

# Dietary pectic substances enhance gut health by its polycomponent: A review

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## Abstract

Pectic substances, one of the cell wall polysaccharides, exist widespread in vegetables and fruits. A surge of recent research has revealed that pectic substances can inhibit gut inflammation and relieve inflammatory bowel disease symptoms. However, physiological functions of pectins are strongly structure dependent. Pectic substances are essentially heteropolysaccharides composed of homogalacturonan and rhamnogalacturonan backbones substituted by various neutral sugar sidechains. Subtle changes in the architecture of pectic substances may remarkably influence the nutritional function of gut microbiota and the host homeostasis of immune system. In this context, developing a structure–function understanding of how pectic substances have an impact on an inflammatory bowel is of primary importance for diet therapy and new drugs. Therefore, the present review has summarized the polycomponent nature of pectic substances, the activities of different pectic polymers, the effects of molecular characteristics and the underlying mechanisms of pectic substances. The immunomodulated property of pectic substances depends on not only the chemical composition but also the physical structure characteristics, such as molecular weight ( $M_w$ ) and chain conformation. The potential mechanisms by which pectic substances exert their protective effects are mainly reversing the disordered gut microbiota, regulating immune cells, enhancing barrier function, and inhibiting pathogen adhesion. The manipulation of pectic substances on gut health is sophisticated, and the link between structural specificity of pectins and selective regulation needs further exploration.

## KEYWORDS

colitis, gut microbiota, inflammatory bowel disease, pathogen infection, RG-I pectin, sidechains

## 1 | INTRODUCTION

A healthy intestine is the foundation of overall wellness in the human body, and gut inflammation is a critical component of many systemic diseases including cancers (Jia et al., 2020). Inflammatory bowel disease (IBD), including ulcerative colitis (UC) and Crohn's disease (CD), are chronic relapsing and idiopathic immune disorders in the gastrointestinal tract (GI), marked by a dysbalanced immune system, leading to a large group of destructive local inflammatory diseases and excessive production of proinflammatory cytokine (Lloyd-Price et al., 2019). Epidemiological studies have suggested that the occurrence of these diseases represent a widespread condition (Mehrman et al., 2021; Ng et al., 2017) and the burden of IBD is constantly rising globally. According to the newest study in *Lancet*, in 195 countries and territories all over the world, the cases of IBD increased from 3.7 million to 6.8 million between 1990 and 2017 (Alatab et al., 2020), indicating the necessity of gut healthcare. Even though IBD has attracted major interest by academic researchers, the etiology of IBD, while still vague, is hypothesized to relate to susceptible genotypes, environmental factors and gut microbiota (Aden et al., 2019).

Despite recently increased advances in IBD treatment, it is still challenging to predict the therapeutic outcome in patients. A high proportion of patients with UC are refractory to medical therapy and sustained remission cannot be achieved in 50% of clinical cases (Verhelst et al., 2020). Moreover, many drugs for IBD were reported with severe adverse effects. However, recent studies have highlighted the important role of dietary fiber in improving gastrointestinal symptoms (Llewellyn et al., 2018; Yue et al., 2015), maintaining homeostasis (Desai et al., 2016; Wu et al., 2013) and lowering the risk of CD in IBD patients (Brotherton et al., 2016).

Pectins, the major water-soluble dietary fiber, exist broadly in the cell walls of various plants and the global pectin market is estimated to account for 1.5 billion dollars in 5 years (Tan & Nie, 2020). Being pervasive in fruits and vegetables, natural pectins contribute to the health-promoting properties as a soluble dietary fiber. In food industries, pectins are extensively used in jams, jellies, fruit drinks, acidified milk, and ice creams as gelatinizer, thickener, stabilizer, or fat replacer. In addition, pectins also can be supplemented as an indigestible nutrient for humans. Nowadays, pectins have been highly regarded as functional ingredients with phenomenal utilization in food. Numerous studies have revealed that pectins exhibit a significant effect on gut healthcare, which is partly attributable to the metabolic function of gut microorganisms, whereby pectins are fermented into large quantities of short-chain fatty acids (SCFAs), which possess anti-

inflammatory activity (Rabbani et al., 2001; Singh et al., 2018). Furthermore, pectins also exert the anti-IBD effect by a microbiota-independent pathway: (1) regular administration of pectins represses erosion of the colonic mucosa barrier (Jin et al., 2019); (2) the immune and nonimmune cells are manipulated by some bioactive fragments such as neutral sugar sidechains in RG-I region (Ishisono et al., 2019); and (3) certain structural domains of pectin molecules bind to foreign pathogens or toxins, appreciably diminishing the incidence of colitis (Gottesmann et al., 2020). Therefore, the wide commercial applications of pectins in healthcare products can be predicted.

However, the discrete structure of pectins is ignored when discussing the protective effects against IBD. Pectic substances extracted from different plant-based sources vary in structural characteristics, but the important "bioactive fragments" of pectin molecules against IBD are currently ill defined (Fan et al., 2020; Ishisono et al., 2019; Markov et al., 2011), due to the lack of targeted extraction of different pectic polymers and the difficulty of laborious separation and purification. The gut inflammatory diseases cannot be rationally modulated by pectic substances without first gaining a thorough understanding of the effects of the polycomponents of pectins. The complex structure of dietary pectins is conducive to the synergy of different components and the diversified development of gastrointestinal microecology. It is urgent to clarify how the important structural regions in pectins perform diverse functions during IBD. Research in recent years has begun to study the complex interactions between pectins and intestinal microbiota and how they can alleviate IBD synergistically. Thus, the aim of the present review is to highlight the activities of key pectic composition on the prevention of IBD and the effects of physical characteristics. This review will also discuss the possible action mechanisms of pectins in alleviating IBD through microbiota-independent and microbiota-dependent manners.

## 2 | THE POLYCOMPONENT NATURE OF PECTIC SUBSTANCES

Pectic substances are a family of structurally complex polysaccharides linked by  $\alpha$ -1,4-D-galacturonic acid (GalA) residues, mainly containing three components: homogalacturonan (HG), rhamnogalacturonan I (RG-I), and substituted galacturonan (Wu et al., 2020). HG is a linear chain consisting of  $\alpha$ -1,4-D-GalA, which is the most abundant region in pectic substances. RG-I is a highly branched polymer, and its backbone consists of repeating disaccharide units  $-2$ - $\alpha$ -L-Rhap-(1 $\rightarrow$ 4)- $\alpha$ -D-GalpA-(1 $\rightarrow$ , where some  $\alpha$ -L-Rhap are substituted by arabinan, galactan, and arabinogalactan (AG I and AG II)

at O-3 or O-4 position. The substituted galacturonan mainly include xylogalacturonan (XGA), apiogalacturonan (ApGA), and rhamnogalacturonan II (RG-II), which is the “hairy” region in pectic polymers with at least 21 kinds of glycosidic linkages and six rare sugar moieties. Apart from these structural domains, the GalA residues could be esterified with methyl groups and acetyl groups to various degrees, which may affect the gastrointestinal immunomodulatory activity (Sahasrabudhe et al., 2018). Also, molecular weight, degree of branching, and chain conformation are pivotal features of pectins. To date, numerous pectins obtained from vegetables and fruits have been reported to suppress IBD, but there is an apparent discrepancy about the value of these features in these pectic samples (Ishisono et al., 2019; Markov et al., 2011). The desired properties of pectins might be achieved through the appropriate selection of the plant source. In addition, polysaccharide–polyphenol interaction by noncovalent or covalent bonding results in pectin extracts accompanied by polyphenols (Liu, Le Bourvellec, & Renard, 2020), especially from berry fruits, which should be taken into consideration when accessing the anti-inflammatory activity. Collectively, these various compositions and structural characteristics present a great challenge in developing a structure-activity-level understanding of how pectins perform their protective effects in gut health.

### 3 | REGULATION OF IBD BY VARIOUS PECTIC SUBSTANCES

Chronic intestinal inflammatory responses trigger IBD. Although the underlying pathogenesis remains elusive, many scientific advances have emphasized the specific roles of genetic, immune, and microbial factors (Franzosa et al., 2019; Liu & Anderson, 2014). The observation that family members of IBD patients have an 8 to 10 times higher risk for developing diseases when compared to the general population highlighted the influence of genetics on immune responses (Liu & Anderson, 2014). Genetic loci related to IBD, which has been reviewed in 2015, regulate epithelial function, innate and adaptive immunity, and cell autophagy (Kaunitz & Nayyar, 2015). Epigenetic regulation of genes is influenced by gut microbiota via their metabolite. Given that no colon inflammation occurs in germ-free rat models, gut microbiota does play a decisive role in the induction and maintenance of intestinal inflammatory conditions (Khan et al., 2019). *Faecalibacterium prausnitzii* and *Bacteroidetes* are widely regarded as the major fecal bacterial groups producing SCFAs that are thought to impact the epigenetic methylation and protect against IBD. However, some sulfite-reducing bacteria such as *Desulfovibrio*, can increase the intestinal content of hydrogen

sulfide (H<sub>2</sub>S) and then impair DNA repair and suppress the protective properties of SCFAs.

As shown in Figure 1, the crosstalk between host cells and gut microbiota is imperative in the pathogenesis of IBD. Nutritional antigens and harmless bacteria will not induce destructive system reactions. However, when the mucosal contents exceed the range of immune tolerance, a substantial amount of immune cells in the intestinal wall exert a series of active and persistent responses to protect against enteric pathogens. The significant player of antigen-presentation cells (APCs) residing in the luminal surface, dendritic cells (DCs), recognize and perceive antigens through their dendrites, followed by more expression of major histocompatibility complex II (MHCII) and some cytokines, such as interleukin (IL)-12, IL-18 and interferon- $\gamma$  (INF- $\gamma$ ) (Coombes & Powrie, 2008). In addition, DCs representing a separate lineage and other antigen-presenting cells in lamina propria like monocytes and macrophages are recruited to the inflammatory location. Some pattern-recognition receptors (PRRs) are expressed on varying cell lines in the innate immune system. For instance, Toll-like receptors (TLRs), sensors of microbial infection, detect bacterial ligands such as lipopolysaccharide (LPS) (Rakoff-Nahoum et al., 2004). Similar to TLRs, NOD-like receptors (NLRs) participate in the recognition of microorganism-associated and host-derived molecules (Robertson & Girardin, 2013). In the secondary lymphoid system, “homing” T cells encounter intestinal antigens presented by DCs, inducing systemic priming (Mowat, 2003). In IBD, the composition of T cells in the lamina propria is typically different from normal one. CD4+ T cells, CD25+ T cells, Type 1 helper T (Th1) cells, and Th2 cells dominate in the regulating system of anti-inflammatory and pro-inflammatory cytokine profile (Bene et al., 2011). Furthermore, TH17 cells, promoted by IL-6 and IL-23, are characterized by producing IL-17, which is involved in the system reactions (Gaublomme et al., 2015). Also, it should be emphasized that autophagy plays an important role in protecting host cells against bacterial toxins. Numerous pathogenic bacteria such as adherent-invasive *Escherichia coli* contain a multitude of virulence factors and hence autophagy is required for immunity homeostasis (Cho & Brant, 2011).

