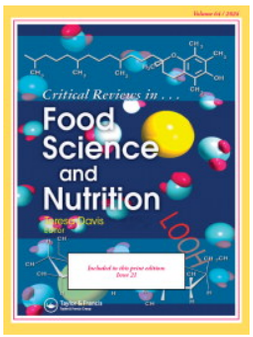

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Oliver W. Meldrum & Gleb E. Yakubov

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REVIEW ARTICLE

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Journey of dietary fiber along the gastrointestinal tract: role of physical interactions, mucus, and biochemical transformations

Oliver W. Meldrum[a] and Gleb E. Yakubov[b]

[a]Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore, Singapore; [b]Soft Matter Biomaterials and Biointerfaces, School of Biosciences, University of Nottingham, Nottingham, UK

ABSTRACT

Dietary fiber-rich foods have been associated with numerous health benefits, including a reduced risk of cardiovascular and metabolic diseases. Harnessing the potential to deliver positive health outcomes rests on our understanding of the underlying mechanisms that drive these associations. This review addresses data and concepts concerning plant-based food functionality by dissecting the cascade of physical and chemical digestive processes and interactions that underpin these physiological benefits. Functional transformations of dietary fiber along the gastrointestinal tract from the stages of oral processing and gastric emptying to intestinal digestion and colonic fermentation influence its capacity to modulate digestion, transit, and commensal microbiome. This analysis highlights the significance, limitations, and challenges in decoding the complex web of interactions to establish a coherent framework connecting specific fiber components' molecular and macroscale interactions across multiple length scales within the gastrointestinal tract. One critical area that requires closer examination is the interaction between fiber, mucus barrier, and the commensal microbiome when considering food structure design and personalized nutritional strategies for beneficial physiologic effects. Understanding the response of specific fibers, particularly concerning an individual's physiology, will offer the opportunity to exploit these functional characteristics to elicit specific, symptom-targeting effects or use fiber types as adjunctive therapies.

KEYWORDS

Mucin; mucoadhesion; gut; microbiota; plant cell walls; food physics

1. Introduction

The human gastrointestinal (GI) tract employs a complex array of biochemical transformations and physical interactions to convert food into energy. A health-promoting diet that includes a generous intake of intact dietary fiber (DF) from whole foods like fruits, vegetables, legumes and whole grains are associated with reduced risk of cardiovascular diseases (Perez-Cornago et al. 2020), Type 2 diabetes (Weickert and Pfeiffer 2018), obesity (Wanders et al. 2014), liver cancer (Singh et al. 2018), and colorectal cancer (Encarnação et al. 2018; Ma et al. 2018). Moreover, DF consumption contributes to enhanced GI health, reducing the likelihood of irritable bowel syndrome (IBS) (So et al. 2021).

The significance of DF in protecting against non-communicable diseases and promoting long-term public health is reflected in nutritional guidelines that advocate for diets rich in plant-based whole foods. These guidelines recommend ~30 g of fiber per day (25 g for women and 38 g for men) (Slavin 2008). They were developed based on a rigorous analysis of available population-based epidemiological studies (Scientific Advisory Committee on Nutrition 2015). While epidemiological data are critically important for demonstrating the importance of DF intake, it has long been acknowledged that statistical associations between DF intake and health outcomes should be supported by mechanistic studies. Transitioning our understanding from correlation to causation necessitates further investigations that aim to uncover and establish the links between DF consumption and its physiological and biochemical effects.

Areas where the mechanistic understanding is particularly robust include the effects of dietary fiber in the upper gastrointestinal tract. Specifically, the consumption of DF leads to the formation of a gel-like substance in the upper gut (McRorie and McKeown 2017). This "viscous" material slows down the enzymatic breakdown of macronutrients, thereby delaying the absorption and re-absorption of small molecules and metabolites from the intestinal lumen (Stribling and Ibrahim 2023; EFSA Panel on Dietetic Products, Nutrition, and Allergies 2011). The impact of this effect can manifest as a decreased rate of starch hydrolysis and reduced diffusion of hydrolysis products, such as maltose, which play a role in improving glycemic control (Feinglos et al. 2013; Anderson et al. 1999). Similarly, the slowed re-absorption of bile acids (BA) due to this gel formation has been shown to contribute to lowering low-density lipoprotein (LDL)-cholesterol (Wolever et al. 2010). A high glycemic index and elevated LDL-cholesterol are well-established risk factors for developing Type 2 diabetes and cardiovascular diseases.

CONTACT Gleb E. Yakubov gleb.yakubov@nottingham.ac.uk; Oliver W. Meldrum oliver.meldrum@ntu.edu.sg

The last decade has seen significant strides in enhancing our understanding of the underlying mechanisms of DF functionality. These advancements concern not only the upper gut and the effects of DF on colonic fermentation and the gut microbiome but also the overall gut physiology, including the impact of DF on the gut-liver, gut-immune system, and gut-brain axes (Ding et al. 2020; Tilg, Adolph, and Trauner 2022). This review focuses on the mechanisms underpinned by the biomolecular and biophysical properties of DF. We summarize the nutritional importance and functionality of DF across physiologically relevant length scales within the GI tract. We begin by examining different types of DF, their supramolecular assembly, and their functionality within the digestive system. Additionally, we discuss emerging evidence regarding the influence of mucus biophysical properties on the mucoadhesive interactions with dietary polysaccharides, providing new insights into the mechanisms underlying DF functionality. Finally, we propose potential avenues for unraveling the intricate web of interactions and present a novel framework for designing food structures in functional and personalized nutrition applications.

1.1. Dietary fiber "goodness"

To date, our understanding of the functionality of DF is limited and incomplete, necessitating further exploration of the fundamental mechanisms encompassing physiological, biochemical, and biophysical pathways. This deeper level of understanding is crucial for addressing practical challenges, such as establishing clear indicators of fiber quality for digestive health, implementing personalized dietary recommendations, and optimizing the nutritional benefits of fiber-rich diets. The variability and structural complexity of DF represent significant factors that influence fiber fermentability and its interactions with digestive processes (Low et al. 2021). For example, different physico-chemical properties, such as particle size, can significantly impact intestinal health. Studies have shown that wheat bran fractions with varying particle sizes have different effects on obesity, inflammation, and gut microbiota (Suriano et al. 2017, 2018). Specifically, smaller particle sizes were associated with reduced hepatic and systemic inflammatory markers upon high fructose intake, likely due to the beneficial modulation of gut microbiota. In contrast, larger particle sizes affected gut microbiota composition and fat binding capacity differently, illustrating the critical role of fiber particle size in determining health outcomes. The continuum between soluble and insoluble fiber (Gidley and Yakubov 2019) presents a need for enhanced analytical methods to assess fiber functionality accurately. Furthermore, the intricate interplay between physiological responses, including motility, hydration, water re-absorption, and the complex flow properties of fiber-rich digesta (chyme), remains inadequately characterized (Low et al. 2020), impeding a comprehensive understanding of fiber transformation throughout the digestive system.

A high fiber diet, primarily derived from fruits and vegetables, has demonstrated efficacy in managing symptoms associated with IBS and inflammatory bowel diseases (Ford et al. 2008; Wedlake et al. 2014). For example, excluding cereal fiber, such as bran and brown bread from the diet while increasing overall fiber intake may prove beneficial in alleviating symptoms of these conditions (Francis and Whorwell 1994; Jalihal and Kurian 1990; Prior and Whorwell 1987; Fernández-Bañares et al. 1999; Welters et al. 2002). However, the available evidence on the subject is limited and conflicting. This is either due to the lack of statistical power or limited experimental control, which leads to numerous confounding factors. The lack of mechanistic insights on the level of digestive physiology or bio-physicochemical interactions also limits the development of foods and beverages with improved DF functionality and, equally, hinders our ability to provide targeted and comprehensive nutritional recommendations.

DF is defined as part of the plant material in the diet that is resistant to enzymatic digestion (Dhingra et al. 2012). This includes both "soluble" and "insoluble" fibers, a simple classification based on the material's behavior when DF is dispersed in water. It is important to note that different types of DF evoke distinct physiological responses due to their unique chemical structures and sizes, which can range from small oligosaccharides (3–9 sugar units long) to intact plant tissue (>1 mm) (Dai and Chau 2017). Each type has distinct sites of action within the GI tract. Soluble fibers are primarily fermented in the colon, producing short-chain fatty acids (SCFAs) that are beneficial for colonic health and have a strong influence on systemic metabolism. In contrast, insoluble fibers are typically poorly fermentable and function as bulking agents, influencing gastric emptying and promoting bowel regularity.

However, traditional categorization of fiber as soluble or insoluble is not always accurate, as certain fibers may be insoluble but readily fermentable (i.e., apple pulp, wheat bran and banana pulp), or soluble but resistant to microbial enzymes due to their complex chemical structure (i.e., some psyllium and mucilage gums) (Marlett, Kajs, and Fischer 2000; Widaningrum et al. 2020). Moreover, the processing of cereal bran particles can influence their solubility and capability to elicit a broad range of microbial functions within the GI tract. For instance, hydrothermal or mechanical processing can enhance the formation of hydrated surface layers composed of "dangling" (exposed) carbohydrate chains that are more readily degraded (Grundy et al. 2017; Boll et al. 2016). This differentiation blurs the categorization of fiber as "soluble" and "insoluble," where "fluffed-up" particles may exhibit poor solubility while still eliciting a broader range of fiber functionality across the GI tract.

To gain a deeper understanding of the health benefits, Gidley and Yakubov (2019) and Williams et al. (2019) have proposed a classification system based on fiber size and density. This approach moves away from the traditional categorization of "soluble" and "insoluble" fibers and instead focuses on the semi-quantitative functional properties, such as their ability to inhibit macronutrient digestibility and availability for fermentation. However, due to the inherent complexity and heterogeneity of fibers and their components, it remains challenging to develop a coherent framework for characterizing fiber at the polymer, cell wall, and tissue levels (Burton, Gidley, and Fincher 2010). Moreover,

establishing a direct link between food components and their specific health benefits is difficult (Capuano 2017), as the mechanisms underlying nutritional functionality vary at different stages of digestion.

To overcome these challenges, researchers must consider the physiological and biochemical mechanisms at play in specific nutritional scenarios, considering the critical length scales at which these interactions occur. This approach will allow for a more detailed understanding of the extent of DF functionality and its impact on health.

To effectively refine dietary recommendations, it is important to address key questions about dietary interventions: "Does it work?," "How does it work?," "For whom does it work?," and "What factors enhance its effectiveness." This approach necessitates a nuanced understanding of DFs, acknowledging their diversity and context-dependent functionality. Different types of DFs exhibit distinct mechanisms of action within the GI tract, which are influenced by the specific dietary and physiological context. This comprehensive perspective is essential for optimizing the application of DFs in individualized nutritional strategies, thereby maximizing their health benefits. The lack of a detailed understanding of the questions above hinders the optimization of fiber types for specific dietary recommendations.

To enhance our comprehension of how DF works and its application in dietary recommendations, it is crucial to delve into the physiological and biochemical mechanisms that drive specific nutritional scenarios, while considering the relevant length scales involved. For instance, the influence of gravity on peristalsis in the ascending colon can affect the duration available for microbial fermentation of DF substrates (Uno 2018). The physical attributes of fiber, including particle size and density, directly impact its fermentability and overall functionality. Refining insoluble fiber through processes like milling or micronization techniques, such as extrusion or ball milling can decrease its bulk density and alter its physicochemical properties toward the improvement of fiber functionality (Chau, Wen, and Wang 2006; Brennan, Monro, and Brennan 2008).

By examining the interplay between molecular, micro, and macro scales within specific fiber chemistries, such as plant tissue and cell wall fragments, we can gain a deeper understanding of the breadth of DF functionality across different length scales. This comprehensive approach holds potential for developing novel tools to balance nutritional requirements and provide a more holistic perspective on the health advantages of DF.

2. Supramolecular assembly of cell walls into a network of food particles

The nutritional benefits of whole foods are influenced by three key structural domains: supramolecular assembly, colloidal microstructure, and polysaccharide primary structure. Whole foods (Figure 1(A)) consist of cellular clusters containing fragments of the epidermis, bran layer, and vascular

