Food Hydrocolloids 127 (2022) 107209

Contents lists available at ScienceDirect

Food Hydrocolloids

journal homepage: www.elsevier.com/locate/foodhyd

Protective effects of six different pectic polysaccharides on DSS-induced IBD in mice

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ARTICLE INFO

Keywords:
IBD
Pectic polysaccharide
Structure
Function
SCFA
Berry

ABSTRACT

Administration of pectic polysaccharides is a therapeutic strategy in the management of gut inflammation. However, the knowledge about the effects of different dietary sources and structure are missing. This study explored the protective effects of six different pectic polysaccharides from Goji berry (G), dragon fruit (D), lemon (L), pomelo (P), potato (T) and raspberry (R) in dextran sulfate sodium (DSS)-induced colitis mice. D mainly contained rhamnogalacturonan (RG) backbone; L had high amount of arabinan sidechains; P was a high-esterified homogalacturonan (HG) pectic polysaccharide; the primary domain in T was galactan sidechains; R and G had the composition of arabinan: galactan: RG: HG = 19: 28: 15: 22 and 36: 17: 21: 14. Our results suggested that G and R were the most effective in alleviating colitis via alleviating tissue damage, promoting the index of immune organs, suppressing the production of TNF-α, IL-1β and IL-17, improving antioxidant status and promoting the total amount of SCFAs. Similarly, the administration of L alleviated colitis mainly by increasing the fermentation products without changes in the composition pattern of SCFAs. The secretion of IL-6 might be suppressed by pectic polysaccharides containing high amount of arabinan sidechains, while anti-inflammatory cytokines and intestinal barrier function tend to be regulated by pectic polysaccharides rich in galactan. In conclusion, pectic polysaccharide containing diversified structural domains (homogeneous proportion of HG, RG, arabinan, and galactan) might be the most effective in alleviating gut inflammation. This unprecedented report revealed the anti-inflammatory effects of different pectic polysaccharides, which was critical for the reasonable selection of dietary fiber to prevent gut inflammation.

1. Introduction

Gut is the essential organ in human body for digestion, fermentation, and nutrients absorption, the intestinal barrier and mucosal layer can protect host from pathogens and harmful substances. Thus, a healthy gut acts as the foundation of human health. Nowadays, with the more intake of processed foods in dietary structure, gut inflammation has become the biggest threat to human benefits (Macdonald & Monteleone, 2005). Globally, gut food allergies and chronically idiopathic inflammation commonplace, thus promoting many systemic diseases including obesity and cancers (Cani et al., 2009; Jia, Rajani, Xu, & Zheng, 2020). Inflammatory bowel disease (IBD), mainly Ulcerative colitis (UC) and Crohn's disease (CD), are chronic diseases of the gastrointestinal system characterized by recurrent inflammation, various complications and unclear etiology. Approximately 6.8 million people had IBD globally in 2017, and the incidence continuously accelerate since 1999 (Mehrmal, Uppal, Nedley, Giesey, & Delost, 2021). It has been estimated that the incidence of IBD in China will reach 1.5 million by 2025. Multiple studies suggested that a number of factors, such as environmental differences, diet habits, pathogen infections and bacteria disorder, can drive the progression of gut inflammation (Aden et al., 2019), among which the dietary pattern plays a particularly significant role. The

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https://doi.org/10.1016/j.foodhyd.2021.107209
Received 12 July 2021; Received in revised form 19 September 2021; Accepted 21 September 2021
Available online 27 October 2021

pharmacological and surgical treatments of IBD have great risks and potentially serious side effects (Verhelst et al., 2020). Therefore, supplementary intervention could be the preferred method to prevent inflammatory response without adverse effects for IBD.

Recently, a clinical research has revealed that 10% of pectic polysaccharide supplemented in diet protected from acute colitis (Silveira et al., 2015). Accumulating experimental data reveal that dietary polysaccharides such as pectic polysaccharide exhibit protective effects against colitis (Fan, Chen, & He, 2020), ulcer (Rajagopal, Manjegowda, Serkad, & Dharmesh, 2018), ileitis (Sahasrabudhe et al., 2018), GI lesions (Jin et al., 2019) and caecal dysfunction (Wu et al., 2019). Our previous study also demonstrated that pectic polysaccharides with different chemical composition attenuated inflammatory parameters in mice model (Mao et al., 2019). Moreover, pectic polysaccharide with more neutral sidechains ameliorates colitis and disorders better (Ishisono, Mano, Yabe, & Kitaguchi, 2019; Sabater et al., 2019).

As one of the most important dietary fiber in the food system, pectic polysaccharide comes from omnipresent sources in the primary cell wall and middle lamella of fruits and vegetables (Wu, Zheng, Mao, et al., 2020). It has been used widely in food industries as a gelling ingredient, emulsifier and stabilizer (Fan et al., 2020). Pectic polysaccharide is multiplex polysaccharide mainly composed of two structural regions, homogalacturonan (HG) and rhamnogalacturonan I (RG-I). HG is a linear homopolymer consisting of α-1,4-linked D-galacturonic acid (GalA) that can be partly esterified and acetylated (Voragen, Coenen, Verhoef, & Schols, 2009). RG-I is regarded as the "hairy" region in pectic polymers formed by rhamnogalacturonan backbone linked by repeating disaccharide units of α-1,2-L-rhamnose-α-1,4-D-galacturonic acid, among which some rhamnose residues are substituted with the vast array of different neutral sugar sidechains, such as galactan, arabinan, arabinogalactan I and arabinogalactan II (Yapo, 2011). The fine structure characteristics of pectic polysaccharide differ due to the extensive array of dietary sources. However, most published papers only focused on one single pectic polysaccharide regulating gut inflammation and neglect the complexity of various dietary sources and discrete pectic polysaccharide structure. Various structural features of pectic polysaccharide have been found in new sources (Park & Shin, 2019; Pieczywek, Kozioł, Płaziński, Cybulska, & Zdunek, 2020; Sowinski, Gilbert, Lam, & Carpita, 2019), and the function is highly dependent on the structure of pectic polysaccharide (Wu et al., 2020b, 2021). Which source or which structure of pectic polysaccharide is the most beneficial to gut health during colitis remains opaque. Here, we hypothesize that different dietary sources could lead to variations in the chemical structure of pectic polysaccharide that would differently alter the intestinal environment during colitis. Clarifying how pectic polysaccharide structure perform diverse functions against IBD could provide guidance on dietary supplement to prevent or alleviate gut inflammation.

In this study, we chose six pectic polysaccharides with specific structural characteristics extracted from different dietary sources to study the structure-function relationship. For this purpose, after physiochemical and structural characterization of pectic polysaccharides, they were administered in the dextran sulfate sodium (DSS)-induced colitis mice to determine the tissue damage, disorder of barrier function, inflammatory response, oxidative stress and changes in bacteria metabolites, so the relationship between the chemical composition of pectic polysaccharide and its anti-inflammation activity was demonstrated.

