



Opinion

Functional reinterpretation of food-medicine homologous polysaccharides: From bioactive macromolecules to multifunctional materials

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Received: 23 July 2026 / Revised: 28 July 2026 / Accepted: 28 July 2026

Citation: Bao C. J., Liu Y. X., Li M. X., et al. Functional reinterpretation of food-medicine homologous polysaccharides: From bioactive macromolecules to multifunctional materials. *Food & Medicine Homology*, 2026, 3: 9420166. <https://doi.org/10.26599/FMH.2026.9420166>

1 Introduction

Precision immune modulation has emerged as a transformative strategy in vaccine development, cancer immunotherapy, chronic disease intervention and preventive healthcare. Advances in immunology, pharmaceuticals and biomaterials science have shifted immune regulation from nonspecific stimulation towards the selective modulation of immune cell populations, immune niches and disease-associated immune states. This conceptual transition has not only reshaped therapeutic paradigms but also generated new demands for immunomodulatory molecules capable of integrating biological activity with controllable delivery and material functionality.

Food-medicine homologous (FMH) substances represent an abundant reservoir of naturally derived bioactive components with favorable safety profiles and long-standing applications in health maintenance. Generally referring to natural resources derived from edible and medicinal biological sources, including plants, fungi, algae and other organisms, FMH substances have been traditionally consumed as foods while also being used for medicinal or health-promoting purposes across different cultural contexts. Among these compounds, polysaccharides have attracted extensive attention owing to their structural diversity, immunomodulatory capacity and intrinsic biocompatibility.

Traditionally, polysaccharides have been investigated primarily as bioactive macromolecules that regulate immune responses through receptor-mediated signaling pathways. However, emerging evidence suggests that their biological significance extends far beyond direct immune activation. Their tunable chemical structures, abundant functional groups and intrinsic biological activities enable polysaccharides to serve as both immunoregulatory molecules and functional building blocks for advanced delivery systems.

Recent progress in glycobiology and pharmaceutical engineering has revealed a paradigm shift in the development of FMH polysaccharides: From identifying bioactive macromolecules towards multifunctional materials. In this context, multifunctional materials refer to polysaccharide-based materials or systems that integrate intrinsic immunological activity with material functions, such as cargo loading, controlled delivery and microenvironment modulation. Their defining feature is therefore not bioactivity or delivery capability alone, but the functional integration of both, enabling the polysaccharide material itself to actively participate in immune regulation rather than serving solely as a passive carrier. This integration of biological activity and material functionality provides new opportunities for precision immune intervention.

In this opinion, we discuss the evolving functional landscape of

FMH polysaccharides from a pharmaceutical perspective. We summarize their transition from immune-active constituents to multifunctional immunological materials, highlight emerging strategies for structure-guided functional design, and discuss the key challenges that must be addressed to enable their translation into precision immune therapeutics. We argue that the future development of FMH polysaccharides should move beyond the conventional paradigm of identifying bioactive constituents and evaluating their biological effects, towards a function-oriented design framework in which polysaccharides are regarded as structurally programmable biological materials that integrate intrinsic immunological activity with material functionality. Such a conceptual shift may enable the rational development of FMH polysaccharide-based systems with predictable immune-regulatory functions and broader pharmaceutical applications.

2 Functional reinterpretation of FMH polysaccharides

The reinterpretation of immune regulation has fundamentally changed the functional positioning of FMH polysaccharides. Historically, polysaccharides were primarily considered natural immune stimulators, and research efforts focused mainly on identifying bioactive fractions and elucidating underlying signaling mechanisms^[1]. However, advances in immunotherapy and drug delivery technologies have revealed that polysaccharides possess broader functional capabilities. Beyond directly regulating immune cells through pattern recognition receptor-mediated pathways, polysaccharides can reshape immune networks, regulate

disease-associated immune microenvironments and serve as biofunctional materials for the delivery of immunotherapeutic agents. This transition represents a conceptual evolution from activity-oriented investigation to function-oriented design, expanding the role of polysaccharides from biological regulators to programmable components for precision immune modulation (Fig. 1).

