Hindawi
Journal of Food Biochemistry
Volume 2023, Article ID 8815971, 12 pages
https://doi.org/10.1155/2023/8815971

Research Article

Development of a Functional Food Based on the Fermentation Broth of Jiegeng for the Treatment of Inflammatory Bowel Disease

Jiahui Peng,[1,2] Chunhai Li,[3] Zhe Wang,[4] Songsen Sui,[5] Chuanzhuang Guo,[5] Ruiting Zhao,[1,2] Haoran Liu,[1,2] Ting Wang ,[1,2] and Zhenshang Xu [1,2]

[1]*State Key Laboratory of Biobased Material and Green Papermaking, Qilu University of Technology, Shandong Academy of Science, Jinan 250353, China*
[2]*School of Bioengineering, Qilu University of Technology, Shandong Academy of Science, Jinan 250353, China*
[3]*Department of Radiology, Qilu Hospital, Cheeloo College of Medicine, Shandong University, Jinan, Shandon 50012, China*
[4]*State Key Laboratory of Food Science and Technology, School of Food Science and Technology, Jiangnan University, 1800 Lihu Avenue, Wuxi 214122, China*
[5]*Zhucheng Dongxiao Biotechnology Co., Ltd., Zhucheng 262200, Shandong, China*

Correspondence should be addressed to Ting Wang; tingwang_97@hotmail.com and Zhenshang Xu; xuzhenshang@qlu.edu.cn

Jiahui Peng and Chunhai Li contributed equally to this work.

Received 3 July 2023; Revised 27 September 2023; Accepted 3 October 2023; Published 12 October 2023

Academic Editor: Rotimi Aluko

The traditional treatment for inflammatory bowel disease (IBD) is often limited by its poor efficacy and high costs. Malnutrition has been closely linked to the occurrence of IBD. Clinical data have revealed that medicinal food ingredients may be more effective and safer, and thus, they can be used as an important part of functional foods. As a high-quality drug-food homologous ingredient, Jiegeng (JG) provides a wide range of pharmacological effects in addition to basic nutrition. In the present study, a functional food (FF) was developed based on the fermentation broth of JG, combined with four nutritional ingredients: Yimi (YM), Chixiaodou (CXD), Baibiandou (BBD), and Shanyao (SY). Subsequently, a 3% Dextran Sulfate Sodium Salt (DSS) water-induced mouse ulcerative colitis (UC) model was established, and the functional validation of the FF was carried out by gavaging the mice with low and high doses of functional foods (250 mg LFF and 500 mg HFF). The results showed that FF restored the body weight of UC model mice by 4.250 ± 0.250 g, reduced the DAI score by 0.255 ± 0.025, restored the colon length by 1.064 ± 0.087 cm, and reduced the spleen index by 0.102 ± 0.019. Furthermore, FF decreased the serum concentrations of the inflammatory factors TNF-α, IL-1βh, and IL-6, while increasing the concentration of the anti-inflammatory factor IL-10 and alleviating the inflammatory response in mice. Pathological analysis of the colonic tissue showed that FF restored the structure of the mouse intestine and reduced the infiltration of inflammatory cells. FF has good stability and is favoured by most people.

1. Introduction

Inflammatory bowel disease (IBD) is a spectrum of chronic inflammatory diseases of the gastrointestinal tract, including ulcerative colitis (UC) and Crohn's disease (CD), as well as some unspecified forms of IBD [1]. In recent years, IBD has become a global issue, with problems such as a long course, difficulty in curing and controlling, an inclination to deteriorate, and potential for disability [2]. Current traditional treatments for IBD offer poor results and a range of side effects, while antibody drugs tend to be expensive and not covered by health insurance [3]. According to statistics, IBD affects over 1 million people in the United States [4] and over 2.5 million people in Europe, with medical costs of 460–560 million Euros per year [5]. This high prevalence and huge medical burden have posed an immense strain on human survival and necessitates a healthier, safer, and sustainable treatment.

Malnutrition in patients with IBD can contribute to major pathogenic factors, such as impaired epithelial barrier function, defective bacterial recognition, antigen delivery,

autophagy, and dysregulated T-cell responses leading to abnormal innate immune responses [6, 7]. Patients with IBD typically experience varying degrees of malnutrition during the early stages of inflammation, which can exacerbate the condition. Furthermore, the progression of IBD inflammation, drug, or surgical treatment can further contribute to malnutrition, and the two interact with each other. As a result, it is difficult to manage the disease long-term with conventional IBD therapy [5]. Consequently, diet plays an essential role in the treatment of IBD as a sustainable treatment strategy [8–13]. Studies have demonstrated that a number of medicinal food ingredients have potential clinical applications in IBD. For example, Ziziphus jujuba var. spinosa (Bunge) Hu ex H. F. Chow contains sour date polysaccharide that can enhance intestinal barrier function and activate AMPK [14]. Fermented *Perilla frutescens* (*L.*) *Britt*, which contains caffeic acid, rosmarinic acid, lignan, and apigenin, can inhibit NF-κB and STAT3-mediated proinflammatory signaling pathways and promote Nfr2-mediated antioxidant defense [15]. In addition, Puerarin obtained from *Radix puerariae lobatae* fermentation can downregulate NF–B and proinflammatory factor secretion, stimulate the Nrf2 pathway, and alleviate intestinal inflammation [16]. Most of the drugs in use for UC patients are limited to targeting a single protein and often cause adverse effects. Therefore, medicinal food ingredients can be utilized as a complementary or alternative therapy for the treatment of inflammatory diseases due to their multitarget, low-side effects, and potential to improve patient nutrition.

Functional food (FF) is a type of food with specific nutritional and health benefits which can reduce the risk of diseases, in addition to providing essential nutrients. It is similar in appearance to traditional food and can be included in a daily diet as a healthy and sustainable option [17–20]. In recent years, the potential benefits of functional foods on human health have been explored [21]. Natural functional nutrients can control proinflammatory cytokines, thus alleviating gastrointestinal inflammation [22, 23]. Clinical trials have demonstrated that, after taking FF as part of a diet plan, a decrease in inflammatory parameters and prevalence of gastrointestinal symptoms can be observed [20]. A well-balanced diet is not only beneficial for the malnutrition associated with IBD but can also help repair intestinal damage and maintain a stable condition. In some cases, such diets may even be used as an alternative to drugs or surgery, making them an important aspect of the treatment strategy for IBD, providing advantages to many IBD patients.

Platycodin D can inhibit inflammatory pathways, promote AMPK expression, and enhance intestinal function [24]. In our previous study [23], Treatment with the fermentation broth of JG significantly reduced the proportion of M1-type macrophages and inhibited the expression levels of NF-κB p65, NLRP3, ASC, and caspase-1 genes and proteins in the DSS-induced colitis model. This is likely due to the fact that the development of IBD inflammation is closely related to malnutrition. In this study, we chose the fermentation broth of JG as the functional ingredient and Yimi (YM), Chixiaodou (CXD), Baibiandou (BBD), and Shanyao (SY) as nutritional ingredients to prepare an FF. We investigated the effect of this FF on the DSS-induced acute UC mouse model, further revealing that JG fermentation broth alleviated the symptoms of UC mice through the AMPK/NF-κB/NLRP3 pathway, confirming the anti-inflammatory effect of FF and its reparative effect on the intestinal tract. Then, we determined the physico-chemical properties of FF and performed sensory evaluation of FF.

2. Materials and Methods

2.1. Food Ingredients, Reagents, and Test Kits. YM, CXD, BBD, and SY were obtained from Jia Qi Tang (Hebei, China), while vitamin complex powder was purchased from Hangzhou Minsheng Health Pharmaceutical Co., Ltd (Shandong, China). DSS was obtained from MP Biomedicals (California, USA), and ELISA kits for the detection of inflammatory factors IL-6, IL-1β, and TNF-α and anti-inflammatory factor IL-10 of mouse serum were acquired from Hangzhou Unitech Biotechnology Co., Ltd. (Zhejiang, China).

