REVIEW
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Utilization of Traditional Chinese Medicine Monomers in the Therapeutic Management of Enteritis-Associated Inflammation

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Abstract: Chronic enteritis with inflammatory characteristics is a persistent and recurring inflammation of the intestinal tract, resulting from a myriad of causative factors. Currently, the customary pharmacological treatments for inflammatory bowel disease (IBD) encompass aminosalicylic acid, glucocorticoids, antibiotics, and other pharmacological agents; however, many of these agents elicit deleterious effects and do not provide a sustainable solution to the issue of recurring symptoms. Therefore, the development of novel medicines for the prevention and cure of IBD holds vast importance. As crude drug constituents, single components of conventional Chinese medicine have the potential to not just mimic their parent drugs but also circumvent the knotty issues of complicated pharmacological ramifications and interpretation faced by their multi-component counterparts. As a result, this write-up outlines the chemical attributes of different mono-constituents of traditional Chinese medicine, namely ginsenoside, puerarin, glycyrrhizin, quercetin, and berberine, along with their exploration and employment in the treatment of IBD.

Keywords: Inflammatory bowel disease; Traditional Chinese medicine monomers; Ginsenoside.

Introduction

The traditional Chinese medicine (TCM) has a rich history and is renowned for its unique approach to treating various ailments, including enteritis. Enteritis, an inflammation of the intestines, often leads to discomfort and discomfort for patients. The application of typical Chinese medicine monomers in the anti-inflammatory treatment of enteritis has garnered significant attention due to their potential therapeutic benefits.

Inflammatory bowel disease (IBD) mainly refers to chronic, inflammatory diseases occurring in the gastrointestinal tract. There are two subtypes of IBD: one is Ulcerative colitis (UC) and the other is Crohn's disease (CD)[1]. The two subtypes are distinguished mainly by the location of the lesion. The lesion sites of UC were mainly concentrated in the rectum and colon, and the main clinical features were abdominal pain, diarrhea, intestinal mucosal inflammation, and hematochezia[2]. Compared with UC and CD, UC and CD occur at any part of the gastrointestinal tract, mainly at the end of the colon and ileum, and the clinical symptoms are mainly abdominal pain, diarrhea, fever, anemia, etc. With the rapid development of the global economy and science and technology, young people's lives and work pressure have increased dramatically. Poor living habits and poor diets with high oil and fat further lead to the frequent occurrence of IBD among young and middle-aged people in developed and even developing countries[3].

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Enteritis-Associated Inflammation

IBD is an autoimmune ailment that displays protracted progression, frequent relapses, and arduous remission, constituting one of the autonomous predispositions of colorectal carcinogenesis. Hence, it fundamentally impairs the well-being of the afflicted individuals. In recent years, more and more scholars have begun to explore the pathogenesis and inducement of IBD. Although current studies cannot fully explain the specific pathogenesis of IBD, a large number of research results show that the occurrence of IBD mainly involves the following factors:

(1) Genetic factors: With the development of gene testing and metabolomics, more and more scholars have begun to pay attention to the gene sequence associated with IBD and the role of heredity in IBD[4]. Some studies have found that the CAD15 (NOD2) gene can lead to the occurrence of IBD in Asia. Meanwhile, recent studies have found that lung surface activity associated with protein D(SFTPD), HSP70-2, IL-23R, IL-8, TNFSF 15, IRGM, and other genes are closely related to the occurrence of IBD. At the same time, it was found that the region encoding the human leukocyte antigen gene in chromosome 6 has obvious specificity in the genetic pathogenesis of IBD, and it was found that the probability of developing IBD in the same family increases with the closeness of the blood relationship.

(2) Environmental factors: Through epidemiological investigations and studies in various places, it is found that smoking, diet structure, and habits are the most common environmental factors that lead to IBD. Smoking: According to the study, smoking is one of the biggest independent hazards of IBD, which can cause further aggravation of the disease, increase the duration of the disease and the number of attacks, and increase the risk of surgical operation. The mechanism of action may be that carbon

monoxide produced by smoking can damage the expansion of microvessels, resulting in intestinal tissue ischemia and chronic inflammation; Diet: Eating habits high in fat and cholesterol, as well as irregular eating habits, increase the risk of IBD. In animal studies, the risk of IBD increases with dietary intake of saturated fatty acids.