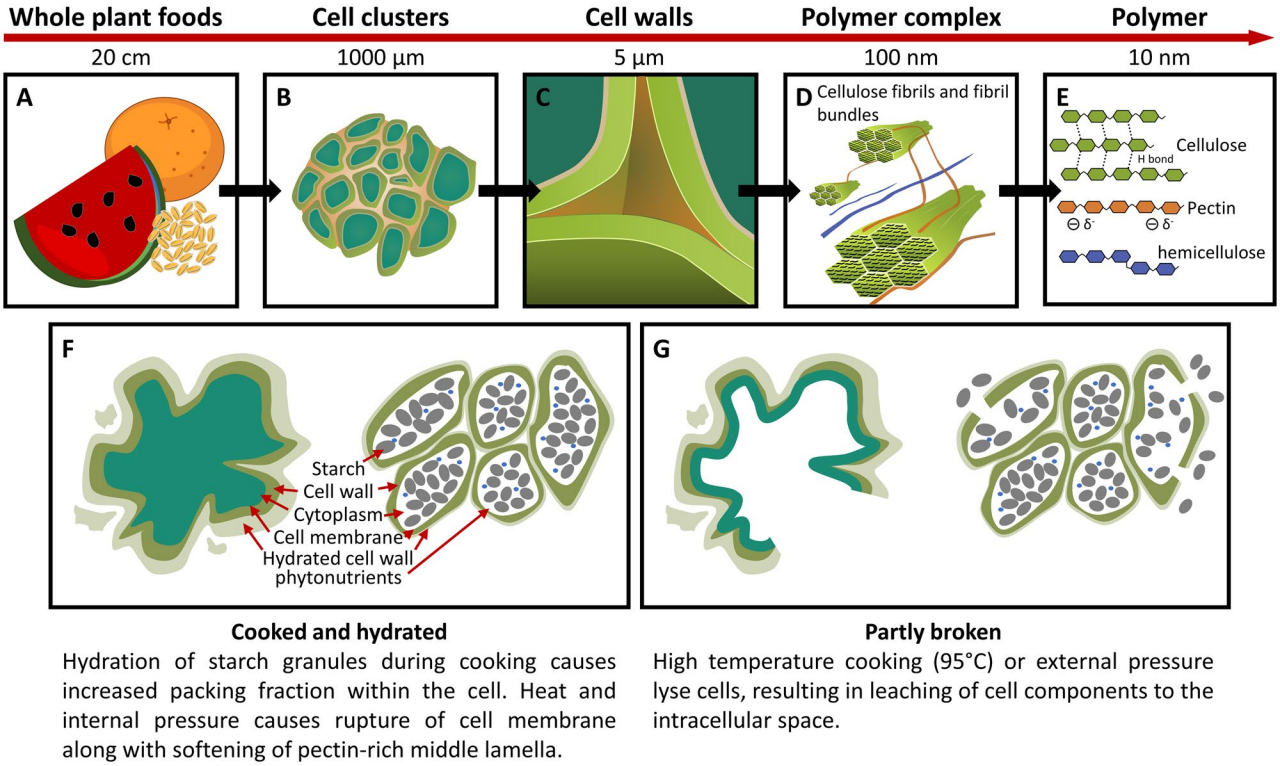

Figure 1. Hierarchical organization of whole plant foods. The horizontal red arrow represents relative sizes, including (A) whole plant foods; (B) cell clusters; (C) cell wall/Middle lamella contacts between adjacent cells; (D) polymer complex of supramolecular assemblies, including cellulose fibrils and fibril bundles containing hemicellulose and pectin; and their (E) individual polymer structures. (F) cell and cell clusters from non-starch (left) and starch-bearing tissues (right), such as legumes and grains, can undergo swelling, rupture, and chemical transformation during crop processing, storage, food manufacture, and digestion, with (G) processing allowing enzymes into the cell interior, facilitating the release of cell contents, including starch, vitamins, and phytonutrients.

tissue (Figure 1(B)). The primary cell walls of these cells are composed of hemicellulose (xylan, mannan, xyloglucan, β-glucan) absorbed onto a network of cellulose microfibrils, with pectin polysaccharides filling the middle lamella to contribute plasticity and lubrication between adjacent cells (Figure 1(C)) (Dolan et al. 2017; Bidhendi, Chebli, and Geitmann 2020; Cosgrove 2018).

At a finer scale, polymer complexes exhibit a range of structural arrangements, from tightly coiled helices to loosely intertwined structures around the cellulose microfibril, driven by intermolecular (exist between molecules) forces that induce various secondary and tertiary conformations (three-dimensional form; Figure 1(D)) (Schefer, Usov, and Mezzenga 2015; Diener et al. 2019). Fiber structures can be categorized as either amorphous or crystalline. Crystalline fibers, like cellulose, consist of linear chains of β-(1,4)-linked glucose units that form microfibrils of 18- and 24-chain structures aligned through hydrogen bonding, rendering them resistant to enzymatic breakdown by the human colonic microbiome (Oehme et al. 2015). On the other hand, amorphous fibers, such as mixed-linkage β-glucans and arabinoxylans, are more readily fermented. It is important to note, however, that the fermentability of hemicellulose dietary fibers, such as arabinoxylans (AXs), is closely linked to their degree of polymerization. Not all AXs are readily fermented (Li et al. 2022). For example, AXs with a higher degree of polymerization tend to be less fermentable compared to those with shorter chains, which can be more easily broken down by colonic bacteria.

The primary structure of cell wall/DF polysaccharides can be characterized by monosaccharide composition (i.e., D-glucose, D-galactose, D-mannose, D-fructose, D-xylose, L-arabinose, L-rhamnose and L-fucose), linkage type (i.e., α(1,4) or α(1,6) which includes anomeric (α or β)) configuration and carbon position, molecular weight and degree of polymerization (molecular size/length), degree and type of branching as well as motif and/or domain structure of polysaccharides (Figure 1(E)) (Hamaker and Tuncil 2014; Diener et al. 2019).

Fruits and vegetables exhibit diverse microstructural properties, including particle size, porosity, and surface area, which directly influence their physiological effects. These properties encompass both soluble and insoluble elements, characterized by their high hydration but low solubility, and vary in terms of plant origin and composition, including the proportion of DF and protein content (Table 1). For example, apples are mainly composed of simple sugars, such as fructose, while their DF is predominantly composed of pectin, along with smaller amounts of hemicellulose, cellulose, and structural proteins (Lopez-Sanchez et al. 2020). In contrast, the primary cell wall of starchy endosperm in cereal grains contains AX (~35%) with ferulic acid crosslinks and a smaller proportion of mixed-linkage (1 → 3) (1 → 4)-β-$_D$-glucan (β-glucan), which aids in maintaining cell wall integrity (Gartaula et al. 2018).

The degree of breakdown, fragmentation, and biophysical transformation of the original plant tissue into DF structures are strongly process-dependent. During oral processing and mastication, the movement of water across the cell wall (turgor pressure) influences the response of plant-based foods to mechanical stress, thereby determining the size of tissue fragments and the degree of liberation of cell wall particles (Mielke et al. 2021).

During ripening, the softening of fruit firmness is attributed to the disassembly of galactan and arabinan side chains in pectin, as well as the depolymerization of other matrix glycans, such as xyloglucan-cellulose networks (Brummell 2006; Videcoq et al. 2017). On one hand, the ripening process positively affects DF solubility but may result in the reduction of the complexity of DF polymer structures, making them more readily fermentable in the colon. This can lead to excessive water retention in the small bowel and/or higher volumes of gas in the colon, resulting in the emergence of adverse GI symptoms (Wilkinson-Smith et al. 2019).

Similarly, the cooking process can modify the porosity of cell walls through physical and chemical alterations of cell wall components (Dhital, Brennan, and Gidley 2019; Bhattarai et al. 2017; Li, Zhang, and Dhital 2019; Moelants et al. 2014) (Figure 1(F)). At elevated temperatures, water imbibition into the plant structures determines the degree of swelling of plant-based food and is partly responsible for the solubilization of hemicellulose and pectin from cell walls. Once liberated, soluble DF polysaccharides can spontaneously form supramolecular aggregates in the digestive tract, such as the formation of pectin gels in the acidic environment of gastric fluid (Khramova et al. 2019; MacDougall and Ring 2003).

Industrialized food processing, such as shell or hull removal, particle size reduction and homogenization (such as chopping, milling, grinding or blending), heat treatment (high pressure cooking or drying), or enzymatic treatment can lead to the highest levels of DF extraction. However, this is often accompanied by the rapture, fragmentation, and separation of plant tissue matrices (Figure 1(G)). Depending on the cell wall structure and the applied force, the resulting fiber fragments may undergo physical degradation of complex molecules, their chemical breakdown, or modification (Kumar et al. 2023).

3. Digestive function, structure, and mucus biology

3.1. Digestive function: a journey along "the tube"

The GI tract comprises a continuous canal that imparts physical, structural, and (bio)chemical transformations to DF from the oral cavity to the colon (Figure 2). The initial step of food digestion occurs in the oral cavity, where chewing, biting, and mixing with saliva disrupt solid and semi-solid foods, breaking them down into smaller particles and reshaping them into a bolus (Witt and Stokes 2015). Using medical terminology, oral processing represents the first "host challenge" for ingested food (Mosca and Chen 2017). Although oral processing is not an obligatory stage of digestion, it is a key factor in a healthy diet. It prepares food for the "journey ahead" and determines food acceptability. Longer chewing time has been linked to lower calorie intake, but not postprandial plasma glucose and insulin levels in healthy young adults (Borvornparadorn et al. 2019).

Table 1. Classification of dietary fiber according to supramolecular assembly, chemical composition, and molecular weight (degree of polymerization/polymer length).

Category	Fiber	Description	Dietary source	References
Cell clusters	Fruits	Fleshy fruits are dominated by parenchyma tissue, which is characterized by thin-walled primary plant cell walls. These cell walls are made up of a cellulose fibrillar framework surrounded by a gelled or partially soluble matrix of pectin, hemicellulose, and glycoproteins.	Fleshy fruits include the flesh or pulp layer of tissue, such as oranges, tomatoes, strawberries, and grapes.	Willats et al. 2001; Posé et al. 2019
	Vegetables	Vegetables are any part of a plant consumed as food. This review refers to fibrous plant tissue that has stopped growing and has a rigid, secondary cell wall. The most common class of cell wall polymer found in these secondary walls is lignin, a resin-like compound that provides structural support to the plant.	Fibrous vegetables include leafy greens, cauliflower, tomatoes, peppers, cucumber, and cabbage.	Padayachee et al. 2017
	Cereal grains and legumes	Cereal grains and legumes contain three main cell types: germ, endosperm, and bran layer. They are primarily composed of encapsulated starch, a small amount of cellulose and lignin, and non-starch polysaccharides, such as arabinoxylan, mixed linkage glucans, xyloglucan, glucomannan, and pectin.	Cereal grains and legumes include whole wheat pasta*, oatmeal, barley, beans, lentils, peas, and corn.	Burton and Fincher 2014; Bader Ul Ain et al. 2019
High molecular weight dietary fiber	Cellulose	Cellulose is an insoluble DF composed of β-(1,4)-linked d-glucose polymers that are assembled side-by-side to form a microfibril, providing tensile strength in cell walls. These microfibrils mesh into a polysaccharide matrix.	An important structural component of the primary cell wall of plants, such as kale and celery stalks, and many forms of algae and oomycetes.	Cosgrove 2005
	Hemicellulose	Hemicellulose is a type of heteropolymer, including xylan, mixed linkage β-glucan, arabinoxylan (AX), glucuronoxylan, glucomannan, and xyloglucan. These hemicelluloses, except mixed linkage β-glucan, contain side-branch structures that may be simple, such as a single monosaccharide with a few linkage types, or very complex with many monosaccharides, linkage types, and varying branching lengths. A common feature is the presence of a continuous β-1,4-linked backbone, except for β-glucan, which contains mixed linkages. The aggregation, binding (to cellulose), secondary structure and partial crystallization, and the ratio of amorphous/paracrystalline domains of the condensed assemblies are important structural features that determine dietary functionality.	Along with cellulose, hemicellulose is an essential structural component of the primary cell wall. The most abundant hemicellulose in annual plants is arabinoxylan and mixed linkage β-glucan, such as wheat, barley, and rice.	Scheller and Ulvskov 2010; Cosgrove 2005
	Pectin	Pectin, also known as pectic polysaccharides, is an acidic polysaccharide containing a linear chain of β-(1,4)-linked d-galacturonic acid with varying amounts of methyl esterified carboxyl groups. The degree of esterification determines the behavior of pectin in food applications, with a high ratio forming a gel under acidic conditions and in the presence of high sugar concentration. Low-esterified pectin, on the other hand, forms ionic bridges between groups of galacturonic acid when it interacts with divalent cations, such as calcium.	Pectin is primarily found in the primary and middle lamella of fruit cells walls, such as oranges, apples, and mangoes, allowing primary cell wall extension and plant growth, or used as food thickeners, fat/sugar replacers in the processed food industry.	Broxterman and Schols 2018
	Seed mucilage	The seed coat of some plants contains mucilage, a polysaccharide-rich hydrogel that protects against dehydration. The composition of the monosaccharides in this hydrogel varies depending on the species and tissue type.	Seed mucilage is released from seed coat epidermal cells. *Salvia hispanica* (chia) and *Plantago ovata* extrude seed mucilage used as gelling agents and food thickeners, egg replacements, and fat alternatives in the food production industry.	Phan and Burton 2018
	Resistant starch	Starch is a branched glucose polymer with α-(1,4) linear links and α-(1,6) branch points, consisting of amylopectin (many short-side branches) and amylose (few long-chains branches). Resistant starch (RS) is a functional description that includes degradation products that are not absorbed in the small intestine. RS can be classified into four types: physically inaccessible or indigestible starch encapsulated within intact plant tissue or processed forms (RS_1); native, semicrystalline, granular forms found in raw foods, such as bananas or high-amylose maize (RS_2); partially recrystallized double-helix structures that form when starch is cooked and cooled, such as cooked and cooled potatoes of stale bread (RS_3); and chemically modified starch (RS_4).	Plants store starch in tightly packed granules containing layers of amylose and amylopectin. The size, shape, and amylose content vary by botanical source. In the diet, starch can be encapsulated by cell walls, including whole grains, legumes, cooked and chilled pasta, potatoes and rice, and unripe bananas.	Lopez-Rubio et al. 2008; Warren et al. 2018
	Lignin	Lignin is a class of complex cross-linked phenolic polymers that fill the spaces between cell walls. These are covalently linked to different plant polysaccharides, conferring mechanical strength to cell wall complexes.	Lignins are commonly produced as a by-product in pulp products, such as okra (Lady's finger).	Terrett and Dupree 2019
	Fructan (high Mw inulin)	Fructan is a general term for various carbohydrates, such as fructooligosaccharides, oligofructans, and inulin, depending on the degree of polymerization.	Fructans represent the main storage carbohydrate found in the vacuole and are found predominantly in plants from temperate climate zones, such as wheat products and legumes.	Vijn and Smeekens 1999
	Bacterial exopolysaccharides	Bacteria produce a variety of extracellular polysaccharides, including xanthan, alginate, and cellulose. These polysaccharides play a role in biofilm formation and pathogenicity.	Synthesized by bacteria of all taxa with distinct chemical properties.	Nwodo, Green, and Okoh 2012

(*Continued*)

Table 1. Continued.