2.2. Preparation of the Fermentation Broth. The fermentation broth of JG was prepared according to the method of Wang et al. [23]. Dried JG was ultramicronized into powder. *L. rhamnosus* 217-1 was cultured in the MRS liquid medium at a constant temperature of 37°C overnight. The fermentation medium consisted of 100 mL of water, 0.5 g of yeast powder and 2 g of glucose, and was sterilised at 85°C for 30 min. After cooling, *L. rhamnosus* 217-1 was inoculated into the fermentation medium at a ratio of 2% and then incubated statically at 37°C for 48 h. After thorough fermentation, the supernatant was taken and centrifuged at 10 000 rpm for 30 min to remove impurities to obtain the JG fermentation broth.

2.3. Preparation of the FF. The nutrient content of the four raw materials (YM, CXD, BBD, and SY) was calculated according to the Chinese Food Composition Table. The amounts of these medicinal food ingredients were determined in accordance with the General Rules for Special Medical Use Formulas (GB 29922-2013). In order to supplement the nutrition of FF, the substances to be added were identified according to the Food Nutrition Fortification Standard (GB 14880-2012) and the General Rules for Special Medical Use Formulas (GB 29922-2013). The 100 g of nutrient powder was mixed with 100 mL of the JG fermentation broth and dried at 55°C until it reached a constant weight. Finally, the mixture was crushed into powder using a crusher and stored in a light-proof seal at room temperature.

2.4. Animal Experiments. Six-week-old male C57BL/6J Kunming mice (No. SCXK (Lu) 20170026) were obtained from Jinan Pengyue Experimental Animal Breeding Co., Ltd. (Shandong, China). The mice were randomly divided into five groups: blank control group (Normal), model group (Model), positive control group (Control), low-dose FF group (LFF), and high-dose FF group (HFF). Each group

contained 30 mice, which were housed in wire mesh cages to prevent fecal ingestion in a temperature of 21 ± 0.5°C and relative humidity of 55 ± 5%. The mice in the model group resumed normal diet, whereas the mice in the positive control group were given mesalazine (0.5 g/kg-d). The mice in the low-dose and high-dose groups were administered FF by gavage (250 mg and 500 mg, respectively, each day) for two weeks (0–14 days). During the feeding process, the mice were weighed at a fixed time every day and the Disease Activity Index (DAI) scores were assessed daily from the day before DSS administration until the end of the experiment (−7 to 14 days). Following the final administration, the mice were fasted and dehydrated for 12 h and then anesthetized with sodium pentobarbital. Blood was collected from the eye vein and then centrifuged at 3500 r at 4°C for 10 min to obtain serum, which was stored at −80°C for measurement. The mice were then euthanized and dissected to obtain spleens, which were immediately stored at −80°C for further measurement.

2.5. Disease Activity Index (DAI) Scores. Daily observations of body mass, fecal traits, and occult blood were conducted on the mice at fixed times. The severity of the disease was determined using the criteria outlined in Supplementary Table 1 to generate a Disease Activity Index (DAI) score.

2.6. Spleen Index. In brief, mice were euthanized by decortication, and the spleen was subsequently immediately dissected and removed. The tissue was washed with physiological saline solution and blotted with filter paper to remove residual water. The spleen was then weighed, and the Spleen Index was calculated using the following formula:

$$\text{spleen index} = \frac{\text{spleen mass (mg)}}{\text{mouse body weight } (g) \times 10}. \quad (1)$$

2.7. Histopathological Examination. The colonic tissues of mice used for histopathological examination were immediately washed with PBS and then fixed in 10% neutral formalin buffer. Following embedment in paraffin, the tissue was sectioned and dewaxed before being stained with H&E. Subsequently, the tissue was sealed with neutral gum and placed under light microscopy to examine pathological changes based on the method of Erben et al. [25]. The score was obtained by summing the degree of inflammatory cell infiltration of intestinal tissue, depth of the lesion, degree of crypt destruction, and extent of the lesion; the scoring criteria are provided in Supplementary Table 2.

2.8. Mouse Serum and Assay. The mice blood of each group was collected by orbital blood sampling and kept at 4°C for two hours. The samples were then centrifuged at 3500 r/min for 10 minutes, and the supernatant was placed in the refrigerator at −80°C. The levels of TNF-α, IL-1β, IL-6, and IL-10 in the serum of the mice were assessed using ELISA kits.

2.9. Physico-Chemical Properties of FF. The physical and chemical properties of FFs largely determine their productivity and mass acceptability. Therefore, the solubility, stability, and pH of FF were evaluated. FF was brewed with different amounts of hot water to see its solubility, its pH change was tested by acid-base titration, and its stability was tested by standing at room temperature for 6 h.

2.10. Sensory Evaluation Methods. As an FF, sensory evaluation by the public is crucial. The acceptability of FF was investigated by randomly inviting 50 people to rate and assess FF with reference to a 9-point hedonic scale [26, 27].

2.11. Statistical Analysis. Each experiment was repeated a minimum of three times, and the results were statistically compared and analyzed using SPSS 26.0 software and expressed as the mean ± standard deviation.

3. Results

3.1. Formulation of the FF. Four drug-food homology ingredients—YM, CXD, BBD, and SY—were chosen for preparation of the FF. The energy content and nutrient content of each 100 g of the four ingredients were determined according to the Chinese Food Composition Table, as shown in Supplementary Table 3. Based on the General Rules for Special Medical Use Formulas, the dosage of each ingredient was determined as 22 g of YM, 5.5 g of CXD, 11 g of BBD, and 49.5 g of SY per 100 g. In accordance with the Food Nutrition Fortification Standard and General Rules for Special Medical Use Formulas, the ingredients and dosage were chosen to supplement the required nutrition of FF. The formulation and nutritional composition of the FF are presented in Tables 1 and 2, respectively.

3.2. Effect of FF on the Body Weight of UC Model Mice. The UC model mouse was successfully established after one week of feeding with 3% DSS. Figure 1 showed the change in body weight of each group of mice at the end of the experiment compared to the beginning. As shown in Figure 1(b), the mice in the normal, control, low FF (LFF), and high FF (HFF) groups all experienced an increase in body weight. The model group, however, still lost an average of 2.096 ± 0.91 g of total body weight after 14 days of normal diet following cessation of the DSS. In comparison, the positive control group gained an average of 5.041 ± 0.42 g, the LFF group gained an average of 3.75 ± 0.21 g, and the HFF group gained an average of 4.08 ± 0.076 g of body weight compared to the baseline body weight. Furthermore, the body weight gain observed in the HFF group was similar to that of the positive control group and 2.72 times more than that of the normal group. This suggests that the LFF and HFF groups exhibited a significant improvement in weight loss caused by UC, particularly in the HFF group. In addition to the therapeutic effects of the JG fermentation broth, a variety of nutritional components may have also contributed to the regulation of appetite and increased nutrition to restore body weight.

Table 1: Formulation of nutritional components of the FF (100 g).

Ingredients	Dosage
Yimi	22 g
Chixiaodou	5.5 g
Baibiandou	11 g
Shanyao	49.5 g
Whey protein concentrates	11 g
Plant menaquinone	4.4 μg
Folate	22.2 μg
D-biotin	2.2 μg
NaCl	30.332 mg
Selenium enriched yeast	1 μg
Glucose	0.86 g
Vitamin complex powder	0.109 g

Table 2: Nutritional composition of the FF (per 100 g).

