

Research Progress of Traditional Chinese Medicine Compound Regulating Intestinal Flora in the Treatment of Rheumatoid Arthritis

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Abstract: This review summarizes the research on the treatment of Rheumatoid arthritis (RA) by traditional Chinese medicine compound and its effect on intestinal flora, including fermented traditional Chinese medicine Qushi Chubi Decoction, Huangqi Guizhi Wuwu Decoction, Huangqin Qingre Chubi Capsule and other traditional Chinese medicine compound. The clinical experiment, animal experiment and the combination of clinical experiment and animal experiment were used in the research, combined with 16 SrRNA sequencing, joint index, pathology, inflammatory factor detection and other techniques to explore the effect of traditional Chinese medicine on RA and the effect of intestinal flora. The results showed that Chinese herbal compounds could alleviate the symptoms of RA by regulating intestinal flora (increasing beneficial bacteria such as Lactobacillus and Bifidobacterium, reducing pathogenic bacteria such as Desulfovibrio and Streptococcus), improving intestinal barrier function or regulating inflammatory factors (reducing pro-inflammatory factors such as IL-1 β and IL-6, and increasing anti-inflammatory factors such as IL-10), and some Chinese herbal compounds (such as fermented Chinese medicine Qushi Chubi Decoction and Zhijing Powder) showed the advantages of rapid onset, long-lasting efficacy, high safety and delaying the recurrence of joint pain. The effect of combined medication (such as Qilong Fengshi Pill combined with L-leucine) was more significant. In summary, Chinese herbal compound can be used as a new clinical choice for RA treatment by regulating intestinal flora.

RA is a chronic autoimmune disease characterized by joint synovitis. Its clinical manifestations are morning stiffness, joint swelling and pain, and dysfunction. In severe cases, it can lead to joint deformity and disability, affecting the quality of life of patients [1]. At present, clinical treatment is mostly dependent on methotrexate, tofacitinib citrate and non-steroidal anti-inflammatory drugs, but long-term use can easily lead to adverse reactions, and some patients have limited efficacy, and the disease is prone to repeated activities. In recent years, the theory of 'intestinal-articular axis' has gradually attracted attention. Studies have found that intestinal flora disorders are common in RA patients, which are manifested as decreased diversity of flora, decreased number of beneficial bacteria, and increased abundance of pathogenic bacteria [2]. The imbalance of intestinal flora can aggravate RA by affecting the differentiation of immune cells and promoting the release of

inflammatory factors. At the same time, traditional Chinese medicine compound has accumulated rich experience in the treatment of RA by virtue of its overall regulation, small side effects and multi-target characteristics. A number of studies have confirmed that traditional Chinese medicine can improve RA symptoms and laboratory data by regulating intestinal microecology [3]. Based on this, it is of great significance to sort out the related research on the regulation of intestinal flora in the treatment of RA by traditional Chinese medicine compound, so as to clarify the treatment mechanism, promote clinical application and reduce toxic and side effects.