2.1 Promotion of antigen presentation

Enhancing antigen presentation represents one of the earliest recognized immunomodulatory functions of FMH polysaccharides and provides the foundation for their application as natural immune adjuvants^[2]. Numerous studies have demonstrated that polysaccharides can be recognized by pattern recognition receptors (PRRs) expressed on antigen-presenting cells (APCs), particularly dendritic cells (DCs), thereby initiating receptor-dependent signaling cascades^[3]. Through these interactions, polysaccharides can facilitate antigen uptake, promote DC maturation and enhance antigen processing and presentation, ultimately leading to the activation of adaptive immune responses involving T cells and B cells^[4]. Importantly, polysaccharides from different biological sources exhibit distinct immunological profiles due to variations in monosaccharide composition, glycosidic linkages and higher-order structures, enabling differential regulation of immune polarization. These findings established polysaccharides as promising natural immune modulators and provided the biological basis for their incorporation into vaccine adjuvant systems and immunotherapeutic platforms.

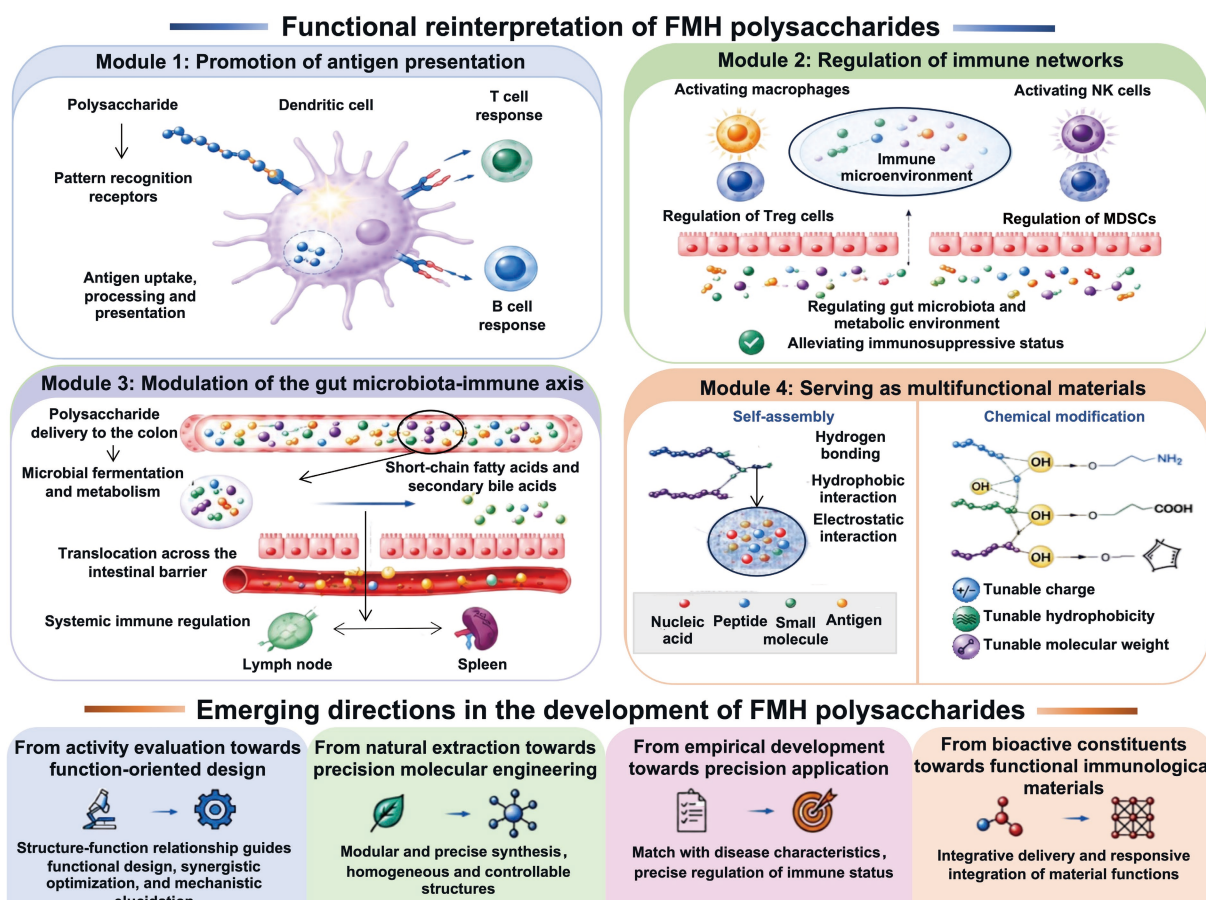


Figure 1 Functional reinterpretation and emerging directions of FMH polysaccharides.

2.2 Regulation of immune networks and microenvironments

The development of modern immunology has highlighted that therapeutic immune modulation is not solely determined by antigen presentation efficiency but also depends on complex interactions among immune cell populations and their surrounding microenvironments. In this context, polysaccharides have increasingly been recognized as regulators of immune networks rather than simple immune stimulators. Accumulating evidence indicates that polysaccharides can enhance the activation and functional maturation of innate immune cells, including macrophages and natural killer (NK) cells, while simultaneously influencing immunosuppressive populations such as regulatory T cells and myeloid-derived suppressor cells (MDSCs)^[5]. Through coordinated regulation of immune cell interactions, polysaccharides may restore immune balance and reshape pathological immune landscapes, particularly within tumor and chronic inflammatory microenvironments.

2.3 Modulation of the gut microbiota-immune axis for systemic immune regulation