Category	Fiber	Description	Dietary source	References
Low molecular weight dietary fiber	Galacto-oligosaccharides	Galacto-oligosaccharides (GOS) are β-galactosides produced by glycoside hydrolases using lactose as a substrate. These galactosides consist of terminal glucose units and remaining galactose units linked together by β-glucosidic bonds.	GOS mixtures of different DP are naturally found in dairy products and legumes or sold commercially as prebiotics.	Torres et al. 2010
	Arabinoxylan-oligosaccharides	Arabinoxylan-oligosaccharides (AXOS) are hydrolysates of AX containing a moderate amount of arabinose substitution and a lower average degree of polymerization. AXOS are derived from the hydrolysis of AX, a type of hemicellulose found in plant cell walls.	AXOS is generated in processed cereal-based food products, including bread, pasta, and beer, through the interaction of endoxylanases with cereal-derived AX.	Broekaert et al. 2011
	Inulin-type fructans	Inulin-type fructans are either oligomers or polymers of fructose, known as fructo-oligosaccharides (with 5–12 monomers) or long-chain inulin (with 13–67 monomers). Fructans with a degree of polymerization (DP) of 3–6 are sweet-tasting and are used as low-calorie food ingredients. Inulin-type fructans are commonly found in plant-based foods and are classified based on their DP.	Fructans are present in vegetables but can also be isolated from non-edible plant sources, such as chicory roots or synthesized from saccharose.	Vijn and Smeekens 1999
	Human milk oligosaccharides (HMO)	HMOs, or human milk oligosaccharides, are complex indigestible sugars that structurally and biologically vary. They play a role in modulating the infant immune system and impacting microbiota development. HMOs are found in human milk and are not digestible by the infant, but instead, are metabolized by gut bacteria.	HMO is the third most abundant solid component in human milk, after lactose and lipids.	Bode 2012

*Whole grains are defined as intact, ground, cracked, or flaked caryopsis, whose principal anatomical components include the starchy endosperm, germ, and bran layer.

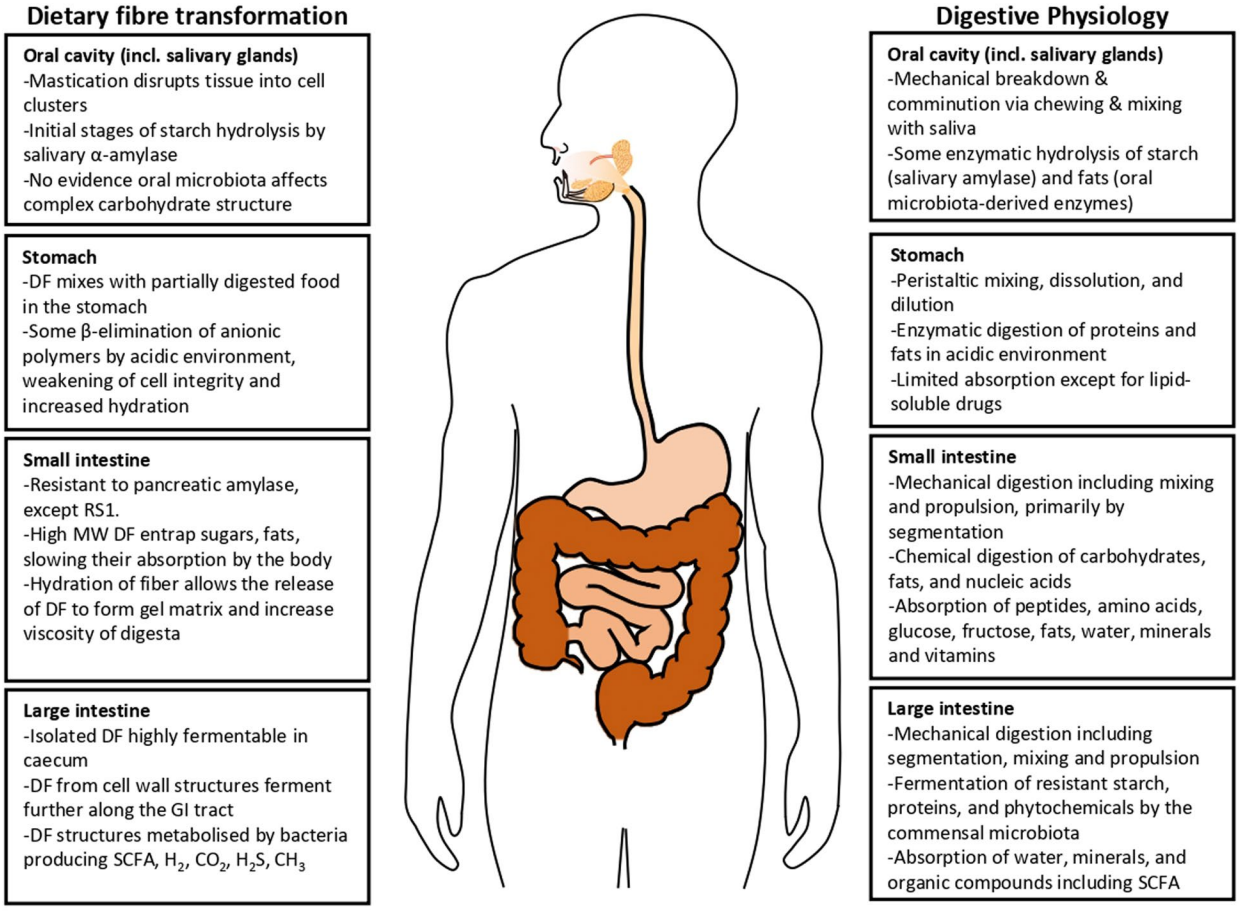

Figure 2. Relationship between dietary fiber transformation and digestive physiology throughout the gastrointestinal tract. Sequential processes that dietary fiber undergoes as it progresses through the various segments of the digestive system, where enzymatic breakdown, fermentation, and absorption of dietary fiber in each anatomical region of the gastrointestinal tract.

The effect is due to a combination of factors, including behavioral, cognitive, and psychophysiological mechanisms affecting satiation (cessation of hunger during eating) and satiety (perception of fullness after a meal).

On the mechanistic level, oral processing prepares the food bolus for further transformation in the stomach. One key mechanism that connects oral processing with the gastric phase is the effect of salivary amylase on the initial

stages of starch hydrolysis. During oral processing the extent of starch conversion is low but becomes significant during the residence of the bolus in the stomach, that is when the pH inside bolus is high (typically above 5) due to buffering effect of saliva, facilitating the action of salivary α-amylase (Woolnough et al. 2010). The presence of DF and delayed gastric emptying may increase the degree of starch hydrolysis and enable an early release of simple sugars into blood circulation, triggering the satiety mechanisms, smoothing the blood glucose absorption, and reducing the occurrence of blood glucose spikes.

The presence of DF also influences the consistency of the bolus in the stomach and the degree of its disintegration before it enters the small bowel and, ultimately, all the way to the colon. Gunn et al. (2022) reported that psyllium fiber appeared as a blob on the magnetic resonance imaging (MRI) image scans, which when combined with FODMAP-rich foods, such as inulin, can reduce colonic gas symptoms associated with its consumption, without disturbing the microbiota or requiring severe dietary restriction.

In the small bowel, DF in the form of plant cell walls can act as an effective barrier that prevents the penetration of digestive enzymes, encapsulating starch and making it inaccessible for enzymatic digestion (Chi et al. 2022). This encapsulation by cell walls exhibits remarkable efficiency in slowing hydrolysis, warranting its classification as Type 1 Resistant Starch due to its resistance to enzymatic breakdown (Rovalino-Córdova, Fogliano, and Capuano 2018; Low et al. 2015). It is important to note that the generic nature of the physicochemical effects of DF may have negative effects too. They may slow protein hydrolysis and delay the adsorption of vitally important amino acids in the blood stream. These effects may result in malnutrition, which is particularly important in elderly and young people, and also within the communities of the developing world where foods may be high in DF but comparatively low in protein (Morais, Chevalier, and Gougeon 2006).

The critical and well-acknowledged effect of DF is its water-holding capacity, which influences water absorption from the lumen and determines digesta viscosity. This, in turn, strongly affects peristalsis across the distal small bowel and colon. In the colon, fiber properties determine fermentation pathways and play an instrumental role in the poorly understood balance between broth fermentation and that accomplished by biofilm consortia formed on the surface of DF/cell wall particles (Dhital et al. 2016; Gorham et al. 2016).

Additionally, in these regions, liquid, solid, and gas phases coexist due to the stabilizing and interfacial activity of hydrocolloids—a complex collective of endogenous and exogenous polymers and surfactants, including fiber. The significance of this lies in the formation of a multi-phase complex fluid with intricate flow and transport properties, which may elicit varying and challenging-to-predict physiological responses. Amongst many polymeric components present in GI tract are polymer, high-molecular weight mucins, the presence of which can have a strong effect on digestion and the fate of DF.

3.2. Secreted polymerizing mucins of the digestive tract

In the GI tract, mucus serves as a critical barrier, composed primarily of mucins—specialized glycoproteins that maintain mucosal integrity against the harsh luminal environment (Table 2) (Johansson et al. 2008). This crucial barrier serves as a primary site for interaction and exchange with the external environment, functioning as the gatekeeper of intestinal health by preventing trillions of microorganisms from directly contacting the intestinal epithelium. Mucus is produced by goblet cells and submucosal glands, with a notable distribution of goblet cells across the intestinal surface, including both the villi of the small intestine and the crypts of the colon, contrary to previous simplifications of their localization (Ermund et al. 2013).

Despite being a dilute aqueous secretion (the content of proteinaceous solids is ca. 1–2 wt%), mucus is a complex fluid. The composition of mucus varies across different sections of the GI tract. Polymerizing mucin glycoproteins, including MUC5AC and MUC6, are dominant in the lining of the stomach, while MUC2 mucins are almost exclusively found in intestinal mucus. Mucin glycoproteins contribute to the viscoelastic and gel-like properties of mucus, which are crucial for incorporating digestive enzymes, salts, lipids, and cellular debris, thus facilitating the formation of a protective layer over the GI mucosa (Johansson et al. 2008; Gustafsson et al. 2012).

Polymerizing mucins are a family of large, complex, glycosylated proteins, featuring densely O-linked polyanionic glycosylated side chains (Figure 3(A)) along the central

Table 2. Composition and location of secreted polymeric mucins along the gastrointestinal tract.

Tissue	Gel-forming mucins	Concentration	pH	Clearance/production rate	Mean layer thickness	Additional defense mechanisms
Oral cavity	MUC5B, MUC7, MUC19 (Wickström et al. 1998)	1% (Iorgulescu 2009)	6.8 (Aframian, Davidowitz, and Benoliel 2006; Dawes 2004)	0.1–0.3 mL/min (Dawes 2004)	7–100 µm (Collins and Dawes 1987)	Tongue/oral movement, lysozymes, flushing of the mouth with saliva
Stomach	MUC5AC, MUC6 (Ho et al. 2004)	3% (Bansil et al. 2013)	1.6 (Fallingborg 1999)	4–5 h (Deshpande et al. 1996)	180 µm (Allen et al. 1990)	Gastric acid, digestive enzymes
Small intestine	MUC2 (Gum et al. 1994)	1.5% (Macierzanka et al. 2014)	6.9 (Fallingborg 1999)	47–270 min (Ermund et al. 2013; Schneider et al. 2018)	37–171 µm (Sarosiek et al. 1991)	Bile acids, digestive enzymes, defensins
Large intestine	MUC2, MUC5AC, MUC6	1.3–1.9% (Howard et al. 2021)	6.7 (Fallingborg 1999)	3 h (Arike et al. 2020); 240 µm/h (Gustafsson et al. 2012)	50 (adherent)–140 (loose) µm (Gustafsson et al. 2012)	Impermeable inner mucus layer, commensal microbiota occupying outer layer

protein region rich in proline, threonine and serine residues (Svensson et al. 2018). These side chains are periodically interrupted by hydrophobic "naked" cysteine-rich regions, giving rise to a flexible "bottlebrush"-like structure (Ambort et al. 2011) (Figure 3(B)). This alternating pattern of negatively charged hydrophilic regions and globular hydrophobic blocks yields a linear conformation resembling the architecture of amphiphilic brush multi-block copolymers (Bates and Fredrickson 1990; Verdugo 2012; Crouzier et al. 2015) (Figure 3(C)). Notably, the complex array of mucin-type O-glycosylation (hereafter referred to as glycans), comprising up to 80% of mucin mass, presents multiple potential ligands for microbial adhesion and serves as an energy source for the commensal microbiota (Arike and Hansson 2016). MUC2, the primary structural polymer in the intestines, exists as a random coil conformation with a molecular mass of ~1.5 MDa and a chain length varying from 50 to 1000 nm (Round et al. 2012; Herrmann et al. 1999). These glycans form homo-oligomers through intermolecular disulfide bonds facilitated by cysteine-rich D-domains (Meldrum et al. 2018) (Figure 3(D)).

