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Review Article

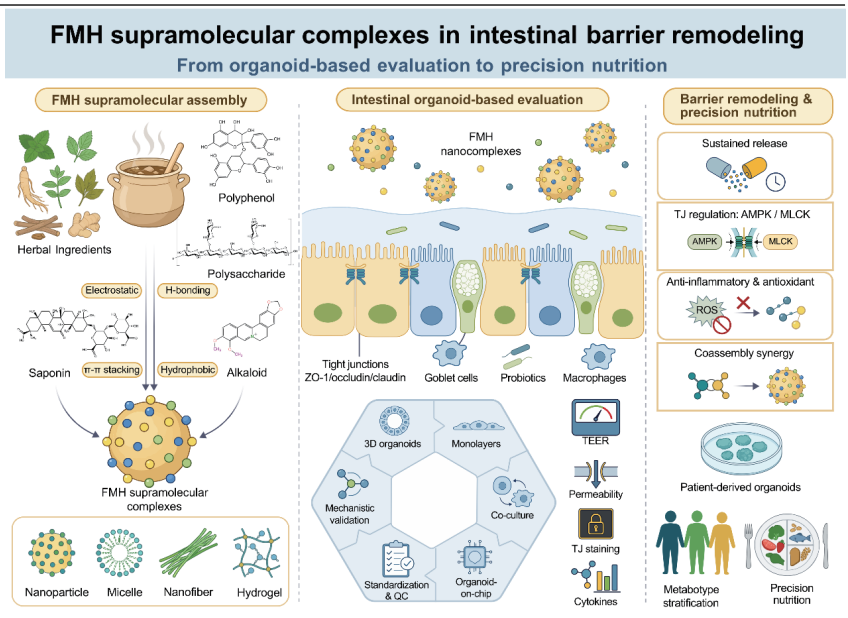
Food and medicine homology supramolecular complexes in intestinal barrier remodeling: From organoid-based evaluation to prospects for precision nutrition

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Abstract: The discovery of supramolecular complexes in traditional food and medicine homology (FMH) resources provides a modern physicochemical perspective on the potential material basis of compatibility effects. These assemblies may form during decoction through non-covalent interactions, including electrostatic attraction, hydrogen bonding, π–π stacking, and hydrophobic interactions, and may influence the stability, dispersion, release, and intestinal fate of bioactive constituents. This review distinguishes decoction-derived assemblies, carrier-free assemblies of unmodified natural constituents, engineered supramolecular formulations, and carrier-based delivery systems. It asks how composition and preparation determine assembly, how gastrointestinal digestion changes the administered structure, and whether barrier effects reflect the assembly state or altered component exposure. We connect physicochemical characterization and digestion to question-specific intestinal organoid models through a five-dimensional evaluation framework. Organoids can provide donor-specific and lineage-resolved epithelial responses, but require complementary digestion, immune, microbial, animal, and human studies. Current evidence and controls needed to test assembly-specific effects are considered in relation to future precision-nutrition applications.



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1 Introduction

The "big food" concept and national health strategies have increased attention to food and medicine homology (FMH) resources, including plant, animal, and fungal resources recognized as both food and medicine. These resources have attracted growing interest for their potential applications in nutrition and disease prevention[1]. Under this strategy, FMH resources are no longer regarded merely as dietary supplements but as functional matrices whose high-value utilization underpins the sustainable development of the agri-food industry and the improvement of public health[2]. Nevertheless, despite millennia of empirical use, the material basis of the synergistic efficacy of classical FMH formulas has never been fully elucidated, which constrains rational design and international acceptance. Therefore, it is necessary to study both the pharmacological properties of the components and the physical state of the formulation-dependent aspects simultaneously.

Traditional decoction preparation can lead to the formation of supramolecular assemblies. During decoction preparation, which is a common form of FMH practice, constituents such as polysaccharides, proteins, polyphenols, saponins, and alkaloids may interact through non-covalent forces and form aggregates ranging from the nanoscale to the microscale. These aggregates can encapsulate unstable bioactive substances, modulate solubility and release kinetics, and may constitute the synergistic material basis long sought by the theory of formula compatibility[3]. This supramolecular interpretation transforms "why decoctions are effective" from a pharmacological conjecture into an addressable physicochemical question, providing a molecular-level entry point into the classical "monarch, minister, assistant, and guide" (jun–chen–zuo–shi) theory[4]. The interactions may modify dispersion, release, and local exposure, but detecting particles alone does not establish molecular organization or explain formula efficacy[5]. Compared with conventional model systems built from purified components at defined ratios, decoctions are heterogeneous mixtures whose constituents may act simultaneously as structural building blocks and bioactive agents[6,7]. Extraction, heating, cooling, concentration, and co-decoction also change composition, making structure–function attribution especially difficult. The preparation methods and molecular interactions that reliably generate reproducible FMH-associated assemblies have yet to be clarified. Systematic evidence is also lacking on which structures or released constituents persist during gastrointestinal transit. Whether such exposure states produce barrier effects beyond those of matched free components or physical mixtures remains to be directly tested in comparative studies.

The intestinal epithelial barrier regulates host contact with luminal contents. Its dysfunction involves changes in junctional permeability, epithelial renewal, mucus, and immune–microbial interactions[8,9]. Orally administered FMH constituents first encounter the gastrointestinal environment; their intestinal effects therefore need to be interpreted in relation to the material species actually present after digestion. This makes barrier remodeling a high-value target for therapeutic and nutritional intervention, and positions the intestine as the primary site at which orally administered FMH supramolecular complexes exert their biological effects.

Conventional Caco-2 monolayers cannot recapitulate the multi-lineage diversity or crypt–villus architecture of the intestinal epithelium, limiting translational fidelity[10]. Intestinal organoids, first established from adult $Lgr5^+$ stem cells by Sato and Clevers in 2009, self-assemble into three-dimensional structures that recapitulate crypt–villus architecture, multi-lineage differentiation, and physiological barrier properties[11,12]. Their evolution into two-dimensional organoid-derived monolayers, gut-on-a-chip, and multi-organ coupled systems has bridged reductionist cell culture and *in vivo* physiology, providing a platform for studying FMH supramolecule barrier interactions. As complementary epithelial models rather than universal replacements, organoids offer luminal-surface access and feasible measurements that depend on culture configuration; no single configuration recreates digestion, a complete microbiota, systemic immunity, or whole-body pharmacokinetics.

This review traces the logical progression from organoid-based evaluation to prospects for precision nutritional intervention. We first summarize the self-assembly behavior and structural features of FMH supramolecular complexes; we then introduce a systematic, multidimensional organoid-based evaluation framework covering model classification, quantitative assessment of barrier function, complex co-culture systems, microfluidic platforms, and standardized quality control; we next elucidate the mechanisms by which supramolecular complexes remodel the intestinal barrier and the prospects for translation toward precision nutrition; and we finally conclude with challenges and future directions. By bridging traditional wisdom, supramolecular chemistry, organoid technology, and precision nutrition, this work establishes a conceptual framework for this previously unexplored interdisciplinary frontier, with important public health implications.

2 Supramolecular complexes in FMH resources: From traditional decoctions to modern characterization

We use "FMH-associated supramolecular assemblies" as an umbrella term for comparison, with four preparation-based categories. Category I denotes assemblies demonstrated in a decoction without deliberate covalent modification or an added external carrier. Category II denotes reconstructed carrier-free assemblies of unmodified natural constituents. Category III denotes engineered supramolecular formulations involving chemical derivatization, conjugation, or designed responsive modifications. Category IV denotes carrier-based delivery systems in which an external protein, polysaccharide, lipid, or synthetic material delivers a cargo. Where a hybrid spans categories, its dominant preparation attribute and additional carrier elements are reported. FMH resource status is not assigned automatically to every cited medicinal herb or derivative. Categories III and IV are used primarily as chemical or evaluation-method analogies, not as

direct evidence for native Category I structures. Table 1 summarizes these boundaries.

2.1 Natural supramolecular sources: Cooperative assembly and self-assembly in decoctions

Decoction preparation extracts constituents into a heterogeneous aqueous matrix and can promote their association during heating and cooling[6,7,21]. Gao *et al.* reviewed evidence for supramolecular structures in traditional decoctions, including colloidal dispersions and multicomponent aggregates[6]. We therefore describe decoctions as potentially containing dissolved species, colloids, and suspended material. Particle-size and concentration ranges should be attributed to specific primary measurements rather than generalized across decoctions. Structures characterized after fractionation should also be distinguished from those demonstrated in the unfractionated, consumed decoction.

Assembly can be examined at the levels of individual resources, herb pairs, and compound formulas[6,7]. However, observations of viscosity, precipitation, or colloidal scattering are insufficient to identify a defined supramolecular structure. Resource-specific assemblies require directly supporting characterization studies. Glycyrrhizic acid (GA, also termed glycyrrhizin) provides a better characterized saponin example; it must be distinguished from glycyrrhetinic acid, its aglycone[22,23].

Two examples illustrate Category I decoction-derived assemblies. Mu *et al.* investigated natural nanoparticles in Gegen–Qinlian Decoction and their effects on colonic absorption of active constituents in DSS-treated mice[13]. Nie *et al.* isolated and characterized nanoparticles from Xie-Bai-San Decoction and assessed oral bioavailability[14]. These studies support preparation-dependent colloidal material and formulation-related exposure effects, but do not prove that an intact structure reaches human epithelium or that an assembly-specific barrier mechanism has been established in human organoids.

Category II reconstructed systems allow more controlled chemical comparison. Rhubarb polysaccharide–berberine (BBR) co-assemblies were evaluated in experimental colitis, and BBR–magnolol co-assemblies were compared with individual components and a non-preassembled combination[15,16]. Reconstructing an assembly from isolated constituents helps test formulation effects, but does not itself establish that the same structure forms in the original decoction. Demonstrating compatibility-related effects requires matched composition, processing controls, and measurement of possible in situ assembly in the mixture group.

2.2 Assembly mechanisms and structural characterization: Non-covalent driving forces and dynamic features

Self-assembly of natural constituents of Chinese medicines is cooperatively driven by multiple non-covalent interactions rather than by a single force[24,25]. Constituents bearing opposite charges can form primary complex units through electrostatic attraction (e.g., cationic alkaloids with carboxyl-containing acidic constituents); the abundant hydroxyl, carboxyl, carbonyl, and amino groups in polysaccharides, polyphenols, saponins, and proteins provide hydrogen-bonding sites; natural small molecules containing aromatic rings or conjugated structures can promote ordered arrangement through π–π stacking; and hydrophobic aggregation of nonpolar backbones in aqueous phase directs hydrophobic regions inward and hydrophilic groups toward the aqueous phase, further stabilizing assembled structures such as nanoparticles, micelles, vesicles, or fibers. In general, electrostatic interactions promote the formation of primary units, while hydrogen bonding, π–π stacking, and hydrophobic interactions jointly participate in the construction and stabilization of higher-order structures. Based on the differences in assembly driving forces and structural motifs, the building blocks and interaction themes were described. We classified the dual-functional supramolecular assemblies for food and medicine into the following four subsections (Fig. 1A), which are different from the four material source categories listed in Table 1.

2.2.1 *Polyphenol–polysaccharide/protein complexes*

Polyphenolic compounds, especially condensed tannins, proanthocyanidins, and tea polyphenols containing catechol and pyrogallol groups, are a widely distributed class of active constituents in FMH resources, abundant in hawthorn, *Phyllanthus emblica*, mulberry, grape seed, green tea, and other foods. The core structural features of these polyphenol molecules, a hydrogen-bond donor/acceptor network formed by multiple phenolic hydroxyl groups and a π-electron system provided by aromatic rings, can facilitate non-covalent association with other biomolecules (Fig. 1A).

The non-covalent assembly of polyphenols with polysaccharides (pectin, cellulose, chitosan, sodium alginate) or proteins (gelatin, soy protein, whey protein) is achieved mainly through the following synergistic driving forces: (1) multiple hydrogen bonds between phenolic hydroxyl groups and polysaccharide hydroxyl groups or protein amide groups; (2) π–π stacking and hydrophobic interactions between aromatic rings and the hydrophobic regions of polysaccharides or aromatic amino acid residues of proteins; and (3) electrostatic attraction between deprotonated phenolate anions and protonated amino groups under certain pH conditions. This synergy of multiple driving forces endows the complexes with high environmental responsiveness. Minor changes in solution pH, temperature, or ionic strength can trigger reversible assembly/disassembly transitions[26](Figs. 1B and C).

A representative example is proanthocyanidin self-assembled nanospheres. Li *et al.*[27] found that proanthocyanidin oligomers extracted from grape seed can spontaneously assemble, under

Table 1 Material categories of supramolecular assemblies and evidence cases

Type	Preparation boundary	Representative evidence
I	Assemblies demonstrated in decoctions; no deliberate covalent modification or external carrier	Gegen–Qinlian and Xie-Bai-San particles[13, 14]
II	Carrier-free assembly of unmodified natural constituents reconstructed under defined conditions	Rhubarb polysaccharide–BBR[15]; BBR–magnolol[16]
III	Engineered assembly after conjugation, derivatization, or designed responsive modification	COS-GL conjugate[17]; multilayer curcumin with carrier elements[18]
IV	External material acts as a cargo carrier	Zein-based β-carotene[19]; polydopamine delivery platform[20]

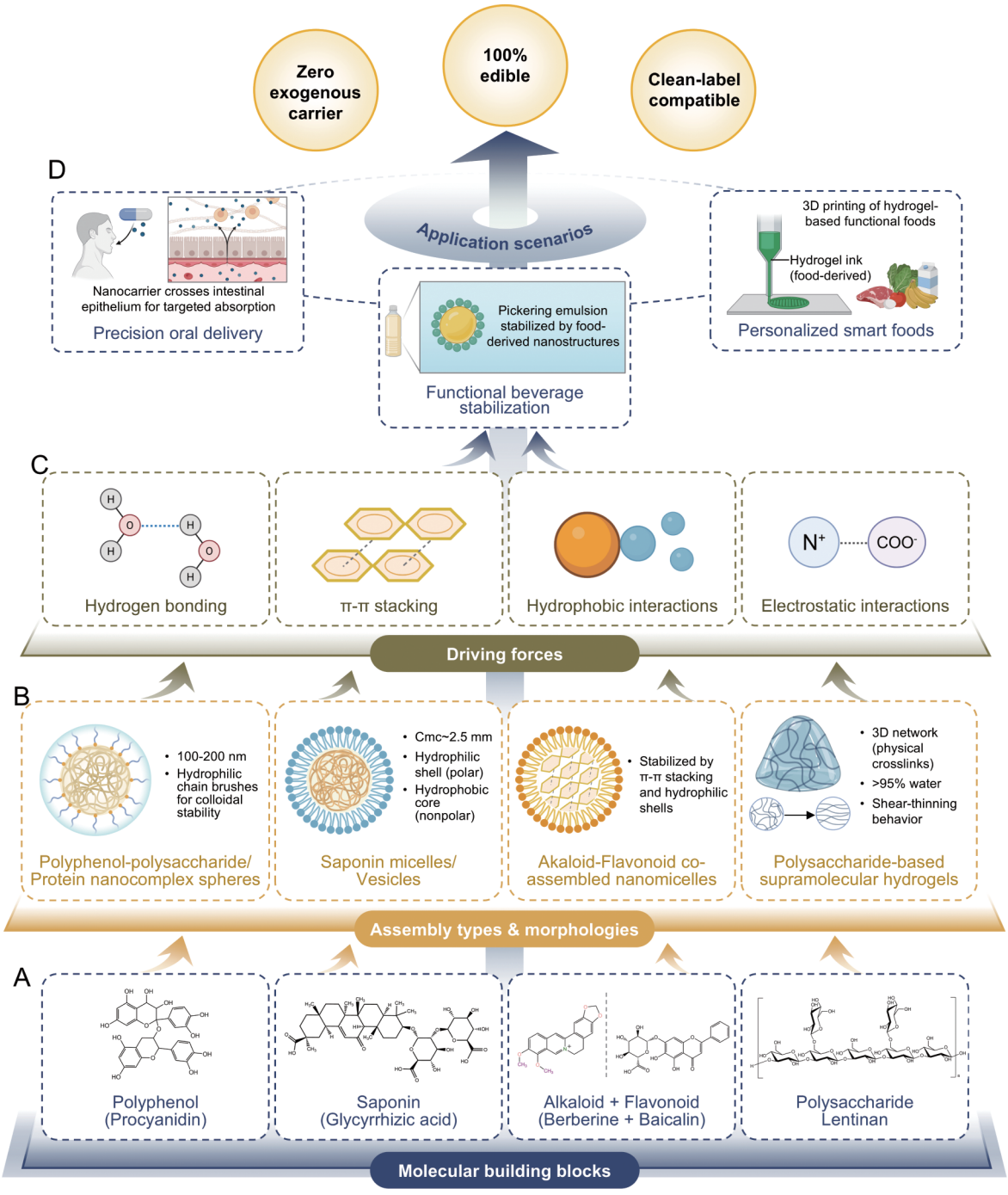


Figure 1 Supramolecular assembly framework related to FMH, from molecular building units to oral application scenarios. (A) Typical FMH active components of supramolecular assembly, including polyphenols, saponins, alkaloids-flavonoids complexes, and polysaccharides. (B) Illustrates four supramolecular assembly forms: Polyphenol-polysaccharide/protein nano-composite spheres, saponin microgel/capsules, alkaloid-flavonoid co-assembled nano-gel, and polysaccharide-based supramolecular hydrogel. (C) Summarizes the four core non-covalent driving forces maintaining the assembly structure: Hydrogen bonds, π-π stacking, hydrophobic interactions, and electrostatic interactions. (D) The three main major application scenarios of this edible supramolecular system, among which precise oral drug delivery aims to enable the nanocarriers to penetrate the intestinal epithelium and promote targeted absorption of the active components. The raw materials of the entire system are all natural dietary components, without exogenous carriers, and compatible with clean labels. This is only a conceptual overview and does not represent the regulatory approval or safety of each separated component or formulation.

specific concentration and pH conditions, into uniform nanospheres of approximately 130 nm with PDI < 0.2 through π–π stacking and intermolecular hydrogen bonding. These nanospheres are injectable and exhibited excellent intra-articular retention and sustained anti-inflammatory effects in an animal model of osteoarthritis. Another notable case is the tea polyphenol–gelatin nanocomplex: Under mild conditions near the isoelectric point of gelatin, epigallocatechin gallate (EGCG) crosslinks with gelatin polypeptide chains through multiple hydrogen bonds to form nanocomposite particles with controllable size (80–300 nm); the encapsulation efficiency for EGCG can reach as high as over 80%, and the particles show marked gastric stability in simulated digestive fluids[28] (Figs. 1B and C).