2. Materials and methods

2.1. Materials

Lemon (*Citrus limon (green)*) peel pectic polysaccharide (L), red pomelo (*Citrus maxima cv. Red pomelo*) peel pectic polysaccharide (P) and red dragon fruit (*Hylocereus undatus*) peel pectic polysaccharide (D) were extracted through a sequential extraction method according to Zhang et al. (2018). After acid extraction, the residue was then resuspended in 0.6% sodium hydroxide solution (1:30), and the extraction procedure with continuous stirring was carried out for 10 min at 32 °C. At the end of extraction, the alkali-extracted pectic polysaccharides (L, P, and D) was recovered after filtration, neutralization and precipitation with 95% ethanol and then, resolved in distilled water and fully freeze-dried. Raspberry pectic polysaccharide (*Rubus ideaus*) (R) was obtained by harsh hydrochloric acid extraction at 80 °C, pH 1.2 for 90 min (Marić et al., 2018). Goji berry (*Lycium barbarum*) pectic polysaccharide (G) was obtained by acid extraction according to Zhou et al. (2020). All the fruit sources used in this study were obtained from the local market in Hangzhou. Potato rhamnogalacturonan I pectic polysaccharide (T) was purchased from Megazyme International Ireland Ltd. (Wicklow, Ireland). Then T was dialyzed (MWCO 8000–14000 Da) and freeze-dried before use. DSS (40 kDa) was purchased from Aladdin Chemical Reagent Co., Ltd. (Shanghai, China). Monosaccharide standards were purchased from Sigma-Aldrich (Shanghai, China). Acetic acid, propionic acid, isobutyric acid, butyric acid, isovaleric acid, and valeric acid were purchased from Macklin Chemical Reagent Co., Ltd. (Shanghai, China). All other chemicals used were of analytical grade and purchased from Aladdin Co. (Shanghai, China).

2.1.1. Characteristics of pectic polysaccharide

Total amount of carbohydrate content of the pectic polysaccharides was analyzed by the to the phenol-sulfuric acid method (Soria et al., 2010). The monosaccharide composition was determined by acid hydrolysis, followed by high-performance anion-exchange chromatography with a pulsed amperometric detection (HPAEC-PAD) (Hu, Ye, Chantapakul, Chen, & Zheng, 2020). The molecular weight was analyzed using a HPSEC-MALLS-RI method (Wu, Zheng, Mao, et al., 2020). The degree of methylation (DM) and acetylation (DAc) were determined by the m-phenylphenol method (Levigne, Thomas, Ralet, Quemener, & Thibault, 2002). After saponification, the pectic polysaccharide samples were prepared to analyzed methanol and acetic acid using High-performance liquid chromatography (HPLC) (Waters 1525, US) equipped with a C18 column (SinoChrom ODS-BP 250 mm × 4.6 mm, 5 mm, Elite, China) and a refractive index (RI) detection (Waters 2414,US). Isopropanol was used as internal standard and 4 mM sulfuric acid was the mobile phase.

2.2. Animal design and colitis scoring

80 male C57BL/6J mice (4–6 weeks old; IACUC-20200525-10) were purchased from Zhejiang Chinese Medical University Laboratory Animal Research Center and housed in specific-pathogen-free conditions (22 ± 1 °C) with a 12 h light/dark cycle. These mice were allowed free access to food and sterile drinking water (DW). After an acclimation period of one week, the mice were randomly divided into eight groups (10 mice in each group, 5 mice per cage), Normal, DSS, DSS-G, DSS-D, DSS-L, DSS-P, DSS-T and DSS-R groups with standard chow diet (Rodent diet, MD171131, Jiangsu Medicine Pharmaceutical Biological Engineering Co, Ltd, Yangzhou China). To investigate the effects of different pectic polysaccharide and compare their effects (Fig. S1), the mice were orally administered with sterile water (vehicle), G (300 mg/kg/d), D (300 mg/kg/d), L (300 mg/kg/d), P (300 mg/kg/d), T (300 mg/kg/d), R (300 mg/kg/d) for two weeks, respectively. The dosage was determined according to the reference (Fan et al., 2020), which revealed that 300 mg/kg/d of low esterified pectic polysaccharide administration could significantly alleviate colitis symptoms in mice. Colitis was induced by drinking water containing 3% DSS for 7 days. The body weight, diarrhea scoring and hematochezia scoring of mice were measured daily. Both of diarrhea and hematochezia scoring were divided into 3 grades (Table 1). At the time indicated, all the mice were fasted for 12 h and anaesthetized, the blood samples were collected from the orbital plexus for subsequent analysis. Thereafter, the mice were sacrificed. The colon, thymus, liver and spleen, caecal contents and colon contents were collected right after sacrifice, frozen in liquid nitrogen and then stored at

Table 1
Scoring standards of the disease activity index.

Parameters		Score
Loss of body weight	0%	0
	0.1–5%	1
	5–10%	2
	>10%	3
Stool consistency	Normal	0
	Loose stools	1
	Stools of irregular shape	2
	Diarrhea	3
Hematochezia	Normal	0
	Presence of blood	1
	Mild bleedings	2
	Gross bleedings	3

−80 °C for following analysis.

The weight of thymus and spleen, the length of colon tissue were measured for calculating organ indexes. The disease activity index (DAI) were recorded according to the grading rules and calculated as follows:

DAI = Loss of body weight scoring + diarrhea scoring + hematochezia scoring

2.3. Hematoxylin and eosin (H&E) staining

Tissue specimens were taken from the distal colon. Colonic tissues of 0.5 cm were fixed using 4% paraformaldehyde and paraffin-embedded, followed by sectioned (4 μm) and stained with H&E to assess the histological injury. The score system was shown in supplementary files (Table S1).

2.4. Preparation of serum sample and biochemical test

Serum samples were separated by centrifugation (4 °C, 12,000 g, 10 min). The serum levels of tumor necrosis factor (TNF)-α and endotoxin lipopolysaccharides (LPS) were measured by enzyme-linked immunosorbent assay (ELISA) kits (Caobenyuan Biotechnology, Nanjing, China). The serum concentration of nitric oxide (NO) was determined by a NO assay kit (Beyotime Technology, Shanghai, China).

2.5. Biochemical analysis of colon tissue

The concentration of interleukin (IL)-10, IL-6, IL-17, interferon gamma (IFN-γ) and interleukin 1 beta (IL-1β) in the colon tissues of mice were evaluated using commercially available ELISA kits (Meilian Biotechnology, Shanghai, China). The determination of superoxide dismutase (SOD) activity in colon tissue was performed by using the kits (Solarbio, Beijing, China).

2.6. Quantification of glutathione/oxidized glutathione in the liver

Determination of glutathione (GSH)/oxidized glutathione (GSSG) in the liver was performed by commercially available kits (Beyotime Technology, Shanghai, China) with the help of a Fluoroskan Ascent FL plate-reader (Thermo Fisher Scientific, USA). Briefly, 0.1 g mouse liver tissue was in PBS and then homogenized in 1 mL cold GSH assay buffer. After centrifugation (10000 g, 10 min, 4 °C), the supernatants was used to perform the assay. The GSH/GSSH level was normalized to the weight of liver.

2.7. Quantification of short-chain fatty acids (SCFA) in intestinal contents

The caecal SCFAs were measured as described by Mao et al. with minor modifications. Briefly, 100 mg of intestinal contents were diluted with 500 μL acidified ethanol (0.5% v/v HCl), vortexed uniformly for 10 min and then subjected to centrifugation at 14,000 rpm for 10 min at 4 °C. The supernatant was filtered through a syringe-filter with the pore size of 0.22 μm and analyzed using the gas chromatography (Agilent Technologies, Stockport, UK) with a 30m × 0.25mm × 0.25 μm HP-INNOWax column (No. 19091N-133; Agilent Technologies, USA) and a flame ionization detector (Agilent Technologies). Quantification of SCFAs of all these samples was achieved by comparing peak areas to those of chemical standards.

2.8. Statistical analysis

All experiments were carried out in triplicate, and the average of three independent experiments was used as the statistical result. The one-way analysis of variance (ANOVA) was conducted, followed by Duncan's multiple range test at a significance level of 0.05 using SPSS software (version 19; IBM Corporation, New York, NY, USA).

3. Results and discussion

3.1. Structural features of pectic polysaccharide samples

The chemical properties of these six pectic polysaccharide samples were provided in Fig. 1. Goji berry pectic polysaccharide had the highest average molecular weight (M_w) amongst the tested samples, of which the M_w were all within 3×10^4–8×10^4 g/mol. M_w is an important factor influencing the function of polysaccharides and the dramatic changes in M_w will change the efficacy of pectic polysaccharides. For instance, Zhu et al. (2020) have compared the effects of the large-M_w pectic polysaccharide (WRP, 535 kDa) and the small-M_w one (DWRP, 12 kDa) on obese mice. The results revealed WRP could significantly prevented bodyweight gain, insulin resistance and enhanced the diversity of gut microbiota but DWRP could not.