(3) Other intestinal diseases and intestinal flora: The occurrence of IBD is often accompanied by the destruction of the intestinal barrier and the disruption of the balance of intestinal flora. Therefore, changes in the composition and proportion of intestinal microorganisms can lead to the occurrence of IBD. At the same time, studies have shown that increasing the content of probiotics in the intestine and improving the microenvironment in the intestine can alleviate the occurrence of IBD.

(4) Immune factors: The occurrence of IBD is closely related to intestinal and intestinal mucosal immunity. Intestinal immunity is a complex immune defense system, in which the presence of intestinal mucosal barrier structure, intestinal-associated lymphoid tissue, and intestinal mucosa can prevent the entry of pathogenic microorganisms and other harmful substances, and ensure the normal immune tolerance of the body. At the same time, the innate and adaptive immunity of the intestine are closely related to the occurrence of IBD. It is found that the decrease of IL-22 + innate lymphoid cells (ILCs) in the mucosa can lead to the occurrence of IBD. Meanwhile, studies have found that the increase of Th17 cells in children patients is related to the occurrence of IBD. Th17 cells can promote the development of IBD by releasing pro-inflammatory factors such as IL-17 and IL-22, and promote the release of TNF-α and IL-6 by intestinal epithelial cells and macrophages.

According to Traditional Chinese Medicine, the emergence of inflammatory enteritis is not solely limited to the intestine; it also holds a profound connection with the five visceral organs. Among them, the spleen stands as the primary organ of dysfunction within the zang-fu system, maintaining a close association with the remaining organs. The majority of spleen-related ailments are attributed to dampness and heat, inappropriate dietary habits, emotional distress, and excessive fatigue. The dampness is considered endogenous, manifesting primarily through the stagnation of Qi, blood collagalories stasis, and even Zang-fu deficiency.

The application of TCM in the IBD anti-inflammatory treatment

In the clinical treatment of IBD, steroids, and antibiotics are mainly used to alleviate the condition, and patients usually need to take medication for life or even surgery. At the same time, the use of steroids and antibiotics in clinical treatment not only easily leads to adverse reactions such as metabolic disorders and obesity, but is also prone to drug resistance, toxic and side effects, antibiotic residues, and other problems, endangering public health safety. With the deepening of relevant research, more and more scholars have confirmed that natural products such as TCM have extensive biological activities and can play a good role in antibacterial[5] and anti-inflammatory[4], anti-tumor, and treatment of various systemic diseases[6]. TCM disease prevention and control is mainly based on the holistic and integrated treatment of diseases through multi-component, multi-pharmacological effects, multi-target, and other TCM formulations. However, due to the complex active ingredients of TCM, unclear pharmacological effects, and low oral availability, the modernization and internationalization of TCM are seriously restricted[7]. Therefore, TCM monomers with specific curative effects and a single active ingredient can be extracted from Chinese herbs. It has become an effective alternative means to treat IBD.

This paper primarily adopts the viewpoint of TCM monomer as listed in Table 1. Based on the research progress of the application of TCM monomers in enteritis at home and abroad, the chemical properties, effects, and mechanisms of TCM monomers were introduced in this paper, providing a reference for promoting the practical clinical application of TCM monomers in IBD.