Beyond directly interacting with immune cells, FMH polysaccharides can exert systemic biological effects through the regulation of the gut microbiota-immune axis^[6]. Due to their complex glycosidic structures and limited digestion in the upper gastrointestinal tract, many polysaccharides reach the colon where they serve as substrates for microbial fermentation and reshape the ecological structure of intestinal communities. Emerging evidence suggests that polysaccharides can selectively enrich specific bacterial populations associated with immune homeostasis, although the determinants governing microbial utilization remain incompletely understood. The structural features of polysaccharides, including monosaccharide composition, glycosidic linkage patterns, molecular size and branching architecture, may collectively influence their microbial accessibility and fermentation profiles. Importantly, the biological effects of microbiota-targeted polysaccharides may not be restricted to local intestinal regulation. Microbial-derived metabolites, including short-chain fatty acids, secondary bile acids and other bioactive molecules, can cross the intestinal barrier and participate in systemic immune regulation through metabolic and immunological communication pathways. These metabolites have been implicated in regulating immune cell differentiation, inflammatory responses and tissue-specific immune microenvironments. These diverse biological functions, together with the inherent structural adaptability of polysaccharides, provide the conceptual and material basis for transforming FMH polysaccharides from bioactive macromolecules into multifunctional immunological materials.

2.4 Integration into multifunctional immunological materials

The development of pharmaceutical technologies has further expanded the application boundaries of FMH polysaccharides. Their diverse chemical structures, abundant reactive groups and inherent biological compatibility provide unique advantages for constructing functional biomaterials. Through self-assembly, chemical modification and molecular conjugation strategies, polysaccharides can be engineered into nanostructures, hydrogels and hybrid delivery platforms capable of carrying diverse

therapeutic cargos, including antigens, nucleic acids, peptides and small-molecule drugs^[7]. For example, Li *et al.* developed a self-adjuvant nanovaccine based on *Astragalus* polysaccharides, in which the polysaccharide simultaneously served as an antigen delivery scaffold and an immune adjuvant to enhance dendritic cell activation and antitumor immune responses^[8]. This dual functionality enables polysaccharides to bridge the gap between bioactive molecules and delivery systems, representing a new generation of naturally derived immunological materials. Such systems provide opportunities to simultaneously control cargo delivery, immune activation and microenvironment remodeling, thereby offering a promising foundation for precision immune intervention.