2.2.2 Saponin-based amphiphilic assemblies

Saponins are a class of naturally occurring amphiphilic molecules in FMH resources, formed by covalent linkage of a hydrophobic triterpenoid or steroidal aglycone core with a hydrophilic sugar chain. This structural feature endows saponin molecules with the essence of surfactants, enabling them to spontaneously form a variety of ordered assembled structures in aqueous solution, such as micelles, vesicles, and liquid-crystalline phases. In the FMH field, GA and ginsenosides are the most representative saponin-based natural supramolecular building blocks (Fig. 1A).

GA is an amphiphilic saponin with condition-dependent self-assembly. Studies report adsorption and association at interfaces, fibrillar assemblies, and gel-like structures; morphology depends on concentration, pH, ionic conditions, temperature, and preparation history[22, 23, 29-33]. Tucker *et al.* investigated GA adsorption and self-assembly, Cai *et al.* examined interfacial assembly and rheology, and Trindade *et al.* characterized GA nanofibrils and reversible temperature-dependent structural changes[22, 23, 30]. Li *et al.* discuss GA assemblies in multiphase foods[31]; the recent reviews by Xiao *et al.* and Wang and Wang place GA hydrogels within biomedical and natural-extract assembly research[32, 33]. These reviews broaden the context, while the primary studies support specific structural observations (Figs. 1B and C).

GA gelation and interfacial activity suggest applications in food structuring and delivery, but those functions do not establish intestinal-barrier repair. Zhao *et al.* investigated a GA-based hydrogel with digestive-tract-responsive behavior[29], illustrating why pre-dose morphology must be reconsidered after digestion. Ginsenoside-based delivery systems are related saponin examples discussed in the broader natural-product literature[28]. Their ability to carry or protect other molecules is formulation-specific and requires separate evidence for digestion behavior, epithelial exposure, and biological activity.

2.2.3 Alkaloid–flavonoid co-assemblies

Supramolecular co-assembly of alkaloids and flavonoids represents the most classic and most thoroughly studied class in FMH self-assembly systems. The core driving force of this assembly mode is the electrostatic neutralization reaction between the quaternary ammonium cations (N^+) of alkaloid molecules and the carboxylate anions (COO^-) of flavonoid glycoside molecules; the resulting primary ion pairs, driven synergistically by hydrophobic interactions and π–π stacking, further assemble into supramolecular ordered structures with well-defined nanostructures[7, 34] (Fig. 1A).

The most representative system is the co-assembly of BBR and baicalin (BA). Yang *et al.*[34], through systematic spectroscopic analysis and molecular dynamics simulations, revealed the assembly mechanism of this system: The quaternary ammonium N^+ of BBR and the COO^- of the glucuronic acid moiety of BA first form a 1:1 ion pair; the isoquinoline aromatic ring of BBR and the flavonoid core of BA are stabilized by π–π stacking, while the hydrophilic glucuronic acid moieties of BA are distributed toward the aqueous phase. This curvature feature of "hydrophilic outside, hydrophobic inside" drives BBR–BA ion pairs to further aggregate through hydrophobic interactions into nanomicelles approximately 200 nm in diameter. Field-emission scanning electron microscopy (FESEM) confirmed that these spherical nanomicelles carry abundant negative surface charge (zeta potential approximately −25 mV), which favors colloidal stability through electrostatic repulsion (Figs. 1B and C).

An important reported feature of BBR–BA nanomicelles is their enhanced pharmacological activity. Antibacterial experiments showed that, compared with an equivalent dose of BBR monomer, BBR–BA nanomicelles increased antibacterial activity against *Staphylococcus aureus* and *Escherichia coli* by 3–8-fold. This antibacterial enhancement stems from the hydrophilic surface of the nanomicelles, which more readily engages in multivalent interactions with the bacterial outer membrane, causing a sharp local increase in drug concentration at the bacterial membrane and promoting the disintegration of mature biofilms[34]. Zhang *et al.*[35] further confirmed that the BBR–BA complex exerts significant protective effects on PC12 neuronal cells injured by $CoCl_2$, and that this protective effect derives from the sustained-release property of the nanomicelles rather than from simple superposition of the two monomers (Figs. 1B and C).

It is worth noting that the naturally occurring alkaloid, flavonoid pairings in food, medicine homology foods are far richer than any single model. The co-decoction system of Coptis (containing BBR, palmatine, and coptisine) with Scutellaria (containing BA and wogonoside), the combined formulation of Phellodendron bark with mulberry leaf, and even the everyday dietary combination of tea (containing caffeine) with hawthorn (containing flavonoids) can all be regarded as natural alkaloid, flavonoid co-assembly reactors, these everyday dietary practices, at the molecular level, embody precisely the intricate logic of supramolecular chemistry.

2.2.4 Oligosaccharide/polysaccharide-based supramolecular hydrogels

Polysaccharides are not only the most abundant macromolecular constituents in FMH resources but also natural building blocks for constructing three-dimensional supramolecular networks. Unlike the first three classes, whose assembly morphologies are dominated by nanoparticles or micelles, the typical product of polysaccharide-based supramolecular systems is the hydrogel, a three-dimensional network structure formed by polysaccharide chain segments through non-covalent crosslinking, with a water content as high as over 95% (Figs. 1A and B).

Among FMH polysaccharides, lentinan (*β*-1,3-glucan with a triple-helical conformation), *Astragalus* polysaccharide (a heteropolysaccharide rich in glucose and arabinose), and *Tremella* polysaccharide (an acidic heteropolysaccharide) are the most representative candidates with supramolecular gelation potential. Zhao *et al.*[36] reported a highly instructive case: *Astragalus* polysaccharide can spontaneously form a physically crosslinked supramolecular hydrogel under appropriate concentration and temperature conditions. The shear-thinning property of this hydrogel confers good injectability; after implantation at the wound site, the gel matrix gradually releases the loaded active constituents through degradation by MMP enzymes in the local microenvironment, while the immunomodulatory activity of *Astragalus* polysaccharide itself provides synergistic support for wound healing. In a full-thickness skin defect model in diabetic rats, the wound closure rate in the *Astragalus* polysaccharide supramolecular hydrogel-treated group reached 92% on day 14, significantly higher than that of the control group. The supramolecular gelation of lentinan, by contrast, is achieved through a different mechanism. In aqueous solution, the triple-helical conformation of lentinan can undergo

conformational transitions (helix→coil→gelation) during heating, cooling cycles, and the resulting physical gel possesses good thermal reversibility, a property that makes lentinan hydrogels an ideal controlled-release matrix for thermosensitive functional constituents. Interestingly, the degradation of lentinan hydrogels responds specifically to β-glucanase secreted by the gut microbiota, providing a natural design rationale for colon-targeted co-delivery of prebiotics and active constituents (Figs. 1B and C).

It is worth emphasizing that the greatest advantage of polysaccharide-based supramolecular hydrogels lies in their dual functionality, the gel matrix is not merely a "carrier" but is itself an "active constituent" (e.g., immunomodulation, prebiotic effects, and regulation of the gut microbiota). This integrated design concept of "carrier-as-active-ingredient" fully conforms to the principle of "minimal processing, maximal efficacy" in functional food development and is highly consistent with the core spirit of clean labeling.

2.3 Structure–function overview: Structural parameters linked to biological effects

When an active constituent transitions from the free state to the assembled state, new structural features are generated beyond the original chemical composition, including particle size, morphology, surface charge, and the spatial distribution of constituents. These parameters collectively influence the dispersion stability of assemblies in aqueous phase, their interactions with biological interfaces, and the loading and release of active constituents; therefore, the biological effects of assemblies cannot be explained solely on the basis of their monomeric constituents.

Existing studies suggest that different structural features may correspond to different biological behaviors. The natural polysaccharide assemblies in Coptis decoction, approximately 100–500 nm in size with a negatively charged surface, can promote the intestinal absorption of BBR, suggesting that nanoscale size and surface properties may participate in its trans-epithelial transport[37]. In BBR co-assembly systems, BA–BBR forms spherical nanoparticles whereas wogonoside–BBR forms nanofibers, and the two exhibit different antibacterial properties, suggesting that molecular packing, microscopic morphology, and surface group exposure can alter the interaction of assemblies with bacteria[38]. Sub-200 nm aggregates tend to undergo transcytosis; larger aggregates may be retained in the mucus layer and exert paracrine signaling effects; positive charge enhances adhesion but may also disrupt membrane structure.

Based on the molecular building blocks and the multilevel self-assembled structures driven by non-covalent forces described above, natural FMH supramolecular systems ultimately serve the core application scenario of oral intestinal delivery. Natural small molecules as building blocks form four types of typical supramolecular assembly morphologies. Assembly is driven by hydrogen bonds, π-π stacking, hydrophobic interactions, and electrostatic interactions in synergy. Ultimately, they are oriented towards three application directions: Precise oral absorption, food stability systems, and intelligent edible materials. Among these, precision oral delivery is directly related to the *in vivo* effects of Chinese medicine decoctions: Natural supramolecular nanocarriers traverse the intestinal epithelial barrier to achieve targeted absorption of active constituents, representing the core pathway by which assemblies in decoctions exert oral biological activity (Fig. 1D).

However, because particle size, morphology, surface properties, and internal composition are usually interrelated, it remains difficult to simply attribute a given biological effect to a single structural parameter. Establishing quantifiable, comparable structure–function relationships still requires validation through more systematic structural characterization and controlled experiments[39]. At the present stage, *in vitro* monolayer cell models cannot readily simulate the complex epithelial structure, cellular heterogeneity, and mucus barrier of the intestine; animal models exhibit species differences and cannot dynamically observe trans-epithelial transport. Therefore, establishing a standardized intestinal organoid evaluation system to quantify the intestinal mucus penetration, epithelial barrier interactions, transcytosis, and intestinal cell responses of different supramolecular assemblies can build a direct bridge from supramolecular microstructure, intestinal-interface biological behavior, and *in vivo* oral efficacy, remedying the current shortcomings in structure–activity relationship research and providing a key evaluation tool for systematically dissecting the oral mechanisms of supramolecular assemblies in FMH compound decoctions.

2.4 Gastrointestinal evolution of FMH-associated assemblies

An administered assembly can undergo disassembly, reassembly, aggregation, constituent exchange, or conversion into other colloidal structures as pH, dilution, ions, bile, enzymes, and food-derived digestion products change. These are candidate processes to be tested in each formulation, not established trajectories shared by all decoction particles[5, 40]. The GA digestive-responsive hydrogel study illustrates formulation-dependent behavior[29]. Structural persistence cannot be inferred from unchanged mean particle size because digestion products may produce a similar scattering signal[5].

A practical approach couples standardized sequential digestion, such as INFOGEST, to orthogonal material analysis[5, 40, 41]. Chemical mass balance and constituent recovery should accompany size distribution, microscopy, and, where feasible, scattering or spectroscopic evidence of organization. Sampling after gastric and intestinal stages should distinguish soluble constituents, persisting particles, new aggregates, and exchanged components[40]. Fluorescent labels require free-dye and label-dissociation controls. Gastric stability alone is insufficient to establish intact intestinal exposure[40].

Characterized digesta can then be tested in apical-out organoids or organoid-derived monolayers with digest-only, vehicle, toxicity, and matched constituent controls[42-44]. Bile and enzymes can injure cells, so dilution or fractionation must be justified and the resulting exposure re-characterized[45]. Correlating post-digestion material species with permeability, junction localization, mucus, and viability makes the connection between assembly chemistry and barrier biology explicit.

3 Intestinal organoids: A systematic multidimensional evaluation system for the barrier effects of FMH supramolecules

The intestinal epithelial barrier is the first line of defense of the body against luminal contents, including food-derived bioactive compounds, microbial metabolites, and exogenous substances. FMH supramolecular complexes, the intestinal barrier is not only a physical obstacle but also an active interface at which these nanoscale self-assembled aggregates exert their core biological effects. Unlike conventional small-molecule drugs or simple plant

extracts, FMH supramolecular complexes possess characteristics such as hierarchically self-assembled structures, multi-component synergistic actions, and stimulus-responsive disassembly kinetics; therefore, the evaluation platform must be able to precisely capture the spatiotemporal behavior of the complexes at the epithelial interface[46-48]. Intestinal organoids can resolve epithelial responses by donor, intestinal segment, lineage, and tissue organization[44, 49, 50]. For assembly–function studies, their specific contribution is to test whether matched exposure states produce different mucus, junctional, viability, and regeneration phenotypes in primary epithelium. As physiologically relevant *in vitro* surrogate models, organoids bridge the gap between conventional cell lines and animal models and have become the core platform for evaluating the regulation of intestinal barrier function by FMH supramolecular complexes[46, 51, 52]. Here, we systematically elaborate the multidimensional organoid system for evaluating the barrier effects of FMH supramolecules from five dimensions: Model classification and construction, quantitative barrier-detection techniques, complex co-culture systems, microfluidic organoid-on-a-chip platforms, and standardization and quality control.

3.1 Classification, construction, and application scenarios of organoid models for supramolecular evaluation

Intestinal organoids are a family of *in vitro* models defined jointly by cell source and culture configuration: The former determines the donor background, intestinal-segment characteristics, and cellular composition, whereas the latter determines the side of the epithelium that contacts the sample, the mode of administration, and the barrier parameters that can be measured. A rational match between the two is a prerequisite for establishing a reliable evaluation system for FMH supramolecules.

3.1.1 Source-based classification of intestinal organoids and their applicability in FMH supramolecular research

Adult stem cell (ASC)-derived intestinal organoids (small-intestinal enteroids and colonic colonoids) are established by embedding $Lgr5^+$ intestinal stem cells in Matrigel, with the culture medium containing a defined combination of growth factors including R-spondin-1, epidermal growth factor (EGF), Noggin, and Wnt pathway activators[46, 47]. This type of organoid has a relatively short culture period, can generate the major cell lineages corresponding to the harvested intestinal segment, retains regional specificity, and possesses long-term genomic stability, and is regarded as the gold standard for recapitulating adult intestinal physiology and patient-specific responses[47, 48]. For FMH evaluation, ASC-derived organoids are particularly suited to donor-/patient-specific barrier-function assessment, for example, organoids derived from patients with inflammatory bowel disease (IBD) can be used to test whether a particular supramolecular formulation can restore barrier function against the disease genetic background[43, 47, 48](Fig. 2A).

Pluripotent stem cell (PSC)-derived organoids are established from embryonic stem cells or induced PSCs through successive differentiation stages, including definitive endoderm, hindgut, and intestinal tissue, and can contain non-epithelial lineages such as mesenchyme; however, their transcriptional programs more closely resemble the fetal state, and the differentiation protocols are longer and more complex, with greater batch-to-batch variation[48, 53]. PSC systems have unlimited proliferative capacity and are amenable to genetic engineering, making them suitable for developmental-stage studies and large-scale biomanufacturing, and they can be used for large-scale high-throughput screening of FMH supramolecular activity[46, 48, 53, 54]. Mature epithelial responses, donor differences, and segmental differences are usually represented by ASC-derived or patient-derived organoids (PDOs), whereas developmental processes, epithelial–mesenchymal interactions, and engineered modification are better suited to PSC systems. When evaluating the effects of FMH supramolecular complexes on differentiated mature barrier function, ASC-derived organoids should be preferred; PSC-derived systems, by contrast, are advantageous for developmental studies, genetic modification, and standardized high-throughput platforms[46, 48, 49, 53, 54] (Fig. 2A).

3.1.2 Question-driven selection of organoid culture configurations

The organoid models should be regarded as complementary tools for addressing different scientific issues, rather than a sequential hierarchy based on technical complexity. The choice of organoid models should be determined by the research question, rather than the complexity of the platform (Table 2).

Conventional 3D organoids are usually embedded in an extracellular matrix and form closed structures with a central lumen, crypt-like budding, and differentiated epithelial regions. They best preserve intercellular spatial connections and are suitable for observing tissue-level morphological and differentiation changes; however, their apical surface lies within the closed lumen, which physically limits direct drug administration and barrier detection, and test compounds usually have to be injected by microinjection[44, 55, 56]. When the question concerns direct luminal-side exposure, some protocols induce eversion of epithelial polarity after matrix removal and suspension culture, generating apical-out organoids that retain three-dimensional tissue morphology while exposing the apical membrane directly and enabling compound–epithelium contact without microinjection[44, 55, 56]. Apical-out organoids thus allow direct luminal-side contact in a 3D configuration[57] (Fig. 2B).

Organoid-derived 2D monolayers open separate apical and basolateral compartments and support transepithelial electrical resistance (TEER), tracer flux, and directional transport measurements, making them the configuration of choice for quantitative permeability and junction-recovery endpoints[44, 57]; their trade-off is reduced spatial organization relative to 3D tissue. Dynamic organoid-on-chip systems are selected when flow, residence time, mechanical stimulation, or controlled oxygen is part of the question, enabling controlled continuous exposure at the cost of device losses, lower throughput, and greater technical complexity (Fig. 2B).

These configurations are complementary rather than hierarchical: Monolayers sacrifice some spatial organization, apical-out models do not inherently provide a separately sampled basolateral chamber, and chips add dynamic control at the expense of throughput. Caco-2 monolayers remain useful for reproducible preliminary permeability and concentration-range studies, although their transformed background and limited lineage diversity constrain physiological interpretation[42, 44]. Primary organoid systems add donor and lineage information at greater cost and with more biological variation. A comparative study should therefore select models by the endpoint and validation requirement rather than assume that the most complex model is the most accurate for every task.

