Review Article

iMedPub Journals
www.imedpub.com

American Journal of Pharmacology and Pharmacotherapeutics
ISSN 2393-8862

2025
Vol.12 No.1:202

Immunopharmacological Mechanisms of Chinese Herbal Medicine in Inflammatory Bowel Disease

Hui Liu*

Center for Traditional Chinese Medicine and Immunology Research, School of Basic Medical Sciences, Shanghai University of Traditional Chinese Medicine, Shanghai, China

***Corresponding author:** Hui Liu, Center for Traditional Chinese Medicine and Immunology Research, School of Basic Medical Sciences, Shanghai University of Traditional Chinese Medicine, Shanghai, China; E-mail: liuhui070020@.com163

Received date: December 23, 2023, Manuscript No. IPAPP-23-18272; **Editor assigned date:** December 26, 2023, PreQC No. IPAPP-23-18272 (PQ); **Reviewed date:** January 10, 2024, QC No. IPAPP-23-18272; **Revised date:** February 14, 2025, Manuscript No. IPAPP-23-18272 (R); **Published date:** February 21, 2025, DOI: 10.36648/ipapp.12.1.202

Citation: Liu H (2025) Immunopharmacological Mechanisms of Chinese Herbal Medicine in Inflammatory Bowel Disease. Am J Pharmacol Pharmacother Vol:12 No:1

Abstract

Background: Inflammatory Bowel Disease (IBD) imposes significant morbidity and healthcare burden globally. Pharmacological therapies typically include 5-aminosalicylic acid, corticosteroids, antibiotics, and other biological agents and cytokine antibodies, but variable treatment efficacy and adverse drug effects remain major problems. Traditional Chinese Medicine (TCM) therapies for IBD have shown good clinical efficacy, low side effects and cost effectiveness. This study aimed to review the immunopharmacological mechanisms of TCM formulae and pure component compounds in the treatment of IBD.

Summary: Evidence for immunological mechanisms involved in mediating the IBD-related clinical effects of Shen Ling Bai Zhu San (SLBZS) and its components Atractylodes macrocephala Koidz ('Baizhu'), Ginseng ('Renshen'), Poria cocos ('Fuling'); Yu Ping Feng San (YPFS) and its component Radix Astragalus ('Huangqi'), Si Shen Wan (SSW) and its component Psoralea corylifolia L ('Buguzhi'), Andrographis paniculata ('Chuanxinlian'), Evodiae fructus ('Wuzhuyu'), and Salvia miltiorrhiza radix ('Danshen') was summarized. These included the modulation of T cell mediated immunological processes, pro and anti-inflammatory cytokine profiles, IFN-γ, and ERK1/2, p38 MAPKs and NF-κB signaling pathways, among others.

Key messages: Available experimental evidence demonstrates several immunological mechanisms of TCM preparations applied in IBD. The regulatory actions of multiple TCM preparations and their components on cytokine production, NF-κB, MAPKs and related signaling pathways in IBD are implicated in mediating their clinical efficacy in IBD. Future research is needed to understand the detailed and comprehensive immunopharmacological mechanisms involved active molecules, and their molecular effects to develop novel TCM-based therapeutic regimes for IBD.

Keywords: Inflammatory bowel; Environmental factors; Intestinal microecology

Introduction

Inflammatory Bowel Disease (IBD) comprises two major forms Ulcerative Colitis (UC), marked by diffuse inflammation of the colon mucosa proximally from the rectum, and Crohn's Disease (CD), marked by granulomatous inflammatory lesions of the digestive tract. The global incidence of IBD is increasing and it poses a public health burden of increasing importance. IBD in clinical practice with recurrent abdominal pain, diarrhea, blood stool as the main manifestations. The etiology of IBD is unknown, traditionally thought to occur as non-specific, and the possible causes found in recent studies are genetic predisposing factors, environmental factors, intestinal microecology and host immune response. Immune deregulation of the mucosal immune system is considered as the central pathogenic mechanism leading to development and perpetuation of mucosal inflammation and barrier disruption characteristic of IBD [1].

