

# Research Progress of Cuttlebone in the Treatment of Chronic Atrophic Gastritis

Yu Jia<sup>1</sup>, Yun Li<sup>1</sup>, Yongpan Xu<sup>2,\*</sup>

<sup>1</sup>The First Clinical Medical College, Shaanxi University of Chinese Medicine, Xianyang 712046, Shaanxi, China

<sup>2</sup>Digestive Department, Affiliated Hospital of Shaanxi University of Chinese Medicine, Xianyang 712000, Shaanxi, China

\*Correspondence Author

**Abstract:** As a common disease of digestive system, atrophic gastritis has the characteristics of high incidence, lingering condition, complex mechanism, and can be further developed into gastric cancer. Western medicine can not reverse the transformation of the disease at present, while traditional Chinese medicine can better improve the clinical symptoms and improve the quality of life through individualized treatment. Chinese medicine cuttlebone has the effects of acid pain relief, convergence hemostasis, bacteriostasis, dampness and sore astringency. It is a commonly used Chinese medicine for the treatment of chronic atrophic gastritis. At present, the research on cuttlebone is mostly focused on clinical efficacy, and the mechanism of action is less. Therefore, this paper reviews the research progress of cuttlebone in the treatment of chronic atrophic gastritis in combination with pharmacological research, famous doctor experience and data mining, so as to provide reference for the future research and treatment of chronic atrophic gastritis.

**Keywords:** Cuttlebone, cAG, Chronic atrophic gastritis, Calcium carbonate.

## 1. Introduction

Chronic atrophic gastritis (CAG) is a common digestive system disease developed from chronic superficial gastritis. Due to the repeated damage of gastric mucosal epithelium, it leads to chronic inflammatory reaction of gastric mucosa and reduction of inherent glands. It occurs in the elderly. It has a slow onset, lingering condition and is difficult to cure [1]. The clinical symptoms of CAG lack specificity and are not completely consistent with the degree of disease development [2]. Some patients with CAG have no obvious discomfort in clinical manifestations, but most patients will have upper abdominal burning pain, swelling pain, aggravation after eating, poor appetite, nausea, acid reflux [3], and other gastrointestinal symptoms. Patients with severe symptoms will have anemia [4]. CAG is often accompanied by different degrees of intestinal metaplasia or atypical hyperplasia. The World Health Organization lists it as a precancerous state of gastric cancer, so CAG is a multi-pathogenic disease and precancerous lesion [5, 6]. Studies have shown that gastric cancer is the fourth most common cancer in the world and the second most common cancer in China [7, 8]. Therefore, CAG patients often have some anxiety, which affects their daily life [9].

Because CAG does not have a corresponding TCM disease name, Because it often appears epigastric pain, stuffiness, chest tightness, belching frequently, anorexia pantothenic acid and other symptoms, so traditional Chinese medicine will be classified as 'stomach pain', 'fullness', 'noisy' and other categories [10]. Its occurrence is mostly due to cold pathogen invading the stomach, internal injury diet, liver qi invading the stomach, spleen and stomach weakness and other factors, and the stomach is a fu-organ with many qi and blood. If the spleen and stomach are deficient, the biochemical source is deficient, which will make qi and blood deficiency, stomach collaterals disharmony, lack of body fluid and blood, qi block, resulting in gastric collateral stasis, which is a syndrome of deficiency and excess [11]. At present, Western medicine believes that Hp infection is the main cause of CAG, and symptomatic treatment is generally adopted. However, due to

the spleen and stomach disease, the condition is repeatedly prolonged, and Western medicine treatment has its limitations. A large number of studies have found that Chinese medicine has a good effect on this kind of chronic disease, with multi-target, multi-level, multi-channel and other advantages [12, 13]. The traditional Chinese medicine cuttlebone has the effect of antacid analgesic, astringent hemostasis, bacteriostatic and astringent sores [14]. Liu Xiangxiang et al. [15] found that the frequency of treatment for stomach pain was the highest and the curative effect was stable through frequency statistics and cluster analysis of 2599 prescriptions using cuttlebone. Zhou Xuewen, a master of traditional Chinese medicine, often uses cuttlebone and other traditional Chinese medicines to treat stomach pain, heartburn, acid regurgitation and other symptoms caused by chronic gastritis in western medicine, and has a good effect [16, 17].

