

# Research Progress of Chinese Medicine Regulating Intestinal Flora to Prevent Chronic Atrophic Gastritis

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**Abstract:** *Chronic atrophic gastritis is a kind of common digestive disease in clinic, because of its insidious symptoms and easy to recur, and accompanied by a certain risk of cancer, in recent years in the clinic more and more attention to the incidence of this disease in the world is rising. This disease has the characteristics of complex pathogenesis, high therapeutic difficulty and prolonged recovery, etc. Western medicine treatment of chronic atrophic gastritis has side effects and the role is not significant, the motherland medicine in the treatment of this disease has a unique advantage, and the advantages of high safety, small side effects, significant efficacy, etc. The author will be from the intestinal flora of the relationship between the traditional Chinese medicine to elaborate the progress of the research on the regulation of intestinal flora of traditional Chinese medicine. In this paper, we reviewed the relevant literature from China Knowledge, Wanfang, Wipro, PubMed and other databases, and screened out 36 pieces of target literature. We will review the relationship between intestinal flora and CAG, and at the same time, we will discuss the feasibility of CAG treatment by TCM based on the regulation of intestinal flora, and we will look forward to the important role of the intestinal microenvironment in the future research on CAG flora. We will also review the relationship between intestinal flora and CAG.*

**Keywords:** Chronic atrophic gastritis, Intestinal flora, Traditional Chinese medicine, Research progress.

## 1. Introduction

Chronic atrophic gastritis (CAG) is a severe chronic gastric disease caused by atrophy of the intrinsic glands of the gastric wall with or without intestinal metaplasia and pseudo-pyloric glandular metaplasia as a result of damage to the gastric mucosal epithelium by a variety of factors [1]. It is a common type of digestive system disease in the clinic. It is in the middle of the Correa gastric cancer cascade sequence and is one of the internationally recognized precancerous states of the stomach. Abdominal pain, bloating, postprandial fullness, early satiety, which can be relieved after eating, may be accompanied by loss of appetite, belching and acid reflux as the main clinical manifestations. *Helicobacter pylori* (Hp), unhealthy diet, duodenal reflux, etc. can induce CAG, and its incidence increases with age. This disease is characterized by complex pathogenesis, high treatment difficulty, and prolonged recovery; some patients may still experience recurrence of the disease after treatment, which seriously affects their daily life and health [2-3]. At present, there is no effective treatment for this disease in modern medicine, and how to reverse the pathological changes such as atrophy has become the focus and difficulty of research in recent years.

The gastrointestinal tract is the largest microecosystem in the human body [4]. Intestinal flora has a close relationship with digestive system diseases, and intestinal flora has important roles in promoting digestion and absorption, regulating immunity and nervous system function [5]. In recent years, it has been found that the diversity of intestinal flora in patients with CAG is reduced, the structure of the flora is altered, the abundance of beneficial bacteria decreases, and the abundance of conditionally pathogenic and harmful bacteria is up-regulated [1, 6]. Gut microorganisms produce progressive changes in gastric carcinogenesis, and immune responses caused by microbial changes may lead to the development and progression of gastric cancer [7]. Thus, it is evident that gut flora disorders play an important role in the progression of

CAG from mild to severe disease course. Therefore, by exploring the relationship between the development of CAG and changes in intestinal flora, this paper provides a reference basis for exploring the intrinsic biological mechanism of the development of CAG in Chinese medicine.

## 2. The Understanding of Chronic Atrophic Gastritis in Chinese Medicine

In the field of traditional Chinese medicine, although there is no name of CAG in the ancient books, most doctors believe that this disease can be attributed to the category of “plumpness”, “gastric pain”, “noisy” and so on. Although the symptoms are different, the etiology of the disease can be attributed to six external influences, uncontrolled diet, unhealthy emotions, uncontrolled labor and leisure, and spleen deficiency [8]. The disease is located in the “stomach”, but it is closely related to the “liver”, “spleen”, “kidney”, and the pathogenesis is characterized by a mixture of deficiencies and realities. Deficiency of spleen and stomach qi is the root of its pathogenesis, and blood stasis in the stomach complex is the key to its pathology [9]. In “Suwen - Assessment of Heat Disease Theory”, it is said that “where the evil comes from, its qi must be deficient”, and there is also the theory that “when the disease is long and deep, the line of Ying and Wei is astringent” which can be preliminarily verified. Li Dongyuan in the “Spleen and Stomach” in the words: “If the stomach gas is weak, diet since the double, the spleen and stomach gas is injured, and the vital energy can not be filled, and all the diseases of the birth of the same”, and puts forward the “spleen and stomach are not enough, all for the blood disease” the theory. Thus, it can be seen that the human body of the gas are generated by the spleen and stomach, the disease at the beginning of the injury to the gas, spleen and stomach qi deficiency, the disease for a long time injury to the blood, qi deficiency and blood stasis, qi and blood with the disease [10]. *Jingyue Encyclopedia* in the cloud: ‘all people's gas and blood, as if the source of the spring is also, full of fluent, less