At present, medical treatment for IBD mainly includes 5-Aminosalicylic Acid (5-ASA), antibiotics, immunosuppressive agents (Azathioprine, 6-mercaptopurine), corticosteroids, and biologicals such as anti-TNF-α agents, and therapy is typically life-long, aimed at remission and relapse prevention. Long term drug therapy is complicated by the risk of drug related adverse events and high costs, while therapeutic de-escalation leads to a high risk of relapse, especially in severe cases which are managed by anti-TNF-α agents. These include a higher risk of bacterial and fungal infections, cervical dysplasia, and neurological disorders, posing serious concerns. Taken together, this indicates an urgent need for the discovery of novel agents for IBD management associated with lower risk of adverse effects [2].

Traditional Chinese Medicine (TCM) has made great achievements in the treatment of gastrointestinal diseases. Clinical trials of Chinese herbal medicines for IBD management have shown positive outcomes with good safety profiles. Increasing evidence from preclinical studies supports the immunoregulatory effects of multiple TCM herbs and their component compounds. Here we reviewed the immunoregulatory effects of TCM and its derived compounds in the treatment of IBD,

particularly with regard to deregulation of T cell mediated immune mechanisms and their downstream effects, thereby highlighting the mechanistic aspects of several promising drug candidates derived from Complementary and Alternative Medicine (CAM) for IBD[3].

Literature Review

The immunological mechanisms underlying the pathology of IBD

Key immunological mechanisms of cell mediated immunity implicated in IBD include the deregulation of T-cell subsets, T-helper 17 (Th17) and regulatory T (Treg) cells, aberrant B cell function, which in turn control macrophage function and cytokine profiles [4].

Th17 cells in IBD: Th17 cells are key effectors of autoimmune disease including IBD, Rheumatoid Arthritis (RA), psoriasis, Multiple Sclerosis (MS). Classically, IBD was thought to be primarily mediated by Th1 cells, but it is now known that Th17 cells and their related cytokines are also crucial mediators in the above-mentioned types of IBDs. Th17 cells act to secrete interleukins and play a key role in mediating intestinal inflammation. In studies showing that massive Th17-cell infiltration and substantial Th17-associated cytokine secretion are seen in the gastrointestinal mucosa of IBD patients. Higher number of mucosal Th17 cells in both active IBD and quiescent IBD [5].

Recent reports suggest that IL-17-secreting Th17 cells secrete chemokines and recruit neutrophils to inflamed tissues. *In vivo* experiments in mice, it has been shown that Th17 cells are involved in the pathogenesis and development of IBD. In addition, the same finding was found that by measuring the proportion of Th17 cells in peripheral blood by flow cytometry, the proportion of Th17 cells in the peripheral blood of patients increased, and in the IL-17 level in Peripheral Blood Mononuclear Cells (PBMCs) by real-PCR, the expression level of IL-17 mRNA in the peripheral blood of IBD patients was significantly increased [6].

In addition, antibodies targeting IL-17F have been shown to be effective in the treatment of IBD. Furthermore, antibodies directed against IL-17F have been shown to have significant efficacy in the treatment of IBD in clinical experiments. Other studies found that the specific gram-positive *Clostridium* species Cluster XIVa (C. XIVa) promoted the quantitative expansion of Treg cells in the colon. Increased bacterial abundance correlated well with the clinical response to Fecal Microbiota Transplantation (FMT) in IBD patients. When C. XIVa or prevot at strain gave Specific Pathogen-Free (SPF) wild-type mice, C. XIVa limits the proportion of Prevotella in the host [7].

The IL-6 and IL-23 factors are known to induce Th17 differentiation *in vivo*, and the concentration of IL-23 determines the polarization of Th17, contributing majorly to IBD progression, and increased production of IL-23 by macrophages, dendritic cells or granulocytes has been observed in various mouse models of colitis and colitis-associated cancer. IL-23 is a critical modulator of differentiation and function of Th17, which secrete downstream IL-17, IL-6, TNF-α and a small amount of interferon γ (IFN-γ), forming a key immune axis in IBD, which is an important therapeutic target [8].