## 2. Research Progress of Cuttlebone

Cuttlebone, first recorded in the 'Yellow Emperor's Internal Classic', also known as squid bone, squid fish bone, is the dry inner shell of needleless squid or golden squid [18]. It belongs to the spleen and kidney meridians, 'Shen Nong's Herbal Classic' says: 'Squid bone, salty and mildly warm, 'is astringent medicine, which is a good product for the treatment of epigastric pain and excessive gastric acid [19]. The use of cuttlebone cuttlebone has a 'small prescription': 'scrape off the skin. " 'Sheng Hui Fang': 'Study carefully. " Bojifang ": " research very fine fly over use. " 'Yicaotingke': 'Remove clothes, grind fine, and rinse with water. " Surgical Dacheng ": " Soup bubble peeling. Now take more of its raw materials, remove excess impurities, rinse with water until there is no obvious salty taste, dry, remove its hard shell, smash into small pieces [20, 21].

Modern pharmacological research [22, 23] found that cuttlebone has a loose and porous network structure, and its chemical composition is complex. The main component is calcium carbonate, which contains more than 70 inorganic elements, 16 protein components, and 168 polypeptide components. The protein components are mainly hemocyanin,

myosin, actin, etc.; polypeptides are mainly derived from actin, histone, tubulin, etc. [24]. Through the detection of the chemical composition of cuttlebone, it was found that cuttlebone contains more trace elements Zn, Fe, Mn, Cu, which are essential for the human body. It has a stable nutritional value, and has pharmacological effects such as neutralizing gastric acid, hemostasis, anti-ulcer, protecting gastric mucosa, antibacterial, osteogenesis, phosphorus reduction, etc. [25, 26]. Liu Yang [27] and others analyzed 1726 papers on the theme of cuttlebone, and found that clinical application accounted for the highest proportion, including 156 articles on the treatment of spleen and stomach diseases and 122 articles on the treatment of chronic gastritis.

It can be seen that cuttlebone is widely used in the treatment of chronic gastritis in clinic, and cuttlebone has the advantages of abundant resources, high quality and low price, so it has rich research value.

### 3. Mechanism of Cuttlebone in the Treatment of CAG

3.1 Analgesic effect of acid CAG patients often appear on the abdomen burning pain, acid reflux and other symptoms, which is related to the reduction of gastric glands. CAG often begins to shrink from the gastric antrum and pylorus. However, a large number of pyloric glands are distributed in the gastric antrum and pylorus. The pyloric glands mainly secrete mucus and  $\text{HCO}_3^-$ , which together form a barrier against gastric mucosal injury, called mucus-bicarbonate barrier. It can effectively prevent gastric acid and pepsin damage to the stomach [28]. However, in the early stage of CAG, the atrophy range is limited, the number of pyloric glands is reduced, the secretion of mucus and  $\text{HCO}_3^-$  is reduced, and the mucus-bicarbonate barrier is thinned, but it will not affect the gastric parietal cells located in the gastric body and the bottom of the stomach (mainly secrete gastric acid). Therefore, the secretion of gastric acid is normal, and CAG patients have symptoms of burning pain and acid reflux [29, 30]. For patients with such symptoms, proton pump inhibitors (PPI) drugs are commonly used in clinical treatment. The drug can reduce the secretion of gastric acid by gastric parietal cells by binding to  $\text{H}^+ - \text{K}^+ - \text{ATPase}$ . However, the combination of PPI and  $\text{H}^+ - \text{K}^+ - \text{ATPase}$  is an irreversible process, so long-term use of the drug can cause a series of adverse reactions [31, 32]. The application of cuttlebone in the treatment of CAG has the advantages of significant curative effect and small adverse reactions. Li Lan et al. [33] found that the calcium carbonate component in cuttlebone accounted for up to 85 % by inductively coupled plasma atomic emission spectrometry (ICP), X-ray diffraction analysis and other methods, which could effectively neutralize gastric acid and relieve the symptoms of burning pain and acid reflux in the upper abdomen. Fanger Li [34] found that the PH value of gastric juice in mice increased significantly after intragastric administration of cuttlebone in rats, and further experiments showed that the increase of PH value of gastric juice was caused by neutralization, and through subsequent experiments, it was found that cuttlebone could significantly increase the content of cAMP in rat gastric tissue. As a second messenger, cAMP is involved in the regulation of digestive tract activity, which can promote the secretion of gastric mucus and enhance the tolerance of

gastric mucosal cells to acid [35, 36]. In addition to a large amount of carbonate, cuttlebone also contains a certain amount of polysaccharide components, mainly chitin, etc. [37]. Chitin can be obtained by soaking squid bone in different concentrations of HCL and NaOH, and washing, drying and weighing. Chitosan is the only alkaline polysaccharide in nature. When it contacts with gastric acid, it will be neutralized with gastric acid, and chitosan can be dissolved into gel solution under acidic conditions, which has good film-forming properties [39, 40]. The above modern pharmacological studies and experimental studies have confirmed that cuttlebone can alleviate the burning sensation and pain caused by excessive gastric acid to a certain extent, and its mechanism may be related to the neutralization of gastric acid by carbonate and chitosan in cuttlebone. Cuttlebone stimulates cAMP secretion to strengthen the gastric mucosal barrier and increase the tolerance of gastric mucosa to acid. Chitosan can also form a harmless biofilm, which enhances the protective effect of gastric mucosal barrier, and is also reflected in many prescriptions for acid and pain relief, such as Weiling Granules, Gastric Ulcer Tablets, Weitongning, Ganwei Qitong Powder, Wubei Powder, Anwei Tablets and so on.

