ISSN 2706-6819 Vol.6, Issue 7: 64-71, DOI: 10.25236/IJFM.2024.060711

Research progress of Chinese medicine regulating intestinal flora in the treatment of autoimmune diseases

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Abstract: *Autoimmune diseases (AIDs) are chronic systemic diseases of unknown etiology that predispose to widespread damage to multiple organs and systems. However, their exact pathogenesis is unclear and clinical treatment is difficult. In recent years, intestinal flora and immune regulatory mechanisms have become a research hotspot. Current studies have shown that intestinal flora plays a significant role in maintaining the immune and metabolic homeostasis of the body. With the increasing maturity of metabolomics and immunomics technologies, studies on the effects of traditional Chinese medicine (TCM) on intestinal flora have shown that TCM can play a positive role in the treatment of autoimmune diseases through the regulation of intestinal flora. This article reviewed the research progress of Chinese medicine regulating intestinal flora in the treatment of autoimmune diseases, and explored the mechanism of intestinal flora involved in immunomodulation in the treatment of diseases, and categorized and summarized the mechanism of immunomodulation between diseases and prescription medicines, which provided a new perspective for the exploration of the mechanism of Chinese medicine in the treatment of autoimmune diseases, with a view to providing a new direction and a new way of thinking for the treatment of autoimmune diseases.*

Keywords: *Intestinal flora; immunomodulation; autoimmune diseases; research progress*

1. Introduction

Autoimmune diseases are a class of diseases caused by autoimmune system dysfunction, and their etiology and pathogenesis have not been clarified so far, which adds many difficulties to the treatment of such diseases. In recent years, with the continuous development of culture technology, multi-omics linkage technology and gene sequencing technology, researchers have been deepening their studies on the interactions among traditional Chinese medicine (TCM), intestinal flora and autoimmune diseases, and the connection between intestinal flora, immune function and diseases has attracted the attention of researchers amidst the interplay between TCM theories and modern medicine. In this article, the research progress of intestinal flora and human immunity as well as Chinese medicine intervention of intestinal flora in the treatment of autoimmune diseases are summarized.

2. Intestinal flora

As the main microorganisms in the intestinal microecosystem, the intestinal flora is up to 1014 in number, with a mass of up to 1. 5kg, which is equivalent to 10 times that of the human body's own cells, and accounts for 99% of the intestinal microorganisms. The intestinal flora is mainly composed of anaerobic bacteria, which are categorized into six phylums, the Firmicutes (Lactobacillus, Enterococcus, Clostridium phylum), Mycobacterium, proteobacteria (Enterobacteriaceae), Actinobacteria (Bifidobacteria), Clostridium, and warty microorganisms, the first four of which are major bacterial phylums of the microbiota in the healthy human body [1-2]. They can be classified into three groups according to their functions: i Physiological bacteria that can live in symbiosis with the host and do not elicit a harmful immune response (commensal bacteria). ii Bacteria that maintain a good survival balance under normal physiological conditions and become invasive and conditionally pathogenic (neutrophilic bacteria) in the presence of a depressed immune function of the organism iii Pathogenic bacteria that elicit an immune response from the human body (harmful bacteria) [3]. The intestinal flora is usually in a state of dynamic equilibrium, and its number and species are susceptible to a variety of factors, such as

ISSN 2706-6819 Vol.6, Issue 7: 64-71, DOI: 10.25236/IJFM.2024.060711

drugs, dietary structure, environment, disease, etc., and at the same time, it has an auxiliary role in the metabolic uptake of nutrients, absorption of non-nutrients, and degradation of toxins. Intestinal flora can maintain the epithelial tissue barrier, reduce intestinal pH, reduce the colonization of pathogenic bacteria, play an important role in the evolution of the disease process, the regulation of the body's immune system, is an important "endocrine organ" [4].

3. Research on the mechanism of intestinal flora regulating immunity

As an important immune organ of the human body, the intestinal tract bears the functions of lymphocytes, immune factors, and intestinal flora collection and dispersal. The normal parasitic flora in the intestine constitutes the biological barrier of the intestine, which together with the mechanical and chemical barriers maintains the balance of the intestinal microecosystem and protects the body from damage in the presence of a large number of bacteria and toxins in the intestinal tract. Therefore, the relationship between gut microorganisms and immune function is close and interactive.