Glycosylation patterns vary along the GI tract and among different mucin forms, influenced by the individual's health status, disease conditions, and the commensal microbiome

A

Monosaccharide type	Physiological charge	pKa (strongest acidic)	pKa (Strongest basic)
N-acetyl-D-galactosamine (GalNAc)	0	11.6	-1.6
N-acetyl-D-glucosamine (GlcNAc)	0	11.6	-0.78
Galactose (Gal)	0	11.3	-3
Fucose (Fuc)	0	11.3	-3.6
Mannose (Man)	0	11.3	-3
Sialic acids (N-Acetylneuraminic acid)	-1	3.02	2.09
or (N-Glycolylneuraminic acid)	-1	2.85	1.19

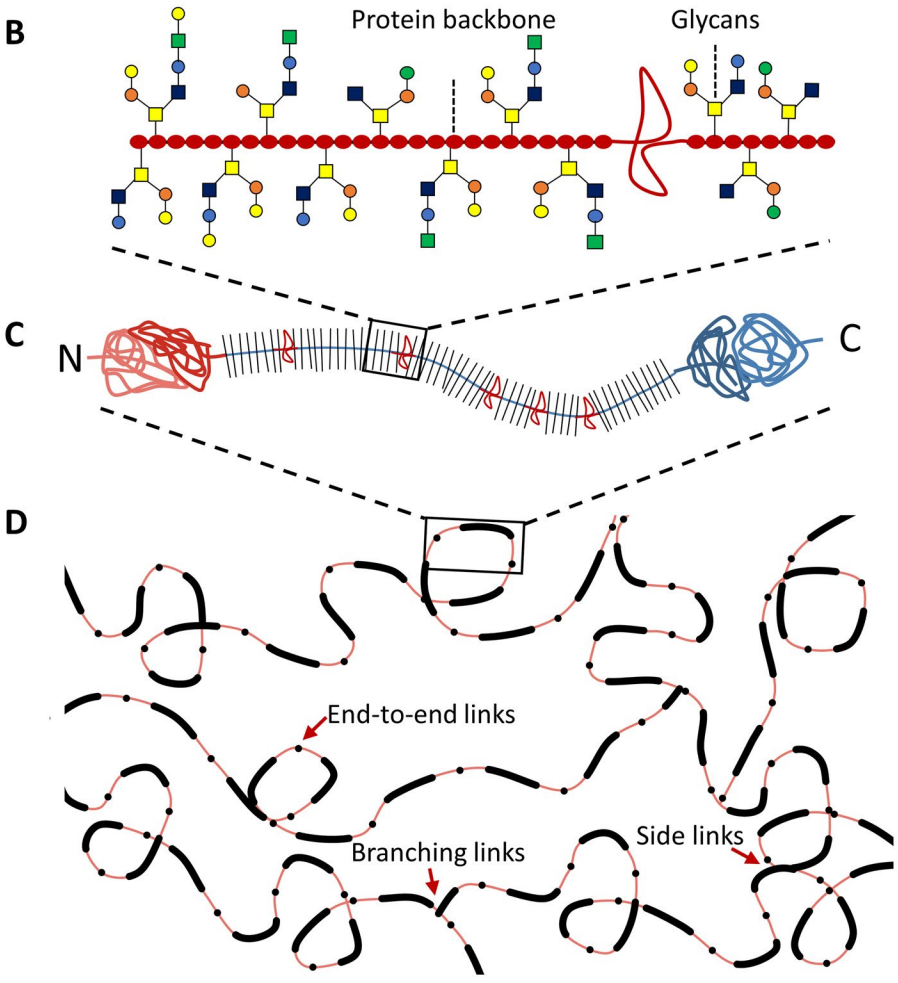

Figure 3. Illustration of the primary structure and assembly of mucin glycoproteins. (A) Table of O-linked mucin glycans, (B) the Central glycosylated protein region; (C) these glycosylated domains are interrupted by non-glycosylated cysteine-rich domains (Cys-D) and capped at each end of N- and C-terminal regions; (D) non-glycosylated terminal and Cys-domains form a network through covalent and reversible interaction between mucin glycoproteins.

(Etienne-Mesmin et al. 2019; Hansson 2020; Holmén Larsson et al. 2013; Jin et al. 2017). Each glycan side chain consists of 2–20 neutral and negatively charged sugars, with N-acetylgalactosamine (GalNAc) being the initial addition to the hydroxyl group of serine or threonine residue (Tran and Ten Hagen 2013). Subsequent stepwise extension involves the stepwise addition of core O-glycan structure with further modified or extended by adding other sugars, such as galactose, GlcNAc, fucose, and sialic acid, leading to the formation of extended linear or branched structures (Tran and Ten Hagen 2013). These sugars may also carry carboxyl (e.g., N-acetylneuraminic acid [Neu5Ac]) and sulfate (e.g., GalNAc, GlcNAc, Gal) groups, contributing to an overall negative surface charge, which renders mucin pH and cation-sensitive in terms of their elastic properties and conformation (Bansil, Stanley, and Lamont 1995; Cao et al. 1999; Wagner et al. 2017). Mucins engage in noncovalent interactions (e.g., electrostatic and hydrophobic interactions, hydrogen bonds, physical entanglement) as well as covalent interactions (e.g., *via* disulfide bonds) with other mucin molecules and various mucus components, including DNA, lipids proteins, salts and cellular debris, resulting in the formation of a mesh-like viscoelastic gel layer (Lai et al. 2009; Meldrum et al. 2018) (Figure 3(D)). In the stomach, approximately half of the MUC5AC O-glycans carry a neutral charge, displaying low sialylation and fucosylation (Robbe et al. 2004).

Another level of complexity of the mucosal barrier is glycocalyx—a layer of membrane-bound mucins that coats the epithelial cells, providing an ultimate defense line against pathogen invasion and enzymatic digestion. Alongside glycocalyx, mucus takes on the form of a 3-layered sandwich. Directly adjacent to the glycocalyx is the tightly adherent layer of secreted mucus, which then transitions to a loosely adherent mucus layer. The distinction between the tightly and loosely adherent layers of mucus is particularly important in mucus turnover and providing a stable barrier to particulate matter and pathogens. Whilst the tightly adherent layer acts as a mesh and diffusive barrier, the loosely adherent layer is more dynamic and can be easily displaced, which is instrumental for the entrapment and elimination of foreign particles. The multi-layered system of mucus is finely regulated and varies in thickness and composition from the stomach to the colon, reflecting the local needs for protection and interaction with pathogens and dietary components. The effect of dietary components and fermentation products on mucus production and its layered structure remains poorly understood, with some reports indicating the possibility of the existence of such mechanisms (Ito et al. 2009; Martínez-Maqueda et al. 2012).

3.3. Assembly and biophysical properties of mucus

In understanding mucus, it is important to define polymer networks and recognize mucus as a chemically cross-linked network. A polymer network refers to a three-dimensional structure formed by linking long polymers together. This network possesses unique physical properties due to the presence of a solvent (typically water), which in turn entraps the solvent to prevent the collapse of the matrix and creates a microenvironment in equilibrium with the surrounding media. Mucus gels represent a specific type of polymer network where the polymers are interconnected through covalent intermolecular bonds as well as other chemical and physical cross-links, such as hydrogen bonds, electrostatic and hydrophobic interactions. The nature of these interactions determines the overall topology and bulk properties of mucus gels, influencing their interactions with small molecules and the commensal microbiome.

Gastric and intestinal mucins have the ability to form linear (unbranched) and branched (e.g., trimer) structures, respectively. These structural characteristics have important repercussions: in the stomach, the large linear conformation allows for the formation of entangled networks (Verdugo 2012) that remain fluid and capable of rearrangement due to chain reptation, a type of diffusive motion through an entangled network (de Gennes and Leger 1982; Hong et al. 2005). In the intestine, mucins undergo dimerization and trimerization through disulfide bonds, resulting in the formation of oligomeric structures that restrict lateral motion (Godl et al. 2002). This arrangement allows for the creation of "lamella networks" within a single plane, which is crucial for mucus assembly (Round et al. 2012; Ambort et al. 2012). However, the role of other molecules, such as proline-rich proteins and keratins, in mucin assembly remains unclear (Meldrum et al. 2018).

The variability in mucus production and clearance rates along the GI tract results in distinct characteristics of viscosity, pH, and composition, crucial for maintaining mucosal integrity (Table 2). Specifically, in the stomach, the transition from a lower pH in the lumen to a higher pH near the mucosal surface is predominantly governed by local buffering mechanisms rather than mere proton diffusion. This buffering capacity is integral to the protective function of mucus against the acidic gastric environment. Notably, when mucin oligomers are enclosed within granules under acidic conditions with high Ca^{2+} concentration (Trillo-Muyo et al. 2018), the negative charges in mucins are protonated (neutralized) and electrostatically screened. Subsequent expansion of mucin molecules through the polyelectrolyte swelling mechanism (Rubinstein et al. 1996) sees the exchange of divalent Ca^{2+} ions, which act as a "crosslinker" between two polymer strands to allow much tighter condensation than when the negative charges of the network are shielded by monovalent cations (Na^+ and K^+) in the lumen (Sircar, Keener, and Fogelson 2013).

Under highly acidic conditions of stomach, protonation of negatively charge sialic acid and carboxylic acid residues occur, inducing alterations in mucin's tertiary structure (Javitt et al. 2020). This exposes hydrophobic regions and facilitates interactions between mucin molecules or with polymers, leading to a transition from a soluble to a gel-like state. For instance, the acidic environment of the gastric environment establishes a highly cross-linked network to impede the diffusion of digestive enzymes toward the underlying epithelial surface (Bahari, Ross, and Turnberg 1982). *Helicobacter pylori*, a pathogen associated with ulcers, produces ureases that hydrolyze urea to produce ammonia,

elevating the pH within the local environment, enabling the penetration into the underlying mucosa, thereby modifying the mechanical properties of mucus (Su et al. 2018).

In the small intestine, under neutral pH conditions, repulsive electrostatic interactions among negatively charge sialic acid and carboxylic acid residues sustain the extended confirmation of mucin. As a result, the mucus exhibits a more fluid nature, which may facilitate the rapid absorption of nutrients (Mackie, Macierzanka, et al. 2016). In contrast, the large intestine possesses two distinct layers of mucus with similar composition but different structure (Johansson et al. 2008; Ambort et al. 2012). The inner layer has a tightly organized MUC2 polymer network, which is stabilized by covalently cross-linked isopeptide bonds formed by the action of transglutaminase 3 (Sharpen et al. 2022). The outer layer originates from the partial degradation of the inner layer; it features a more open MUC2 polymer structure, providing a niche for microbial colonization (Johansson et al. 2008). The microbial colonization of the outer mucus layers is facilitated by the ability of bacteria to utilize mucin glycans as a carbon source. The majority of taxa express endo-acting O-glycanases, which enable cleavage of O-glycans and play a part in mucin breakdown (Crouch et al. 2020). This arrangement, couple with molecular components of the innate immune system like secreted IgA, ensures the separation of commensal and/or opportunistic microbiota from the epithelium, which is crucial for intestinal homeostasis (Meyer-Hoffert et al. 2008).

Past investigations on mucus in the stomach and intestine have faced challenges due to the utilization of inadequately processed samples, leading to potential alterations in the structure and properties of mucins. The use of mucin derived from the porcine stomach or dissected tissue samples from the porcine stomach and intestine has been associated with disruptions in protein conformation during processing. This, in turn, can impact mucin gelation, as observed in previous experiments (Meldrum et al. 2018). To ensure accurate interpretation of experimental findings, it is imperative to appropriately process and handle mucin samples (Sardelli et al. 2019).

4. Physical interactions and biochemical transformations

4.1. Functional characteristics of dietary fiber in the gastrointestinal tract

The intricate structure of plant cell walls in fruits, vegetables, and grains poses challenges in comprehending their functionality within the GI tract and their contribution to health. Although a diverse array of fiber types are present in a typical diet, there remains a need for a more comprehensive understanding of the specific chemical and physical interactions that underlie the reported health benefits (Mackie, Macierzanka, et al. 2016). Furthermore, the impact of fiber material dilution on the viscosity of fiber-containing meals and its consequent influence on physiological effects of fiber is poorly understood (Grundy et al. 2017). Current studies on DF often focus on isolated model systems with limited chemical and physical structures (Wolever et al. 2010), neglecting the complexity inherent in whole food systems encompassing plant tissues, cell clusters, and cell wall assemblies (Low et al. 2015, 2021). The complex chemistry of food mixtures and constituent components often makes it challenging to understand their effects on digestion throughout the entire GI tract when studied in isolation (Davies et al. 2014; Georgiades et al. 2014; Meldrum et al. 2017). Consequently, linking food composition to perceived health benefits necessitates a more holistic understanding of the properties and physiological pathways of DF throughout the GI tract (Capuano 2017; Gidley 2013). The following sections describe the mechanisms through which DF can function, classified into five categories.

4.2. Transport properties ("viscosity" and diffusion)

The digesta, a mixture of liquid and solid particles, exhibits properties influenced by the concentration, shape, size, and buoyancy of the particulate matter. Both soluble polysaccharides and insoluble materials, such as bran, fruit fibers, and vegetable fibers, can contribute to a "viscosifying" effect, reducing mechanical mixing within the GI tract (Dikeman, Murphy, and Fahey 2006). However, it is essential to acknowledge that the concept of "viscosity" is more complex. Fluids exhibit a wide range of responses to applied stress, influenced by several factors, such as dynamic viscosity (resistance to flow), viscoelasticity (a combination of viscous and elastic behavior), thixotropy (time-dependent shear thinning behavior), and yield stress (the minimum stress required to cause permanent deformation or plastic flow in a solid). As the liquid fraction diminishes in the distal segments of the intestine, the remaining solid fraction becomes more aggregated and develops visco-mechanical properties influenced by its constituent components. These components include viscous or semi-solid materials like mucus or food chyme, as well as DF polymers and particles that can exhibit viscous or semi-solid characteristics.

In the dynamic and time-dependent environment of the digestive system, viscosity plays a significant role in retaining materials at the mucosal surface and controlling diffusivity. According to the Stokes–Einstein equation (Einstein 1905), viscosity and the diffusion coefficient are inversely related, meaning that as viscosity increases, diffusivity decreases. The reduction in diffusivity can restrict or slow down the transport of hydrolytic enzymes through mucus or DF porous particles, such as cell wall fragments (Capuano 2017). Additionally, factors, such as hydrophobicity, steric interactions, and electrostatic interactions can further alter the transport of molecules and colloidal particulates through the mucus (Rovalino-Córdova, Aguirre Montesdeoca, and Capuano 2021).

Furthermore, viscosity influences the phenomenon of poroelasticity (MacMinn, Dufresne, and Wettlaufer 2016). Typically, poroelasticity is considered in the context of the mechanics of articular cartilage immersed in synovial fluid (Li, Buschmann, and Shirazi-Adl 2000). However, poroelastic effects can also occur in mucus membranes during the swelling and expansion of the mucus gel as part of its turnover mechanism (Corfield 2015).

4.3. Binding

Enzyme reactions occur at the interface of liquid and solids and are important for the efficient utilization of starch and cell wall degradation, with the presence of carbohydrate-binding modules or domains that enable binding to their substrate, particularly insoluble substrates (Cockburn et al. 2018). For starch, enzymatic digestive processes determine the digestibility and nutritional value, where enhancing their catalytic activity increases the surface area of the substrate through the formation of pores on starch granules (Valk et al. 2015). Amylose-content is shown to provide structural differences to starch granules, increasing their resistance to degradation by reducing the availability of attack sites on the granular surface, that are further diminished as degradation reduced the number of available attack sites (Tian et al. 2023). Further levels of structural complexity, such as protein-starch and lipid-starch complexes, can additionally suppress the swelling of starch granule, thereby further reducing enzyme accessibility (Yang et al. 2019; Chao et al. 2020; Eliasson, Finstad, and Ljunger 1988).