Ginsenosides

Ginsenosides are important active ingredients in ginseng, belonging to triterpenoids. Ginsenosides have been proven to have various therapeutic effects such as anti-oxidation， anti-inflammation, anti-allergy, and anti-tumor. Ginsenosides are mainly divided into Rh2[8], Rb1, Rb2, Rg3, Rc, CK, and so on according to their structural differences[9], among which ginsenosides Rg3 is the first class of new anticancer drugs in China[10]. In the study of IBD, it was found that ginsenosides Rg3 (20 mg/kg, 40 mg/kg) could regulate the expression of Th1 and Th2 cells, inhibit the expression of TNF-α and IL-6-related cytokines, and promote the expression of IL-10 cells. Studies have shown that ginsenoside Rd can promote autophagy and explain NLRP-3 inflammasome through the AMPK-ULK1-p62 signaling pathway, reduce the secretion of IL-1β by macrophages, and inhibit the occurrence of IBD. In the mouse IBD disease model, ginsenoside Rh2 was found to promote TGF-β expression, increase mRNA expression and protein phosphorylation of TGF- β receptor I, and significantly increase the phosphorylation of downstream targets SMAD2 and SMAD3, inhibit the occurrence of enteritis, and inhibit the expression of TGF-β[3]. The therapeutic effect of ginsenoside Rh2 was decreased. Ginsenosides Rd, Rb1, and CK can also relieve intestinal tissue injury, inflammatory cell infiltration, and pro-inflammatory factor release by regulating NF-kB and MAPK signaling pathways[8].

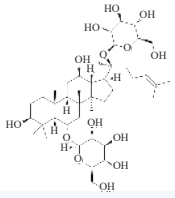
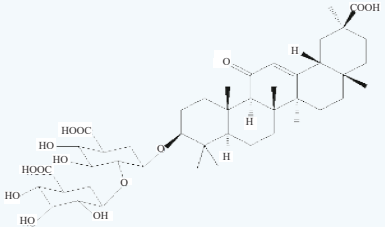
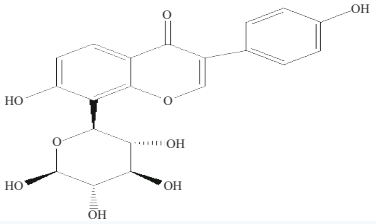
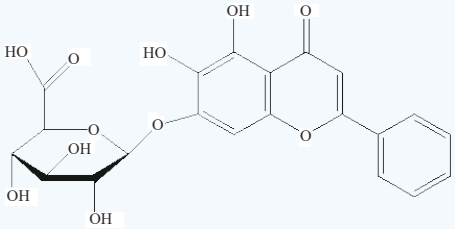
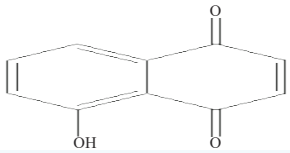
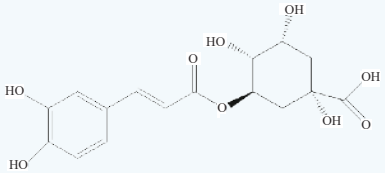
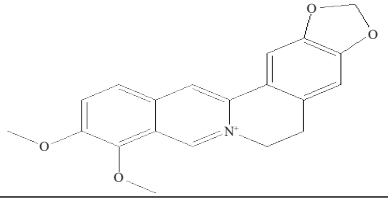
Glycyrrhizin

Glycyrrhiza uralensis Fisc, as the "king of medicines", has been recorded in Chinese herbal medicine books in successive dynasties. It has the effects of tonifying the spleen and qi, moistening the lungs relieving cough, clearing heat, and detoxifying[8].

According to the chemical composition, licorice is divided into: triterpenoids glycyrrhizic acid and glycyrrhetinic acid, flavonoids glycyrrhizin, glycyrrhizin flavones, alkaloids tetrahydroquinoline compounds, and licorice extract is also listed as safe and non-toxic substances by the US FDA. In IBD research, glycyrrhizin and glycyrrhizin were studied more. Glycyrrhizin forms a white crystalline powder, which has a special sweet taste and is insoluble in oil. It can be dissolved in hot water and becomes sticky after cooling.

Studies suggest that endoplasmic reticulum stress promotes ex-

Table 1. Chemical formula of Chinese medicine monomer.