congestion, so the gas and blood is not stagnant, not stagnant, there is no stagnation of the virtual', from the virtual stasis, stasis in the combination of virtual. The symptoms of CAG have been recorded in the Yellow Emperor's Classic of Internal Medicine (HUNDI NEIJING). The Su Wen - Zhi Zhen Yao Da Lun (素问-至真要大论) says: "The victory of the Shaoyang, the heat guest in the stomach, the annoyance of the heart heartache." [11] "Su Wen - Six Yuan Zheng Ji Da Lun" said, "Wood Depression of the hair ..... Min disease stomach and epigastric when the heart and pain, on the support of the two hypochondriacs, diaphragm and pharynx can not be passed, food and drink can not be." The Treatise on Typhoid Fever suggests, "If the heart is full and hard and painful under the heart, this is the knot chest also ..... but full and not painful, this is the plump. The Jingyue Encyclopedia - Plankton" contains: "Plankton, Plankton can not be said; full, full of fullness can not be said. Covering the full is close to bloating, and plumping is not necessary to bloat." "Where there is evil and stagnation and the disease, the real plumping is also; there is nothing and no stagnation and the plumping is also false plumping. If there is pain and fullness, it is real fullness; if there is no pain and fullness, it is false fullness." Elaborating on the identification of deficiency and reality of plumpness [12].

Modern medical practitioners have conducted more in-depth research on the pathogenesis of CAG on the basis of previous researchers. Most of them believe that CAG is located in the stomach and is closely related to the liver and spleen. Dietary disorders, weakness of the spleen and stomach, emotional and emotional disorders, and external evils in the stomach can all lead to the occurrence of CAG, and the interaction of multiple factors can lead to the development of CAG due to the weakness of the stomach and stasis of the veins and channels, which is a kind of deficiency of the root cause and symptoms of CAG, or a mixture of deficiencies and deficiencies, with deficiency of the spleen and stomach qi being the root of CAG, and stasis of blood in the gastric channels being the key to its pathology [13-14]. Xu Jingfan, a master of Chinese medicine, focuses on the treatment of chronic gastralgia from the perspective of "blood stasis" and believes that qi deficiency, qi stagnation, yin deficiency, bleeding and other factors can lead to the formation of "blood stasis" in the spleen and stomach diseases, which is classified into qi deficiency and blood stasis, qi stagnation and blood stasis, yin deficiency and blood stasis and heat breakage and blood stasis, among which qi deficiency and blood stasis are the most common ones. Among them, qi deficiency and blood stasis is the most common [15]. Zhang Zesheng pointed out that CAG is mostly characterized by deficiency and stagnation of qi in the middle, and as qi disease affects blood over a long period of time, both qi and blood should be taken into account, so the medication should focus on benefiting qi and activating blood [16]. According to Shan Zhaowei, this disease is characterized by a mixture of deficiency and reality, starting from spleen deficiency, spreading to liver depression, being heavy in dampness and heat, and being tied to blood stasis. The pathogenesis of the disease is mainly attributed to qi deficiency and blood stasis, and dampness and heat are internalized. And because the stomach is an internal organ with many qi and blood, it is valuable to regulate qi and blood, and all kinds of internal and external factors can make the qi and blood of the stomach function abnormally and lead to qi

stagnation and blood stasis, so the treatment is centered on regulating qi and blood [17].