A growing number of studies have confirmed the modulatory activities of pectic substances in the intestinal immune system (Suh et al., 2013; Chung et al., 2017). Pectins exhibit protective effects against many bowel symptoms (Table 1). These findings uncover a critical role of pectin molecules in the regulation of inflammatory-oriented cytokines, protective chemokines, intercellular adhesion molecules, and symbiotic flora (Singh et al., 2018; Sanders et al., 2019). However, the factors determining the effect of pectins on IBD remain unknown. Recently, due

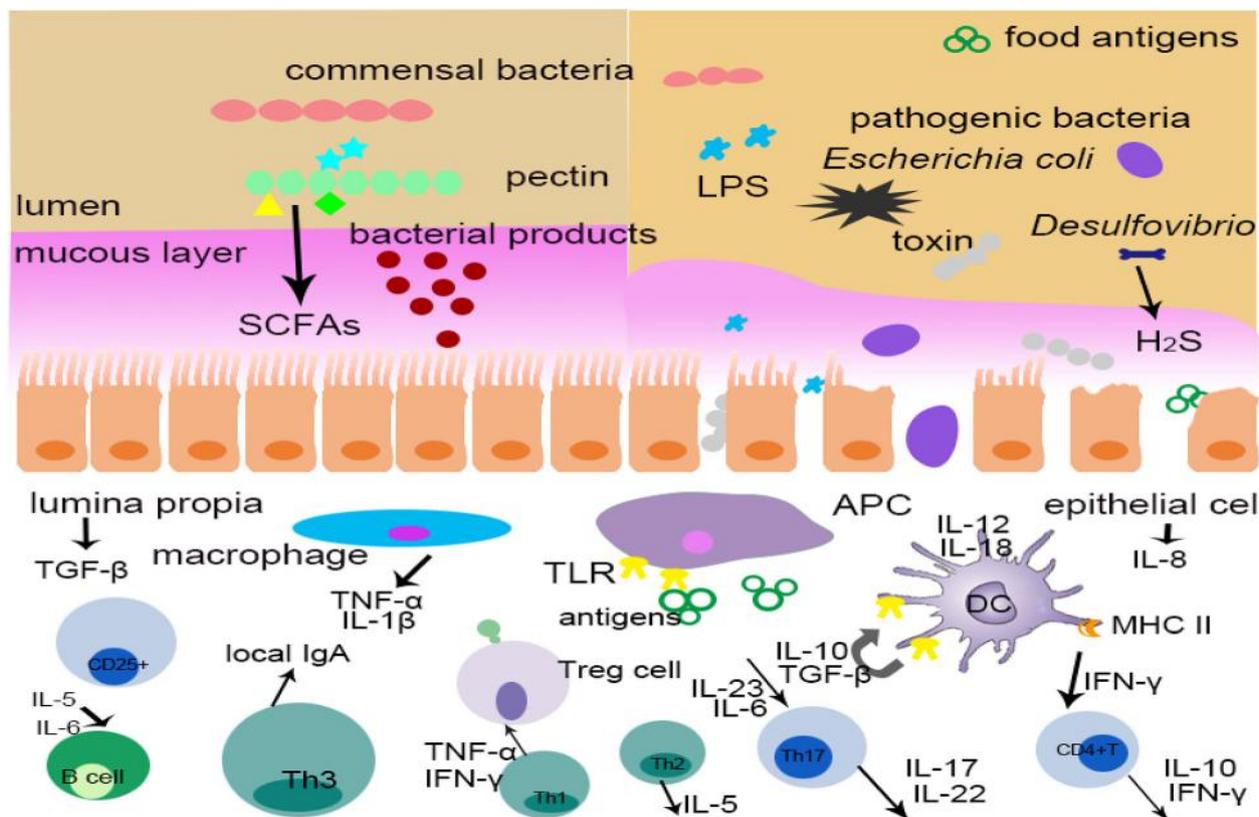


FIGURE 1 Dysbiosis and gut inflammation in inflammatory bowel disease (IBD)

*Note:* This schematic depicts obvious observations in microbial composition, mucus layer (pink region) and epithelium (orange region), and multiple associated pathways modulating inflammation. The gut houses trillions of commensal bacteria. Some food components such as pectins can be metabolized into short-chain fatty acids (SCFAs) by certain microbial species. These bacterial products nourish the colon cells. But it also contains harmful substances in the lumen, such as food antigens, pathogenic bacteria and toxins, which can lead to chronic inflammatory disorders in gut. Then, reduced mucous layer and destroyed intestinal barrier facilitate antigens passing into lumina propria, which is populated with a large proportion of innate immune cells, such as dendritic cells (DCs), macrophages and adaptive immune cells, such as T cells and B cells. Pattern-recognition receptors (PRRs), such as Toll-like receptors (TLRs) in immune cells participate in the recognition of exogenous antigens, and major histocompatibility complex (MHC) plays a key role in antigen presentation. All of these epithelial cells, antigen-presentation cells (APCs) and lymphocytes can produce inflammatory cytokines, such as interleukin (IL), interferon (IFN), tumor necrosis factor (TNF)- $\alpha$ , and transforming growth factor (TGF)- $\beta$ . The immunological outcomes are local IgA production and systemic immune homeostasis. Abbreviations: LPS, lipopolysaccharide; Th cell, T helper (Th) cells; Treg cell, regulatory T (Treg) cells.

to the structural diversity and complexity of pectins, many investigations have focused on main identifying macromolecular domains (HG, RG-I, and RG-II) and major characteristics of physical structure, to describe variable pharmacological efficacies and specificities as compared to whole pectic heteropolysaccharides.

### 3.1 | Galacturonan backbone of HG pectin

It has been 20 years since clinical data revealed that HG type pectin was beneficial in the dietary intervention of persistent diarrhea in children (Rabbani et al., 2001). Recently, a series of research suggested that HG

type pectins from various plant sources possessed anti-inflammation activity (Wang et al., 2014). Distinguishing of HG backbones irrespective of various branching regions in initial pectin are reportedly responsible for its anti-colitis effects (Markov et al., 2011). In the GI, HG type pectin can indirectly act on host cells or the intestinal system by regulating some anti-inflammatory commensal bacteria belonging to *Firmicutes* (Singh et al., 2018), but HG pectin with different degree of esterification (DE) or molecular weight ( $M_w$ ) might be fermented in different locations and then act on the intestinal epithelium in ileum, cecum, or the proximal colon (Wu et al., 2019; Tian et al., 2017). In vitro models provide important tools for investigating the regulation of HG pectin on specific strains. For instance, purified galacturonan oligomers with the degree of

TABLE 1 The protective effects of pectic substances against gut symptoms

Pectin sources	Symptoms	Assays	References
Pectin/alginate mixture	Colitis	Rat model	Voltes et al. (2020)
Artichoke pectin	DSS-induced colitis	Mice model	Sabater, Olano, Montilla, and Corzo, 2020
Citrus pectin and lemon pectin	TNBS- and DSS-induced colitis	Mice model	Ishisono, Mano, Yabe, and Kitaguchi, 2019
Noni pectin	DSS-induced bowel disease	Mice model	Jin et al., 2019
<i>Rauvolfia verticillata</i> (Lour.) Baill pectin	DSS-induced ulcerative colitis	Mice model	Miao et al., 2018
LMP	Caecal dysfunction	Mice model	Wu et al., 2019
HG	$\alpha$ IL-10R-induced colitis	Mice model	Singh et al., 2018
Orange by-products	DSS-induced colitis	Mice model	Pacheco et al., 2018
Dietary fiber	DSS-induced colitis	Mice model	Llewellyn et al., 2018
Turmeric pectin	LPS and swim stress-induced ulcer	Rat model	Rajagopal, Manjegowda, Serkad, and Dharmesh, 2018
Lemon pectin	Doxorubicin-induced ileitis	Mice model	Sahasrabudhe et al., 2018
Citrus pectin	DSS-induced colitis	Mice model	Silveira et al., 2015
Citrus pectin	Ulcerative colitis	Patients	Wei et al., 2016
<i>Comarum palustre</i> L. pectin	Acetic acid-induced colitis	Mice model	Popov, Ovodova, Markov, Nikitina, and Ovodov, 2006
Apple pectin	DSS-induced colitis	Mice model	Lim et al., 2003

polymerization (DP) 4 and 5 were prepared from beet pectin. In the flora-based assays, DP4 and DP5 were utilized by *Eubacterium eligens* and *F. prausnitzii* species, which are the main pectin-degrading strains in *Firmicutes* phylum. These oligomers can induce significant production of anti-inflammatory cytokine IL-10, but levels of production of other cytokines like IL-1 $\beta$  and IFN- $\gamma$  in human peripheral blood mononuclear cells (PBMCs) are extremely low (Chung et al., 2017), indicating that HG pectin has an effect on the immune system via interacting with gut microbiota. However, the anti-inflammatory substances secreted by *E. eligens* or *F. prausnitzii* have not been taken into consideration. These representative anti-inflammatory flora play an important role in the rehabilitation of IBD, and in the in vitro fermentation of pectins, HG polymers mainly increased the abundance of *F. prausnitzii*. Intriguingly, RG-I pectin maintained or decreased the level of *F. prausnitzii* in in vitro fermentation system (Larsen et al., 2019). But in the microbiota of IBD models, there is a lack of research focusing on the effects of HG or other pectic domains on the anti-inflammatory capacity of gut bacteria (Singh et al., 2018; Kang et al., 2018).