TCM	Source	Chemical Formula	Structural Formula
Ginsenoside-Rg1	Ginseng	$C_{42}H_{72}O_{14}$	
Glycyrrhizic acid	Glycyrrhiza uralensis Fisch	$C_{42}H_{62}O_{16}$	
Puerain	Pueraria lobata	$C_{12}H_{18}O_{11}$	
Baicalin	Scutellaria baicalensis Georgi	$C_{21}H_{18}O_{11}$	
Juglone	Walnut	$C_{10}H_6O_3$	
Chlorogenic acid	Lonicera japonica Thunb	$C1_6H_{18}O_9$	
Berberine	*Coptis chinensis* Franch	$C_{20}H_{18}NO_4$	

Note: In this table, we present the sources, chemical formulas, and structural formulas of the seven traditional Chinese medicine (TCM) monomers discussed in the paper. For instance, berberine is derived from Coptis chinensis Franch with a chemical formula of $C_{20}H_{18}NO_4$.

cessive activation of intestinal NF-kB, which in turn leads to immunoinflammatory injury and apoptosis of intestinal epithelial cells, thus destroying the intestinal mucosal barrier and causing IBD. Therefore, by using H_2O_2 stimulation to establish the ERS model of cells, glycyrrhizin was found to inhibit apoptosis caused by hydrogen peroxide, and at the same time inhibit the decreased expression of phosphorylated protein kinase-like ER kinase (p-PERK) and NF-kB. In addition, glycyrrhizic acid can also inhibit the abnormal expression of tight junction protein in intestinal epithelial cells and promote the growth of mucosal cells.

Puerarin

It is recorded in "On Febrile Diseases" that Gegen Qinlian decoction is often used for ulcerative colitis and diarrheal irritable bowel syndrome of spleen and stomach damp-heat syndrome. Puerarin is the main active ingredient and quality standard of pueraria in Chinese Pharmacopoeia. In mouse experiments, puerarin can restore the change of colon length induced by DSS, reduce the expression of IL-6, IL-1β, and TNF-α in serum, increase the expression of intestinal epithelial cup cell compact linking protein (ZO-1) and Muc2, enhance the abundance of intestinal flora in mice, improve diarrhea, relieve colitis, and improve the quality of intestinal flora. At the same time, puerarin can also play an anti-inflammatory role in alleviating colitis by regulating tryptophan, niacin, lysine, and other metabolic pathways.

Baicalin

Baicalin (BG) is a kind of flavonoid chemical extracted from the dried root of scutellaria baicalin. At room temperature, baicalin is a pale yellow powder with a bitter taste[11]. The compound is almost insoluble in water but slightly soluble in chloroform and nitrobenzene. Baicalin has significant biological activity, which can inhibit bacteria, reduce inflammation, clear heat, and relieve fire, and has the effects of anti-thrombosis, hemostasis, fetal peace, and cholesterol reduction[11]. Baicalin has been proven to play a good role in the prevention and treatment of chronic migraine diseases, rheumatoid arthritis, epilepsy, liver cancer, and other diseases.

Studies on baicalin in IBD diseases have found that baicalin (80 mg/kg) can relieve the decrease of body weight and change of colon length in mice induced by DSS, and baicalin can effectively reduce the expression of protein and mRNA in Fascin, an actin-binding protein Fascin. Fascin Fascin has fascin as a candidate biomarker and a potential therapeutic target for multiple cancers. The high expression of fascin can promote tumor invasion and migration.

Therefore, this study believed that baicalin can effectively improve colitis injury in mice and inhibit the occurrence of colon cancer to a certain extent. In the study on the specific mechanism of baicalin in enteritis, it has been found that baicalin can inhibit the release of inflammatory factors, restore the intestinal flora barrier, and alleviate the occurrence of IBD by regulating MLCK/pMLC2 and MPD-NOD2 signaling pathways[12].

Juglone

Juglone the scientific name 5-hydroxy-1, 4-naphthoquinone, is a naphthoquinone compound extracted from the immature outer peel of walnut and its isotope black walnut, easily soluble in ethanol, ether, and slightly soluble in hot water. It has antibacterial, anti-tumor, antiviral, and other pharmacological activities[13].

