DOI: 10.15806/j.issn.2311-8571.2016.0043 World J Tradit Chin Med 2017; 3(2): 20–30

Review

Mechanism of Traditional Chinese Medicine on Intestinal Mucosal Immunity in Chronic Intestinal Diseases

Lin Lv[a#], Feng-Yun Wang[a#], Xiang-Xue Ma[a], Ting Chen[a], Hai-Jie Ji[a], Zheng-Yi Chen[a], Ya-Xin Tian[a], Li-Qun Bian[a], Bei-Hua Zhang[a], Xiao-Lan Yin[b], Xu-Dong Tang[a]*

[a]Gastroenterology Department, Xiyuan Hospital of China Academy of Chinese Medical Sciences, 1, Xi Yuan Yard Road, Beijing 100091, China
[b]School of China Academy of Chinese Medical Sciences Beijing,100700
[#]These authors contributed equally to this work
**Correspondence:* Xu-Dong Tang, MD, Professor of Medicine, Director of the hospital, Gastroenterology, Gastroenterology Department, Xiyuan Hospital of China Academy of Chinese Medical Sciences, 1, Xi Yuan yard Road, Beijing 100091, *E-mail:* China.txdly@sina.com

ABSTRACT

Although irritable bowel syndrome (IBS) and inflammatory bowel disease (IBD) are clinically common diseases with unclear pathogenesis, both of them are related to the immune system. With progress in studies on their pathogenesis, the two diseases are currently believed to be associated with the presence of intestinal inflammation and intestinal mucosal immune disorder. In recent years, a new approach for the prevention and treatment of chronic intestinal disease is to protect the complete structure and normal immunity of the intestinal mucosal barrier during the treatment of intestinal diseases. However, traditional Chinese medicine (TCM) may have more advantages in regulating the imbalance of the intestinal immune microenvironment, as various single herbs and compounds of TCM have been investigated from the perspective of immune regulation. The use of TCM is prevalent in China. The effectiveness of these therapies appears to be supported by preliminary evidence and clinical experience, although the mechanisms that underlie these effects will require further research. In this paper, with common chronic bowel diseases including IBS, ulcerative colitis and Crohn's disease as the research objects, the relationship between TCM and immunity was explored from the perspectives of the pathogenesis of intestinal mucosal immune injury, the correlation between TCM syndromes and immune disorders, and TCM immune regulation. Moreover, the problems and limitations of the present study were pointed out, and several suggestions were proposed. The purpose of this article is to explore the potential mechanism of TCM on intestinal mucosal immunity in chronic intestinal diseases.

Key words: Irritable Bowel Syndrome, Inflammatory Bowel Disease, Immune Disorder, TCM Immune Regulation
Received 16 September 2016; Accept 29 March 2017

Introduction

Chronic bowel diseases are common, frequently-occurring digestive diseases, with an overall incidence of nearly 20% of the population. Although their pathogenesis still remains unclear, some factors, such as gastrointestinal motility disorders, visceral hypersensitivity, immune activation, brain-gut axis dysfunction, and psychological factors, play an important role in the pathogenesis and progression[1,2]. As the causes of chronic intestinal diseases, gastrointestinal infection and mucosal inflammation have drawn increasing concern in recent years. In this paper, with irritable bowel syndrome (IBS) and inflammatory bowel disease (IBD) as representative examples, the role of gastrointestinal mucosal inflammation and immunity in the pathogenesis was investigated, and the mechanism of TCM in treating chronic gastrointestinal diseases through immune regulation was described. On this basis, the advantages of TCM in the treatment of chronic gastrointestinal diseases were put forward.

The main symptoms of IBS include abdominal pain or discomfort, which can be improved after a bowel movement. The syndrome is often accompanied by a functional bowel disorder that leads to change in bowel habits, but the cause has not yet been clear. In recent years, the role of low-grade bowel inflammation in the intestinal immune mechanism of IBS has gained increasing attention[3,4]. Intestinal immune disorders affect the immune barrier function of the intestinal mucosa, thereby causing IBS symptoms. Immune disorders in patients with IBS are reflected in the generally increased levels of peripheral blood cytokines IL-1β, IL-8, IL-10, and TGF-β[5,6], and an increase in the number of mast cells of the terminal ileum, ileocecal junction, cecum, colon and rectal mucosa[7]. This immune disorder is primarily resulted from an imbalance between the anti-inflammatory cytokines and pro-inflammatory cytokines, manifesting as increased levels of pro-inflammatory cytokines, such as IL-6, IL-8, TNFα and IL-1β[8], decreased levels of anti-inflammatory cytokines like IL-4 and IL-10[9], resulting in damages to the intestinal mucosal barrier. Thus, immune disorders are not only manifested locally in the intestinal mucosa, but also involve the systemic peripheral blood, eventually leading to damages to the intestinal mucosal barrier and giving rise to IBS symptoms.

IBD includes ulcerative colitis (UC) and Crohn's disease (CD). IBD is an idiopathic inflammatory bowel disease, involving the ileum, rectum, and colon, with main clinical manifestations of diarrhea, abdominal pain, and even blood in stool. UC is a continuous inflammation of the colonic mucosa and submucosa, which usually first involves the rectum and gradually spreads to the entire colon. CD is a non-continuous transmural inflammation that may affect the

whole digestive tract, with the terminal ileum, colon and anus as its most commonly sites of involvement. Although etiology and pathogenesis of both diseases have not yet been entirely clear, it is currently known that inflammations induced by abnormal responses in the intestinal mucosal immune system play an important role in the pathogenesis of IBD[10-12], and the role of the intestinal epithelial barrier and intestinal mucosal immunity in the pathogenesis of IBD has also been verified[13]. In terms of immune disorders, CD is manifested as overexpression of IL-12 and (or)IL-23 and IFN-γ and (or) IL-17 observed in the intestinal mucosa[14,15], while UC is manifested as increased levels of IL-1β, TNF-α, IFN-γ and IL-13 in the intestinal mucosa[16,17]. Both UC and CD show increased intestinal mucosal immune responses, resulting in damages to the intestinal mucosal barrier.

Since IBS and IBD share similar damages to the intestinal mucosal barrier, involving the immune system, the pathogenesis of both diseases is related to the damages to the intestinal mucosal immune barrier. At present, clinical treatment is basically symptomatic management, while IBS is also confronted with the troublesome problem of side effects that are prone to occur after the combined use of biological agents and immuno suppressive agents. However, TCM has a good clinical efficacy in the treatment of IBS and IBD. In further studies on the mechanism of single herbs and compounds of TCM, it was also found that many classic compounds used for treatment of chronic bowel diseases could regulate immunity, with rarely reported adverse effects. Since there are still some problems existing in the TCM treatment of chronic bowel diseases, it is necessary to carry out further studies on the regulation mechanism of TCM on the intestinal immune barrier in the treatment of chronic bowel diseases.

Intestinal Mucosal Inflammation and Chronic Intestinal Disease

Intestinal Mucosal Inflammation and Immune Barrier

The intestinal mucosal immune barrier is one of the most important barrier to the body, and its function is implemented by the gut-associated lymphoid tissue (GALT) located under the intestinal mucosa[18], including the intestinal aggregated lymph nodes, mesenteric lymph nodes, intraepithelial and lamina propria diffuse lymphoid tissue, and the cytokines and immunoglobulins produced by them[19]. The surface of intestinal lymphoid follicles is covered with a layer of follicle associated epithelium, composed of microfold cells (M cells), intestinal epithelial cells, and lymphocytes, all of which can capture, process and present the antigens to the effector cells, such as T cell, B cell and natural killer cell. It is generally believed that the mucosal follicles are the inductive sites of immune response, while the diffuse lymphoid tissues are the outgoing sites of immune response, to where the sensitized lymphocytes are migrated. By the secretion of cytokines, the immunoglobulins and cytotoxicity exert biological effects, which are primarily the humoral immunity mediated by secretory immunoglobulin A (sIgA), supplemented by the cellular immunity mediated by cytotoxicity[20].

More and more studies have found that the complex constellation of symptoms of chronic gastrointestinal diseases can only be interpreted as paresthesia and motility disorders, however, more attention has been paid to low-grade inflammation and mucosal immune disorder in recent years[21]. The changes in local immune microenvironment after intestinal infection affect the immune and neural regulation of the intestinal tract, causing visceral sensory dysfunction and intestinal motility disorders and generating associated symptoms.

