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Exploration on the mechanism of TCM treatment for systemic sclerosis based on intestinal flora

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Abstract. Systemic sclerosis (SSc) is a rare chronic disease, it is characterized by immune dysregulation, vascular lesions, and skin and multi-organ fibrosis. The disease is difficult to cure and it is important to find safe and effective complementary therapies.TCM is one of the important complementary therapies of SSc, however, the specific mechanism of action is unclear. In recent years, studies on intestinal flora have provided new ideas for the pathogenesis and treatment of diseases. Intestinal flora has been shown to influence the function of the immune system and play an important role in the development of autoimmune diseases. Modifying intestinal flora disorders and regulating inflammation-associated cytokines may be the basic mechanism of action of TCM for disease treatment. This review combines SSc, intestinal flora, and TCM to explore the mechanism of TCM's therapeutic effect on SSc by regulating intestinal flora, to provide a reference for subsequent studies, and offer new ideas for clinical treatment.

Keywords: systemic sclerosis, TCM, intestinal flora, Autoimmune diseases.

1. Introduction

Systemic sclerosis (SSc) is a disease in which progressive auto-microangiopathy and abnormal synthesis of extracellular matrix proteins in tissues are caused by abnormal auto-antibody production. Research has performed that SSc patients show abnormal levels of oxidative stress markers in the blood and a state of oxidative and antioxidant imbalance, which regulates immunity, promotes inflammation and contributes to the maintenance of fibrosis in systemic sclerosis [1]. The process of its fibrosis is thought to be associated with increased collagen, and the inhibition of excessive collagen production in SSc cells and reduction of collagen accumulation in tissues have become important mechanisms of action of clinical drugs to improve and treat SSc [2]. Immunomodulatory therapies, nonsteroidal anti-inflammatory drugs, glucocorticoids, and biologics are used clinically, but the side effects that occur with the treatments cannot be ignored.

TCM is highly individualized and flexible. It has few side effects and is often used as a complementary treatment for patients with SSc. However, there is no clear and rational explanation for the mechanism of the therapeutic effect of TCM on SSc, which makes it difficult to promote TCM in the clinical treatment of SSc.

The alteration of intestinal flora in SSc patients, which affects human health, may be used to elucidate the pathogenesis, guide therapeutic use, and further explain the mechanism of action of TCM in treating SSc.

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2. SSc and intestinal flora

2.1. Intestinal flora and immunity

The state of good immune system function is decided by the balance between tolerance to its commensal microorganisms and response to external influences determines. The intestine is considered to be one of the most immunologically active organs, and the intestinal mucosa possesses a large number of innate and adaptive immune lymphocytes [3], at the same time there is a large number of colonized microorganisms called Gastrointestinal Microbiota(GM), it plays an important role in human intestinal immunity and systemic immunity, and the disruption of immune homeostasis is the causative mechanism of some autoimmune diseases [4]. Among GM, bacteria, fungi, etc. make up the intestinal flora, with bacteria accounting for the largest proportion. Changes in the composition and abundance of intestinal flora compared to healthy individuals are known as intestinal dysbiosis, which can cause inflammation, metabolic diseases, etc [5].

2.2. Changes in SSc intestinal flora

Although according to the classification criteria currently followed by SSc, the gastrointestinal tract (GIT) is not counted, it is undeniable that up to 90% of patients can present with GIT, and the symptoms of GIT are also thought to influence the morbidity and mortality of SSc disease [6], and its occurrence is not related to the clinical classification of SSc. Although biomarkers of GIT are lacking, the presence of intestinal flora aberrations in GIT is thought to be associated with its symptoms in some studies. Inflammatory bowel disease (IBD) is an autoimmune disease of the gastrointestinal tract, which is a type of GIT and is closely associated with microbial community dysbiosis, presenting with reduced butyrate-producing flora and abnormal inflammatory response [7]. Meanwhile, the pathological mechanism of intestinal fibrosis seen in IBD is similar to that of cutaneous organ fibrosis in SSc [8]. This suggests that our treatment of the same pathological mechanisms may have a modifying effect on the body as a whole.