3.1. Up-regulate the relative abundance of beneficial bacteria

The number and species of intestinal flora maintain a dynamic equilibrium in the intestinal microenvironment, and once this equilibrium is disturbed and the intestinal microecosystem is out of balance, it will cause dysfunction and thus lead to the occurrence of diseases. It has been found that restoring the dynamic balance of intestinal flora by up-regulating the relative abundance of beneficial bacteria and reducing the number of pathogenic bacteria can enhance the immune function, and Chang [5] et al. found that Bifidobacterium fragilis could alter the inflammatory response induced by bacterial lipopolysaccharide LPS (LPS) to alter regulatory T lymphocyte (Treg)/helper T cell 17(T helper 17) (T helper 17) (T helper 17) (T helper 17) (T helper 17) (T helper 17) (T helper 17) (T helper 17)). 17 (T helper 17) balance, thus exerting an immunomodulatory effect. Jiang [6] et al. found that umeboshi pills could reduce the number of anopheles phylum, increase the abundance of Firmicutes thus adjusting the structure of intestinal flora, and down-regulate the NF-kB/IL-6/STAT3 pathway synergistically to inhibit the transformation of inflammation to cancer. Vieira A T [7] et al. found that the effects of bacterial pneumonia on the mice orally administered the symbiotic probiotic Bifidobacterium longum, which activated the TLR signaling pathway to produce reactive oxygen species (ROS) and regulate the inflammatory response in the lungs. Therefore, clinical regulation and enhancement of immune function can be achieved by enhancing the abundance of beneficial bacteria and optimizing the flora structure.

3.2. Involved in metabolizing bile acids (BAs)

Bile acids can act on immune cells through activation of farnesol receptor (FXR), pregnane X receptor (PXR), and G protein-coupled bile acid receptor 1 (GPBAR1/ TGR5), and have important regulatory roles in immune responses [8-9]. The small portion of primary bile acids that are not reabsorbed at the end of the ileum can be hydrolyzed and metabolized by the intestinal flora to produce secondary bile acids after entering the colon [10]. It has been shown that secondary bile acids can bind to the TGR5 receptor to activate part of the macrophage's action, thereby determining whether TGR5 activation stimulates a pro- or anti-inflammatory response and intervenes in immune modulation [11]. Secondly, changes in intestinal flora can influence the bile acid receptor FXR and TGR5 to reduce the expression of pro-inflammatory factors in immune cells and achieve immunomodulation [12]. In conclusion, the metabolism of bile acids by intestinal flora can influence the immunomodulatory factors and positively regulate the immune function.

3.3. Increased expression of short-chain fatty acids (SCFAs)

Short-chain fatty acids (SCFAs) are important mediators in the regulation of a wide range of cells and the maintenance of intestinal homeostasis, and are key factors in the regulation and maintenance of the normal function of the immune system, regulating the differentiation and function of intrinsic and adaptive immune cells [13]. The main components of short-chain fatty acids are acetate, propionate and butyrate. Acetate and propionate are mainly produced by the phylum Bacteroidetes and butyrate is mainly derived from the phylum Bacteroidetes thickettsiae [14]. Butyrate can be involved in the intestinal immune response to chemokines such as responsive cytokines and microbial-derived molecules (e.g. , peptidoglycans) regulating through the intestinal mucosal epithelial cells IL-8, Monocyte Chemoattractant Protein -1 MCP-1) and growth-associated oncogene (GRO) expression and release,

ISSN 2706-6819 Vol.6, Issue 7: 64-71, DOI: 10.25236/IJFM.2024.060711

blocking the expression of interferon (IFN) and chemoattractant-γ-inducible protein-10 (IP-10, CXCL-10) in T lymphocytes and monocytes through the intestinal mucosal epithelium [15]. Yang [16] found that butyrate could regulate the expression of Aryl Hydrocarbon Receptor AhR and Hypoxic Hydrocarbon Receptor AhR through up-regulation of Aryl Hydrocarbon Receptor and Hypoxic Hypoxia. Receptor AhR) and Hypoxia-inducible Factors 1α HIF1α to promote the production of IL-22 in CD4 T cells and thus enhance intestinal immune function. Thus, it is evident that SCFAs, while enhancing intestinal immune function, can also influence the regulation of overall immune function through the modulation of immune factors.