Intestinal Mucosal Immune Mechanism of IBS

Irritable bowel syndrome is the most common type of chronic bowel diseases, whose pathogenesis is generally believed to be associated with the "brain-gut axis" dysfunction, and it can be divided into four subtypes, i.e., constipation-predominant IBS, diarrhea-type IBS, mixed IBS, and uncertain form IBS. Some data showed that 1/3 of patients with IBS were found with symptoms after acute intestinal infection, and after intestinal infection, 1/4 patients were found with symptoms alike IBS. Compared with the healthy control group, after infection, the intestinal tract in patients with IBS was found with mild inflammation[22], proliferation of inflammatory cells and immune cells such as mast cells, macrophages and endocrine cells[23,6], increased epithelial permeability, accumulation of inflammatory cells, and increased release of inflammatory mediators[2]. Further studies found that IBS patients without a history of infection also showed inflammatory cell infiltration in the intestinal mucosa. Recently, it has been hypothesized that IBS is a type of chronic low-grade inflammatory disease[24], which may also be related to the activation of intestinal immune effector cells induced by factors like stress and food allergies[9]. Studies found that patients with IBS showed significantly increased amounts of mast cells and lymphocytes in the intestinal mucosa[25], and especially the activation of the intestinal mucosa mast cells and the occurrence of IBS have become a hot topic of research[26]. Mast cell is a kind of important immune cells with immune activity that can secret a variety of mediators. The intestinal mucosa mast cells are extremely close to the course of the intestinal nerve fibers, and even a small number of mast cells were observed to have connected with the nerve fiber cells via cell membranes[27]. The intestinal mast cells in patients with IBS release media (mainly composed of histamine and tryptase) that excite the visceral sensory nerves in rats, while antihistamines can inhibit the conduction of excitement through its dorsal root ganglion. Hence, it is speculated that the activation of mast cells is closely related to the incidence of intestinal visceral hypersensitivity[28]. Recent researches showed that inhibiting the degranulation of mast cells could increase the tolerance of visceral sensitivity in patients with IBS, and reduce diarrhea and improve quality of life[29,30]. The specific mechanism is related to the cell adhesion molecule-1 (CADM1), which has been newly identified. The interactions between mast cells, nerve cells and smooth muscle cells increase the nerve sensitivity to stimulus and the contraction of smooth muscle cells.

In addition,the imbalance of intestinal mucosa cytokines of IBS is also a manifestation of intestinal mucosal inflammation. Studies found that, for PI-patients with IBS (Post infectious or post inflammatory irritable bowel syndrome,PI-IBS), expression levels of IFN-γ in the colonic mucosal tissues were significantly higher than the control group, while the levels of IL-10 were significantly lower than the control group[31]. Animal studies have also shown that mice with PI-IBS were found with significant increase in IFN-γ and IL-17 in the duodenum and ileum, while IL-10 was significantly decreased in the jejunum, ileum and colon[32]. These results suggest that, in IBS, imbalance between the intestinal mucosal anti-inflammatory cytokines and pro-inflammatory cytokines occurs, inducing the intestinal inflammation and immune activation, and the gastrointestinal motility and visceral sensitivity are affected by the release of a large number of inflammatory cytokines, which act on the gastrointestinal smooth muscle, enteric nervous system, and interstitial cells of Cajal.

Intestinal Mucosal Immune Mechanism of IBD

IBD is characterized by infiltration of local intestinal inflammatory cells and aggregation of soluble inflammatory mediators. A large number of neutrophils, lymphocytes, plasma cells, macrophages and eosinophils appear alternatively during the active stage, remission stage, and chronic stage of IBD[33]. As the central part of immunity, T lymphocytes play an important role in the development of IBD. With the deepening of the studies on the pathogenesis of IBD, scholars have found some new cell subsets, among the CD4+T cells, such as the regulatory T cell (Treg), helper T celll7 (Thl7)[34], with the former mainly involved in anti-inflammatory activities and immune tolerance and the latter mainly involved in pro-inflammatory activities. The balance between the Th17 cells and Treg cells is the key factor in maintaining intestinal immune homeostasis[35]. Patients with IBD could secret more Th17-associated cytokines, and colonic mucosal local and serum levels of Th17/IL-17 in active patients with IBD were significantly higher than the control group[36]. Increased levels of interleukins IL-21,IL-22 and IL-23, which are secreted by Th17, promote Th1 response, thus exacerbating the disease. IL-17 which is secreted by Th17 is also verified to be closely related to the incidence of inflammatory bowel disease[37], playing an important role in inducing and maintaining the inflammatory bowel disease and mucosal inflammation.

Patients with UC can be found with abnormal secretion of various cytokines in the local colonic mucosa, as well as the imbalance between the pro-inflammatory and anti-inflammatory effects. With the actions of various factors, the intestinal local chemokines aggregate a large number of activated macrophages, engulfing and processing the antigens, and maintaining a high level of IL-12, which in turn promotes the synthesis of TNF-α by macrophages and the secretion of IFN-γ by T cells, inducing the macrophages to secret a variety of pro-inflammatory cytokines, such as IL-6, TNF, IL-1, NO, and prostaglandin E2 (PGE2), thereby inducing inflammation[38]. In patients with UC, the number of cells secreted by IL-4 was reduced, and both the expression of IL-4 mRNA and the secretion of protein were significantly reduced, and therefore, IL-4 could be used as one of the indicators in monitoring the severity of UC. In active patients with UC, serum IL-10 levels were significantly lowered, especially significant in severe patients with large lesions, which showed an improvement during the remission stage but were still lower than the control group; the expression of IL-10 was also associated with the disease activity, showing a decreasing trend along with the aggravation of the disease. The serum IL-10 levels were negatively correlated with both the activity index of UC and CRP, and thus could be used as a reference indicator in assessing the status of UC. In patients with UC, both the serum and colonic mucosa IL-6 level were higher than those of the control group; in active patients with UC, the colonic mucosa IL-6 level was higher than that in the remission stage, but it had nothing to do with the lesion site or scope. The colonic mucosal expression of IL-1 and IL-8 mRNA was negatively correlated with the degree of inflammation of UC, and therefore could be used as an indicator in determining the clinical severity and efficacy of the disease[39]. Patients with UC also showed imbalance between subsets of lymphocytes $CD4^+$ and $CD8^+$, with reduced $CD4^+/CD8^+$[40].

CD is a kind of non-specific enteritis manifested as chronic granulomatous inflammatory lesions. Intestinal inflammation and mucosal tissue injury are the important features of CD. It is currently believed that the inflammation induced by the immune system abnormalities in the intestinal mucosa plays an important role in the pathogenesis of IBD. As the central part of immune regulation, T cells play an important role in the pathogenesis and development of the disease, and participate in a variety of immunity response to mucosal inflammation. Inappropriate increase or decrease in immune response can cause persistent tissue damages or inflammation[41]. Studies have shown that patients with CD might show increased proportions of $CD3^+$, $CD4^+$ and $CD8^+$ T along with the disease activity, positively correlated with CRP and negatively correlated with hemoglobin[42]. The pathogenesis of CD was also closely related to the imbalance in the differentiation of Treg cells/Thl7 cells, that is, inadequate Treg cells and excessive Thl7 cells[43,44].

The pathogenesis of chronic gastrointestinal diseases is still unclear, but associated with the immune system in many aspects (as shown in Table 1), including humoral immunity and cellular immunity. This leads to the prolonged, recurrent features of chronic gastrointestinal diseases.

Immune Mechanism of Various Syndromes of Chronic Bowel Diseases From the TCM Perspective

The main symptoms of chronic bowel disease include abdominal pain, diarrhea, pus and blood in stool, and constipation, which are recurrent, refractory and protracted. TCM believes that the spleen governs transportation and transformation, the stomach governs intake, the small intestine governs the transfusion of the clear and turbid, the large intestine governs the transferring of the dregs, and all of them jointly completed the digestion and absorption of water and grain, as well as

Table 1. Immune mechanism for chronic Intestinal diseases.