1. Clinical experiment of Chinese herbal compound regulating intestinal flora in the treatment of RA

RA belongs to the category of ' arthralgia syndrome ' in traditional Chinese medicine. Arthralgia syndrome is caused by the obstruction of qi, blood and meridians caused by wind, cold and dampness, which is caused by joint muscle swelling, pain, numbness and urgency [2]. Since ancient times, doctors in China have made many contributions to ' Bi syndrome ', and have drawn up many classic prescriptions, which have been widely used in clinical practice. From ancient times to the present, doctors have tried to study and treat the disease from different ways. Hao Gaoting, a scholar, explored the effect of fermented Chinese medicine Qushi Chubi Recipe on RA and intestinal flora. The compound is Professor Wei Zhonghai's 'Qushi Chubi Recipe' empirical prescription. The results showed that the fermented traditional Chinese medicine Qushi Chubi Decoction was effective in the treatment of RA, with rapid onset and long duration of curative effect. It could effectively improve the clinical symptoms of patients, and had obvious advantages in regulating the microecological balance of intestinal flora in patients compared with unfermented traditional Chinese medicine preparations. The fermentation of traditional Chinese medicine can reduce the toxic and side effects of drugs, improve the bioavailability of active ingredients, enhance the efficacy, reduce the use of medicinal materials when ensuring the same efficacy, and improve the taste of traditional Chinese medicine, which is more easily absorbed by the human body [4]. Jiang Yan conducted a study on the effects of Huangqi Guizhi Wuwu Decoction combined with Tofacitinib Tablets on patients with RA of the qi - blood deficiency type. They found that Huangqi Guizhi Wuwu Decoction combined with Tofacitinib Citrate Tablets was effective in the treatment of RA patients with deficiency of both qi and blood, which could significantly improve the M1 and M2 inflammatory reactions, improve the intestinal flora disorder, and did not increase adverse reactions. Tofacitinib citrate tablets can bind to the ATP site of JAK structure, inhibit the phosphorylation and activation of JAK / STAT, and block the inflammatory cascade amplification reaction. Astragalus saponins in Huangqi Guizhi Wuwu Decoction may induce the polarization and transformation of M1 macrophages to M2 macrophages by activating $\alpha 7$ nicotinic acetylcholine receptor. Total glucosides of paeony can regulate the over-activated JAK2/STAT3 signaling pathway. Ginger can regulate immune function, and the combined treatment can produce synergistic effect, enhance the treatment intensity, induce the polarization of related macrophages, and has good safety [5].

2. Animal experimental study on the regulation of intestinal flora and RA by traditional Chinese medicine compound

In addition to the above clinical trials, the researchers also focused on animal experiments, the whole process of multi-channel observation of traditional Chinese medicine compound on the intestinal flora of rheumatoid joints. In order to clarify the mechanism of Huangqin Qingre Chubi Capsule(HQC)in the treatment of RA especially its effect on intestinal flora and intestinal barrier, Peng et al. conducted animal experiments and cell experiments. By observing and analyzing the

data of incidence, joint score, serum, intestinal flora and other related indicators, Peng Yanhui et al. concluded that HQC had obvious anti-inflammatory and anti-rheumatic effects on CIA mice. The intestinal flora imbalance and intestinal barrier damage in CIA mice are potential new targets for the diagnosis and treatment of RA ; hQC improves RA by regulating intestinal flora and intestinal barrier and inhibiting intestinal LPS translocation into blood, and its anti-arthritis effect depends on the regulation of intestinal flora. This study explores the mechanism of HQC in the treatment of RA from the perspective of ' intestine-peripheral blood-joint ' axis, and provides a new perspective for the treatment of RA with traditional Chinese medicine [6]. Sun Yehong et al. continued to take Huangqin Qingre Chubi Capsule (HQC) as the object, and explored its mechanism of action by constructing a rat model for RA (RA) damp-heat obstruction syndrome, combined with 16SrRNA gene sequencing (intestinal flora), LC-MS / GC-MS non-targeted metabolomics (fecal metabolites) and Pearson correlation redundancy analysis (RDA). The results showed that HQC could significantly improve the symptoms of arthritis in model rats, protect joint pathological damage, and down-regulate serum pro-inflammatory factors(TNF- α , IL-1 β , etc.);regulate the intestinal flora (reverse the abundance of Muribaculaceae, Lactobacillus and other bacteria, correct the flora disorder); reversal of various differential metabolites(such as xanthine, palmitoylethanolamide, etc.), improve purine metabolism, tryptophan metabolism and other pathways ; muribaculaceae was positively correlated with anti-inflammatory metabolites such as perilloside E, and negatively correlated with TNF- α /IL-1 β . Finally, it was confirmed that HQC played a role in improving RA damp-heat obstruction syndrome by regulating intestinal flora-metabolite balance, improving immune inflammation and oxidative stress [7].