3.4. Regulation of Th17/Treg cell homeostasis

Studies have shown that the gut microbiota and its metabolites can influence Th17 / Treg differentiation [17], Th17 cell-mediated adaptive immunity is important for the pro-inflammatory nature of host immunity, whereas Treg cells have anti-inflammatory functions and play an important role in suppressing immune responses and maintaining immune tolerance [18]. Th17 cells and Treg cells share a common TGF-β-mediated signaling pathway, and the presence of inflammatory factors such as TGF-β induces naïve CD4 T cells to differentiate into different immune cells, causing an imbalance of Th17/Treg cells [19]. Th17/Treg cell imbalance has been shown to affect intestinal mucosal immunoregulation [20] and play an important role in the pathogenesis of autoimmune diseases. Xu [21] found that the inhibition of inflammatory response by compound bitter ginseng decoction in mice with colitis may be related to the reduction of Th17 cell differentiation and up-regulation of the percentage of Treg cells, which regulates the Th17/Treg cell balance. This shows that through the interaction between intestinal flora and Th17/Treg cells, the inhibition of intestinal immune-inflammatory response and the intervention of systemic immune regulation is not a new direction for the treatment of AIDs.

4. Chinese medicine intervenes in the intestinal flora to achieve immunomodulation

4.1. Chinese medicine and intestinal flora

Chinese medicine is a traditional medical science system formed by studying the reaction state of the organism at the holistic level. Exploring the relationship between the spleen and stomach and disease from the perspective of Chinese medicine, it is recorded in the Nei Jing: "Drinking into the stomach, overflowing essence and qi, up to the spleen ..... in the four seasons of the five viscera and yin and yang, premise degree to think of the normal also." Reflects the key role of the spleen in maintaining the normal state of life by transporting water, grain and essence. The physiological function of the spleen and the intestinal flora in the human digestive process plays an important role coincides. "Medical Treasures of the Golden Chamber" said: "The strong function of the spleen can make people less susceptible to pathogenic invasion throughout the year", it indicates that the normal function of the spleen and stomach in transportation and digestion is a prerequisite for the sufficiency of positive qi. This, in turn, makes the body less susceptible to diseases and pathogens. From this theory, it can be seen that strengthening the spleen and stomach can prevent diseases.

Herbal medicine has a long history in China, and the gastrointestinal tract is the main place where herbal medicine exerts its effect, and as the largest microbiota in the gastrointestinal tract, herbal medicine is essential for the intervention and regulation of intestinal flora. Chinese medicines can protect the gastrointestinal mucosal barrier function, protect the intestinal microecological balance [22], reduce intestinal pH, provide a suitable growth environment for gastrointestinal flora [23], selectively promote the growth of probiotics in the intestinal tract [24], accelerate intestinal peristalsis, and timely exclude pathogenic bacteria and undesirable metabolites so as to improve the condition of bacterial imbalance [25], in addition to this, intestinal flora can also participate in the metabolism of Chinese medicines through the action of a variety of biological enzymes, and participate in the metabolism of Chinese medicines. In addition, the intestinal flora also participates in the metabolism of traditional Chinese medicine through a variety of biological enzymes, increasing its bioactivity and bioavailability, so that it has stronger physicochemical activity and produces different chemical effects on the organism [26], and the metabolites of the intestinal flora, such as lipid alkaloids, have a toxicity-reducing effect on traditional Chinese medicines [27], which improves the safety of traditional Chinese medicine in clinical use.