Items	Per 100 g	Nutrient reference value (%)
Energy	1201.3 kJ	14.3
Protein	21.74 g	36.23
Fat	1.36 g	2
Carbohydrates	58 g	19.3
Dietary fiber	2.717 g	10.87
VA	151.43 μgRE	18.93
VD_2	1 μg	20
VE	3.303 mg	23.59
VB_1	0.71 mg	50.7
VB_2	0.69 mg	49.29
VB_6	0.05 mg	3.57
VB_{12}	0.1 μg	4.17
VC	5 mg	5
VK	4.4 μg	5.5
Biotin	2.2 μg	7.3
Pantothenic acid	0.5 mg	10
Choline	5 mg	1.11
Niacin	2.226 mg	15.9
Folate	22.2 μg	5.55
Fe	3.024 mg	20.16
Cu	0.52 mg	34.67
Zn	1.09 mg	7.27
Mg	29.86 mg	9.95
Ca	107.61 mg	13.45
Mn	0.61 mg	20.3
K	270.23 mg	13.5
P	93.06 mg	13.29
Se	3.7 μg	7.4
Na	83 mg	4.15

3.3. Effect of FF on DAI in UC Model Mice. As illustrated in Figure 2(a), Dextran Sulfate Sodium (DSS) administration in mice resulted in weight loss and bloody diarrhea, which are similar to the clinical features of human ulcerative colitis (UC). These inflammation-related parameters were measured to calculate the Disease Activity Index (DAI) score. After one week of DSS treatment, the DAI score was around 2.2 in all groups of mice, indicating consistent severity of IBD symptoms. Following the cessation of DSS treatment and the introduction of drug or fructo-oligosaccharides (FF) intervention, the DAI score gradually decreased in each group. On day 14, the DAI score of the mesalazine-treated group had decreased to approximately 0.4, which was similar to that of the high-dose group and slightly higher than that of the low-dose group (Figure 2(b)). These results indicate that the administration of FF had a beneficial effect on the weight loss and blood stool of the DSS-induced UC model mice.

3.4. Effect of FF on Colonic Length in UC Model Mice. At the end of the experiment, the mice were dissected in order to measure their colon length. Figure 3(a) reveals an intuitive representation of the treatment effect of each group. Compared to the normal group, the colon length of all other groups was significantly lower ($P < 0.01$). However, the colonic length was significantly higher in the mesalazine and FF-treated groups ($P < 0.01$) compared to the model group. The control group had a colon length of 7.460 ± 0.26 g, which was slightly higher than 6.557 ± 0.43 g in the LFF group, and 6.733 ± 0.48 g in the HFF group. The ability to alleviate colon shortening in the high-dose group was not significantly different from that in the low-dose group, indicating a lack of dose-dependent relationship.

3.5. Effect of FF on the Spleen Index of UC Model Mice. The spleen is rich in lymphocytes and macrophages, which are closely associated with humoral immunity. The spleen index can be used as a marker to assess the strength of the body's immune system. As shown in Figure 4, at the end of the experiment, the spleen weights of all groups increased compared to the normal group, with the model group exhibiting the highest spleen index ($P < 0.05$). These results suggest that DSS ingestion stimulated the mice's autoimmune system and caused inflammation or reduced the effects of inflammation. However, the spleen weights of the control, LHH, and HFF groups were reduced by 0.19 ± 0.06 g, 0.08 ± 0.24 g, and 0.14 ± 0.09 g, respectively, when compared to the model group. This suggests that the inflammation in the mice treated with the drug or FFC was improved and the treatment effects were ranked in order of mesalazine, high-dose, and low-dose groups.

3.6. Effect of FF on Colonic Histopathology in UC Model Mice. As shown in Figure 5(a), the colonic wall of the normal group mice was structurally intact. The mucosal and submucosal layers formed folds that protruded into the intestinal lumen, and there were a small number of contents in the lumen. In the model group mice, whole-layer necrosis (including the mucosa, submucosa, and muscle layer), edema, and massive inflammatory cell infiltration were observed in the intestinal wall, with the mucosa being detached. The control group mice exhibited only localized mucosal degeneration, with little to no necrosis. The lesion scores in the LFF and HFF groups were limited to superficial mucosal degeneration and necrosis, not involving the submucosa or muscle layer. As shown in Figure 5(b), the lesion score in the model group was 14, while the control and HFF groups scored consistently 3 and the LFF group scored

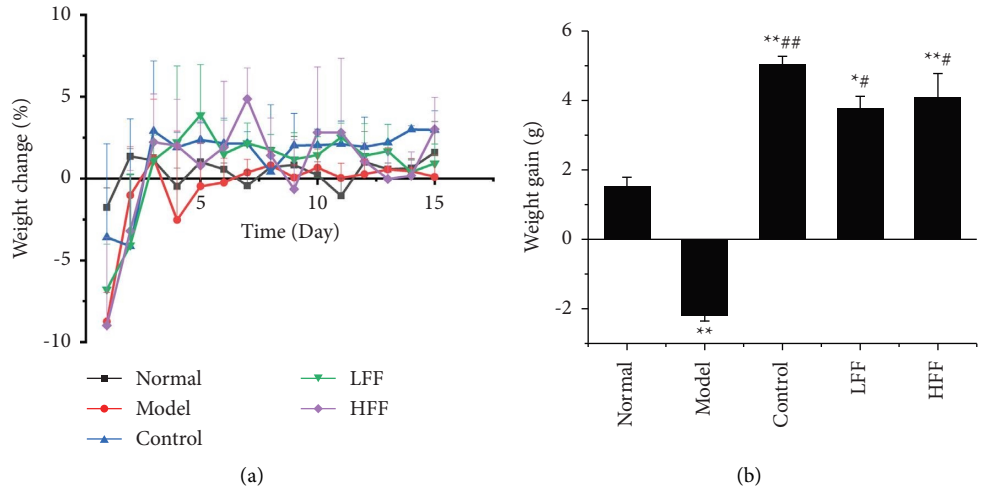

Figure 1: Effect of FF on body weight of mice in the IBD model. (a) Body weight changes in the mice. (b) Weight change compared to the initial period (*: $P < 0.05$, **: $P < 0.01$ vs. normal; #: $P < 0.05$, ##: $P < 0.01$, ###: $P < 0.001$ vs. model).

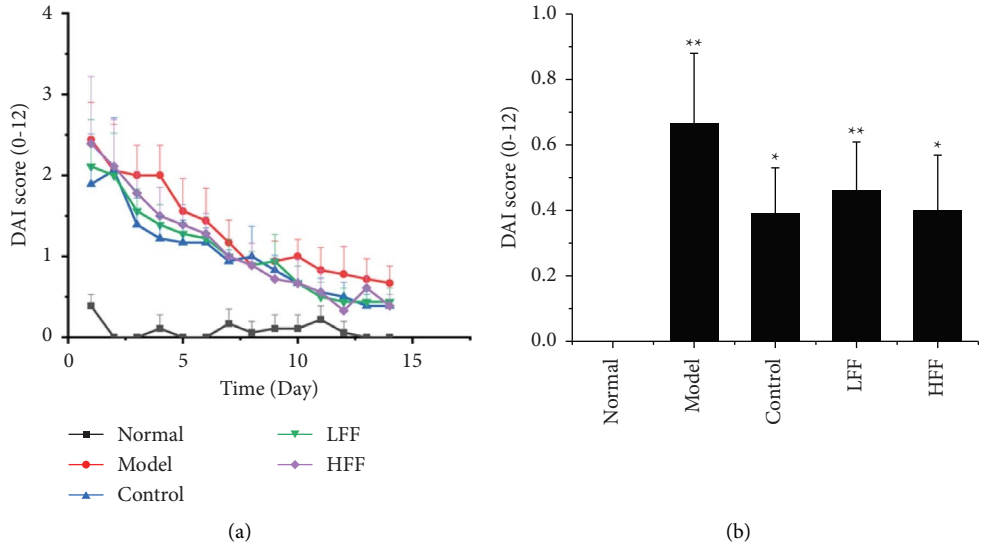

Figure 2: Effect of FF intervention on DAI of mice and DAI values of each group of mice at the end of the experiment. (a) Effect of FF on DAI scores of UC model mice. (b) DAI scores of mice in each group at the end of the experiment (*: $P < 0.05$, **: $P < 0.01$ vs. normal).