Wu Ziyang and other scholars found that heat-clearing and blood-activating decoction can effectively alleviate the joint swelling of CIA rats, reduce the clinical score of joints, inhibit synovial inflammation and joint destruction, reduce the expression of synovial CD31 and WEGFR2, and inhibit the number and progress of angiogenesis. The compound can increase the abundance, species and evenness of intestinal flora in CIA rats, and reduce the difference between the normal group and the normal group. In the CIA model group, Lactobacillus is the dominant flora. Heat-clearing and blood-activating decoction up-regulates the proportion of other genera by down-regulating the proportion of Lactobacillus, and regulates the imbalance of intestinal flora to the intestinal flora of normal rats. At the same time, the team found that Qingre Huoxue Recipe can up-regulate the proportion of Treg cells in the spleen of CIA rats, down-regulate the proportion of Th17 cells, regulate the homeostasis of Th / Treg, and regulate the body 's immunity by up-regulating serum IL-10, down-regulating IL-17 and other immune effectors to control synovial inflammation and angiogenesis to alleviate the clinical symptoms of CIA rats [8].

The joint synovium and intra-articular blood vessels of RA are important organs for the occurrence of disease. Improving the inflammation of the joint synovium and blood vessels is also an important way. From the perspective of intestinal microecology, Ling Yuanyuan and other scholars revealed the mechanism of Yishen Juanbi Pills in the treatment of RA, and studied the effects of Yishen Juanbi Pills on serum inflammatory factors (IL-10, IL-17A)and intestinal flora in mice (CIA). The results showed that Yishen Juanbi Pills could significantly reduce the arthritis index score of CIA mice, increase the level of serum anti-inflammatory factor IL-10, reduce the level of pro-inflammatory factor IL-17A, inhibit synovial hyperplasia and pannus formation, and alleviate joint pathological damage. At the same time, Yishen Juanbi Pill can improve the abundance (Chao index, Observed species index)and diversity(Shannon Wiener index) of intestinal flora in CIA mice, reshape the structure of flora and promote the balance of intestinal microecology. Ling Yuanyuan et al. believed that the mechanism of Yishen Juanbi Pill in the treatment of RA may be related to the regulation of Th17/Treg cytokine balance. Intestinal flora may be one of the effective targets of Yishen Juanbi Pill in the treatment of RA. Itplays a therapeutic role by

regulating intestinal microecology and immune balance, and provides a new direction for the treatment of RA with integrated traditional Chinese and Western medicine[9].

While exploring the regulation of intestinal flora by traditional Chinese medicine compound in the treatment of rheumatoid joints, modern technology is also introduced to explore the toxic and side effects and medication safety of traditional Chinese medicine compound. Wang Zhiheng and other scholars took bovine type II collagen-induced CIA mice as the object, and set up normal control group, model group, methotrexate group and antispasmodic powder group for intragastric administration. By recording the body weight and joint swelling degree of mice, the intestinal flora and organ pathology were detected, and the acute toxicity test and subacute toxicity test were also carried out. The results showed that Zhijing Powder could significantly alleviate the joint swelling of mice, reduce the arthritis score and the expression of IL-2 and IL-6 in the joint, and reduce the number of osteoclasts. In terms of intestinal flora, the Chao1 and Shannon indexes of rectal flora were significantly reduced, the abundance of Bacteroidetes and Actinobacteria in rectum and cecum was increased at the phylum level, and the abundance of Firmicutes was decreased. Through experiments and data, it is concluded that Zhijing Powder can improve RA by regulating intestinal flora, increasing beneficial bacteria in rectum and cecum, reducing harmful bacteria in intestine, and restoring intestinal microbial homeostasis. There are no obvious toxic and side effects in the process of medication, which provides a new safe and effective choice for RA treatment [10].