In the mouse model, researchers can easily observe the improvement of the entire intestinal tissue. The beneficial effects of HG pectin are primarily manifested in mucosal

content, intestinal barrier function, cytokines levels, and the distribution of immune cells. Jin et al. (2019) observed that the polysaccharides extracted from *Morinda citrifolia*, mainly containing HG pectin, possessed protective effects in gut inflammatory disease through increasing the secretion of mucus and promoting the colonic barrier function. Apart from interacting with intestinal mucosa, the pectic polysaccharides obtained from *Rauvolfia serpentina* L could inhibit infiltration of neutrophils in the intestinal wall, according to the decreased colonic myeloperoxidase (MPO) activity (Popov et al., 2006). Recently, reducing the level of oxidative stress, maintaining collagen homeostasis and accelerating the wound healing by HG pectin have been also reported in the dextran sodium sulfate (DSS)-induced colitis mouse model (Fan et al., 2020; Maria-Ferreira et al., 2018b). Nevertheless, different regulation was found, such as the downregulation of anti-inflammation cytokine IL-10 and enhancement of the lesion area according to Fan et al. (2020) and Markov et al. (2011). The inconsistency of these results may be due to different  $M_w$ , DE, branching regions, and pectin dosage, which will be discussed further. In addition, varying methods of model establishment and the modeling cycle will also make the finally observed effects different (Jakobsdottir et al., 2013; Sahasrabudhe et al., 2018). Given the

discrepancies between these studies, more research work is needed to discuss the effects of HG pectin on GI tract during IBD.

As the structure of HG pectin is similar to the structure of glycoconjugates on the cell membranes, the linear galacturonan chain in HG polymers can competitively bind pathogenic toxins as a ligand. LPSs are common endotoxins secreted by Gram-negative bacteria and can trigger intestinal inflammation. The HG oligomers from chemically modified apple pectin can block LPS binding to the membrane TLR4 and, thus, reduce colonic toxicities and immune response (Liu et al., 2010). Likewise, two HG oligosaccharides obtained through controlled enzymatic hydrolysis, POS I from HMP (high-methoxy pectin) and POS II from LMP (low-methoxy pectin), were used as soluble receptor molecules to bind Shiga toxin, which was produced by *E. coli* and could cause hemorrhagic colitis. Due to the similar structure with globoseries receptors (Gal $\alpha$ 1 $\rightarrow$ 4Gal $\beta$  disaccharide) and the increased accessibility to binding sites on the toxin, GalA oligosaccharides showed better inhibitory effects than polymers. Apart from the polymerization, the degree of methylation also impacted the binding ability and a high amount of methyl groups could impair the inhibitory effects of pectins. Five different pectic oligosaccharides (POSSs) from orange peel have been analyzed and a high DE in POS limited its toxin-binding activity (Di et al., 2017). Moreover, technology in the food industry employing pectins to remove mycotoxins from food, feed and beverages has been reported recently (Gonzalez-Jartin et al., 2019). Thus, HG pectin possesses great potential to prevent host from toxin-induced gut inflammation and oligosaccharides may show better protective effects. However, at present, no other studies on the molecular level have confirmed that pectins antagonize the intestinal toxins. Some molecular interaction techniques such as surface plasmon resonance (SPR) technology, enzyme-linked immunosorbent assay (ELISA), and immunofluorescence technique can be applied to visualize the binding affinity, binding site, and dissociation constant. The construction of some in vitro models also helps to provide better insight into the effects of DP and DE of HG pectin on its toxin-binding capacity.

In contrast to the results of previously cited studies, Jimenez et al. (2019) discussed the role of diet-derived GalA in the infection and gut colonization of two enteric pathogens, *Enterohaemorrhagic Escherichia coli* and *Citrobacter rodentium*. Saccharolytic strains of gut microbiota can break down HG pectin into GalA oligomers or residues, which were able to promote pathogen expansion in the initial stage of infection and enhance *E. coli* growth (Chang et al., 2004; Fabich et al., 2008). According to Jimenez et al. (2019), sensing of GalA regulated through ExuR transcription factor could aid the pathogen

to initiate infectious colitis. However, the concentration of GalA after fermentation is hard to control and the effects of parental pectins on this system were not determined. In addition, the anti-pectin antibodies in host may help to prevent chronic inflammatory autoimmune disease (Dai et al., 2014).

In summary, the regulatory effect on IBD of HG pectin is strongly related to the galacturonan backbone, which promotes the growth of main anti-inflammatory bacteria, alleviates intestinal tissue damage, reduces the infiltration of inflammatory cells, and enhances antioxidant capacity. Meanwhile, HG pectin is effective in binding microbial toxins. The DP and the DE in galacturonan backbone have a great impact on the toxin-mitigation activity. Furthermore, the ester group in GalA residues may determine the action of HG pectin in the intestinal mucosa.

### 3.2 | Sidechains of RG-I pectin

The ramified RG-I of the pectin from *Bupleurum falcatum* L. was regarded as the bioactive part in proliferating B cells (Sakurai et al., 1999). Nevertheless, Markov et al. (2011) observed that not all RG-I pectins have anti-inflammation activity and some even promote colitis severity. This may be determined by the position and arrangement of neutral sugar chains in RG-I region. Furthermore, the importance of branches in the immunological activity has been emphasized in recent studies (Meijerink et al., 2018; Zhang et al., 2019; Tamiello et al., 2018; Georgiev et al., 2017).

The neutral sidechains in RG-I may regulate the intestinal immunity through their fermentation products, but in some in vitro models, RG-I pectin also shows direct modulation on intestinal immune cells. Macrophages are significant players involved in intestinal inflammation, non-migratory in the lamina propria and are characterized by the large production of IL-10 and IL-6. LPS-treated macrophage usually serves as an in vitro inflammation model. The competition between pectic substances and LPS in combining TLR4 has been revealed by assays based on cell lines (Tan & Nie, 2020). RG-I pectin can directly inhibit TLR1/2 and TLR4 activation, thus, suppressing IL-6 production of macrophages (Ishisono et al., 2019). While HG pectin tend to activate all the TLRs as well as the NOD receptors (Prado et al., 2020), indicating that HG might tend to interact with the receptors in the surface of immune cells, RG-I prefer to bind to the ligands of these receptors. Herein, it seems that RG-I suppresses the inflammation, while HG promote healthy immune responses in cells. The co-culture system composed of colonic epithelial cells and macrophages has also been used to investigate the activity of RG-I pectin. In the assay based on co-culture of Caco-2 and THP1 cells, arabinogalactan (AG) significantly

increased the transepithelial electrical resistance (TEER) of the Caco-2 monolayer, representing enhanced gut barrier function and cell integrity. The immune parameters revealed a large decrease in NF- $\kappa$ B/AP-1 activity and IL-6 level but a significant increase in the production of IL-10 in AG-treated group by comparison with the control (Daguet et al., 2016). The lamina propria also contain rich amount of DCs, which acquire antigens by extending dendrites and then present antigens to T cell. Sahasrabudhe et al. (2018) concluded that HG pectin can inhibit IL-6 production on DCs in DM-dependent manner, while few publications studied the effects of RG-I pectin on DCs. The RG-I from *Diospyros kaki* can inhibit B lymphocyte proliferation during inflammation (Duan et al., 2010). The natural killer (NK) cells might be also involved in the activity of RG-I, due to that galacto-oligosaccharides lead to the higher activity of NK cells and, thus, promotes gastrointestinal immune function (Vulevic et al., 2015). RG-I pectin may be able to manipulate the NK cell by the galactan sidechains. In these cell models, pectins have direct contact with cells, but in the in vivo environment, pectin molecules are poorly absorbed. It is still not established whether pectin molecules will reach and act on immune cells in the intestine.

Some researchers have focused on the microbial pathogen-induced immune abnormality and RG-I pectin has shown the potential to reduce the infection risks by their anti-adherence properties. Many enteric pathogens bind to intestinal epithelial cells by recognizing the carbohydrate moieties coating the host cells and then induce intestinal inflammation. For instance, *E. coli* and *Fusobacterium nucleatum* are found to adhere to colonic mucosa and reduce the abundance of *F. prausnitzii* in the IBD model (Gevers et al., 2014; Lopez-Siles et al., 2016). Galactan oligosaccharides can competitively inhibit the epithelial adherence of intestinal pathogens, thus, promoting gut health (Quintero et al., 2011). *Helicobacter pylori* infection can induce overt gastrointestinal symptoms, which begins with the adhesion of *H. pylori* to host cells via receptor binding, such as LPS interacting with galectin-3 on the epithelial cell surface. A highly esterified RG-I extracted from okra apparently reduced the molecular interaction as well as the adhesion of *H. pylori* to gastric adenocarcinoma epithelial (AGS) cell after pretreatment with the bacterium. The esterification and the highly branched structure were suggested to be a prerequisite for its anti-adhesive property (Gottesmann et al., 2020). A similar research work revealed that okra RG-I could exert anti-adhesive activity against *Campylobacter jejuni* (Lengsfeld et al., 2007), which definitely enhances the severity of colitis. However, these studies only represented in vitro attachment of pathogens to

cell lines and it is unknown whether these anti-adhesive RG-I pectins can still work after oral administration in human intestinal tract. The degradation of the RG-I sidechains in the stomach acid will lead to a decline in the anti-adherence activity. According to Kittana et al. (2018), administration of galacto-oligosaccharides (GOS) in mice could protect against intestinal inflammation and prevented the colonic tissue from damage without inhibition on the bacterial colonic adherence, which may because *Citrobacter rodentium* cultured in the lab resulted in differential gene expression including GOS-sensitive adhesins. In this sense, whether some pectin-sensitive adhesins exist in vivo needs further investigation under the establishment of a bacteria-induced colitis model (Bronner et al., 2018).

