



Opinion

# Addressing the Precision Delivery Challenges of Food-Medicine Homologous Active Polysaccharides (F-MHAPs): A Synergistic Strategy of "Carrier Adaptation-Targeted Modification-Environmental Response"

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Received: 11 September 2025 / Revised: 20 October 2025 / Accepted: 23 October 2025

**Abstract:** Active polysaccharides from food-medicine homologous sources are pivotal for the modernization of Food-Medicine Homologous substances. However, their clinical translation and efficacy exertion are hindered by three critical bottlenecks: inadequate targeting ability (prone to dispersion in non-target tissues, thus limiting efficient accumulation at lesion sites), low bioavailability (some polysaccharides with large molecular weights are susceptible to glycosidase degradation or unable to penetrate physiological barriers), and poor stability (vulnerable to pH fluctuations and enzymatic hydrolysis in the gastrointestinal tract). This paper proposes a "carrier adaptation-targeted modification-environmental response" synergistic strategy. Carrier adaptation provides a stable transportation foundation for polysaccharides, targeted modification achieves precise positioning, and environmental response ensures on-demand release at target sites. The synergistic effect of the three constructs a precise delivery system for active polysaccharides. This strategy not only addresses the delivery dilemmas of these polysaccharides but also enhances their targeting precision, bioavailability, and stability, advancing functional foods toward precision nutrition and aiding chronic disease prevention.

**Keywords:** F-MHAPs; Precision delivery; Carrier adaptation; Targeted modification; Environmental-Responsive Release

**Citation:** Wang C. Y., Fan P., Yang N. X., et al. Addressing the Precision Delivery Challenges of Food-Medicine Homologous Active Polysaccharides (F-MHAPs): A Synergistic Strategy of "Carrier Adaptation-Targeted Modification-Environmental Response". *Food & Medicine Homology*, 2026, 3: 9420132. <https://doi.org/10.26599/FMH.2026.9420132>

Active polysaccharides derived from Food-Medicine Homologous sources (e.g., *Lycium barbarum* polysaccharides [1], *Dendrobium officinale* polysaccharides [2]) have become a core research focus in the modernization process of Food-Medicine Homologous substances. Their attractiveness lies in their extensive physiological activities, including immunomodulatory effects, anti-tumor activity, and anti-inflammatory properties, combined with low toxicity and high biocompatibility. However, their clinical application and efficacy are hindered by three critical bottlenecks:

insufficient targeting (prone to dispersion in non-target tissues, limiting efficient accumulation at lesion sites), low bioavailability (large molecular weights of some polysaccharides render them susceptible to degradation by glycosidases or inability to penetrate physiological barriers), and poor stability (vulnerable to pH and enzymatic effects in the gastrointestinal tract). To address these aforementioned challenges, a synergistic strategy that integrates 'carrier adaptation-targeted modification-environmental response' is proposed in this study. This strategy enables precise delivery,

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efficient accumulation, and on-demand release of active polysaccharides through well-designed delivery systems (Fig 1).

In this figure, the “carrier adaptation-targeted modification-environmental response” strategy are designed. The core circle replaced the different carrier adaptation styles: polysaccharide-, protein-, lipid-, and inorganic nanomaterial-based carrier. The environmental response systems are also dividly placed at the edge of the figure, including enzyme-responsive, pH-responsive, and redox-responsive delivery systems. The “tumor cells” are the target sites of the precision targeted delivery. The delivery system is designed to specifically recognize and bind to the target cells. The interaction logic is that the delivery system, equipped with specific ligands or targeting moieties, can selectively bind to the receptors or over - expressed proteins on the surface of target cells. Once bound, the active polysaccharides are then released into the target cells through endocytosis or other mechanisms, exerting their functions such as anti-tumor, immunomodulatory effects specifically within the target cells, achieving the goal of precision targeted delivery.

## 1 Carrier Adaptation

Tailoring “Carrier-Active Ingredient” Matching Based on Polysaccharide Characteristics Carriers serve as the “transport units” for active polysaccharides, with core functions including stable loading, prevention of premature leakage, protection against degradation, and enabling barrier penetration. Carrier selection should be tailored to the physicochemical properties of polysaccharides, such as charge, molecular weight, and and hydrophilicity/hydrophobicity, to ensure optimal compatibility.

