powders, capsules, and decoctions, generally provide limited control over release kinetics and gastrointestinal site specificity, potentially resulting in variable dissolution, absorption, and exposure of bioactive constituents [16]. Importantly, the gastrointestinal fate of herbal bioactive is closely associated with their interaction with the gut microbiota, as microbial enzymes can transform phytochemicals into metabolites with altered biological activity and bioavailability [17]**.** Therefore, delivery strategies capable of protecting herbal bioactive during passage through the upper gastrointestinal tract and facilitating controlled or site-specific release in the intestine or colon may improve their exposure to the gut microbiota and enhance their potential for microbiome-mediated biotransformation [18]. These challenges underscore the need for advanced delivery systems capable of protecting herbal substances and achieving controlled delivery to the colon and lower intestine.

1.3 Rationale for Hydrogel Microsphere–Based Delivery

Three-dimensional polymeric frameworks, percentage of water, and modifiable physicochemical properties of hydrogel microspheres combine to render them a viable oral delivery system. These systems can entrap sensitive phytochemicals, shield them during the hostile environment of the stomach, and release them in a controlled or stimuli-regulated manner. H-sensitive, enzyme-responsive, and microbiota-responsive hydrogels are particularly useful for colon-targeted administration, where microbial populations with high density facilitate phytochemical biotransformation; hydrogel microspheres can be manufactured with sustained release,

mucoadhesion, and longer intestinal residence to enhance local therapeutic levels and minimize systemic exposure. Due to these properties, hydrogel microspheres are especially suitable for the delivery of herbal medicines that can be used to change the composition and activity of the gut microbiome. [19,20,21]

1.4 Scope and Objectives of the Review

Based on *Panax quinquefolius* L. as a model example of phototherapeutic drug, the present review critically investigates the hydrogel microsphere-based delivery approach for gut microbiota control. This article provides the pharmacological significance of *Panax quinquefolius*, as well as its interactions with gut flora and the disadvantages of conventional delivery methods.[22] Special considerations are given to hydrogel design strategies, encapsulating, and stimuli-responsive release strategies that are relevant to oral and colon-targeted delivery. A prospective perspective of the clinical potential of herbal delivery systems based on hydrogels is also provided through a critical analysis of molecular concepts, therapeutic applications, health problems, and translational challenges. [23]

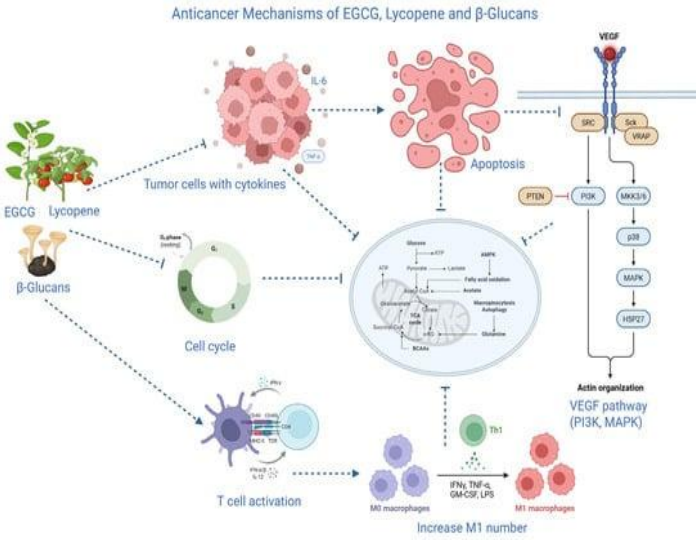


Figure 1: Overview of gut microbiome–targeted delivery challenges and the rationale for hydrogel microsphere–based phytochemical systems

2. *Panax quinquefolius*L. and Its Pharmacological Relevance

Panax quinquefolius L., commonly known as American ginseng, is a perennial medicinal plant belonging to the family Araliaceae. The plant has a long history of use in traditional medicine because of its health-promoting and therapeutic properties [24, 25], and its pharmacological potential is largely attributed to diverse bioactive constituents, particularly ginsenosides, polysaccharides, polyacetylenes, and phenolic compounds [26]**.** Increasing scientific evidence has highlighted the potential of *Panax quinquefolius* in areas including immune regulation, metabolic health, intestinal function, and inflammation [27], of which ginsenosides can undergo intestinal microbial biotransformation, while ginseng-derived constituents may also influence gut microbial composition and metabolism, suggesting a bidirectional relationship between *Panax* bioactives and the gut microbiota. [28]

2.1 Botanical Background and Traditional Uses

Panax quinquefolius L. (American ginseng) is a slow-growing perennial herb native to eastern North America, and its root is the principal medicinally utilized part of the plant **[29]**. It grows naturally in cool, shaded, temperate forest environments and is also cultivated commercially for medicinal use [30]. American ginseng has a long history of use in traditional Chinese medicine and among Indigenous peoples of North America, where its root has traditionally been consumed as a tonic for promoting vitality and general well-being **[30]**. Traditional applications include the management of fatigue, stress, digestive complaints, and inflammatory conditions**.** In traditional Chinese Medicine, *Panax quinquefolius*is generally considered to have a more “cooling” or less warming character than *Panax ginseng* (Asian ginseng), which has contributed to differences in their traditional applications. These historical applications have contributed to contemporary research investigating the pharmacological effects of *Panax quinquefolius*, particularly its potential roles in immune regulation, metabolic homeostasis, inflammation, and gastrointestinal health [31].