Author	Year	Journal	disease	Mechanism
Ashwood P	2004	Innamm Res	UC	IL-1↑,IL-8↑
Lee KJ	2008	J Gastroenterol Hepatol	IBS	MC↑
Kobayashi T	2008	Gut	IBD	Th17/IL-17↑
Zhou L	2008	Nature	CD	Treg↓,Thl7↑
Himmel M E	2008	Immunology	CD	Treg↓,Thl7↑
Spiller R	2009	Gastroenterology	IBS	MC↑
Matricon J	2012	Aliment Pharmacol Ther	IBS	MC↑
Chen J	2012	Gastroenterol	IBS	IFN-γ↑,IL-10↓
Monteleone I	2012	Curt Mol Med	IBD	IL-17↑
Liu SY	2013	Chin J Padia	UC	IL-12↑,IFN-γ↑,IL-6↑,IL-1↑
Yang DS	2014	Chin J Diabetes	UC	$CD4^+$↓,$CD4^+/CD8^+$↓
Yang B	2015	Gastroenterol	IBS	IFN-γ↑,IL-17↑,IL-10↓
Yuan BS	2015	Chin J Gastroenterol	CD	$CD3^+$↑,$CD4^+$↑,$CD8^+$↑

IBS: irritable bowel syndrome; IBD: inflammatory bowel disease; UC: ulcerative colitis; CD: crohn's disease; MC: mast cells; Treg: regulatory T cell; Thl7: helper T celll7; IFN-γ: Interferon-γ; IL-6:Interleukin-6.

the distribution of essence. In the presence of dysfunctions in the spleen, stomach, large and small intestines caused by the stimulation of various factors such as exogenous pathogenic factors, diets and emotions, symptoms including abnormal stools, diarrhea, constipation, or pus and blood in stool may occur. If the circulation of Qi and blood is blocked, or if Qi and blood are insufficient to keep warm, abdominal pain can occur. Clinically, the common syndromes of IBS include liver Qi stagnation, liver depression and spleen deficiency, and spleen-stomach deficiency; the common syndromes of IBS include large intestine dampness-heat, spleen-stomach deficiency, spleen-kidney yang deficiency, and blood stasis in intestine.

Various Syndromes and Immune Disorders of IBS

Ma Junjie et al.[44] found that, compared with healthy individuals, PI-patients with IBS showed increased Th1 (INF-γ, IL-2) but decreased Th2 (IL-4, IL-5), with a shift of Th1 /Th2 (INF-γ/IL-4, IL-2/IL-5) in the left. Serum Th1 (INF-γ, IL-2) indicator contents were ordered from high to low as liver Qi stagnation group, liver depression and spleen deficiency group, and spleen-stomach deficiency group; Th2 (IL-4, IL-5) indicator contents were ordered from high to low as spleen-stomach deficiency group, liver depression and spleen deficiency group, and liver Qi stagnation group; Th1/Th2 (INF-γ/IL-4, IL-2/IL-5) indicator contents were ordered from high to low as liver Qi stagnation group, liver depression and spleen deficiency group, and spleen-stomach deficiency group, three of which are the clinically common syndromes of IBS[45]. Through comparison of the three syndromes--liver depression, spleen deficiency, and liver depression and spleen deficiency--in rat immunity model, Zhao Ronghua et al.[46] found that immune dysfunction existed in the three syndromes to some degree, and that compared with the control group, serum IL-2, IL-6, and thymus and spleen indicators in rats of all the 3 groups were significantly decreased (P<0.05); in liver depression group, serum IL-1 was significantly decreased, and TNF-α was significantly increased (P<0.05); in liver depression and spleen deficiency group, serum IL-1 and TNF-α were significantly increased (P<0.05), and T lymphocytes proliferation in the spleen was significantly decreased (P<0.05).

Various Syndromes and Immune Disorders of IBD

In the syndrome distribution of TCM, UC is mainly manifested as the large intestine dampness-heat and the spleen-kidney yang deficiency, followed by the blood stasis in intestine. In particular, UC syndromes in the active stage are ordered from common to uncommon as large intestine dampness-heat, liver depression and spleen deficiency, and blood stasis in intestine; syndromes in the remission stage are primarily the spleen and stomach Qi deficiency and the spleen-kidney yang deficiency[47]. In order to clarify the immunological characteristics of different TCM syndromes of UC, Zhang Shumei et al[48] found that, comparing the excess syndromes of UC (the dampness-heat and the Qi stagnation and blood stasis) with spleen-kidney yang deficiency, T cell subsets were changed in both the excess and deficiency syndromes, with the former largely manifested as hyperthyroidism of helper T cells functions, and the latter largely manifested as hyperthyroidism of suppressor T cells functions. Since the excess syndromes of UC showed higher levels of IL-6 and IL-8 than the deficiency syndromes and the mixed syndromes, IL-6 and IL-8 could be used to classify the TCM syndromes and to provide a reference in determining excess and deficiency syndromes, especially; since IL-6 and IL-8 levels in the active stage were higher than in the remission stage, IL-6 and IL-8 were also of a certain reference value in the stage classification of UC[47]. Through observation on the expression of T lymphocytes subsets in the colonic mucosa in patients with UC, Change Tingmin et al.[49] found that $CD4^+$ was significantly decreased and $CD8^+$ was significantly increased in the dampness-heat; $CD4^+$ was significantly decreased and $CD8^+$ was slightly increased in the Qi stagnation and blood stasis; $CD4^+$ was slightly decreased and $CD8^+$ was slightly increased

in the spleen-kidney deficiency; $CD4^+$ was slightly decreased and $CD8^+$ was significantly increased in the yin-blood deficiency. Immune disorders of the Th cells subsets extensively exist in the development and progression of IBD. Through studies on the correlation between TCM Syndromes and T cell subsets in patients with IBD, Gao Yan et al.[50] discovered that, for patients with UC in the active stage, the changes in T lymphocytes subsets of the peripheral blood were mainly manifested as increased levels of $CD3^+$ and $CD8^+$, decreased level of CD4 and ratio of $CD4^+/CD8^+$; patients with CD mainly manifested as decreased levels of $CD3^+$, $CD4^+$ and $CD8^+$, and increased ratio of $CD4>CD8^+$. With the increase in severity, for UC, $CD4^+$ level was decreased, and $CD8^+$ level was increased; for CD, $CD4^+$ level was increased, and $CD8^+$ level was decreased. According to the above findings, both UC and CD are immunological diseases caused by the imbalance of $CD4^+/CD8^+$ and the broken immune homeostasis in the body. According to the above studies, in the active stage of UC, the mechanism of immune injury is related to the pathogenesis of TCM excess syndromes, while in the remission stage, the mechanism of immune injury is related to the pathogenesis of TCM deficiency syndromes. This implies that the TCM understanding of the pathogenesis of IBD, "deficiency in origin and excess in superficiality, with origin deficiency in the attack stage, and superficiality in the remission stage", is consistent with the immune pathogenesis in the active stage and the remission stage proposed by modern medicine.

Immune Regulation of TCM

Over the years, in the numerous studies on the related mechanism of TCM, many single herbs and compounds have been discovered to be able to regulate immunity. TCM theory holds that spleen and stomach disorders, i.e., disorders of the ascending and descending of Qi activities, are the major pathogenesis of gastrointestinal diseases, including non-digestion and non-absorption of food, no ascending or descending of Qi, and exessive driness and dampness in nature. Therefore, the treatment for chronic gastrointestinal disease is to regulate these abnormal states. By tonifying deficiency and expelling excess and regulating Qi activities, the spleen-stomach system is promoted to restore the interdependence of ascending and descending, the coordination between containing and digestion, and balance between dryness and dampness. "Regulation" is the key focus. See details in single herbs and compounds. Compounds are often used in a way of "invigorating spleen and supplementing qi" both for cold and heat, activating Qi and blood circulation.

Immune Regulation by Single Herbs

Total glucosides of paeonia (TGP) is the effective composition extracted from the root of paeonia Lactiflora, including paeoniflorin, albiflorin, oxypaeoniflorin, and paeonin. Researches[51] showed that total glucosides of paeony can significantly improve the colonic morphology and histopathology in rats with experimental colitis, thereby protecting the rats; it can inhibit pro-inflammatory cytokines like TNF-α and promote anti-inflammatory cytokines like IL-10; it can also inhibit the activation of ρ38MAPK and secretion of TNF-α, promote the secretion of IL-10, and improve immune disorders. Wang Bin et al.[52] also found that, after treatment with paeoniflorin for UC model rats, serum IL-2,IL-6 levels were both significantly decreased, while IL-10 level was significantly increased. Thus it was speculated that paeoniflorin may regulate the intestinal abnormal immune response by expression of pro-inflammatory and anti-inflammatory cytokines, thereby taking therapeutic effects.