The results of monosaccharide composition analysis showed that every pectic polysaccharide sample exhibited specific structural characteristics. Goji berry pectic polysaccharide contained 74% of RG-I structure, and the monosaccharide ratio was as GalA: Rha: Ara: Gal = 3.4: 1: 3.6: 1.7. In the ^{1}H spectra of G, the high peaks at 5.16 ppm, 4.50 ppm, 4.09 ppm and 3.86 ppm were derived from Ara-H_1, Gal-H_1, Ara-H_2 and GalA-H_3, respectively (Chen et al., 2020; Xu, Qi, Goff, & Cui, 2020; Zhou et al., 2018). The signal at 5.34 ppm was assigned to Rha-H_1. Dragon fruit pectic polysaccharide was enriched in the rhamnogalacturonan (RG) backbone (almost 60%) and the total amount of RG-I of D was 83%. Lemon pectic polysaccharide have 49% of arabinose, which mainly existed as the sidechains of RG-I pectic polysaccharide. In the ^{1}H spectra of L, the high peak at 4.23 ppm was assigned to Ara-H_4. Red pomelo pectic polysaccharide was categorized as HG type pectic polysaccharide. Potato pectic polysaccharide contained 88% RG-I, of which 51% was galactan sidechains, which was reflected by the obvious signal at 4.53 ppm in the ^{1}H spectra. Raspberry pectic polysaccharide have a multicomplex composition of arabinan: galactan: RG backbone: HG backbone = 19: 28: 15: 22. In the ^{1}H spectra of R, the two highest peaks were attributed to GalA residue and Gal residue. Most of these structural domains have been reported to be protective against dietary diseases. HG could maintain the collagen homeostasis and accelerate the wound healing in DSS-induced colitis mice (Fan et al., 2020). The high amount of arabinan sidechains could promote the intestinal probiotic effect of citrus pectic polysaccharide (Mao et al., 2019). Furthermore, galactan sidechains in artichoke pectic polysaccharide exert greater activity against colitis than arabinan sidechains by down-regulating the level of proinflammatory markers TNF-α and ICAM-1 and increasing the expression of mucosal protein MUC-3 (Sabater et al., 2019). However, the anti-inflammatory effects of RG backbone remained to be determined.

All of the pectic polysaccharides have low DAc. The DM of P was

A

Pectin	Monosaccharide composition (mol %)						HG (mol%)	RG-I (mol%)	RG (mol%)	GalA/Rha	GalA/(Ara+Gal)	Total sugar (mg/g)	Mw (g/mol)	DM (%)	DAc (%)
	Arabinose	Galactose	Rhamnose	Galacturonic acid	Glucose	Xylose									
G	35.95±2.02	17.07±0.22	10.31±0.86	33.65±0.34	1.54±0.08	1.48±0.02	23.34	73.64	20.62	3.26	0.63	637±8	$(2.18\pm0.03)\times10^5$	N	0.39
D	13.18±0.21	11.12±0.16	29.38±0.46	41.35±1.02	2.89±0.02	2.08±0.47	11.19	83.06	58.76	1.41	1.70	703±9	$(5.74\pm0.06)\times10^4$	N	2.18
L	49.02±0.32	13.74±0.07	2.58±0.08	25.6±0.22	2.30±0.10	6.99±0.42	23.02	67.92	5.16	9.92	0.41	721±13	$(4.21\pm0.03)\times10^4$	N	0.48
P	9.35±2.1	3.29±0.2	1.47±0.15	78.01±3.21	4.65±0.55	3.12±0.74	75.07	15.58	2.94	53.07	6.17	787±16	$(8.39\pm0.03)\times10^4$	67	7.27
T	9.23±1.6	50.78±1.15	14.09±0.22	16.67±1.33	7.77±0.95	1.45±0.21	2.58	88.19	28.18	1.18	0.28	719±8	$(3.03\pm0.03)\times10^4$	N	0.70
R	18.97±2.53	28.25±5.19	7.37±0.67	29.25±4.94	7.86±1.20	5.30±0.27	21.88	61.96	14.74	3.96	0.62	828±17	$(4.69\pm0.08)\times10^4$	19	3.00

*HG mol%=GalA mol%-Rha mol%; RG-I mol% = 2Rha mol% + Ara mol% + Gal mol%; RG = 2Rha mol%

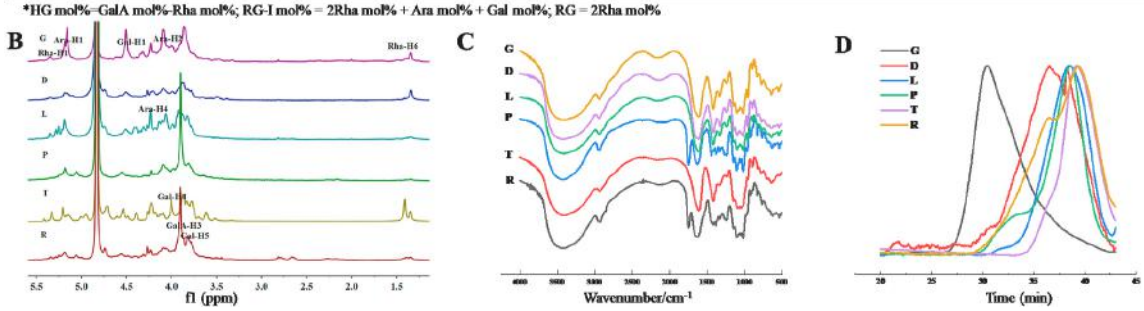

Fig. 1. Structural features of six pectic polysaccharides. G: Goji pectic polysaccharide; D: dragon fruit pectic polysaccharide; L: lemon pectic polysaccharide; P: red pomelo pectic polysaccharide; T: potato pectic polysaccharide; R: raspberry pectic polysaccharide. (A) Chemical composition and molecular features of six pectic polysaccharides. N: not detected (B) ^{1}H NMR spectra (C) FT-IR spectra (D) HPGPC profiles. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

67%, more than 50%, and others were all low-methylation pectic polysaccharide (LMP), which was in accordance with the results of the infrared spectrum. Usually, the peak at 1740 cm^{-1} was due to the stretching vibration of C═O and C–O of the ester group (–COO–R). The peak at 1630 cm^{-1} corresponds to the existence of COO- in polysaccharides. Thus, all of the G, D, L and T were almost non-esterified pectic polysaccharide since none peak occurred at 1740 cm^{-1}. The evident peaks at 1740 cm^{-1} of P and R spectra indicated that some