Although there are no human experiments, some studies have used mice models of IBD to verify the effect of RG-I pectin on regulating gut inflammation. For instance, black cumin RG-I containing  $\beta$ -1,4-galactan and  $\alpha$ -1,5-arabinan sidechains could accelerate the gastric ulcer healing and increase the mucin content (Manjegowda et al., 2017). There has been a well-designed study to examine the effects of sugar sidechains in murine models of IBD, independent of its prebiotic effect (Ishisono et al., 2019). Orange pectin and citrus pectin (CP) were prepared and the significant differences in neutral sidechain content between these two pectins existed (higher amount of sidechains in orange pectin). In the 2,4,6-trinitrobenzene sulfonic acid (TNBS)-induced colitis model, low levels of epithelial damage and inflammatory cell infiltration were found only in orange pectin-fed mice, indicating that neutral sugar chains had a profound impact on the prevention of IBD. In this context, colonic Th1 cells, believed to aggravate TNBS-induced colitis, decreased significantly. Also, the level of inflammatory cytokines including IL-1 $\beta$ , IL-6, and TNF- $\alpha$  were much lower than those in the CP treated group. Furthermore, orange pectin, not CP exhibited protective effects against DSS-induced colitis with a significant decline in the level of IL-6, suggesting that macrophages were involved in the anti-colitis activity of orange pectin. After the treatment of antibiotics in mice, alleviating colitis of orange pectin still could be observed (Ishisono et al., 2019). Collectively, the neutral sidechains could directly influence the intestinal host cells and modulate inflammatory responses. However, there was no determination of the sample purity in these studies, whether these pectic materials contain other substances such as protein, polyphenols, and flavones were unclear. Further investigation is required to fully understand the differences between orange pectin and CP. Other factors need to be kept unchanged to establish the impact of specific structural element. Thus, enzyme hydrolysis,

having high selectivity, is the preferred method to demonstrate the protective effects of sidechains content against IBD. Sabater et al. (2020), for example, carried out a study using two enzymes to remove specific sidechains and concluded that the  $\beta$ -1,4-galactan was more important than  $\alpha$ -1,5 arabinan in maintaining the bioactivity of artichoke pectin.

Considering all have mentioned above, the modulation of RG-I pectin on gut barrier function and immune homeostasis are highly dependent on the neutral sugar sidechains. RG-I pectin can inhibit the activation of macrophages and DCs, thereby decreasing the production of inflammatory cytokines. RG-I also exerts the anti-adhesion activity and reduces the risk of infectious colitis induced by pathogens. However, the effect of the RG backbone on gut health remains unclear. Regarding the regulatory effects of RG-I pectin on intestinal inflammation, the distribution of sidechains, the length of branches, and the coordination between RG and few oligosaccharide sidechains should be considered.

### 3.3 | RG-II and other substituted galacturonan domains

RG-II is one of the most branched regions in pectic polymers, which contains a galacturonan backbone substituted by various carbohydrate oligomers (Park & Shin, 2019). Due to the low amount in plant cell walls and the complexity of their fractionation, pure RG-II is difficult to be obtained and only limited studies discuss the impact of RG-II on IBD. In the assay based on LPS-treated RAW264.7 cells, RG-II isolated from *Korean mondshood* root significantly inhibits the inflammatory response by disturbing the NF- $\kappa$ B signal pathways (Li et al., 2014), indicating the potential of RG-II in making direct contact with host cells. In an animal model of obesity, RG-II decreased the serum concentration of inflammatory factors IL-6, IL-1 $\beta$ , TNF- $\alpha$ , and also reduced the distribution of proinflammatory macrophages in adipose tissue (Su et al., 2020). Therefore, RG-II might possess the ability to alleviate IBD in an in vivo model. ApGA, another minor pectin type, can consistently promote the phagocytosis of macrophages in a dose-dependent manner (Lv et al., 2015). However, in a mouse model of colitis, the linear HG pectin with branched ApGA significantly increased the lesion area in the large intestinal wall and remarkably enhanced MPO activity (Markov et al., 2011), indicating that apiose may activate inflammatory response after tissue damage. However, limited data are available on the protective effects of RG-II and ApGA in colitis animal models and herein this subject will not be further discussed.

## 4 | THE EFFECTS OF MOLECULAR CHARACTERISTICS AND PHYSICAL STRUCTURE

The intrinsic capacity of pectic polysaccharides to modulate inflammatory response have been investigated over the years. It can also be observed in the published researches that structural modification of pectins may result in different effects on the immune system. For example, the bioactivity of CP and modified CP (MCP) has been investigated, and the results revealed that MCP possessed better immunomodulatory properties (Merheb et al., 2019). However, not all modifications can improve the bioactivity of the parental pectin. According to Sabater et al. (2020), elimination of galactose by enzyme digestion induced a loss of protective effects of artichoke pectin against colitis. Similarly, the pectin treated by chemical hydrolysis suppress the production of anti-inflammatory IL-10 (do Nascimento, Winnischofer, Ramirez, Iacomini, & Cordeiro, 2017). Therefore, chemical modification or ultrasonic degradation, where the reaction is messy and disorderly, cannot effectively retain the bioactive domains within pectins, and may even increase potential safety risks. Currently, most research covering modified pectins are only concerned about the reduction of molecular weight, which indeed can improve the solubility and availability of pectin. However, other structural characteristics such as DE and sidechain content were mostly overlooked and these can be as important as molecular weight on preventing IBD.

### 4.1 | Molecular weight

The molecular weight of pectic polymers is important in the immunomodulatory activity. Usually, acid, heat, and ultrasound modification can significantly decrease molecular weight, thus, leading to better bioactivity (Ogutu et al., 2017). Rajagopal and his colleagues have demonstrated a pH-modified low- $M_w$  pectin (MTrPP) from turmeric possessing modulatory effects on gastric inflammation. In this study, pretreatment with MTrPP reduced the production of pro-inflammation cytokines and ulcer-specific markers in the rat model and the overexpression of IL-10 switched the inflammatory phase to the anti-inflammatory one (Rajagopal et al., 2018), indicating that reduction of molecular weight might enhance pectin's inhibitory effects on IBD. Comparison of natural pectins also consistently demonstrates the advantage of smaller ones. In an assay based on HT29 cells, two POSs of different molecular weight (73 KD and 811 KD) were used to investigate their antibacterial adhesion activity. POS1, the smaller one,

exhibited relatively better effects, which not only inhibits the interaction between Shiga toxin 2 and the receptor, but also reduces cytotoxicity (Di et al., 2017). However, according to Vogt et al. (2016), the important role of intact backbone structure in immune cell activation was suggested because a reduction of molecular weight resulted in a loss of effect. Likewise, the reduction of molecular weight caused by chemical hydrolysis led to a decreased level of TNF- $\alpha$  and IL-10 (do Nascimento et al., 2017), and the downregulation of both pro-inflammation and anti-inflammation cytokines cannot explain the enhancement of pectin's bioactivity. In our recent studies on the obesity mice model, both RG-I pectin and degraded RG-I pectin alleviated the systematic inflammation. There were no significant differences in the anti-inflammatory effects between the large pectin and the smaller ones, but the parental RG-I produced more SCFAs (Mao et al., 2019).

Thus, the decrease of molecular weight does not necessarily guarantee better properties of pectins in alleviating intestinal inflammation. Pectic polymers and oligosaccharides might be utilized by different intestinal microorganism. And we speculated that pectins of a certain  $M_w$  range may not lead to significant changes in the anti-inflammatory activity. Moreover, the anti-colitis activity of pectins is not related to molecular weight alone but is determined by various factors.

## 4.2 | Degree of esterification

Different effects related to the DE have been observed. Recently, research on the protective effects of pectins with different DE on colitis was carried out in colitis mice and the results revealed that low esterified pectin was more protective by improving the intestinal barrier and reducing the infiltration of immune cells and the level of oxidative stress (Fan et al., 2020). Also, Popov and Ovodov (2013) reviewed that free carboxyl groups were involved in the inhibitory effects of pectins on leukocytes and LMP could easily penetrate the mucin layer and interact with the epithelial cells. However, different experimental models can lead to different results. The apple pectin with 70% to 75% esterification could alleviate systemic inflammation in a rat model of a high-fat diet, which was manifested in the lower serum level of cytokine MCP-1 and the loss of spleen weight (Jakobsdottir et al., 2013). Moreover, a highly esterified pectin (RGal), mainly containing HG, increased gastric mucus content and reduced oxidative stress in a chronic ulcer model (Maria-Ferreira et al., 2018a). It has also been reported that RGal contributes to collagen homeostasis and accelerates wound healing in DSS-induced colitis mouse model (Maria-Ferreira et al., 2018b). It is noteworthy that the sample purity and the

detailed monosaccharide composition are not provided in these studies. The variability of molecular weight most likely impacts the anti-colitogenic effects of dietary pectins (Fan et al., 2020). In a study on an obese mouse model, only the serum level of MOP and spleen weight was employed to serve as the judgment index for pectin's effects, so the inhibitory effects on gut inflammation were opaque (Jakobsdottir et al., 2013). In these two studies based on a colitis model, different mice (Swiss mice and C57BL/6 J mice), DSS concentration (3% to 5%) and modeling period (5 days and 7 days) definitely result in different disease stages (Fan et al., 2020; Maria-Ferreira et al., 2018a). Moreover, the ester group may exert anti-inflammatory activity in various locations such as the stomach, ileum, cecum, and proximal colon (Maria-Ferreira et al., 2018a; Tian et al., 2017; Wu et al., 2019). LMP is efficiently fermented in the ileum and cecum, while HMP is mainly fermented in the proximal colon. Hence, it is necessary to consider the model characteristics and the location of injury to discuss the effects of DE on the anti-colitogenic activity of pectins.