Astragalus polysaccharide is extracted from astragalus mongholicus bunge or astragalus membranaceus, and concentrated and purified into water-soluble heteropolysaccharide, which has the effects of anti-aging, antioxidant and immunity-regulating. Gao Yongjian[53] found that Astragalus polysaccharides regulates the immune function in two ways, and the different doses show different effects on the colitis, as a small dose of Astragalus polysaccharides can promote the expression of anti-inflammatory cytokines, increasing the levels of IL-4 and IL-10 expressions to take protective effect against colitis; since the expression of the transcription factor Tbet/GATA3 affects the balance of Th1/Th2, a small dose of Astragalus polysaccharides can increase the ratio of Tbe/GATA3 that was decreased abnormally due to immune regulation; while a large dose of Astragalus polysaccharides will instead aggravate the severity of colitis. Ko et al.[54] verified that both oral dose and colonic administration of Astragalus polysaccharides could ease the colitis and protect the colon in mice, by regulating the colonic cytokines.

Also known as Chinese goldthread, berberine is an alkaloid extracted from coptis and cortex phellodendri, with heat-clearing and detoxifying effects. It is proven effective in antibacterial treatment of diarrhea, with immunomodulatory and other pharmacological effects. Shu Dezhong et al.[55] suggested that the antioxidant effect of berberine hydrochloride could reduce the injury induced by dextran sulfate sodium to colonic mucosa in mice, and simultaneously reduce the infiltration of inflammatory cells, reducing colonic mucosal inflammation in mice. By inhibiting activation of NF-κB, the transcription of inflammatory cytokines was prevented, and inflammation was therefore reduced. Hong et al.[56] found that berberine hydrochloride could regulate the balance between Th1 and Th2 in mice with experimental colitis by promoting expressions of IFN-γ and IL-12 and inhibiting expressions of IL-4 and IL-10, thereby reducing inflammation. Cao et al.[57] found that berberine could protect the intestinal mucosal barrier in patients with IBS, by antagonizing the structural and functional damages of pro-inflammatory cytokines TNF-α and IFN-γ to the intestinal epithelial tight junction, via the signal pathway of MLCK-MLC phosphorylation.

Originated from the dried rhizome of Turmeric of zingiberaceae, curcumin is abundant and cheap, with fewer adverse reactions, and can take anti-inflammatory effects by regulating the release of cytokines[58]. Curcumin can decrease the levels of pro-inflammatory cytokines IL-1α, IL-1β, IL-2, IL-6, IL-8, IL-12, IL-17 and IL-23, all of which are closely related to the pathogenesis and development of UC. Meanwhile, curcumin can increase the levels of anti-inflammatory cytokines IL-4,

IL-10, and IL-13, thereby reducing inflammatory responses[59]. Yi Jinxia et al.[60] treated UC with curcumin combined with marrow mesenchymal stem cell (MSCs), and the mechanism of the immune regulation was achieved by controlling the percentage of Th17 and Treg cells.

Hedyotis diffusa is a plant in the Hedyotis genus of the Rubiaceae family, whole plant with roots, also known as snake tongue grass, with the heat-clearing, detoxifying, inducing diuresis, reducing edema, analgesic, anti-cancer, and enhancing immunity effects. Its extract, total flavones of oldenlandia diffusa (FOD) shows an obvious anti-inflammatory effect for mice with UC, and its mechanism may by related to inhibiting the activation of NF-κB p65, reducing the expression of pro-inflammatory cytokines IL-8 and TNF-α, and increasing the expression of anti-inflammatory cytokines IL-10[61].

Triptolide is a kind of diterpene lactone epoxide compounds extracted from the Celastraceae Tripterygium, as one of the active components of Tripterygium, with anti-inflammatory and immunosuppressive effects. Triptolide can reduce the severity of inflammatory bowel diseases in mice by lowering the expression of TLR2 and TLR4 in CD colon, inhibiting the expression of MyD88, NFκBp65, and IL-17, and inhibiting the conduction of transcription factor STAT-3 via trans-signaling induced by IL-6[62]. Tripterygium glycosides have a therapeutic effect on CD, and its mechanism may be related to interference of TGF-β1/Smad signaling pathway. The expressions of mRNA of colonic tissues Smad3 and Smad4 were decreased, expression of mRNA of Smad7 was increased, and expressions of TGF-β1 and p-Smad2/3 proteins were decreased[63].

Patrinia is the rhizome and whole plant with roots of perennial herbs, Patrinia scabiosaefolia Fisch and Patrinia villosa Juss, with effects of heat-clearing, detoxifying, discharging pus, and promoting blood circulation to remove blood stasis. After treatment with this extract, in UC model rats, colonic tissue lesions were obviously eased, the ulcer was healed, crypt abscess disappeared, congestion and edema were significantly mitigated, inflammatory cell infiltration was significantly reduced, and serum TNF-α and IL-1β levels were significantly lowered[64].

Sinomenine is an alkaloid monomer extracted from caulis sinomenii or Sinomenium acutum var. cinereum. Studies found that it had anti-inflammatory and immunomodulatory pharmacological effects. Studies have shown that Sinomenine can significantly improve the intestinal mucosal inflammation in rats with colitis, and inhibit the secretion of IL-1β and TNF-α[65]; Sinomenine can improve the severity of colitis in UC model mice, by down-regulating the levels of miRNA155 and other inflammatory cytokines[66].

Immune Regulation by Classic Formula

By determining etiologic factor based on differentiation and thus determining treatment methods, according to the principles of formulating prescription, TCM classic formula selects the appropriate combination of drugs and decides the usage and dosage. The classic formulas are the representative prescription for a certain syndrome, which have been clinically used repeatedly with exact clinical efficacy.

Liu[67] found that Huoxiang Zhengqi Liquid (Patchouli Qi-Righting Liquid) could significantly improve the tight junctions of intestinal epithelium in rats with PI-IBS, regulating the expression and distribution of ZO-1 and Occludin protein, thereby strengthening the function of intestinal mucosal barrier, and improving the increased intestinal mucosal permeability caused by inflammation. Studies have shown that[68] Sijunzi Decoction (Four Gnetlemen Decoction) could enhance the function of intestinal mucosal barrier in children with megacolon. The formula can not only enhance the intestinal immunity, but also maintain the integrity of the intestinal mucosal barrier. Sishen Pill (Four Miracle Pill) regulates the intestinal abnormal immune response by down-regulating the expressions of IL-1β and TNF-α and increasing the expression of IL-4[69]. Through investigations on Tongxieyao Formula (Pain and Diarrhea Formula)in UC model rats, Zhu Xiangdong et al.[70] found that the immune regulation might be related to the activation of the signal pathway of PPAR-1/NF-κB. However, the inflammation reduction in UC model rats by Glycyrrhizae Decoction for Clearing Stomach-Fire is related to the expression of NF-κB p65[71]. Through treatment with Flavored Coptis Rectifying Decoction combined with mesalazine, Wang Weifeng et al.[72] found increased level of serum IL-10 and decreased level of TNF-α in patients with UC in the active stage. Cheng Chanhe[73] and Liu Xiping[74] et al. found that Shenling-Atractylodes Powder (whose sovereign medicinals are ginsen, poria and white Atractylodes rhizome) could not only improve the spleen index and promote the phagocytosis of peritoneal macrophages in mice with chronic diarrhea, but also lower the expressions of CD44 and (soluble adhesion molecules P-selectin) CD62p in rat model with spleen deficiency, thereby improving the positive response of the intestinal mucosa. Sun Yang et al.[75] found that dark plum pill (dark plum, asarum, dried ginger) could decrease the expression levels of TLR4,NF-κBp65 proteins of the colonic mucosal tissues in UC rat model, thereby regulating immunity.

Immune Regulation by Self-Designed Formula

Under the guidance of TCM theory, combining our own clinical experience with the basis of classic formulas, it is a common clinical practice to employ self-designed formula by combining the drugs for treatment. The self-designed formulas have supplemented and improved the prescriptions which are clinically effective but have not been previously recorded, thus enriching the content of TCM formulas.