The binding of enzymes to the substrate is influenced by the chemical properties (degree of polymerization, charge, and complexity), density of interactions (degree of physical entanglement and the presence of low/high energy bonds), the conformation of the substrate (availability of reaction sites), and physical barriers that reduce enzyme accessibility and suppress binding. As a result, the extent of interaction within the complex food matrix determines the bioaccessibility and bioavailability of macronutrients, which constitutes a key factor in the multi-pronged effect of DF on the digestive process.

4.4. Entrapment

The physical form of foods, ranging from fresh whole fruits and vegetables to whole grain bread and meats, significantly affects their digestibility. Food structuring has been shown to inhibit gastric retention time, stimulate GI motility, and modulate postprandial satiety by the release of GI hormones, such as cholecystokinin (CCK) (Khramova et al. 2019). Foods with a complex, less processed structure tend to be digested more slowly, enhancing satiety compared to more processed, softer food forms. This slower digestion process is partly due to the mechanical properties of these foods, which resist rapid breakdown, thus prolonging gastric retention and stimulating a more substantial release of CCK by I-cells in the duodenum, particularly in response to fats and proteins. Viscous, gel-forming soluble DFs are commonly believed to provide physiological benefits, such as delaying gastric emptying, reducing cholesterol levels, and attenuating postprandial blood glucose responses (Khramova et al. 2019; Cassidy, McSorley, and Allsopp 2018; Tamargo et al. 2020). This is attributed to the increased luminal viscosity, which hampers the interaction between digestive enzymes, nutrient substrates, and their respective transporters, thereby reducing nutrient absorption in the intestine (Sadakiyo et al. 2017; Gunness and Gidley 2010).

Despite some inconsistencies across trials, the overall evidence supports the notion that the consumption of viscous, gel-forming DFs has been shown to smooth the postprandial blood glucose surge following a high-carbohydrate meal. Variations possibly occur due to differences in polymer concentration, types of gel-forming fibers, and the physical availability of fibers affected by grain processing or meal preparation techniques (Shen et al. 2016; Wolever et al. 2010; Biörklund et al. 2005).

It is crucial to consider that the viscosity of soluble fibers and their impact on gastric emptying and satiety is subject to shear-thinning behavior, which can be significantly reduced or nullified by peristaltic forces during intestinal digestion (Kale et al. 2015; Dhital et al. 2014). Studies comparing the effects of food structure alone on satiety and gastric processing have faced challenges due to the design of isocaloric food forms. These forms can segregate or sediment into an energy-rich phase in the stomach, potentially inducing a higher degree of satiety compared to meals that remain homogeneous under gastric conditions.

4.5. Interaction with mucosa

The interaction between DF and the luminal surface of the GI tract remains an area of active research, with questions remaining unanswered regarding the protective role of fibers. Typically, digestible carbohydrates are broken down by salivary and pancreatic alpha-amylase, with di- and oligosaccharide fragments subsequently hydrolyzed into monosaccharides by brush border enzymes and absorbed through transporter proteins. Soluble DF, such as β-glucan from barley, are notable for their ability to penetrate the intestinal mucus layer. This penetration significantly increases the mucus layer's viscosity and reduces its mean pore size, altering its physical properties and potentially influencing its protective function (Mackie, Rigby, et al. 2016).

This modification of the intestinal mucus layer by soluble DFs is critical for modulating nutrient absorption rates and the composition of the gut microbiota. By increasing mucus viscosity and reducing pore size, soluble DFs may influence the rate and efficiency of nutrient and microbial translocation across the mucus barrier. Furthermore, soluble DFs have been observed to attenuate the post-prandial glycemic response, not by inhibiting brush border enzyme or α-amylase activity involved in starch digestion but by restricting the activity of intestinal glucose transporters (SGLT1 and GLUT2) (Malunga et al. 2021). This suggests that the action of β-glucan membrane-active proteins, and possibly its viscosity-increasing effect within the mucus layer, plays a significant role in modulating starch digestion and glucose absorption.

Additionally, the impact of dietary polymers on the mucus layer's structure and function extends to the large intestine, where it serves as a critical barrier against bacterial penetration and colonization (Johansson et al. 2008). Soluble DFs can induce reversible compression of the mucus layer, influenced by the polymers' size, charge (for polyelectrolytes), and interactions (Preska Steinberg, Wang, and Ismagilov 2019; Preska Steinberg et al. 2019).

This phenomenon aligns with the Flory-Huggins solution theory, indicating that penetrating polymers can reduce the hydrated volume of the mucus layer through enthalpic and entropic effects, further supported by the observation that high polymer concentrations in the intestinal lumen can lead to osmotically induced mucus layer compression (Preska Steinberg et al. 2019).

4.6. Hypocholesterolemic effect

DF plays a crucial role in regulating cholesterol levels in the human body, contributing significantly to its hypocholesterolemic effect. This effect is primarily attributed to the interaction of soluble DFs with BA in the GI tract, which significantly impacts cholesterol metabolism and excretion. Soluble fibers, such as mixed-linkage glucan, pectins, and chitosan have been shown to bind BA or their salts (Massa, Compari, and Fisicaro 2022; Mikkelsen et al. 2014). In the bound state, the rate of reabsorption in the ileum is greatly reduced.

A decrease in BA reabsorption triggers a complementary mechanism wherein the liver increases the synthesis of BA from circulating cholesterol, leading to a reduction in serum cholesterol levels (Ames et al. 2017). Interestingly, despite the high-fat content found in nuts and avocados, these foods have been associated with a decrease in circulating triglyceride levels, accompanied by an increased excretion of fecal fat and BA (Henning et al. 2019; Thompson et al. 2021; Guarneiri, Paton, and Cooper 2021). Additionally, alterations in the composition of the gut microbiota have been observed to enhance the synthesis of SCFAs, particularly butyrate and propionate. These fatty acids are known for their beneficial effects on cholesterol metabolism, further reinforcing the hypocholesterolemic role of DF.

4.7. Fermentation

It is noteworthy that the human genome encodes only a limited number of enzymes, <20, which target specific carbohydrate structures of sucrose, lactose, and some starch structures. Consequently, the digestion of complex carbohydrates relies solely on the activity of the commensal microbiome (Flint et al. 2012). When these components are not readily accessible for digestion, they may be transported to the large intestine where they undergo partial or complete fermentation (Jones 2014). The micro- and nanoscale structure of different physical forms of food significantly influences the composition of the microbiome, including species that are key in degrading polysaccharides (such as *Firmicutes* and *Prevotella*), thereby affecting digestion kinetics and fermentation outcomes (Warren et al. 2018; Guan et al. 2020; Deehan et al. 2020).

To understand the human commensal microbiome, it is essential to identify the diverse range of carbohydrate-active enzymes (CAZymes) that target complex carbohydrates and glycoconjugates like mucin (Kaoutari et al. 2013). Although these enzymes exhibit varying substrate specificities, the glycosyl hydrolase families are known to have specific functions restricted to one or a few types of carbohydrates, enabling predictions of their general substrate specificity. The composition of the diet is a major determinant of the microbiota configuration, influencing the abundance of specific species and their metabolic functions, whether individual or collective. The impact of a particular diet on an individual may be influenced by a combination of host and microbial factors, with microbial factors being more responsive to interventions (Thomson et al. 2019).

5. Mucoadhesion: plant cell walls and mucin

5.1. Types of mucoadhesive interactions

Mucoadhesion, encompassing adhesive and binding interactions between a material and biological substrate like the mucus layer, is often overlooked when considering the nutritional and physiological effects. However, attributes, such as entanglement, entrapment, and the viscous effects on nutrient absorption and the commensal microbiota are relevant factors in mucoadhesion. Understanding the mucoadhesive properties of DFs is crucial for assessing their functionality.

Mucin glycoproteins, characterized by O-linked regions, proton acceptor and donor groups, and cysteine-rich naked regions, can be regarded as a highly complex gel (Menchicchi et al. 2015). This complexity provides diverse opportunities for various forces to interact during protein-polysaccharide interactions. Mucoadhesive interactions refer to the entire range of biological material-mucus and mucous membrane interactions, including interfacial adhesion, dynamic and topological interactions (e.g., entanglement), molecular binding, and even chemical bonds like disulfide bonds formed by thio-functionalized mucoadhesive polymers attached to mucin glycoproteins (Leitner, Walker, and Bernkop-Schnürch 2003). In this review, the term "mucoadhesion" will be used in its broadest definition to encompass mucosal binding and mucosal interfacial adhesion. The interaction between DFs and mucin is influenced by intrinsic factors, such as molecular weight, surface charge, and conformation, as well as environmental factors like the location within the GI tract. Concentration plays a crucial role in studying these interactions, as polymer chains above the critical concentration (C^*) form entangled networks that limit their interaction with mucin, instead forming an interfacial layer with the mucus.

5.1.1. Macroscopic interactions

Physicochemical interactions occur at the interface across multiple scales, ranging from individual atoms and functional groups to molecular clusters and supramolecular and colloidal interactions within the 5–1000 nm range. The categorization between supramolecular and colloidal domains is somewhat arbitrary, where the former represents molecular assemblies lacking a defined interface, while the latter involves interfaces that significantly contribute to the system's total Gibbs free energy. In low-concentration mucus systems within the small intestine, a distinct interface does not exist due to full hydration. Conversely, DF particles can

exist as loosely gelled structures within defined interfaces (e.g., pectin gels) or as particles with well-defined interfaces (e.g., cereal brans). The concept of an interfacial layer becomes relevant when describing interactions confined to the molecular interaction scale or spanning a few hundred nanometers, leading to a diverse range of physicochemical interactions.

5.1.2. Interfacial layers

The concept of molecular topologies has been previously described in the mucoadhesion for drug delivery (Mayol et al. 2008; Urbanova et al. 2016). For further information, we suggest referring to the work of Yang et al. (2020) to explore its relevance to the specific case at hand. While numerous potential interactions can be identified, we will focus on the topologies of adhesion likely to occur within the GI tract.

Based on available evidence, we propose two biological perspectives on topological interactions between plant cell walls (PCWs) and mucin: bond topology and stitch topology. Bond topology involves complementary functional groups between mucin and DF, leading to strong adhesion through the formation of bridging polymer chains (Figure 4(A)). Stitch topology occurs when adherents lack complementary functional groups, yet adhesion is still achieved through the presence of sparse and robust polymer networks (Figure 4(B)). This topology may arise when mucin diffuses into preformed supramolecular assemblies, becoming topologically entangled with the polymer network. However, it is important to note that PCWs' functionality within the GI tract exists across a continuum of length scales, making it challenging to account for all possible interactions. The role of macroscale interactions between plant tissue aggregates and cell walls in this process remains understudied but may contribute to the observed research phenotypes.

5.1.3. Molecular interactions

Noncovalent interactions between functional groups in different molecular topologies and chemistries play a crucial role in adhesion (Figure 4(C)). These interactions can result

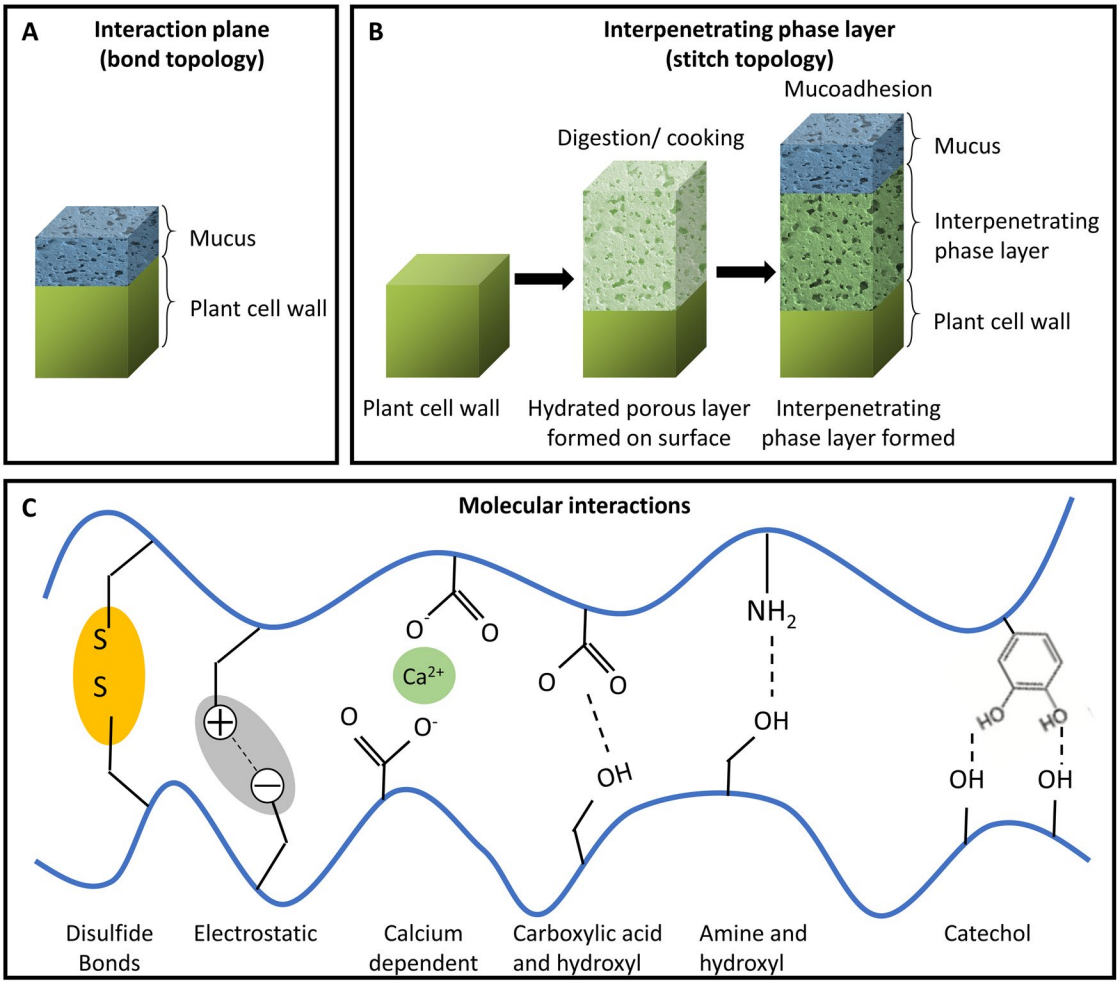

Figure 4. The molecular topologies of mucoadhesion interactions. These interactions can be broadly categorized into two main groups: (A) adhesion between mucus and plant cell walls: This interaction creates an interaction plane through the formation of either covalent bonds or noncovalent interactions between mutually reactive functional groups. (B) Formation of a hydrated porous layer on the surface of plant cell walls: This process involves mechanical interlocking and leads to the creation of an interpenetration phase layer through mucoadhesive interactions. (C) These interactions can be facilitated through a range of molecular mechanisms, such as disulfide bonds, electrostatic interactions, divalent ion interactions (predominantly Ca^{2+}-mediated), carboxylic acid and amine interactions, and catechol hydrogen bonding.

in strong polymer adhesion and prolong the association between mucus components. At the molecular level, ionic, hydrogen, and dipole interactions give rise to van der Waals interactions, which operate within a few nanometers on the supramolecular and colloidal scales. The strength of these non-covalent interactions covers a broad spectrum, with stacking interactions, for instance, forming strong associations through supramolecular complexes capable of adapting to strain, breaking, and reforming under suitable conditions, such as time, temperature, and pH (Nieto-Orellana et al. 2017). The interaction between mucin and anionic polysaccharides, like pectin, is influenced by factors, such as molecular weight, charge, and the degree of polymer contraction (Nordgård and Draget 2011).