Jungen Tang et al. found that the intestinal flora of SSc patients showed a decrease in Bacteroidetes and an increase in Firmicutes at the phylum level, and the ratio of Firmicutes to Bacteroidetes also showed an increase. At the genus level there was an increase in Lactobacillus, but a decreasing trend in Bifidobacterium. In contrast, De Luca et al. found an increase in Lactobacillus and Bifidobacterium in the intestinal flora of SSc patients [9]. At the same time, symbiotic beneficial bacteria such as Faecalibacterium, Clostridium, and Rikenella decreased in the intestine of SSc patients, while potentially pathogenic bacteria Fusobacterium, Prevotella, Ruminococcus, Akkermansia, γ-Proteobacteria, Erwinia, and Trabsulsiella increased. Faecalibacterium prausnitzii, which has immunomodulatory properties, also showed a decrease, which is consistent with that in the IBD study [10].In several studies, the presence and severity of intestinal infections in SSc patients also influenced the changes in the intestinal flora, such as a decrease in Bacteroides fragilis, higher levels of Lactobacillus, Blautia, and Coprococcus and lower levels of Faecalibacterium and Roseburia in patients with combined GIT[11]. Another study found that Turicibacter was reduced in the intestine of SSc patients and the abundance of Desulfovibrio increased with increasing severity of GIT [12].

2.3. Effect of SSc intestinal flora

The intestinal flora and the immune cells in the body cooperate and together they form the intestinal immune barrier that affects the development of disease inflammation. The SCFA formed by the intestinal flora after fermentation of food mainly consists of butyrate and propionate, butyrate is mainly produced by thick-walled bacteria and Faecalibacterium prausnitzii, and propionate is mainly synthesized by Bacillus mimicus. The vagus nerve can sense SCFA produced by microbiota and transmit the signal to the central system, and its stimulation has anti-inflammatory effects [3]. At the same time, SCFA contributes to the generation of extra-thymic and peripheral neoplastic Treg cells [13]. Treg and Th17 cells share a TGF-β-mediated pathway for differentiation, and the balance between Treg cells, which have the function of controlling intestinal inflammation and suppressing autoimmunity, and Th17

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cells, which have the opposite effect, affects the development of inflammatory and immune diseases [14]. At the same time, T-cell imbalance may also lead to colony displacement and increased innate immune activation [15].

The elevation of Bifidobacterium in disease may be related to its protective effect of anti-indole phenolate, which induces endothelial aromatic hydrocarbon receptor (AhR) activation for endothelial damage, pro-inflammatory transcription factors such as NF-κB or AP-1 to promote inflammation, and pro-oxidant effects [16]. It has been shown that supplementation with Lactobacillus intestinalis can correct the Treg/Th17 imbalance and lead to a reduction in colonic collagen deposition [17]. Probiotic supplementation did not reduce the patient's symptoms, but also did not worsen, and it reduced Th17 levels in the patient [18]. Probiotics can inhibit the fibrosis of SSc by suppressing T cell-mediated cytokines and inhibit the adhesion of pathogenic bacteria in the intestine thus improving GM [19]. The presence of elevated Bifidobacterium and Lactobacillus as consensus beneficial bacteria in SSc may be a compensatory change in the organism for the appearance of disease inflammation, but the positive effect it produces does not extend beyond the development of the disease process.