In vivo and in vitro experiments in animal models demonstrated that juglone at a dose of 150 mg/kg can significantly reduce the expression levels of TNF-α, MPO, and TLR-4, inhibit the expression of IL-1β and TNF-α, and improve the occurrence of IBD by reducing inflammatory cytokines and neutrophil infiltration.

Chlorogenic acid

Chlorogenic acid is one of the main antibacterial and antiviral pharmacological components extracted from honeysuckle. Chlorogenic acid is soluble in ethanol, and acetone is slightly soluble in ethyl acetate[14].

Chlorogenic acid has a wide range of biological activities, which have been proven to be antibacterial, antiviral, blood pressure lowering, blood lipid-lowering, anti-aging, and other functions. Studies have shown that chlorogenic acid can inhibit the expression of MLCK, inhibit the depolymerization of F-actin, and at the same time, alleviate the damage of intestinal mucosal barrier and relieve TNBS-induced enteritis by up-regulating the expression of tight junction proteins Occludin and Claudin -1 on the cell membrane[15].

Berberine

Berberine is an alkaloid isolated from Coptis chinensis. It is the main active component of Coptis chinensis antibacterial[10]. Berberine is a yellow needle-like crystal with a bitter taste[16]. Berberine is mainly absorbed in the gastrointestinal tract. Studies have shown that after oral administration of 25 mg/kg berberine in rats for 15 minutes, the maximum concentration of berberine is 16.74 ng/ml. The plasma concentration rapidly decreases within 12 hours but remains at an extremely low plasma concentration of 36 hours.

Berberine is one of the most commonly used traditional Chinese medicine ingredients in the treatment of inflammatory enteritis. It mainly treats enteritis through antibacterial, anti-inflammatory, analgesic, antioxidant, and protecting the intestinal epithelial barrier. Firstly, the infection of harmful bacteria in the intestine is a key factor in inducing IBD, and berberine, as a positively charged compound, can directly interact with LPS in the bacterial cell wall and cell surface proteins, thereby interfering with harmful bacterial metabolism. It can also inhibit bacterial DNA replication, RNA transcription, and protein expression[17]. Secondly, in the TNBS-induced CD model, berberine can reduce TNF by inhibiting the expression of Th17-related cytokines- α、The expression of IL-23 and IL-6 can also inhibit Th1 differentiation by inhibiting p38 mitogen-activated protein kinase (MAPK) and JNK activation[18]. Meanwhile, berberine can alleviate pain caused by IBD in patients, and research has shown that berberine can pass through mouse m-berberine and mouse m-opioid receptors (μ- MOR and δ- The (DOR) dependent effect reverses the excessive movement, secretion, and pain induced by diarrhea induced irritable bowel syndrome (IBS-D), and increases the expression of MOR and DOR in mouse gut and rat embryonic cortical neurons[17,19]. At the same time, berberine has antioxidant effects, which can inhibit oxidative stress, increase the activity of intracellular antioxidant enzymes, reduce the occurrence of intracellular lipid peroxidation, and enhance the defense ability of antioxidant enzymes[20,21].

In Fig. 1, we have mapped seven TCM monomers involved in signaling pathways or targets in the treatment of enteritis. For example, the main targets of Puerain are IL-6,IL-1β and TNF-α.

Conclusions and prospects

Inflammatory enteritis, as a disease that is difficult to cure, has a long course, and the incidence is increasing in modern society, which constantly troubles patients and clinical treatment. Al-