Mucins, as glycoproteins, have a pI value between 2 and 3. At pH values higher than the pI, mucin acquires a negative charge, resulting in electrostatic repulsion forces and an extended confirmation of the chain (Lieleg, Vladescu, and Ribbeck 2010). Electrostatic complexation between mucin and fiber is likely favored within a pH range of 2.4 and 6.3 (Veerman, Valentijn-Benz, and Nieuw Amerongen 1989). Conversely, *O*-glycosylation in mucin introduces positively charged trimethylammonium groups and negatively charged sulfonate groups, leading to a stable polymer network crosslinked by randomly formed ionic bonds (Navarro, French, and Zauscher 2018). The non-glycosylated domains of mucin contain significant hydrophobic regions (globular terminal and Cys-D domains), contributing to entropic interactions through hydrophobic attraction. Simultaneously, highly hydrated sugars create a repulsive barrier in the form of hydrophilic repulsion or hydration shell repulsion, particularly important in fucose-terminated glycans, which lack negative charges compared to their sialic acid-terminated counterparts.

5.2. Physical entanglement in the context of DF polymers

The interactions between mucin and DF molecules and particles are influenced by factors, such as geometric complexity, physical entanglement, topological adhesion, and Velcro effects (Meldrum et al. 2017). At the sub-micrometer scale, mucus forms a sparse network with elastic properties (E′ or G′) resulting from both an entropic spring component (typical for polymers) and mechanical resistance (typical for fibrous structures). Charged polysaccharides with low molecular weight and rigid polyanions preferentially interact with the globular regions of mucin without significantly altering its conformation or rheological properties (Menchicchi et al. 2015). In contrast, high molecular weight polyanions are more flexible and can bridge distant sites, influencing the conformation of mucin and leading to a reduced hydrodynamic volume. Interactions between mucin and low and high molecular weight neutral or highly branched DF, such as dextran, have been found to be minimal (Menchicchi et al. 2015; Meldrum et al. 2017).

The behavior of concentrated polymer systems, such as gels or polymer blends, depends on the intrinsic mobility of the components and the local compositional heterogeneity arising from concentration fluctuations. When mobility is constrained in one dimension, the system exhibits snake-like motion and is referred to as entangled. The effect of geometric constraints (entanglements) on molecular motion depends on polymer-polymer and polymer-solvent interactions. Repulsive interactions can slow diffusion by increasing the effective radius of reptating chains, while attractive interactions lead to binding and unbinding events that reduce motion. This sub-diffusive motion emphasizes the dynamic nature of mucus as a biomaterial that responds to the polymeric composition of its environment, as well as thermal energy and hydrodynamic drag.

5.3. Physical entrapment and viscous effects in the context of DF particles

Adhesion between two adherends can occur through a combination of topological adhesion and mechanical interlocking, without the need for covalent bonds or noncovalent interactions. This adhesive strength relies on the fiber's topology, and mucin can fill surface irregularities based on the surface roughness, resulting in closed pores (lock-key topology) or open pores (thread-hole topology). However, the physicochemical properties of polysaccharides within a cellulosic network can vary, requiring a case-by-case evaluation of their interaction with mucin. During cooking and digestion, cell walls can develop closed pores or asperities on the surface, forming an array of dense pores (Li, Gidley, and Dhital 2019; Paciulli et al. 2016; Dhital et al. 2016). The interaction between cell walls and mucin likely involves two steps: topological adhesion without functional groups and physical entanglement or un-crosslinked mucin chains diffusing into DF supramolecular assemblies. The cell wall surface exhibits three characteristic deformation models with a spatial distribution of elastic moduli at the nanometer length scale (Yakubov et al. 2016). Across length scales of 0.1–1 micrometer, "hard" and "soft" domains exist (Yakubov et al. 2016), which are significantly larger than the typical pore size of mucin oligomer mesh size (20–200 nm for Muc2) (Round et al. 2012).

Hemicellulose and pectin undergo annealing above their glass transition temperature within the cellulosic network of plant cell walls (Lin, Yuen, and Varner 1991). When they encounter mucin, physical entanglement occurs through chain diffusion, filling the pores and forming a lock-key topology (Figure 5(A)). However, if the adhesive strength of the cell wall is greater than the underlying mucus layer, dissociation will occur during intestinal transit. In some foods, open pores can exist due to food processing or cooking, allowing mucin polymers to infiltrate pores and crate a thread-like topology upon adhesion (Figure 5(B)). This process may facilitate the translocation of mucus-associated hydrolytic enzymes and commensal microbes, offering a competitive advantage over lumen-associated bacteria that may have difficulty closely associating with food structures within the GI tract (Crouch et al. 2020).

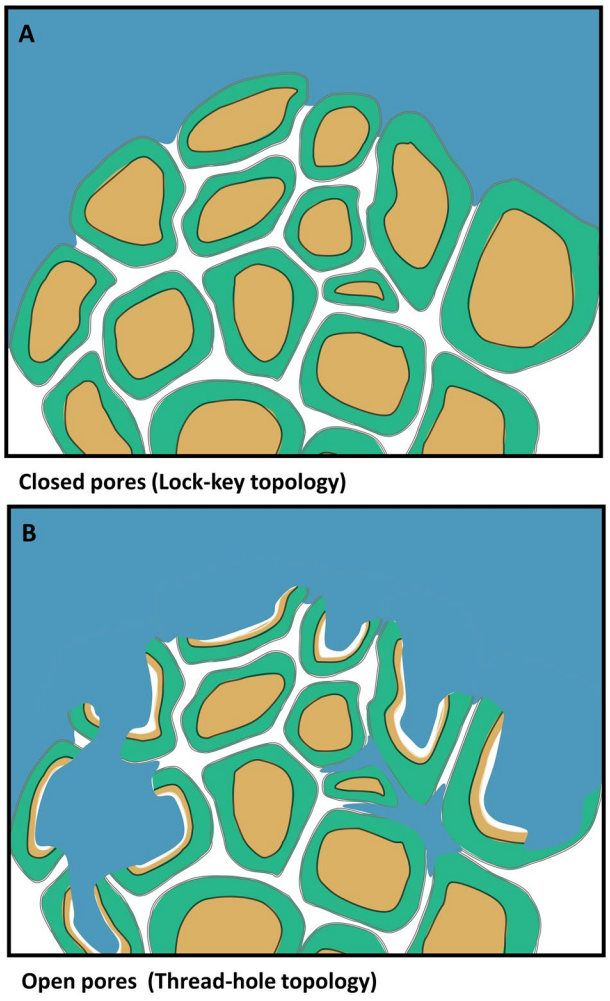

Figure 5. Macroscopic topologies of mucoadhesion with plant cell walls. (A) Where the adherent contains closed pores, a lock-key topology is formed when mucin glycoproteins interact with the plant cell walls. (B) When the adherend has open pores, which could result from processing or cooking, the mucin glycoprotein can occupy a significantly larger surface area created by these open pores, leading to what is referred to as a thread-hold topology. Figure adapted from Yang et al. (2020).

5.4. Mucoadhesion along the GI tract

In this section, we examine further the physiological effects of mucin adhesion induced by DF within the GI tract, which may confer specific health benefits. Our analysis extends to the biophysical mechanisms involved, with a specific focus on mucoadhesion, a phenomenon widely noted in pharmaceutical applications and nutrient delivery systems, including vitamins and micronutrients (Dalmoro et al. 2019).

As DFs travel through the oral cavity, stomach, and small intestine, their macrostructure (supramolecular assembly) and microstructure (colloidal) play vital roles in determining nutrient availability and the rate of prebiotic fermentation by the gut microbiome. In the stomach, the activity of enzymes, such as amylase is not merely time-dependent but is significantly influenced by the local pH levels. This aspect is crucial in understanding the biochemical interactions within the GI tract. Furthermore, mucoadhesive interactions are capable of encapsulating and/or entrapping nutrients, altering the viscosity of digesta, and profoundly affecting microbial attachment within the GI tract. It is also important to note that gastric emptying is governed not only by these mucoadhesive interactions but also by the structure and energy density of the gastric chyme. This aspect, although briefly mentioned earlier, warrants specific attention due to its substantial impact on the digestive process and subsequent nutrient absorption.

5.4.1. Physical effects of fiber during oral processing

During oral processing, the physical properties of fiber exert important effects on the digestion and absorption of nutrients and bioactive compounds. Chewing not only facilitates the mechanical breakdown of food particles but also is essential for the integration of salivary secretions with the food, leading to the formation of a coherent bolus (Witt and Stokes 2015). This process is crucial for foods of all textures, including those high in DF, which are resistant to enzymatic degradation and remain largely intact during oral processing. Moreover, the texture of carbohydrate-based meals profoundly affects oral processing behaviors. For instance, differences in texture—such as those between white rice and rice cake—significantly influence bolus particle size and surface area, which can impact the ease of swallowing and subsequent digestive processes (Choy et al. 2021). In addition, prolonged chewing can reduce total calorie intake, though its impact on postprandial glucose and insulin levels appears negligible in both healthy and overweight individuals (Borvornparadorn et al. 2019).

Saliva acts as a lubricant and binder. Salivary secretions, which mix with chewed food, facilitate the agglomeration of chewed food into a cohesive mass that can be easily swallowed. Although saliva contains α-amylase, the formation of a coherent, swallowable bolus is primarily governed by the physical interaction of saliva with food particles, rather than the enzymatic breakdown of starch by α-amylase (Mackie and Pangborn 1990; Froehlich, Pangborn, and Whitaker 1987; Joubert et al. 2017). Saliva is secreted into the oral cavity *via* salivary ducts from the three pairs of major salivary glands: the parotid, submandibular, and sublingual glands. Additionally, numerous minor salivary glands positioned on soft oral surfaces contribute to the overall volume of saliva, albeit to a lesser extent. Each type of salivary gland has a distinct contribution to the composition of saliva. While all three glands secrete electrolytes and digestive enzymes, such as amylase for starch breakdown and lysozyme for bacterial lysis, it is specifically the submandibular and sublingual glands that produce non-polymerizing mucin glycoproteins, namely MUC5B (polymerizing) and MUC7 (non-polymerizing). These mucins play a crucial role in forming a protective and lubricating film over the oral mucosa and in co-localizing digestive enzymes with ingested food particles, thus facilitating the preliminary digestion of starches (Yakubov et al. 2014).

Stimulated by chewing, the parotid glands do not produce mucins but secrete large amounts of salivary α-amylase, thus highlighting their specialized function among the salivary glands (Piras et al. 2010). Given the limited oral

residence time of food, the extent of starch hydrolysis in the mouth is minimal; however, this process is significantly extended into the stomach, especially while the postprandial pH remains elevated, allowing amylase to continue its action beyond the oral phase.

Lastly, microorganisms present in the oral cavity (i.e., oral microbiome) can utilize carbohydrates as a carbon source to support bacterial biofilms (Ribeiro et al. 2005). While the use of "simple" plant carbohydrates, such as sucrose and degraded starch, by oral microbiome is well documented (Keller et al. 2017), the impact of fiber is poorly understood. Some evidence from the murine dental models suggests that the presence of fiber in the diet results in the significant changes in dental microbiome beta diversity at the genus level (Sedghi et al. 2019).

5.4.2. Physical effects of fiber in the stomach

As the food bolus transitions from the esophagus to the stomach, it undergoes a series of transformations. Contrary to the previous suggestion that salivary α-amylase remains active in the bolus for a fixed duration (10–30 min) after entering the stomach (Freitas et al. 2018), it is important to note that the enzyme's activity is dependent on the local pH of the stomach environment, where the acidic nature of the gastric juices can significantly influence its enzymatic activity. In addition to mechanical contractions, the digestion process in the stomach involves acidic gastric juices, mechanical mixing, and the enzymatic activity of pepsin and gastric lipase, transforming the bolus into chyme (Ferrua and Singh 2010).