Th17/Treg ratio in IBD: The dynamic balance of the Th 17/ Treg ratio plays an important role in intestinal homeostasis and IBD. The anti-inflammatory mediators IL-10 and TGF-β are the main cytokines produced by T reg, and the forkhead box protein P3 (Foxp 3) is an essential transcription factor for IL-10 and TGF-β in IBD. TGF-β induces the transformation of naive T cells to Treg and suppresses autoimmunity. The combined effects of IL-6 and TGF-β promoted Treg differentiation, while IL-23 promoted Th 17 differentiation.

The vitamin A metabolite retinoic acid, which is a major regulator of TGF-β dependent immune responses, blocks the secretion of IL-6 by Th17 cells and promotes Treg differentiation. The nuclear receptor RARα is an important downstream molecule of retinoic acid. Activated RAR α increased Foxp 3 expression and downregulated RORγt expression, thereby inducing Treg polarization and inhibition of Th17 polarization. Thus, retinoic acid can play a beneficial role in the progression of IBD by restoring the Th17/Treg ratio, thereby maintaining the balance of immune homeostasis *in vivo*.

Th1/Th2 ratio in IBD: The Th1/Th2 imbalance is a characteristic feature of the IBD. Th1 cells produce large amounts of IFN-γ, IL-2, and IL-18, while Th2 cells secrete IL-4, IL-5, IL-10, and IL-13. UC is associated with an aberrant th2-mediated response, and is characterized by elevated levels of IL-4, IL-5, IL-10, and IL-13; While CD was associated with an increased th1-mediated response and was accompanied by an elevated production of IFN-γ, IL-2, and IL-18. In ulcerative colitis, a non-classical Th 2 response is mediated by Natural Killer (NK) t-cells, leading to an increase in IL-13, which in turn leads to intestinal epithelium damage. Both cytokine profiles and Th subsets discriminate UC and Crohn's disease. The modulation of Th1/Th2 by infliximab can reverse colitis. In addition, altered Th1/Th2 ratio is considered a biomarker for interferon therapy and leucocytapheresis [9].

The immunoregulatory therapeutic roles of TCM in IBD

An evidence based, rational combination of TCM can have a synergistic effect in the management of IBD or reduce the side effects of drugs. The application of TCM (such as SLBZS, YPFS and SSW) on the basis of syndrome differentiation and treatment is a promising alternative therapy to treat IBD [10].

Shen Ling Bai Zhu San (SLBZS) and IBD: Shen Ling Bai Zhu San (SLBZS) is one of the most commonly used TCM formulations for the treatment of IBD patients. SLBZS comprised of ten commonly used herbs: *Atractylodes macrocephala* Koidz (Baizhu), *Ginseng* (Renshen), *Poria cocos* (Fuling), *Dolichos lablab* L (Baibiandou), *Dioscorea opposita* Thunb (Shanyao), *Glycyrrhiza uralensis* Fisch (Gancao), *Plumula Nelumbinis* (Lanzi), *Fructus amomi* (Sharen), *Semen coicis* (Yiyiren), and *Radix platycodonis* (Jiegeng). The most important individual herb of a formula is usually called as 'sovereign drug'. *Atractylodes*

macrocephala Koidz, Ginseng and *Poria cocos* are the sovereign drugs of SLBZS.

SLBZS is effective in ameliorating the clinical symptoms of IBD, such as diarrhea, abdominal pain and anorexia. SLBZS attenuated dss-induced colitis symptoms in mice by inhibiting the activation of ERK/p38 MAPK and NF-κ B signaling and showed that SLBZS treatment significantly decreased IL-1 β, IL-6, IL-8 and TNF-α and increased IL-4 and IL-10 levels in the intestinal mucosa [11].

