

# ***Potential of Traditional Chinese Medicine in Treating Helicobacter pylori Infection***

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**Abstract.** *Helicobacter pylori* (Hp), as a significant pathogenic factor for gastric cancer, is closely related to chronic gastritis, peptic ulcer and other diseases. Eradicating it is a key strategy to reduce the risk of gastric cancer. At present, traditional Chinese medicine (TCM) has demonstrated unique advantages in the prevention and treatment of Hp infection and related diseases. Through a multi-target collaborative mechanism of "inhibiting bacteria - repairing - regulating", it can increase the eradication rate, improve symptoms, alleviate antibiotic resistance and adverse reactions, and maintain the balance of intestinal microecology. However, the research on the anti-Hp effects of TCM still faces several key issues such as the lack of standardization, insufficient mechanism elucidation, and the absence of high-quality clinical evidence. This article systematically reviews the understanding of the etiology and pathogenesis of Hp infection in TCM, summarizes the clinical efficacy and potential mechanisms of commonly used Chinese medicines (single herbs and compound formulas), and analyzes their pathological basis from the perspective of gastrointestinal microecology. At the same time, it deeply examines the challenges and limitations present in current research. This study provides innovative ideas for the prevention and treatment of Hp infection and related diseases using TCM, emphasizing the value of multi-target integrated intervention. Future research urgently needs to strengthen the construction of the standardization system for TCM, deepen the analysis of the mechanism of compound drugs (especially by using single-cell sequencing and other technologies), etc., in order to promote the standardized application of TCM in this field and the early intervention of precancerous lesions of gastric cancer.

**Keywords:** *Helicobacter pylori* infection, Traditional Chinese medicine, Multi-target mechanism, Banxia Xiexin Decoction

## **1. Introduction**

The prevalence of *Helicobacter pylori* (Hp) infection shows significant regional differences. In developing countries, over 80% of the population is infected with Hp, while in industrialized countries, it is usually below 40% [1]. At present, Hp infection remains a major public health issue worldwide. In 2015, it was estimated that approximately 4.4 billion people worldwide had a positive reaction to Hp. This is the most comprehensive and up-to-date systematic review of the global prevalence of HP. It has been proven that the prevalence of Hp varies significantly among different

regions and countries. The prevalence of Hp has continued to decline in industrialized countries in the Western world, while it remains at a relatively high level in developing countries and emerging industrialized countries [2]. Hp has been classified as a Group I carcinogen by the International Agency for Research on Cancer. It is closely associated with chronic gastritis, gastric ulcers, duodenal ulcers, and gastric cancer. In particular, it plays a central role in the onset of gastric adenocarcinoma, low-grade B-cell gastric lymphoma (MALT lymphoma), and gastric cancer. Timely eradication of Hp infection is currently the only evidence-based strategy, which can effectively reduce the risk, incidence and mortality of Hp-related gastric cancer [3].

The current mainstream modern medical treatments (such as standard triple therapy and bismuth quadruple therapy) are facing severe challenges. The rising resistance rates of key antibiotics (such as clarithromycin and metronidazole) have led to a significant decline in the eradication rate (the eradication rate of the traditional triple therapy can be as low as 56%), accompanied by adverse reactions such as severe imbalance of intestinal flora and weakened gastric acid barrier function. In this context, traditional Chinese medicine (TCM) has demonstrated unique multi-dimensional clinical advantages in the prevention and treatment of Hp infections and related diseases. Based on the core concepts of "strengthening the body resistance and eliminating pathogenic factors" and "dialectical treatment", a wide range of single herbs (such as *Coptis chinensis* and *Astragalus membranaceus* which have significant antibacterial effects, as well as *Astragalus membranaceus* and *Evodia rutaecarpa* which can repair the mucosa and regulate immunity) and classic formulas (such as Banxia Xiexin Decoction, Zuojin Formula, Anwei Decoction, etc.) are commonly used in clinical practice. These therapeutic approaches, through a multi-targeted synergistic mechanism of "bacteriostasis - repair - regulation", not only can significantly improve patient symptoms, increase the eradication rate of Hp, and reduce the risk of recurrence, but also can effectively alleviate the problem of antibiotic resistance, reduce treatment-related adverse reactions, and help maintain the stability of the intestinal flora. This integrated therapeutic model has become an important research direction in the current anti-Hp studies. This article systematically reviews the understanding of the etiology and pathogenesis of Hp infection in TCM, summarizes the commonly used diagnostic and therapeutic methods and their mechanisms in clinical practice, and analyzes the pathological basis from the perspective of gastrointestinal microecological balance. It also discusses the issues of insufficient explanation of existing mechanisms and the lack of standardized diagnosis and treatment plans, providing innovative ideas for the prevention and treatment of Hp infection-related diseases.