### 3. Intestinal Flora and Chronic Atrophic Gastritis

The gastrointestinal tract is the largest microecosystem in the human body, and the function of gut microorganisms in the human body is closely related to human health, which not only affects nutrient supply and energy balance, but also participates in a variety of physiological processes, such as immune defense, endocrine regulation, and inhibition of pathogen colonization [18]. It is estimated that there are about 1, 014 species of bacteria in the human gut, whose genomes are more than 150 times larger than the host genome, and these bacteria are called intestinal flora. The human intestinal flora consists mainly of the phylum Thick-walled Bacteria, Bacteroidetes, Ascomycetes, and Actinobacteria. Among them, the thick-walled phylum and the anaplasma phylum account for about 90% of all intestinal microflora [19]. The ability of intestinal flora to harmoniously and stably inhabit the intestinal tract can be attributed to the following functions: (1) the ability to ingest and synthesize nutrient metabolites, such as bile acids, vitamins, and short-chain fatty acids; (2) to maintain the integrity of intestinal epithelium by regulating intestinal pH and competing for nutrients to resist pathogenic bacterial colonization; and (3) to regulate the development, homeostasis, and function of intrinsic and adaptive immune cells [20]. Stabilized intestinal flora protect host intestinal health in a symbiotic manner, resisting external interference and maintaining normal structural and metabolic functions. The composition structure and number of these microbiota may vary depending on the host's age, sex, anatomical site, dietary habits, physicochemical and immunological factors. Intestinal dysbiosis has been defined as the loss of the fragile balance of various microorganisms in the intestinal ecosystem in the organism [4].

Intestinal flora is closely related to digestive diseases, and intestinal flora has important roles in promoting digestion and absorption, regulating immunity and nervous system function. In normal intestinal microecology, the intestinal flora maintains a dynamic balance, with beneficial and pathogenic bacteria interdependent and mutually restraining each other to achieve a dynamic flora balance and play the role of an immune barrier, but when the homeostasis of the intestinal flora is disrupted, some conditionally pathogenic bacteria can rapidly proliferate and mediate inflammatory responses [21]. The current study found that in the normal human intestinal microflora, the phylum Bacteroidetes and the phylum Firmicutes are the most dominant phyla, but when the gastric inflammation attacks, which leads to the gradual atrophy of the gastric mucosa, the intestinal homeostasis will be tilted and altered, and the abundance of dominant flora and the structure of the flora clustering will be changed as well [22].

Gut microflora and their metabolites play a central role in regulating intestinal health and disease. Changes in the composition of the gut microbiota are associated with inflammation and metabolic disorders. The gut flora plays a key role in the development of CAG. Studies have shown that the intestinal flora of patients with CAG differs significantly from that of the healthy population in terms of flora

abundance, structure and composition [23]. Xie Bean Bean and Zhu Long et al. showed that there is a tendency for beneficial bacteria to decrease in patients with CAG compared to the healthy population [24]. Huang Diem Yu and Lin Xuejuan et al. showed that the top ten genera in abundance in patients with CAG were *Anaplasma*, *Prevotella*, *E. faecalis*, *Anaplasma paraphyllum*, *Megachilus*, *Caulobacter*, *Clostridium*, *Anaplasma paraphyllum*, *Rhodobacter*, *Trichosporon*, *Eubacterium eligens* group of genera, and that there was a some degree of disproportion. Among them, the abundance of *Bifidobacterium* spp. was significantly reduced in group C-3 compared with group C-1 ( $P < 0.05$ ), while the abundance of *Prevotella* spp. was significantly enriched ( $P < 0.05$ ), and LEfSe analysis showed that *Bifidobacterium* spp. and *Cetylloccoccus* spp. were the characteristic genera [7]. With the increasing research on intestinal flora, it has been found that intestinal flora can accelerate the risk of gastrointestinal intraepithelial neoplasia, and intestinal flora may promote the development of gastric cancer [25]. Thus, it is evident that intestinal flora disorders play an important role in the development of CAG from mild to severe disease course.