SLBZS is also effective in curing Colitis Associated Colorectal Cancer (caCRC). Multiple studies have shown that SLBZS relieves gut microbial dysbiosis. Polysaccharides derived from SLBZS have shown the ability to alleviate microbial dysbiosis in UC and upregulate tryptophan metabolism of gut microbiota, leading to upregulation of Aryl-hydrocarbon Receptor (AhR) and Cyp1A1 to promote colonic IL-10 expression. An increase in Short Chain Fatty Acid (SCFA) producing microbiota and decrease in dysbiosis markers has been noted. Transcriptomic studies indicate that SLBZS can restore the function of MAPK signaling in colitis. Mechanistically, SLBZS can restore Th1/Th2 balance by downregulating the TLR7/NF-κB pathway.

Atractylodes macrocephala Koidz ('Baizhu' in Chinese): Atractylenolide I (AT-I) and Atractylenolide III (ATL-III) are the naturally occurring sesquiterpene compounds found in the rhizome of *Atractylodes macrocephala* antioxidant effects and can facilitate gastrointestinal motility, with gut microbial modulation. Ji, et al. showed that ATL-I inhibited the activation of ERK1/2, p38 MAPKs and NF-κB signaling pathways in RAW264.7. ATL-III inhibited the activation of ERK, p38, MAPKs and NF-κB, and in turn inhibited the expression of Nitric Oxide (NO), Prostaglandin E2 (PGE 2), TNF-α and IL-6 in mouse intestinal mucosal macrophages. Furthermore, ATL-I induced a stronger inhibition of TNF-α and NO production by lps-activated primary peritoneal macrophages than ATL-III. *Atractylodes macrocephala* administration promotes a Th2 type of response, with increased IL-4 and decreased interferon-γ production.

Ginseng ('Renshen' in Chinese): Ginseng Polysaccharide (GPS) or Panax polysaccharide comprises of polysaccharide compounds extracted from Ginseng. GPS inhibits colitis by reducing intestinal inflammation and its anti-inflammatory properties may play an important role in the chemoprevention of colorectal cancer.

In the TNBS-induced colitis model, the protective effect of GPS is associated with a reduction of colonic oxidative stress and C-Reactive Protein (CRP) due to a range of immunomodulatory activities including decreased IL-1 β, INF-γ, TNF-α, and IL-6. In another study, Wang, et al. found that oral GPS significantly reduced abdominal pain and diarrhea symptoms in an Azomethane (AOM)/dss-induced colitis-associated Colonic CRC (caCRC) mouse model by inhibiting IL-1 α, IL-1 β, and IL-6. The Treg differentiation assay showed decreased differentiation of CD4+ FoxP 3+ cells, showing Treg frequency and stronger inhibition by GBPE treatment [12].

***Poria cocos* ('Fuling' in Chinese):** *Poria cocos* is a saprophytic fungus growing in a variety of pine species. Kumalan is a polysaccharide compound extracted from *Poria cocos*. Several studies have shown that papaya exhibits significant anti-inflammatory activity in different experimental models of acute or chronic inflammation. Poria polysaccharides exert immunomodulatory activity by regulating the TLR4/TRAF6 signaling pathway. In a model of colitis, lower levels of pro-inflammatory cytokines and increased ant-inflammatory cytokines of the Pachyraman derivative CMP33 treatment were noted, and oleic acid and dihydrotestosterone emerged as probable targets. To increase the solubility of the polysaccharide, carboxymethylation was performed to obtain a carboxymethyl Poria cocos polysaccharide CMP33. Jeong, et al. showed that the ethanol extract (EPC) reduced LPS-induced NO and PGE 2 production in RAW264.7 macrophages in mouse intestinal mucosa by downregulating the protein iNOS and COX-2 levels and mRNA levels. In addition, EEPC also reduced LPS-induced production of proinflammatory cytokines, IL-1β, and TNF-α. These effects are mediated by the inhibition of the nuclear translocation of NF-κB. *Poria coccus* extracts have shown the ability to promote Treg differentiation *via* aryl hydrocarbon receptor activation [13].