### 1.1 Polysaccharide-based carriers

Homologous adaptation from natural sources Natural polysaccharide carriers, due to structural homology with active

polysaccharides, achieve efficient loading via hydrogen bonding or electrostatic interactions, retain natural properties, and even enhance synergistic effects. For instance, positively charged chitosan and negatively charged alginate can self-assemble into composite nanoparticles via electrostatic adsorption. The encapsulation efficiency of chitosan-alginate composite nanoparticles for *Lycium barbarum* polysaccharides (LBPs) reaches over 85%; Additionally, after 2 hours of incubation in simulated gastric fluid, the molecular weight retention rate of LBPs in the nanoparticles is  $91.5 \pm 2.4\%$ , while free LBPs show a retention rate of only  $62.3 \pm 3.1\%$ . Chitosan exhibits mucoadhesive properties, which can prolong the retention time of the delivery system in the intestine. This not only enables targeted intestinal delivery to avoid gastric degradation but also increases the interaction time with intestinal mucosal immune cells, thereby fully activating the immunomodulatory functions of the polysaccharides.

Additionally, polysaccharides like hyaluronic acid and dextran can be modified (e.g., cross-linking, grafting) to adjust particle size and hydrophilicity, adapting to polysaccharides of varying molecular weights and addressing barrier penetration issues for large molecules.

### 1.2 Protein-based carriers

Targeted delivery via “hydrophobic-hydrophilic” interactions Protein carriers bind to hydrophilic groups of polysaccharides through hydrophobic regions, forming nanoparticles or microspheres via emulsification or self-assembly—ideal for gastrointestinal delivery. For instance, whey protein nanoparticles loaded with Astragalus polysaccharides (APs) utilize whey protein’s gastric acid resistance to prevent premature release in the stomach. For APs, The encapsulation efficiency of whey protein nanoparticles for APs reaches over 82%; In SIF (pH 6.8, containing trypsin), the nanoparticles release  $81.5 \pm 3.2\%$  of APs

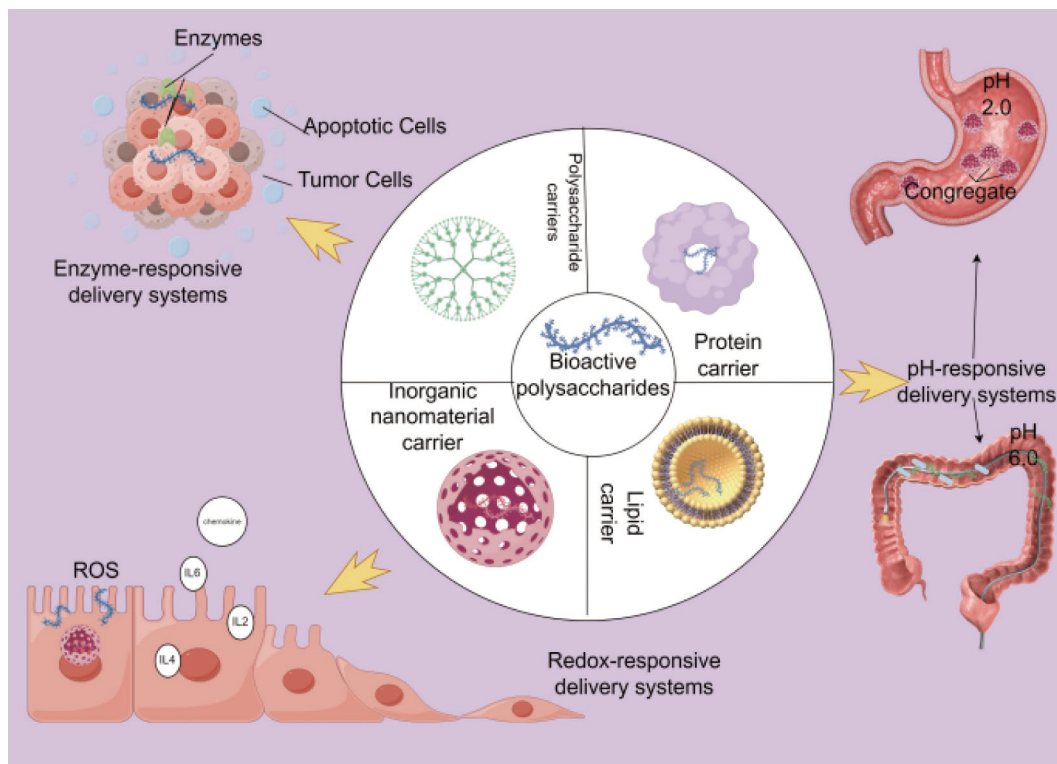


Figure 1 Precision targeted delivery of active Polysaccharides.