Liu Tielong et al.[76] adopted self-designed formula (fried white peony,fried Atractylodes, and radixsileris) in the treatment for IBS, and results showed that $CD4^+$ level was increased and $CD8^+$ level was decreased. Liu Jiemin et al.[77] and Liu Xianzhi et al.[78] adopted self-designed formula (Bupleurum, Codonopsis pilosula, white peony, Immature Bitter Orange, cape jasmine, and rhizomabletillae) in a study on rats with IBS and obtained similar results.

Li Guoxia et al.[79] adopted self-designed formula (Bupleurum, rhizomacyperi, and white peony) in the treatment for IBS, and results showed that IgM level was decreased, inhibitory T lymphocytes (T8+) was restored to normal level, and

IL-2 level was increased. Li Chen et al.[80] adopted self-designed formula (coptis, white peony, and areca) in the treatment for patients with UC in the active stage, and results showed that serum TNF-α, IL-17 and IL-21 levels were significantly decreased. Xiang Fengmei et al.[81]adopted self-designed formula (American ginseng, astragalus, and Atractylodes) in the treatment for patients with IBS, and results showed that serum TNF-α level was lowered, and expression of IL-10 was increased. Ma Junjie et al.[82] used self-designed formula (Pulsatilla, coptis, cortex phellodendri, and fructus forsythiae) in combination with SASP (Sulfasalazine Suppositories) enema in the treatment for patients with UC in the active stage, and results showed that serum TNF-α and IL-2 were lowered, IL-4 and IL-5 were increased, and Th1/Th2 was decreased. Fu Yongjin et al.[83] employed self-designed formula (coptis, Astragalus, and typhae pollen) in studies on UC model rats induced by immune complex method, and results showed that the mechanism might be related with increased level of sIgA in colonic tissues and decreased expression of P-selectin.

Zhang Wan et al.[84] used self-designed formula (eupatorium, oriental wormwood, phoenix-tail fern, and hairy euphorbia) in the treatment for 108 patients with UC, and found that the levels of plasma interleukins IL-13 and TNF-a were lower than the treatment before, and the symptoms of mucosal congestion and edema, erosion, and ulcer were significantly improved. Further researches[84] found that this formula was effective in reducing the number of subsets of $CD4^+$/CD29+T cells in UC model rats. Liu Zifeng et al.[85] found that the mechanism of Kuijieling Decoction (Atractylodes, white peony, leech, and licorice) in the treatment for UC might be related to the increased proportions of $CD4^+$ Foxp3+Treg cells and decreased proportions of CD4+IL-17A+ Th17 cells in the peripheral blood, and the resulting balance of Treg/Th17 in the body. Chen Wengang et al.[86] cited the Xiezhuojiedu Decoction (Turbidity-Purging and Detoxification Decoction, herba houttuyniae, patrinia, and Sargent gloryvine) in the treatment for UC model rats and found that the expression levels of TLR4/ NF-κB in the treatment group were significantly lower than the model group, indicating that Xiezhuojiedu Decoction might take effect by lowering the transcription level of TLR4 mRNA, reducing the synthesis and expression of TLR4 proteins, blocking the conduction of signal pathway of TLR4 and NF-κB, decreasing the release of pro-inflammatory cytokines, inhibiting the excessive activation of the immune system, and rectifying the abnormal immune inflammation of the colon.

In summary, along with the deepening of the researches on gastrointestinal diseases, a lot of attention has focused on the efficacy-centered advantage of TCM in the prevention and treatment of chronic gastrointestinal disease. TCM showed therapeutic characteristics and advantages for functional gastrointestinal diseases (FGID) (e.g., functional dyspepsia (FD), IBS, non-specific mucosal inflammation), malignant transformation (e.g., chronic gastritis, precancerous lesions), and (e.g.,ulcerative colitis (UC)). In the treatment of these diseases, while addressing gastrointestinal symptoms, TCM has been proven excellent in preventing mucosal inflammation and improving the cure rate of UC. Therefore, it is necessary to further strengthen the immune system research on TCM. The immune mechanisms of single herbs and compounds of TCM are listed in Table 2 and 3.

Table 2. Immune mechanism for chronic Intestinal diseases treated by Traditional Chinese Medicine monomer.

Author	Year	Journal	disease	Single Chinese herbs	TCM monomer	Mechanism
Sanchez M F	2008	World J Gastroenterol	colitis	Rhizoma curcumae longae	curcumin	IL-1α, IL-1β, IL-2, IL-6, IL-8, IL-12, IL-17 and IL-23↓, IL-4, IL-10 and IL-13↑
Zhou J	2009	Anhui Medical University[D]	UC	radices paeoniae alba	total glucosides of paeony	TNF-α↓, IL-10↑
Zhou GS	2009	Anhui Medical University[D]	UC	caulis sinomenii or Sinomenium acutum va	Sinomenine	IL-1β and TNF-α↓
Li Y	2010	Mol Immunol	CD	Tripterygium	Triptolide	TLR2, TLR4, MyD88, NFκBp65, IL-17 and IL-6↓
Gao YJ	2010	Peking Union Medical College[D]	colitis	Astragalus mongholicus	Astragalus polysaccharides	IL-4↑, IL-10↑
Hong T	2012	Immino pharmaol Ommunotoxicol	colitis	rhizoma coptidis	Berberine hydrochloride	IFN-γ and IL-12↑, IL-4 and IL-10↓
Zheng Y	2013	Chin J Gen Surg	CD	Tripterygium	Tripterygium glycosides	Smad3 and Smad4 mRNA↓, Smad7 mRNA↑
Wang B	2013	Chin J Integr Trad West Med Dig	UC	radices paeoniae alba	paeoniflorin	IL-2↓, IL-6↓, IL-10↑
Luo SY	2014	Chin J Tradit Chin Med Pharm	UC	Hedyotis diffusa	FOD	IL-8 and TNF-α↓, IL-10↑

UC: ulcerative colitis; CD: crohn's disease; FOD: total flavones of oldenlandia diffusa willd;TNF-α: tumornecrosisfactor-α; IL-10: interleukin-10; IFN-γ: Interferon-γ; Smad: Intracellular signal transduction molecules of TGF- β cell factor super family; TLR4: Toll-like receptor-4; MyD88: myeloid differentiation factor 88.

Table 3. Immune mechanism for chronic Intestinal diseases treated by Traditional Chinese Medicine compound.

Author	Year	Journal	disease	TCM compound	mechanism
Li GX	2011	J Tianjin Med Univ	IBS	harmonizing the liver and spleen	IL-2
Chen WG	2012	J Hebei Med Univ	UC	XiezhuoJiedu decoction	TLR4/NF- B
Li C	2013	World Chin J Dig	UC	Shaohuang Anchang decoction	TNF-, IL-17 and IL-21
Zhang W	2013	Chin J Exp Tradit Med Form	UC	Lanyin Fengyang Huazhuo Jiedu Prescription	IL-13 and TNF-
Liu TL	2014	Chin arch Tradit Chin Med	IBS	Inhibiting Wood Decoction	$CD4^+$, $CD8^+$
Zhu XD	2014	Chin J Integr Trad West Med Dig	UC	Tongxie Yaofang	NF- B p65
Xiao FM	2014	Chin J Integr Trad West Med Dig	IBS	Shengqing Jiangzhou herbs	TNF-, IL-10
Ma JJ	2014	Chin J Tradit Chin Med Pharm	UC	Baitouweng decoction and Liangge san	TNF- and IL-2, IL-4 and IL-5, Th1/Th2
Wang FF	2015	Chin Arch Tradit Chin Med Pharm	UC	Lianli Decoction	TNF-, IL-10
Wang Y	2015	Chin J Geront	UC	Si Shen Pill	IL-1 and TNF-, IL-4
Liu Z F	2015	Tradit Chin Drug Res Pharmaco	UC	Kuijielingdecoction	$CD4^+$ Foxp3+Treg, CD4+IL-17A+ Th17

UC: ulcerative colitis; IBS: irritable bowel syndrome; TNF-α: tumornecrosis factor-α; IL-2: interleukin-2; NF-κB: nuclear factor kappa B; TLR4:Toll-like receptor-4.