Yu Ping Feng San (YPFS) and IBD: Yu Ping Feng San (YPFS) is a classic herbal formula that has been widely used in clinical treatment of various inflammatory diseases. YPFS comprises of three commonly used TCM herbs: *Radix astragalus* (Huangqi), *Atractylodes macrocephala* Koidz (Baizhu), *Saposhnikoviae radix* (Chuanxiong). *Radix astragalus* is the sovereign drug of YPFS. In a cell model, YPFS supressed iNOS and COX-2 expression in macrophages while promoting intestinal alkaline phosphatase in enterocytes, to produce anti-inflammatory effects. Zang, et al. found that YPFS powder can shorten the duration of disease and reduce the recurrence rate of diarrhea, and the potential mechanism of YPFS in IBD treatment may be related to the inhibition of NF-κB signaling pathway and regulate the colonic tryptophan metabolism. YPFS promotes IL-10 expression in a dose-dependent manner in LPS-stimulated macrophages, thus suggesting that the anti-inflammatory effect of YPFS may be mediated through IL-10. Macrophages express inflammatory mediators, including inducible Nitric Oxide Synthase (iNOS) and Cyclooxygenase 2 (COX-2), which are key enzymes in acute or chronic inflammation, including IBD [14].

Radix *Astragalus* ('Huangqi' in Chinese): *Astragalus* polysaccharides are a kind of polysaccharide compound extracted from Radix *Astragalus*. It can regulate T cell differentiation of and has immunomodulatory properties both *in vitro* and *in vivo*. *Astragalus* polysaccharides have been reported to promote the proliferation of B cells and increase cytokine production in B cells or macrophages. *Astragalus* polysaccharides could inhibit the expression of iNOS through NF-κB pathway in macrophages. In RAW264.7 APS has been shown to significantly inhibit no generation, the pro-inflammatory cytokine IL-1 β, TNF-α and the anti-inflammatory activity of APS is activated by inhibition of NF-κB.

Si Shen Wan (SSW) and IBD: SSW comprises of ive commonly used herbs: *Psoralea corylifolia* L (Buguzhi), *Ziziphus Jujubae* Mill (Dazao), Rutaecarpae (Wuzhuyu), *Semen myristicae* (Roudoukou) and Fructus *Schisandrae chinensis* (Wuweizi), which are used to treat diarrhea. *Psoralea corylifolia* L is a major

component of SSW. Recently, it has been used in the treatment of IBD, allergic colitis, and irritable bowel syndrome, among others [15].

Liu et al. reported that SSW increased the mRNA expression of IL-4 and IL-10, which in turn inhibited the production of proinflammatory cytokines TNF-α and IL-1 in dss-induced mouse colitis, and had the same mechanism in the treatment of TNBS-induced colitis in rats. Wang et al. showed that SSW downregulated the expression of inflammatory factors (IFN-γ, IL-1 β and IL-IL-17), as well as increased the expression of IL-4. Moreover, some reports have suggested that the therapeutic effect of SSW on chronic colitis is mediated by the inhibition of NF-κB activation by inhibiting the NEMO/NLK signaling pathway. Other researchers have also reported that SSW regulates the function of T follicular helper cells by inhibiting Bcl-6/Blimp-1 signaling and JAK/STAT pathway, thus achieving therapeutic effects on IBD.

***Psoralea corylifolia* L ('Buguzhi' in Chinese):** Bavachin is a flavonoid compound isolated from the Chinese herb *Psoralea corylifolia* L. psoralin has been used to treat clinically presenting gastrointestinal symptoms and various forms of inflammatory disease [16].

The Bavachin protein inhibited NO production in RAW 264.7 macrophages activated by IFN-γ. Mechanistic studies showed that Bakciol inhibited iNOS mRNA expression by inactivating NF-κB. The Bavachin protein decreased the Lps-induced production of IL-6 and IL-12p40, and decreased the activation of MAPKs and NF-κB. Bavachin Also inhibited inflammatory cytokine production and activation in LPS-stimulated mouse peritoneal macrophages. And the inhibition of inflammatory factor production in the RAW 264.7 cell line by inhibiting NF-κB [17].

Discussion

Other compous of TCM in the treatment of IBD

***Andrographis paniculata* ('Chuanxinlian' in Chinese):** *Andrographis paniculata* is a polysaccharide compound isolated from the Chinese herbal medicine *L. andrographia*. *Andrographis paniculata* has been used to treat inflammatory diseases, such as IBD [18].