#### 4. Chinese Medicine Regulates Intestinal Flora to Prevent Chronic Atrophic Gastritis

The development of CAG is closely related to the intestinal flora, and the clinical symptoms of CAG patients can be improved by regulating the imbalance of the flora and restoring the normality of the flora in clinical treatment, and Chinese medicine is actively exploring and researching in this aspect. The formula follows the method, the method follows the evidence, the formula is formed by the medicine, and the method is used to unify the formula. In previous studies, Chinese medicine scholars believe that the treatment of CAG should be based on the main therapeutic direction of nourishing the stomach, benefiting the qi and strengthening the spleen, etc. The dosage of traditional Chinese medicine can be increased or decreased according to the patient's disease, in which *Angelica Jianzhong Tang* has the efficacy of warming and tonifying the qi and blood, easing the urgency and relieving the pain, etc. The traditional Chinese medicines of *Angelica sinensis* and white peony have the efficacy of strengthening the spleen and benefiting the qi and regulating the spleen and stomach, etc. Licorice can achieve the efficacy of clearing away heat and removing toxins, regulating the whole formula, and neutralizing the properties of all the drugs, etc. [1]. Intestinal flora is an important part of the biological basis of CAG, and is also an important way for Chinese medicines to exert their therapeutic effects.

##### 4.1 The Role of Chinese Medicine Compound Prescription and Preparation in Regulating Intestinal Flora to Prevent Chronic Atrophic Gastritis.

Chinese medicine compound prescription can be added or subtracted according to different types of diseases, and it is widely used in clinic. Du Mingmin, Lang Xiaomeng et al. found through modern pharmacological research that the treatment of liver-sparing and turbidity-reducing formula can improve the antibacterial effect, inhibit the propagation of *Helicobacter pylori*, and significantly improve the clinical symptoms of dyspepsia and other symptoms of the patients

[26]. Xu Yapei et al. used the formula of Chai Shao Liu Jun Zi Tang plus and minus to treat patients with chronic atrophic gastritis of liver depression and spleen deficiency type, and the results showed that the total effective rate of the experimental group was higher when compared with the control group that was treated with western drugs alone during the same period of time [27]. Half-summer diarrhea heart soup is a conciliatory agent, which has the effects of harmonizing the liver and spleen, leveling cold and heat, and eliminating plaques and dispersing knots. The half-summer in the formula has the effects of dispersing knots and eliminating plaques, descending rebelliousness and stopping vomiting, which is the monarch's medicine, and with dried ginger, it can achieve the effect of warming the center and dispersing evils; Huanglian and *Scutellaria baicalensis*, which can drain heat and eliminate plaques, are the ministers' medicines, and ginseng and jujubes, which can achieve the effects of sweetness and warmth and benefit the vital energy and tonify the vital energy of the spleen. Finally, licorice is used to neutralize the medicinal properties, which can help to improve the safety and efficacy of the treatment [28]. Strengthening the spleen and clearing heat and dampness soup is often used to improve the patient's spleen and stomach disharmony, dampness and heat trapped spleen symptoms, the formula selected lotus seed, lily, yam and other traditional Chinese medicines can achieve the effectiveness of strengthening the spleen and eliminating dampness, clearing heat and assisting yang, etc., and its application in the treatment of chronic atrophic gastritis can help to improve the patient's Chinese medicine syndrome, alleviate the discomfort of the epigastric region, and help to promote the recovery of the post-treatment period compared with the conventional treatment [29].

##### 4.2 The Role of Chinese Medicine Monomers and Active Ingredients in Regulating Intestinal Flora to Prevent and Control Chronic Atrophic Gastritis

Studies have shown that the monomers, active ingredients or components of many traditional Chinese medicines have the effect of regulating the intestinal microecology of CAG and improving the intestinal flora disorders of CAG. By making CAG mouse model, Zhang Shiyang et al. found that the effective components of ginseng and *Atractylodes macrocephala* could significantly improve the degree of gastric mucosal atrophy and the level of inflammation in rats, which had a mitigating effect on chronic atrophic gastritis and to some extent reversed the declining abundance and diversity of the intestinal flora, and reduced the number of pathogenic bacteria in the intestine [30]. Liu Y et al. experimentally proved that *Astragalus* could regulate serum pepsinogen PGI through regulating serum pepsinogen PGI, PG II and PGR levels play an important role in the treatment of CAG patients, and for the regulation of intestinal microorganisms in CAG model rats, it was found that *Astragalus* could effectively dial back the abundance of the beneficial bacterium *Acetobacter* spp. and the pathogenic bacterium *Escherichia* spp. [31]. It has been shown that the intestinal flora structure of CAG patients changed as follows after the use of sour horse milk: *E. faecalis* *Faecalibacterium prausnitzii*, *E. rectale*, *Eubacterium rectale*, *Bacteroides uniformis* and *Roseburia* spp. The relative content of beneficial bacteria increased, while the relative content of conditionally pathogenic bacteria such as

Parabacteroides parabacteroides and Shigella spp. Shigella decreased [32].