5.5. From these results, it can be concluded that drug or FF treatment can reduce colonic lesions. The effect of the HFF group was comparable to that of mesalazine, and the LFF group showed a great improvement compared to the model group.

3.7. Effect of FF on the Level of Inflammatory Factor Content in Serum of UC Model Mice. Analysis of the serum levels of IL-6, IL-1β, TNF-α, and IL-10 in mice revealed significant differences among the model group, normal group, and the intervention groups. As shown in Figure 6(a), IL-6 levels in the serum of model group mice were significantly higher than that of the normal group ($P < 0.01$), while IL-6 levels in all three intervention groups were not significantly different from the normal group. The control group with mesalazine intervention had the greatest reduction effect, with only 8.516 ± 2.09 pg/mL higher IL-6 inflammatory factor levels than the normal group, followed by the LFF and HFF groups. As shown in Figure 6(b), IL-1β levels in the model group increased significantly after DSS administration and were significantly different from the normal group ($P < 0.01$). In the three intervention groups, the serum IL-1β levels in mice decreased to near the levels of the normal group. Further, Figure 6(c) revealed that the levels of serum TNF-α in the remaining four groups of mice were significantly different with the normal group ($P < 0.01$), indicating that DSS could increase the concentration levels of TNF-α in the serum of mice. Compared with the model group, treatment with mesalazine and HFF significantly reduced the concentration of TNF-α by 30.025 ± 2.05 pg/mL and 13.366 ± 1.89 pg/mL, respectively,

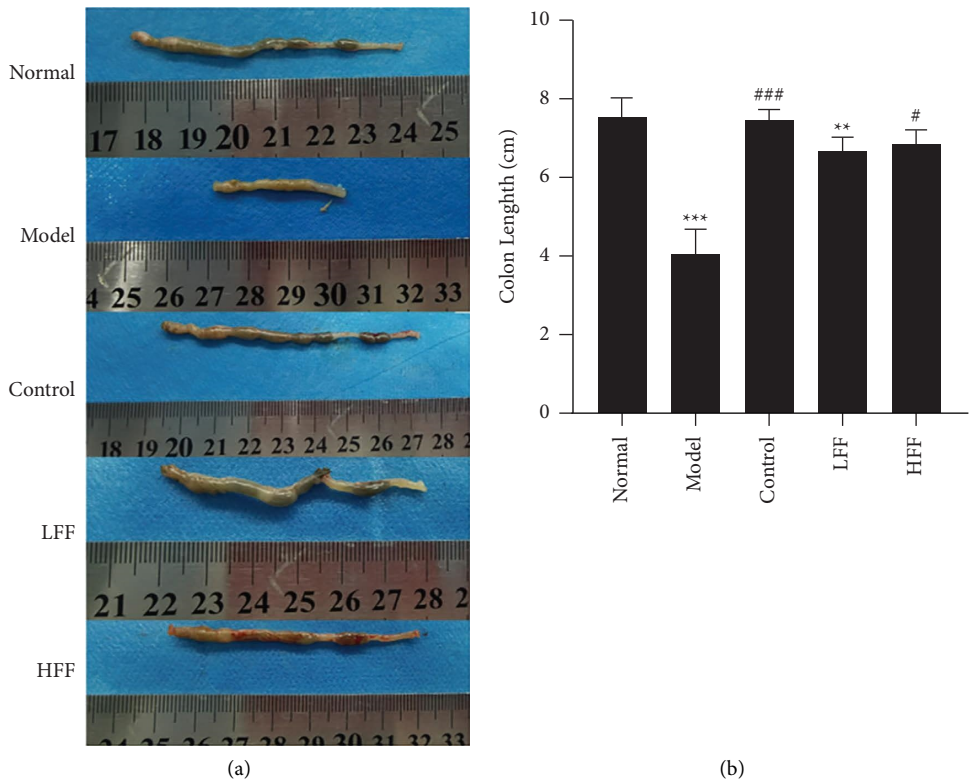

Figure 3: Colonic length of each group of mice (**: $p < 0.01$, ***: $p < 0.001$ vs. normal; #: $P < 0.05$, ###: $P < 0.001$ vs. model).

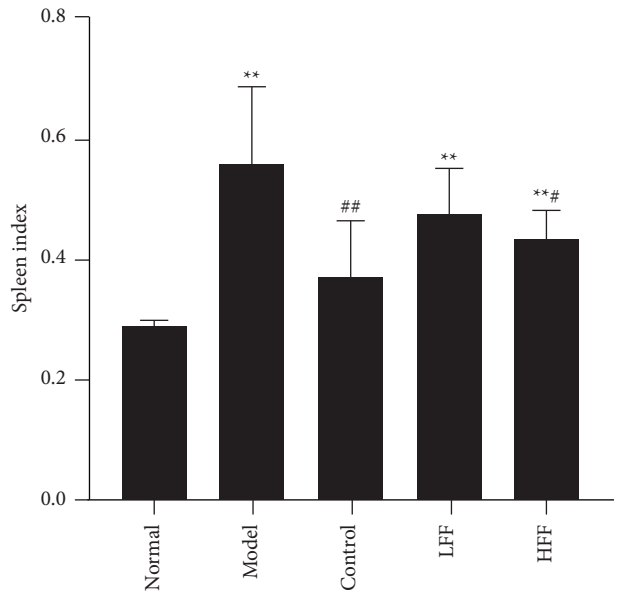

Figure 4: Spleen index of mice in each group (**: $P < 0.01$ vs. normal; #: $P < 0.05$, ##: $P < 0.01$ vs. model).

though there was still a significant gap to the concentration of the normal group. Lastly, Figure 6(d) showed that the concentration of IL-10 in the HFF group was 33.863 ± 1.75 pg/mL, which was the closest to the normal group, followed by mesalazine and LFF. Compared with the model group, treatment with mesalazine and HFF significantly increased the serum IL-10 levels in the UC mouse model, demonstrating their beneficial effects in reducing the inflammation caused by DSS.

3.8. Determination of Physico-Chemical Properties of FF. FF was obtained by adding (not adding) different amounts of hot water, and it can be seen from Figure 7(a) that different concentrations of FF had moderate pH values and did not differ much from each other. Figure 7(b) clearly shows that FF has good solubility. The concentration of 50% FF was sufficiently thick that it could stand on a toothpick, could be shaken by hand without spilling, and could be hung in a glass. FF at 25% and 20% had good flowability and a yoghurt-like texture, and only a small amount hung on the wall of the glass. FF at 10% and 5% has a similar texture to soya milk and milk. FF without hot water is crispy and without hard lumps. After standing at room temperature (25°C) for 6 h, a small amount of precipitation was produced at the bottom of samples III–V. Sample II was thick and homogeneous without precipitation. Sample VI was completely dissolved without precipitation. The physical and chemical properties of substances affect production and marketing. Brewed FF is stable in nature and hardly affects consumption. For long-term consumption and preservation, we also consider making it into biscuits.