2.2 Phytochemical Composition and Bioactive Constituents

Panax quinquefolius L. contains a diverse range of phytochemicals, with triterpenoid saponins known as **ginsenosides** representing the major and most extensively investigated bioactive constituents. More than 50 ginsenosides have been identified in *Panax quinquefolius*, including major constituents such as **Rb1, Rb2, Rc, Rd, Re, and Rg1**, although their relative abundance varies according to plant part, cultivation conditions, geographical origin, age, and processing methods **[32]** In addition to ginsenosides, American ginseng contains polysaccharides, polyacetylenes, phenolic compounds, flavonoids, amino acids, volatile oils, and other minor constituents that may contribute to its overall

pharmacological activity **[33]** Ginsenosides are particularly important because their biological activities include immunomodulatory, anti-inflammatory, antioxidant, metabolic, and gastrointestinal effects **[34]** Importantly, many naturally occurring ginsenosides have relatively limited absorption in their intact forms and can undergo extensive biotransformation by intestinal microbiota into deglycosylated metabolites with different pharmacological [35] Therefore, the phytochemical composition of *Panax quinquefolius*, particularly its ginsenoside profile, provides an important basis for understanding its pharmacological effects and its potential interactions with the gut microbiome.

2.3 Challenges in Oral Bioavailability and Stability

Panax quinquefolius L. is pharmacologically promising; however, the therapeutic utilization of its ginsenosides is constrained by their generally low oral bioavailability and complex gastrointestinal disposition [36]. The relatively high molecular size, extensive glycosylation, limited membrane permeability, and physicochemical characteristics of many ginsenosides contribute to their poor intestinal absorption [37]**.** In addition, ginsenosides undergo chemical and metabolic transformations within the gastrointestinal tract, including acid-catalyzed degradation in the stomach and extensive deglycosylation mediated by intestinal microbiota [38]. These biotransformation processes can generate metabolites with absorption and pharmacological properties that differ substantially from those of the parent ginsenosides [39]. Furthermore, differences in intestinal microbiota composition and metabolic activity may contribute to interindividual variability in ginsenoside biotransformation and systemic exposure. The complex chemical composition of *Panax quinquefolius*extracts and the diverse physicochemical characteristics of their constituents also present challenges in achieving consistent formulation performance and predictable bioavailability. Therefore, advanced delivery systems capable of improving the stability, protection, controlled release, and gastrointestinal site-specific delivery of ginseng bioactives are of great interest. [40]

Table 1: Major bioactive constituents of *Panax quinquefolius*L. and their reported biological activities related to gut health and immunity

S. No.	Constituent	Class	Gut-Related Activity	Immunological Effect	Microbiome Involvement	Therapeutic Relevance	Ref.
1.	Ginsenoside Rb1	Protopanaxadiol	Enhances gut barrier integrity	Anti-inflammatory	Microbial deglycosylation	IBD, metabolic disorders	41
2.	Ginsenoside Rb2	Protopanaxadiol	Reduces intestinal inflammation	Cytokine suppression	Converted by gut bacteria	Colitis	41
3.	GinsenosideRc	Protopanaxadiol	Antioxidant in gut epithelium	Immune regulation	Microbial metabolism-dependent	Gut inflammation	41
4.	Ginsenoside Rd	Protopanaxadiol	Protects mucosal lining	Anti-oxidative	Colonic biotransformation	Barrier dysfunction	42
5.	Ginsenoside Re	Protopanaxatriol	Modulates gut immune balance	Macrophage regulation	Alters microbial composition	Immune disorders	42
6.	Ginsenoside Rg1	Protopanaxatriol	Supports epithelial repair	Immune stimulation	Partial microbial conversion	Gut–brain axis	42
7.	Ginsenoside Rg3	Rare ginsenoside	Reduces gut-derived inflammation	Immunosuppressive balance	Formed via microbiota	Cancer-related inflammation	43
8.	Ginsenoside Rh2	Rare ginsenoside	Improves intestinal homeostasis	Anti-inflammatory	Microbial conversion product	IBD, cancer	43
9.	Compound K	Ginsenoside metabolite	High colonic absorption	Potent immunomodulation	Direct microbiota-derived	Metabolic disease, IBD	43
10.	Ginseng polysaccharides	Polysaccharides	Prebiotic activity	Enhances innate immunity	Promotes beneficial flora	Gut microbiome balance	43
11.	Acidic polysaccharides	Polysaccharides	Improves microbial diversity	Immune activation	Fermented by gut microbiota	Immune support	44
12.	Neutral polysaccharides	Polysaccharides	Supports gut homeostasis	Mild immunostimulation	Microbial fermentation	Digestive health	44
13.	Ferulic acid	Phenolic acid	Antioxidant in gut lumen	Anti-inflammatory	Influences microbial metabolism	Gut inflammation	44
14.	Vanillic acid	Phenolic acid	Protects intestinal cells	Reduces oxidative stress	Microbial metabolite	Barrier protection	44
15.	Panaxynol	Polyacetylene	Modulates gut inflammation	Anti-inflammatory	Limited microbiome interaction	GI protection	45
16.	Panaxydol	Polyacetylene	Preserves epithelial integrity	Immunomodulatory	Synergistic microbiome effects	Gut health	45
17.	Ginseng oligopeptides	Peptides	Promotes mucosal repair	Immune signaling	Indirect microbiome effects	Barrier restoration	45
18.	Essential amino acids	Nutritional components	Supports gut cell metabolism	Immune nourishment	Enhances microbial growth	General gut health	46

19.	Trace minerals (Zn, Fe)	Micronutrients	Maintains gut enzyme function	Immune competence	Microbial growth support	Immune balance	47
20.	Volatile oils	Minor phytochemicals	Regulates gut motility	Anti-microbial balance	Modulates microbial load	Digestive disorders	48

3. Interaction of *Panax quinquefolius*L. with the Gut Microbiome

The interaction between *Panax quinquefolius*L. and the gut microbiome is increasingly recognized as an important factor influencing the pharmacological behavior of its bioactive constituents. Following oral administration, several ginsenosides undergo extensive biotransformation by intestinal microorganisms, particularly through stepwise deglycosylation, producing metabolites such as ginsenoside F2 and compound K that may exhibit different absorption and biological activities from their parent compounds [49,50]**.** In addition to being metabolized by gut microorganisms, ginseng-derived constituents may also influence the composition and metabolic activity of the intestinal microbiota. Therefore, the relationship between *Panax quinquefolius* and the gut microbiome is considered bidirectional, involving microbiota-mediated metabolism of phytochemicals as well as potential modulation of microbial communities and host–microbe signaling pathways [51**]**. These interactions may contribute to variations in bioavailability, pharmacological response, and therapeutic outcomes among individuals, making *Panax quinquefolius* a promising microbiome-interacting phototherapeutic agent.