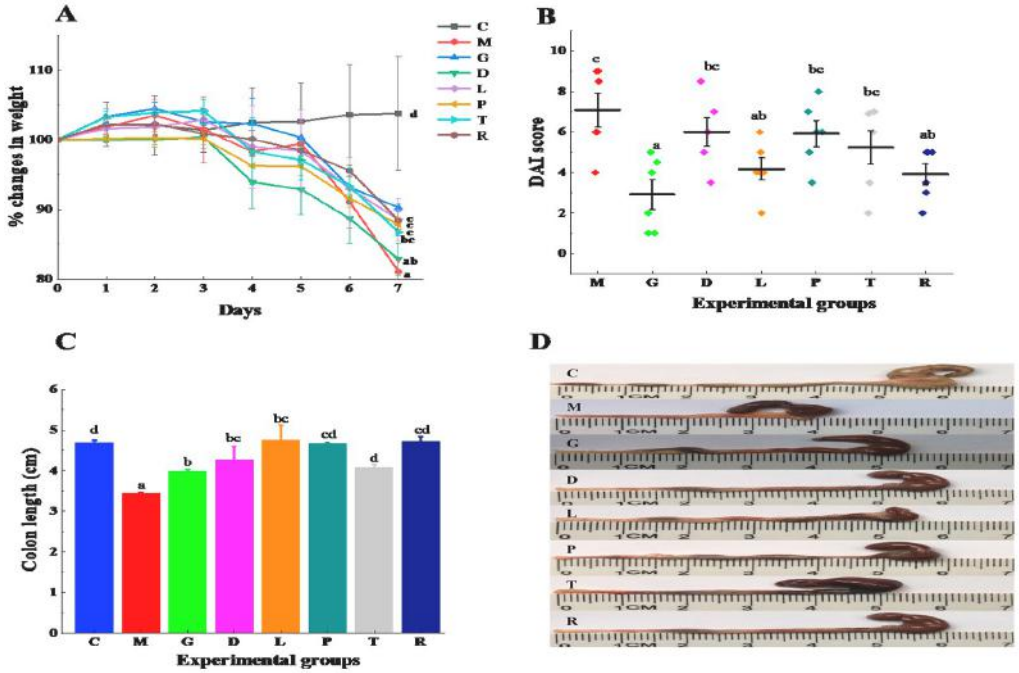

Fig. 2. Impact of six pectic polysaccharides on the severity of colitis, including (A) the loss of body weight (n = 6 per group), (B) the DAI scores (n = 6 per group), (C) length of colon (n = 6 per group) and (D) pictures of colon tissues. Groups with different letters are significantly different ($p < 0.05$).

portions of the two pectic polysaccharides were esterified. The differences in DM were due to different extraction methods, because the alkaline environment led to de-esterification of pectic polysaccharide, while acid did not, which was in accordance with previous studies (Nguyen et al., 2018; Zhang et al., 2018). Previous studies have suggested de-methylesterified and de-acetylated cacao pod husks pectic polysaccharide exhibited better properties than native polymers in enhancing the cytotoxic phenotype in macrophages (Amorim, Vriesmann, Petkowicz, Martinez, & Noleto, 2016). The ester groups in GalA could hinder the molecules interaction between pectic polysaccharide and the pattern-recognition receptors in immune cells and thus, destroy the immunomodulatory activity of pectic polysaccharide (Sahasrabudhe et al., 2018). However, apple pectic polysaccharide with 70–75% esterification could also reduce systemic inflammation in obese rat by inhibiting the production of cytokines MCP-1 and the enlargement of spleen (Jakobsdottir, Xu, Molin, Ahrne, & Nyman, 2013). So, the function of pectic polysaccharides are regulated by many other factors, such as M_w and different structural domains.

3.2. The disease symptoms of DSS-induced colitis in mice

The body weight changes are significant indicators to represent the physical conditions of mice in IBD. During one week of DSS exposure, the weight of the colitis model group decreased since the 3rd day compared to that of the control group, as shown in Fig. 2A. On the 7th day, the body weight decreased by 18.94% in model (M) group. The pectic polysaccharide treatment groups showed attenuation of loss weight, but there was no significant difference between D group and M group. Goji pectic polysaccharide, which has been reported to be protective for colitis (Kang, Yang, Zhang, Ross, & Zhu, 2018), was the best effective treatment to maintain the body weight during the experimental period. However, there was no significant difference observed in the body weight changes of the G, L, P, T and R groups. As shown in Fig. 2B, G, L and P significantly decreased the DAI scores of colitis mice on the 7th day, while there were no significant differences between other groups and model group. The shortening of the colon caused by colitis can be considered as indicator of disease severity (Han et al., 2019). Our results suggested that administration of all the pectic polysaccharide significantly palliated the colonic shortening, indicating that all kinds of pectic polysaccharides could relieve DSS-induced colitis to a certain extent. Collectively, G, L, and R exhibited the better effects in alleviating the diseases symptom of colitis in mice than D, P, and T. Both of D and T contained more than 80% of total RG-I, whereas these two pectic polysaccharides showed less protective effects than G, L, and R, suggesting the total amount of RG-I was not closely related to the function of pectic polysaccharides in mice of colitis.

The thymus is a vital lymphoid organ closely related to immune function (Lev, Simon, Amariglio, Rechavi, & Somech, 2012). The thymus index (thymus weight/body weight) was calculated to assess the anti-inflammatory effects of pectic polysaccharide in colitis mice. As shown in Fig. 3A, the thymus index remarkably decreased in colitis mice, while pectic polysaccharide treatment could attenuate the shrinking of thymus induced by DSS. Compared to that of model group, G, D, L, P, T and R increased the thymus index by 21.05%, 2.8%, 6.3%, 11.5, 17.54% and 71.93%, respectively. However, only the R group showed a significant difference from the M group, indicating the better protective effects of raspberry pectic polysaccharide than that of the other pectic polysaccharides. In addition, the spleen plays a vital role in the immune system, and the swelling of the spleen is an indicator of colitis severity (Mok et al., 2020). As shown in Fig. 3C, the spleen enlarged and darkened in colitis mice. Our results showed that G, L and R suppressed the enlargement of spleen in colitis mice. Compared to M group, G significantly decreased the spleen index in colitis mice, suggesting the protective effects of G in colitis mice.

Histopathological examination of the colon of mice can reveal the tissue injuries in the intestinal wall (Singh et al., 2018; Han et al., 2019). As shown in Fig. 4, the healthy colon tissues in the control group have intact colonic mucosa with erect and parallel crypts and rich goblet cells (black arrow), which can secrete mucin to contribute to the intestinal mucus barrier (Cornick, Kumar, Moreau, Gaisano, & Chadee, 2019). A small number of inflammatory cells (neutrophils, lymphocytes, monocytes and eosinophils) are located in the mucosal muscularis (black star), but almost none was observed in the submucosa (red arrow). H&E staining of the colonic segments from DSS-induced colitis mice indicated thinned mucosa, severe damage of crypt structure, visible depletion of goblet cells and infiltration of inflammatory cells in the submucosa (red circle in Fig. 4). In contrast, pectic polysaccharide treatments remarkably mitigated the morphological alterations caused by DSS, especially G, T and R (Fig. 4). The preserved colon architecture, such as increased mucosa thickness, distinct crypt structures, more goblet cells, and cleaner submucosa, suggested the protective effects of dietary pectic polysaccharide from Goji berry, raspberry, and potato against DSS-induced colonic injuries.

Collectively, these results shed light on the contribution of pectic polysaccharide from Goji berry and raspberry on relieving the symptoms in colitis mice, especially the raspberry pectic polysaccharide.

3.3. The content of inflammatory cytokines in serum and colon

Inflammatory cytokines play a significant role in driving and mediating colitis. The up-regulation of pro-inflammatory cytokines can increase the severity of colitis (Bevivino & Monteleone, 2018). In our study, we detected the TNF-α level (Fig. 5A) in serum and IL-1β, IL-6, IL-10, IL-17, INF-γ (Fig. 6) in the colon using the ELISA method. After induction of DSS, the concentration of pro-inflammatory cytokines TNF-α, IL-1β, IL-6, IL-17 and INF-γ in colitis mice increased by 53%,

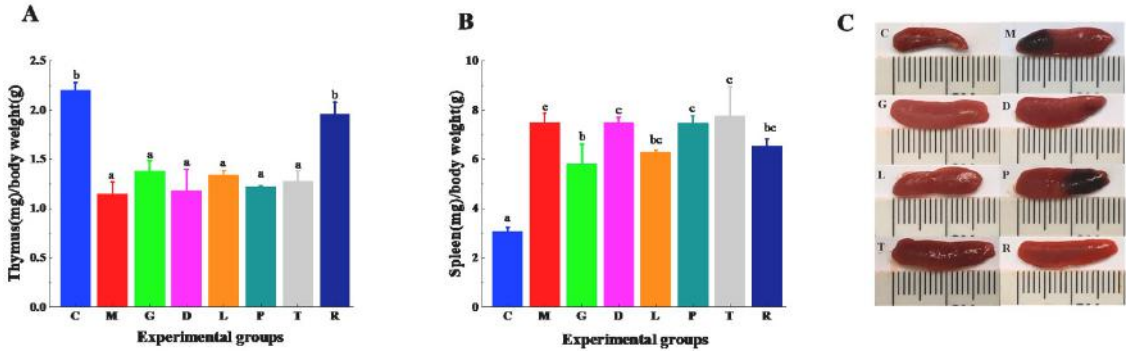

Fig. 3. Thymus index (A) and Spleen index (B) of colitis mice (n = 6 per group) and (C) pictures of spleen. Groups with different letters are significantly different ($p < 0.05$).