3 Emerging directions in the development of FMH polysaccharides

3.1 From activity evaluation towards function-oriented design

For decades, research on FMH polysaccharides has largely followed a discovery-driven paradigm, focusing on resource screening, activity evaluation and mechanistic investigation. Although this strategy has led to the identification of numerous immunomodulatory polysaccharides, activity-based classification alone is insufficient to explain their complex biological behavior or to guide the rational development of precision immunological interventions. Accordingly, the development of polysaccharides should increasingly adopt a function-oriented design strategy in which structural characteristics, material properties and biological functions are considered as an integrated system. Such an approach may enable the coordinated optimization of immune activity, delivery behavior and material performance, thereby moving the field from the discovery of active polysaccharides towards the design of polysaccharides with predefined functions.

3.2 From natural extraction towards precision molecular engineering

Natural extraction remains an important route for obtaining bioactive polysaccharides and can preserve the compositional complexity that may contribute to their biological effects. However, naturally derived polysaccharides are inherently heterogeneous. Variations in botanical source, cultivation conditions, processing procedures and purification strategies can lead to substantial differences in molecular composition, structural organization and biological activity. This heterogeneity complicates structure-function analysis, limits batch-to-batch consistency and presents challenges for the development of reproducible therapeutic products. Precision molecular engineering provides a complementary strategy to overcome these limitations. Chemical synthesis, enzymatic assembly and chemoenzymatic approaches can generate structurally defined oligosaccharides and polysaccharide mimetics with controlled sequence, linkage and branching patterns^[9,10]. These approaches also enable the construction of structure-defined molecular libraries and functional probes for systematically interrogating the relationship between glycan structure and immune activity.

Natural polysaccharides can provide structurally and biologically relevant templates, whereas synthetic and enzymatic strategies can help identify functional motifs and reconstruct defined structural features. Importantly, the objective of precision

engineering is not necessarily to fully reproduce or replace the structural complexity of natural polysaccharides. Heterogeneous polysaccharides may generate polyvalent interactions or synergistic effects that cannot be recapitulated by a single structurally defined oligosaccharide. Instead, structurally characterized natural polysaccharides can serve as biologically relevant templates for the reconstruction of selected structural features through chemical, enzymatic or chemoenzymatic approaches. The biological activities of these defined structures can then be compared with those of their natural counterparts to determine which functions are retained, which depend on structural complexity or multivalency, and where further structural optimization may be possible. The optimal balance between structural complexity and precision should therefore be determined by the therapeutic context and the functional requirements of the intended application.

3.3 From empirical development towards precision application

FMH substances have traditionally been developed on the basis of accumulated empirical knowledge and their broad effects on health maintenance. This approach has provided an important foundation for the long-term application of these substances but is not sufficient to meet the requirements of modern precision immunology. Immune responses are highly context dependent. The same immunomodulatory intervention may produce distinct outcomes depending on disease type, immune status, tissue microenvironment and treatment stage. Accordingly, the future application of polysaccharides should consider not only their intrinsic immunological activity but also the specific immune context in which they are administered. A major objective will therefore be to establish design principles that connect polysaccharide structure and formulation properties with disease-associated immune states. Such principles could guide the development of polysaccharides that selectively modulate immune cell populations, remodel pathological immune microenvironments, influence the gut-immune axis or improve the response to existing immunotherapies. Importantly, precision immune modulation does not imply a universal direction of immune activation, but rather the ability to achieve context-dependent immune regulation according to specific disease states and therapeutic requirements. For example, polysaccharide-based materials may be designed to enhance antigen presentation and antitumor immunity in cancer and vaccination, while promoting immune balance and controlling excessive inflammation in autoimmune disorders or infectious diseases. Therefore, future polysaccharide development should focus on establishing adjustable relationships among molecular structure, material properties and immune outcomes, enabling tailored regulation of distinct immune states.