3.1 Microbiota-Mediated Biotransformation of Ginsenosides

Ginsenosides are the major bioactive constituents of *Panax quinquefolius*L. and are primarily glycosylated triterpenoid saponins with generally limited intestinal absorption in their parent forms [52, 53]. Following oral administration, many ginsenosides undergo extensive biotransformation by gut microbial enzymes, particularly glycosidases such as β-glucosidases, which sequentially remove sugar moieties and generate less glycosylated metabolites [54**]**. These metabolites, including ginsenoside F2 and compound K, may exhibit physicochemical and pharmacokinetic properties that differ from those of their parent compounds and, in some cases, improved intestinal absorption and distinct biological activities**.** The composition and metabolic activity of an individual's gut microbiota can substantially influence the efficiency and profile of ginsenoside biotransformation, contributing to interindividual variability in metabolite production, bioavailability, and pharmacological responses [55]. Several gut microorganisms can convert major ginsenosides into bioactive metabolites that exhibit anti-inflammatory, immunomodulatory, antioxidant, and other pharmacological activities [56].

Therefore, microbiota-mediated metabolism is an important determinant of the biological fate of orally administered ginsenosides. This provides a scientific rationale for developing intestinal or colon-targeted delivery systems that can facilitate the interaction between ginsenosides and dense microbial populations in the lower gastrointestinal tract. However, the therapeutic advantages of such targeted delivery systems should be experimentally established for individual formulations.

3.2 Prebiotic, immunomodulatory, and anti-inflammatory effects

The bioactive constituents of *Panax quinquefolius*L. can interact with gut microbiota both as substrates for microbial metabolism and as potential modulators of microbial composition and activity. Ginsenosides and ginseng-derived polysaccharides have been reported to influence gut microbial communities and promote beneficial microbial populations while reducing dysbiosis-associated changes in experimental models [57, 58, 59]. Polysaccharides from *Panax quinquefolius* have demonstrated microbiota-modulating effects associated with improvements in intestinal microbial balance, short-chain fatty acid production, intestinal barrier function, and inflammatory responses **[**60].These findings suggest that ginseng polysaccharides may exert prebiotic-like effects**,** although the term "prebiotic" should be used cautiously unless the constituent fulfills the established criteria. Microbiota-mediated pathways may also contribute to the immunomodulatory and anti-inflammatory effects of *Panax quinquefolius* constituents. Microbial biotransformation of ginsenosides produces metabolites, such as compound K and other deglycosylated derivatives, that can exhibit anti-inflammatory and immunomodulatory activities [62]. Experimental studies

have shown that ginsenosides and their metabolites can influence inflammatory signaling pathways, cytokine production, intestinal barrier integrity, and immune responses, while alterations in the gut microbiota may contribute to these effects [61]. Collectively, these microbiota-associated actions may help reduce intestinal inflammation and support immune and microbial homeostasis, making *Panax quinquefolius*and its bioactive constituents relevant for further investigation in chronic inflammatory and dysbiosis-associated disorders.

3.3 Role in Metabolic and Barrier Function Regulation

*Panax quinquefolius*L. affects intestinal barrier integrity and host metabolic control, which are vital gut microbiota functions. Ginsenosides regulate lipid and glucose metabolism, improve insulin sensitivity, and modify biliary acid signaling through microbiota-mediated events. [62] These effects are closely connected with changes in microbial-derived metabolites that change host metabolic pathways; chemicals generated by *Panax quinquefolius*contribute to preserving the activity of the intestinal epithelial barrier through the enhancement of tight junction protein expression and reduction of inflammation associated with permeability. [63, 64].Enhanced barrier integrity reduces metabolic load and systemic inflammation —as well as translocation of microbial endotoxins. Combined, these activities complement the effectiveness of *Panax quinquefolius*in the curative of inflammatory and metabolic diseases through derivative regulation of the gut microbiome and host physiology. [65, 66].

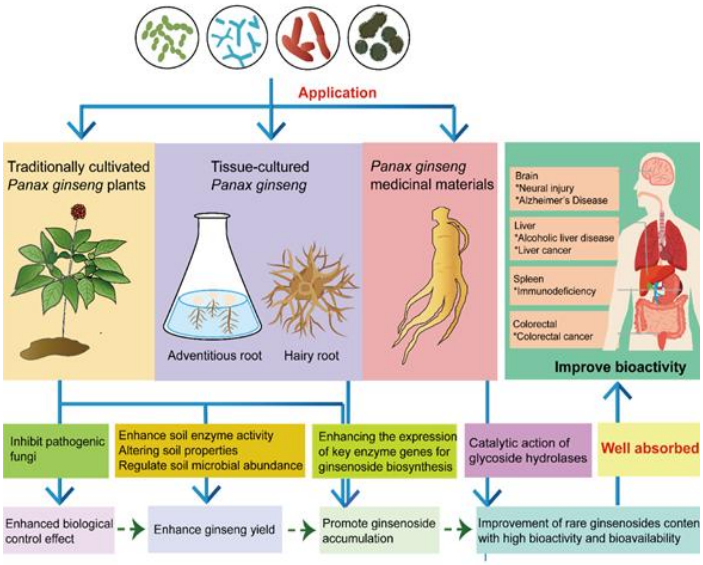


Figure 2: Microbiota-driven biotransformation of Panax quinquefoliusL. ginsenosides and downstream host signaling pathways.