Some cell models were used in these studies. Based on a macrophage cell model, CP at a higher DE exhibited better effects on inhibiting expression of inducible nitric oxide synthase and cyclooxygenase 2, which promoted the development of inflammation (Chen et al., 2006). The immunological activity of these lemon pectins with DM of 30%, 56%, and 74% was investigated in THP1 MD2-CD14 cell. TLRs played a significant role in the cell activation and the TLR-induced activation of NF- $\kappa$ B/AP-1 signal pathway increased due to the increasing DM value (Vogt et al., 2016). Conversely, different effects can be found on different cell lines within immune system. DE30, DE60, and DE90 refer to CPs with 30%, 60%, 90% esterification. After incubated with human PBMC, DE60, and DE90 promoted the production of two anti-inflammatory cytokines, IL-1ra and IL-10, whereas DE30 reduced the secretion of IL-10 and had no effects on that of IL-1ra (Salman et al., 2008). Similar research was carried out by Amorim et al. (2016) and they concluded that the de-acetylated and de-esterified pectin from cacao pod husks possessed better properties than the native pectin in activating the cytotoxic phenotype in macrophages, presenting the possibility of lowering intestinal susceptibility to microbial infection. Collectively, even on the same cell line, completely opposite conclusions were represented in different papers, which might be related to the sample concentration and the parameters measured in these experiments.

As mentioned above, various effects could be observed when pectins act on different players in the intestinal immune system, which might be due to different membrane receptors expressed in the cell surface and different inflammatory signaling pathways. In a short, a high number of nonesterified GalA residues facilitates

pectin-binding to TLRs. In in vitro model, HMPs tend to exert the protective effects via enhancing the mucosal barrier, while LMPs can penetrate the mucous layer to interact with epithelial cells. However, not only the number of methyl-esters but the distribution will influence the anti-inflammatory effects of pectins and more in vivo experiments are needed to determine the impact of the degree of blockiness (Beukema et al., 2021).

### 4.3 | Degree of branching

De-branching of pectins not only impairs the prebiotic activity (Zhu et al., 2019), but also impacts the function of pectins on immune cells. The branched regions in pectic substances, such as ramified galacturonan, seem to enhance both the phagocytosis of macrophages and antibody production (Popov & Ovodov, 2013). do Nascimento et al. suggested that the sidechains removal of sweet pepper pectin induced lower secretion of TNF- $\alpha$  and IL-10 in THP-1 macrophages (do Nascimento et al., 2017). Debranching of the pectin from *Dendrobium nobile* decreased the proliferative activities on T- and B-lymphocytes (Wang, Lou, & Zha, 2010). Furthermore, galactan sidechains exert greater activity against colitis than arabinan (Sabater et al., 2020). The galactose-free pectin (APwG) and arabinose-free pectin (APwA) were obtained through enzyme modification. In the study based on colitis mice, only APwA maintained the bioactivity of the parental pectin, suggesting that the elimination of galactan sidechains in RG-I region impaired the anti-inflammatory properties of pectins. Moreover,  $\beta$ -1,4-galactan sidechains are more competitive to antagonize the pro-inflammatory protein, galactin-3 (Gao et al., 2013).

In conclusion, higher RG-I and neutral sugar in pectins contribute to better function and galactans turn to be the principal bioactive sidechains in RG-I region. Also, the coordination of arabinans, galactans, and AGs plays a crucial role in the activity of pectins. However, no systematic evaluation of the specific length and the sidechains location required for anti-colitis activity has been carried out. The diversity and complexity of branches may lead to considerable variability in pectin function.

### 4.4 | Effects of physical properties

Another important point correlates to the function of pectins involves physical structural characteristics, such as viscosity. High dosage may lead to increases in viscosity, thus, leading to the changes in physical accessibility and

glycolysis rate of pectic substances (Tamargo et al., 2018). However, when discussing the dose-dependent effect, Fan et al. suggested that LMP of 100 and 300 mg/kg could significantly downregulate the oxidative stress but 200 mg/kg dose did not lead to obvious effects. Similarly, no statistically significant differences were observed between 40 and 80 mg/kg, indicating that there might be no dose-dependent effects within a certain range of pectin dosage. Differences in chain conformation are particularly important in the functional activity of pectins. Pectic polysaccharides existing as a random coil conformation or a globular shape with branching are reported to possess antioxidant properties (Xia et al., 2020a, 2020b). However, this structural feature provide an additional challenge for interaction between pectin molecules and immune cells. Also, the insolubility degree may reduce the physical accessibility of pectic substances by gut microorganisms, thus, hindering enzymatic degradation. Therefore, the physical accessibility of pectins will directly impact the fermentation and bacterial metabolic outcomes. And whether the insoluble pectin has specific way to achieve health outcomes during IBD remains unclear.

## 5 | DISCUSSION AND ANTI-IBD MECHANISM HYPOTHESIS OF PECTINS

Intestinal homeostasis is increasingly recognized as the most important factor driving human health, which is impacted by nutrient intake and the living microorganisms. The intestinal epithelial cells, intestinal immune cells and a plethora of microorganisms interact with each other within the ecosystem and simultaneously respond to environmental changes. Pectic polysaccharides, an important slowly fermented carbohydrate, regulate IBD by not only promoting the abundance of an intestine-friendly microbial community, but also interacting with the host immune system including the mucosa layer, pathogenic bacteria, and host cells. The mechanism of action of pectins is proposed to involve microbiota-dependent and microbiota-independent factors. As the substrate of bacterial fermentation, pectins are converted to SCFAs, directly impacting colonocyte growth and cellular inflammation. It has been suggested that microbiota-degraded products exert greater immunomodulatory properties than parental pectin (Rösch et al., 2017), while recent studies have revealed that pectins can regulate barrier function, the immune system, and the mucosal layer as the parental molecule (Ishisono et al., 2019). These findings have enabled us to gain a preliminary understanding of the protective effects of pectic polymers against IBD.

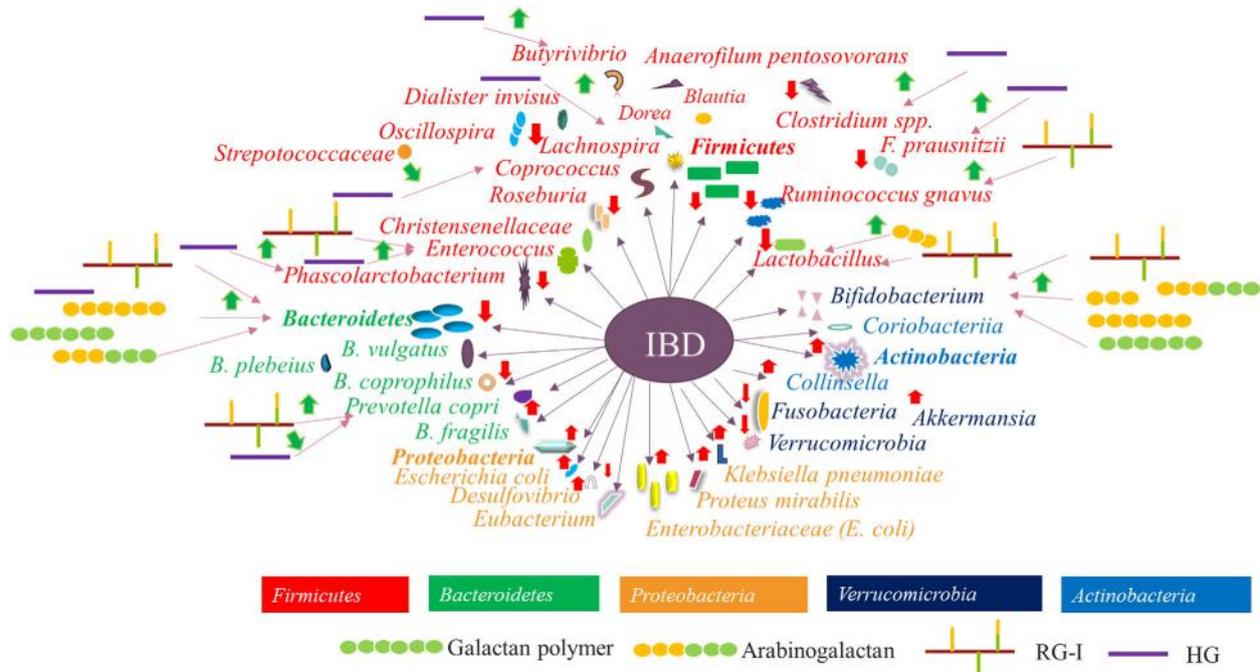


FIGURE 2 Comprehensive profiles of pectic substances in regulating IBD-related intestinal microbiota

Note: Different colors indicate different bacterial phyla. Green arrows indicate the regulation of pectic substances toward bacteria, and red arrows reveal the positive or negative correlation between IBD and specific microbiota.

## 5.1 | Microbiota-dependent pathway

The GI harbors the trillions of microorganisms, specifically bacteria, which exert a crucial role in the development of chronic inflammation. IBD is associated with an altered structure of the microbial community and decreased bacterial diversity, whereas it remains unknown whether a specific bacterial strain/species might be cause or alleviate IBD. Many studies employed mice models to assess the colitogenic ability of certain individual bacterial species/strains, while none was shown to convincingly lead to IBD. The correlations between these pathogenic organisms and pro-inflammatory cytokines have been discussed, implicating the effects of gut microbiota on mucosal autoimmunity (Li, Han, et al., 2020). The dominant bacterial phylotypes in the human gut are *Firmicutes*, *Bacteroidetes*, *Proteobacteria*, and *Actinobacteria*. These major microbiome members further expand host metabolic fitness through utilizing undigested polysaccharides in food intake, producing SCFAs and energy, synthesizing vitamins, maintaining the mucosa and intestinal barrier integrity, and interacting with the host immune system (Cui, Lian, et al., 2019). Some microbiota members have been considered of key importance to immune homeostasis. For instance, *F. prausnitzii* is characterized as a type of significant beneficial strain and some

strains of *Bacteroides* and *Clostridia* genera could induce anti-inflammatory responses (Atarashi et al., 2013; Tilg et al., 2020). Also, *Bifidobacterium* and *Lactobacillus* have exhibited protective effects against intestinal inflammation (Han et al., 2019; Wang et al., 2020). Conversely, the abundance of certain pro-inflammatory bacterial species, like *Bilophila*, *Clostridioides difficile*, *E. coli*, and *γ-proteobacteria* could be increased during IBD (Ramos & Papadakis, 2019). Although a novel promising probiotics, the anti-inflammatory activity of *Akkermansia muciniphila* is strain-specific, indicating that some strains may not have immune-regulatory capacities (Zhai et al., 2019; Roy et al., 2017). As shown in Figure 2, a gut microbial dysbiosis exists in patients with IBD. Many gut bacterial members are associated with IBD. For instance, the increase of some potential pathogenic microorganisms like *Collinsella*, *Escherichia*, *Fusobacterium*, and the decreased beneficial microorganisms (*F. prausnitzii*, *Christensenellaceae*, *Oscillospira*, *Enterococcus*, *Ruminococcaceae*, *Lachnospiraceae*, *Roseburia*, *Clostridium cluster*, *B. coprophilus*) were observed under the disease condition. However, the dysbiosis pattern varies in IBD cases due to different disease states, sample types, genetic inheritance and methods of analysis. And the changes of some beneficial bacteria like *Coprococcus* and *Prevotalla copri* during IBD is undefined.