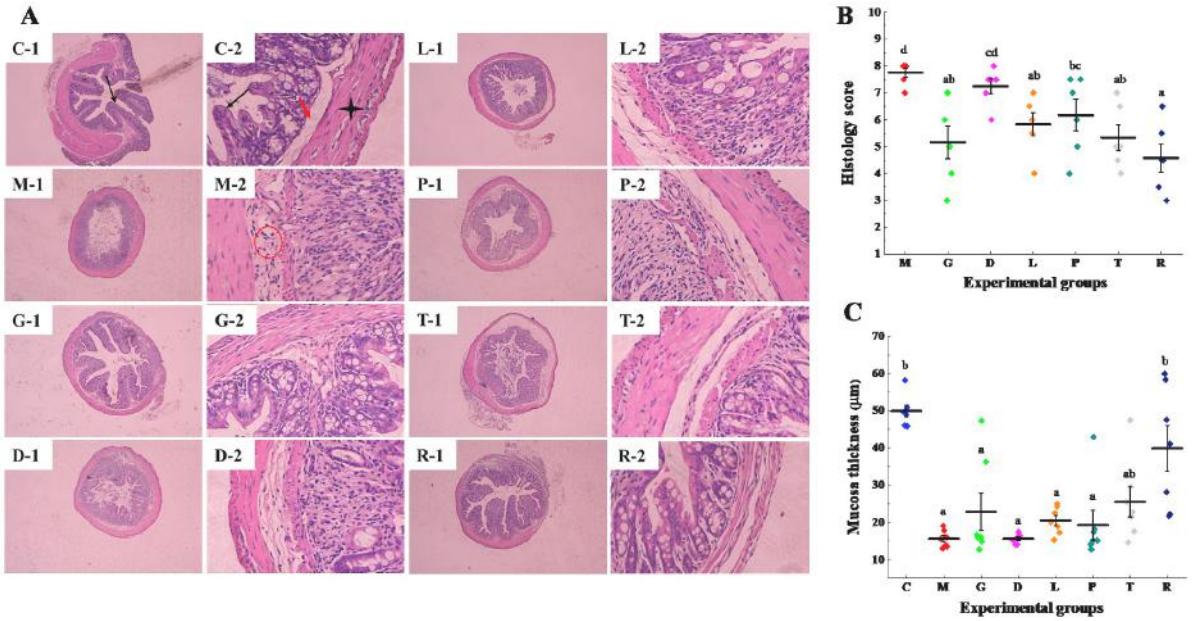

Fig. 4. H&E staining of colons from untreated mice or mice treated with DSS (3%) and pectic polysaccharide under the light microscope ($p < 0.05$) (A); histological scores of crypt structure and infiltration of inflammatory cells (B); colonic mucosa thickness (C). Number 1 and 2 meant 50x and 400x of magnification, respectively. Black star, black arrow, red arrow, and red circle represented the mucosal muscularis, crypt structure, submucosa, and infiltration of immune cells, respectively. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

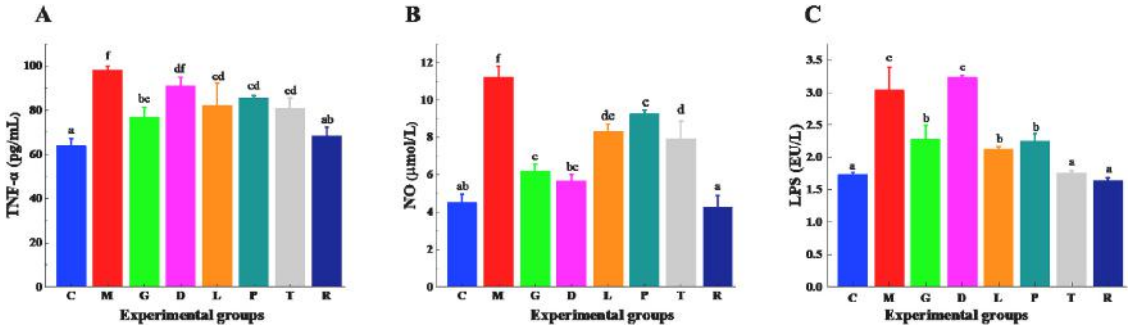

Fig. 5. TNF-α concentration (A), NO production (B) and the level of LPS (C) in serum (n = 6 per group). Groups with different letters are significantly different ($p < 0.05$).

57%, 34%, 61% and 96% compared to that in the control (C) group (before DSS treatment), respectively, which suggested strong inflammatory responses occurred in the colon. For the anti-inflammatory cytokine IL-10, the content in colitis mice was still much higher than that of healthy mice, which might be due to that severe colitis induced the self-defense response. This was consistent with the previous research (Han et al., 2019; Li et al., 2020). Reversing the changes of cytokines will help to alleviate colitis (Han et al., 2020; Singh et al., 2018). Our results showed that administration of pectic polysaccharide led to significant decreases in the levels of pro-inflammatory cytokines. Particularly, G significantly decreased the levels of TNF-α, IL-1β, IL-6, IL-17, INF-γin colitis mice by 21%, 23%, 25%, 32%, 41%, respectively. R significantly reduced the contents of TNF-α, IL-1β, IL-6, IL-17 by 30%, 24%, 20%, 31%, respectively, which is similar to the results of a previous study (Xiao et al., 2015). Also, L significantly decreased the concentration of IL-6 by 23%. These results illustrated that DSS induced severe inflammation, whereas G, R, and L could significantly suppress pro-inflammatory cytokines in the colon of DSS-induced colitis mice.

Inflammatory cytokines play a crucial role in the development of IBD, and the dysregulation of inflammatory cytokines is a critical component in IBD (Kaunitz & Nayyar, 2015). TNF-α, IL-6 and IL-1β, mainly secreted by monocytes, macrophages and neutrophils, are the dominant pro-inflammatory cytokines, causing colon damage, destroying the epithelial barrier and inducing cell apoptosis (Bevivino & Monteleone, 2018). Reports indicate that INF-γ participates in the MyD88 signaling in myeloid cells, which is required for colitis development (An, Li, Bhang, Song, & Youn, 2020; Eftychi et al., 2019). IL-17 is also a prominent effector in inflammation, and the serum concentration will increase significantly during colitis (Lee et al., 2020). Our results demonstrated that pectic polysaccharide administration treatments could inhibit the level of INF-γ and IL-17, especially G and R. It has been reported that polysaccharides, mainly containing β-glucan, can regulate the NF-κB, MAPK and PI3K/AKT signal pathway to down-regulate the pro-inflammatory cytokines (Lv et al., 2017; Ren et al., 2018). Our results suggested that administration of pectic polysaccharide can significantly change the levels of some cytokines, and different structures could target different cytokines. This might be because that pectic polysaccharide with different structures can influence different signal