4. Gut Microbiome Modulation as a Therapeutic Strategy

The gut microbiome plays an important role in host metabolism, immune regulation, intestinal barrier maintenance, and inflammatory homeostasis, making microbiome modulation an increasingly investigated therapeutic strategy [67]. Unlike conventional pharmacological approaches that commonly target specific host receptors, enzymes, or signaling pathways, microbiome-directed interventions aim to modify the microbial composition, function, or microbial-derived metabolites to influence host physiology [68]. Such approaches include the use of probiotics, prebiotics, synbiotics, postbiotics, dietary interventions, fecal microbiota transplantation, and selected microbiota-targeting pharmacological or phytochemical interventions.

4.1 Dysbiosis and Disease Pathogenesis

Reduced microbial diversity, loss of helpful commensal species, and the growth of harmful or opportunistic microbes are hallmarks of gut dysbiosis. These changes hinder the formation of short-chain fatty acids, alter bile acid profiles, and enhance the production of pro-inflammatory metabolites by interfering with microbial metabolic output. These alterations cause chronic low-grade inflammation, encourage endotoxin transfer, and jeopardize intestinal barrier integrity. Numerous illnesses, such as inflammatory bowel diseases, metabolic syndrome, type 2 diabetes, neurological diseases, and several types of cancer, have been linked to dysbiosis. Crucially, microbial profiles linked to disease are frequently disease-specific, indicating that focused microbiome modification may offer therapeutic precision. Restoring microbial equilibrium is therefore a logical way to prevent the spread of disease at an upstream, systems-level interface. [69, 70]

4.2Phytochemical-Driven MicrobiomeRemodeling

Phytochemicals are ideal for modulating the microbiota because of their unique properties. Since many substances produced from plants are poorly absorbed in the upper gastrointestinal system, they can enter the colon undamaged and directly interact with the microbiota. Phytochemicals can alter the form and function of microbial communities through signaling interactions, substrate provision, and selective antimicrobial activities. Bioactive metabolites produced by microbiota-mediated phytochemical metabolism further affect host metabolic and inflammatory pathways. [71].Because of this

reciprocal relationship, phytochemicals alter the microorganisms, and microbial enzymes activate or improve the effectiveness of phytochemicals. The restoration of microbial metabolic equilibrium, suppression of pro-inflammatory species, and increased abundance of beneficial taxa have all been linked to microbiome remodeling, underscoring the therapeutic value of phytochemical-based therapies. [72]

4.3 Importance of Site-Specific and Colon-Targeted Delivery

for the local therapy of several bowel conditions, including ulcerative colitis, Crohn's disease, amebiosis, and colonic cancer, local treatment of colonic pathologies, and systemic distribution of protein and peptide medications. [73]The colon-specific drug delivery system (CDDS) should safeguard the medication while it is being transported to the colon; that is, drug release and absorption should not occur in the stomach or small intestine, and the bioactive agent should only be released and absorbed once the system reaches the colon. The colon is an appropriate location for absorption of peptides and protein medications: [74] CDDS protects peptide drugs from hydrolysis and enzymatic degradation in the duodenum and jejunum. Eventually, the drug is released into the ileum or colon, increasing systemic bioavailability. Finally, the colon has a long residence time of up to five days and is highly responsive to absorption enhancers. [75]

5. Hydrogel Microspheres as Advanced Drug Delivery Platforms

"Because of their unique ability to combine high drug loading, environmental responsiveness, and biocompatibility, hydrogel microspheres have become a versatile drug delivery technology. They are especially well suited for oral administration and gut-targeted therapeutics because their three-dimensional polymeric networks provide precise control over swelling behavior, release kinetics, and site-specific delivery. These characteristics make hydrogel microspheres promising platforms to overcome the limitations of traditional phytochemical and microbiome-directed drug delivery."[76, 77]

5.1 Definition and Structural Characteristics

Spherical, cross-linked polymeric particles absorb large amounts of water or biological fluids without breaking down. Their structure consists of a network of hydrophilic polymers that are cross-linked chemically or physically to create a porous structure that can retain drugs. To manipulate the release rate, biodegradation, and diffusion of hydrogel microspheres, different internal structures may be constructed to achieve this goal.[78,79]

The effectiveness of hydrogel microspheres in the digestive system is also greatly influenced by their size, cross-link density (linked molecules), porosity (the amount of space between molecules), and charge. The density of crosslinking determines the mechanical stability and responsiveness to physiological stimuli, and the size of the microspheres determines mucosal interaction and gastrointestinal transit characteristics. Hydrogel microspheres can protect unstable compounds from degradation in the stomach and release them in defined regions of the intestine based on these adjustable parameters.[80]

5.2 Advantages over Conventional Nanocarriers

Hydrogel microspheres offer unique advantages over common nanocarriers, such as polymeric nanoparticles, liposomes, and solid lipid nanoparticles, for oral and gut-targeted delivery. Their long-term use is based on their soft nature and high water content, which improve biocompatibility and minimize cytotoxicity of the drug. Hydrogel microspheres can also deliver hydrophilic and hydrophobic bioactive substances. [81, 82]Rigid nanocarriers may undergo rapid systemic absorption or clearance, whereas hydrogel microspheres are better suited for restricting gastrointestinal activity. Their capacity to induce pH-sensitive swelling, enzyme-triggered breakdown, and microbiota-responsive release allows for better control over the timing and location of drug administration. These features make hydrogel microspheres especially helpful for applications requiring prolonged intestinal retention and targeted microbiota manipulation. [83]

5.3 Natural versus Synthetic Polymer-Based Hydrogels

Natural, (produced by people/not naturally occurring), or a combination of two things/gas-electric vehicle polymers can be used to create hydrogel microspheres; each has (like nothing else in the world) benefits and (bad results or effects). Because of their built-in bioactivity, biocompatibility, and (ability to break down naturally into harmless things), natural polymers, including proteins and polysaccharides, are prized. These materials are appropriate for the microbiome.[84]Molecular weight, allowing for exact customization of release (movement-related) s and (firm and steady nature/lasting

nature/strength). To (promise that something will definitely happen or that something will definitely be described) biocompatibility and legal/law-based acceptance, materials might need to be carefully improved. [85, 86]provide a balanced approach for oral delivery, combination of two things/gas-electric vehicle hydrogel systems that combine natural and (produced by people/not naturally occurring) polymers try to take advantage of the (related to the body function of living things) benefits of natural materials with the (related to what holds something together and makes it strong) toughness of (produced by people/not naturally occurring) partners. [87]