Dietary pectins can keep the composition of healthy microbiota by reducing the amount of pathogens or mucin-degrading microorganism. Recent research has reported that a fiber-deprived diet in mice model leads to the mucus layer and intestinal barrier degraded mainly by *A. muciniphila* and *Bacteroides caccae*, which forage on these colonic barrier and cause inflammation and increased infection (Desai et al., 2016). As the most important dietary fiber, varying pectic substances can reach the colonic cavity and promote the intestine-friendly environment. Many published researches have revealed the regulation of pectins on *Bacteroidetes* spp., *Bifidobacterium*, *Lactobacillus*, and *Enterococcus*. The diversity and composition of healthy gut commensals are highly dependent on the distinct structural characteristics of pectins, such as various degrees of esterification, amidation, and branched chains (Tan & Nie, 2020; Beukema et al., 2020; Garcia-Carrizo et al., 2019). All pectic substances exhibit the regulatory role toward *Bacteroidetes* and *Bifidobacterium* (Figure 2) (Tingirikari, 2019; Khan et al., 2019; Ji et al., 2020; Patnode et al., 2019). In addition, in vitro fermentation of different pectins were performed using the TIM-2 model of proximal colon, and the results suggested that amidated HG can increase the proportion of *Coprococcus* and *Christensenellaceae*, and decrease that of *F. prausnitzii*. Similarly, HG of different DE induced various compositions of commensal flora (Larsen et al., 2019). In line with this, *F. prausnitzii* can be stimulated by HMP rather than LMP, but LMP efficiently reduces the level of *Prevotalla copri* in mice model of insulin resistance (Cui, Lian, et al., 2019), which may be due to the different digestibility between HMPs and LMPs (Beukema et al., 2020). Thus, certain structural blocks may require sophisticated machinery of specific bacteria to be accessed and utilized. According to Jiang et al. (2016), based on the obese mice model, the increase in *Firmicutes* phylum and the decrease in *Bacteroidetes* were restored to approximately normal levels by oral administration of apple-derived pectin but the sample structure was not provided. Collectively, pectic polysaccharides can, to some extent, reverse flora disorders during diseases, and specific regions appear to increase a target group of bacteria with specificity. In our previous studies, the probiotic effects of commercial HG pectin (CP), RG-I pectin (WRP), and depolymerized RG-I (DWRP) were determined in mice model. RG-I pectin alleviated the inflammation with a reduction in serum LPS level, which was partly via enriching the total amount of SCFAs in the colon (Mao et al., 2019). Compared to that of HG pectin, fermentation of RG-I in the colon produced more butyrate, which might contribute to the inflammation-regulating properties. There were evident changes in the overall gut microbiota structure. All of the pectic substances significantly promoted the growth of *Ruminococcaceae*. WRP adminis-

tration notably increased the amount of *Bacteroides* genus and *Ruminococcus*, while only DWRP treatment remarkably increased the abundance of *Bifidobacterium* and *Lactobacillus* in mice. This study confirmed that the changes of flora are closely related to the molecular weight and chemical structure of pectins for the first time. RG-I pectin shows superiority in promoting the growth of *Bifidobacterium*, *Lactobacillus*, and *Ruminococcus* within the gut microbiota in the obese mice model (Zhu et al., 2020). These species may possess a specialized and complete glycobiome for RG-I pectin degradation (Ndeh & Gilbert, 2018; Luis et al., 2018). However, different results are observed in the in vitro TIM-2 fermentation system. Compared to HG pectin, RG-I or RG-I-enriched pectins evidently reduce or maintain the abundance of *Ruminococcus* in vitro fermentation model (Larsen et al., 2019), indicating that RG-I pectin may show different effects on some species in the healthy gut or in a colitis model. However, the effect of pectin structure on the gut microbiota during IBD is scarce and more further researches are needed.

The SCFAs are regarded as the most important metabolite of the intestinal flora, which play a vital role in protecting human gut from pathogens and regulating several immune pathways of cells in the intestinal wall including epithelial cells, neutrophils, monocytes, macrophages and DCs (Tingirikari, 2019; Cui, Lian et al., 2020). The microbial fermentation of dietary fibers usually starts in the caecum and colon. SCFAs produced by the microbial metabolism not only show beneficial effects on the epithelial cells, but also can be absorbed into the bloodstream and regulate systemic inflammation. Among SCFAs, butyrate nourishes the colonocytes and suppresses colonic tumors, thus, exhibiting the local health-promoting properties in the large intestine. Yet, the loss of butyrate producers, mainly belonging to *Firmicutes* phylum, is suggested to be one feature of microbial dysbiosis during IBD (Table 2). Hence, butyrate supplementation is presumed to be effective in treating IBD. It has been reported that Goji polysaccharides notably promote the growth of *Lachnospiraceae-Ruminococcaceae*, *Roseburia* spp., *Clostridium cluster*, *F. prausnitzii*, and thus, remarkably increase the amount of butyrate, relieving IL-10-deficient colitis in mice (Kang et al., 2018). However, Singh et al. (2018) have compared the effects of pectin and inulin in colitis mice, and the results revealed that fermentation of inulin preferentially enhances the level of butyrate but did not reduce the colitis, even potentiated the severity; while pectin significantly increases acetate and markedly abrogated the chronic inflammation. Therefore, we should know that some dietary fibers could exacerbate bowel disease while others could not, which may be due to the different intestinal sites of fermentation, the dosage and the coordination of other SCFAs. Different fibers fermented in the

TABLE 2 The major short chain fatty acid (SCFA) producing bacteria pertinent to IBD

Phyla/domain	Strains	SCFA production
Firmicutes	<i>Clostridium cluster</i>	Butyrate
	<i>Faecalibacterium prausnitzii</i>	Butyrate
	<i>Lactobacillus</i>	Acetate, propionate
	<i>Ruminococcaceae</i>	Butyrate
	<i>Lachnospiraceae</i>	Butyrate
	<i>Oscillospira</i>	Butyrate
	<i>Christensenellaceae</i>	Butyrate
	<i>Roseburia</i>	Butyrate
	<i>Dorea</i>	Butyrate
	<i>Butyrivibrio</i>	Butyrate
Bacteroidetes	<i>Bacteroides fragilis</i>	Acetate, propionate
Actinobacteria	<i>Escherichia coli</i> ,	Butyrate
	<i>Eubacterium</i>	Butyrate
Proteobacteria	<i>Bifidobacterium</i>	Acetate, lactic acid
Archaea	<i>Methanobrevibacter</i>	Butyrate

cecum could produce butyrate of the same concentration, but the effects on colitis were completely different. This might be due to the different effects of fermented substrates on the absorption of epithelial cells. Thus, targeting in promoting butyrate-producing bacteria as a therapeutic strategy for IBD needs to be carefully investigated. Butyrate and butyrate-producing bacteria may not be the key to disease recovery. According to Morita et al. (1982), the benefit of butyrate is thought to be dose-related and higher concentrations of butyrate lead to toxicity in colon epithelial cells. In addition, whether butyrate is harmful to the colonic epithelium after tissue injury remains unknown. And the nuance of the location where different dietary fibers are fermented into SCFAs may lead to different absorption rates of acetate and propionate, which may also augment the production of butyrate in the colonic environment (Koropatkin et al., 2012). Moreover, the molecular characteristics of pectins determine the composition of fermentation products and different polymers of pectins result in different composition of SCFAs. Fermentation of RG-I produces more acetate and less butyrate in mice of the obesity model (Zhu et al., 2020). Amidated HG preferentially turned into acetic acid and HMP led to more propionic acid than LMP in in vitro fermentation (Larsen et al., 2019). This demonstrates that the composition of SCFAs is closely related to the structure of pectins. In these studies, pectins can promote the growth of many butyrate-producers in Firmicutes phylum, but SCFAs are not the only important metabolite playing a major role in regulating inflammation. For example, *F. prausnitzii* is a butyrate-producing species and is also an anti-inflammatory bacterium. According

to Quevrain et al. (2016), *F. prausnitzii* could secrete an anti-inflammatory protein suppressing the NF- $\kappa$ B pathway in colitis mice. Similarly, the administration of pectins during colitis might be able to promote the production of pathogen-sensitive bacteriocins such as nisin and thuricin to alleviate inflammation (Tan & Nie, 2020). Therefore, the anti-inflammatory substances produced by the human gut microflora and the influence of pectins on the anti-inflammatory bacteria are more worthy of investigation.

Apart from the substantial chemical-structure heterogeneity, complex physical structure also requires certain targeted bacteria that have specific machinery to degrade these substrates. Recently, Cantu-Jungles and Hamaker (2020) have proposed that physical properties, such as particle size, physical accessibility, insolubility degree, and viscosity, can be manipulated to change the fiber specificity to gut bacteria. Furthermore, the effects of dietary fiber were suggested to be dose dependent (Deehan et al., 2020). Thus, these physical characteristics definitely allowed the elucidation of structure-function relationships between pectins and the microbiome during IBD. Moreover, the spatial conformation of the sugar chain might have a greater effect than the primary structure on the activity of pectins. For instance, pectin with majority of linear chains contributes to better proliferation of *Bacteroides fingoldii* than that of branched pectin (Centanni et al., 2019). In addition, all members of the gut commensals participate in the beneficial function of pectins, so the establishment of “unhealthy” microbiome in vitro model is helpful to further decipher the gut microbiota features shaped by different dietary pectins during IBD.