In the study of the effect of traditional Chinese medicine compound on the regulation of intestinal flora on rheumatoid, more and more bacteria have been discovered and valued. For example, Bacteroidetes and Firmicutes are the main related bacteria of RA. In the study of the effect and mechanism of Qiwei Tongbi Oral Liquid on RA rats, Tong Xiaoyu found that each dose of Qiwei Tongbi Oral Liquid could effectively reduce the foot swelling of model rats and inhibit the inflammatory response. The structure and composition of intestinal flora in rats treated with Qiwei Tongbi Oral Liquid were closer to those in normal rats. The abundance of Firmicutes in feces decreased, the abundance of Bacteroidetes and Proteobacteria increased, and the abundance of Bacteroides and Heterobacteroides increased. Tong Xiaoyu believes that Qiwei Tongbi Oral Liquid can inhibit the secretion of inflammatory factors by regulating the abundance and composition of intestinal flora, improve the ecological environment of intestinal flora, and improve the condition of RA rats. Among them, Bacteroidetes and Firmicutes are the main related bacteria of RA, some bacteria in Firmicutes are pathogenic bacteria, and Bacteroidetes in Bacteroidetes are probiotics. Qiwei Tongbi Oral Liquid can effectively inhibit pathogenic bacteria and protect probiotics [11].

The representative prescription for treating cold-dampness obstruction syndrome in arthralgia syndrome is Wutou decoction. It is composed of Chuanwu, Mahuang, Huangqi, Baishao, Gancao. Guo Wentao's team used collagen-induced arthritis(CIA)rats with cold-dampness arthralgia syndrome as a model. The study was conducted through multi-dimensional experiments, including the detection of arthritis index, foot swelling, serum inflammatory factor levels, intestinal barrier repair, analysis of intestinal flora and fecal metabolites, and fecal transplantation (FMT) experiments. The results showed that Wutou decoction could repair the intestinal barrier injury by regulating the ' intestinal barrier-joint axis ', regulate the distribution of immune cells in the intestine-blood-joint, reduce the level of pro-inflammatory factors, regulate the intestinal flora and fecal metabolites, and achieve the therapeutic effect of RA through the coordinated regulation of ' intestinal barrier-immunity-joint ', which provided a new mechanism explanation and effective prescription for RA treatment . Especially in the clinical diagnosis and treatment of traditional Chinese medicine , Wutou decoction is a reliable choice for cold - dampness arthralgia syndrome [12].

In recent years, many studies have found that the diversity, uniformity and abundance of intestinal flora in patients with RA have changed, It is interesting that Chinese herbal compound has

the effect of inhibiting harmful bacteria in intestinal flora and protecting beneficial bacteria. Sun Huihui and other scholars are studying the mechanism of intestinal microecology using traditional Chinese medicine compound Lijie capsule to treat RA. This study found that the diversity of intestinal flora in collagen-induced arthritis(CIA)mice decreased, and the composition of flora changed significantly. The most obvious is the increase of *Desulfovibrio* and *Clostridium* XIVa and the decrease of *Bifidobacterium*; lijie capsule can improve the diversity of intestinal flora in CIA mice and improve the uniformity of flora components. In particular, it can inhibit the growth of *Streptococcus* in the intestine of diseased mice, and has a significant effect on the cultivation of *Bifidobacterium*. By regulating the structure of intestinal flora in CIA mice, it can alleviate joint inflammation and control the progression of RA[13].

In traditional medicine, Tibetan medicine also occupies an indispensable position. We found that some Tibetan medicines can also effectively improve RA. Wang Tong took the traditional Tibetan medicine Siwei Tibetan Maoru Decoction(SXD)as the object, and established a rat model of RA(CIA)to explore its effect and mechanism of improving RA from the perspective of 'intestinal flora-short-chain fatty acid(SCFAs)metabolism'-balance. Seven active ingredients such as gallic acid and loganic acid were found in the study. Researchers have found that SXD can significantly improve the symptoms of arthritis in CIA rats(increase body weight, inhibit joint swelling, and balance serum cytokines), protect articular cartilage and intestinal mucosal barrier(reduce intestinal permeability indicators, increase tight junction protein expression), and regulate intestinal flora, increase α diversity, promote the growth of beneficial bacteria *Prevotellaceae*_UCG-001 and *Bacteroides*, inhibit harmful bacteria *Lactobacillus* and *Desulfovibrio*, and increase SCFAs content. SCFAs were positively correlated with anti-inflammatory factors, beneficial bacteria abundance and tight junction proteins. Finally, it was confirmed that SXD played an anti-RA role based on the balance of 'intestinal flora-SCFAs metabolism ', which provided a theoretical basis for its development and utilization[14].