5.4 Microsphere Fabrication Techniques for Oral Administration

A range of manufacturing techniques, including ionic gelation, emulsion-based crosslinking, spray drying, and microfluidic techniques, have been used to create hydrogel microspheres with regulated size, shape, and drug-loading efficiency.[88]

Particle homogeneity, encapsulation effectiveness, and scalability are all affected by the fabrication method selection. Microfluidic technologies allow for the precise manufacture of monodisperse microspheres with customizable topologies, whereas spray drying has advantages in terms of large-scale production and particle size control. [89, 90]

Table 2: Hydrogel polymers used for gut-targeted delivery: key physicochemical and biological attributes

S.No.	Category	Polymer	Physicochemical Features	Responsiveness	Gut-Targeting Advantage	Uses	References
1.	Natural	Alginate	Anionic, Ca^{2+} crosslinked, pH-sensitive	pH	Gastric protection, intestinal release	Colon delivery, probiotics	91
		Chitosan	Cationic, mucoadhesive	pH	Prolonged intestinal residence	Local gut therapy	91
		Pectin	High swelling, microbiota-degradable	Enzymatic	Colon-specific degradation	Microbiome targeting	91
		Dextran	Neutral, MW-tunable	Enzymatic	Controlled microbial activation	Smart colon systems	91
		Guar gum	High viscosity, fermentable	Microbial	Selective colonic breakdown	Sustained colon release	91
		Xanthan gum	High gel strength	pH	Delayed intestinal release	Oral sustained delivery	91
		Inulin	Prebiotic polysaccharide	Microbial	Enhances beneficial microbiota	Microbiome modulation	91
		Pullulan	Film-forming, hydrophilic	Enzymatic	Stable oral delivery	Colon targeting	91
2.	Semi-synthetic	HPMC	Controlled swelling, stable	pH	Reproducible GI release	Sustained oral systems	92
		CMC	Hydrophilic, viscous	pH	Improved matrix integrity	Oral controlled delivery	92
		Ethyl cellulose	Hydrophobic, low permeability	Time-dependent	Delayed drug release	Colon protection	92
3.	Synthetic	Eudragit® S/L	pH-dependent solubility	pH	Ileum/colon-specific release	Marketed colon DDS	93
		Poly(acrylic acid)	High swelling at alkaline pH	pH	Sharp colon release trigger	Controlled colon DDS	93
		Poly(methacrylic acid)	Strong ionic interactions	pH	Precise site-specific delivery	Targeted gut release	93
		PVA	High mechanical strength	Limited	Structural support matrix	Hybrid hydrogels	93
		PEG-based hydrogels	Tunable crosslinking	Multi-stimuli	Controlled diffusion	Oral drug carriers	93
4.	Hybrid	Alginate–chitosan	Dual charge system	pH + enzyme	Enhanced stability & targeting	Colon-specific delivery	94
		Pectin–Eudragit	Improved mechanical strength	pH + microbial	Colon-selective release	Advanced oral DDS	94
5.	Smart	Enzyme-cleavable hydrogels	Dynamic crosslinks	Microbial	Microbiota-specific activation	Precision gut therapy	95

		pH–enzyme dual hydrogels	Programmable swelling	Dual-responsive	Highly selective colon delivery	Personalized DDS	95

6. Design Strategies for *Panax quinquefolius L.*– Loaded Hydrogel Microspheres

The design of hydrogel microspheres for *Panax quinquefolius*L. should consider both the protection of its bioactive constituents during gastrointestinal transit and their subsequent availability for interaction with the intestinal microbiota. Ginsenosides, the major bioactive saponins of *Panax quinquefolius*, undergo extensive biotransformation by intestinal microorganisms, and their biological activity and absorption can therefore depend on microbial metabolism [96]. An appropriately designed hydrogel system may help protect these constituents from premature degradation or release in the upper gastrointestinal tract while providing controlled release in the intestine or colon.The selection of polymer is a critical design consideration. Natural polysaccharides, such as alginate, chitosan, pectin, dextran, and guar gum, can provide favorable swelling, gel-forming, mucoadhesive, and/or microbial degradation characteristics, whereas synthetic or semi-synthetic polymers can provide greater control over mechanical strength, swelling, and release kinetics [97,98]. Hybrid polymer systems may further combine the biological and microbial responsiveness of natural materials with the structural stability and tunability of synthetic polymers. The encapsulation method and formulation architecture should be optimized to achieve adequate loading and retention of ginsenosides while maintaining their chemical stability. Parameters such as polymer concentration, crosslinking density, microsphere size, encapsulation efficiency, swelling behavior, and surface characteristics can substantially influence gastrointestinal release and intestinal residence [98]**.** Stimuli-responsive approaches based on pH, enzymes, or microbial activity may provide additional control over release, allowing the formulation to remain relatively stable during passage through the upper gastrointestinal tract and undergo enhanced release under conditions encountered in the lower intestine [99].

For *Panax quinquefolius*L., the ultimate objective is not simply to maximize systemic absorption but, where appropriate, to increase the exposure of ginsenosides and their precursors to the intestinal microbial community. Controlled colonic release could provide a greater opportunity for the microbial conversion of major ginsenosides into deglycosylated metabolites, potentially influencing their biological activity and host–microbiome interactions [100,101]. Thus, an effective formulation should balance gastrointestinal protection, controlled release, microbial accessibility, residence time, and the preservation of bioactivity**.** However, these proposed benefits require experimental validation, as the relationship between formulation-mediated delivery, microbiota composition, ginsenoside biotransformation, and clinical outcomes remains unclear. [102]

6.1 Polymer Selection and Crosslinking Approaches

One of the most vital features of microsphere technology is its versatility. Polymer selection affects the stability, swelling, and release rates of bioactive materials derived from *Panax quinquefolius*. The desired properties of gut-targeted delivery systems include pH sensitivity, enzyme degradability, and mucoadhesive Ness. Natural polysaccharides are useful options that also have an affinity for herbal extracts and respond to degradation by the gut microbiome.