To investigate the effect of *Andrographis paniculata* on Th cell-specific cytokine production, we generated Peripheral Blood Mononuclear Cells (PBMCs) isolated from IBD patients and treated with 10, 20 or 30 μg/ml *Andrographis paniculata*. Another meaningful study involving HMPL-004 (Andrographia extract), the expression levels of pro-inflammatory factors (TNF-α, IL-1 β, IL-22, IN-2 and IFN-γ) significantly decreased in HMPL-004, but the IL-10 increased. These results suggest that andrographolide and HMPL-004 are potentially applicable in IBD therapy.

Wormwood ('Kuai' in Chinese): Two active substances have been shown to be responsible for the anti-inflammatory effect against Artemis in IBD. The first one is the cardamonin. Cardamom is a sulfur species isolated from wormwood. The second is flavonoids isolated from wormwood.

Cardamonin reduces NO release and iNOS expression in human intestinal epithelial cells. Cardamonin has also been shown to reduce TNF-α in mouse peritoneal macrophages after LPS treatment. A flavonoid isolated from wormwood was also shown to exhibit anti-inflammatory activity [19].

Evodiae fructus ('Wuzhuyu' in Chinese): Eodiamine (EVO) is a quinolone alkaloid that is an essential ingredient from fruit. EVO has been shown to have antitumor, anti-inflammatory, antioxidant, and other therapeutic capabilities.

The inability of EVO to inhibit TNF-α production activates peritoneal macrophages *in vitro*, thus suggesting that EVO may directly affect the way macrophages behave or may have other target cells. EVO can produce TNF-α, such as activated NK cells, T cells, including: γδ T cells and natural killer T cell. Furthermore, Fan et al showed that EVO promotes the secret of IL-10 and reduces the production of IL-1 β, IL-6, and TNF-α in lps-stimulated microvascular endothelial human colonic cells.

Salvia miltiorrhiza radix ('Danshen' in Chinese): Tanshinone IIA (Tan IIA) is a diterpene quinone compound that can be purified from *Salvia miltiorrhiza*. Tan IIA inhibited NO production and expression of iNOS and interleukin IL-1 β in activated RAW 264.7 cells. Furthermore, Jang et al showed that Tan IIA inhibited the production of NO, TNF-α, IL-1 β and IL-6 and inhibited the expression of iNOS in activated RAW 264.7 cells. Bai et al. reported that Tan IIA improved TNBS-induced cells and reduced the production of TNF-α, IL-1 β, IL-IL-6 and INF-γ in inflammatory tissues in colitis [20].

Conclusion

TCM has a long history in treating IBD. Elucidating the molecular mechanisms related to the role of TCM in this context is crucial to defining the active ingredients, standardizing and establishing efficacy. The role of TCM in treating IBD mainly involves immune regulation of T cell responses and inhibition of MAPK/NF-κB ERK1/2 and p38NEMO/NLK, p38 MAPK and Bcl-6/Blimp-1 signaling, inhibition of TNF-α IL-1 IL-6 IL-8 IL-12 p 40 IL-22, IL-23 and IFN-γ upregulate anti-inflammatory cytokines IL-4 and IL-10. Taken together, the available data clearly demonstrate that SLBZS, YPFS, and SSW induce a mechanistic role in alleviating IBD.

TCMs (such as SLBZS, YPFS and SSW) that exhibit clear molecular effects in IBD and may provide new drug candidate therapeutic or adjuvant drugs for the clinical treatment of IBD. Moreover, from the perspective of health economics, the promotion and use of TCM may offer significant benefits in the management of IBD. However, systematic reviews have highlighted significant clinical heterogeneity and quality issues. Further clinical and experimental studies are needed to study the exact molecular mechanism and drug compatibility of TCM components to expand their application in clinical practice.

Conflict of Interest Statement

The authors declare no conflicts of interest.