3.2 Bacteriostatic effect Helicobacter pylori (Hp) infection is one of the important causes of CAG, and Hp infection is easy to aggravate the malignant transformation of CAG [41, 42]. Yin et al. [43] found that the prevalence of CAG was about 25 %, and the risk of CAG in HP-positive patients was about 2.4 times that of HP-negative patients. It is not difficult to find through the data that the prevalence of CAG is very high in the world, and HP infection is the primary risk factor for CAG. Therefore, the eradication of Hp can effectively improve the gastric inflammatory response, delay the progression of the disease, and prevent the deterioration of the disease.

A large number of studies have found that the sterilization effect of most antibiotics decreases rapidly under acidic conditions, and increasing the pH value can down-regulate the MIC value (minimum inhibitory concentration) of various antibiotics [45]. As mentioned above, cuttlebone contains a large amount of calcium carbonate and chitosan, which can regulate the gastric environment, neutralize gastric acid, and increase the pH value of the gastric cavity, which is conducive to the eradication of Hp. In addition to increasing the pH value and destroying the living environment of Hp, calcium carbonate will also release calcium ions during the neutralization process, and calcium ions will produce electrostatic interaction with the cell membrane of bacteria, thus changing and destroying the cell membrane structure of bacteria, resulting in the rupture and death of bacteria [46]. In addition, studies have shown that chitosan has broad-spectrum antibacterial activity [47, 48]. Zhu Wenjing [49] took the inner bones of three kinds of squid (golden squid, squid, cuttlefish) and dried the powder, added 80 % ethanol to make a suspension, and cultured a variety of bacteria. The results showed that the three kinds of squid bones had inhibitory effects on a variety of bacteria. Jiao Tianyu [50] et al. made chitosan / polyvinyl alcohol nanofiber membrane, which was wrapped on the surface of levofloxacin, and combined the strong inhibitory effect of levofloxacin on Hp with the structure of chitosan / polyvinyl alcohol nanofiber membrane. In vivo and in vitro experiments, it was found that

the nanofiber membrane loaded with levofloxacin had a broad-spectrum and long-term antibacterial effect on *Helicobacter pylori*, and the effect was better than the traditional quadruple therapy. Hp-positive patients often show a certain degree of family aggregation. For Hp-positive members in the same family, they are in a dangerous environment [51, 52]. Therefore, how to prevent Hp infection has become a hot topic in the latest research. Xie et al. [53] divided 30 mice into three groups: HP antigen group, Hp antigen + chitosan acid solution group, Hp antigen + immune adjuvant cholera toxin (CT) group. After three times of intragastric administration, it was found that the immune protection rate of Hp antigen with chitosan as adjuvant could reach 60 %, while that with CT as adjuvant was 58 %. Both of them were significantly higher than that of Hp antigen group alone, which could effectively prevent Hp infection. Therefore, in summary, whether it is for the eradication of Hp patients, or the prevention of infection in high-risk groups, cuttlebone has a good effect.