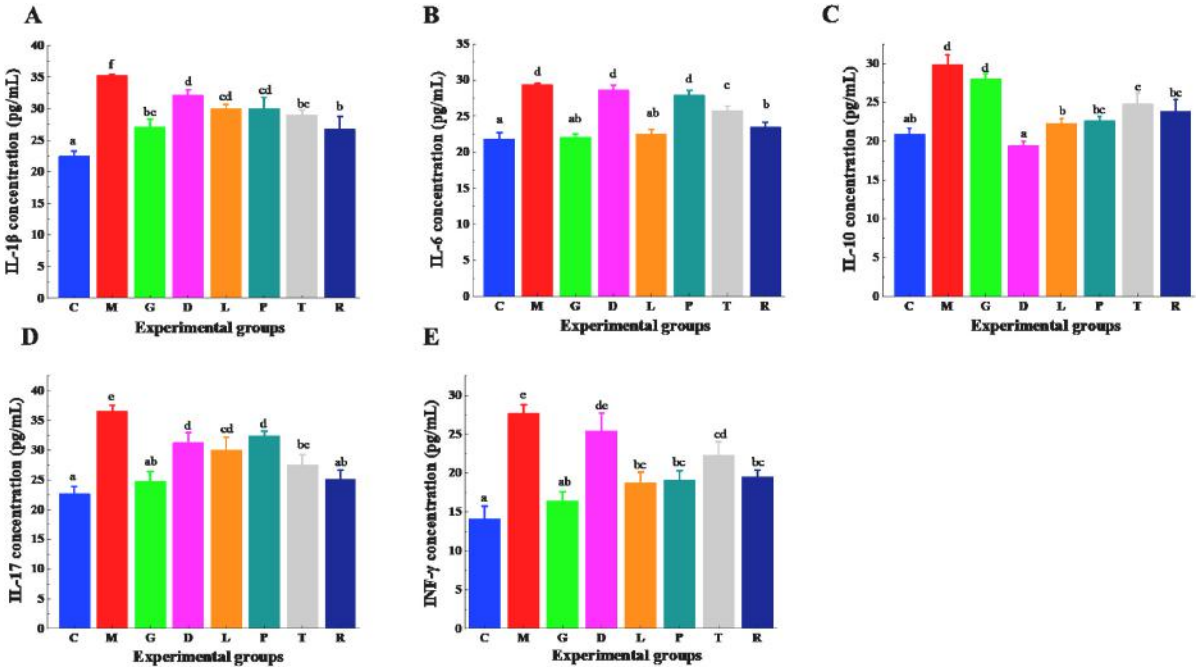

Fig. 6. Effect of different pectic polysaccharides on inflammatory cytokines in colon tissue (n = 6 per group). (A) IL-1β, (B) IL-6, (C) IL-10, (D) IL-17 and (E) TNF-γ. Groups with different letters are significantly different ($p < 0.05$).

pathways and pattern recognition receptors (Sahasrabudhe et al., 2018). It has been reported that pectic polysaccharide can directly regulate the inflammatory response of intestinal host cells through its sidechains (Ishisono et al., 2019). L-arabinose administration could inhibit the mRNA level of TNF-α (Li et al., 2019), but Sabater et al. (2019) suggested that arabinan sidechains in artichoke pectic polysaccharide was not the key to regulate TNF-α. However, the G, L and R, which contain more amount of arabinan than other pectic polysaccharides (Fig. 1), exhibited better inhibitory effects on TNF-α. We speculated that these conflicting conclusions were due to different doses, sugar linkage and M_w. Many studies have suggested that the production of IL-6 can be inhibited by HMP (Fan et al., 2020), LMP (Sahasrabudhe et al., 2018), neutral sugar chains (Ishisono et al., 2019; Li et al., 2019). The orange pectic polysaccharide can directly suppresses IL-6 secretion in macrophages by the neutral sidechains (Ishisono et al., 2019). Our results indicated that G, L, and R, which contain a higher amount of arabinan sidechains in RG-I than that of the other pectic polysaccharides, were more effective in regulating the level of IL-6. There might be some interaction between the arabinan sidechains and the Toll-like receptors in the surface of immune cells. IL-10, as an anti-inflammatory cytokine, plays a critical role in preventing inflammatory and autoimmune pathologies, and its mechanism of action could be mediating the metabolic program in macrophages (Eddie Ip, Hoshi, Shouval, Snapper, & Medzhitov, 2017). There was no significant difference between the G group and the M group regarding the regulation of IL-10, while all of the other pectic polysaccharides remarkably decreased the level of IL-10 in colitis mice. Furthermore, the IL-10 level in T and R groups were higher than that of other groups, indicated that up-regulation of IL-10 might be the potential mode of pectic polysaccharide containing higher amount of galactan to maintain immune homeostasis. It has been reported that LMP can remarkably down-regulate the level of IL-10 in IBD (Fan et al., 2020; Sahasrabudhe et al., 2018). However, in our studies, P (a high-methoxy pectic polysaccharide, HMP) still can significantly decrease the production of IL-10, which might be due to the presence of neutral sidechains.

Considering all the above mentioned, berry pectic polysaccharide could alleviate colitis by significant suppression on the level of IL-6, TNF-α, IL-1β and IL-17. The marked reduction in IL-6 production might be attributable to the arabinan sidechains in RG-I. Moreover, pectic polysaccharide containing a high amount of galactose may tend to regulate IL-10.

3.4. Intestinal barrier function

The serum concentration of LPS was applied to evaluate the effects of pectic polysaccharides on mucous barrier damage. As a result of the defects in intestinal barrier function and increased gut permeability, LPS migrate into the blood and cause inflammatory responses. So the serum concentration of LPS was applied to evaluate the effects of pectic polysaccharide on gut barrier damage (Fan, Chen, & He, 2020). The serum level of LPS in the M group increased significantly by 75.72% compared to that of the C group, indicating severe epithelial destruction caused by DSS, which is in agreement with the results of H&E staining. However, except the dragon fruit pectic polysaccharide, treatment of G, L, P, T and R remarkably decreased the serum content of LPS by 25%, 20%, 26%, 42% and 46% compared with that of the model group (Fig. 5C). R and T showed better effects in keeping the integrity of the whole intestinal barrier than the G, L and P significantly. Previous studies have indicated that RG-I-enriched pectic polysaccharide and LMP can remarkably reduce the concentration of LPS in serum (Fan et al., 2020; Mao et al., 2019). However, the important structural regions remained unclear. Herein, our results suggested the total amount of RG-I was not closely related to the improving effects of pectic polysaccharide on gut permeability. For instance, the dragon fruit pectic polysaccharide was not effective in maintaining barrier function, even though it contained 83% RG-I. Pectic polysaccharide containing high amount of galactose (T and R) might have better bioactivity in protecting intestinal barrier from chemical damage. It has been reported that galactose in pectic polysaccharide can increase the expression of MUC-1 and MUC-3 (Sabater et al., 2019). Consumption of dietary fiber remarkably increased the thickness of inner mucus layer and prevented degradation of the intestinal mucus barrier (Desai et al., 2016). Also, Goji berry arabinogalactan

could enhance the intestinal barrier function in colitis mice by promoting the expression of mucin-2 and tight junction proteins (Cao et al., 2021). In the evaluation of colonic histopathology (Fig. 4C), R and T did increase the mucosa thickness in colitis mice, and R exhibited superior effect on preserving the structure of colonic mucosa, so R and T pectic polysaccharides might protect the intestinal barrier through increasing the thickness of colonic mucosa that overlies the epithelium in colitis mice.