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4.2. Chinese medicine treats autoimmune diseases by treating intestinal flora

4.2.1. Inflammatory Bowel Disease (IBD)

Inflammatory bowel disease (IBD) is a chronic inflammatory disease whose etiology is still unclear, including ulcerative colitis UC and Crohn disease CD. With the incidence of inflammatory bowel disease rising year by year, many studies have shown that the inflammatory disease is closely related to the dysregulation of intestinal flora [28]. Shao [29] et al. found that Anabaena fragilis could inhibit the NLRP3-mediated inflammatory signaling pathway by promoting the secretory intervention of butyrate, thus alleviating intestinal inflammation. Yang Shuhui [30] used high-throughput 16S rRNA sequencing and found that P. flavus could effectively improve the survival of IBD mice and repair intestinal lesions by up-regulating the relative abundance and bacterial diversity of the intestinal phylum Pseudomonas, and decreasing inflammatory factors. Moreover, Hua [31] found that the administration of the formula Pulsatilla decoction could regulate the balance of the ratio of intestinal flora, increase the relative abundance of beneficial bacteria such as Lactobacillus, and inhibit the activity of NF-κB through the participation of intestinal flora in the metabolism of bile acids and the activation of bile acid receptor TGR5 and FXR to inhibit the inflammation and block the mucosal damage, which could help the recovery of ulcerative colitis. Wu [32] and others found that the Chinese herbal medicine compound formula Sanhuangshuai Tang (San Huang, Scutellariae, Baicalin, Scutellariae and Ai Tang) could effectively improve the survival condition of IBD mice by reducing the inflammatory factors. Ai Tang (Huanglian, Scutellaria baicalensis, Cyperus rotundus, and Ai ripening) prevented the reduction of intestinal beneficial bacteria such as Lactobacillus brevis in mice with colitis, significantly reduced the levels of pro-inflammatory cytokines IL-6, IL-1β, and TNF-α in colon tissues, and improved the symptoms of UC in mice with colitis by inhibiting NF-κB signaling, suppressing oxidative stress, and increasing ROS. All of the above studies have shown that Chinese medicines regulate can intestinal flora and thus affect immune regulation, is IBD symptoms are effectively alleviated, in the process of Chinese medicine clinical treatment of inflammatory bowel disease, the reliability of Chinese medicines has been confirmed [33], but its mechanism of action and target point still need to be further studied.

4.2.2. Primary Dryness Syndrome

Primary Sjögren's syndrome (pSS) is a chronic inflammatory autoimmune disease characterized by dry mouth, dry eyes and joint pain. The pathogenesis of this disease is still unclear, and recent studies have found a close relationship between autoimmune diseases and intestinal microecological dysregulation. Sun Wenying [34], in a study of the intestinal flora of patients with pSS, found that there was intestinal dysbiosis in patients with pSS, and the abundance of pro-inflammatory bacteria in their intestines was elevated, but the abundance of metabolizing flora of Prevotella, a group that is closely related to tear secretion, and of SCFAs, which are helpful for immune regulation, was reduced, and it was found that for the first time that the abundance of E. Coli in the diseased population was significantly higher than that in the healthy population, and that this type of flora could induce intestinal inflammation and compete with probiotics for survival space and nutrients, thus aggravating intestinal dysbiosis. Liu Xingyan [35] found that total glucosides of Paeonia lactiflora (TGPs) could promote the growth of bifidobacteria, Lactobacillus, and other beneficial bacteria, alleviate the imbalance of intestinal flora in patients with pSS, increase the content of acetic acid and butyric acid to promote the balance of Th17/Treg cells, and play a role in protecting the intestinal mucosal barrier to alleviate the gastrointestinal discomfort in patients with pSS. pSS belongs to the category of "dry paralysis" in Traditional Chinese Medicine (TCM). In Chinese medicine, pSS belongs to the category of "dryness paralysis", and dryness is related to the imbalance of fluid transmission. In the theory of five organs, the lung is the main propagator of purging and descending, which is closely related to fluid transmission, and the lung is a delicate organ that can be easily injured by dryness, and Zou Fangxia [36] applied the nourishing yin and moistening dryness pills, which was created by Prof. Wang Gang, to the treatment of patients with pSS based on the theory that the lung and the large intestine are mutually superficial. The medicine was made from the addition and subtraction of Zengyi Tang, adopting the concept of combined treatment of the lung and the large intestine, and the patient's symptoms of dry mouth were significantly improved after 2 months of treatment with a combination of traditional Chinese and Western medicine. It proves that the regulation of intestinal function in the treatment of pSS can produce positive feedback on this disease, which further supports the close correlation between intestinal immune function and this disease. As the disease is insidious and there is no systematic treatment plan, Chinese medicine has unique advantages in the treatment of difficult and complicated diseases, and the regulation of intestinal microecology and the enhancement of intestinal immune function through Chinese medicine and the intervention of immune regulation provide a new way of thinking for the treatment of this disease.