**3.3 Anti-inflammation and protection of gastric mucosal inflammation** As one of the main pathological manifestations of chronic atrophic gastritis, it is caused by the atrophy of glands, the decrease of mucus secretion, the decrease of gastric mucosal barrier function, and the long-term stimulation of gastric acid to gastric mucosa [54]. The occurrence of inflammation is inseparable from the role of inflammatory mediators, and arachidonic acid is the main source of inflammatory mediators [55]. The determination of traditional Chinese medicine cuttlebone also contains coumarin and other components [56], and studies [57] have found that coumarin compounds can affect the metabolic pathway of arachidonic acid by inhibiting lipoxygenase and cyclooxygenase, thereby exerting anti-inflammatory effects. In addition, chitin in cuttlebone can also inhibit inflammation and promote inflammation recovery by reducing the expression of pro-inflammatory cytokines, such as TNF- $\alpha$  and IL-6 levels [58]. Je Kwan Jang et al. [59] immersed the shaved dorsal area of rats in hot water to produce burns, and applied chitin locally. After 14 days of histological analysis, it was found that chitin significantly increased the recovery of wound inflammation, reduced the white blood cell count and the expression of pro-inflammatory factors TNF- $\alpha$  and IL-6, and had a good anti-inflammatory effect. Qiu et al. [60] prepared a rat model of acute mucosal injury induced by indomethacin and added cuttlebone as a preventive administration. It was found that the gastric mucosal injury index and inflammation score of rats were lower than those of the control group, and there was a positive dose correlation. The concentration of EGF and PGE2 in serum of rats was increased. It was found that cuttlebone could protect gastric mucosa by activating the expression of EGF and increasing the secretion of PGE2. Zhao Wenling [61] et al. pretreated 20 mice with different doses of cuttlebone polysaccharide, and then gavaged with anhydrous ethanol to detect the degree of gastric mucosal injury. It was found that different doses of cuttlebone polysaccharide could protect the integrity of gastric mucosal cells. At the same time, it also protected the integrity of gastric muscle cells and increased the inhibition rate of injury. Cuttlebone polysaccharide increased the local blood circulation of the stomach and reduced the damage of gastric mucosa, thereby strengthening the functional mechanism of gastric mucosal defense stimuli. Guo Yifeng

[62] determined the nitric oxide (NO) and glutathione (GSH) of gastric mucosa by using cuttlebone polysaccharide to pretreat gastric mucosal injury model mice. It was found that the NO and GSH in the cuttlebone polysaccharide pretreatment group were significantly higher than those in the simple model group. NO is an endogenous substance that regulates the blood flow of gastric mucosa and maintains the integrity of gastric mucosa. It has the effect of relaxing blood vessels. GSH is helpful to protect the immune system of gastric mucosa. Therefore, cuttlebone polysaccharide protects gastric mucosa by increasing the concentration of NO and GSH. Zhang Zhengli et al. [63] first intragastrically administered ethanol to mice, and then intragastrically administered cuttlebone. It was found that high doses could increase the content of aminohexose and effectively reduce gastric mucosal damage. Aminohexose [64] and PGE2 [65] are important components of the gastric mucosal barrier. Aminohexose is the main component of glycoprotein in the mucous layer of the mucosa, maintaining the normal structure and function of the mucous layer. PGE2 can increase the secretion of gastric mucus, bicarbonate, and surfactant phospholipids, thereby strengthening the protective function of the gastric mucus-bicarbonate barrier.

In summary, calcium carbonate and other components in cuttlebone can neutralize gastric acid and reduce the stimulation of gastric acid to gastric mucosa; a variety of components such as coumarin can inhibit the release of inflammatory factors and alleviate local inflammatory reactions, thus alleviating the existing symptoms. It can also increase the concentration of NO, GSH, increase local blood flow, promote the repair of damaged mucosa, and promote the secretion of hexosamine and PGE2 to increase the barrier function of gastric mucosa. The anti-inflammatory effect of cuttlebone and the promotion of gastric mucosal repair are also reflected in many prescriptions, such as Baifen Powder, Gastric Ulcer Tablets, Jingji Powder, Weitongning, Kuiyang Powder, Qishao Jicao Decoction and so on.

**3.4 Other effects** Studies have shown that CAG patients are often accompanied by symptoms of anemia and wasting, which is related to the lack of iron ions and the lack of internal factors [66]. As mentioned above, in addition to a large amount of calcium ions, there is a certain amount of iron ions in cuttlebone. Therefore, taking cuttlebone can improve iron deficiency anemia. Qiu Lingling et al. [67] studied the composition of cuttlebone by microwave digestion-inductively coupled plasma mass spectrometry and found that it contains 18 common amino acids and some trace elements necessary for human body, which can play a certain role in nutritional support for CAG patients. In summary, cuttlebone can play a role in nutritional support for anemia and emaciation caused by chronic diseases.

## 4. Summary and Prospect

As an ancient Chinese medicine, cuttlebone has undergone several tests in the long history and has important medicinal value. It comes from the inner shell of marine biological squid. It has a wide range of raw materials, affordable prices, and high safety. Therefore, it has broad development prospects and is also a hot research topic in recent years. In this paper, from the analysis of the chemical composition of cuttlebone, it

was found that it had the effects of acid-producing and analgesic, protecting gastric mucosa, bacteriostasis and anti-inflammation. Both pharmacological effects and clinical application of traditional Chinese medicine had a good effect on CAG and better improved the quality of life of patients. However, due to the complex pharmacological properties of traditional Chinese medicine, the current research on its mechanism of action is lacking. Therefore, this article reviews the research progress of traditional Chinese medicine cuttlebone in the treatment of chronic atrophic gastritis, hoping to provide reference for future CAG research and treatment.

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