This increases the stability and reactivity of the microspheres. Although covalent crosslinking is more mechanically stable and has a longer release profile, ionic crosslinking has more favorable processing conditions, which are suitable for heat- and pH-sensitive ginsenosides. Although triggered release is permitted in the intestinal or colonic environment, optimal crosslinking density ensures protection against the gastric environment.

6.2 Encapsulation Techniques and Drug Loading Efficiency

To ensure phytochemical stability and a constant dose of *Panax quinquefolius*extracts, they need to be encapsulated in hydro–gel microspheres. Scalability, particle size, and solubility of the extracts are considered when selecting the encapsulation technique. Gelation-based encapsulation methods are preferred because of their suitability for complex herbal extracts. Polymer concentration, polymer–drug interactions, and manufacturing factors all affect drug loading efficiency. A high loading capacity is ideal for a lower dose volume while maintaining sustained release. Controlled encapsulation improves phytochemical stability and

boosts microbiome exposure by lowering early drug loss in tupper gastrointestinal tract. [103,104]

6.3 pH-Responsive and Enzyme-Responsive Systems

PH-responsive hydrogel microspheres are designed to remain compact under acidic stomach conditions while expanding or disintegrating in the neutral to alkaline pH of the colon and intestine. This feature is particularly useful for protecting ginsenosides from stomach digestion and enabling site-specific release. [105]

Enzyme-responsive systems exploit the enzymatic activity of intestinal and colonic bacteria to release drugs. Precise activation is made possible by polymers that are broken down by microbial enzymes in the colon, where ginsenoside biotransformation is highest. Treatment selectivity is enhanced, and off-target effects are decreased by this dual pH-enzyme responsiveness. [106,107]

6.4 Microbiome-Responsive and Smart Hydrogel Designs

Gut microbial ecology interacts dynamically with the microbiome-reactive components of advanced hydrogels in a micro-sized format. These biosystems effectively regulate the release of pharmacological agents through responses to metabolites, microbial enzymatic activity or components in the immediate area.. These enhancements improve the transformation of ginsenosides into bioactive metabolites by coordinating release with microbial activity. [108,109]Additionally, the ability to adapt to disease-related dysbiosis is made possible by microbiome-responsive hydrogels, which opens the door to personalized treatment. Smart hydrogels are positioned as next-generation platforms for precise gut microbiota management, owing to their numerous stimuli-responsive mechanisms that offer fine control over release behavior. [110,111]

6.5 Mucoadhesive and Colon-Targeting Strategies

The mucoadhesive properties are used to extend the residence time of the drug in the intestine and increase its concentration at the mucosal surface. [12, 13]

The use of polymers with mucoadhesive properties increases the interaction between the microbiome and phytochemicals by improving their retention in the gut. tThe upper gastrointestinal tract. These strategies include pH-sensitive polymers, microbiota-degradable matrices, and time-controlled-release systems. When mucoadhesion occurs, colon-targeted hydrogel microspheres with *Panax quinquefolius*bioactives can be delivered locally and sustainably [14].

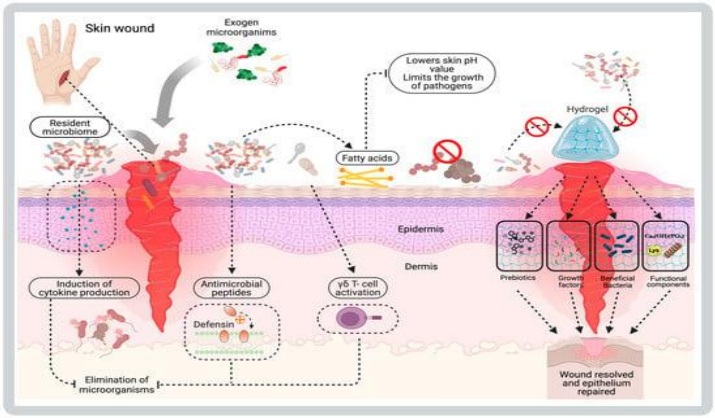


Figure 3: Design strategies for hydrogel microspheres, including pH-, enzyme-, and microbiome-responsive release mechanisms

7. Mechanistic Insights into Gut-Targeted Delivery

To optimize the effectiveness of therapy targeted at the gastrointestinal tract, it is necessary to understand the molecular basis of hydrogel microsphere-mediated delivery. In the gastrointestinal tract, hydrogel systems actively control the protection, release, positioning, and biological interactions of *Panax quinquefolius*L. bioactive compounds instead of acting as passive carriers. The safety and efficacy of therapy depend on these mechanisms.[115]

7.1 Protection from Gastric and Intestinal Degradation

Oral phytochemicals are highly sensitive to degradation in the acidic environment of the stomach and undergo enzymatic hydrolysis in the upper intestine. Hydrogel microspheres form a polymeric matrix that protects *Panax quinquefolius*ginsenosides from the acidic pH and digestive enzymes in the stomach. When placed in an acidic environment, the polymeric matrix is very dense and resists solvent diffusion; therefore, the release is controlled by the polymeric matrix itself. In addition, as polymeric microspheres progress through the colon, their controlled swelling properties allow for reduced interaction with digestive enzymes. [116] This ensures that a greater concentration of phytochemicals reaches the colon, where activation by the microbiota is maximized. Barrier protection is critical for maintaining drug consistency. [117]

7.2 Controlled and Sustained Release in the Colon

Colon-specific controlled and extended release is made possible through the engineered swelling, erosion, or degradation rates of the hydrogel matrix. [118]