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4.2.3. Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is a chronic progressive autoimmune disease that occurs mostly in women of reproductive age, and its onset is mostly related to genetics and the environment, and its pathogenesis involves multiple organs such as the skin, joints, kidneys, lungs, heart, and gastrointestinal tract, etc. Clinically, glucocorticosteroids and immunosuppressant drugs are mostly used to control the disease, which have a good effect, with certain side effects and complications. Glucocorticosteroids and immunosuppressants are often used to control the disease, which are effective and have certain side effects and complications, and there are some limitations in clinical treatment. Numerous studies have shown that patients mostly suffer from an imbalance of intestinal flora (e.g. , decreased ratio of Firmicutes to Mycobacterium anisopliae) and their metabolites [37]. Therefore, the treatment of SLE by intervening the intestinal flora has attracted the attention of researchers, who have successively conducted studies on the intestinal flora regulating effect of the traditional Chinese medicine compound Detoxification, Dispelling Stasis and Resolving Yin Formula on SLE mice and its therapeutic effect on SLE, and found that the Detoxification, Dispelling Stasis and Resolving Yin Formula could change the structure of the intestinal flora and correct the imbalance of intestinal flora of SLE mice [38], and upregulate the abundance of flora that were negatively related to SLE and had an immune-regulating function. It can up-regulate the abundance of bacteria negatively related to SLE and with immunomodulatory functions (such as the genera Bacteroides and Sutterella), reduce the serum inflammatory factor level of mice, and improve the spleen index and localized renal lesions of mice to a certain extent [39], which confirms that the regulation of the intestinal flora of diseased mice by traditional Chinese medicines can have a certain therapeutic effect on SLE. Based on the formula for detoxification, elimination of blood stasis and transformation of yin, Lin Xiaoying [40] investigated the effect of the core medicines of this formula on mice with SLE, and found that the intestinal flora positively related to the disease such as Clostridium and Ruminococcus were significantly down-regulated and increased in the mice that were given the formula of Artemisia annua - Tetragonolactone. The abundance of Clostridium and Ruminococcus in the mice with positive correlation with the disease was significantly down-regulated, and the relative abundance of Clostridium and Paracoccus with negative correlation with the disease was increased. This demonstrates the effectiveness of Chinese medicine in intervening the intestinal flora in the treatment of SLE, and provides a safer and more effective target for the treatment of SLE.

4.2.4. Psoriasis

Psoriasis (psoriasis) is a group of autoimmune diseases with a poor prognosis and a high relapse rate caused by the interaction between hyperproliferative keratinocytes and infiltrating immune cells. Numerous studies have confirmed the close relationship between intestinal dysbiosis and psoriasis. For example, Huang [41] et al. found that the Firmicutes was a key factor contributing to the distribution of the microbiota in healthy subjects, whereas Mycobacterium avium was a key factor contributing to microbiota dysregulation in patients with psoriasis, and Afifi [42] et al. found that the induced overactive Th17 response was a potential causative factor for psoriasis, and that the intestinal flora could regulate the Th17/Treg cell balance, thus the disease may be caused by the intestinal flora through the interaction between immune cells. Therefore, this disease may be prevented and alleviated through the regulation of the flora. Zákostelská Z [43] found that imiquimod induced milder psoriasis-like skin inflammation in germ-free mice than in conventional mice by enhancing the Th17 response, and all of the above confirms that intestinal ecological dysregulation is closely related to the pathogenesis of psoriasis. In the theory of Chinese medicine, the spleen is responsible for transportation of water, grain and fluid, and when the spleen is not healthy, phlegm and dampness are easy to be generated, and the spleen is the source of dampness, and dampness is easy to block the orifices, which is the main pathogen of skin diseases. The herbal compound with the effect of benefiting the stomach and strengthening the spleen can help to regulate the intestinal flora to achieve the purpose of treating the disease. Based on Chinese medicine theory, Liu Xin and Wang Xiaojin [44,45] discussed the correlation between intestinal microecology and psoriasis and the current progress of Chinese medicine treatment based on the relationship between meridians, veins and collaterals, the etiology of sores and ulcers, as well as the symptomatic signs and symptoms of psoriasis, which has found a new way of treating psoriasis with Chinese medicine. Cao Shuang [46] summarized the mechanism of action of TCM monomers and TCM combinations to regulate the balance of Th17/Treg cells in the treatment of psoriasis, and since the immunoregulatory function of intestinal flora is related to this mechanism, its role as a target of TCM in the treatment of psoriasis needs to be confirmed by further research. (Table 1)