Peristaltic motion in the stomach and intestines aids in propelling the chyme forward. A unique gastric phenomenon, retropulsion, occurs when a constriction in the stomach creates a jet-like motion, pushing gastric contents back into the proximal antrum. This effect is more pronounced with denser food boluses (Li et al. 2021). During this process, food particles interact with the mucosal lining, composed of columnar epithelial cells and mucus, which is crucial for efficient digestion, increasing the surface area for this interaction. The rate at which these transformations occur in the stomach appears to be influenced by the dry matter content of the ingested food. Higher dry matter content leads to delayed emptying, indicating a concentration-dependent solid-like response ($G' > G''$), whereas lower concentration digesta results in rapid initial emptying with a more liquid-like response ($G'' > G'$) (Wu et al. 2017; Camilleri et al. 1985).

Additionally, DF, resistant to hydrolysis by human digestive enzymes, can undergo glycosidic hydrolysis induced by gastric acid, depending on its type and composition. Neutral DFs, such as xylan and mixed-linkage β-glucan are more resistant to low pH than polyanionic DFs like pectin (Johansson et al. 2006; Smirnov et al. 2017). Pectin exposed to simulated gastric fluid has been shown to hydrolyze galactose side chains, resulting in complexes with antioxidant properties (Garna et al. 2006).

In studies comparing diets containing viscous gel-forming DF, it was observed that a starch-based diet supplemented with 10% AX (arabinoxylan) exhibited delayed gastric emptying of solid and liquid contents, along with prolonged retention time in the small and large intestines. However, a diet supplemented with 10% mixed-linkage β-glucan did not show the same effect (Low et al. 2020). Furthermore, when comparing a diet supplemented with a viscous gel-forming pectin powder to one with mango pulp, a significant decrease in gastric emptying was observed. This decrease may be attributed to the increased solubility of pectin, hindering the free movement, and mixing of digesta during digestion (Wu et al. 2016; Low et al. 2021). The viscous nature and high water-holding capacity of pectin likely contribute to the hindrance of digestion and mixing processes.

Anionic polysaccharides, such as gellan gum and pectin have exhibited pH-sensitive mucoadhesive interactions, forming a three-dimensional, interconnected network with mucin after the transition to neutral pH (Cardoso, Gremiao, and Cury 2020; Wu et al. 2016). The pH changes experienced during transit from the oral cavity to the stomach and intestine (pH changes from ~7 to 3) result in reversible aggregation changes of anionic polysaccharides due to the screening of electrostatic charges. This process leads to the formation of dynamic and static complexes within the stomach (Yuan, Ritzoulis, and Chen 2019). In contrast, the interaction with resistant starch has demonstrated a weak interaction that remains insensitive to changes in pH, indicating its limited impact on mucus' rheological and barrier properties (Cardoso, Gremiao, and Cury 2020). The presence of a physical bran layer on white rice has also been found to delay gastric emptying, irrespective of amylose content or thermal treatment (Pletsch and Hamaker 2018). This delay can be explained by two potential mechanisms: the addition of a physical bran layer, which takes longer to break down or reduce in size within the stomach (Wang et al. 2015), and the slower digestion rate of the resulting particles compared to white rice particles. These factors partly account for the comparatively low glycemic response observed for brown rice. Similarly, Mackie et al. (2017) demonstrated that the particle size of flake oat porridge influenced the gastric emptying rate and the availability of starch-associated glycemic response compared to flour. Consumption of flour oat porridge resulted in an extended period of satiety, likely attributed to the increased solubility of β-glucan in the stomach. The effects of particle-particle interactions among insoluble fiber and their complexation with solution fiber have not been extensively explored, but they are crucial in understanding the factors governing digestion and the flow and mixing processes within the stomach.

5.4.3. Physical effects of fiber in the small intestine

The physical effects of fiber in the small intestine play a significant role in transit time, release of bioactive compounds, and nutrient absorption at the mucosal surface. Highly viscous, gel-forming fibers, such as mixed-linkage β-glucan, guar gum, psyllium, and alginate have demonstrated the ability to reduce postprandial blood glucose and insulin levels after high carbohydrate meals, with their health

benefits strongly correlated to their viscosity (Smith and Holm 1982; Kamalpour, Ghalandari, and Nasrollahzadeh 2018; Fuse et al. 2020; Kato et al. 2018; Wolever et al. 2010). On the other hand, non-viscous soluble fiber supplements (e.g., inulin, wheat dextran) and insoluble fiber (e.g., wheat bran) do not exhibit the same beneficial effects on glycemic control (Jenkins et al. 2002; Pourghassem Gargari et al. 2013).

While high viscosity, soluble DF provides advantages for glycemic control and lipid absorption, there are challenges associated with their sensory properties and modification during food processing, which can lead to depolymerization (Tosh et al. 2010). It should be noted that while gel-forming fiber can delay nutrient absorption until they reach the distal ileum, thereby triggering the "ileal brake phenomenon" and slowing gastric emptying and small bowel transit to minimize nutrient loss in the large intestine (Chegeni et al. 2022).

In addition to the viscosity effects and aggregation behavior of gel-forming polymers in the intestinal lumen, DF also strongly interacts with intestinal mucus secretion. For example, pectin reduces mucus permeability, while alginate and mixed-linkage β-glucan affect the diffusivity and pore size of the mucin network, affecting the diffusion of nutrients and lipids down to the 100 nm scale (Hino et al. 2012; Mackie, Macierzanka, et al. 2016; Mackie, Rigby, et al. 2016). The entrapment of fiber within mucus depends on the relative sizes of the fiber polymer and the pores in the mucus network. While uncharged fiber does not exhibit attractive interactions with mucus at the macroscale (Yuan, Ritzoulis, and Chen 2019), soluble DF embedded within the cellulosic network of fruits (e.g., parenchymal apple tissue) and grains (e.g., wheat endosperm) enhances intestinal mucin (Muc2) binding to cell walls (Meldrum et al. 2017). This binding occurs through two distinct mechanisms: mucoadhesive interactions mediated by pectic polysaccharides in fruits and vegetables, and polysaccharide network properties associated with neutral polysaccharides like arabinoxylan and β-glucan in cereal grains.

Fiber aggregation in the small SI lumen can be controlled by adjusting the size and concentration of DF polymers (Preska Steinberg et al. 2019). This phenomenon aligns with the behavior observed in the aggregation of nanoparticles in aqueous solutions, which is driven by depletion-type interactions due to the presence of large polymers (Kumar et al. 2013). While host polymers like MUC2, extracellular DNA, and F-actin have been found to aggregate microbes (Secor et al. 2018), their role in particle aggregation is relatively minor yet significant (Preska Steinberg et al. 2019). Dynamic interactions involving high-concentration gradients within the GI tract play a crucial role in the interaction between DF and mucus. These gradients involve salt, water pH, and solutes, such as BA, leading to diffusive and Brownian motion-related phenomena that contribute to micro-flows within villi. Interfacial-driven phenomena, like the Marangoni effect, generate significant flow around bubbles formed during peristaltic motion, particularly in the colon where gas is produced as a byproduct of fermentation. The viscous effect caused by DF can result in adhesive-like phenomena, causing particles to linger and adhere to the intestinal wall or in the vicinity of DF particles.

Simple sugars (e.g., fructose, galactose, glucose), amino acids, and fatty acids are absorbed across the mucosa by membrane-bound and brush-border transporters. While DF passes through the small intestine with limited ileal fermentation, the intactness of cell wall structures control starch digestion by pancreatic amylase, with as little as a single cell wall able to deliver entrapped swollen starch granules and oil bodies to the large intestine (Zoetendal et al. 2012; Grundy et al. 2015; Dhital et al. 2016). Solubility is limited when cell walls partially lose their structural integrity due to stronger chemical interactions with other components (Comino et al. 2014). For example, the activity of proteases (enzymes that break down proteins) on the periphery of cell walls increases the solubility and permeability of DF to digestive enzymes (Robertson et al. 1997; Bhattarai et al. 2017). This leads to an increase in particle size and surface structure, creating gaps between particles and inter-particle voids, which may improve the hydration and binding properties of the remaining material. As DF passes through the small intestine, its concentration increases as other food components are absorbed. However, the impact of this increase on the physical interactions between amorphous DF and aggregated food particles is not yet fully understood.

Studies examining the impact of whole-grain rye bread consumption on postprandial insulin response and satiety have provided valuable insights, with an intervention study involving 19 healthy post-menopausal women, showed how different structural features between rye and wheat bread have a significant effect on reducing postprandial insulin response (Juntunen et al. 2003). Microstructural differences between rye bread and wheat bread were observed, with rye bread exhibiting a continuous phase of amylose surrounding closely packed starch granules, while wheat bread contained starch granules trapped within an extensible gluten network. During heating, the encapsulated starch granules in wheat bread undergo gelatinization, making them more accessible to hydrolytic enzymes. In contrast, amylose leaches out and coats the starch granules in rye bread, creating a structure that is more resistant to starch hydrolysis after cooling (Liljeberg and Björck 1994). As a result, rye bread has a less porous and mechanically firmer structure, leading to a slower rate of starch hydrolysis. These structural differences likely contribute to the observed effects on postprandial insulin response and satiety associated with whole-grain rye bread consumption. The unique microstructure of rye bread, characterized by a continuous phase of amylose and closely packed starch granules, distinguishes it from wheat bread, where starch granules are entrapped within a gluten network. These structural disparities are thought to contribute to the slower rate of starch hydrolysis in rye bread.

5.4.4. Physical effects of fiber in the large intestine

In the large intestine, the digesta is composed of undigested food, water, electrolytes, microbial byproducts, and cellular debris. As the digesta passes through the colon, water and electrolytes are absorbed, leading to the progressive consolidation of the digesta. The interaction between uncharged polymers (such as polyethylene glycol or PEG) and

polyelectrolyte polymers (such as carboxymethyl cellulose) has been shown to induce osmotic compression with mucus (Datta, Preska Steinberg, and Ismagilov 2016; Preska Steinberg, Wang, and Ismagilov 2019). This mucoadhesive mechanism can be adjusted by increasing the ionic strength, which decreases the extent of polyelectrolyte-induced compression without affecting uncharged polymers. Uncharged polymers induce compression by interacting with mucin polymers through enthalpic interactions, causing mucus to reduce its hydrated volume (Datta, Preska Steinberg, and Ismagilov 2016). As a result, the polymer concentration increases, driving water out of the polymer network and causing the mucus network to compress. This behavior aligns with the Flory-Huggins theory of polymer-induced compression, which states that the gel equilibrium depends on the balance between compression and mixing pressure, as well as the pressure associated with the elastic deformation of the network chains (Sierra-Martin et al. 2011). On the other hand, polyelectrolyte polymers compress mucus based on the degree of polymer charge, following a modified Flory-Huggins theory known as the Donnan partitioning theory. The preferential partitioning of ions between phases results in an increase in polyelectrolyte osmotic pressure compared to the external solution phase it comes into contact with (Preska Steinberg, Wang, and Ismagilov 2019).

These concepts are particularly relevant when considering the restructuring of mucus that occurs with DFs, leading to the compression of the mucus hydrogel. However, mucus-associated gut microbes can also influence mucus structure by degrading interpenetrating polymers. Prebiotic supplements, often containing purified soluble fibers like inulin, arabinoxylan, and mixed-linkage β-glucan, do not effectively mitigate microbial erosion of mucus, despite their impact on gut community composition (Desai et al. 2016). Therefore, the specific role of different DF polymers and their interactions with the mucus layer are still not fully understood and require further investigation (Suriano et al. 2022).

5.4.5. Microbiome

The final step in the biotransformation of DF involves the production of key metabolites, such as SCFAs by the gut microbiota. It is widely acknowledged that the fecal microbiome does not fully represent the composition and genetic repertoire of the mucosa-associated microbiome (Luis and Hansson 2023). This limitation hampers our ability to identify specific diet-related microbes, particularly in the less defined outer layer of mucus, which consists of mucus, gut microbes, and dietary material. Consequently, it is reasonable to speculate that mucosa-associated microbes will have a more substantial impact on DF utilization compared to lumen-associated microbes. The nano- to micro-scale structure of DF plays a significant role in modulating the composition, diversity, and richness of the gut microbiome, which in turn affects digestion kinetics and fermentation outcomes (Warren et al. 2018). The ability of an individual's microbiota to respond to specific prebiotic treatment depends on their habitual dietary intake and microbiome metabolic plasticity (Holmes et al. 2022). DF provides substrates for fermentation reactions carried out by specific microbial species with the necessary enzymes to degrade complex carbohydrates. However, the impact of a particular diet on the gut microbiome varies from person to person, influenced by a combination of host and microbial factors, with the latter potentially being more responsive to intervention. Different physical forms of the same DF can lead to specific shifts in microbiota composition and alter the production of SCFAs, such as butyrate, which have protective roles in the gut (Peng et al. 2009).

The organization of plant cells and cell walls are linked to variations in gut microbial fermentation properties, with faster and more complete fermentation occurring with higher levels of pectin and primary cell walls (e.g., in apples and celery), and slower and incomplete fermentation occurring with more robust secondary-thickened cell walls, starch, and lignin (e.g., in bananas, spinach) (Widaningrum et al. 2020). The variety and structure of DFs also influence the composition of the gut microbiota, with the presence of complex fruit particles containing high levels of pectin, cellulose, hemicellulose, and phytonutrients increasing the diversity and metabolic products produced by these microbes (Grant et al. 2019). Studies have shown that diet-induced changes in the gut microbiome can occur within just four days when transitioning from an animal-based to a plant-based diet (David et al. 2014). Animal-based diets have been found to increase the abundance of bile-tolerant microorganisms (such as *Alistipes*, *Bilophila*, and *Bacteroides*) while decreasing the levels of *Firmicutes* and *Prevotella*, which are involved in DF metabolism. On the other hand, dietary interventions with specific fibers have been shown to increase the abundance of beneficial bacteria like *Bifidobacterium* and *Lactobacillus* species, as well as fecal butyrate concentration (So et al. 2018). However, it is important to note that changes in the gut microbiota are maintained only as long as the substrate (fiber) is consumed, and not all individuals possess the same repertoire of bacteria capable of degrading any given DF substrate (Zhao et al. 2018).