Through pH-sensitive swelling and enzyme-catalyzed degradation of the hydrogel matrix, the release of

ginsenosides can be controlled based on the local physiological environment. The slow-release profile ensures that the concentration of the drug is maintained at a therapeutically appropriate level for an extended period. Through the extension of the interaction time between the phytochemicals and local bacteria, the colon-specific extended-release formulation makes possible the efficient bio transformation – of phytochemicals into bioactive metabolites.[119] Through the reduction of peak-to-trough variation, reduction of systemic exposure, and reduction of the frequency of dose, continuous dosage administration enhances patient safety and compliance.[120]

7.3 Interaction with Intestinal Mucus and Epithelial Barriers

The mucus layer in the intestine plays a very important role in drug localization and retention. Mucoadhesive hydrogel microspheres provide sustained localization at the epithelial interface through binding with mucin glycoproteins. Through the binding process, the duration of presence in the gut is prolonged, and the local bioavailability at the interface. Controlled drug delivery promotes barrier homeostasis by limiting over-permeability and irritation at the epithelial interface. Together, these mechanisms greatly influence metabolic and inflammatory diseases when mucosal barrier integrity is disrupted. [121]

7.4 Hydrogel–Microbiome–Host Crosstalk

Hydrogel microspheres serve as dynamic surfaces that facilitate interactions between the drug delivery platform, gut microflora, and host tissue. The hydrogel matrix is enzymatically degraded by the microbiome, thereby causing the ginsenosides derived from ~~the~~ microbes to be dependent on where the hydrogel is located. [122] Metabolic products produced between the host and gut microbes have a reciprocal relationship; they are metabolic byproducts of each other that assist in the creation of molecular signals affecting host metabolism, inflammatory processes, immune regulation, and epithelial barrier integrity. [123] The hydrogel matrix also serves as a means to modulate microbial activity through changes in the microenvironment surrounding the participating microbes. Collectively, these interactions highlight the ability of hydrogel-based systems to behave as dynamic modulators of host–microbiome interactions rather than simply delivery systems. [124]

8. Therapeutic Uses of Hydrogel-Based *Panax quinquefolius*L. Delivery

Microspheres may represent a general platform for the treatment of various diseases, and the potential ability of stabilizing, localizing, and microbiota-activating ginsenosides characterized by dysbiosis, inflammation, and barrier weakness may be most effectively treated using delivery devices. delivery systems enhance the therapeutic efficacy of *Panax quinquefolius*L. Examples of conditions related to chronic By allowing for sustained GI-localized bioavailability and interaction with gut microbiota, use of hydrogel-based

8.1 Inflammatory Bowel Diseases

This formulation reduces pro-inflammatory cytokines and restores immunological homeostasis. This formulation is useful as an oral colon-targeted drug delivery system to enhance local anti-inflammatory potential with minimal systemic exposure, with the advantage of localized production of ginsenosides in the inflamed regions of the colon. Ginsenosides are converted into bioactive substances by microbiota, and ulcerative colitis is characterized by microbial dysbiosis, impaired integrity of the epithelial barrier, and chronic intestinal inflammation. *Panax quinquefolius*-loaded hydrogels could prove effective for inflammatory bowel disease (IBD), including Crohn's disease. Furthermore, sustained release from hydrogel microspheres promotes barrier reinforcement and epithelial regeneration, making this strategy particularly suitable for long-term IBD treatment. [125]

8.2 Metabolic Disorders and Diabetes

Panax quinquefolius bioactives delivered via hydrogel modulate microbe-interacting pathways, controlling basal insulin sensitivity, lipid homeostasis, and glucose metabolism in the colon. gut microbiome destabilization. Type 2 diabetes and obesity, for instance, are the result of a metabolic disorder triggered by efficacy of hydrogel phytochemical delivery as an adjunct or alternative therapy for metabolic disorders is made possible by exposure to the colon leads to beneficial bacterial modifications and metabolic signaling-linked metabolites being synthesized. In addition, a prolonged colon-targeted microbiome-mediated approach was adopted. [126]

8.3 Immune Modulation and Gut–Brain Axis

Sustained contact with immune cells and gut microbiota. is all interconnected via the gut-brain axis, a bidirectional communication system. In particular, hydrogel delivery systems enhance the ability of *Panax quinquefolius*to

modulate the gut-brain axis because immune responses, gut microbiota, and CNS activity derived from ginsenosides can alter neuroimmunesignaling. Microbial metabolites, stress responses, and inflammatory mediators. Thus, localized delivery in the gut can be beneficial in immune-mediated neurological disorders, stress-related disorders, and cognitive impairment where systemic exposure to drugs could be harmful. [127,128]

8.4 Emerging Applications in Cancer and Neuroinflammatory Disorders

There is an emerging literature on gut microbiome composition in treatment outcomes, cancer development, and immune monitoring. The hydrogel-based delivery of *Panax quinquefolius*may have the potential to enhance anti-cancer effects by decreasing the inflammation caused by tumors and increasing the immune response through. Microbiome-mediated mechanisms. Neuroinflammatory diseases are also increasingly recognized as being associated with intestinal dysbiosis and systemic inflammation. Inflammatory signal-suppressing and microbiome-restoring delivery technologies offer promising avenues for complementary therapies. Although there is no clinical validation for hydrogel-based phytochemical delivery, it offers a new and flexible approach to managing complex microbiome-related diseases. [129]

9. Safety, Biocompatibility, and Regulatory Considerations [130,131,132,133]

The use of hydrogel-based delivery systems for *Panax quinquefolius* L. in a clinical setting requires a comprehensive evaluation of safety, biocompatibility, and regulatory issues. The delivery systems are intended for long-term oral administration and interaction with the gastrointestinal tract; therefore, it is necessary to consider the formulation and consistency of the delivery systems.

9.1 Biodegradability and Toxicological Aspects

One crucial safety feature of hydrogel microspheres intended for intestinal delivery is biodegradability. The polymers used in these delivery systems continuously break down into safe byproducts that the body can readily eliminate. Because of their proven biocompatibility and ability to be broken down by gastrointestinal tract enzymes, natural and semi-synthetic polymers are typically used. Potential local and systemic effects, such as mucosal irritation, immunological activation, and accumulation of breakdown products, must be considered in toxicological examinations. Long-term exposure studies are especially crucial. For both clinical acceptance and regulatory approval, it is essential to ensure little cytotoxicity and no negative immunological reactions.