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Table 1: Regulatory mechanism of Chinese medicine in treating autoimmune system diseases through intestinal flora

Diseases	Chinese Medicines and Formulas	Associated bacterial community	Mechanisms of Immunological regulation
inflammatory bowel disease (IBD)	Hibiscus esculentus	Mycobacterium↓ Firmicutes↑	Promotes MUC2, inhibits TNF-α expression and ameliorates intestinal inflammation [30].
	Pulsatilla decoction	lactobacillus↑	Regulation of the size and composition of the abnormal BA pool increases TGR5 and FXR expression and inhibits NF-κB activity [31].
	Sanhuang and mugwort soup	lactobacillus↑	Reduces the levels of pro-inflammatory cytokines IL-6, IL-1β and TNF-α, inhibits NF-κB signalling, and inhibits oxidative stress to increase ROS [32].
Primary Sjögren's syndrome	Total glucosides of paeonia	Bifidobacteria↑ lactobacillus↑	Increased levels of butyric acid acetate promote Th17/Treg cell homeostasis[35]
Ystemic lupus erythematosus	Artemisia annua-Turtle Shell	Clostridium↓ Lactococcus↓ Bacteroides↑ Parabacterium↑	Reduces creatinine and TNF-α expression [40]
	Detoxification, elimination of blood stasis and nourishment of yin	Colibacillus↓ Enterococcus↓ Bacteroides↓ Bifidobacteria↑ lactobacillus↑	Reduced levels of serum autoantibodies (anti-dsDNA and ANA) and the inflammatory factor IL-6, down-regulation of splenic index, percentage of splenic plasma cells, and percentage of B-cells in splenic germinal centres [38-39]

5. Summarizing and looking forward

As the research on the relationship between traditional Chinese medicine, intestinal flora and the development of diseases continues to deepen, the connection between intestinal flora and various organs of the human body is also being unveiled one by one. Studies based on the interaction mechanism between the intestinal immune system and intestinal microecology have confirmed that intestinal flora and its metabolites can indeed intervene in immune regulation and help the body to restore a healthy state. Due to the complexity and diversity of the causes of autoimmune diseases, a complete cure cannot be achieved clinically, and research based on the target of Chinese medicine can provide more directions for disease treatment, and provide a scientific theoretical basis for Chinese medicine to promote the recovery of the organism through the regulation of intestinal environmental homeostasis. However, in the current study, the effectiveness of TCM in treating autoimmune diseases has been confirmed experimentally and clinically, but the correlation between its mechanism of action and intestinal flora still needs to be confirmed by further research. At present, there are still limitations on the intervention of Chinese medicine in immune system diseases through intestinal flora, and most of the studies remain at the stage of animal experiments, lacking multi-center and large-sample clinical observation studies. Most of the clinical studies related to intestinal flora are on gastrointestinal diseases, and there are still fewer studies on immune system diseases. In the future, the mechanism of Chinese medicine in treating immune-related diseases through intestinal flora should be studied in depth, and it can also be combined with the advantages of genomics and metabolomics to provide a more effective method for treating autoimmune diseases.

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