Conclusions

In conclusion, from the intestinal mucosal immune mechanism of various types of chronic bowel diseases including IBS, UC and CD, as well as the correlation between TCM syndromes and immunity and TCM regulation, this paper summarized the latest research results of the important relationship and interactions between TCM and the pathogenesis and development of chronic bowel diseases, explored the relationship and regulation between TCM and immune response, and further interpreted the immune mechanism of TCM in the treatment of chronic gastrointestinal diseases. However, researches on the mechanism of TCM in improving immunity remain to be further strengthened.

Theory of Struggle and Immunity

TCM has its own unique theoretical system, especially the "Theory of Struggling between Healthy Qi and Pathogenic Factors", which is rich in immunology theories and practices. Modern immunology holds that the immune system is the body's own defense mechanism, which maintains the body's physiological balance by identifying endogenous and exogenous components (virus and bacteria), and generating immune response to expel the exogenous ones. However, the Theory of Struggle holds that the body constantly undergoes the struggle between "good and evil", where the good" refers to the healthy Qi, that is, the body's ability to resist evil, representing the internal normal immune function, while the "evil" refers to all the external pathogenic factors, including bacteria and virus. The so-called "healthy Qi" exists in your heart, hence that the evil won't disturb you in the "*Inner Canon*" has made it clear that normal immune function is the prerequisite for maintaining the overall balance of physiological functions in the body. As the healthy Qi remains powerful, the pathogenic factors cannot invade, and diseases do not occur. Therefore, it is particularly advocated in clinical treatment to strengthen the healthy Qi. In chronic bowel diseases, instead of merely using the invigorators, such as ginseng, Astragalus, Angelica, and Donkey-hide gelatin, the method of supporting the healthy Qi should be to focus on physiological characteristics of the liver, spleen and kidney, regulating their functions to achieve the interdependence of ascending and descending, and the balance between dryness and dampness. On the other hand, instead of simply using heat-clearing and detoxicating drugs, such as Oldenlandia diffusa, Scutellaria Barbata, and Indian Iphigenia Bulb, the method of expelling the pathogenic factors should be to correspondingly use the drug combination for the determined syndrome, on the basis of mastering the efficacy and potency of the various types of drugs. Qi stagnation should be treated with Qi-regulating medicinal, blood stasis should be treated with stasis-resolving medicinal, spleen dampness should be treated with spleen-invigorating medicinal to eliminate dampness, Qi deficiency should be treated Qi-tonifying medicinal, and heat-toxin should be treated with heat-clearing and detoxification medicinal, accordingly.

TCM and Intestinal Immunity

The holistic concept is the feature of TCM theoretical system, both emphasizing the overall balance of the human body, and stressing the internal balance between the organs. For this reason, TCM may have more advantages in regulating the imbalance of intestinal immune microenvironment. The intestinal homeostasis is a crucial part of the body's overall balance, as the intestinal tract is also an important part of the body's immune system, distributed with a variety of immune factors with different functions. The regulation of intestinal immune response depends on the involvement of immune cells, cytokines and immunoglobulins. This paper summarized the related researches on the regulations TCM on immune cells CD4 and CD8, cytokines IL-2, IL4 and IL-10, and immunoglobulins IgA and IgM. The researches limited to the expression level of a certain cell or cytokine can hardly perform a comprehensive evaluation of the pharmacological mechanisms of TCM. Only by exploring an instructive starting point,

it is possible to achieve the ultimate goal of immune regulation through overall regulation of the body by TCM.

Problems and Countermeasures

So far, researches of TCM immune regulation on chronic bowel diseases have made some achievements, but there are also several problems. 1) There is currently a lack of clinical trials with standardized, large samples and high-level evidence TCM to support the determination of the efficacy advantages of TCM immune regulation. The clinical trials include evaluation of the efficacy of TCM treatment for chronic bowel diseases, multicenter randomized controlled trial (RCT), and data analysis of real clinical diagnosis, all of which are the current focus of clinical researches on TCM; 2) The pharmacological mechanism of TCM needs to be further investigated. The immune system is composed of immune organs (bone marrow, spleen, lymph nodes, tonsils, aggregated lymph nodes of small intestine, appendix, thymus, etc.), humoral immunity, and cellular immunity. Due to the complex composition of the formulas, researches on TCM compounds are currently limited to the TCM regulation on the expressions of immune cells, immune factors, and immune proteins, but the deep mechanism causing the rise and drop in expressions remains to be further explored; 3) The common mechanism of the efficacy for chronic bowel diseases is the bottleneck of the present study. The clinical manifestations and core pathogenesis of IBS, UC and CD all agree uniformly with the syndrome of spleen deficiency. For spleen dysfunction due to dampness, the representative formula is Shenling-Atractylodes Formula; for liver depression and spleen deficiency, the representative formula is Tongxieyao Formula (Pain and Diarrhea Formula); for spleen Qi deficiency, the representative formula is Sijunzi Decoction (Four Gentlemen Decoction); for spleen-kidney yang deficiency, the representative formula is Aconite Middle-Regulating Pill. The author believes that "spleen transportation" and "spleen transformation" are the guarantee for the body's normal physiological function. As for mechanism of the "non-transportation" and "non-transformation" of the spleen, on the levels of whole body, tissue, cell, and molecule, it seems to be an important area that requires theoretical innovation of TCM and also an important target of TCM compound therapy; 4) A lack of suitable animal model brought about great limitations to the related researches on the pharmacological mechanism of TCM. This study first proposed an idea of "combining disease and syndrome, and classifying diseases with syndromes", and carried out some establishment and evaluation of animal models combining disease and syndrome (including animal models of gastroesophageal reflux disease, functional diarrhea, and IBS, with all of which combining disease and syndrome), providing solid foundation for the further studies on the pharmacological mechanism of TCM.

Acknowledgements

This work was supported by Major State Basic Research Development Program of China (973 Program) (No.2013CB531703) and the General Program of National Nature Science Foundation of China (No. 81373580, 81503567 and 81173209) and the Visiting Scientist Program of China Academy of Chinese Medical Sciences (No. ZZ070801).

Conflict of interest

The authors declare that there are no conflicts of interest.

Reference

1. Simsek I. Irritable bowel syndrome and other functional gastrointestinal disorders. *J Clin Gastroenterol* 2011;45(Suppl):S86–88.
2. Ohman L, Simrén M. Pathogenesis of IBS:Role of inflammation, immunity and neuroimmune interactions. *Nat Rev Gastroenterol Hepatol* 2010;7(3):163–173.
3. Long Y, Wang W, Wang H, et al. Characteristics of intestinal lamina propria dendritic cells in a mouse model of postinfectious irritable bowel syndrome. *Clin Gastroenterol Hepatol* 2012;27(5):935–944.
4. Cerf-Bensussan N, Gaboriau-Routhiau V. The immune system and the gut microbiota: friends or foes? *Nat Rev Immunol* 2010;10(10): 735–744.
5. Macsharry J, O'Mahony L, Fanning A, et al. Mucosal cytokine imbalance in irritable bowel syndrome. *Scand J Gastroenterol* 2008; 43(12):1467–1476.
6. Dinan TG, Clarke G, Quigley EM, et al. Enhanced cholinnergic-mediated increase in the inflammatory cytokine IL-6 in irritable bowel syndrome: role of muscarinic receptor. *Am J Gastroenterol* 2008;103(10):2570–2576.
7. Ortiz-Lucas M, Saz-Peiro P, Sebastian-Domingo JJ. Iriritable bowel syndrome immune hypothesis. Part two: the role of cytokines. *Rev Esp Enferm Dig* 2010;102(12):637–647.
8. Scully P, McKernan DP, Keohane J, et al. Plasma cytokine profiles in females with irritable bowel syndrome and extra-intestinal co-morbidity. *Am J Gastroenterol* 2010;105(10):2235–2243.
9. Matricon J, Meleine M, Gelot A, et al. Review article: Associations between immune activation, intestinal permeability and the irritable bowel syndrome. *Aliment Pharmaco Ther* 2012;36(11-12):1009–1031.
10. Martins GA, Cimmino L, Shapiro-Shelef M, et al. Transcriptional repressor Blimp-1 regulates T cell homeostasis and function. *Nat Immunol* 2006;7(5):457–465.
11. Kallies A, Hawkins ED, Belz GT, et al. Transcriptional repressor Blimp-1 is essential for T cell homeostasis and self-tolerance. *Nat Immunol* 2006;7(5):466–474.
12. Spahn TW, Herbst H, Rennert PD, et al. Induction of colitis in mice deficient of Peyer's patches and mesenteric lymph nodes is associated with increased disease severity and formation of colonic lymphoid patches. *Am J Pathol* 2002;161(6):2273–2282.
13. Gassler N, Rohr C, Schneider A, et al. Inflammatory bowel disease is associated with changes of enterocytic junctions. *Am J Physiol Gastrointest Liver Physiol* 2001;281(1):G216-G228.
14. Parronchi P, Romagnani P, Annunziato F, et al. Type 1 T-helper cell predominance and interleukin-12 expression in the gut of patients with Crohn's disease. *Am J Pathol* 1997;150(3):823–832.
15. Round JL, Mazmanian SK. The gut microbiota shapes intestinal immune responses during health and disease. *Nat Rev* Immunol 2009;9(5):313–323.
16. Bruno LS, Li X, Wang L, et al. Two-hybrid analysis of human salivary mucin MUC7 interactions. *Biochim Biophys Acta* 2005;1746(1): 65–72.
17. Iontcheva I, Oppenheim FG, Offner GD, et al. Molecular mapping of statherin-and histatin-binding domains in human salivary mucin MG1 (MUC5B) by the yeast two-hybrid system. *J Dent Res* 2000;79(2):732–739.