In FMH evaluation, these models can be used as complementary modules within a tiered strategy: Caco-2

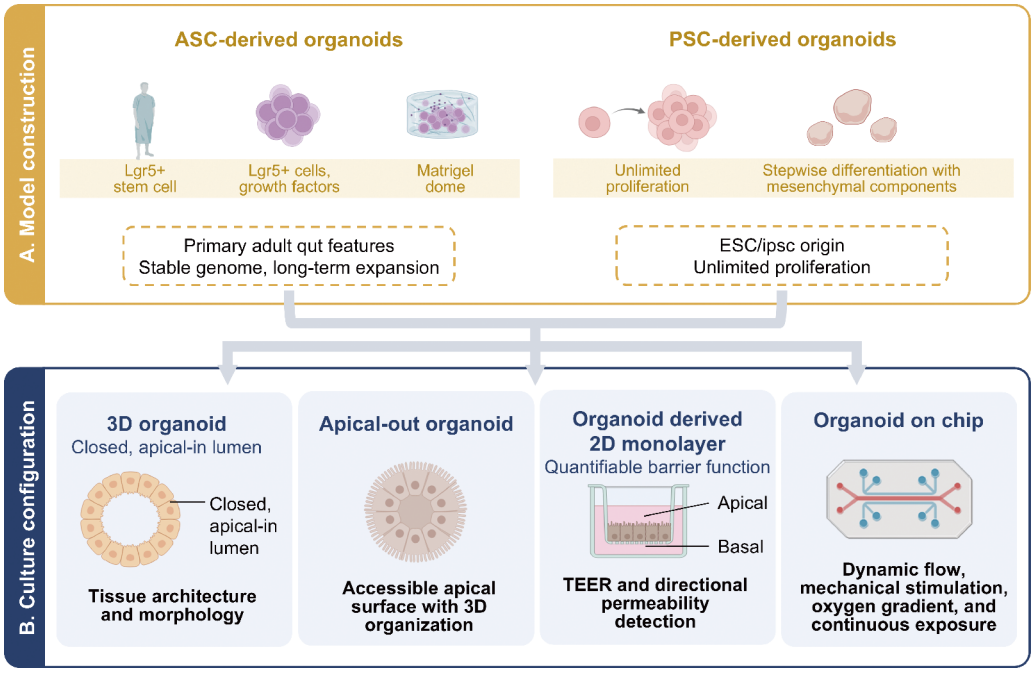


Figure 2 Intestinal organoid model for evaluating the functional supermolecular complexes derived from FMH. (A) Organoids derived from ASCs retain the adult intestinal characteristics and stable genome specific to the donor/patient, suitable for evaluating the donor-specific FMH barrier; organoids derived from PSCs can proliferate indefinitely, are easy to genetically edit, and are compatible with high-throughput screening. (B) Four types of organoid culture models: Three-dimensional organoids in closed chambers are used for morphological and long-term effect studies; organoids growing upward and outward are used for direct contact with compounds; 2D single-layer cells derived from the organoids are used on Transwell for quantitative barrier function analysis (TEER, FITC-dextran/fluorescein yellow permeability) and high-throughput screening. Organoids on the chip can simulate dynamic fluid, mechanical stimulation, oxygen gradients, and continuous exposure.

Table 2 Organoid configurations recommended by research question, with main strengths and limitations

Research question	Model	Main strength	Main limitation
Architecture and renewal	Conventional 3D	Tissue organization and lineage information	Closed apical lumen; exposure/sampling constraints
Direct luminal contact	Apical-out 3D	Accessible apical surface with 3D organization	No separated basolateral sampling; polarity QC
Barrier permeability and transport	Organoid-derived 2D	TEER and directional tracer or constituent flux	Reduced spatial organization; differentiation dependence
Flow residence time or mechanical cues	Organoid-on-chip	Controlled dynamic exposure; optional oxygen/strain	Device losses, cost, scaling and lower throughput

monolayers take charge of concentration-range exploration and preliminary permeability screening; organoid-derived monolayers provide mechanistic confirmation of barrier function; conventional 3D or apical-out organoids support tissue-level observation of morphology, mucus secretion, and long-term effects; and animal-model validation is added when whole-organism confirmation is necessary[44, 46]. Finally, whatever the configuration, organoid readouts identify epithelial responses rather than supramolecular structure: Neither fluorescence nor a barrier phenotype confirms that an intact assembly reaches the epithelium. Composition-matched controls, measured exposure, post-digestion structural analysis, and perturbation of candidate pathways are required to link epithelial effects causally to assembly.

3.2 Core quantitative detection techniques for intestinal barrier function

In *in vitro* models, changes in the intestinal barrier are mainly observed through the ability of substances to cross the epithelium, mucus coverage, and the status of epithelial cells. The rise or fall of a single tight junction protein or inflammatory factor provides only fragmentary information; a multidimensional readout combination covering the physical, biochemical, and immune-inflammatory layers of the barrier is needed [58, 59] (Fig. 3).

3.2.1 *Assessment of epithelial tight junction integrity*

The paracellular pathway is regulated by the apical junctional complex, in which tight junctions (TJs), composed of transmembrane proteins (claudins, occludin, tricellulin) and cytoplasmic scaffold proteins (zonula occludens, ZO-1/2/3), exert multifunctional molecular gating[60]. Paracellular transport occurs through two distinct pathways, the pore pathway, mediated by claudin channels with size and charge selectivity, and the regulated leak pathway, which accommodates larger molecules, both of which can be modulated by inflammatory cytokines and dietary bioactive compounds[42, 61].

TEER and tracer permeability reflect the epithelial barrier from the perspectives of ionic conductance and molecular crossing, respectively. TEER is suitable for real-time, label-free monitoring of monolayer ionic conductance on Transwell membranes or chip interfaces and is the gold standard for evaluating barrier integrity[43, 44, 60, 61]. However, it should be noted that TEER reflects the overall ionic permeability state of the epithelium; resistance changes may arise from tight junction rearrangement but can also

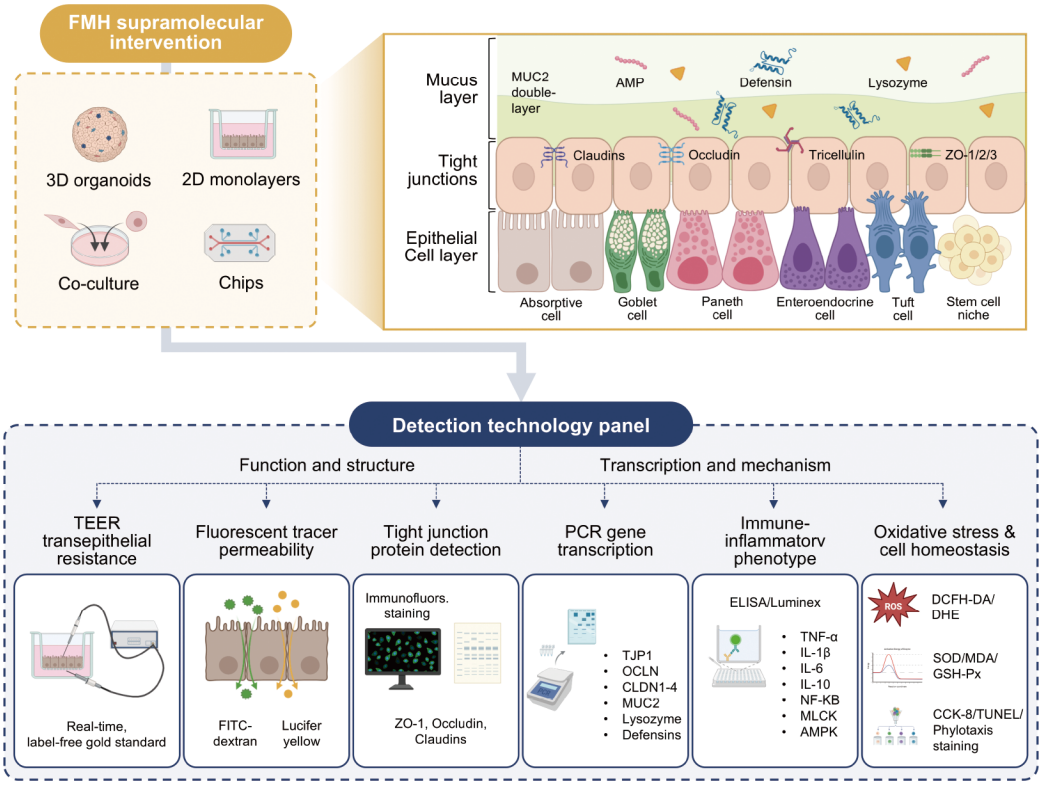


Figure 3 The multi-dimensional quantitative detection panel for evaluating the intestinal barrier function of FMH supramolecular complexes. The FMH supramolecular formulation can be applied to four complementary intestinal organoid platforms: Three-dimensional organoids, two-dimensional monolayers, co-culture systems, and microfluidic chips. The intestinal barrier is depicted as a three-layer structure: Mucus layer (MUC2, antimicrobial peptides, defensins, lysozyme), tight junction network (claudins, occludin, tricellulin, ZO-1/2/3), and epithelial cell layer (absorptive cells, goblet cells, Paneth cells, endocrine cells, cluster cells, and stem cell niches). The six detection modules connect the anatomical structure of the barrier with functional/mechanism readings: TEER transepithelial resistance (real-time unlabeled, ionic conductance, gold standard for barrier integrity), fluorescent tracer permeability (FITC-dextran quantitative leakage pathway, Lucifer yellow detection pore pathway), tight junction protein molecule detection (immunofluorescence assessment of continuity of the junction belt, Western blot precise quantification, ZO-1/occludin/claudins target protein spectrum); gene transcription qPCR (TJP1/OCLN/CLDN1–4 barrier genes, MUC2/lysozyme/defensin mucin genes), immune inflammatory phenotype (cytokine ELISA/Luminex multiplex detection, TNF-α/IL-1β/IL-6/IL-10, NF-κB/MLCK/AMPK pathways), oxidative stress and cell homeostasis (ROS probe DCFH-DA/DHE, SOD/MDA/GSH-Px enzyme activity, CCK-8/TUNEL/lineage staining).

be affected by cell density, transcellular ion transport, and cell damage, and therefore need to be interpreted in combination with other readouts[43,44]. Tracer flux assays use size-graded fluorescent tracers, 4 kDa FITC-dextran for the leak pathway and Lucifer yellow for the pore pathway, providing molecular-scale information complementary to TEER[44,61]. Tight junction proteins provide structural evidence for functional changes: Immunofluorescence of ZO-1, occludin, and different claudin subtypes can reveal whether the junctional belt is continuous, while immunoblotting and transcriptomics provide quantitative expression data[44,60,61] (Fig. 3). For FMH supramolecular complexes, their protective or restorative effects are manifested as maintenance of TEER, reduced FITC-dextran flux, and maintained or upregulated expression of ZO-1 and occludin under inflammatory stimulation (e.g., TNF-α/IFN-γ) [43,44,61].

3.2.2 Assessment of intestinal mucosal secretory function: Mucus barrier and antimicrobial defense

The mucus layer constitutes the first biochemical barrier of the intestine. In the colon, the gel-forming mucin MUC2 secreted by goblet cells forms a two-layer mucus system, a dense, bacteria-impermeable inner layer and a loose outer layer that accommodates the commensal microbiota[62]. Mucus dysfunction (reduced MUC2 production, altered glycosylation, or goblet cell depletion) is a hallmark change in IBD and is increasingly regarded as a target of dietary intervention[59,62]. In organoid models, the mucus barrier is evaluated by the following methods: (1) quantification of goblet cell numbers and MUC2 expression by periodic acid–Schiff (PAS)/Alcian blue staining, immunofluorescence, and single-cell transcriptomics; (2) measurement of secreted mucin levels in conditioned medium (ELISA, mass spectrometry); and (3) assessment of mucus thickness and penetrability in 2D monolayer or apical-out configurations[44,59,62] (Fig. 3). Secretions in conventional 3D organoids tend to accumulate in the closed lumen, which is suitable for observing goblet cell differentiation and luminal mucus changes but limits continuous sampling; 2D monolayers facilitate kinetic sampling but have limited mucus accumulation. Because standard intestinal organoids are dominated by enterocytes with a relatively low proportion of goblet cells, differentiation protocols induced by Notch inhibition (e.g., DAPT) or specific microenvironmental factors are usually required to obtain mucus-producing models suitable for evaluating mucus-targeting FMH compounds[59,62].

The small-intestinal barrier also includes antimicrobial peptides produced by Paneth cells (defensins, lysozyme, RegIII proteins). Immunostaining can reveal the presence and distribution of Paneth cells, whereas transcriptional and immunological assays (qPCR, ELISA) reflect the production levels of the relevant antimicrobial molecules[56,59]. For FMH evaluation, Paneth cell

abundance and antimicrobial output are sensitive indicators that can reflect whether supramolecular complexes maintain the antimicrobial arm of the chemical barrier and preserve epithelial homeostasis under stress conditions[56, 59].

3.2.3 *Assessment of intestinal epithelial cell homeostasis*

Barrier readouts need to be understood in the context of epithelial cell status, extensive cell death, epithelial shedding, or marked changes in lineage proportions can all affect TEER, tracer flux, and junctional protein signals. Absorptive cells, goblet cells, Paneth cells, enteroendocrine cells, and stem/progenitor cells can be localized and quantified using their corresponding markers (villin, MUC2, lysozyme, chromogranin A, Lgr5, etc.)[47, 56, 59]. Morphological parameters of 3D organoids, such as budding, lumen, and wall thickness, reflect tissue-level homeostasis. Cell viability and apoptosis can be assessed by ATP/metabolic activity assays (CCK-8), membrane-integrity dyes, Annexin V and nucleic acid dyes, TUNEL staining, and live/dead cell imaging[55, 59]. Oxidative stress, elevated reactive oxygen species (ROS) accompanied by depletion of SOD and GSH-Px and elevation of MDA, is another convergent mechanism by which pro-inflammatory stimuli and food-derived oxidants impair junctional integrity; it can be examined with ROS fluorescent probes such as DCFH-DA to visualize the control-verified relative oxidation-sensitive signal and its spatial distribution, combined with measurements of SOD, MDA, and GSH-Px activities[58, 63] (Fig. 3).

3.2.4 *Inflammatory responses of the organoid epithelium and mechanistic validation*

Barrier function is closely related to the immune-inflammatory state of the epithelium. Cytokines such as TNF-α, IFN-γ, and IL-13 directly regulate TJ expression and internalization through signaling cascades such as MLCK and NF-κB, whereas anti-inflammatory mediators such as IL-10 promote barrier repair[58, 61]. Conventional ASC-derived organoids mainly reconstruct the epithelium and can present epithelial cell responses to inflammatory factors or microbe-associated stimuli, and can also detect chemokines and some cytokines released by the epithelium. Immuno-inflammatory phenotypic analysis includes: (1) cytokine/chemokine profiling of conditioned medium (multiplex ELISA, Luminex); (2) pathway-activation analysis, immunoblotting and imaging of phosphorylated NF-κB p65, p-MLCK, and STAT signaling; (3) detection of oxidative stress markers; and (4) epithelial stress transcriptional signatures (endoplasmic reticulum stress, apoptosis), bulk or single-cell RNA sequencing[44, 58, 61, 63] (Fig. 3).

The interpretation of inflammatory outcomes also depends on the source of the stimulus: TNF-α or IL-1β can be used to establish a background of barrier injury; when the same factor has already been added externally to the culture system, detection of that factor in the culture supernatant is of limited value. Candidate mechanisms can be progressively narrowed down from the functional phenotypes that emerge, temporal relationships, and existing studies, against backgrounds such as inflammatory barrier injury, energy metabolism, or cytoskeletal rearrangement, the NF-κB, Nrf2, AMPK, and MLCK/ROCK pathways are priority targets for validating the mechanisms of action of FMH supramolecular complexes[58, 61, 63]. In this context, dietary alkaloids such as BBR have been confirmed to maintain junctional integrity through a combined mechanism of antioxidant, anti-inflammatory, and microbiota-regulating actions, exemplifying the multi-target mode of action expected of FMH compounds[64, 65].

3.3 Complex co-culture organoid evaluation systems

Organoids dominated by the intestinal epithelium are suitable for observing TJs, mucus secretion, and injury repair, but cannot present barrier changes under the continuous participation of luminal microorganisms and the mucosal immune system. Introducing non-epithelial components such as microorganisms and immune cells can extend the organoid platform into an integrated model of host, microbe, immune interactions, which is crucial for evaluating FMH supramolecular complexes that exert biological activity through microbial or immune mediators[66-68].

3.3.1 *Organoid–probiotic co-culture and prebiotic intervention systems*

Probiotics (e.g., *Lactobacillus*, *Bifidobacterium*) and their metabolites regulate barrier function through multiple mechanisms, including strengthening TJs, inducing mucin secretion, and competing with pathogens[66, 67]. In organoid systems, probiotic co-culture is achieved by: (1) microinjection into the lumen of 3D organoids; (2) apical seeding on organoid-derived monolayers; or (3) incubation with apical-out organoids[56, 66, 67]. Quantitative readouts include bacterial viability and adhesion, epithelial TEER and permeability, TJ and mucin gene expression, and secretion of short-chain fatty acids (SCFAs) and cytokines [66, 67]. Notably, organoid models have revealed that the barrier-protective effects of specific probiotic strains cannot always be recapitulated by cancer cell lines, highlighting the necessity of evaluating FMH–probiotic combinations based on primary epithelium[66, 67] (Fig. 4A).