## 5.2 | Microbiota-independent pathway

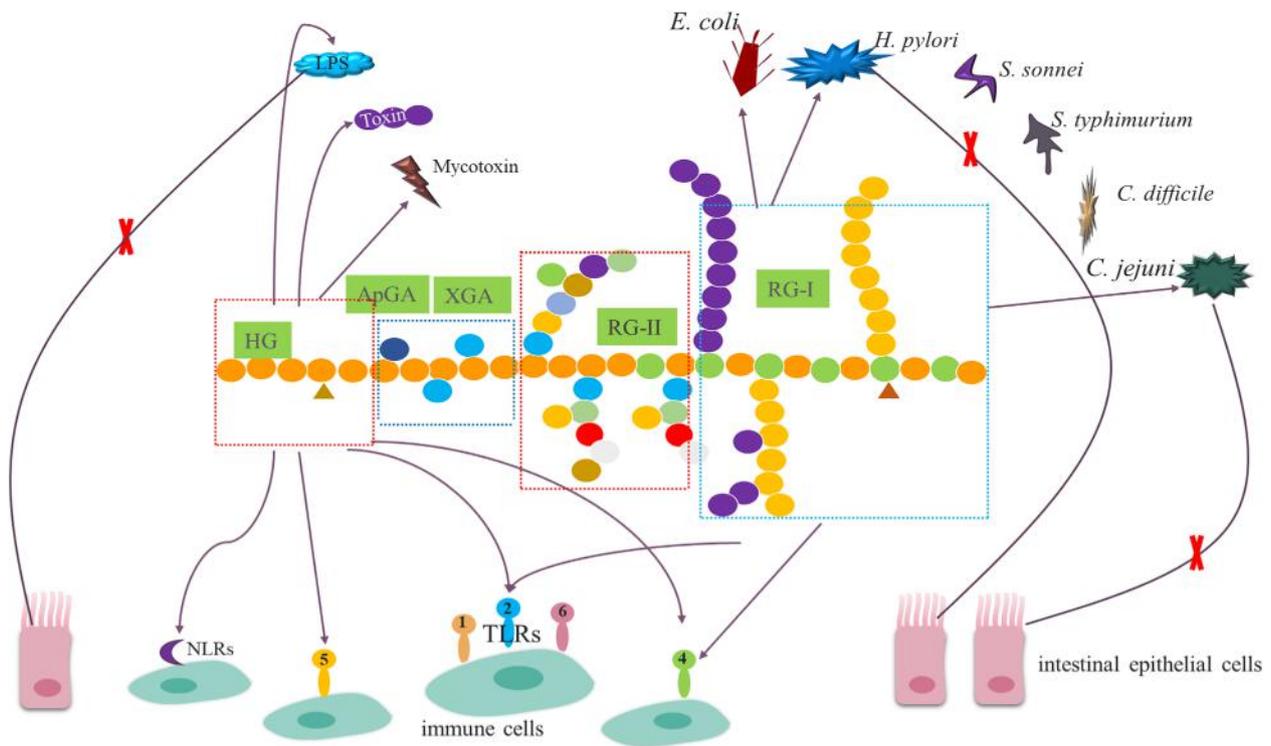
### 5.2.1 | Mucus layer

The intestinal mucosal layer plays an important role in maintaining the homeostasis of gut function via keeping the immune system maintenance of commensal microorganisms and regulation of foreign pathogens (Martens et al., 2018). The mucosa acts as a thick barrier between luminal components and intestinal epithelial cells, which protects sensitive stem cells from harmful substances in the colonic lumen like excess butyrate (Cummings et al., 1987). Mucin-2 glycoprotein (MUC) secreted by goblet cells, a major component of the colonic mucosa, forms a disulfide-linked network. Mucosal degradation by pathogens can induce lethal colitis (Desai et al., 2016). Pectic substances can stimulate the secretion of mucins via interacting with PRRs on the surface of goblet cells or by the microbial metabolites SCFAs. Pectin of low DM is regarded to be possible to penetrate the mucus layer and combine to the epithelial cells, while high DM pectin can enhance the mucosal barrier through interacting with mucins (Beukema et al., 2020). The HG pectin from noni (NFP) regulates the production of colonic mucosa in colitis mice. The goblet cells per crypt are increased and the amount of crypt damage is decreased in NFP-fed mice. More mucus is also observed in the lamina propria (Jin et al., 2019). Similarly, the expression of MUC3 is improved in orange pectin-treated mice (Pacheco et al., 2018) and turmeric pectin-treated mice (Rajagopal et al., 2018). Currently, SCFAs have been shown to enhance the mucosal layer and reduce intestinal inflammation. But there may still be the possibility that pectins directly interact with goblet cells through their galacturonan chains and then stimulate signaling pathways secreting mucus as that pectin could alleviate colitis without a remarkable increase in SCFAs (Ishisono et al., 2019). In addition, RG-I pectin possess the ability to inhibit adhesion and translocation of many pathogenic bacteria, such as *E. coli*, *Shigella sonnei*, *Salmonella typhimurium*, and *Clostridioides difficile* in in vitro model (Roberts et al., 2013). Due to the structure of the glycan chains similar to those on the epithelial cell surface, HG pectin exerts the binding activity to inhibit the adherence of bacterial toxins, which represent another mechanism by which HG pectin improve the mucus barrier function. However, the location where pectins inhibit bacterial adhesion is predicted to be within the terminal ileum and the proximal colon, as pectins are thought to be quickly fermented into SCFAs in the colon. But whether there are pectins remaining in the feces needs to be further determined. Therefore, it remains unclear whether

pectins can directly stimulate the epithelium in the large intestine (Beukema et al., 2020). Anti-adhesion activities (Figure 3) are regarded as the pivotal function of pectins in the mucosal layer, but more work is needed to clarify which type of pectins show the strongest binding affinity to pathogenic bacteria or the toxins.

### 5.2.2 | Epithelial barrier

The intestinal barrier, comprised predominantly by a single epithelial cell layer, is the final barrier separating gut lumen from the circulatory system. The intestinal cells mainly consist of enterocytes, microfold (M) cells, Paneth cells and goblet cells, which function to preserve the integrity of epithelium. Some dietary compositions could impact the gastrointestinal permeability, inducing pathogen invasion and translocation of gut microbiota and eventually exacerbating inflammatory diseases in IBD patients. However, pectins can enhance the barrier integrity, which is manifested in the increased expression of related proteins. Administration of pectins in mice usually upregulates the expression of main tight junction proteins such as occludens-2 and claudin 1 (Yue et al., 2015; Pacheco et al., 2018; Wu et al., 2019). The mechanism of pectic substances regulating epithelial cells is thought to be through the activation of PRRs. Dietary pectins might stimulate the secretion of antimicrobial components from Paneth cells by interacting with PRRs (Wang et al., 2017). But whether HG, RG-I or RG-II will induce different effects is unclear. HG could increase the content of mucin by directly acting on goblet cells in rats models (Hino et al., 2013), while the high DM or  $M_w$  may hinder the combination between HG and PRRs on the cell surface due to the mucoadhesive property of pectins (Sriamornsak et al., 2010). In the in vitro model based on Caco-2 epithelial cell line, HG could improve the claudin-1 expression and enhance the tight junctions (Maria-Ferreira et al., 2018b). Furthermore, glycosylation changes occur in the colonic cells, such as O-glycans on transmembrane glycoconjugates that serve as the receptors for lectins such as galectin-3, which exerts a crucial role in promoting inflammation. RG-I pectin can antagonize galectin-3 in intestinal cells and alleviate inflammatory responses and even precancerous adenomas in *C. rodentium*-induced colitis mice (Gottesmann et al., 2020; Kittana et al., 2018). Therefore, HG and RG-I might act on intestinal cells via interacting with different receptors. However, the effects of the secondary and the tertiary structures of pectins on their activity as inhibitors require further exploration.



**FIGURE 3** The interaction between pattern-recognition receptors (PRRs) and pectic substances, and their anti-adhesion activity

*Note:* HG pectin could affect the activation of inflammatory signal pathway by binding to TLR2, TLR4, TLR5, and some nod-like receptors (NLRs). Also, HG could disturb the damage of microbial toxins on epithelial cells via combination with toxin molecules. Apart from interacting with TLR2 and TLR4, RG-I pectin tend to inhibit the adhesion of many pathogenic bacteria (*Escherichia coli* [*E. coli*], *Helicobacter pylori* [*H. pylori*], *S. sonnei*, *S. typhimurium*, *Clostridioides difficile* [*C. difficile*], *Campylobacter jejuni* [*C. jejuni*]) to intestinal epithelium by linking to these microorganisms. Abbreviations: LPS, lipopolysaccharide; TLR, toll-like receptor.

### 5.2.3 | Immune cells

Approximately 75% of the inherent immune function resides in the digestive tract. The intestinal immune system, composed of innate and adaptive immunity, regulates the composition of gut microbiota and the protective immune responses against the environmental antigens. Multiple immune cells are involved, including lymphocytes, macrophages, NK cells and DCs. Studies based on animal models have revealed that pectins can regulate the activity of Th1 cells, Treg cells, DCs, and so on. Moreover, in cell models, pectic polysaccharides exert their immunological properties via interacting with PRRs (Vogt et al., 2016; Li et al., 2014; Lv et al., 2015). Thus, in the human body both the fermentation products and parental pectins can directly regulate the immune system.