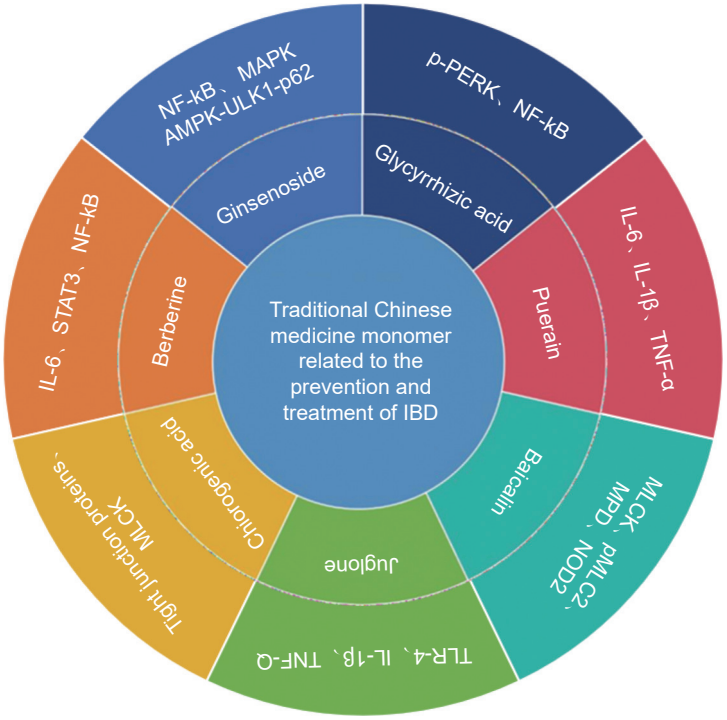


Fig. 1. TCM commonly utilized in clinical treatment for IBD and their effective mechanisms of action.

though the amino acid hydrochlorate and steroid hormone used in clinical medicine can alleviate the disease to a certain extent, the side effects, complications, and threats to public health security can not be ignored. TCM monomer has the advantages of clear chemical structure, obvious efficacy, small toxicity, and low raw materials, not only in inflammatory enteritis but also in other diseases to show good disease resistance and broad application prospects. Therefore, this paper presents the research progress of seven TCM monomers including Ginsenosides in enteritis at home and abroad. These seven traditional Chinese medicines all show good disease resistance in animal disease models and have a good effect in the treatment of enteritis. However, most traditional Chinese medicine monomers still lack practical clinical studies, and sufficient clinical experimental data are needed to evaluate the effectiveness of traditional Chinese medicine monomers in the treatment of IBD. Therefore, it is hoped that some scholars can conduct deeper studies on this.

Abbreviations

CARD15, capase recruitment domain protein 15; DSS, Dextran Sulfate Sodium Salt; HSP70, heat-shock protein 70; IL, interleukin; MLCK, myosin light chain kinase; MPO, myeloperoxidase; NF-kB, nuclear factor-k-gene binding; NOD2, nucleotide-binding oligomerization domain 2.

Authors' contributions

HYH wrote the manuscript, analyzed all data, prepared all tables and figures, and conducted the most of the work. HYT assisted in analyzing all the data. ZCL assisted analyzed all data and revised the manuscript. JL designed and analyzed all data and revised the manuscript. All authors read and approved the final manuscript.

References

[1] Neurath M, Vieth M. Different levels of healing in inflammatory bowel diseases: mucosal, histological, transmural, barrier and complete healing. Gut, 2023, 72(11): 2164-2183.

[2] Gilliland A, Chan J, De Wolfe T, et al. Pathobionts in Inflammatory Bowel Disease: Origins, Underlying Mechanisms, and Implications for Clinical Care. Gastroenterology, 2023.

[3] Bernstein C, Fisk J, Dolovich C, et al. Understanding predictors of fatigue over time in persons with IBD: The importance of depressive and anxiety symptoms. AM J gastroenterol, 2023, 10-14309.

[4] Dai Y, Lu Q, Li P, et al. Xianglian Pill attenuates ulcerative colitis through TLR4/MyD88/NF-κB signaling pathway. J Ethnopharmacol, 2023, 300: 115690.

[5] Yang Z, Lin S, Feng W, et al. A potential therapeutic target in traditional Chinese medicine for ulcerative colitis: Macrophage polarization. Front Pharmacol, 2022, 13: 999179.