Unlike probiotics, which are living co-culture partners, prebiotics mainly enter the model as intervention substrates utilizable by microorganisms, and their study involves at least two types of actions: One is serving as microbial fermentation substrates (e.g., polysaccharides metabolized by the microbiota into SCFAs); the other is direct effects on the epithelium or microorganisms. After FMH supramolecular complexes enter this system, changes on both the microbial and epithelial sides need to be observed simultaneously: On the microbial side, attention is paid to strain retention, contact with the epithelium, and metabolic output; on the epithelial side, attention is paid to barrier parameters and mucin expression[56, 66, 67]. Studies showing that *Limosilactobacillus reuteri* affects intestinal epithelial stem cell maintenance and post-injury regeneration suggest that probiotic–epithelial interactions also involve stem cell niche regulation, expanding the observational dimensions of FMH–probiotic synergy evaluation[56, 67].

3.3.2 *Organoid–intestinal immune cell co-culture models*

The relationship between the intestinal epithelium and immune cells is not a unidirectional inflammatory stimulation, macrophages can participate in barrier support, phagocytic clearance, and injury repair, while T cells and intraepithelial lymphocytes play roles in maintaining immune surveillance and tolerance[69]. Organoid, immune co-culture strategies can be divided into two architectures: (1) "outside-in" reconstruction, adding immune cells (macrophages, T cells, NK cells, intraepithelial lymphocytes) to the basolateral compartment of 2D monolayers, or co-embedding them with 3D organoids in Matrigel; and (2) "inside-out" approaches, retaining endogenous immune cells within patient-derived tumor organoids[69]. The spatial location of immune cells determines which type of interaction the model can present: Embedding immune cells in 3D organoids is more suitable for observing cell–cell contact,

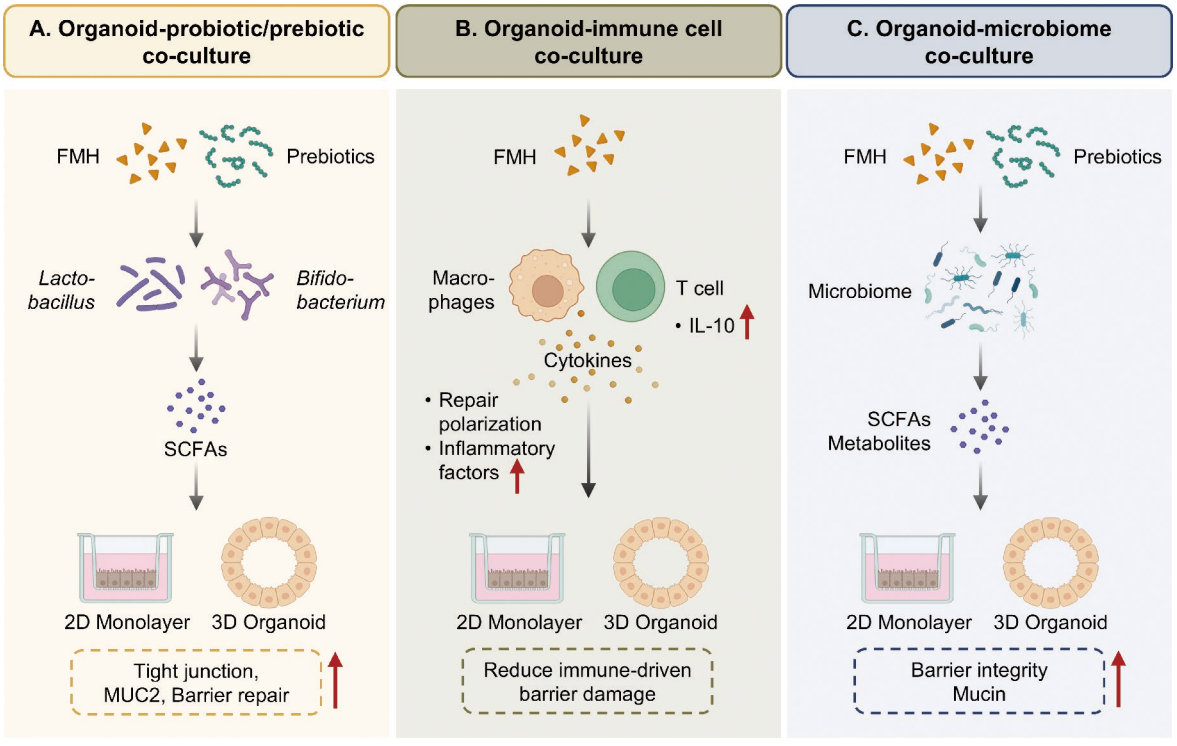


Figure 4 Composite co-culture intestinal organoid systems for evaluating FMH supramolecular complexes. (A) Organoid–probiotic/prebiotic co-culture: *Lactobacillus* and *Bifidobacterium* are introduced into the luminal side of 2D monolayers or 3D organoids together with FMH constituents or prebiotics; microbial metabolism produces SCFAs that can reinforce TJs, MUC2 expression, and barrier repair. (B) Organoid–immune cell co-culture: Macrophages and T cells are added to 2D monolayers or embedded in 3D organoids; FMH exposure may promote repair-like macrophage polarization and enhance IL-10 secretion while attenuating cytokine-driven barrier damage. (C) Organoid–microbiome co-culture: Complex microbial communities are co-cultured with organoids under controlled oxygen gradients; FMH constituents and/or prebiotics modulate community-derived SCFAs and metabolites, thereby influencing barrier integrity and mucin production.

intratissue migration, and localized injury; basolateral co-culture on Transwell is suitable for studying soluble-mediator-mediated barrier regulation (Fig. 4B).

For barrier-centric FMH research, basolateral co-culture of macrophages or activated T cells with epithelial monolayers can recapitulate cytokine-mediated barrier disruption and can be used to test whether FMH supramolecular complexes attenuate immune-driven TJ loss, promote repair-like macrophage polarization, or enhance IL-10 production[58, 69]. Key readouts combine the barrier panel with immune phenotypic analysis (flow cytometry, cytokine arrays) and Transwell migration assays[69]. It should be noted that evaluation of macrophage status should not be confined to the M1/M2 binary framework, pro-inflammatory-like and repair-like states can serve as shorthand for describing functional tendencies, but the phenotypes of intestinal macrophages are continuously shaped by microenvironmental signals. Existing immune co-culture studies demonstrate that this type of model can support epithelial–immune interaction analysis, but direct evidence that FMH supramolecules modulate macrophages or intraepithelial lymphocytes still awaits accumulation[68, 69].

3.3.3 *Organoid–intestinal microbiome co-culture systems*

When moving from single strains to the gut microbiome, the model must also handle ecological variables such as community competition, metabolic complementarity, and donor differences. Long-term co-culture is technically challenging, bacterial overgrowth can rapidly compromise epithelial viability; current solutions include anaerobic microinjection, maintenance media supplemented with antibiotics, 2D monolayer co-culture with controlled apical seeding, air, liquid interface systems, and microfluidic platforms with continuous perfusion[56, 66, 70]. A practical guide for designing bacterial, epithelial interaction experiments emphasizes matching bacterial species with appropriate organoid configurations, controlling oxygen gradients, and verifying bacterial colonization sites by confocal imaging[56] (Fig. 4C).

Evaluation of complex microbial communities requires linking community changes to host outcomes: In addition to community composition and diversity, metabolites, biotransformation products, and host readouts such as epithelial permeability, mucus, and junctional proteins should be integrated[56, 66, 70]. This model helps distinguish the direct epithelial effects of FMH supramolecules, microbiota-mediated effects, and secondary effects generated by microbial transformation products, constituting a key tool for evaluating the core precision-nutrition hypothesis that "supramolecular complexes remodel the microbiota and thereby enhance barrier integrity"[56, 66, 67, 70].

3.4 Advanced microfluidic organoid-on-a-chip evaluation platforms for supramolecular dynamics simulation

Static organoids can preserve donor-related epithelial features, yet it is difficult to continuously control mass flow, oxygen gradients, and the mechanical environment. Microfluidic organoid-on-a-chip platforms place organoid-derived cells in a perfusable microenvironment capable of applying mechanical stimuli, integrating dynamic perfusion, peristalsis-like strain, and serial connection of multiple tissues, thereby overcoming the limitations of static culture and enabling dynamic, systematic evaluation of FMH supramolecular complexes[71-73].

3.4.1 *On-chip single-intestine microfluidic systems*

A typical intestinal chip consists of microchannels representing the luminal side and the vascular side, with the epithelium and endothelium separated by a porous membrane or extracellular matrix; the membrane-based structure has clear apical–basal compartmentalization, supports the reconstruction of polarized epithelium under continuous flow and cyclic mechanical strain, and permits long-term (days to weeks) co-culture with commensal bacteria and immune cells while maintaining physiological TEER[70,72,74]. Fluid shear and peristalsis-like deformation are two related but distinct physical stimuli: Continuous perfusion renews nutrients and oxygen supply and removes metabolites while generating shear stress on the epithelial surface; cyclic pressure deformation simulates intestinal peristalsis (Fig. 5).

Compared with static Transwell and organoid systems, intestinal chip platforms offer: (1) physiologically relevant shear stress and peristalsis-like deformation; (2) stable oxygen gradients that support aerobic–anaerobic microbial co-culture; (3) real-time, label-free barrier monitoring integrated with on-chip sensors (integrated electrodes, oxygen sensors); and (4) controlled, reproducible dosing protocols for pharmacokinetics-style studies[70-72,75]. Disease modeling further extends the utility of this platform, for example, elderly ulcerative colitis involves simultaneous gut microbiota imbalance, mucosal epithelial injury, and immunoregulatory abnormalities, and the chip can dynamically integrate these factors; when the chip uses organoids derived from patient biopsies, it can also compare barrier phenotypes and intervention responses between healthy donors and patients and among different patients[73,74,76]. For FMH supramolecular complexes whose biological effects depend on concentration, residence time, and dynamic exposure, chip-based dynamic dosing offers a decisive advantage over static culture in evaluating dose–response relationships, reversibility, and sustained-release formulations[70,71,73,77].

3.4.2 *Multi-organ linked microfluidic chips*

A single intestinal chip mainly answers whether substances can cross the intestinal barrier and how the barrier itself changes; multi-organ chips bring the post-barrier fate into observation. Multi-organ chips connecting the intestine and liver recapitulate first-pass metabolism, enterohepatic circulation, and organ crosstalk, thereby filling a key gap in evaluating food-derived bioactive compounds: Distinguishing the effects of parent compounds from those of their hepatic metabolites[77,78]. Gut–liver axis chips have been used to simulate inflammatory crosstalk, bile acid signaling, and drug/nutrient toxicity in non-alcoholic fatty liver disease (NAFLD), with readouts covering barrier integrity, hepatocyte function (albumin, CYP450 activity), and systemic inflammatory markers[77,78]. Gut–brain axis chips connect intestinal organoids with neural/neuronal compartments to study how diet- and microbiota-derived metabolites (e.g., SCFAs, serotonin precursors) affect neural function, and conversely, how neural signals regulate intestinal permeability[77] (Fig. 5).

For FMH evaluation, multi-organ chips can test how supramolecular complexes are processed along the gut–liver axis, whether microbial metabolites are further transformed by hepatocytes, and whether liver-derived signals (e.g., bile acids, FGF19) feedback-regulate intestinal barrier function[77,78]. If a complex remains mainly in the intestinal lumen, its effects may derive from microbiota remodeling or local barrier regulation; if some components or their metabolites enter the circulation, their distal effects need to be tracked.

3.4.3 *Features of microfluidic chips in evaluating sustained-release supramolecular delivery*

Static organoids usually observe an endpoint after a single addition of the sample. As constituents are released, taken up by cells, and metabolites accumulate in the culture medium, the actual exposure conditions change continuously, yet it is difficult to determine whether a barrier change at a given time is caused by which constituent or which assembly state. Chip platforms enable dynamic evaluation of sustained-release formulations: Sustained-release and nano-encapsulated FMH complexes can be perfused through chip channels at programmed flow rates, with longitudinal monitoring of their release kinetics, epithelial uptake, and barrier effects[71,77,78]. Dynamic perfusion also enables assessment of the reversibility of barrier responses. TEER, oxygen environment, and some secretory signals can be recorded continuously, while permeability, outflow constituents, and

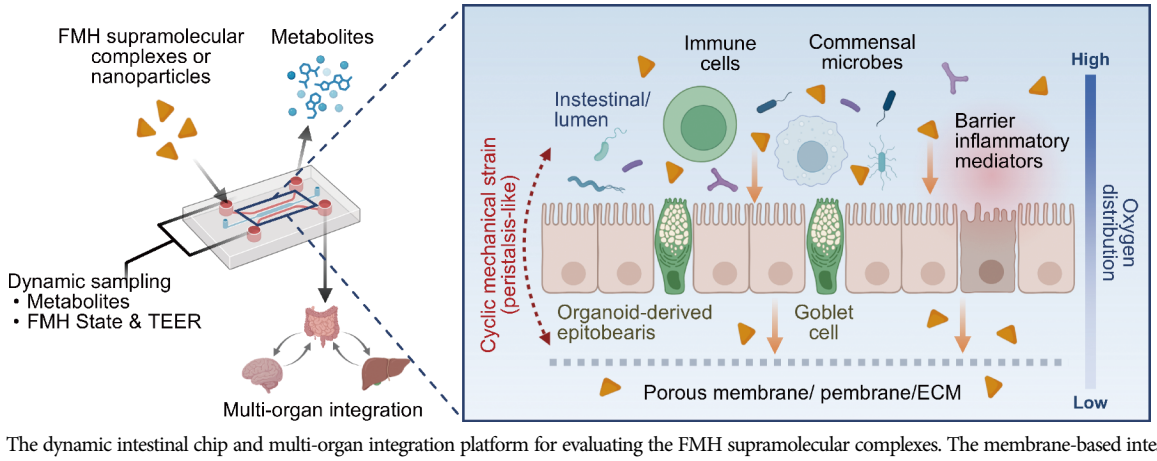


Figure 5 The dynamic intestinal chip and multi-organ integration platform for evaluating the FMH supramolecular complexes. The membrane-based intestinal chip reconstructs intestinal epithelium with apical-basal polarity on a porous membrane. This platform enables: (1) continuous perfusion of FMH supramolecular complexes or nanoparticles on the luminal side of the intestine; (2) periodic mechanical strain to simulate peristaltic movements; (3) controlled oxygen gradients across the epithelial layer; (4) real-time, label-free monitoring of barrier integrity through integrated TEER and O_2 sensors. Co-culturing with immune cells and symbiotic bacteria can evaluate host-microbiota-immune interactions and barrier inflammatory responses. Dynamic sampling at the outlet end can simultaneously detect metabolites, FMH assembly status, and TEER readings. At the same time, the intestinal chip is connected to the liver and the brain/neurogenic compartments to simulate the intestinal-liver axis and intestinal-brain axis.

supramolecular assembly states can be sampled at corresponding time points, thereby distinguishing reversible effects from irreversible damage[71, 77, 79] (Fig. 5).

It should be noted that the chip material and flow path themselves may alter the actual exposure of supramolecules: The commonly used polydimethylsiloxane (PDMS) adsorbs some hydrophobic small molecules, and tubing retention, minute volumes, and flow shear may also affect the integrity of supramolecular assemblies; therefore, material controls should be set up and the assembly state of the outflow should be monitored in experiments[71, 77, 79]. Intestinal chips and static organoids have different applicable scopes: 3D organoids are more suitable for batch expansion, morphological observation, and relatively simple preliminary screening; chips have irreplaceable advantages in directional transport, continuous exposure, multi-organ linkage, and sustained-release kinetics evaluation[75, 79, 80].

3.5 Standardization, quality control, and current limitations of the FMH supramolecular organoid evaluation system

3.5.1 *Standardized operating procedures and quality control*

Quality control of human intestinal organoids (HIOs) should begin with the cell source. Studies need to record the starting cell type, donor background, harvested intestinal segment, and tissue status, and to specify the passage and cryopreservation history of the organoids[46, 50, 53]. Before FMH intervention, quality-control indicators, such as morphology and growth, sample identity, chromosomal stability, cell viability, contamination control, and epithelial markers, can be selected according to existing standards and quality-assessment recommendations, depending on the intended use of the model. In addition, independent experimental units should be defined before statistical analysis, multiple organoids observed within the same culture well are nested subsamples and cannot be used directly to inflate the sample size; multiple wells from the same batch do not constitute biological replicates either[50, 53].

Quality control of FMH samples needs to proceed in parallel with organoid quality control. Classifying a sample as FMH does not mean that a stable, compositionally well-defined supramolecular entity has already formed in it. In addition to the source of raw materials and the preparation process, the assembly state (particle size, zeta potential, morphology, and stability) should also be confirmed. Control designs should be able to distinguish compositional effects from assembly effects, besides untreated, vehicle, or model controls, when feasible, sample controls with matched composition and processing history but different assembly states can be included[46, 50].

At a more macroscopic level, recent initiatives have begun to promote the establishment of industry standards: The Minimum Information about Organoid Research (MIOR) framework defines reporting standards covering six modules, specimen, derivation, culture, characterization, functional assays, and quality, and mainstream the MIOR framework has been proposed to promote standardized reporting[81]. Parallel efforts focus on scalable, GMP-compliant manufacturing of organoids (including bioreactor expansion, defined media, and synthetic hydrogels) and living organoid biobanks linked with clinical annotations, which are crucial for reproducibility, regulatory acceptance, and patient-derived precision evaluation[50, 82, 83]. For FMH research, standardization of culture conditions (Matrigel batches, growth factor combinations), assay protocols (TEER measurement timing, tracer concentrations), and data reporting is a prerequisite for achieving cross-study comparability and, ultimately, acceptance under regulatory frameworks such as new approach methodologies (NAMs) [46, 81, 82].

3.5.2 *Current bottlenecks of the evaluation system*

Despite its transformative potential, organoid-based barrier evaluation still faces several limitations: (1) the absence of a fully standardized, xeno-free culture system; (2) ASC-derived intestinal organoids mainly recapitulate the epithelium and typically lack vasculature, stroma, nerves, immune cells, and a stable luminal microbiota, and the absence of vascularization and systemic immune circulation limits chronic-toxicity and pharmacokinetic studies; (3) the limited proportion of goblet and Paneth cells under default differentiation protocols; (4) batch-to-batch variation in Matrigel systems; and (5) the unresolved validity of extrapolating organoid results to *in vivo* barrier physiology[44, 46, 50, 53]. In addition, neither static organoids nor intestinal chips fully replicate sequential oral, gastric, small-intestinal, and colonic digestion, so a separate digestion stage remains necessary. Chip-based platforms carry further system-specific limitations, including material adsorption, tubing losses, difficulties in scale-up, and constraints imposed by shared medium[84-87].