3.4 From bioactive constituents towards functional immunological materials

The development of modern pharmaceutical and biomaterials technologies has fundamentally expanded the functional definition of natural bioactive molecules. For FMH polysaccharides, biological activity represents only one dimension of their pharmaceutical value. Their structural tunability, physicochemical versatility and capacity for chemical modification provide additional opportunities for material engineering. A polysaccharide can potentially function simultaneously as an

immunomodulatory molecule, a structural material and a delivery platform. For example, a single polysaccharide-based system may provide a matrix for cargo loading, regulate the release of therapeutic molecules and directly modulate the immune microenvironment. This convergence of biological and material functions suggests that polysaccharides should no longer be viewed solely as active ingredients or passive excipients. Instead, they may serve as integrated functional materials in which the carrier and the therapeutic component are not necessarily separate entities. Such systems could provide new opportunities for the development of immunotherapies that combine immune modulation, controlled delivery and microenvironment regulation within a unified platform.

4 Key challenges in the functional expansion of FMH polysaccharides

4.1 Deciphering higher-order structures of polysaccharides for functional design

The inherent complexity of polysaccharides, including diverse monosaccharide compositions, heterogeneous chain lengths, extensive branching patterns and dynamic conformational properties, presents substantial challenges for precise structural elucidation. Current characterization strategies primarily focus on relatively basic structural parameters, such as monosaccharide composition, molecular weight distribution and glycosidic linkage patterns. However, these descriptors may not fully capture the functional properties of polysaccharides. Increasing evidence suggests that higher-order structural features, including three-dimensional conformations, chain organization, supramolecular assembly and spatial presentation of functional domains, can critically influence molecular recognition, receptor engagement, biological distribution and immunomodulatory activity. Therefore, a major challenge in advancing polysaccharides from bioactive constituents to functional immunological materials is the establishment of high-resolution structural analysis platforms capable of linking complex glycan architectures with biological functions. Emerging approaches integrating advanced spectroscopy, computational modeling, cryogenic imaging and molecular engineering may enable the identification of functional structural motifs within heterogeneous polysaccharide systems.

4.2 Establishing structure–function relationships that support functional design

The structure–function relationships of polysaccharides remain incompletely understood. Conventional studies have primarily attempted to associate structural parameters with biological activity, often using a limited number of structural descriptors and endpoint assays. However, the functional performance of a polysaccharide-based immunological material is determined by multiple interconnected properties, including molecular structure, physicochemical characteristics, supramolecular organization, pharmacokinetic behavior and immune activity. Future studies should therefore develop integrated structure–function frameworks that consider these parameters simultaneously. Such an approach could enable the identification of structural determinants that control specific functional outputs, including receptor recognition, cellular uptake, tissue distribution, cargo loading and immune microenvironment regulation. The ultimate objective should be to move beyond merely characterizing

naturally occurring structures towards establishing design principles that enable the creation of polysaccharides with predictable functions.

4.3 Developing evaluation systems that capture the properties of functional materials

Current evaluation strategies are often divided between biological activity assays and pharmaceutical characterization. This separation is insufficient for polysaccharides that simultaneously function as bioactive molecules and delivery materials. A more comprehensive evaluation framework should integrate three complementary dimensions. First, material properties should include structural integrity, physicochemical stability, degradation behavior and long-term safety. Second, biological behavior should encompass cellular uptake, biodistribution, pharmacokinetics and cargo delivery efficiency. Third, immunological function should include immune cell activation, immune polarization, therapeutic efficacy and remodeling of disease-associated immune microenvironments. Importantly, these parameters should not be evaluated independently. The relationship between material properties and biological outcomes should be explicitly established. For example, changes in molecular weight, charge or supramolecular organization may influence both cargo loading and immune receptor recognition. An integrated evaluation framework would therefore provide a more accurate understanding of polysaccharide function and facilitate the comparison of materials derived from different natural sources.