18. Mowat AM, Viney JL. The anatomical basis of intestinal immunity. *Immunol Rev* 1997;156(1):145–166.
19. Bellot P, Francés R, Such J. Pathological bacterial translocation in cirrhosis: pathophysiology, diagnosis and clinical implications. *Liver Int* 2013; 33(1): 31–39.
20. Wittig BM, Zeitz M. The gut as an organ of immunology. *Int J Colorectal Dis* 2003;18(3):181–187.
21. Stuller KA, Ding HR, Redline RW, et al. CD25+ T cells induce Helicobacter pylori-specific CD25-T-cell anergy but are not required to maintain persistent hyporesponsiveness. E*ur J Immunol* 2008; 38(12):3426–3435.
22. Bercik P, Verdu EF, Collins SM. Is irritable bowel syndrome a low grade inflammatory bowel disease. *Gastroenterol Clin North Am* 2005;34(2):235–245.
23. Spiller R, Garsed K. Postinfectious irritable bowel syndrome. *Gastroenterology* 2009;136(6):1979–1988.
24. Philpott H, Gibson P, Thien F. Irritable bowel syndrome—An inflammatory disease involving mast cells. *Asia Pac Allergy* 2011;1(1):36–42.
25. Wouters MM, Vicario M, Santos J. The role of mast cells in functional GI disorders. *Gut* 2016;65(1):155–168.
26. Barbara G, Stanghellini V, De Giorgio R, et al. Activated mast cells in proximity to colonic nerves correlate with abdominal pain in irritable bowel syndrome. *Gastroenterology* 2004;126(3):693–702.
27. Barbara G, Wang BX, Stanghellini V, et al. Mast cell-dependent excitation of visceral-nociceptive sensory neurons in irritable bowel syndrome. *Gastroenterology* 2007;132(1):26–37.
28. Lee KJ, Kim YB, Kim JH, et al. The alteration of enterochrom affin cell, mast cell, and lamina propria T lymphocyte numbers in irritable bowel syndrome and its relationship with psychological factors. *J Gastroenterol Hepatol* 2008;23(11):1689–1694.
29. Klooker TK, Braak B, Koopman KE, et al. The mast cell stabiliser ketotifen decreases visceral hypersensitivity and improves intestinal symptoms in patients with irritable bowel syndrome. *Gut* 2010; 59(9):1213–1221.
30. Chen J, Zhang Y, Deng Z. Imbalanced shift of cytokine expression between T helper 1 and T helper 2 (Th1/Th2) in intestinal mucosa of patients with post-infectious irritable bowel syndrome. *BMC Gastroe terol* 2012; 12(27): 1–6.
31. Yang B, Zhou X, Lan C. Changes of cytokine levels in a mouse model of post-infectious irritable bowel syndrome. *BMC Gastroenterol* 2015; 15(1):1–7.
32. Hisamatsu T, Kanai T, Mikami Y, et al. Immune aspects of the pathogenesis of inflammatory bowel disease. *Pharmacol Ther* 2013;137(3): 283–297.
33. Huang Z, Jiang Y, Yang Y, et al. 3,3′-Diindolylmethane alleviates oxazolone-induced colitis through Th2/Th17 suppression and Treg induction. *Mol Immunol* 2013;53(4):335–344.
34. Chen Z, Lin F, Gao Y, et al. Foxp3 and RoRrt:transcriptional regulation of Treg and Th17. *Intimmun opharmacol* 2011;11(5):536–542.
35. Kobayashi T, Okamoto S, Hisamatsu T, et al. IL-23 differentially regulates the Th1/Th17 balance in ulcerative colitis and Crohn's disease. *Gut* 2008;57(12):1682–1689.
36. Monteleone I, Sarra M, Pallone F, et al. Th17-related cytokines in inflammatory bowel disease: friends or foes? *Curt Mol Med* 2012;12(5):592–597.
37. Liu SY, Zang MX, Zhao Q. Detection of serum SIL-2R, cow's milk specificity IgG and IgE in infancy with persistent and chronic diarrhea. *Chin J Pract Padia* 2013;28(1):29–30.
38. Ashwood P, Harvey R, Verjee T, et al. Functional interactions between mucosal IL-1, IL-ra and TGF-beta 1in ulcerative colitis. *Innamm Res* 2004;53(2):53–59.
39. Yang DS, Kang YH, Suo ZM. The periheral blood T cell subsets imbalance in patients with latent autoimmune diabetes in adult and ulcerative colitis and its clinical signifncance. *Chin J Diabetes* 2014;22(9):824–826.
40. Silverberg MS, Satsangi J, Ahmad T, et al. Toward an integrated clinical, molecular and serological classification of inflammatory bowel disease: report of a Working Party of the 2005 Montreal World Congress of Gastroenterology. *Can J Gastroenterol* 2005; 19(Suppl A):5A-36A.
41. Yuan B, Jin X, Youke LU, et al. Relationship between peripheral blood $CD3^+$, $CD4^+$ and $CD8^+$ T cells and inflammation markers in patients with Crohn's disease. *Chin J Gastroenterol* 2015; 20(3):143–145.
42. Zhou L, Lopes JE, Chong MM, et a1. TGF-β-induced Foxp3 inhibits THl7 cell differentiation by antagonizing ROR-γ function. *Nature* 2008; 453(7192):236–240.
43. Himmel ME, Hardenberg G, Piccirillo CA, et al. The role of T-regulatory cells and Toll-like receptor in the pathogenesis of human inflammatory bowel disease. *Immunology* 2008;125(2):145–153.
44. Ma JJ, Zhang YL. Study on the relationship between syndromes of TCM and Th1/Th2 drift in post infectious irritable bowel syndrome patients. *Chin J Tradit Chin Med Pharm* 2014;29(2):592–594.
45. Wang HB, Zhang SS. Characteristics of Chinese medicine syndromes of irritable bowel syndrome: understandings and thoughts. *World Chin J Dig* 2010;18(21): 2210–2215.
46. Zhao RH, Xie M, Li C, et al. Changes of ilEinlune functions in rat models of liver depression syndrome, spleen deficiency syndrome and syndrome of liver depression and spleen deficiency. *J Beijing Univ Tradit Chin Med* 2013;36(12):821–824.
47. Lv YH, Cong LL. Study on the Chinese medical syndrome distribution of ulcerative colitis. *Chin J Integr Tradit West Med* 2012;32(4): 450–454.
48. Zhang SM, Chan LL, Li GY, et al. The study of T lymphocyte subet in different kinds of Chinese type of patients with ulcerative colitis. *Chin J Med Guide* 2008;10(8):1232–1233.
49. Chang TM, Lix IM, Zhao XD. Study on the relationship between Chinese medicine grouping of ulcerative colitis and T cell subgroup. *Liaoning J Tradit Chin Med* 2008;35(12):1803–1805.
50. Gao Y. Research on the relationship between inflammatory bowel disease syndromes and T cell subgroup. Beijing: Beijing University of Traditional Chinese Medicine 2013.
51. Zhou J. Effect and mechanism of total glucosides of paeony on experimental colitis. Hefei: Anhui Medical University 2009.
52. Wang B, Zhu XD, Duan YQ, et al. Effect of paeoniflorin on colon tissue pathological morphology and the balance of anti-inflammatory and proinflammatory factors in rats with ulcerative colitis. *Chin J Integr Trad West Med Dig* 2013;2l(1):1–4.
53. Gao YJ. Astragalus polysaccharide on the therapeutic effect of TNBS induced experimental colitis in rats and effects on immune function. Beijing: Peking Union Medical College 2010.
54. Ko JK, Chik CW. The protective action of radix astragalus membranaceus against hapten induced colitis through modulation of cytokines. *Cytokine* 2009;47(2):85–90.
55. Shu DZ, Wan XH, Liu HR, et al. Effect of berberine chloride on experimental murine colitis induced by dextran sulfate sodium. *J chin Pharm Sci* 2006;15(3):182–187.
56. Hong T, Tang Z, Lv CF, et al. Supressive effect of betterineon experimental dextran sulfate sodium induced colitis. *Immino pharmaol Ommunotoxicol* 2012;34(3):391–397.
57. Cao M, Wang P, Sun C, et al. Amelioration of IFN-γ and TNF-α-induced intestinal epithelial barrier dysfunction by berberine via suppression of MLCK-MLC phosphorylation signaling pathway. *PLos One* 2013;8(5):e61944.
58. Srivastava RM, Singh S, Dubey SK, et al. Immunomodulatory and therapeutic activity of curcumin. I*nt Immunopharmacol* 2011; 11(3):331–341.
59. Sanchez MF, Dominguez LA, Yamamoto-Furusho JK. Role of cytokines in inflammatory bowel disease. *World J Gastroenterol* 2008; 14(27):4280–4288.
60. Yi JX, Fei SJ, Pang XL, et al. Therapeutic effects of curcumin combined with MSCs against ulcerative colitis in rats. *World Chin J Dig* 2014; 22(12):1642–1650.
61. Luo SY, Le Z, Lv XH, et al. Study on effect of total flavonoids of Oldenlendia difflusa on ulcerative colitis and its immunological mechanism. *Chin J Tradit Chin Med Pharm* 2014;39(5):896–900.