Variation among organoids themselves remains a major obstacle to cross-study comparison: donor age, disease status, and intestinal segment introduce genuine biological differences, whereas medium formulations, growth factor activity, matrix batches, and passage strategies add technical variation[50, 53]. PSC-derived systems can remain developmentally immature. The FMH samples introduce a further layer of uncertainty: The chemical composition of natural multi-component materials may vary with raw material and preparation batch, and assembly states driven by non-covalent interactions are highly sensitive to concentration, temperature, pH, and time. Exposure itself poses an additional translation problem: An *in vitro* concentration cannot be equated directly with dietary intake without considering digestion volume, dilution, binding, bioaccessibility, and luminal residence time.

Both cost and throughput limitations are prominent. The expansion and differentiation of organoids still require a significant amount of manpower, with the costs of media, growth factors, and matrices being high, and three-dimensional imaging and multi-cell analysis being more expensive than traditional cell experiments[46, 50, 58]. Detection interference may also further limit their routine application. Therefore, as a supplementary model connecting traditional cell experiments with animal and human research, organoids still need more improvement and optimization.

3.5.3 *Technical solutions optimized for the current limitations*

Emerging solutions include vascularized organoids, synthetic and defined hydrogels, automated high-content screening, and the integration of organoid-on-a-chip with multi-omics readouts[50, 71, 72]. Subsequent standardization can adopt a layered approach of "general quality requirements and use-specific requirements": The general layer is used to confirm sample identity, contamination status, genetic stability, viability, and basic cellular composition; the use-specific layer sets corresponding indicators for specific scenarios such as barrier evaluation, microbial interaction, or dynamic transport[46, 50, 81]. Improvements in culture materials and assay workflows are expected to reduce

technical fluctuation, matrices with more defined composition, batch-validated culture factors, and standardized cryopreserved cell banks can reduce interference from raw-material variability, while multiple donors and independent preparation batches assess reproducibility[50,82]. Model complexity can be increased stepwise according to the evidence chain: 3D organoids or organoid-derived monolayers are suitable for preliminary comparisons of epithelial effects, cytotoxicity, and barrier tolerance; issues involving microbial metabolism, immunomodulation, or dynamic exposure then introduce co-culture or chip systems, rather than as a mandatory escalation in model complexity[50,72].

For FMH samples that may form supramolecular aggregates, a minimal information chain of "chemical composition, assembly state, actual exposure, biological effect" can be further adopted. Organoid donors and preparation batches are independent sources of variation and should be analyzed separately. Different preparation batches should report chemical composition and assembly-state parameters, and experimental designs should specify the actual exposure concentration and time and interpret differences in biological effects accordingly[46,50,88]. Digestion should precede epithelial exposure, with digest-only controls, a justified dilution or fractionation step, and confirmation that the processed exposure retains the relevant chemical and structural features[41]. Functional permeability, junction localization, and viability are core complementary endpoints; additional mechanistic assays should follow a defined hypothesis. This approach tests assembly–function relationships without assuming that a benefit has already been established for natural FMH systems. A direction of particular interest for FMH research is the emerging self-assembled nanoparticles from natural polyphenols, which exploit supramolecular chemistry (including metal–polyphenol networks) to simultaneously regulate the microbiota, inflammation, and barrier integrity[88]. Looking ahead, the convergence of organoid technology and food-science evaluation, as exemplified by recent high-impact reviews on organoid-based evaluation of food-derived bioactive peptides and functional molecules[51,52], provides a clear roadmap for rigorously evaluating FMH supramolecular complexes using standardized, multidimensional organoid platforms, accelerating the translation from laboratory to nutritional intervention, and ultimately realizing individualized dietary recommendations[46,51,52,54,88,89].

4 Supramolecule-mediated barrier remodeling: From organoid evidence to translational prospects

After FMH bioactive components enter the gastrointestinal tract, their barrier effects are governed jointly by chemical composition and assembly state: The mode of aggregation can alter digestive stability, mucus behavior, local exposure, and immune responses, and organoids allow these changes to be observed at the tissue level[21,90]. The supramolecular assembly state of FMH bioactive components differs fundamentally from the free state in remodeling the intestinal epithelial barrier, by enhancing bioavailability, sustained-release properties, and emergent synergistic interactions, the supramolecular architecture can amplify and qualitatively change effects that free compounds cannot reproduce[90-92]. Whether the supramolecular state itself endows bioactive components with superior barrier-regulatory capacity relative to the free state, and how this physical-state difference translates into precision-nutrition intervention practice, are key questions in the field of nutritional delivery that urgently need to be clarified.

4.1 Supramolecular state versus free state: Differential barrier regulation by FMH bioactive components

A formulation may alter constituent protection, release, and tissue contact, but these effects are not equivalent to an assembly-specific signaling mechanism. Evidence is assessed by material category, actual exposure state, comparator, model, and functional endpoint. Table 3 summarizes representative studies and their limits. Judging whether the supramolecular state is superior to the free state requires separately examining formulation protection, component synergy, and signaling mechanisms, and the results from cells, organoids, and animals should be interpreted in a tiered manner[93,94] (Fig. 6).

4.1.1 Digestive stability, bioavailability, and cellular uptake

Assemblies and nanocarriers can modify bioaccessibility and release, but their gastrointestinal behavior depends on formulation and digestion conditions[93,94]. Mucus adhesion, mucus penetration, epithelial uptake, and basolateral appearance require separate measurements. Uptake of a fluorophore does not establish uptake of an intact assembly, and improved constituent exposure does not demonstrate intact-particle passage. Ngew *et al.* compared free β-carotene with a zein-based, surface-modified nanocarrier (Category IV), including simulated digestion, artificial-mucus assays, and patient-derived organoid inflammatory outcomes[19]. Xu *et al.* compared BBR–magnolol carrier-free co-assemblies (Category II) with individual constituents and their combination in animal studies[16]. These results support the model of engineered nanocarrier systems regarding the dependent exposure and efficacy of the formulation. They also suggest the

Table 3 Representative evidence and limitations related to supramolecular state and free state

Study and material category	Model and comparison	Representative evidence	Limitations
Xu *et al.*[16]; II BBR–magnolol	Cells and animals; single constituents and combination	Formulation-associated exposure and colitis outcomes	No human organoid validation; mixture may assemble in situ
Ngew *et al.*[19]; IV β-carotene carrier	Digestion, artificial mucus, PDOs; free β-carotene	Formulation-dependent inflammatory and viability responses	Native decoction structure; direct functional barrier recovery
Lim *et al.*[17]; III COS-GL conjugate	Cell systems, intestinal organoids and animals	Engineered conjugate outcomes involving inflammation and junctions	Chemical identity and assembly effects not fully separated; human native-assembly evidence
Wang *et al.*[95] and Wang *et al.*[96]; free constituents	BBR or sclareol pathway studies	Component-level candidate signaling	Assembly-versus-free causal comparison
Qiao *et al.*[97]; II BBR/ matrine–GA	Experimental DSS colitis	Constituent co-assembly-associated anti-inflammatory outcomes	Native structural identity and human organoid mechanism
Han *et al.*[18]; III hybrid	Cell and animal models	Engineered responsive-delivery outcomes	No organoid validation; multilayer contribution confounding

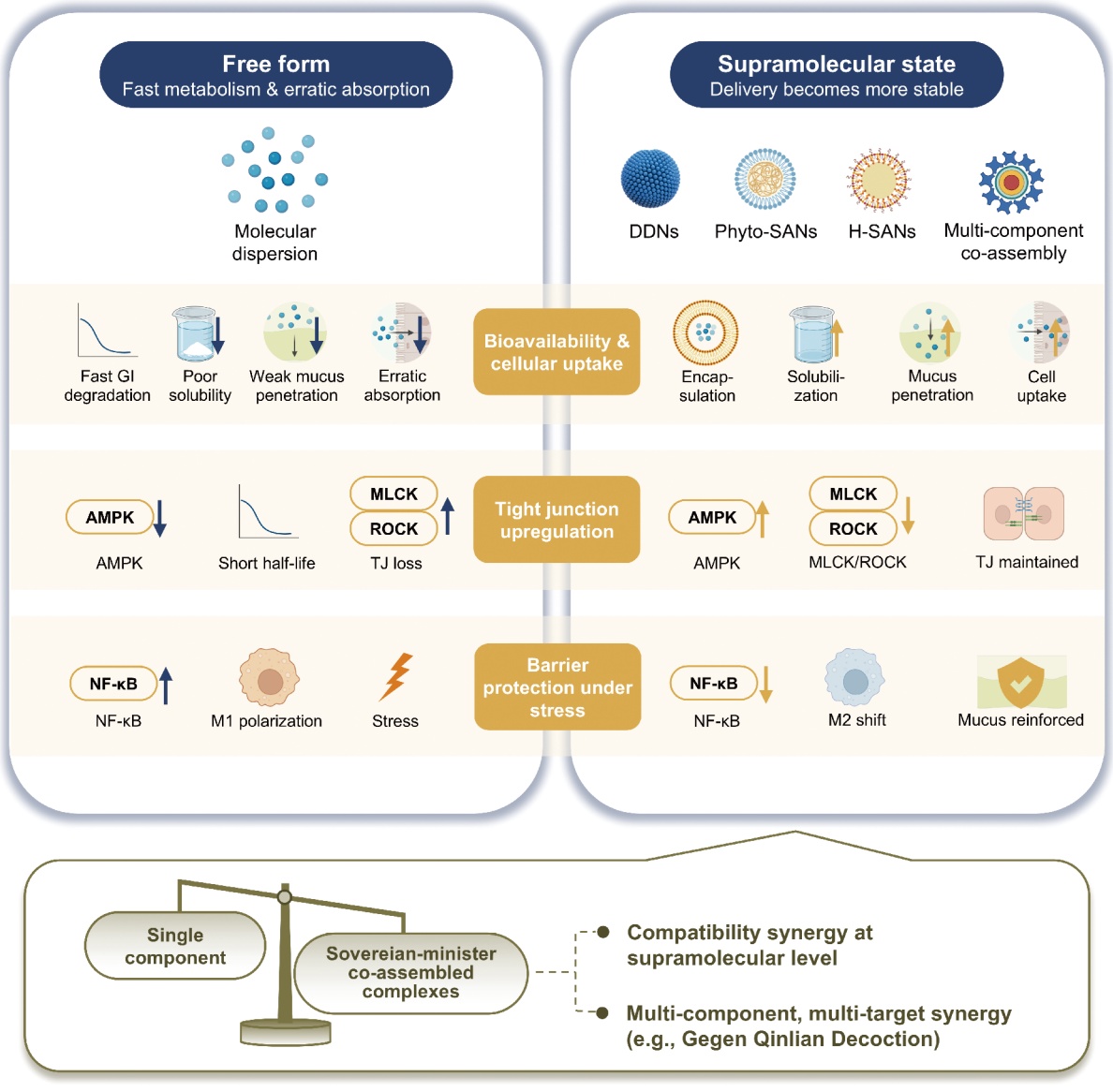


Figure 6 The differential regulatory mechanisms of intestinal barrier function by supramolecular and free state bioactive components of food and medicine. The free state exists in a molecular dispersed form and is prone to rapid metabolism and large fluctuations in absorption; while the supramolecular state forms decoction-derived nanoparticles (DDNs), phyto-self-assembled nanoparticles (Phyto-SANs), hybrid self-assembled nanoparticles (H-SANs), or multi-component co-assemblies through non-covalent self-assembly, which have more stable delivery characteristics. The supramolecular state outperforms the free state in barrier regulation pathways: (1) bioavailability and cell uptake; (2) tight junction upregulation; (3) barrier protection under stress. The pathways of the free components or engineered preparations shown in the figure are not the established mechanisms shared by natural FMH aggregates. Additionally, the supramolecular complexes formed by the combination of sovereign, ministerial, and assistant ingredients have multi-component and multi-target synergistic effects, superior to single-component preparations, suggesting that the supramolecular structure itself may be the modern material carrier of traditional compatibility rules.

potential advantages of natural decoction assemblies in HIOs.

4.1.2 *Tight junction regulation and its mechanistic boundaries*

Tight-junction organization depends on claudins, occludin, ZO proteins, and cytoskeletal regulation[60,61]. Evidence that free constituents affect AMPK, NF-κB, Nrf2, or MLCK provides hypotheses for assembly studies, not proof that a flavonoid–polysaccharide assembly sustains AMPK activation or inhibits MLCK/ROCK. Direct comparisons of assembled, free, and mixture states are needed before assigning sustained signaling or coordinated junctional effects to a formulation. Lim *et al.* chemically conjugated glycyrrhizin to chitosan oligosaccharide and evaluated self-assembled COS-GL nanoparticles (Category III) in cell systems, intestinal organoids, and experimental colitis[17]. This is engineered conjugate evidence, not a native decoction assembly. Wang *et al.* investigated free BBR and the AMPK/MLCK pathway, while a separate study examined free sclareol and Nrf2/NF-κB/MLCK signaling[95,96]. These component studies nominate candidate pathways. Demonstrating an assembly-specific mechanism requires matched free and mixture controls in the same organoid experiment, measured post-digestion exposure, functional permeability, and pathway perturbation.

4.1.3 *Barrier protection under inflammation and oxidative stress*

Inflammation and oxidative injury can disrupt epithelial junctions through interacting signaling and cytoskeletal processes[58,61]. Qiao *et al.* evaluated BBR–GA and matrine–GA complexes associated with Qingchang wenzhong decoction in

DSS-induced colitis[97]. The reconstructed complexes are classified here as Category II, with decoction relevance distinguished from direct isolation of an identical native structure. Reported inflammatory changes do not establish that those complexes are the sole or principal cause of formula efficacy, or that their signaling is assembly-specific in human epithelium.

In PDOs, the engineered β-carotene formulation provides evidence of formulation-dependent inflammatory and viability responses[19]; those endpoints are distinct from TEER or directional permeability. Han *et al.* used a multilayer responsive curcumin formulation incorporating yeast-derived particles (Category III with carrier elements), with cellular and animal rather than organoid validation[18]. Epithelial-only organoids cannot establish macrophage reprogramming. Such conclusions require an immune compartment and appropriate phenotyping.

4.1.4 *Co-assembly synergy inspired by herb-pair compatibility*

BBR–magnolol co-assembly is a Category II example with individual-component and non-preassembled combination controls in experimental colitis[16]. Its improved outcomes support a formulation-associated benefit, but the study does not supply human intestinal organoid evidence or rule out in situ assembly in the mixture group. Qingchang wenzhong-related complexes provide additional animal evidence[97]. These findings justify testing compatibility-associated assemblies; they do not establish a universal supramolecular explanation for traditional formula efficacy.

A stronger organoid experiment should compare constituents, a freshly prepared physical mixture, a preformed assembly, and, when relevant, an empty carrier or conjugate control. Chemical modification must be accounted for because it changes molecular identity as well as assembly. Matching nominal dose is insufficient if bioaccessible or epithelial-associated exposure differs. Time-resolved structural measurements and concentration-matched released-component controls can help distinguish delivery effects from a residual assembly-dependent mechanism.

4.2 From organoid evaluation to precision nutritional intervention: Translational prospects and challenges

Translating organoids requires establishing a reproducible correspondence among formulation state, local exposure, and functional outcomes; existing evidence is scattered across different models, which is suitable for building a tiered validation workflow on this basis. The regulatory wind has shifted toward human-relevant platforms: The U.S. FDA's Modernization Act 2.0 and NAMs guidance recognize HIOs, organ chips, and AI-integrated analysis as alternatives to animal testing, in response to the more than 85% failure rate of intestinal drug candidates in clinical trials[98, 99].

4.2.1 *Standardized platforms for functional evaluation of FMH supramolecules*

Intestinal organoids, whether derived from ASCs or PSCs, can recapitulate key features of the crypt–villus architecture, multilineage differentiation, and intestinal barrier function. Compared with simplified *in vitro* models, they provide a more physiologically relevant system for studying intestinal responses, while offering a human-derived model that complements animal experiments[98-100]. Rubert *et al.* confirmed that organoids respond to microbiota metabolites and phytochemicals more closely to *in vivo* physiology than Caco-2 monolayers[101]; organoid-derived 2D monolayers provide an apically accessible quantitative format for TEER, paracellular flux, and TJ imaging[98, 100, 102]. Standardization is the key bottleneck: Model-selection frameworks for dietary components must cover stem cell origin, matrix composition, culture medium formulation, passage heterogeneity, and quality-assessment criteria[98, 102]. When used for physical-state comparison, donor origin, passage number, and differentiation state should be controlled, free-state, non-pre-assembled mixed-state, supramolecular-state, and blank-carrier groups should be set at equal bioactive-component doses, and particle size, surface charge, and drug loading before and after simulated digestion should be recorded simultaneously; after administration, viability, morphology, cytokines, TJ localization, and functional permeability should be measured in combination[100, 103]. Engineered platforms are addressing reproducibility: Brandenberg *et al.* confined cell aggregation location and scale using PEG-hydrogel microcavities and integrated seeding, medium exchange, dosing, and high-content imaging into an automated workflow, achieving a correlation coefficient of 0.90 between two experiments in screening 80 compounds in colorectal cancer PDOs, but this has not yet been applied to FMH supramolecule or barrier evaluation[104]. A standardized pipeline should include: An accredited biobank, a validated apical-dosing protocol, core readout indicators (TEER, FITC-dextran flux, TJ localization, cytokine panel), and batch-equivalence reference materials[98, 100, 102, 103] (Fig. 7A).