Funding Sources

This work was supported by National Key Research and Development Program of China (2020YFC0845400), National Natural Science Foundation of China (82073901), Shanghai Scientific Research Program on Prevention and Treatment of COVID-19 in Traditional Chinese Medicine (2020XGKY10), Shanghai Science and Technology Innovation Action Plans (20S21901500) and a high-level project of Shanghai University of traditional Chinese Medicine.

Author Contributions

Hui Liu conceptualized the study, performed the literature search, data compilation, manuscript drafting, editing and revision.

References

1. Xavier RJ, Podolsky D (2007) Unravelling the pathogenesis of inflammatory bowel disease. Nature 448:427-434
2. Ng SC, Shi HY, Hamidi N, Underwood FE, Tang W, et al. (2017) Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. Lancet 390:2769-2778
3. Flynn S, Eisenstein S (2019) Inflammatory bowel disease presentation and diagnosis. Surg Clin North Am 99:1051-1062
4. Peyrin-Biroulet L, Panes J, Sandborn WJ, Vermeire S, Danese S, et al. (2016) Defining disease severity in inflammatory bowel diseases: current and future directions. Clin Gastroenterol Hepatol 14:348-354
5. Guan Q (2019) A comprehensive review and update on the pathogenesis of inflammatory bowel disease. J Immunol Res 2019:7247238.
6. Neurath MF (2019) Targeting immune cell circuits and trafficking in inflammatory bowel disease. Nat Immunol 20:970-979
7. Ahlawat S, Kumar P, Mohan H, Goyal S, Sharma KK (2021) Inflammatory bowel disease: tri-directional relationship between microbiota, immune system and intestinal epithelium. Crit Rev Microbiol 47:254-273
8. Sulz MC, Burri E, Michetti P, Rogler G, Peyrin-Biroulet L, et al. (2020) Treatment algorithms for Crohn's disease. Digestion 101:43-57
9. Nakase H, Uchino M, Shinzaki S, Matsuura M, Matsuoka K, et al. (2021) Evidence-based clinical practice guidelines for inflammatory bowel disease 2020. J Gastroenterol 56:489-526
10. Zhang B, Gulati A, Alipour O, Shao L (2020) Relapse from deep remission after therapeutic de-escalation in inflammatory bowel disease: a systematic review and meta-analysis. J Crohns Colitis 14:1413-1423
11. Marehbian J, Arrighi MH, Hass S, Tian H, Sandborn WJ (2009) Adverse events associated with common therapy regimens for moderate-to-severe Crohn's disease. Am J Gastroenterol 104:2524-2533
12. Ng SC, Lam YT, Tsoi KK, Chan FK, Sung JJ, et al. (2013) Systematic review: the efficacy of herbal therapy in inflammatory bowel disease. Aliment Pharmacol Ther 38:854-863
13. Yuan S, Li Y, Li J, Xue JC, Wang Q, et al. (2022) Traditional Chinese medicine and natural products: potential approaches for inflammatory bowel disease. Front Pharmacol 13:892790
14. Yan JB, Luo MM, Chen ZY, He BH (2020) The function and role of the Th17/Treg cell balance in inflammatory bowel disease. J Immunol Res 2020:8813558
15. Brandtzaeg P, Carlsen HS, Halstensen TS (2006) The B-cell system in inflammatory bowel disease. Adv Exp Med Biol 579:149-167
16. Castro-Dopico T, Colombel JF, Mehandru S (2020) Targeting B cells for inflammatory bowel disease treatment: back to the future. Curr Opin Pharmacol 55:90-98
17. Mahida YR (2000) The key role of macrophages in the immunopathogenesis of inflammatory bowel disease. Inflamm Bowel Dis 6:21-33
18. Zenewicz LA, Antov A, Flavell RA (2009) CD4 T-cell differentiation and inflammatory bowel disease. Trends Mol Med 15:199-207
19. Dige A, Stoy S, Rasmussen TK, Kelsen J, Hvas CL, et al. (2013) Increased levels of circulating Th17 cells in quiescent versus active Crohn's disease. J Crohns Colitis 7:248-255
20. Murphy KM, Reiner SL (2002) The lineage decisions of helper T cells. Nat Rev Immunol 2:933-944