Moreover, the ability of a microbe to benefit from a specific DF goes beyond its capacity as a primary fiber degrader. It also depends on factors, such as adherence to the substrate, tolerance to the micro-environmental conditions associated with the fiber, and the ability to utilize carbohydrate breakdown products and metabolites through cross-feeding interactions with secondary fiber degraders (Deehan et al. 2017).

Recently, short-term dynamics of microbial succession in human fecal microbiota revealed an abrupt shift in the microbial community during in vitro wheat bran colonization and fermentation (De Paepe et al. 2020). Monitoring the succession of gut microbiota during wheat bran fermentation revealed *Enterobacteriaceae* and *Fusobacterium* species dominated the early stages of incubation by feeding on carbohydrate-low and protein-rich medium in which wheat bran supplementation. A second fermentation stage was observed in which wheat bran fermentation resulted in a rapid rise in SCFA production and increased butyrate proportion and endo-1,4-β-xylanase activity, reflecting the

increased abundance of bacterial taxa associated with insoluble wheat bran fermentation.

These insights raise an important question about the balance between broth and biofilm fermentation pathways. This balance may depend on the physicochemical properties of DF particles or aggregates, such as mechanical properties, hydrophobicity, surface roughness, and particle size. Suriano et al. (2017) explored the effect of wheat bran particle size on microbiota, its metabolic activity, and its implications for inflammatory markers, such as the expression of interleukin (IL) 1β in the gut. Specifically, wheat bran fractions with sub-millimeter particle size (average diameter ~ 150 µm) as opposed to millimeter-sized particles (average diameter ~ 1.7 mm) have been shown to selectively influence changes in gut microbiota induced by high fructose intake, particularly by suppressing the bloom of *Enterobacteriaceae* (Suriano et al. 2018). The latter is known to be associated with dysbiosis, which in turn has demonstrable links to liver inflammation and nonalcoholic fatty liver disease (NAFLD) (Bauer et al. 2022).

In the context of dysbiosis, it is important to point out that the colonic mucin layer and gut microbiota maintain bidirectional interactions that are essential to the development of the mucus layer and microbial colonization of the gut (Jakobsson et al. 2015). Structurally diverse DF results in dramatic changes in mucin O-glycosylation profiles and microbiome profiles, revealing how individual colonic mucin glycan structures associated with specific gut bacteria (Gamage et al. 2020; Zhao et al. 2023). SCFAs have been proposed to regulate colonic mucin O-glycosylation through their impact on the expression of host glycosyltransferases (Wrzosek et al. 2013). Additionally, DF particles have been proposed to mechanically stimulate mucus secretion by the intestinal epithelium (McRorie and McKeown 2017). Reduced consumption of DF leads to decreased diversity of the gut microbiota and SCFA production, shifting microbial metabolism toward utilizing dietary and endogenous protein sources, such as mucins, which may have detrimental effects on the host (Desai et al. 2016; Schroeder et al. 2018). The accumulation of cytotoxic and pro-inflammatory metabolites derived from protein fermentation contributes to chronic diseases, such as ulcerative colitis and colorectal cancer (Windey, De Preter, and Verbeke 2012). Recent research has revealed that microbial metabolism influences not only the GI tract mucosa but also extends to the microbiota-gut-brain axis (Ousey, Boktor, and Mazmanian 2023).

The structural characteristics of DF are important factors that influence their utilization in the GI tract and their ability to favor specific beneficial commensal microbiota phyla. The structural features of pectin can also modulate the composition and activity of the gut microbiota, including the degree of esterification, neutral sugar composition, degree of branching, and presence of amino groups (Larsen et al. 2019). Certain keystone species in the microbiota can target specific fiber structures for degradation. However, since different types and structures of fiber are present in plant cell walls, a collective effort of multiple microbial species is required to efficiently degrade the supramolecular aggregate of different fiber types. Mucus entrapment containing commensal microbiota may also facilitate the access to carbohydrates that may be somewhat hidden in the food matrix as it enters the colon. This can be advantageous when designing fiber chemical structures and mixtures to achieve desirable effects on the microbiota in the colon.

Overall, the structural complexity of DF, along with its interaction with the microbiome and the production of metabolites like SCFAs, plays a critical role in maintaining gut health and influencing various physiological processes in the host. Further research is needed to better understand the specific effects of DF structures on their utilization in the GI tract and their impact on the composition and function of the commensal microbiota.

6. Concluding remarks

6.1. The significance of the DF-mucus-microbiome axis

We are beginning to unravel the intricate relationship between DF, the mucus layer, and the commensal microbiota in the gut, shedding light on its profound impact on health and nutrition. The emerging field of study known as the DF-Mucus-Microbiome axis has revealed that the mucus layer plays a crucial role in guiding the journey of DF through the gut. There are still limitations that impede a comprehensive comprehension of these interactions beyond basic solubility categories despite making significant progress in our understanding of this axis. As a result, our current ability to define the functionality properties of DF is constrained. This limitation further hampers the development of technological solutions aimed at selecting and modifying fiber structures to optimally support human nutrition and foster a healthy commensal microbiome. A systematic approach must be developed to better comprehend the role of mucin glycosylation in signaling the regulation of pathogens within specific disease states. Furthermore, the impact of mucus-associated commensal microbiota on chronic conditions, such as metabolic syndrome, obesity, inflammatory bowel disease (IBD), and cardiovascular diseases, requires in-depth investigation (Jaurigue and Cappell 2014).

By addressing these knowledge gaps and enhancing our understanding of the DF-mucus-microbiome axis, we can pave the way for developing targeted interventions and therapies to promote better human health. Characterizing the mucosa-associated microbiome is challenging, as it requires colonoscopy biopsies compared to stool samples typically used to characterize the luminal microbiome. The mucosa-associated microbiota, which includes mucus, gut microbes, and dietary material, is likely to have a more significant impact on DF utilization than the luminal microbiota. These advances hold the potential to revolutionize dietary recommendations and personalized nutrition, leading to improved management and prevention of various chronic diseases linked to the gut microbiota. The intimate affiliation between gut bacteria and mucin glycan structures that line the colon surface is critical yet hugely unexplored. Coupling microbiota study with glycomic mucin analysis should become a more common practice in the field of nutrition research.

6.2. Multi-fiber nutritional recommendations

When considering DF, it is essential to move beyond merely examining its chemical composition and to also focus on structural aspects at different length scales. The structural characteristics of fiber exist across a range of length scales and play a significant role in determining their health benefits (Figure 6). While the chemical composition provides insights into the types of fibers present, it is the structural properties that govern their interactions within the GI tract. To design food polymer mixtures with optimal health effects, a multi-prong approach can be adopted. For example, incorporating bioflocculating functional RG-I pectins (Mao et al. 2020) can enhance food aggregation in the small intestine, leading to delayed nutrient absorption. Similarly, the addition of oat mixed-linkage glucans can delay bile salt re-absorption (Gunness and Gidley 2010), which can have positive implications on health. To stimulate colonic fermentation while reducing gas production and associated symptoms, propiogenic psyllium fiber fractions can be added to the mixture (Harris et al. 2023; Gunn et al. 2022). Cereal (arabino-) xylans have to potential to increase mucus viscosity and contribute to the mucus barrier function, adding another layer of benefit (Meldrum et al. 2017).

However, creating effective multi-fiber mixtures goes beyond simple strategies for ingredient mixing. It is essential to identify natural composites based on plant cell wall assemblies that offer such multicomponent functionality. These composites should act as substrates for bacterial communities in the gut, maintaining a delicate balance between functionality and avoiding adverse reactions and symptoms (Yao et al. 2023).

6.3. Importance of mechanistic studies for future research

Understanding the link between DF structure and its physiological function opens new hypotheses to drive future clinical and epidemiological research, guiding DF recommendation policy to improve the intake of functional DF globally. One significant area of investigation involves unraveling the mechanisms by which the mucus layer acts as a selective barrier and how it responds to changes induced by enzymes,

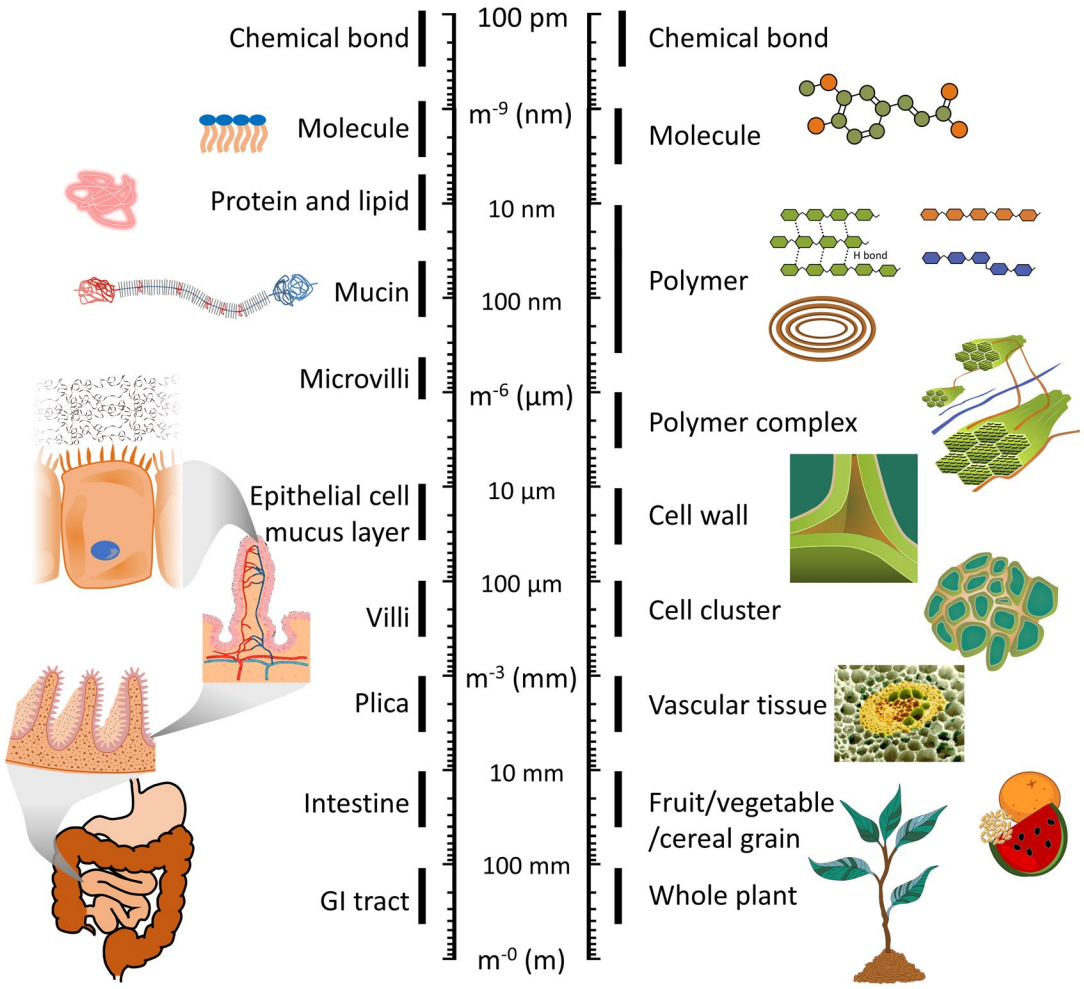

Figure 6. Illustration of length scales and sizes in the interactions between dietary fibers and the gastrointestinal tract. A 100-picometre (100 pm; 1 Å) is the approximate size of a covalent bond holding two molecules together at the tangible end of consideration. Comparing the length-scale proportionality, plants to cell clusters have the same length-scale gap between cell clusters and individual polymers. Similarly, the distance between the gastrointestinal tract and epithelial cells are proportionally comparable to the cellular lipid bilayer.

food components, and the commensal microbiota. Such insights can pave the way for rational approaches to engineer a mucosal barrier that efficiently delivers nutrients and bioactive ingredients, thus promoting a healthy gut microbiome. When developing food formulations and microstructure, it is essential to adopt a rational approach, considering the molecular, microstructural (colloidal), and macroscopic levels, with the aim of either adhering to or evading the mucus layer. While exploring methods to enhance the permeability of the mucus layer, it is crucial to consider the potential impact of dietary components that may compromise its integrity. Such compromises could lead to the exposure of underlying tissues to harmful microbes, viruses, and endogenous factors present in the GI tract.

The demand for improved DF functionality is a pressing concern for both developed and developing countries. In developed nations, there is a need to increase DF intake, while in regions with high consumption of coarse or nonfunctional DF, malnutrition may result due to inhibited absorption of proteins and lipids. The growing body of evidence highlights the importance of studying the mechanisms of interaction between different DF structures and mucus, emphasizing the necessity for systematic in-vitro research and well-designed clinical intervention studies. Combining human- and organoid-based studies can provide valuable insights into the degradation of proteins, DF, and fatty acids under various healthy and disease conditions, contributing to a better understanding of nutrient cycling in gut microbial systems.

One crucial aspect yet to be addressed is the systematic characterization of DF composition, particle size, and mechanical properties. Paying special attention to the mechanical properties is vital for advancing the area of minimally processed food, where retaining the natural structure of DF is essential, with "soft" components (high molecular weight polysaccharides) integrated within solid-like particles (biofilm substrates). The conceptual approach presented in Figure 6 illustrates how DF interactions within the GI tract can be mapped to study their impact on GI physiology, physicochemical properties, nutrient uptake, and interactions with the microbiome. The successful implementation of these proposed research avenues hinges on our ability to develop and validate new characterization methods for the fine structure of polysaccharides. This includes exploring distributions of functional groups or side chains that influence DF properties beyond just molecular weight and monosaccharide/linkage composition. Further advancements in in vivo and ex vivo imaging methods are crucial to enable monitoring the effects of DF-rich foods on gut physiology and mucus barrier function.

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Author contributions

O.W.M. and G.E.Y. conceptualized, wrote, and edited the manuscript.

Disclosure statement

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