4.2.2 *Organoid validation of supramolecular delivery systems*

Organoids can reproduce some key features of the intestinal environment relevant to responsive release, including changes in pH, redox state, enzyme activity, and the mucus layer, providing a useful model for evaluating delivery systems. Herbal self-assembled nanoplatforms (H-SANs) achieve high drug loading and can undergo stimuli-responsive structural changes under disease-relevant cues[92]; polyphenol-based nanoparticles are stable in the acidic gastric environment and release controllably in the neutral-to-alkaline intestinal lumen[21]; SDDSs respond to the microenvironment of each site from the oral cavity to the GI tract to achieve spatiotemporally controlled release[94]. NAMs-based biopharmaceutic assessment has integrated permeability, solubility, organoid, and chip models to predict oral absorption[105]. Delivery validation can sequentially observe component protection, release location, mucus behavior, cellular uptake, and transepithelial transport; organoid-derived monolayers allow head-to-head testing: Mucus-containing monolayers evaluate mucus penetration and adhesion, conditioned apical medium evaluates stimuli-responsive release, and quantitative apical uptake with basolateral appearance evaluates intestinal targeting[103, 105, 106] (Fig. 7B). Organoids reproduce selected epithelial functions; they do not inherently reproduce the changing pH, enzymes, bile, dilution, and transit of the whole gastrointestinal tract. Release and digestion should be evaluated separately, with characterized digest fractions then introduced to an appropriate apical model[41]. For responsive systems, the imposed trigger and its physiological relevance must be stated. Mucus contact, cell association, internalization, and transepithelial transfer should be quantified separately.

Tong *et al.* converted mouse intestinal organoids into Transwell monolayers and induced M cells with RANKL: A carrier conjugated with a σ1-targeting protein and coated with poly-*L*-lysine transported model cargo 61% more than the uncoated carrier over 48 h, and M-cell number was the determinant of

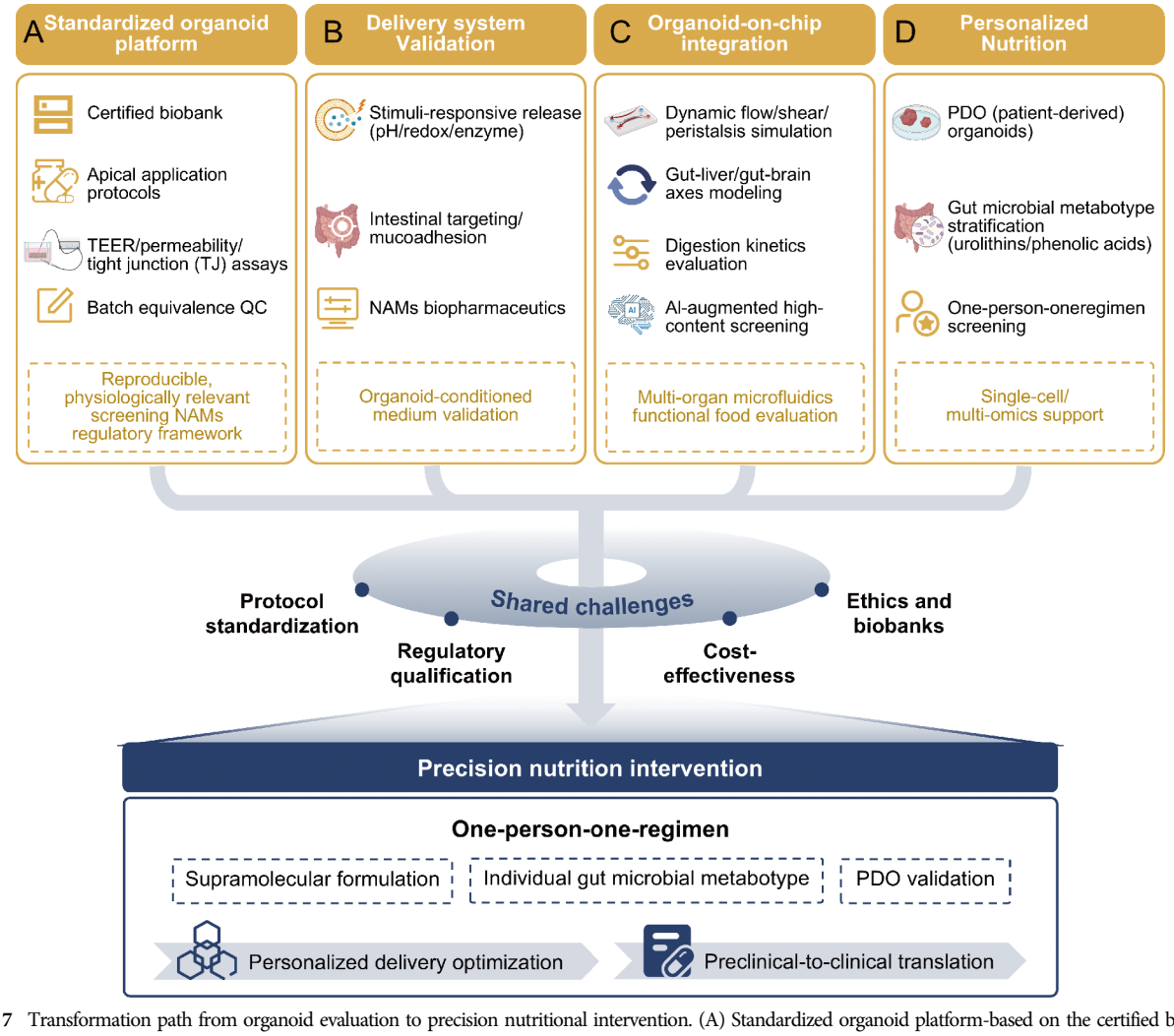


Figure 7 Transformation path from organoid evaluation to precision nutritional intervention. (A) Standardized organoid platform-based on the certified biological library, establish a repeatable intestinal organoid model, standardize the top-down administration protocol, use indicators such as TEER, FITC-dextran permeability, and TJ staining to evaluate the barrier function, and establish a batch equivalence quality control system to make it comply with the regulatory framework requirements of NAMs. (B) Delivery system verification-verify the release behavior, intestinal targeting and mucosal adhesion characteristics, as well as oral biopharmaceutical parameters of pH-responsive, redox-responsive, and enzyme-responsive supramolecular delivery systems in organoid monolayers or chip platforms. (C) Organ chip integration-through dynamic fluid, mechanical shear and peristaltic simulation, construct intestinal-liver and intestinal-brain inter-action models, combine digestive kinetics evaluation and artificial intelligence-enhanced high-content screening to achieve multi-dimensional evaluation of functional foods and supramolecular formulations. (D) Personalized Nutrition-Utilize PDO and intestinal microbiome metabolic stratification (such as urinary sterols, phenolic acids, etc. metabolic phenotypes) to conduct "one person, one strategy" supramolecular nutritional intervention screening. The transformation to an intervention mode centered on the integration of supramolecular formulations, individual intestinal microbiome metabolic types and PDO verification faces common challenges such as standardization of the plan, regulatory qualification recognition, cost-effectiveness, ethics and biological sample libraries.

transport efficiency[107]. Guan *et al.*'s polyacrylic acid-coated mesoporous polydopamine system (PAA@MPDA-SAP) released less than 17% at pH 1.2 and 4.5 and approximately 82% over 36 h at pH 7.0; in human colonic organoids, particle internalization, reduced inflammatory factors, and restoration of ZO-1/occludin were observed[20]. This system uses a synthetic carrier and sulfasalazine and is suitable as a technical reference for combined pH-responsive and human-organoid evaluation. These Category IV studies supply evaluation methods, not evidence for native FMH assemblies. Han *et al.*'s curcumin system showed that acid and ROS accelerate release, but it did not enter organoid validation[18]; Ngew *et al.* completed simulated digestion, mucus, and PDO inflammation evaluation, but did not measure transepithelial flux[19]. Subsequent studies should connect these links within the same model and report adhesion, penetration, uptake, and transport separately, avoiding the use of a single fluorescent signal to summarize overall delivery efficiency[18-20].

4.2.3 *Organoid chips and multi-organ axes*

Organoids lack the dynamic mechanical forces (fluid shear, peristalsis), vascularization, and multi-organ communication present *in vivo*; organ-on-a-chip (OOC) technology compensates for these deficiencies through microfluidic perfusion, mechanical stimulation, and multi-compartment design[106, 108, 109]. Organoid-chip systems reproduce key features of the intestinal mucosal barrier and have been used for modeling mucosal injury and repair and for drug screening[109]; GOC platforms integrate organoids, vascularization, and 3D bioprinting, providing mature strategies for barrier evaluation, disease modeling, and nano-formulation evaluation[106]. Multi-organ configurations enable pharmacokinetic and pharmacodynamic studies across organ boundaries. Bein *et al.* dissociated pediatric duodenal organoids

and seeded them into dual-channel chips, forming villus-like epithelium and a mucus layer under flow and cyclic mechanical deformation. Niacinamide and tryptophan deficiency led to villus shortening, mucus thinning, increased permeability, and reduced fatty acid uptake in chips from both healthy and environmental enteric dysfunction (EED) donors, with a stronger inflammatory response in EED donors. The dynamic platform enables simultaneous assessment of barrier function and nutrient absorption and can capture differences between donor backgrounds[110]. Trapecar *et al.* connected human intestinal, hepatic, and brain microphysiological modules through a shared recirculating medium and added Treg/Th17 cells. SCFAs generally reduced several inflammatory mediators, but also induced some disease-related transcriptional changes in the Parkinson's disease-derived brain module. These findings suggest that responses observed in an isolated intestinal model may differ when multiple organs are considered together[111]. This system is a multi-organ microphysiological system (organoid-derived intestinal epithelium + primary hepatocytes + iPSC-derived brain cells), and the framework could be borrowed in the future to track the hepatic metabolism and neural effects of FMH supramolecules after they cross the barrier[111]. Microfluidic GOC systems are being used to track the gastrointestinal fate of bioactive components from digestion kinetics to the absorption barrier[108]; artificial intelligence converts high-content imaging and sensor data into reproducible, pharmacologically interpretable readouts and drives screening decisions[112]. The integration of organoid chips provides the most complete *in vitro* architecture currently available for tracking the multi-organ consequences of supramolecular barrier remodeling[106, 108, 110, 111, 113] (Fig. 7C).

4.2.4 *PDOs and personalized nutritional screening*

The ultimate translational vision of FMH supramolecules is personalized nutrition: Matching supramolecular formulations to an individual's intestinal physiology, microbiota, and disease background. PDOs retain the epithelial architecture, cellular heterogeneity, and patient-specific genetic features of the original tissue and can enable functionally relevant screening at the individual level[100]. Sugihara *et al.* reviewed the clinical translation trajectory of intestinal organoids, emphasizing the growing evidence for PDOs as patient-specific surrogates for predicting drug responses[53]. The use of gastrointestinal cancer PDOs for drug screening, CRISPR/Cas9-based mechanistic studies, and tumor microenvironment co-culture provides useful methodological approaches that could be adapted for individualized screening of FMH supramolecules[53, 114].

Inter-individual differences, rather than dose, dominate the biological effects of dietary polyphenols: Most natural polyphenols are poorly absorbed in the upper gastrointestinal tract, a considerable proportion reaches the colon, and they are converted by microbiota metabotypes into low-molecular-weight metabolites such as urolithins, phenyl-γ-valerolactones, and phenolic acids[115]. Stratification by metabotype is therefore the rational basis for "one person, one strategy": For example, individuals who produce the anti-inflammatory metabolite urolithin A are expected to respond differently to ellagitannin-rich supramolecular formulations[115]. PDO screening puts this concept into practice: Ngew *et al.* demonstrated that UC-PDOs can distinguish the inflammatory effects of nBC from those of free β-carotene[19]; Bein *et al.* showed that donor disease background alters barrier, absorption, and inflammatory phenotypes under nutritional deficiency[110]. These results provide preliminary support for using PDOs to screen FMH formulations, but donor numbers are limited, and no personal nutrition plan has been developed from *in vitro* results with clinical follow-up. A feasible workflow is: Establish a multi-donor PDO biobank; compare three formulation states at equal doses while controlling passage number and experimental batch; narrow candidate ranges by combining inflammatory typing and clinically achievable luminal concentrations; then calibrate through prospective human intervention and test cross-batch/cross-center reproducibility[100, 102, 115] (Fig. 7D). Key challenges include: Standardizing PDO biobanks while maintaining the barrier phenotype, high-throughput screening of supramolecular formulation libraries, integrating multi-omics readouts to identify responders and non-responders, and resolving the ethical and regulatory framework for nutrition-oriented PDOs [53, 102, 114]. The convergence of PDOs with organ chips and AI data analysis can form a precision-nutrition workflow: Multi-patient PDOs screen formulation libraries on microfluidic platforms, generate barrier-function datasets, and train models that predict individualized dietary recommendations[100, 102, 112]. "One person, one prescription" is rooted in the individualized tradition of traditional Chinese medicine dietary therapy and is empowered by modern organoid and microfluidic technologies, representing the most promising translational frontier of FMH supramolecular barrier-remodeling research.

5 Current limitations and key scientific issues

Within the studies examined in this narrative review, we did not identify a primary study that jointly demonstrated a native Category I FMH decoction assembly, tracked its post-digestion structural identity, and compared its barrier effect with matched free or mixture controls in HIOs. This is an evidence gap in the reviewed literature, not a systematic census proving that no such study exists. The human β-carotene PDO example is Category IV[19], and COS-GL is a Category III conjugate evaluated in intestinal organoids[17]. Neither is counted as direct native-decoction human-organoid validation.

Whether an assembly remains intact through digestion is formulation-dependent and unresolved for many native systems. Recovered constituents, soluble complexes, persistent particles, and newly formed bile-associated or digestion-derived colloids may all contribute to exposure. Orthogonal time-resolved characterization is needed before attributing an epithelial effect to the originally administered structure[29, 41].

Higher biological activity can arise from improved solubility, protection, retention, or release without a new signaling mechanism intrinsic to the assembly. Tests should include equal-composition free constituents, physical mixtures, preformed assemblies, empty carriers where relevant, and released-component controls matched to measured exposure. Mixture groups should also be checked for spontaneous assembly. A residual functional difference after exposure matching, together with causal pathway perturbation, would strengthen evidence for an assembly-dependent mechanism[16, 17].

Particle-associated fluorescence or tissue constituent concentration alone does not establish intact assembly arrival. Direct evidence requires chemical co-localization, controls for free dye and label exchange, recovery of material at the epithelial interface, and orthogonal assessment of its organization[5, 116]. Luminal retention, mucus binding, epithelial association, internalization, and basolateral transport are distinct endpoints. An assembly may act locally without crossing the epithelium.

Multiple donors, disease backgrounds, intestinal segments, and independent preparation batches should be incorporated with prespecified endpoints and appropriate nested analysis. Repeated wells or organoids from one donor do not establish population reproducibility. Effect sizes should be reported for permeability, viability, and junction localization, and the influence of passage, matrix, differentiation, and digestion conditions should be examined before proposing responder stratification[44, 50].

A proposed quality package includes resource and constituent identity; raw-material provenance; preparation conditions; chemical fingerprints; particle distribution and morphology; constituent recovery and release after digestion; storage and batch consistency; contaminants; and dose-dependent toxicity. Barrier tightening and permeability enhancement must be assessed separately, including reversibility and microbial-translocation risk. Regulatory classification depends on intended use, jurisdiction, chemical modification, and carrier materials[98, 102]. The proposed package is a research recommendation rather than an established FMH-specific regulatory standard[81, 98, 102]. Prospective human studies are needed to connect organoid responses to safety and dietary benefit.

6 Conclusions and perspectives

FMH supramolecular complexes may contribute to the efficacy of traditional decoctions and represent an intervention dimension with distinct biological effects. Their effects on intestinal barrier function and nutrient interactions can be further investigated using human-relevant platforms such as organoids. The establishment of this understanding provides a molecular-level reinterpretation of the classical compatibility theory and anchors a scientific coordinate for the modern development of FMH resources.

Supramolecular complexes constitute the material basis of the synergistic effects of traditional decoctions. From the GQD nanomicelles formed by the electrostatic pairing of BA and BBR in Gegen Qinlian Decoction to the natural encapsulation of paeoniflorin by glycyrrhizin micelles in Shaoyao Gancao Decoction, "co-decoction differs from mixing" has obtained direct physicochemical evidence[6, 16]. These assemblies are not merely by-products of separation processes but may represent physical states present in traditionally prepared decoctions. Their multicomponent composition and potential multi-target effects provide a possible material basis for the “monarch, minister, assistant, and courier” (jun-chen-zuo-shi) compatibility theory and offer a framework for studying this principle from a supramolecular chemistry perspective[90, 117]. Supramolecular complexes thus become the "material bridge" that links traditional FMH wisdom to modern nutritional science, and also provide a testable scientific hypothesis for understanding why decoctions are more effective than single herbs.

Organoids contribute donor-specific and lineage-resolved epithelial information, and organoid-derived monolayers allow quantitative permeability studies. These advantages complement chemical measurements, digestion assays, conventional cells, animals, and human research. AMPK, NF-κB, Nrf2, MLCK, and ROCK remain candidate pathways for assembly-specific experiments where direct formulation comparisons and causal perturbation are missing[118-121]. Because current studies often assess different formulations, models, and endpoints, the causal relationship among assembly state, barrier function, and mechanism cannot always be established across studies. Therefore, the key task for the next step is to clearly define at what time point and how to achieve a certain specific supramolecular state, and to demonstrate that compared to the free or unpre-assembled control group in the same experimental system, it brings repeatable functional advantages.