3.5. Antioxidative status

Many human studies have suggested a strong association between oxidative stress and inflammation (Hussain et al., 2016; Pavlick et al., 2002). During colitis, the antioxidant response system of colon tissue is defective and pro-inflammatory cytokines lead to significant production of reactive oxygen species (ROS) such as hydroxylated radicals and nitric oxide (NO) (Simmonds et al., 1992). As is shown in Fig. 5B, colitis leads to large quantities of NO released, while administration of pectic polysaccharide significantly decreased the level of NO in the serum; especially, dietary R, G and D almost reversed the NO's production. The downregulation of antioxidants such as superoxide dismutase (SOD) has been found in DSS-induced colitis and antioxidants effectively alleviate colitis (Dziabowska-Grabias et al., 2021). Our results (Fig. 7) revealed that almost all of these pectic polysaccharides reversed the activity of SOD in colon tissue, primarily, R increased it by 94.8%. GSH is regarded as the most important free radical scavenger. Compared to the healthy mice, GSH/GSSG was remarkably reduced in colitis mice. As shown in Fig. 7B, G and R significantly increased the GSH/GSSG ratio by 3.96- and 4.78-fold, respectively, indicating the protective effects of berries pectic polysaccharide against ROS during colitis. ROS existing in inflamed colonic mucosa might exert a pathogenic role, and many drugs with antioxidant activity such as aminosalicylates (5-ASA) appear to be clinically effective in curing IBD (Langmead et al., 2002). Many studies have confirmed that administration of antioxidants or overproduction of antioxidant enzymes attenuates IBD (Dashdorj et al., 2013), thus suggesting that raspberry pectic polysaccharide and Goji pectic polysaccharide could alleviate colitis by regulating the antioxidant response system. Lots of articles have revealed that polysaccharides possess antioxidant activity (Huang et al., 2017; Jian et al., 2018). Yan et al. (2021) have reported that higher GalA content contributed to the antioxidant activity of bitter gourd polysaccharides, but just *in vitro* experimental data could not represent the *in vivo* results. Our results suggested that high amount of HG (75% in P) could not show the best antioxidant activity in colitis mice, but the structure of G, L and R, which have 20% HG and the value of GalA/(Ara + Gal) was 0.4–0.6, might be the key factor for antioxidant potential *in vivo*. Furthermore, R group exhibited better effect on alleviating oxidative stress than that of the G group, which might be due to the different M_w. Collectively, the antioxidant activity of pectic polysaccharide in colitis mice was determined by the monosaccharide composition and M_w. The pectic polysaccharide of smaller M_w (<200 kDa) might possess stronger antioxidant property (Sun, Wang, Shi, & Ma, 2009).

3.6. The production of SCFAs in cecum

It is well proven that SCFAs are the most important metabolites produced upon pectic polysaccharide degradation by microbiota, which promote immunity and suppress inflammatory responses in the intestine and other organs (Morrison & Preston, 2016). Considering the differential effects of these pectic polysaccharide on the severity of colitis, we investigated the concentration of SCFAs in the cecum of the mice. Notably, our results showed that the total amount of SCFAs and the level of acetate, propionate, I-butyrate, butyrate, I-valerate and valerate in colitis mice decreased by 78%, 76%, 78%, 27%, 85%, 91% and 78% compared to that of the control group, respectively (Fig. 8). It has been shown that colitis could cause adverse effects on the abundance of *Firmicutes* and *Bifidobacterium*, which are the major players involved in the production of SCFAs (Canfora, Jocken, & Blaak, 2015). All of the G, L, T

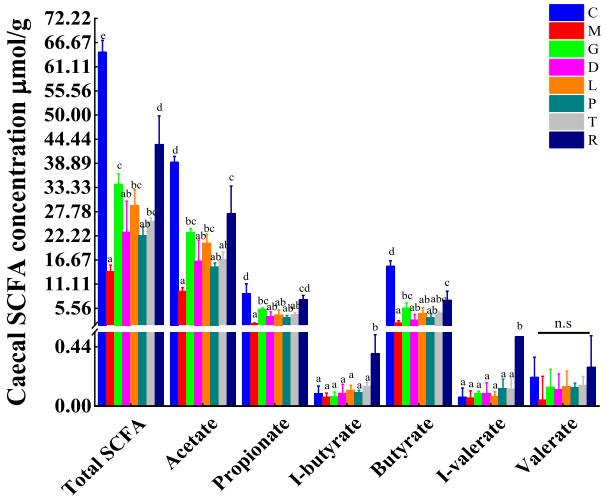

Fig. 8. The concentration (μmol/g) of acetate, propionate, butyrate, I-butyrate, valerate, and I-valerate in the caecal contents (n = 6 per group). Groups with different letters are significantly different ($p < 0.05$).

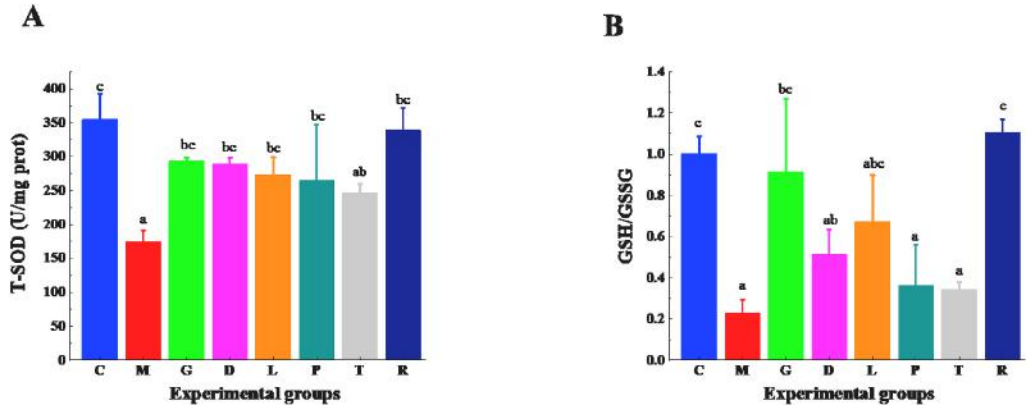

Fig. 7. Effects of six pectic polysaccharides on the oxidative stress-associated indicators. (A) the colonic concentrations of T-SOD (n = 6 per group) and (B) the ratio of GSH/GSSG in the liver (n = 6 per group). Groups with different letters are significantly different ($p < 0.05$).

and R could significantly increase the total level of SCFAs in colitis mice, but there was no significant difference between D, P groups with M group. This might be due to the high amount of RG bone and high-esterified HG are hard to be degraded by gut bacteria. Not the level of the total amount of SCFAs formed in the pectic polysaccharide-treated groups was higher, but the level of specific SCFAs was also higher than that of the model group. Among the six pectic polysaccharide groups, the total SCFAs in G and R groups were remarkably higher than the other groups. Acetate, propionate and butyrate are the major SCFAs metabolized by the gut microbiota. G, L and R groups showed remarkably higher acetate level than that of the model group and all the three pectic polysaccharides contained a higher amount of arabinan sidechains than other pectic polysaccharides (Fig. 1), indicated that maybe arabinan sidechains could help gut microbiota utilize the whole pectic polysaccharide domains during colitis to produce more SCFAs. Arabinan-enriched pectic polysaccharide could increase the abundance of *Bacteroides* spp., *Bifidobacterium* spp. and *Ruminococcaceae* and the production of acetate and butyrate (Mao et al., 2019). Arabinose could increase the production of SCFAs and organic acids in the intestine and promote the growth of anti-inflammatory bacterium *Actinobacteria* in DSS-induced colitis mice (Li et al., 2019). In the studies of *in vitro* TIM-2 fermentation, arabinan-enriched lime pectic polysaccharide also increased the production of butyrate (Larsen et al., 2019). The amount of propionate was higher in the G and R group than any other pectic polysaccharide group, but not significantly ($P > 0.05$). As for the production of butyrate, G and R groups were significantly higher than that of the model group, but only the R group showed a significant difference compared to the model and other pectic polysaccharide groups. Intriguingly, there were a tendency toward a higher level of minor acids (I-butyrate and I-valerate) formed in mice fed R than any other groups. A recent new research in Science has discovered the immunomodulatory property of iso-butyrate and iso-valerate (Guo et al., 2019). Thus, the higher amount of these minor acids might contribute to the anti-inflammatory effects of raspberry pectic polysaccharide as well.