## 5. Concluding Remarks

Chronic superficial gastritis will develop to atrophic gastritis, and then intestinal epithelial hyperplasia will occur, which will lead to heterogeneous hyperplasia, and ultimately to gastric cancer, and in the process of gastric cancer, chronic atrophic gastritis is the central link, and it plays an extremely important role in the process of blocking the occurrence of gastric cancer, therefore, if it is found that the chronic superficial gastritis has transformed to atrophic gastritis, then it is necessary to be highly vigilant, and to actively prevent the occurrence of gastric cancer.

Intestinal microecology not only has an important impact on gastrointestinal function, but also the imbalance of intestinal flora is an important reason for the progression of gastrointestinal diseases. Imbalance of intestinal flora is a risk factor for chronic atrophic gastritis accompanied by intestinal epithelial chemotaxis lesions. Currently, the literature mainly focuses on the relationship between the intestinal monospecies, phylum, and complexity of the flora and the progression of chronic atrophic gastritis, and a comprehensive summary of the literature shows that beneficial intestinal bacteria include Bifidobacterium, Prevotella, and Mycobacterium, and harmful bacteria are mainly Dorea, of which Bifidobacterium is one of the main probiotic bacteria in the human body, which participates in the digestive, absorptive, metabolic, nutritional, and immune processes, and plays a role in maintaining the intestinal mucosa and maintaining the intestinal epithelial chemosis. Bifidobacterium spp. is one of the major probiotic bacteria in the human body, participating in digestion, absorption, metabolism, nutrition, immunity and other processes, and plays an important role in maintaining the integrity of the intestinal mucosal barrier [33]; Prevotella spp. has a close correlation with chronic functional gastrointestinal dysfunction, and is an indispensable beneficial bacterial genus for the maintenance of gastrointestinal function [34, 35]; Bacteroides spp. have a mitigating effect on the inflammation of chronic atrophic gastritis [36]; and the harmful bacterial genus Dorea has been associated with the exacerbation of the inflammation of chronic atrophic gastritis [2]. All these studies suggest that there is a close correlation between the morbid body condition of patients with chronic atrophic gastritis with intestinal epithelial hyperplasia and the abundance of intestinal flora, the complexity of the flora species, and the diversity of the flora community.

It is the focus of future work to construct a perfect TCM evidence model from the ideas of holistic concept and evidence-based treatment, and to conduct high-quality, large-sample, multi-center clinical trials with relevant targets. It can be seen that there is still a lot of room for the development of TCM in regulating intestinal flora in the treatment of CAG, combining TCM evidence-based thinking with modern medical principles, and taking intestinal flora as a research focus, so as to achieve effective prevention and control at the stage of CAG or even earlier, researching and developing TCM based on the precise regulation of intestinal flora, and exploring the prospects for the application of TCM

in the treatment of CAG. The basic pathomechanism of CAG is spleen deficiency and blood stasis. The basic pathogenesis of CAG is spleen deficiency and blood stasis, which is the key to the pathology of the disease, and is found throughout the development of the disease; therefore, clinical evidence of qi deficiency and blood stasis is common. In recent years, a number of studies have shown that Chinese medicine regulates intestinal flora therapy in CAG, which has a high efficiency through data control, and plays the roles of increasing blood flow in mucosal microcirculation, down-regulating inflammatory response, regulating uncontrolled cell proliferation-apoptosis, repairing damaged mucosa, and reversing pre-cancerous lesions, etc. [1]. Various medical practitioners have adopted self-proposed formulas for treatment, which always focus on benefiting qi and strengthening the spleen, regulating qi and activating blood circulation and removing blood stasis. In this paper, we summarize the research results of various authors, and from the perspective of intestinal flora, we sort out the theoretical origin, microdiagnosis, traditional Chinese medicine (TCM), and the combination of TCM and western and traditional Chinese medicine (WCM) in order to provide references for the clinical treatment and research of CAG.

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