To move FMH supramolecular complexes from organoid evaluation into clinical practice, quality evaluation should integrate resource identity, preparation reproducibility, chemical composition, assembly parameters, post-digestion exposure, functional permeability, and safety. Regulatory acceptance depends on jurisdiction, intended food or therapeutic use, and degree of engineering; natural origin and organoid data alone do not establish approval. To address donor heterogeneity, batch-to-batch variation, matrix uncertainty, and vascular–immune deficiency, the MIOR framework should be used for unified reporting of sample source, passage history, and assembly status. A "chemical composition-assembly state-actual exposure-biological effect" minimal information chain should be established, and at the same dose, free state, unpre-assembled mixed state, and supramolecular state controls should be set side by side, with functional permeability rather than single protein expression as the necessary readout[98, 100, 102, 103]. At the same time, clinical translation must be carried out simultaneously with safety assessment. Leveraging the NAMs framework to promote the regulatory approval of organoid data, systematically evaluating the long-term exposure safety and batch consistency, and verifying the *in vitro* results through prospective human studies, to clarify the hierarchical validation relationship among organoid, animal and human research[53, 99, 105, 113]. Furthermore, the integration of artificial intelligence with multi-omics will drive rational supramolecular engineering, constructing a "structural parameters-barrier endpoints-microbial metabolic types" prediction model, and promoting the shift from trial-and-error screening to on-demand customization in design[99, 108, 112, 115].

Ultimately, the convergence of organoid evaluation and precision nutritional intervention opens a sustainable pathway for the high-value utilization of FMH resources. Personalized stratification based on gut microbial metabotypes, such as the different responses of urolithin A producers and non-producers to different ellagitannin-containing formulations, could support a “one person, one strategy” approach to supramolecular nutritional intervention[108, 115]; PDO biobanks combined with multi-omics analysis can prospectively identify high-response subgroups from population cohorts, guiding the targeted development of FMH by-products and low-value parts and precision formulation design[53, 115]. This "evaluation-driven development" paradigm not only enhances the scientific added value of FMH resources but also aligns with the strategic needs of the "big food" concept and the construction of sustainable agri-food systems. When supramolecular chemistry, organoid technology, and precision nutrition converge within the same framework, traditional FMH resources will be upgraded from empirical dietary supplements to evidence-driven personalized health assets.

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 Associate Editors of Food & Medicine Homology Resources, but was not involved in the processing, peer review or decision making of this article.

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Author contribution statement

Qing-Ru Song, Xiao-Meng Li and Juan Liu contributed to the study design and drafting and writing of the manuscript. Yu-Xin Su and Yu-Tian Feng contributed to figure preparation. Ming-Yue Pan, Wen-Rui Ma and Qi Wang participated in manuscript revision. Peng-Fei Li, Wen-Zhen Yin, Tan-Qing Long, Ni An and Shu-Yi Li were responsible for data collection. Chun-Qiu Zhang, Xiang-Dong Zheng, Juan Liu, Jia-Lun Duan and Zhi-Yuan Hu supervised the writing of the manuscript. All authors read and approved the final manuscript.

Informed consent

Not applicable.

Ethics statement

Not applicable.

Use of AI statement

None.

References

[1] Cai, L., Hu, X. Y., Liu, S., et al. China is implementing the national nutrition plan of action. *Frontiers in Nutrition*, **2022**, 9: 983484. https://doi.org/10.3389/fnut.2022.983484

[2] Hou, Y., Jiang, J. G. Origin and concept of medicine food homology and its application in modern functional foods. *Food & Function*, **2013**, 4: 1727–1741. https://doi.org/10.1039/c3fo60295h

[3] Chu, Z., Yang, T., Zhang, Y., et al. Self-assembled nanoparticles from Xiexin Decoction attenuate ulcerative colitis by targeting VDAC1-mediated NLRP3 inflammasome activation. *Materials Today Bio*, **2026**, 38: 103078. https://doi.org/10.1016/j.mtbio.2026.103078

[4] Niu, Y. H., Chen, F. B., Guo, X. R., et al. Thermodynamic selectivity and kinetic control in the encapsulation of spiropyran derivatives by cucurbit[8]uril. *Physical Chemistry Chemical Physics*, **2026**, 28: 15898–15909. https://doi.org/10.1039/d6cp00611f

[5] Wang, C. L., Zong, S. Y., Zhang, H., et al. Supramolecular nanocomplexes in traditional Chinese medicine decoctions: Challenges and methodologies for structural characterization. *Talanta*, **2026**, 312: 130468. https://doi.org/10.1016/j.talanta.2026.130468

[6] Gao, Y., Dong, Y. Y., Guo, Q., et al. Study on supramolecules in traditional Chinese medicine decoction. *Molecules*, **2022**, 27: 3268. https://doi.org/10.3390/molecules27103268

[7] Fang, C., Liu, Z. Formation of self-assembly aggregates in traditional Chinese medicine decoctions and their application in cancer treatments. *RSC Advances*, **2025**, 15: 5476–5506. https://doi.org/10.1039/d4ra07212j

[8] Miller, C., Jiménez-Flores, R. The milk fat globule membrane increases bacterial serotonin and exopolysaccharide production for maintenance of intestinal cell differentiation. *Journal of Dairy Science*, **2026**, 109: 4201–4215. https://doi.org/10.3168/jds.2026-28296

[9] Li, P. H., Zhang, Y. K., Guo, S. Q., et al. Transient receptor potential vanilloid channels in inflammatory bowel diseases: Linking inflammation, angiogenesis, and oxidative stress. *Inflammopharmacology*, **2026**, 34: 5305–5327. https://doi.org/10.1007/s10787-026-02311-5

[10] Zhang, Q., Chai, L., Liu, H., et al. Colon-targeting pH-responsive *Bletilla striata* polysaccharide coacervate microdroplets for ulcerative colitis therapy *via* macrophage reprogramming. *Journal of Nanobiotechnology*, **2026**, 24: 811. https://doi.org/10.1186/s12951-026-04824-1

[11] Wang, R. T., Liang, J. L., Wu, H. X., et al. Intestinal organoids as models to study viruses: Current application and future perspective. *Journal of Microbiology and Biotechnology*, **2026**, 36: e2603016. https://doi.org/10.4014/jmb.2603.03016

[12] Wijnakker, J. J. A. P. M., Lim, S., Schreurs, R., et al. Invasin-functionalized PIC hydrogels enable long-term 3D culture of epithelial organoids. *Proceedings of the National Academy of Sciences of the United States of America*, **2025**, 122: e2507500122. https://doi.org/10.1073/pnas.2507500122

[13] Mu, S., Zheng, Z. J., Lu, J. Z., et al. Natural nanoparticles in Gegen–Qinlian decoction promote the colonic absorption of active constituents in mice with dextran sulfate sodium-induced ulcerative colitis. *Pharmaceuticals*, **2025**, 18: 1718. https://doi.org/10.3390/ph18111718

[14] Nie, W. L., Liu, Y., Lan, J. S., et al. Self-assembled nanoparticles from Xie-Bai-San Decoction: Isolation, characterization and enhancing oral bioavailability. *International Journal of Nanomedicine*, **2024**, 19: 3405–3421. https://doi.org/10.2147/IJN.S449268

[15] Feng, Y. F., Wu, C. Y., Chen, H., et al. Rhubarb polysaccharide and berberine co-assembled nanoparticles ameliorate ulcerative colitis by regulating the intestinal flora. *Frontiers in Pharmacology*, **2023**, 14: 1184183. https://doi.org/10.3389/fphar.2023.1184183

[16] Xu, Y. D., Chen, Z. J., Hao, W., et al. Berberine and magnolol exert cooperative effects on ulcerative colitis in mice by self-assembling into carrier-free nanostructures. *Journal of Nanobiotechnology*, **2024**, 22: 538. https://doi.org/10.1186/s12951-024-02804-x

[17] Lim, G., Kim, H. R., Yoo, C., et al. Mucoadhesive and self-assembled chitosan oligosaccharide-glycyrrhizin nanoparticle for oral nanotherapeutic in inflammatory bowel disease. *ACS Nano*, **2025**, 19: 31169–31182. https://doi.org/10.1021/acsnano.5c09985

[18] Han, X. Q., Luo, R. F., Qi, S. S., et al. "Dual sensitive supramolecular curcumin nanoparticles" in "advanced yeast particles" mediate macrophage reprogramming, ROS scavenging and inflammation resolution for ulcerative colitis treatment. *Journal of Nanobiotechnology*, **2023**, 21: 321. https://doi.org/10.1186/s12951-023-01976-2

[19] Ngew, E., Kollipara, R., Bessissow, T., et al. Nanoencapsulation enhanced the performance of β-carotene for ameliorating inflammation in patient-derived organoids. *Nanomedicine*, **2025**, 20: 663–675. https://doi.org/10.1080/17435889.2025.2465247

[20] Guan, H. D., Xu, Z. W., Du, G. S., et al. A mesoporous polydopamine-derived nanomedicine for targeted and synergistic treatment of inflammatory bowel disease by pH-responsive drug release and ROS scavenging. *Materials Today Bio*, **2023**, 19: 100610. https://doi.org/10.1016/j.mtbio.2023.100610

[21] Chen, Y. Y., Wang, L., Song, X. J., et al. Decoction-derived nanogranules from traditional Chinese medicine for drug delivery. *Journal of Controlled Release*, **2026**, 396: 115099. https://doi.org/10.1016/j.jconrel.2026.115099

[22] Trindade, S. G., Okasaki, F. B., Williams, A. P., et al. The self-assembly of glycyrrhizic acid into nanofibrils. *Journal of Colloid and Interface Science*, **2025**, 699: 138280. https://doi.org/10.1016/j.jcis.2025.138280

[23] Tucker, I. M., Burley, A., Petkova, R. E., et al. Adsorption and self-assembly properties of the plant based biosurfactant. *Journal of Colloid and Interface Science*, **2021**, 598: 444–454. https://doi.org/10.1016/j.jcis.2021.03.101

[24] Assunção Bicca, S., Sieczkowski, N., Doco, T., et al. Polysaccharide structure of Mannoproteins influences the colloidal outcome of their interactions with grape seed tannins. *Carbohydrate Polymers*, **2026**, 388: 125562. https://doi.org/10.1016/j.carbpol.2026.125562

[25] Li, J. Q., Liu, N. J., Qin, F. R., et al. Preparation, binding behavior and molecular simulation of binary complexes of phloridzin with whey protein isolate. *Foods*, **2026**, 15: 2089. https://doi.org/10.3390/foods15122089

[26] Li, C. H., Li, C., Sun, J., et al. Research progress on the *in vivo* fate of self-assembled traditional Chinese medicine ingredients: Absorption. *Chinese Chemical Letters*, **2026**, 37: 111888. https://doi.org/10.1016/j.cclet.2025.111888

[27] Li, G. J., He, F., Feng, J. B., et al. Injectable self-assembling procyanidin nanospheres for effective osteoarthritis treatment. *International Journal of Nanomedicine*, **2025**, 20: 1133–1145. https://doi.org/10.2147/IJN.S496827

[28] Guo, X. H., Luo, W. K., Wu, L. Y., et al. Natural products from herbal medicine self-assemble into advanced bioactive materials. *Advanced Science*, **2024**, 11: 2403388. https://doi.org/10.1002/advs.202403388

[29] Zhao, X. R., Liu, M. Q., Ma, Z. C., et al. Constructing a hydrogel based on self-assembly properties of glycyrrhizic acid: A drug delivery system with digestive tract responsive. *Colloids and Surfaces A: Physicochemical and Engineering Aspects*, **2024**, 697: 134497. https://doi.org/10.1016/j.colsurfa.2024.134497

[30] Cai, J. Y., Wu, J. H., Yu, X. K., et al. Interfacial assembly and rheology of multi-responsive glycyrrhizic acid at liquid interfaces. *Soft Matter*, **2024**, 20: 1173–1185. https://doi.org/10.1039/d3sm00973d

[31] Li, Q., Wan, Z. L., Yang, X. Q. Glycyrrhizic acid: Self-assembly and applications in multiphase food systems. *Current Opinion in Food Science*, **2022**, 43: 107–113. https://doi.org/10.1016/j.cofs.2021.11.008

[32] Xiao, L. W., Ding, J. X., Cao, R. T., et al. Glycyrrhizic acid-based supramolecular hydrogels as multifunctional platforms for biomedical applications. *Advanced Healthcare Materials*, **2026**, 15: e05953. https://doi.org/10.1002/adhm.202505953

[33] Wang, S. C., Wang, R. Supramolecular self-assembly of natural herb extracts: From molecular interactions to functional biomaterials. *The Innovation Materials*, **2026**, 4: 100206–100220. https://doi.org/10.59717/j.xinn-mater.2026.100206

[34] Yang, H., Wang, J., Tan, Q. R., et al. Supramolecular interaction between berberine hydrochloride and baicalin in aqueous solution: Reaction kinetics. *Heliyon*, **2024**, 10: e29992. https://doi.org/10.1016/j.heliyon.2024.e29992

[35] Zang, Z. Y., Zhang, Y. Z., Zhao, Y. H., et al. Research progress on carrier-free and carrier-supported supramolecular nanosystems of traditional Chinese medicine anti-tumor star molecules. *Acta Pharmaceutica Sinica*, **2024**, 59: 908–917. https://doi.org/10.16438/j.0513-4870.2023-1169

[36] Zhao, M. Y., Xiang, J. W., Meng, Y., et al. *Astragalus* polysaccharide hydrogels with drug-carrying super self-assembly from natural herbs promote wound healing. *ACS Nano*, **2025**, 19: 21571–21588. https://doi.org/10.1021/acsnano.5c03744

[37] Ding, Y. K., Chen, J. P., Xu, Y. J., et al. Perfect partner for a dietary alkaloid: Dual role of *Coptis chinensis* polysaccharide in berberine taste masking and immune amplification. *Plant Foods for Human Nutrition*, **2026**, 81: 43. https://doi.org/10.1007/s11130-026-01494-0

[38] Uekusa, Y., Tanioka, C., Nakamoto, K., et al. Compound–compound interaction analysis of baicalin and berberine derivatives in aqueous solution. *Journal of Natural Medicines*, **2024**, 78: 590–598. https://doi.org/10.1007/s11418-024-01804-3

[39] Yu, H., Yang, Q., Li, C. H., et al. Supramolecular nanogel aggregate as injectable regulatory barrier for preventing postoperative adhesion in diabetic colonic anastomosis. *Biomaterials*, **2027**, 336: 124479. https://doi.org/10.1016/j.biomaterials.2026.124479

[40] Nie, W., Zhang, X., Kang, P., et al. Exploring the influence of polysaccharide on gastrointestinal stability. *Scientific Reports*, **2025**, 15: 8293. https://doi.org/10.1038/s41598-024-82130-2

[41] Brodkorb, A., Egger, L., Alminger, M., et al. INFOGEST static *in vitro* simulation of gastrointestinal food digestion. *Nature Protocols*, **2019**, 14: 991–1014. https://doi.org/10.1038/s41596-018-0119-1

[42] Youhanna, S., Lauschke, V. M. The past, present and future of intestinal *in vitro* cell systems for drug absorption studies. *Journal of Pharmaceutical Sciences*, **2021**, 110: 50–65. https://doi.org/10.1016/j.xphs.2020.07.001

[43] Flood, P., Hanrahan, N., Nally, K., et al. Human intestinal organoids: Modeling gastrointestinal physiology and immunopathology — current applications and limitations. *European Journal of Immunology*, **2024**, 54: 2250248. https://doi.org/10.1002/eji.202250248

[44] Lechuga, S., Braga-Neto, M. B., Naydenov, N. G., et al. Understanding disruption of the gut barrier during inflammation: Should we abandon traditional epithelial cell lines and switch to intestinal organoids? *Frontiers in Immunology*, **2023**, 14: 1108289. https://doi.org/10.3389/fimmu.2023.1108289

[45] Camporesi, G., Canzian, C., Bordoni, A. Optimizing INFOGEST digest conditioning for reliable *in vitro* assessment of nutrient bioavailability using Caco-2 cell models. *Nutrients*, **2026**, 18: 339. https://doi.org/10.3390/nu18020339

[46] Wang, D. S., Villenave, R., Stokar-Regenscheit, N., et al. Human organoids as 3D *in vitro* platforms for drug discovery: Opportunities and challenges. *Nature Reviews Drug Discovery*, **2026**, 25: 204–226. https://doi.org/10.1038/s41573-025-01317-y

[47] Wang, Q. Y., Guo, F. Y., Jin, Y. T., et al. Applications of human organoids in the personalized treatment for digestive diseases. *Signal Transduction and Targeted Therapy*, **2022**, 7: 336. https://doi.org/10.1038/s41392-022-01194-6

[48] Tang, X. Y., Wu, S. S., Wang, D., et al. Human organoids in basic research and clinical applications. *Signal Transduction and Targeted Therapy*, **2022**, 7: 168. https://doi.org/10.1038/s41392-022-01024-9

[49] Kim, J., Koo, B. K., Knoblich, J. A. Human organoids: Model systems for human biology and medicine. *Nature Reviews Molecular Cell Biology*, **2020**, 21: 571–584. https://doi.org/10.1038/s41580-020-0259-3

[50] Hofer, M., Lutolf, M. P. Engineering organoids. *Nature Reviews Materials*, **2021**, 6: 402–420. https://doi.org/10.1038/s41578-021-00279-y

[51] Wan, A. C. A. Evaluating the nutritional value of functional molecules for food processing using tissue and organoid models. *Trends in Food Science & Technology*, **2025**, 156: 104834. https://doi.org/10.1016/j.tifs.2024.104834

[52] Chen, H. W., Wang, S. G., Wu, J. P., et al. The convergence of food-derived bioactive peptides and organoids: Model construction, application, challenges and outlooks. *Trends in Food Science & Technology*, **2026**, 174: 105800. https://doi.org/10.1016/j.tifs.2026.105800

[53] Sugihara, H. Y., Okamoto, R., Mizutani, T. Intestinal organoids: The path towards clinical application. *European Journal of Cell Biology*, **2025**, 104: 151474. https://doi.org/10.1016/j.ejcb.2024.151474

[54] Andersson-Rolf, A., Clevers, H. New developments and applications of human organoids. *Nature Reviews Molecular Cell Biology*, **2026**, 27: 543–558. https://doi.org/10.1038/s41580-026-00974-0

[55] Günther, C., Winner, B., Neurath, M. F., et al. Organoids in

gastrointestinal diseases: From experimental models to clinical translation. *Gut*, **2022**, 71: 1892–1908. https://doi.org/10.1136/gutjnl-2021-326560