within 4 hours, moreover, the released APs retain 92% of their original immunomodulatory activity

In the intestine, whey protein is hydrolyzed by intestinal proteases, and the released polysaccharides target macrophages via specific receptor binding, activating macrophage functions and enhancing immunomodulation.

### 1.3 Lipid-based carriers

"Transmembrane tools" for barrier penetration. For large-molecular-weight polysaccharides that cannot cross cell membranes independently, lipid carriers (e.g., liposomes, solid lipid nanoparticles) can utilize the lipophilicity of phospholipid bilayers to provide transmembrane transport channels for polysaccharides, thereby promoting their entry into target cells. For example, encapsulating high-molecular-weight anti-tumor polysaccharides in liposomes enables passive targeting via the Enhanced Permeability and Retention (EPR) effect [3] in tumors. Liposomes fuse with tumor cell membranes to release polysaccharides, enhancing anti-cancer efficacy. Solid lipid carriers, with superior stability, extend polysaccharide half-life for sustained release and prolonged biological activity.

### 1.4 Inorganic nanocarriers

"Responsive reservoirs" with biosecurity Biocompatible inorganic nanomaterials (e.g., mesoporous silica nanoparticles) act as "smart reservoirs," loading active polysaccharides via pore design and enabling targeted release through surface modification. For example, mesoporous silica nanoparticles loaded with anti-tumor polysaccharides are capped with MMP-2 enzyme-sensitive peptides (highly expressed in the tumor microenvironment). MMP-2 in tumors cleaves the peptides, releasing polysaccharides and increasing their concentration at tumor sites. On the basis of achieving efficient matching between carriers and active polysaccharides, targeted modification is further used to endow the delivery system with 'active navigation' capability, so as to improve the enrichment efficiency of polysaccharides in target tissues.

## 2 Targeted Modification

"Active Navigation" via Ligand Modification Passive targeting, such as the EPR effect and the inherent organ tropism of carriers, is insufficient in targeting precision. Active targeting, achieved by modifying carriers with ligands that specifically bind to target cells/tissues, guides precise localization and accumulation of active polysaccharides:

### 2.1 Folic acid modification

Tumor cells (e.g., liver, breast cancer cells) overexpress folate receptors, making folic acid ideal for modifying anti-tumor polysaccharide delivery systems. Folate-modified delivery systems can actively bind to folate receptors overexpressed on the surface of liver cancer cells, which not only improves the endocytosis efficiency of the system but also enhances the accumulation of polysaccharides in tumor cells. Experimental data shows that folic acid modification increases the uptake amount of polysaccharides by liver cancer cells by 2-3 folds compared with the unmodified group.

### 2.2 Mannose modification

Macrophages and dendritic cells highly express mannose

receptors, making mannose suitable for immunomodulatory polysaccharide systems. Mannose guides the delivery system to target macrophage mannose receptors, enhancing polysaccharide uptake, strengthening cytokine secretion, and improving immunomodulatory functions, e.g., increasing the secretion levels of cytokines such as IL-2 and TNF- $\alpha$ . In vivo, mannose-modified liposomes loaded with *Lycium barbarum* polysaccharides (LBPs) accumulated in the spleen at a concentration 2.1 times higher than unmodified liposomes, confirming its ability to enhance site-specific delivery to immune tissues and amplify the immunomodulatory functions of F-MHAPs.