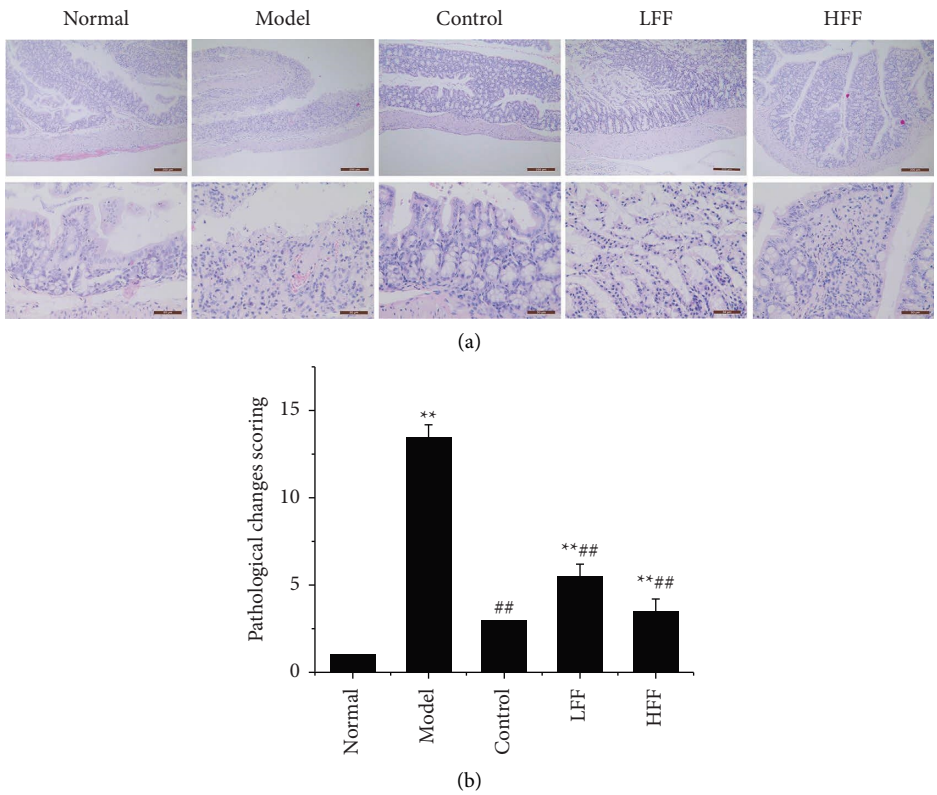

Figure 5: Effects of FF on colonic histopathology. (a) HE staining of mouse colonic tissue in each group (top: 100x, bottom: 400x). (b) Colonic tissue score (**: $P < 0.01$ vs. normal; ##: $P < 0.01$ vs. model).

3.9. Sensory Evaluation of FF. Participants tasted and rated the FF on a 9-point hedonic scale, and the feedback is shown in Table 3. The FF was approved by 88% of the participants. 46% said that they enjoyed it a lot and gave it a very high score (>7), rating the FF as having an even colour, a delicate taste, and an intense aroma. Of these, 36% said they would like to have another drink, while 10% thought it had the colour and texture of cooked cereal, with good taste and nutrition. Similarly, 46% of the participants expressed an average level of liking and the colour looked appetising but not as tasty as expected. However, as a FF, we have tried to make it effective and at the same time bring enjoyment to people's tongue. Compared to traditional food, FF still falls short in terms of flavour and texture, but there is no denying that FF has been a great success. Only 12% thought that it was a little yellow in colour and tasted a little strange. No participants showed any complaints about the FF. This positive feedback was to be expected, as JG is fermented by lactobacilli to give it a fermented aroma in itself, and we added a variety of carefully selected nutrients. Prior to the study, participants were asked to confirm that they were not allergic to cereal-based foods, without being made aware of the efficacy of this food. It is encouraging to note that, even just as a common food, it was well received by almost half of the participants. The taste and aroma can be further adjusted according to the desired outcome during the production process. If a special diet could be developed to provide a sustainable treatment for IBD, this would be highly attractive to patients.

4. Discussion

Dietary changes can promote the formation of either anti-inflammatory or proinflammatory components [28, 29], leading to the development of FF to treat a variety of diseases, such as diabetes, cardiovascular diseases, gastrointestinal inflammation, and neurological diseases [30–32]. Plant-derived foods contain a plethora of nutrients, fibers, and polyphenols, which are increasingly popular for the use of probiotics to ferment them, as demonstrated to be of great benefit to overall health [33–39]. These findings demonstrate the potential of developing nutritional formulas for IBD patients by combining medicinal ingredients rich in plant polysaccharides, unsaturated fatty acids, and small-molecule active ingredients with probiotics with explicit functions. Fewer studies have been conducted on the treatment of IBD with JG, and there is no development of FF for IBD patients based on the JG fermentation broth. In this study, *L. rhamnosus* 217-1 was used to ferment JG and effectively release its active components. The JG fermentation broth was used as a functional component, and YM, CXD, BBD, and SY were added as nutrients to cultivate FF for IBD patients.

UC usually inevitably leads to weight loss and exacerbates malnutrition. Both HFF and LFF restored the body weight of the UC model mice well, 4.250 ± 0.250 g and 3.891 ± 0.175 g, respectively. This was accompanied by a reduction in the DAI score of 0.255 ± 0.025 and a restoration of

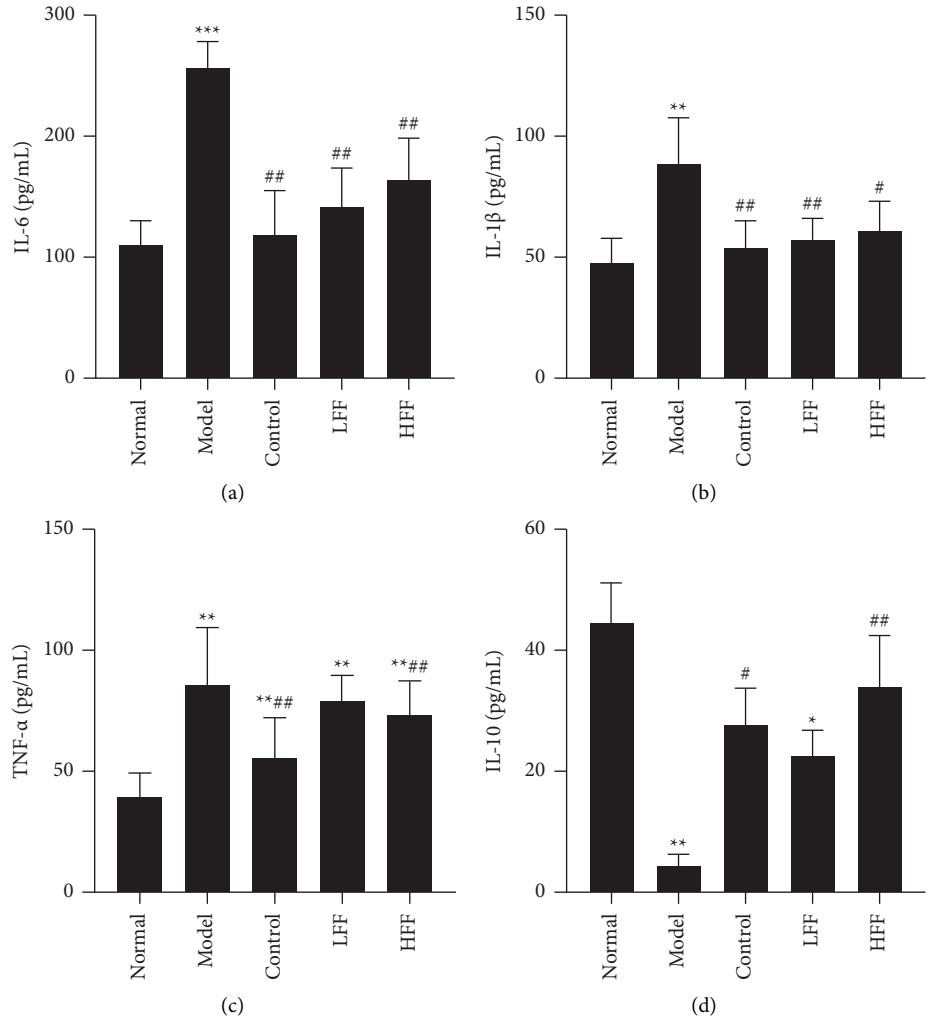

Figure 6: Effect of FF on the levels of inflammatory factors in serum of UC model mice. Figures (a–c) and (d) show the changes of IL-6, IL-1β, TNF-α, and IL-10 inflammatory factors in serum of mice, respectively.