It has been shown that increased levels of Akkermansia cause a decrease in levels of the anti-inflammatory cytokines IL-10 and IL-4 and an increase in levels of the pro-inflammatory cytokines TNF-a and IFN-c [20]. Clostridium IV and XIV flora induce Treg cell differentiation. Bacteroides fragilis can deliver immunomodulatory molecules to immune cells by secreting outer membrane vesicles (OMV), inducing IL-10 production by Treg cells to suppress inflammation and promoting mucosal tolerance to microbiota. These two florae also present protective roles in other autoimmune diseases [21]. However, as typical of Gram-negative bacteria, Bacteroides fragilis can secrete a complex mixture of neurotoxins, including LPS, which can stimulate an immune response and cause inflammation by inducing VPO1 expression and promoting an oxidative response leading to NF-κB phosphorylation and nuclear translocation [22]. In the meanwhile, Fusobacterium is also gram-negative anaerobic bacteria. However, probiotics have been shown to downregulate serum LPS and inhibit inflammationcan[23].

There is growing evidence that a stable state of the immune system is the foundation of human health, and that any cytokine-mediated pathway that is overactive can cause different disease states, i.e., immune overload or immune underload. The search for "immune stabilizers", which can maintain a stable state of immunity by adjusting cytokines and inflammatory pathways in the body, may be a future research direction.

3. Progress of research in Chinese medicine for SSc

It was found that Chinese medicine could significantly alleviate the clinical symptoms of SSc. The Yiqihuoxue formula can attenuate bleomycin-induced fibrosis, downregulate SSc dermal fibroblast number, and inhibit TGF-β1-induced ECM gene expression and high-level phosphorylation in NIH/3T3 fibroblasts as well as collagen production [24]. Various herbal extracts have also been studied for their therapeutic effects, such as Icariin (ICA), which has anti-dermal fibrosis effects by activating AMPK signaling and inhibiting WNT/β-linked protein signaling [25]. Dihydroartemisinin significantly inhibits skin fibroblast activation and collagen-1 production by modulating the PI3K-Akt pathway [26]. As a commonly used herbal medicine for SSc to de-liverize the liver and regulate qi, Radix Bupleuri has a main bioactive compound, Saikosaponins, which has anti-inflammatory, immunomodulatory, anti-cancer, and anti-oxidative stress effects [27].

4. Progress of research on regulation of intestinal flora in Chinese medicine

TCM can be fermented or transformed by microbes through the stomach to the intestines to form bioactive or bioavailable metabolites.

Rhubarb Peony soup (RPD) can restore intestinal flora homeostasis and Th17/Treg balance while increasing Treg-related cytokine TGF-β concentration [28]. Modified Gegen Qinlian Decoction (MGQD) can significantly increase the number of SCFA-producing flora and promote Treg cell development to inhibit Th17 cell differentiation, thus re-establishing immune homeostasis [29]. Lycium

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barbarum glycopeptide (LbGP) extracted from Lycium barbarum can increase the abundance of beneficial bacteria such as Turicibacter, Bacteroides, and Lactobacillus and change the intestinal flora to prevent the development of colitis [30], Lycium LBP-3 can also regulate the structure and abundance of intestinal flora to reduce the symptoms of chronic colitis[31]. Pulsatilla decoction is often used to treat "damp-heat dysentery", in recent studies, it has been shown to modulate intestinal homeostasis by upregulating the abundance of Bacteroidetes, Clostridium, and Lactobacillus, and increasing propionate and SCFA content to achieve therapeutic effects in ulcerative colitis [32].

5. Conclusion

SSc causes alterations in the intestinal flora, which is mainly reflected in the decrease of beneficial bacteria and the increase of harmful bacteria. Probiotic supplementation is considered a complementary therapy for SSc, but its specific types and dosage standards cannot be standardized at present. The therapeutic mechanism of TCM as an important complementary therapy for the disease is not clear. Intestinal flora influences the production of inflammatory and fibrotic mediators in SSc, which in turn exerts a facilitating or inhibiting effect on SSc progression. TCM achieves therapeutic effects on SSc by regulating intestinal flora, restoring its homeostasis, and inhibiting the development of oxidative stress, inflammation, and fibrosis. There are countless individual and compound medicines used in TCM for the treatment of SSc, but only a few of them have been investigated. Future studies are necessary to further understand their effective specific components and related effects to rationalize the use of TCM and improve clinical efficacy.

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