62. Li Y, Yu C, Zhu WM, et al. Triptolide ameliorates IL-10-deficient mice colitis by menchanism involving suppression of IL-6/STAT 3 signaling pathway and down-regulation of IL-17. *Mol Immunol* 2010; 47(15):2467–2474.
63. Zheng Y, Tao QS, Ji ZL, et al. The protective effects and mechanisms of tripterygium wilfordii polyglycosidium in Crohn's disease model of rats. *Chin J Gen Surg* 2013; 22(12):1650–1654.
64. Liang H, Liu CH. Impact of herba patriniae on TNF-α, IL-1β and IL-10 expression in colonic tissue of rats with experimental ulcerative colitis. *Pharmacy Today* 2013;23(2):78–79.
65. Zhou GS. Mechanism of action research for Sinomenine on trinitrobenzene sulfonic acid induced experimental colitis in rats. Hefei: Anhui Medical University 2009.
66. Yu Q, Zhu S, Zhou R, et al. Effects of sinomenine in the expression of micro RNA 155 in 2,4,6 trinitro benzenesul fonicacid induced colitis in mice. *Plos One* 2013;8(9):e73757.
67. Liu Y, Liu W, Peng QX, et al. Protective effect of huoxiang zhengqi oral liquid on intestinal mucosal mechanical barrier of rats with post-infectious irritable bowel syndrome induced by acetic acid. *Evid Based Complement Alternat Med* 2014;2014:218383–218383.
68. Zhu Y, Yao MH, Wang X. Clinical observation of effects of modified SiJunzi Decoction on the intutlnal mucosal barrier of giant colon children patients. *Chin J Integr Tradit West Med* 2012;32(2): 199–203.
69. Wang Y, Cao YF, Zhu XD, et al. Influence of the Si Shen Pill on the content of interleukin-1β, interleukin-4 and TNF-α in rats with ulcerative colitis. *Chin J Geront* 2015;35(1):127–129.
70. Zhu XD, Mei XY, Wang Y, et al. Influence of Tong Xie Yao Fang on the PPAR-y mRNA and protein expressions of colonic mucosa in rats with experimental ulcerative colitis. *Chin J Tradit Chin Med Pharm* 2013; 28(4):941–945.
71. Chen SF, Gao ZX, Huang H, et al. Effect of Gancao Xiexin Decoction on expression of NF-κB and IL-10 in rats with ulcerative colitis. *J Fujian Univ Tradit Chin Med* 2014;24(4):39–41.
72. Wang FF, Zhou F, Fwng YL, et al. Influence of TNF-α and IL -10 expressions of active ulcerative colitis with Lianli Decoction. *Chin Arch Tradit Chin Med Pharm* 2015;33(2):381–383.
73. Cheng CH, Zhu XD, Li LZ, et al. Mechanism of Xiebikang in treating chronic diarrhea. *Chin J Integr Trad West Med Dig* 2004; 12(2):86–89.
74. Liu XP, Jia YX, Liu Q, et al. Effects of Shenglingbaizhusan Decoction on CD44, D62p and CD54 in ulcerative colitis rats with asthenia of spleen. *Lishizhen Med Mater Med Res* 2011;22(11):2671–2674.
75. Sun Y, Zhang X, Li YH, et al. Treatment effects of Wumei Pill on rats with ulcerative colitis and the mechanisms. *Mil Med J S Chin* 2013;27(1):5–9.
76. Liu TL, Lu Y, Yao QY. Effect of Inhibiting Wood Decoction by detecting T-lymphocyte subsets of patients with disharmony between liver and spleen D-IBS. *Chin arch Tradit Chin Med* 2014;32(5):1053–1054.
77. Liu JM, Lin XY, Hu H, et al. Effects of Fu-an Decoction on T-lymphocyte subsets in rats of diarrhea-predominant irritable bowel syndrome. *Liaoning J Tradit Chin Med* 2010;37(10):2061–2062.
78. Liu XZ, Wang C, Liu HJ, et al. Study of the mechanism of Qingweilichang Capsule in rats with experimental ulcerative colitis (UC). *J Emerg Tradit Chin Med* 2011;20(2):262–263.
79. Li GX, Ning ZF, Li JX. Immunology mechanism of harmonizing the liver and spleen on irritable bowel syndrome. *J Tianjin Med Univ* 2011;17(3):317–319.
80. Li C, Fan YF, Liu H, et al. Therapeutic effect of Shaohuang Anchang Decoction on active ulcerative colitis and serum levels of TNF-α, IL-17 and IL-21. *World Chin J Dig* 2013;21(32): 3580–3584.
81. Xiao FM, Jiang YP, Deng KS. Effect of Shengqing Jiangzhou heibs on the level of TNF-α and IL-10 in serum of patients with IBS. *Chin J Integr Trad West Med Dig* 2014;22(11):638–640.
82. Ma J, Dou Y, Zhang Y, et al. Study on Effect of Regulation to Th1/Th2 in AUC Patients with Chinese medicine combined with SASP enema under guidance of synchronous treatment of lung and intestine. *World Sci Tech: Mod Tradit Chin Mater Med* 2014;16(4):769–773.
83. Fu YJ, Zhang XM, Lian DW, et al. Effects of Changyanqing Decoction on the expressions of sIgA and P-selection in ulcerative colitis rats. *Chin J Exp Tradit Med Form* 2014;20(3):148–152.
84. Zhang W, Wang ZK, Dong L, et al. Effect of Lanyin Fengyang Huazhuo Jiedu Prescriptionon immune regulation mechanism in rats with ulcerative coliti. C*hin J Exp Tradit Med Form* 2013;19(1):236–239.
85. Liu ZF, Guo Z, Li YW, et al. Effects of Kuijieling on balance of peripheral blood Treg/Th17 in experimental ulcerative colitis rats. *Tradit Chin Drug Res Pharmaco* 2015;26(1):1–4.
86. Chen WG, Chen JQ, Liu JP, et al. Effect of XiezhuoJiedu Decoction in colon tissue of rats with ulcerative colitis by TLR4/NF-nuclear factor kappa B signal pathway. *J Hebei Med Univ* 2012;33(7):803–805.