the colonic length of 1.064 ± 0.087 cm. The increase in the spleen index was caused by the increasing number of macrophages that infiltrated the spleen. Treatment with FF reduced the splenic index by 0.102 ± 0.019, demonstrating that FF attenuates the abnormal immune response induced by macrophages. Damage to the intestinal barrier leads to an increase in intestinal permeability and serum levels of LPS, which further aggravate colitis [40]. Pathological analysis of colonic tissues revealed that FF significantly improved the total necrosis of the intestinal wall, reduced edema and inflammatory cell infiltration, decreased mucosal detachment, and restored the intestinal barrier, effectively alleviating the inflammatory response of the mouse colon. Moreover, a dose-dependent relationship was observed, with the intervention effect of high-dose FF being greater than that of low-dose. Furthermore, FF also decreased the concentration of inflammatory factors in the serum of mice, with the concentrations of TNF-α, IL-1βh, and IL-6 f decreasing by 9.518 ± 2.986 pg/mL, 29.253 ± 1.734 pg/mL, and 104.365 ± 11.483 pg/mL, respectively. The concentration of the serum inflammatory factor IL-10 increased by 23.623 ± 5.624 pg/mL. This finding is consistent with the research of Guo et al. [24], who found that platycodon saponin-D significantly reduced the levels of proinflammatory cytokines TNF-α, IL-6, and IL-1β and increased the levels of anti-inflammatory cytokine IL-10 in DSS-induced mice, suggesting that the active ingredient of the FF was Platycodon saponin.

Comparing with previous studies [23], the effect of FF was highly consistent with treatment with fermentation alone and the anti-inflammatory indexes of UC mice treated with FF were not lower than those of fermentation treatment. *In vitro* and *in vivo* studies have demonstrated the potential clinical application value of homologous raw materials for IBD [41–45]; however, their composition is complex and their pharmacological effects are wide-ranging. Though the preparation of FF diluted the JG ferment, the addition of YM, CXD, BBD, and SY supplemented a variety of nutrients, which undoubtedly ameliorated malnutrition in IBD patients to some extent and repaired intestinal damage in synergy with the JG fermentation broth. Unlike expensive drugs with side effects and unacceptable ferments,

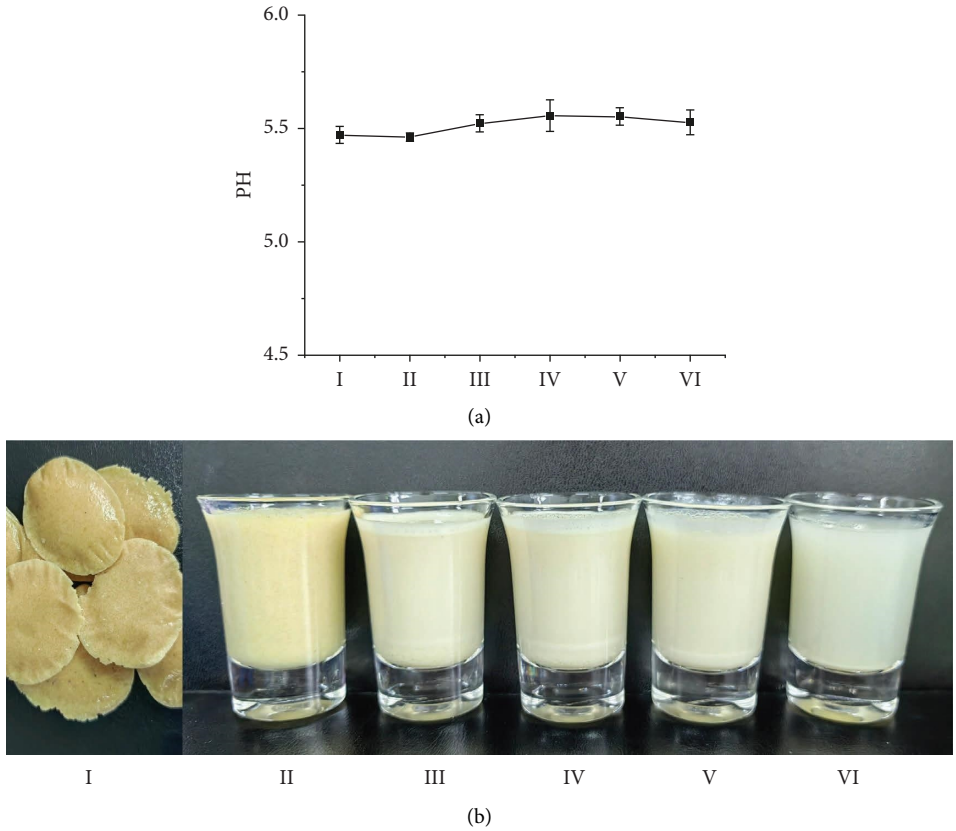

Figure 7: Physico-chemical property tests of FF (I, II, III, IV, V, VI FF with 96%, 50%, 25%, 20%, 10%, and 5% solids content, respectively) (a) pH of FF with different solids content. (b) Solubility of FF with different solids content (standing at room temperature for 6 h).

Table 3: Sensory evaluation of FF.

Grade	Scores	Percentage (%)	Evaluation
Like extremely	9	0	—
Like very much	8	10	Rich cereal aroma
Like moderately	7	36	Would love to try
Like slightly	6	30	A bit like
Neither like nor dislike	5	12	Acceptable
Dislike slightly	4	12	Tastes a bit strange
Dislike moderately	3	0	—
Dislike very much	2	0	—
Dislike extremely	1	0	—

FF has been carefully formulated and its excellent appearance and product stability along with good flavour and nutritional value are accepted by the majority of the population and preferred by 46% of the population. What is more convenient is that FF can be brewed in different consistencies according to personal preference. FF has good productivity and mass acceptance and has undoubtedly been a notable success as a therapeutic food and, to a certain extent, meets the needs of the IBD population. We are constantly innovating FFs with different flavours and serving styles on the one hand, and on the other hand, we are also working on creating better and more complete nutritional formulations, by replacing the functional ingredients in FF and tailoring it to the needs of people with specific diseases.

Previous studies have demonstrated that mesalazine (5-aminosalicylic acid) can improve intestinal inflammation by activating AMPK in macrophages and inhibiting NF-κB activation [46]. Guo et al. [24] treated LPS-stimulated RAW264.7 cells with platycodon saponin-D and found that AMPK activation enhanced the PI3K/Akt signaling pathway and impaired the NF-κB pathway. In this study, we investigated the effect of FF on a mouse model of DSS-induced UC, further confirming the anti-inflammatory effect of the JG fermentation broth as a mechanism of action of the AMPK/NF-κB/NLRP3 pathway. The quest for healthy, green, and wholesome foods has become a growing trend. Countless IBD patients are now seeking alternative dietary treatments [21, 22, 47]. This is expected to have a positive impact on the development and expansion of the food and pharmaceutical industries. Nevertheless, as an FF, further studies are needed to assess its safety and efficacy in humans before it can be marketed. In addition, the ingredients of the recipe should be clearly identified, and people with special constitutions such as those who are allergic to grains should not consume it. In the future, cooperation with medical institutions should be explored in order to complete the clinic-related study of the FF. We sincerely hope that the dream of sustainable treatment and prevention of the occurrence of IBD through daily diet will be realized soon, and the pain and burden of the majority of patients will be alleviated.