9.2 Compatibility of Herbal Extracts with Hydrogel Matrices

Reproducible release profile. The herbal extracts were more diverse than those of other formulations. The hydrogel matrices and medicinal bioactives should be compatible for chemical stability, biological activity, and ginsenosides and its related drugs. adverse interactions. Consequently, optimization of formulation should focus on hydrogel matrices that can provide protective encapsulation with intact pharmacological activity of the polymer and phytochemicals is important as they might. Bioactives can precipitate or degrade due to from shelf stability, percentage release, loading efficacy, and drug entrapment. The interaction phytochemical constituent of *Panax quinquefolius* influence

9.3 Manufacturing, Scalability, and Quality Control

These are important considerations in the manufacturing of such a product to achieve reproducibility of particle size, drug loading levels, and release rates. is an important consideration for translating Hydrogel Microspheres from lab to industry. Scalability, cost-effectiveness, and feasibility for mass production at a conscionably low concentration. purity. This is especially important for herbal medicines, where the drug may act externally. A robust quality control system is necessary, monitoring critical parameters such as microbiological safety, encapsulation efficiency, cross-link density, and polymer.

9.4 Regulatory Challenges and Clinical Translation

Efficacy should be based on well-documented preclinical and clinical data. Incorporates properties of drugs, excipients, and devices. Tangible evidence in terms of quality, safety, and The herbal-delivery systems fabricated in hydrogel face difficulty obtain clearance from the regulatory bodies as the system release mechanisms, standardization of herbal extracts, and polymer selection rationale. Authorities should consider the assessment.

10. Current Challenges and knowledge Gaps

However, in view of the encouraging preclinical data, there are still some key questions that must be answered before the hydrogel-based delivery systems for *Panax quinquefolius* L. can be successfully applied in a clinical setting. Individual differences in gut microbiota composition are currently the biggest challenge. The ginsenoside biotransformation process is very sensitive to

differences in microbial diversity and enzyme activity, which in turn affects bioavailability, efficacy, and individual response to treatment.

Another challenge is the standardization of *Panax quinquefolius* extracts. The differences in phytochemical composition among batches, which are caused by differences in plant availability, growth conditions, harvesting, and processing, are currently a major obstacle.The absence of generally accepted criteria for the classification of extracts also affects their clinical consistency, approval, and quality. Moreover, most of the information currently available to support *Panax quinquefolius*hydrogel-based delivery is based on in vitro studies or animal models, which fail to reflect the complexity of the human gut microbiota. and disease pathophysiology, although these studies have provided valuable mechanistic insights. Thus, well-designed in vivo and clinical studies are essential to assess the efficacy, safety, and microbiome-related processes of these agents in humans. *Panax quinquefolius* delivery systems is to transition from laboratory-based research to practical microbiome-targeted treatments. on demand performance. Filling these knowledge voids needs to be undertaken if hydrogel-based not been widely investigated. The large-scale preparation and long-term use of the formulation also require extensive investigation to guarantee its long-term safety and tolerability. [134]

11. Future Perspective and Emerging Trends

Transcriptomics can provide a broader readout of host-microbe-phytochemical crosstalk. Formulation, dosage, and drug selection for more reproducible and personalized treatments. The combined use of microbiomeomics tools, such as metagenomics, metabolomics, related to progressive growth in specific and personalized approaches, can modulate gastric microflora. Unique microbiota fingerprints, functions, and disease-associated dysbiosis profiles will increasingly contribute to the adjustment of It is anticipated that future advances in the application of hydrogels as carriers for *Panax quinquefolius* L. would be closely and help to identify biomarkers for stratification. These data sources may offer insights into intricate regulatory networks that control microbial metabolism, immune modulation, and epithelial barrier function when combined with systems biology tools. Given their capacity to forecast polymer and microbiome responses, artificial intelligence/machine learning techniques are expected to be crucial for hydrogel design and optimization. From a translational standpoint, hydrogel-based phytochemical therapy is positioned as a viable strategy owing to the expanding recognition of the gut microbiome as a therapeutic target, as well as developments in biomaterials and regulatory frameworks. These technologies have great potential for tailored microbiome-directed therapy in neuroimmune, metabolic, and chronic inflammatory diseases with enhanced standardization, safety validation, and clinical understanding.

12. Conclusions

Hydrogel microsphere-based methods for delivering substances show much promise for enhancing the medicinal effects of *Panax quinquefolius* L. through their ability to accurately target the gut microbiome, often referred to as gut flora'. These methods also address many of the significant shortcomings associated with the use of dietary or herbal medicines because they can facilitate site-specific and sustained (slow) release of the active components in the colon, while providing protection from the effects of degradation of the active components (ginsenosides) before reaching the colon during normal digestion. Their ability to incorporate pH-sensitive, enzyme-sensitive, and microbiome-sensitive materials, which together facilitate the successful biotransformation of phytochemicals (ginsenosides) and successful management of phytochemical delivery via the microbiome (microorganisms living in the gut), will enable the accomplishment of these desired results. Furthermore, owing to the potential limitations associated with systemic circulation, hydrogel-based delivery systems may be ideal for delivering therapeutic agents for chronic diseases associated with gut dysbiosis, inflammation, and metabolic disorders. Although there were some positive outcomes seen in preclinical trials of *Panax quinquefolius*, there are several limits and barriers to moving forward with this product, including, but not limited to microbiota diversity, lack of standardization of plant extracts, no data on its long-term safety, and need for clinical validation. Therefore, to be able to translate this work successfully, interdisciplinary approaches will have to occur, as well as developing innovative biomaterials and more clinical studies. After considering these factors, the development of *Panax quinquefolius*delivery systems based on hydrogels could represent an exciting new means to deliver microbiome-based therapies, which have considerable potential to lead

to the second generation of functional phytopharmaceuticals.

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