Even though the underlying mechanism is vague, many studies have paid attention to the direct interaction between pectins and the PRRs on the cell surface, which is the primary microbiota-independent pathway, by which pectins regulate gut inflammation. Different PRRs in intestinal cells may be the potential targets for pec-

tic polymers to regulate innate immunity. The involvement of TLR adaptor MyD88 has been investigated in the attenuating-cytokine activity of HG pectin (Bermudez-Brito et al., 2015) and the binding force between pectins and the receptors is also reasonably explained. Low-DM pectin is protective in mice with TLR-dependent ileitis. Anti-inflammatory effects of lemon pectins with different DM values (7%, 22%, 45%, 60%, 75%) were studied in cell lines expressing different TLRs (TLR2, TLR4 and TLR5), which can be activated by P3CSK4, LPS, and flagellin, respectively. The results suggest that HG pectin could not activate these receptors but exhibit a strong inhibitory effect on TLR2 activation in a DM-dependent manner and pectins only impact the pro-inflammatory TLR2-TLR1 pathway, the TLR2-TLR6 heterodimers remain unaltered. Lower DM pectin show more pronounced effect than that of the higher DM pectin in HEK TLR2 reporter cells. When DM value is less than 22%, pectins can remarkably suppress the NF- $\kappa$ B activation (Sahasrabudhe et al., 2018). Then the molecule-interaction between pectins and TLR2 was confirmed via immunofluorescence and ELISA experiments, which illustrate that pectins bound to TLR2 ectodomain

TABLE 3 Applications of pectins in food system

Source	Application form	Food system	References
Citrus	Sugar replacer	Batter	Chan et al., 2018
Sugar beet	Structuring agent	Meat dispersions	Zeeb et al., 2018
Banana peel	Fat replacer	Salad cream	Maneerat et al., 2017
Low-methoxyl pectin	Emulsion	Meat batter	Silva-Vazquez et al., 2018
Apple	Sugar replacer	Cake	Chan et al., 2019
High-methyl pectin	Fat mimetic	Mayonnaise	Sun et al., 2018
Citrus	Thickener	Dairy desserts	Protte et al., 2019
Citrus peel	Pickering high internal phase emulsion (HIPE)	Curcumin in HIPEs	Zhou et al., 2018
Citrus peel	Inulin/fructooligosaccharides/pectin-based emulsion	Encapsulating matrices of polyphenols	Tarone et al., 2021
Low-methoxyl pectin	Stabilizer	Yogurt	Khubber et al., 2021
GENU	Delivery vehicle	Co-encapsulation of curcumin and resveratrol	Guo et al., 2021
Citrus peel	Pectin-iron capsule	Delivery of probiotics	Ghibaud et al., 2017
Citrus peel	Bovine serum albumin-pectin conjugated hydrogel	Delivery of vitamin C	Peng et al., 2016
Carrot	Gelatizer	Oil-in-water emulsion	Idrovo Encalada et al., 2020
Sugar peel pulp	Emulsion	Oil-in-water emulsion	Ai et al., 2020
Citrus	Emulsion	Micelles in water	Fan, Chen, and He (2020)
Sugar beet and citrus	Stabilizer and Emulsifier	Oil-in-water-emulsions	Schmidt et al., 2015
Citrus canning water	Fat replacer	Ice cream	Zhang et al., 2018
Sunflower head	Edible coating	Fried potato chips	Hua et al., 2015
Citrus peel	Antimicrobial pectin-inulin particle	–	Krivorotova et al., 2016
Citrus fruit	Edible coating	Fresh-cut apples	Moreira et al., 2015
Mexican lime bagasse and pomace	Edible film	–	Sánchez Aldana et al., 2015

through electrostatic forces and the ester group might reduce the attraction (Sahasrabudhe et al., 2018). Similarly, Un-2-WSF, the pectin of 15% DM from papaya, obviously decreased the NF- $\kappa$ B release in the activated HEK TLR2 cell lines (Prado et al., 2020). According to these findings, pectins with a low DE (DM < 20%) have a stronger interaction with TLR2 than high-esterified HG pectins in cell models. Also in the case of RG-I pectin, sidechains can suppress the production of IL-6 by stimulating TLR1/2 and TLR4 in macrophages (Ishisono et al., 2019), but the binding mechanism remains vague. In addition, HG pectin can interact with more PRRs, such as TLR4, TLR5, NOD1, and NOD2 (Prado et al., 2020), but whether the methoxyl group can disturb the combination between pectins and all of these receptors remains unclear. Hence, there is a lack of

systematic research on the interaction specificity of pectins with PRRs.

## 6 | FOOD APPLICATIONS

In recent years, continued researches have reported the applications of pectins in the food system (Table 3), indicating the various intake forms of pectins, not merely by fruits, vegetables or nutraceuticals. Due to its probiotic nature, pectins find the potential for new-generation probiotics, which can selectively improve the growth of beneficial bacteria in human gut (Singh et al., 2020). Given the gelling properties and the resistance to acidic stomach conditions, pectins act as a delivery vehicle in food

TABLE 4 Commercial pectin products and related studies

Pectin	Suppliers	Catalogue	Functions	Studies
Citrus pectin	Sigma-Aldrich		Regulating colitis	Singh et al., 2018
Citrus pectin	Creamsa	Creampectin RS4700	Regulation metabolism of microbiota	Patnode et al., 2019
Apple pectin	Herbafoods Ingredients GmbH	Herbapek SF 50 LV		
High-esterified pectin	Sigma-Aldrich	Ref76282	Regulating metabolic diseases	Garcia-Carrizo et al., 2019
Commercial pectin	Sigma-Aldrich		Suppress systemic inflammation	Mao et al., 2019
Commercial pectin	Sigma-Aldrich		Regulating obesity	Zhu et al., 2020
PectaSol-C	EcoNugenics	80029662	Enhancing the PTX effect on ovarian cancer cells	Hossein et al., 2019
Commercially extracted lemon pectins	CP Kelco (Lille Skensved, Denmark).		Attenuating immune responses	Hu et al., 2021
Persimmon pectin	IchimaruPharcos Company Ltd. (Gifu, Japan)		Improving aging-related impairment of nutrient absorption	Othman et al., 2020

products, thus, maintaining the stability of functional agents. For instance, citrus peel pectin can be prepared into a delivery system for loading vitamin C (Peng et al., 2016). In addition, excellent surface activity and hydrophobicity enable pectins employed as emulsifying agents in yoghurt (Khubber et al., 2021), mayonnaise (Sun et al., 2018), dairy desserts, and fruit drinks (Schmidt et al., 2015). And pectins can be developed as a novel detoxification agent to eliminate toxic compounds in beverages due to the binding ability of microbial toxins (Gonzalez-Jartin et al., 2019). Also, pectins show the potential for water treatment as biopolymer-based nanomaterials (Nasrollahzadeh et al., 2021). To date, it has been confirmed that MCP could significantly promote the excretion of lead, arsenic, cadmium and uranium in clinical studies without any side effects (Eliaz et al., 2006; Eliaz et al., 2019). Moreover, pectins have found usage as an edible coating in the field of food preservation (Idrovo Encalada et al., 2020). Therefore, pectins have been pervasively present in the dietary system, not only in natural fruits and vegetables or their products. However, the properties of pectins are highly dependent on the structural characteristics. Pectins of different architecture form a component of food and are taken into the GI together, so the nutritional effects of these pectic substances should be considered.

Many experimental diets mixed with commercial pectins have confirmed the health effects. A prospective phase II study on prostate cancer patients have suggested the safety and potential benefit of the dietary supplement PectaSol-C (Keizman et al., 2019), which mainly contains CP. The pro-inflammatory protein, galectin-3 may be the target of PectaSol-C to promote healthy immune

responses. In our previous studies, the arabinan-enriched RG-I pectin showed better effects than that of commercial pectin on alleviating fat accumulation and systemic inflammation (Mao et al., 2019; Zhu et al., 2020). As listed in Table 4, the administration of pectins is mixed with the diet during some studies, which indicated that supplementation of pectins in food products could increase the health benefits and the pectic substances existing in fruits and vegetables definitely contributes to the health-promoting properties. Moreover, pectic substances still exert the functions in the mixture of pectins and other food ingredients, but whether other nutrients such as proteins, polyphenols and flavonoids in diet could interact with pectins and then impact the activities is obscure.

Therefore, the discussion of the structure–activity relationship of pectins on regulating gut inflammation could provide important insight for developing better functional agents and specific applications in food products.

## 7 | CONCLUDING REMARKS

Considering the physicochemical structural complexity of pectic substances, various structural domains show different properties, supporting or attenuating intestinal inflammation. The function of HG pectin is closely related to the ramified regions,  $M_w$  and DE. Not all the RG-I pectin possess anti-inflammatory activity, but the importance of neutral sidechains in RG-I region has been demonstrated. In addition, physical properties such as chain conformation, viscosity, and solubility are important factors in the discussion of the structure-activity relationship. Currently

published papers arrive at different conclusions, which might be due to the low purity of these pectic polymers, discrete fiber structure, different dosages and various experimental models.

1. Most reports suggest that pectins are beneficial for the treatment of IBD, but the important bioactive structural regions are unclear and whether every domain act on a specific target involved in intestinal health or on common receptors requires additional investigation. Anti-colitis studies about various pure pectic polymers such as HG, RG-I, and RG-II should be designed in the same model to compare the effects, which contributes to design the most effective nutraceutical. Maintaining pectin structure using novel production processes is certainly important. In addition, physical accessibility also should be taken into account in the discussion of structure-function relationship.
2. Current studies focus on the regulation of immune cells, mucosal layer, colonic barrier function, but the effects of different pectins on the gut bacteria during IBD is understudied. The variability of certain strains pertinent to inflammation and the anti-inflammatory compounds most likely impinges on mitigating this disease. The enrichment of metabolites induced by pectins can promote positive health outcomes.
3. Some experiments are needed to confirm the antagonist property of pectins, including SPR, ELISA, or immunofluorescence. Pectic polymers have the potential to interact with PRRs, pathogenic bacteria or toxins, but the binding affinity, binding sites, and structural specificity remain unclear.
4. Characterization of pectin purity is very important as extracted pectins are usually accompanied by proteins, phenolics, and Amadori compounds. In this context, it is controversial to conclude that only pectins in the extracted complexes contribute to the beneficial effects.
5. There is a lack of systematic research about the effects of pectins in different stages of IBD and the effects of different dosages. After the gastrointestinal epithelium is damaged, pectins may appear to function less effectively (Silveira et al., 2015; Ishisono et al., 2019). It is necessary to distinguish therapeutic and prophylactic effects of pectins. Moreover, some studies have suggested that the administration of pectins at certain high dosage will improve the symptoms of colitis, but the reasons remain unclear.

At this stage, it is necessary to conduct extensive studies on the structure-function relationship of pectic substances in attenuating IBD.

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## CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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