5. Conclusions

In this study, a functional food (FF) was developed for the treatment of IBD based on the fermented liquid of JG and four medicinal food ingredients including YM, CXD, BBD, and SY. Its efficacy was further evaluated in a DSS-induced UC mouse model. Results demonstrated that the FF inhibited the release of the inflammatory factors TNF-α, IL-1β, and IL-6 and increased the expression of the anti-inflammatory factor IL-10. In summary, the FF developed in this study effectively alleviated the inflammatory response of the mouse colon. Although the FF is not as effective as traditional drugs in the treatment of IBD, it offers numerous nutrients and is produced from healthy, low-cost ingredients with no side effects and can be utilized as a diet to achieve a sustainable treatment of IBD. In addition to the production stability and mass popularity of FF, this FF developed utilizing drug-food homology ingredients is expected to be a viable treatment strategy for IBD, enriching the food repertoire for IBD patients and paving the way for the future application of FF in medical and food industries.

Data Availability

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethical Approval

Institutional Review Board Statement. All animal experiments were approved by the Experimental Animal Ethics Review Committee of Yantai Raphael Biotechnology Co., Ltd (permit number: M20-RB062-ph).

Disclosure

Chunhai Li as a co-author.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

Writing and original draft preparation, writing of the review and editing, validation were performed by Jiahui Peng; methodology and software were handled by Zhe Wang; software was handled by Chunhai LI, Songsen Sui, and Chuanzhuang Guo; methodology was conducted by Ruiting Zhao and Haoran Liu; conceptualization, validation, writing of the review and editing, supervision, and funding acquisition were carried out by Ting Wang and Zhenshang Xu. The authors Jiahui Peng and Chunhai Li contributed equally to this study.

Acknowledgments

This work was financially supported by the Key Research and Development Program of Shandong Province (Grant no. 2020CXGC010602), the Science and Technology Support Plan for Young People in Colleges and Universities of Shandong Province (Grant no. 2020KJE005), the National Natural Science Foundation of China (Grant no. 31901665), Key innovation Project of Qilu University of Technology (Shandong Academy of Sciences) (Grant nos. 2022JBZ01–06), and the Basic Research of Pilot Project for the Integration of Science, Education and Industry, Qilu University of Technology, Shandong Academy of Sciences (Grant no. 2022PY074).

Supplementary Materials

Supplementary Table 1 describes the disease activity index of mice (DAI score). Supplementary Table 2 describes the pathological changes scoring criteria. Supplementary Table 3 shows the content of energy and nutrients per 100 g of medicinal food ingredients. (*Supplementary Materials*)

References

[1] S. Alatab, S. G. Sepanlou, K. Ikuta et al., "The global, regional, and national burden of inflammatory bowel disease in 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017," *The Lancet Gastroenterology & Hepatology*, vol. 5, no. 1, pp. 17–30, 2020.

[2] V. Jairath and B. G. Feagan, "Global burden of inflammatory bowel disease," *The Lancet Gastroenterology & Hepatology*, vol. 5, no. 1, pp. 2-3, 2020.

[3] A. Damião, M. F. C. D. Azevedo, A. D. S. Carlos et al., "Conventional therapy for moderate to severe inflammatory bowel disease: a systematic literature review," *World Journal of Gastroenterology*, vol. 25, no. 9, pp. 1142–1157, 2019.

[4] J. Burisch, T. Jess, M. Martinato, and P. L. Lakatos, "The burden of inflammatory bowel disease in Europe," *Journal of Crohn's and Colitis*, vol. 7, no. 4, pp. 322–337, 2013.

[5] G. G. Kaplan, "The global burden of IBD: from 2015 to 2025," *Nature Reviews Gastroenterology & Hepatology*, vol. 12, pp. 720–727, 2015.

[6] Y. Z. Zhang and Y. Y. Li, "Inflammatory bowel disease: pathogenesis," *World Journal of Gastroenterology*, vol. 20, no. 1, pp. 91–99, 2014.

[7] A. Schirbel and C. Fiocchi, "Inflammatory bowel disease: established and evolving considerations on its etiopathogenesis and therapy," *Journal of Digestive Diseases*, vol. 11, no. 5, pp. 266–276, 2010.

[8] D. Owczarek, T. Rodacki, R. Domagała-Rodacka, D. Cibor, and T. Mach, "Diet and nutritional factors in inflammatory bowel diseases," *World Journal of Gastroenterology*, vol. 22, no. 3, pp. 895–905, 2016.

[9] J. D. Lewis and M. T. Abreu, "Diet as a trigger or therapy for inflammatory bowel diseases," *Gastroenterology*, vol. 152, no. 2, pp. 398–414.e6, 2017.

[10] J. K. Hou, B. Abraham, and H. El-Serag, "Dietary intake and risk of developing inflammatory bowel disease: a systematic review of the literature," *American Journal of Gastroenterology*, vol. 106, no. 4, pp. 563–573, 2011.

[11] A. N. Ananthakrishnan, H. Khalili, M. Song et al., "High school diet and risk of Crohn's disease and ulcerative colitis," *Inflammatory Bowel Diseases*, vol. 21, no. 10, pp. 2311–2319, 2015.

[12] A. N. Ananthakrishnan, H. Khalili, G. G. Konijeti et al., "Long-term intake of dietary fat and risk of ulcerative colitis and Crohn's disease," *Gut*, vol. 63, no. 5, pp. 776–784, 2014.

[13] C. H. Lo, P. Lochhead, H. Khalili et al., "Dietary inflammatory potential and risk of Crohn's disease and ulcerative colitis," *Gastroenterology*, vol. 159, no. 3, pp. 873–883.e1, 2020.

[14] Y. Yue, S. Wu, Z. Li et al., "Wild jujube polysaccharides protect against experimental inflammatory bowel disease by enabling enhanced intestinal barrier function," *Food & Function*, vol. 6, no. 8, pp. 2568–2577, 2015.

[15] B. R. Jin, K. S. Chung, S. Y. Cheon et al., "Rosmarinic acid suppresses colonic inflammation in dextran sulphate sodium (DSS)-induced mice via dual inhibition of NF-κB and STAT3 activation," *Scientific Reports*, vol. 7, no. 1, Article ID 46252, 2017.

[16] Y. D. Jeon, J. H. Lee, Y. M. Lee, and D. K. Kim, "Puerarin inhibits inflammation and oxidative stress in dextran sulfate sodium-induced colitis mice model," *Biomedicine & Pharmacotherapy*, vol. 124, Article ID 109847, 2020.

[17] K. Topolska, A. Florkiewicz, and A. Filipiak-Florkiewicz, "Functional food-consumer motivations and expectations," *International Journal of Environmental Research and Public Health*, vol. 18, no. 10, p. 5327, 2021.

[18] J. Roosen, M. Bruhn, R. A. Mecking, and L. S. Drescher, "Consumer demand for personalized nutrition and functional food," *International Journal for Vitamin and Nutrition Research*, vol. 78, no. 6, pp. 269–274, 2008.

[19] J. A. Giménez-Bastida and H. Zieliński, "Buckwheat as a functional food and its effects on health," *Journal of Agricultural and Food Chemistry*, vol. 63, no. 36, pp. 7896–7913, 2015.

[20] J. F. Lacerda, A. C. Lagos, E. Carolino, A. S. Silva-Herdade, M. Silva, and C. Sousa Guerreiro, "Functional food components, intestinal permeability and inflammatory markers in patients with inflammatory bowel disease," *Nutrients*, vol. 13, no. 2, p. 642, 2021.