### 2.3 Peptide modification

Peptide ligands, with high specificity and barrier penetration, target disease-specific tissues. For example, RGD peptide (recognizing integrin  $\alpha\beta_3$  receptors on tumor cells)-modified systems actively bind to tumor cells, prolonging polysaccharide retention, activating tumor-infiltrating lymphocytes, and enhancing anti-tumor efficacy. For instance, RGD-modified mesoporous silica nanoparticles loaded with Ganoderma lucidum polysaccharides (GLPs) exhibited a 4.5-fold higher uptake rate by MDA-MB-231 breast cancer cells than unmodified nanoparticles. Polysaccharides modified with cell-penetrating peptides (CPPs) can cross biological barriers such as the blood-brain barrier (BBB), thereby increasing the concentration of polysaccharides in the brain and enabling them to exert their biological functions.

## 3 Environmental Response:

Ensuring On-Demand Release at Target Sites Active polysaccharides must be released precisely at target sites to avoid enzymatic degradation or ineffective consumption in non-target areas. Environmental responsiveness is triggered by the target microenvironment, compatible with delivery scenarios of food-medicine homologous polysaccharides:

### 3.1 pH-responsive release

This strategy utilizes the pH differences in the gastrointestinal tract (i.e., gastric pH ranging from approximately 1.5 to 3.5 and intestinal pH ranging from approximately 6 to 7.5) to achieve site-specific release. The delivery system remains stable in the acidic stomach (no release) but swells and disintegrates in the neutral intestine by pepsin and pancreatic amylase, releasing polysaccharides to improve absorption, regulate immunity, and enhance the intestinal mucosal barrier. In tumors (acidic microenvironment), pH-sensitive carriers release polysaccharides specifically at tumor sites.

### 3.2 Enzyme-responsive release

Targets enzymes highly expressed at specific sites. For example, intestinal enzymes cleave the delivery system to release polysaccharides, targeting intestinal probiotics, promoting gut health, and preventing premature degradation in the stomach. Tumor-specific enzymes (e.g., overexpressed proteases) can cleave the carriers, leading to the release of polysaccharides. This process inhibits tumor growth while avoiding damage to normal tissues.

### 3.3 Redox-responsive release

Suitable for inflammatory sites (e.g., joint cavities in rheumatoid arthritis) with high redox potential. Redox-sensitive carriers, such as disulfide bond-crosslinked delivery systems, can decompose

under high glutathione concentrations in inflammatory sites (e.g., joint cavities in rheumatoid arthritis). This decomposition allows the controlled release of polysaccharides, which then exert local anti-inflammatory effects. The other redox sensitive carriers, hyaluronic acid-chitosan carriers modified with disulfide bonds, can release rate reaches 90% within 4 hours in a high-glutathione environment. In conclusion, the synergistic strategy of 'carrier adaptation-targeted modification-environmental response' offers a comprehensive solution to the challenges associated with the precision delivery of F-MHAPs. This approach not only enhances the targeting precision, bioavailability, and stability of F-MHAPs but also promotes the development of functional foods and nutritional supplements toward the direction of precision nutrition and targeted intervention. Furthermore, it provides new insights and approaches for the prevention of chronic diseases and the management of human health.

## 4 Discussion

### 4.1 Current Limitations and Challenges

Despite the promising potential of the "carrier adaptation - targeted modification - environmental response" synergistic strategy for the precision delivery of F-MHAPs, there are still several limitations and challenges that need to be addressed.

One of the major concerns is the potential toxicity of carriers. Although many carriers, such as polysaccharide - based, protein - based, lipid - based, and inorganic nanocarriers, are claimed to be biocompatible, long - term and high - dose use may still pose risks. For example, some inorganic nanocarriers, like mesoporous silica nanoparticles, may accumulate in the body over time, and their long - term effects on human health are not yet fully understood. The release of nanoparticles from the carriers in the body may also cause unknown biological responses, which could potentially lead to toxicity issues.

The high - cost production is another obstacle. The synthesis and modification of carriers, as well as the preparation of the delivery systems, often involve complex processes and expensive raw materials. For instance, the production of liposomes requires high - purity phospholipids, and the modification of carriers with specific ligands like folic acid or peptides can be costly. These high production costs limit the large - scale application of the precision delivery systems, making it difficult to translate the technology from the laboratory to the market.

In terms of large - scale application, there are also limitations. The production processes of the delivery systems may not be easily scalable. The quality control during large - scale production is also a challenge. Ensuring the consistency of the encapsulation efficiency, targeting ability, and environmental - responsive release properties of the delivery systems in large - scale production is crucial but difficult to achieve. Additionally, the regulatory approval for these novel delivery systems is complex and time - consuming, which also hampers their large - scale application.