3. Combination of clinical trials and animal experiments

In the long-term clinical practice of traditional Chinese medicine, it was found that the intervention of Qilong Fengshi Pill on RA was particularly obvious, so Li Na 's team found the difference between RA patients and healthy people through clinical trials. The intestinal flora (enrichment of *Zurich bacillus*, reduction of *Burkholderia*, etc.)and amino acid metabolism (L-leucine) were significantly abnormal in RA patients, and mTOR was the dominant pathway. In order to further verify the effects of Qilong Fengshi Pill and L-leucine on RA and intestinal flora, Li Na 's team further carried out animal experiments. The results showed that Qilong Fengshi Pills or L-leucine could reduce the AI index and serum IL-6 and TNF- α levels in rats, and improve joint swelling and synovial lesions. The combined treatment group can also increase the abundance of *Clostridium butyricum* and *Akkermania*, regulate the balance of intestinal flora, and the combined treatment effect of the two is significantly better than that of the single drug. It is confirmed that Qilong Fengshi Pill can play an anti-RA role by synergistically regulating intestinal flora and amino acid metabolism with L-leucine [15]. This study provides a scientific basis for the development of RA drugs targeting intestinal microorganisms and the role of traditional Chinese medicine in the treatment of RA.

4. Conclusion

The joint synovial membrane of rheumatoid patients is the target tissue of inflammatory cytokines, so protecting the joint synovial membrane and inhibiting inflammatory cytokines is the primary task of clinical treatment. At present, the relationship between intestinal flora and RA is a

research hotspot in recent years. As an important flora in the intestinal microenvironment, beneficial bacteria can protect the intestinal mucosal barrier, reduce the production of pro-inflammatory metabolites, and reduce side effects. At the same time, scholars have also found the mechanism of action of intestinal flora and RA, which provides a new clinical choice for the treatment of RA from new multiple targets. The above studies provide a scientific basis for the development of RA drugs targeting intestinal microorganisms and the role of traditional Chinese medicine in the treatment of RA. At the same time, there are also deficiencies in the research. Many studies only stay in animal experiments. Under the premise of ensuring drug safety and reducing side effects, more clinical studies should be carried out in the future. Clinical studies should expand the sample size and make the data and results more convincing. By understanding these studies, we found that relatively few clinical trials, the future to increase research in this area.

Traditional Chinese medicine is a long and great discipline. Many treatments for RA now have many side effects such as infection, tuberculosis, liver and kidney damage in the blood system. We should give full play to the advantages of traditional Chinese medicine to seek the effect of expelling evil qi without damaging healthy qi when treating diseases. Chinese doctors have been trying to explore ways to treat RA. In clinical practice, they have also received the treatment results of patients' subjective feelings and objective data improvement, summed up experience and actively explored. Innovation in the form of medication, such as the fermentation of traditional Chinese medicine compound fermentation to achieve amazing results, and less than half of the conventional compound measurement. This method also improves safety and reduces the burden on liver and kidney. Through long-term clinical experience, it was found that the intervention of some traditional Chinese medicine compounds was particularly obvious. At the same time, compared with RA and healthy people, amino acid metabolism (L-leucine) was found to be a differential metabolite, and mTOR (the dominant pathway) was significantly abnormal. In order to verify, animal experiments were further carried out. The results showed that the effect of traditional Chinese medicine compound combined with L-leucine was better than that of single drug, and the clinical symptoms, serum indexes, joint indexes and intestinal microecology were improved. The prescriptions of traditional Chinese Tibetan medicine have obvious effects in the treatment of RA, and many rare and effective ingredients have been found through modern scientific research. These explorations provide reliable data support for future clinical practice and provide some unique ideas and ideas.

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