[6] Wu H, Chen Q, Wang W, et al. Compound sophorae decoction enhances intestinal barrier function of dextran sodium sulfate induced colitis via regulating notch signaling pathway in mice. Biomed Pharmacother, 2021, 133: 110937.

[7] Wei Y, Fan Y, Ga Y, et al. Shaoyao decoction attenuates DSS-induced ulcerative colitis, macrophage and NLRP3 inflammasome activation through the MKP1/NF-κB pathway. Phytomedicine, 2021, 92: 153743.

[8] Lu Q, Wu X, Han W, et al. Effect of Glycyrrhiza uralensis against ulcerative colitis through regulating the signaling pathway of FXR/P-gp. Am J Transl Res, 2021, 13(8): 9296-9305.

[9] Zhou P, Xie W, He S, et al. Ginsenoside Rb1 as an Anti-Diabetic Agent and Its Underlying Mechanism Analysis. Cells, 2019, 8(3).

[10] Dong Y, Fan H, Zhang Z, et al. Berberine ameliorates DSS-induced

intestinal mucosal barrier dysfunction through microbiota-dependence and Wnt/β-catenin pathway. Int J Biol Sci, 2022, 18(4): 1381-1397.

[11] Hu Q, Zhang W, Wu Z, et al. Baicalin and the liver-gut system: Pharmacological bases explaining its therapeutic effects. Pharmacol Res, 2021, 165: 105444.

[12] Li M, Li M, Lei J, et al. Huangqin decoction ameliorates DSS-induced ulcerative colitis: Role of gut microbiota and amino acid metabolism, mTOR pathway and intestinal epithelial barrier. Phytomedicine, 2022, 100: 154052.

[13] Akutsu Y, Fujiwara T, Suzuki R, et al. Juglone, a plant-derived 1, 4-naphthoquinone, binds to hydroxylamine oxidoreductase and inhibits the electron transfer to cytochrome. Appl Environ Microbiol, 2023: e0129123.

[14] Yao L, Zhao M, Luo Q, et al. Carbon Quantum Dots-Based Nanozyme from Coffee Induces Cancer Cell Ferroptosis to Activate Antitumor Immunity. ACS nano, 2022, 16(6): 9228-9239.

[15] Han D, Wu Y, Lu D, et al. Polyphenol-rich diet mediates interplay between macrophage-neutrophil and gut microbiota to alleviate intestinal inflammation. Cell Death Dis, 2023, 14(10): 656.

[16] Zhu L, Gu P, Shen H. Protective effects of berberine hydrochloride on DSS-induced ulcerative colitis in rats. Int Immunopharmacol, 2019, 68: 242-251.

[17] Chen C, Lu M, Pan Q, et al. Berberine Improves Intestinal Motility and Visceral Pain in the Mouse Models Mimicking Diarrhea-Predominant Irritable Bowel Syndrome (IBS-D) Symptoms in an Opioid-Receptor Dependent Manner. PLoS One, 2015, 10(12): e0145556.

[18] Cui G, Qin X, Zhang Y, et al. Berberine differentially modulates the activities of ERK, p38 MAPK, and JNK to suppress Th17 and Th1 T cell differentiation in type 1 diabetic mice. J Biol Chem, 2009, 284(41): 28420-28429.

[19] Eans SO, Ganno ML, Mizrachi E, et al. Parallel Synthesis of Hexahydrodiimidazodiazepines Heterocyclic Peptidomimetics and Their in Vitro and in Vivo Activities at μ (MOR), δ (DOR), and κ (KOR) Opioid Receptors. J Med Chem, 2015, 58(12): 4905-4917.

[20] Chen C, Tao C, Liu Z, et al. A Randomized Clinical Trial of Berberine Hydrochloride in Patients with Diarrhea-Predominant Irritable Bowel Syndrome. Phytother Res, 2015, 29(11): 1822-1827.

[21] Li H, Fan C, Lu H, et al. Protective role of berberine on ulcerative colitis through modulating enteric glial cells-intestinal epithelial cells-immune cells interactions. Acta Pharm Sin B, 2020, 10(3): 447-461.