Next, we analyzed the proportion of each fatty acid in the total amount of SCFAs and the ratio of propionate/acetate and butyrate/acetate, in order to determine whether the administration of different pectic polysaccharide led to different composition patterns of fermentation products. As was listed in Table 2, a significant difference was observed in the ratio of butyrate (from 25% to 13.2–17.5%) and the ratio of But/Ace (from 0.41 to 0.29–0.28) between the control group and all the colitis groups, indicating the inability of colitis dysbiotic microbiota to produce butyrate. All of the pectic polysaccharide treatments presented no changes in the proportion of butyrate, suggesting that these pectic polysaccharides does not relieve inflammation by regulating butyrate production, consistent with previous findings (Singh et al., 2018). The composition pattern of the SCFAs in G, P, T and R groups is similar to that of the normal group, except that the proportion of iso-butyrate and valerate in the R group was significantly increased. There was no significant difference between the D and L groups, but L showed much better protective effect than D, indicating that the total amount of SCFAs played an important role. The different structures of pectic polysaccharides extracted from different sources resulted in a different amount of SCFAs, but the proportion of each SCFA in the whole SCFAs was not much different.

Considering all of these results in fermentation products, G and R could produce a much higher amount of SCFAs than any other pectic polysaccharide, and they also exhibited the best protective effect against colitis according to the results of DAI scores, colon length, inflammatory cytokines, gut permeability and antioxidative status, suggesting SCFAs were the important metabolites to regulating gut inflammation. Compared to other pectic polysaccharides, diversified structure features can be observed in G and R, which contain 21–23% HG and the ratio of GalA/(Ara + Gal) was 0.6. While the amount of RG-I was not directly associated with the function of pectic polysaccharides. Thus, pectic polysaccharide with multicomplex composition might be the predominant bioactive dietary fiber. In previous studies, the antioxidant activities of raspberry pectic polysaccharide were determined on human hepatic L02 cells (Chen et al., 2020), but the anti-inflammatory activity remained unknown. Goji berry exhibited protective effects against gut inflammation in DSS-induced colitis mice (Kang, Xue, Du, & Zhu, 2017) and IL-10-deficient mice (Kang et al., 2018). Goji berry pectic substance (arabinogalactan, named LBP-3) was extracted by hot water, which could alleviate DSS-induced colitis by down-regulating the production of proinflammatory cytokines, up-regulating expression of mucin-2 and tight junction proteins, enriching intestinal probiotic bacteria and promoting SCFAs production (Cao et al., 2021). Compared to LBP-3, the protective effect of G on the colonic mucosa barrier was relatively lower, which might be due to the lower amount of galactose in G. LBP-3 mainly increased the concentration of acetate, valerate, and iso-valerate, while G significantly enriched the content of acetate, propionate, and butyrate. This was attributable to different monosaccharide composition, M_w, and different gut microbiota in different mice. In this study, R group produced higher level of SCFAs than that of the G group, which might be attributable to the smaller M_w. The larger M_w (218 kDa) of G might increase the physical inaccessibility of pectic polysaccharide, and thus gut microbiota could not fully degrade Goji berry pectic polysaccharide.

4. Conclusion

Our studies confirmed that the differential effects of pectic polysaccharides against DSS-induced gut inflammation were highly structure-dependent. In detail, the function of pectic polysaccharides was not closely related to the total amount of RG-I. The administration of the Goji pectic polysaccharide and raspberry pectic polysaccharide showed superior effects on alleviating colitis in mice model via promoting the index of immune organs, ameliorating colonic injuries, reducing the production of TNF-α, IL-17 and IL-1β, attenuating oxidative stress and increasing the production of total SCFAs. Given the structure feature, both of G and R contained diversified domains. While others, lemon peel pectic polysaccharide mainly containing arabinan sidechains, potato pectic polysaccharide rich in galactan sidechains, dragon fruit pectic polysaccharide with 59% RG backbone and pomelo pectic polysaccharide dominated by HG region showed less effective in attenuating colitis, even though they might have beneficial effects on increasing the production of SCFAs, promoting the antioxidative statues

Table 2
The proportion of acetate, propionate, butyrate, I-butyrate, valerate, and I-valerate, Pro/Ace and But/Ace values in the caecal contents.

Groups	Acetate (%)	Propionate (%)	I-butyrate (%)	Butyrate (%)	I-valerate (%)	Valerate (%)	Pro/Ace	But/Ace
C	60.75 ± 0.42a	13.81 ± 3.07a	0.14 ± 0.09a	24.88 ± 2.88b	0.10 ± 0.01a	0.33 ± 0.22a	0.23 ± 0.05a	0.41 ± 0.04c
M	68.10 ± 1.48abc	14.18 ± 1.59a	0.48 ± 0.19 ab	15.96 ± 2.00a	0.42 ± 0.34a	0.33 ± 0.10a	0.22 ± 0.02a	0.23 ± 0.03 ab
G	67.47 ± 2.09abc	15.46 ± 0.06a	0.21 ± 0.10 ab	16.26 ± 2.11a	0.27 ± 0.06a	0.42 ± 0.13a	0.23 ± 0.01a	0.24 ± 0.04 ab
D	71.38 ± 3.44c	14.09 ± 0.52a	0.38 ± 0.16 ab	13.28 ± 3.73a	0.36 ± 0.23a	0.52 ± 0.14a	0.20 ± 0.01a	0.19 ± 0.06a
L	70.72 ± 2.36bc	13.91 ± 3.00a	0.41 ± 0.10 ab	14.17 ± 4.11a	0.25 ± 0.09a	0.50 ± 0.14a	0.20 ± 0.04a	0.20 ± 0.06 ab
P	67.82 ± 3.30abc	15.11 ± 1.19a	0.45 ± 0.04 ab	15.46 ± 3.28a	0.58 ± 0.27a	0.64 ± 0.18a	0.22 ± 0.02a	0.23 ± 0.06 ab
T	64.16 ± 2.07abc	16.21 ± 2.14a	0.58 ± 0.10b	17.57 ± 0.9a	0.50 ± 0.29a	0.61 ± 0.26a	0.25 ± 0.04a	0.28 ± 0.02b
R	62.68 ± 5.83 ab	17.85 ± 5.39a	0.90 ± 0.24c	16.7 ± 2.15a	1.19 ± 0.16b	0.71 ± 0.56a	0.29 ± 0.12a	0.27 ± 0.05 ab

Means with different letters are significantly different between rows ($p < 0.05$). Pro (propionate); But (butyrate).

and enhancing the intestinal barrier. In conclusion, G and R, which contained homogeneous proportion of HG, RG, arabinan, and galactan, possessed the best protective effects against colitis in mice model. Collectively, our findings provided a significant scientific basis for the study on the structure-function relationship of pectic polysaccharides, which will contribute to developing of novel probiotic products or functional food for the prevention and attenuation of colitis. However, whether different extraction methods will change the structural composition and the function of Goji pectic polysaccharides and raspberry pectic polysaccharides remains to be solved. And more research is needed to reveal the mechanism and pathways involved.

Authors contributions

Dongmei Wu: Conceptualization; Investigation; Methodology; Roles/Writing- original draft; **Weiwei Hu:** Software; **Kai Zhu:** Software; **Chengxiao Yu:** Software; **Robert J. Linhardt:** Writing - review & editing; **Shokouh Ahmadi:** Writing - review & editing; **Qiaojun He:** Resources; **Huan Cheng:** Resources; **Xingqian Ye:** Funding acquisition; Resources; **Shiguo Chen:** Methodology; Funding acquisition; Writing - review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

This work was supported by National Key Research and Development program of China (2017YFE0122300).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.foodhyd.2021.107209.

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