[56] Han, X., Mslati, M. A., Davies, E., et al. Creating a more perfect union: Modeling intestinal bacteria-epithelial interactions using organoids. *Cellular and Molecular Gastroenterology and Hepatology*, **2021**, 12: 769–782. https://doi.org/10.1016/j.jcmgh.2021.04.010

[57] Co, J. Y., Margalef-Català, M., Li, X., et al. Controlling epithelial polarity: A human enteroid model for host-pathogen interactions. *Cell Reports*, **2019**, 26: 2509–2520.e4. https://doi.org/10.1016/j.celrep.2019.01.108

[58] Turner, J. R. Intestinal mucosal barrier function in health and disease. *Nature Reviews Immunology*, **2009**, 9: 799–809. https://doi.org/10.1038/nri2653

[59] Peterson, L. W., Artis, D. Intestinal epithelial cells: Regulators of barrier function and immune homeostasis. *Nature Reviews Immunology*, **2014**, 14: 141–153. https://doi.org/10.1038/nri3608

[60] Zihni, C., Mills, C., Matter, K., et al. Tight junctions: From simple barriers to multifunctional molecular gates. *Nature Reviews Molecular Cell Biology*, **2016**, 17: 564–580. https://doi.org/10.1038/nrm.2016.80

[61] Horowitz, A., Chanez-Paredes, S. D., Haest, X., et al. Paracellular permeability and tight junction regulation in gut health and disease. *Nature Reviews Gastroenterology & Hepatology*, **2023**, 20: 417–432. https://doi.org/10.1038/s41575-023-00766-3

[62] Johansson, M. E. V., Sjövall, H., Hansson, G. C. The gastrointestinal mucus system in health and disease. *Nature Reviews Gastroenterology & Hepatology*, **2013**, 10: 352–361. https://doi.org/10.1038/nrgastro.2013.35

[63] Wang, M. Y., Zhao, H., Wen, X., et al. Citrus flavonoids and the intestinal barrier: Interactions and effects. *Comprehensive Reviews in Food Science and Food Safety*, **2021**, 20: 225–251. https://doi.org/10.1111/1541-4337.12652

[64] Habtemariam, S. Berberine and inflammatory bowel disease: A concise review. *Pharmacological Research*, **2016**, 113: 592–599. https://doi.org/10.1016/j.phrs.2016.09.041

[65] Tang, J. L., Wang, C. H., Yang, Y., et al. Berberine in inflammatory bowel disease: Integrative regulation of the microbiota–immune–barrier axis. *International Journal of Molecular Sciences*, **2026**, 27: 5220. https://doi.org/10.3390/ijms27125220

[66] Puschhof, J., Pleguezuelos-Manzano, C., Clevers, H. Organoids and organs-on-chips: Insights into human gut-microbe interactions. *Cell Host & Microbe*, **2021**, 29: 867–878. https://doi.org/10.1016/j.chom.2021.04.002

[67] Bozzetti, V., Senger, S. Organoid technologies for the study of intestinal microbiota–host interactions. *Trends in Molecular Medicine*, **2022**, 28: 290–303. https://doi.org/10.1016/j.molmed.2022.02.001

[68] Al-Qadami, G., Raposo, A., Chien, C. C., et al. Intestinal organoid coculture systems: Current approaches. *American Journal of Physiology-Gastrointestinal and Liver Physiology*, **2025**, 328: G252–G276. https://doi.org/10.1152/ajpgi.00203.2024

[69] Yuki, K., Cheng, N., Nakano, M., et al. Organoid models of tumor immunology. *Trends in Immunology*, **2020**, 41: 652–664. https://doi.org/10.1016/j.it.2020.06.010

[70] Bein, A., Shin, W., Jalili-Firoozinezhad, S., et al. Microfluidic organ-on-a-chip models of human intestine. *Cellular and Molecular Gastroenterology and Hepatology*, **2018**, 5: 659–668. https://doi.org/10.1016/j.jcmgh.2017.12.010

[71] Park, S. E., Georgescu, A., Huh, D. Organoids-on-a-chip. *Science*, **2019**, 364: 960–965. https://doi.org/10.1126/science.aaw7894

[72] Leung, C. M., de Haan, P., Ronaldson-Bouchard, K., et al. A guide to the organ-on-a-chip. *Nature Reviews Methods Primers*, **2022**, 2: 33. https://doi.org/10.1038/s43586-022-00118-6

[73] Özkan, A., LoGrande, N. T., Feitor, J. F., et al. Intestinal organ chips for disease modelling and personalized medicine. *Nature Reviews Gastroenterology & Hepatology*, **2024**, 21: 751–773. https://doi.org/10.1038/s41575-024-00968-3

[74] Wang, H. Y., Li, X., Shi, P. C., et al. Establishment and evaluation of on-chip intestinal barrier biosystems based on microfluidic techniques. *Materials Today Bio*, **2024**, 26: 101079. https://doi.org/10.1016/j.mtbio.2024.101079

[75] Pimenta, J., Ribeiro, R., Almeida, R., et al. Organ-on-chip approaches for intestinal 3D *in vitro* modeling. *Cellular and Molecular Gastroenterology and Hepatology*, **2022**, 13: 351–367. https://doi.org/10.1016/j.jcmgh.2021.08.015

[76] Fu, M., Wang, Q. W., Liu, Y. R., et al. The role of the three major intestinal barriers in ulcerative colitis in the elderly. *Ageing Research Reviews*, **2025**, 108: 102752. https://doi.org/10.1016/j.arr.2025.102752

[77] Guo, Y. X., Chen, X. F., Gong, P., et al. The gut–organ-axis concept: Advances the application of gut-on-chip technology. *International Journal of Molecular Sciences*, **2023**, 24: 4089. https://doi.org/10.3390/ijms24044089

[78] Hu, W. L., Wang, Y. S., Han, J. L., et al. Microfluidic organ-on-a-chip models for the gut–liver axis: From structural mimicry to functional insights. *Biomaterials Science*, **2025**, 13: 1624–1656. https://doi.org/10.1039/d4bm01273a

[79] Iwao, T., Matsunaga, T. Development of intestinal organoids and microphysiological systems and their application to drug discovery. *Drug Metabolism and Pharmacokinetics*, **2025**, 60: 101045. https://doi.org/10.1016/j.dmpk.2024.101045

[80] Antfolk, M., Jensen, K. B. A bioengineering perspective on modelling the intestinal epithelial physiology *in vitro*. *Nature Communications*, **2020**, 11: 6244. https://doi.org/10.1038/s41467-020-20052-z

[81] Lou, L., Wang, K., Cai, C. H. Minimum information about organoid research (MIOR): A framework for reproducibility, interoperability, and translation. *Cell Organoid*, **2026**. https://doi.org/10.26599/co.2025.9410020

[82] Kim, D., Youn, J., Kim, J., et al. From organoid culture to manufacturing: technologies for reproducible and scalable organoid production. *npj Biomedical Innovations*, **2026**, 3: 12. https://doi.org/10.1038/s44385-025-00054-6

[83] Zhou, Z., Cong, L., Cong, X. Y. Patient-derived organoids in precision medicine: Drug screening, organoid-on-a-chip and living organoid biobank. *Frontiers in Oncology*, **2021**, 11: 762184. https://doi.org/10.3389/fonc.2021.762184

[84] Alver, C. G., Drabbe, E., Ishahak, M., et al. Roadblocks confronting widespread dissemination and deployment of organs on chips. *Nature Communications*, **2024**, 15: 5118. https://doi.org/10.1038/s41467-024-48864-3

[85] Shirure, V. S., George, S. C. Design considerations to minimize the impact of drug absorption in polymer-based organ-on-a-chip platforms. *Lab on a Chip*, **2017**, 17: 681–690. https://doi.org/10.1039/c6lc01401a

[86] Wikswo, J. P., Curtis, E. L., Eagleton, Z. E., et al. Scaling and systems biology for integrating multiple organs-on-a-chip. *Lab on a Chip*, **2013**, 13: 3496–3511. https://doi.org/10.1039/c3lc50243k

[87] Rogal, J., Probst, C., Loskill, P. Integration concepts for multi-organ chips: How to maintain flexibility?! *Future Science OA*, **2017**, 3: FSO180. https://doi.org/10.4155/fsoa-2016-0092

[88] Liu, Q. L., He, Y. X., Fang, Y., et al. Emerging self-assembled nanoparticles constructed from natural polyphenols for intestinal diseases. *Advanced NanoBiomed Research*, **2023**, 3: 2300046. https://doi.org/10.1002/anbr.202300046

[89] Feng, J., Liu, S. B., Huang, W. Y., et al. Supramolecular self-assembly of enzymatically hydrolyzed food protein polypeptides: Versatile architecture for enhancing the intestinal absorption of natural bioactive compounds. *Advances in Colloid and Interface Science*, **2026**, 349: 103734. https://doi.org/10.1016/j.cis.2025.103734

[90] Li, J., Zhang, W., Ye, J., et al. Self-assembled structures as a material basis for indirect pharmacology in traditional Chinese medicine. *Chinese Medicine*, **2026**, 21: 205. https://doi.org/10.1186/

s13020-026-01471-4
[91] Ma, G., Li, H., Sang, X. F., et al. Phytochemicals self-assemblies: Bridging biomedicine and agriculture for next-generation crop protection. *Advances in Colloid and Interface Science*, **2026**, 350: 103785. https://doi.org/10.1016/j.cis.2026.103785
[92] Zou, X. Y., Liu, J., Ren, X. H., et al. Advanced herbal self-assembled nanoplatforms: Targeted, stimuli-responsive, and precision therapeutics for human diseases. *Journal of Nanobiotechnology*, **2026**, 24: 946. https://doi.org/10.1186/s12951-026-04798-0
[93] Zhong, Q., Zeng, J., Jia, X. J. Self-assembled aggregated structures of natural products for oral drug delivery. *International Journal of Nanomedicine*, **2024**, 19: 5931–5949. https://doi.org/10.2147/IJN.S467354
[94] Chen, J., Liu, T., Wang, M., et al. Supramolecular oral delivery technologies for polypeptide-based drugs. *Journal of Controlled Release*, **2025**, 381: 113549. https://doi.org/10.1016/j.jconrel.2025.02.045
[95] Wang, Z., Zhong, Y., Xin, M., et al. Swiprosin-1 participates in the berberine-regulated AMPK/MLCK pathway to attenuate colitis-induced tight junction damage. *Phytomedicine*, **2024**, 135: 156111. https://doi.org/10.1016/j.phymed.2024.156111
[96] Wang, L., Song, X. Y., Zhou, Y., et al. Sclareol protected against intestinal barrier dysfunction ameliorating Crohn's disease-like colitis *via* Nrf2/NF-κB/MLCK signalling. *International Immunopharmacology*, **2024**, 133: 112140. https://doi.org/10.1016/j.intimp.2024.112140
[97] Qiao, Z., Zhang, Y. N., Xu, R. Y., et al. Therapeutic effects of self-assembled berberine-glycyrrhizic acid and matrine-glycyrrhizic acid complexes from qingchang wenzhong decoction on DSS-induced ulcerative colitis: Mechanisms of anti-inflammatory action. *Journal of Ethnopharmacology*, **2025**, 352: 120169. https://doi.org/10.1016/j.jep.2025.120169
[98] Patra, D., Sayed, I. M., Mukherjee, S., et al. Integrating human intestinal organoids into FDA's new approach methodologies for drug discovery. *Advanced Science*, **2026**, 13: e22276. https://doi.org/10.1002/advs.202522276
[99] Liu, W. Q., Pang, P. D., Wu, C. A., et al. New approach methodologies for drug discovery. *Cell*, **2026**, 189: 1877–1903. https://doi.org/10.1016/j.cell.2026.02.012
[100] Caruso, A., Hamrouni, Y., Delvecchio, A., et al. Patient-derived organoids in gastrointestinal disease: Current applications, limitations, and future perspectives. *International Journal of Molecular Sciences*, **2026**, 27: 6949. https://doi.org/10.3390/ijms27156949
[101] Rubert, J., Schweiger, P. J., Mattivi, F., et al. Intestinal organoids: A tool for modelling diet–microbiome–host interactions. *Trends in Endocrinology & Metabolism*, **2020**, 31: 848–858. https://doi.org/10.1016/j.tem.2020.02.004
[102] Li, H., Pan, Y., Zheng, Z., et al. Organoid models: Regulations and prospects for the development of investigational new drugs. *Chinese Medical Journal*, **2026**, 139: 1303–1316. https://doi.org/10.1097/CM9.0000000000004067
[103] Ye, G. Q., Liu, Z. Y., Wang, Z. Y., et al. Intestinal organoid models as emerging tools to investigate the impact of dietary components on gut health. *Journal of Agricultural and Food Chemistry*, **2026**, 74: 14704–14720. https://doi.org/10.1021/acs.jafc.5c14263
[104] Brandenberg, N., Hoehnel, S., Kuttler, F., et al. High-throughput automated organoid culture *via* stem-cell aggregation in microcavity arrays. *Nature Biomedical Engineering*, **2020**, 4: 863–874. https://doi.org/10.1038/s41551-020-0565-2
[105] García, M. A., Cabrera-Pérez, M. Á., González, P. M., et al. Application of new approach methodologies to improve oral biopharmaceutic assessments. *Pharmaceutics*, **2026**, 18: 552. https://doi.org/10.3390/pharmaceutics18050552
[106] Lin, Q. Q., Zhou, F. S., Hao, W. S., et al. Gut-on-a-chip: From biomimetic design to precision biomedical applications. *ACS Applied Materials & Interfaces*, **2026**, 18: 42241–42260. https://doi.org/10.1021/acsami.6c10688
[107] Tong, T. J., Qi, Y. J., Rollins, D., et al. Rational design of oral drugs targeting mucosa delivery with gut organoid platforms. *Bioactive Materials*, **2023**, 30: 116–128. https://doi.org/10.1016/j.bioactmat.2023.07.014
[108] Yao, F., Chen, L. C. Microfluidic gut-on-a-chip models for functional food evaluation: From digestion kinetics to personalized nutrition. *Comprehensive Reviews in Food Science and Food Safety*, **2026**, 25: e70549. https://doi.org/10.1111/1541-4337.70549
[109] Qian, K., Wang, Y. W., Li, R., et al. Application and prospects of organoid-on-a-chip in research on the intestinal mucosal barrier. *Burns & Trauma*, **2026**, 14: tkag029. https://doi.org/10.1093/burnst/tkag029
[110] Bein, A., Fadel, C. W., Swenor, B., et al. Nutritional deficiency in an intestine-on-a-chip recapitulates injury hallmarks associated with environmental enteric dysfunction. *Nature Biomedical Engineering*, **2022**, 6: 1236–1247. https://doi.org/10.1038/s41551-022-00899-x
[111] Trapecar, M., Wogram, E., Svoboda, D., et al. Human physiomimetic model integrating microphysiological systems of the gut. *Science Advances*, **2021**, 7: eabd1707. https://doi.org/10.1126/sciadv.abd1707
[112] Song, C. X., Li, T. Y., Guan, H., et al. Artificial intelligence-augmented organ- and organoid-on-a-chip for drug screening. *Lab on a Chip*, **2026**, 26: 4384–4417. https://doi.org/10.1039/d6lc00365f
[113] Zhou, Y. Y., Wang, F. R., Zhao, R., et al. Advanced strategies in organoid/organ-on-a-chip for food safety and nutrition. *Food Research International*, **2025**, 219: 117011. https://doi.org/10.1016/j.foodres.2025.117011
[114] Yan, S. C., He, Y. X., Zhu, Y. H., et al. Human patient derived organoids: An emerging precision medicine model for gastrointestinal cancer research. *Frontiers in Cell and Developmental Biology*, **2024**, 12: 1384450. https://doi.org/10.3389/fcell.2024.1384450
[115] Perrone, P., D'Angelo, S. Gut microbial metabotypes shape polyphenol bioactivity: Toward precision nutrition strategies for human health. *Nutrients*, **2026**, 18: 2396. https://doi.org/10.3390/nu18142396
[116] Snipstad, S., Hak, S., Baghirov, H., et al. Labeling nanoparticles: Dye leakage and altered cellular uptake. *Cytometry Part A*, **2017**, 91: 760–766. https://doi.org/10.1002/cyto.a.22853
[117] Hou, Y. J., Wang, H., Li, J. T., et al. Gegen Qinlian decoction, a classic traditional Chinese medicine formula: A potential therapeutic strategy for ulcerative colitis and colorectal cancer. *Frontiers in Pharmacology*, **2026**, 17: 1868875. https://doi.org/10.3389/fphar.2026.1868875
[118] Gong, J., Guan, G. P., Wang, S. S., et al. The *Aloe vera* polysaccharides in inflammatory bowel disease: An ethnopharmacological review on the mechanisms of intestinal barrier repair and immunomodulation. *Journal of Ethnopharmacology*, **2027**, 373: 122286. https://doi.org/10.1016/j.jep.2026.122286
[119] Suo, X. J., Wang, X. L., Liang, P., et al. Based on the "gut microbiota-barrier-immunity" axis to explore the mechanism of action of traditional Chinese medicine polysaccharides in the treatment of inflammatory bowel disease and structure-activity relationship: A review. *International Journal of Biological Macromolecules*, **2026**, 378: 153802. https://doi.org/10.1016/j.ijbiomac.2026.153802
[120] Zhu, W. Y., Jia, C. Y., Fei, T. Y., et al. Baicalin as a multifunctional regulator of gut health: Integrative mechanisms involving inflammation. *Drug Design, Development and Therapy*, **2026**, 20: 585486. https://doi.org/10.2147/DDDT.S585486
[121] Khasanov, R., Boettcher, M., Wessel, L. M., et al. All roads lead to NF-κB: The NF-κB pathway as a major target for intestinal inflammatory disorders. *Frontiers in Immunology*, **2026**, 17: 1816653. https://doi.org/10.3389/fimmu.2026.1816653