### 4.2 Future Research Directions

To overcome the current limitations and challenges, several future research directions can be proposed.

First, the development of more biocompatible and cost - effective carriers is essential. Researchers can explore new natural materials or modify existing materials to improve their biocompatibility and reduce costs. For example, further research can be done on natural polymers from renewable sources to

develop more efficient and affordable polysaccharide - based carriers. The use of genetic engineering techniques to modify proteins or polysaccharides to enhance their performance as carriers can also be investigated.

Second, an in - depth study of the interaction mechanism between polysaccharides and carriers is needed. Understanding how polysaccharides interact with carriers at the molecular level can help optimize the design of the delivery systems. This includes studying the binding forces between them, the influence of carrier structure on polysaccharide loading and release, and the impact of the interaction on the biological activity of polysaccharides. Such knowledge can guide the development of more efficient and stable delivery systems.

Finally, the exploration of new application scenarios for F-MHAPs and their delivery systems should be encouraged. Besides the traditional applications in functional foods, nutritional supplements, and anti-tumor and immunomodulatory therapies, F-MHAPs could potentially be used in other fields such as tissue engineering, wound healing, and drug delivery for other diseases. For example, F-MHAPs could be used to develop bioactive scaffolds for tissue engineering, taking advantage of their biocompatibility and bioactivity.

## 5 Outlook

### 5.1 Potential Impact on Precision Nutrition and Chronic Disease Prevention

The precision delivery of F-MHAPs holds great promise in promoting the development of functional foods and nutritional supplements towards precision nutrition and targeted intervention. In the realm of precision nutrition, it allows for the customization of nutritional products based on an individual's specific physiological conditions, genetic makeup, and health goals. For example, by precisely delivering immunomodulatory polysaccharides to individuals with weakened immune systems, these polysaccharides can be effectively absorbed and utilized to enhance their immune functions. This personalized approach can improve the efficiency of nutrition supply, ensuring that nutrients are delivered to the right place at the right time, and minimizing waste and potential side-effects.

In terms of chronic disease prevention, F-MHAPs with precise delivery can play a significant role. Chronic diseases such as cardiovascular diseases, diabetes, and cancer are often related to long - term imbalances in the body's physiological functions. F-MHAPs with anti-inflammatory, anti -oxidative, and immunomodulatory properties, when precisely delivered to the target tissues, can help regulate the body's internal environment. They can reduce chronic inflammation, which is a common underlying factor in many chronic diseases. For instance, anti-inflammatory polysaccharides can be precisely delivered to the sites of chronic inflammation in the body, alleviating the inflammatory response and potentially preventing the progression of related chronic diseases.

### 5.2 Broadening the Horizons of Food - Medicine Homologous Research

This research on the precision delivery of F-MHAPs can open up new areas of research and application in the field of Food-Medicine Homologous substances. It encourages the exploration of more novel carriers and modification methods, which can lead to the discovery of new delivery systems with better performance.

For example, the development of new polysaccharide -based carriers or the modification of existing carriers with unique ligands may enable the delivery of F-MHAPs to previously inaccessible target sites.

Moreover, it promotes the combination of Food-Medicine Homologous research with other disciplines such as nanotechnology, materials science, and molecular biology. The integration of nanotechnology can lead to the development of more advanced nanocarriers for F-MHAPs, while materials science can provide new ideas for the design of carriers with improved properties. Molecular biology can help in understanding the interaction mechanisms between F-MHAPs and cells at a deeper level, guiding the optimization of the delivery system.

In the context of human health management, this research provides a new paradigm. It enables a more targeted and effective approach to maintaining and improving human health. By precisely delivering F-MHAPs, we can better utilize the health-promoting properties of Food-Medicine Homologous substances, which is of great significance for disease prevention, health maintenance, and the improvement of the overall quality of life.

### Acknowledgment

The authors would like to thank the financial supported by the

Key Technology R&D and Industrialization of Polysaccharide-Rich Dietary Health Products (S2024KJCY2222), by the Scientific research project of Jiangxi Medical Products Administration (No.2024GL19).

### Conflicts of interest

The authors declare that there are no conflicts of interest in this work.

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