4.4 Establishing a translational framework adapted to multifunctional polysaccharides

The multifunctional nature of polysaccharides creates challenges for their pharmaceutical translation. Unlike conventional natural products, their development requires simultaneous consideration of biological activity, material performance and formulation behavior. Conversely, unlike conventional delivery systems, polysaccharide-based materials may directly participate in immune regulation. This dual nature necessitates a translational framework that integrates basic glycobiology, pharmaceutical engineering, quality control, safety assessment and regulatory science. Particular attention should be given to critical quality attributes that determine both biological activity and material performance. These may include molecular composition, molecular weight distribution, structural integrity, degree of modification, impurity profiles, physicochemical stability and batch-to-batch consistency. Establishing robust relationships between these quality attributes and biological function will be essential for improving reproducibility and supporting the translation of polysaccharide-based immunological materials.

5 Outlook

The development of FMH polysaccharides is entering a phase in which their pharmaceutical value can no longer be adequately described by their biological activity alone. The central question is gradually shifting from “What activity does a polysaccharide possess?” to “What biological and pharmaceutical functions can its structure be designed to achieve?” This shift reflects a broader transformation in natural product research. Rather than treating natural molecules solely as sources of pharmacological activity, modern pharmaceutical science increasingly seeks to understand how their intrinsic structural properties can be harnessed to create

multifunctional therapeutic systems.

FMH polysaccharides are particularly well positioned within this transition because they combine structural diversity, biological activity, biocompatibility and material adaptability. Future progress will depend on closer integration of glycobiology, immunology, pharmaceuticals, biomaterials science and computational approaches. Advances in glycan structure elucidation, structure-guided design, molecular engineering and precision delivery may enable the development of polysaccharide-based systems with increasingly predictable biological functions. Looking ahead, a systematic classification and comparative evaluation of native, chemically modified, synthetic, conjugated and hybrid polysaccharide systems will be essential, as these categories differ substantially in their production routes, mechanisms of action, safety profiles and regulatory requirements. Such comparative frameworks will not only facilitate material selection for specific therapeutic contexts but also inform the rational design of next-generation polysaccharide-based platforms. Ultimately, the most important conceptual shift may be the recognition that a polysaccharide does not need to be classified exclusively as either a bioactive molecule or a delivery material. Its biological activity and material properties can be integrated within the same molecular or supramolecular system. This convergence may establish FMH polysaccharides as an important class of naturally derived functional immunological materials and provide a new framework for translating traditional natural resources into precision immune interventions.

Data availability

Not applicable.

Conflicts of interest

The authors declare that there are no conflicts of interest in this work. Jia-Lun Duan is an Editorial Board Member of Food & Medicine Homology, but was not involved in the processing, peer review or decision making of this article.

Acknowledgements

None.

Funding

This work is granted by National Key Research and Development Program of China (Young Scholars, No. 2025YFC3512200), National Natural Science Foundation of China (Grant No. 82405025), Natural Science Foundation of Jiangsu Province (Grant No. BK20230462, BK20240749) and CAMS Innovation Fund for Medical Sciences (2023-I2M-2-006).

Author contribution statement

Chun-Jie Bao: Writing—original draft. Yi-Xuan Liu: Writing—original draft. Mei-Xia Li: Writing—original draft. Huan Yi: Writing—original draft. Xue-Tao Li: Writing—original draft. Xiang-Wei Chang: Writing—original draft. Wei-Jia Zhang: Writing—original draft. Xian-Jin Qin: Project administration, writing—review & editing. Yi-Qun Geng: Project administration, funding acquisition, writing—review & editing. Jia-Lun Duan: Project administration, funding acquisition, writing—review & editing. All the authors have approved the final manuscript.

Informed consent

Not applicable.

Ethics statement

Not applicable.

Use of AI statement

None.

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