[21] T. Larussa, M. Imeneo, and F. Luzza, "Potential role of nutraceutical compounds in inflammatory bowel disease," *World Journal of Gastroenterology*, vol. 23, no. 14, pp. 2483–2492, 2017.

[22] D. W. Shin and B. O. Lim, "Nutritional interventions using functional foods and nutraceuticals to improve inflammatory bowel disease," *Journal of Medicinal Food*, vol. 23, no. 11, pp. 1136–1145, 2020.

[23] Z. Wang, C. Li, X. He et al., "Platycodon grandiflorum root fermentation broth reduces inflammation in a mouse IBD model through the AMPK/NF-κB/NLRP3 pathway," *Food & Function*, vol. 13, no. 7, pp. 3946–3956, 2022.

[24] R. Guo, Q. Meng, B. Wang, and F. Li, "Anti-inflammatory effects of Platycodin D on dextran sulfate sodium (DSS) induced colitis and *E. coli* Lipopolysaccharide (LPS) induced inflammation," *International Immunopharmacology*, vol. 94, Article ID 107474, 2021.

[25] U. Erben, C. Loddenkemper, K. Doerfel et al., "A guide to histomorphological evaluation of intestinal inflammation in mouse models," *International Journal of Clinical and Experimental Pathology*, vol. 7, no. 8, pp. 4557–4576, 2014.

[26] Y. Xia, J. Song, F. Zhong, J. Halim, and M. O'Mahony, "The 9-point hedonic scale: using R-Index Preference Measurement to compute effect size and eliminate artifactual ties," *Food Research International*, vol. 133, Article ID 109140, 2020.

[27] S. Wichchukit and M. O'Mahony, "The 9-point hedonic and unstructured line hedonic scales: an alternative analysis with more relevant effect sizes for preference," *Food Quality and Preference*, vol. 99, Article ID 104575, 2022.

[28] L. A. David, C. F. Maurice, R. N. Carmody et al., "Diet rapidly and reproducibly alters the human gut microbiome," *Nature*, vol. 505, no. 7484, pp. 559–563, 2014.

[29] G. D. Wu, J. Chen, C. Hoffmann et al., "Linking long-term dietary patterns with gut microbial enterotypes," *Science*, vol. 334, no. 6052, pp. 105–108, 2011.

[30] M. Elbandy, "Anti-inflammatory effects of marine bioactive compounds and their potential as functional food ingredients in the prevention and treatment of neuroinflammatory disorders," *Molecules*, vol. 28, no. 1, p. 2, 2022.

[31] S. Ballali and F. Lanciai, "Functional food and diabetes: a natural way in diabetes prevention?" *International Journal of Food Sciences & Nutrition*, vol. 63, no. 1, pp. 51–61, 2012.

[32] J. N. Losso, "Food processing, dysbiosis, gastrointestinal inflammatory diseases, and antiangiogenic functional foods or beverages," *Annual Review of Food Science and Technology*, vol. 12, no. 1, pp. 235–258, 2021.

[33] H. Karakula-Juchnowicz, J. Rog, D. Juchnowicz et al., "The study evaluating the effect of probiotic supplementation on the mental status, inflammation, and intestinal barrier in major depressive disorder patients using gluten-free or gluten-containing diet (SANGUT study): a 12-week, randomized, double-blind, and placebo-controlled clinical study protocol," *Nutrition Journal*, vol. 18, no. 1, p. 50, 2019.

[34] T. Wang, Z. Wang, Z. Yang et al., "Effect of the fermentation broth of the mixture of pueraria lobata, *Lonicera japonica*, and crataegus pinnatifida by lactobacillus rhamnosus 217-1 on liver health and intestinal flora in mice with alcoholic liver disease induced by liquor," *Frontiers in Microbiology*, vol. 12, Article ID 722171, 2021.

[35] B. Ran, C. E. Guo, W. Li et al., "Sea buckthorn (*Hippophae rhamnoides* L.) fermentation liquid protects against alcoholic liver disease linked to regulation of liver metabolome and the abundance of gut microbiota," *Journal of the Science of Food and Agriculture*, vol. 101, no. 7, pp. 2846–2854, 2021.

[36] W. Zhao, D. Peng, W. Li et al., "Probiotic-fermented Pueraria lobata (Willd.) Ohwi alleviates alcoholic liver injury by enhancing antioxidant defense and modulating gut microbiota," *Journal of the Science of Food and Agriculture*, vol. 102, no. 15, pp. 6877–6888, 2022.

[37] H. Li, J. Shi, L. Zhao et al., "Lactobacillus plantarum KLDS1.0344 and lactobacillus acidophilus KLDS1.0901 mixture prevents chronic alcoholic liver injury in mice by protecting the intestinal barrier and regulating gut microbiota and liver-related pathways," *Journal of Agricultural and Food Chemistry*, vol. 69, no. 1, pp. 183–197, 2021.

[38] J. E. Kwon, J. W. Lee, Y. Park et al., "Biotransformation of pueraria lobata extract with lactobacillus rhamnosus vitaP1 enhances anti-melanogenic activity," *Journal of Microbiology and Biotechnology*, vol. 28, no. 1, pp. 22–31, 2018.

[39] Y. Tao, M. Yue, C. Lv et al., "Pharmacological activation of ERβ by arctigenin maintains the integrity of intestinal epithelial barrier in inflammatory bowel diseases," *The FASEB Journal*, vol. 34, no. 2, pp. 3069–3090, 2020.

[40] X. Bian, W. Wu, L. Yang et al., "Administration of akkermansia muciniphila ameliorates dextran sulfate sodium-induced ulcerative colitis in mice," *Frontiers in Microbiology*, vol. 10, p. 2259, 2019.

[41] M. Fujisawa, K. Oguchi, T. Yamaura, M. Suzuki, and J. C. Cyong, "Protective effect of hawthorn fruit on murine experimental colitis," *American Journal of Chinese Medicine*, vol. 33, no. 2, pp. 167–180, 2005.

[42] S. Y. Lee, S. J. Lee, and S. J. Hur, "Effects of Prunus mume Sieb. et Zucc. extract and its biopolymer encapsulation on a mouse

model of colitis," *Journal of the Science of Food and Agriculture*, vol. 97, no. 2, pp. 686–692, 2017.

[43] J. W. Park, H. Bae, G. Lee et al., "Prophylactic effects of *Lonicera japonica* extract on dextran sulphate sodium-induced colitis in a mouse model by the inhibition of the Th1/Th17 response," *British Journal of Nutrition*, vol. 109, no. 2, pp. 283–292, 2013.

[44] L. Wang, C. Chen, A. Su, Y. Zhang, J. Yuan, and X. Ju, "Structural characterization of phenolic compounds and antioxidant activity of the phenolic-rich fraction from defatted adlay (Coix lachryma-jobi L. var. ma-yuen Stapf) seed meal," *Food Chemistry*, vol. 196, pp. 509–517, 2016.

[45] Y. Jing, A. Li, Z. Liu et al., "Absorption of codonopsis pilosula saponins by coexisting polysaccharides alleviates gut microbial dysbiosis with dextran sulfate sodium-induced colitis in model mice," *BioMed Research International*, vol. 2018, Article ID 1781036, 18 pages, 2018.

[46] S. Banskota, H. Wang, Y. H. Kwon et al., "Salicylates ameliorate intestinal inflammation by activating macrophage AMPK," *Inflammatory Bowel Diseases*, vol. 27, no. 6, pp. 914–926, 2021.

[47] M. A. Mijan and B. O. Lim, "Diets, functional foods, and nutraceuticals as alternative therapies for inflammatory bowel disease: present status and future trends," *World Journal of Gastroenterology*, vol. 24, no. 25, pp. 2673–2685, 2018.