## 2. Multi-stage analysis of the causes of Hp infection

Hp is able to successfully colonize in the harsh gastric environment and cause diseases, relying on a series of complex mechanisms, which can be mainly divided into three stages: colonization, the action of virulence factors, and the imbalance of host immune response: First, it successfully colonizes, relying on 4-8 unbranched flagella with sheaths for "swimming", "diffusion" or "swarm" movements, penetrating the gastric mucus layer [4]. The key urease breaks down urea into ammonia and carbon dioxide, effectively neutralizing gastric acid and creating a slightly alkaline environment around the bacteria, which is the core of colonization. Nickel is crucial as a cofactor for urease and hydrogenase [5]. Subsequently, Hp specifically recognizes and binds to the receptor molecules on the surface of the host gastric epithelial cells through its outer membrane adhesins, achieving tight adhesion. For example, BabA (a blood group antigen-binding Adhesin) mainly binds to gastric epithelial cells and the Lewis b antigen present in mucus (a specific carbohydrate structure synthesized by specific glycosyltransferases and expressed on the surface of gastric epithelial cells and the secreted mucin glycoproteins). This combination enables bacteria to anchor themselves on

the mucosal surface rich in Lewis b, resisting the clearance by gastric peristalsis and mucus flow. It is one of the key steps for bacteria to establish a persistent colonization in the stomach. HopQ (Helicobacter outer membrane protein Q) mainly recognizes and binds to CEACAMs (Carcinoembryonic Antigen-related Cell Adhesion Molecules, especially subtypes 1, 3, 5, and 6) on the surface of host cells. CEACAMs are a type of immunoglobulin superfamily receptors expressed on epithelial cells. The binding of HopQ to CEACAMs is not merely a physical adhesion; more importantly, it establishes a crucial bridge for the subsequent translocation of the virulence factor CagA: This interaction can facilitate the effective docking of the Hp type IV secretion system (T4SS) with the host cell membrane, thereby mediating the efficient "injection" of the CagA protein into the host cytoplasm [6,7]. This specific adhesion mechanism (such as BabA-Lewis b, HopQ-CEACAMs) is not only the basis for the physical anchoring of bacteria, but also the starting point that triggers the subsequent pathogenic signal cascade reaction (such as CagA translocation). Then, the host cell damage mediated by the virulence factors, CagA, is a bacterial protein. This core virulence factor is phosphorylated at the EPIYA motif (A, B, C/D types, region and disease risk related) after entering the cell [8]. Phosphorylated CagA activates host signaling pathways (such as SHP-2), leading to cytoskeleton rearrangement ("hummingbird" phenotype), loss of polarity, and release of pro-inflammatory factors, which is closely related to the occurrence of gastric adenocarcinoma. Ultimately, the various antigen components continuously released by Hp (such as lipopolysaccharide, lipoprotein, lipoteichoic acid, heat shock protein 60, neutrophil-activating protein A, bacterial DNA and RNA) are specifically recognized by the Toll-like receptors (TLRs) on the surface of gastric epithelial cells. These TLRs (particularly TLR2, 4, 5, 9) are activated, triggering the key intracellular nuclear factor  $\kappa$ B (NF- $\kappa$ B) signaling pathway and c-Jun N-terminal kinase (JNK) signaling pathway, resulting in the massive release of pro-inflammatory cytokines [9,10]. Subsequently, the gastric mucosa is infiltrated by inflammatory cells, recruiting neutrophils, monocytes, generating ROS, NO and lymphocytes CD4<sup>+</sup>, CD8<sup>+</sup> T cells. There may be a preferential activation of CD4<sup>+</sup> cells, which could damage CD8<sup>+</sup> cells and lead to a specific response to bacteria [11]. Hp infection induces a Th1 polarization immune response, one of the characteristics of which is the reduction of the key factor of Th2-type immune response, interleukin-4 (IL-4); IFN- $\gamma$ , TNF, IL-1 $\beta$ , etc. (especially in adults) significantly increase, mainly exerting pro-inflammatory effects; IL-10 increases but has anti-inflammatory functions [12]. In terms of humoral immunity: specific IgM appears 4 weeks after infection, and specific IgA and IgG are produced in the chronic phase. Although this chronic inflammation often has no symptoms, it significantly increases the risk of peptic ulcers and gastric cancer.

The mainstream treatment for Hp in modern medicine is the standard triple therapy, which consists of a standard dose of proton pump inhibitor (PPI), clarithromycin (500 mg), and amoxicillin (1 g), taken twice a day for 7 days. Additionally, there is the bismuth quadruple therapy (with an added 120 mg of bismuth). However, there are still deficiencies in the current treatment for Hp. The key antibiotics have developed resistance (the resistance rates of clarithromycin, metronidazole, and quinolones are >15%), which directly leads to the eradication rate of the traditional triple therapy dropping to 56%, and causes severe imbalance of the intestinal flora and a reduction in the gastric acid barrier [13].

### 3. Clinical research progress of TCM in treating Hp infection

From the perspective of TCM, the infection of Hp can be classified under the category of "pathogenic factors or toxins" in TCM. The "Synopsis of the Golden Chamber" states: "Toxin refers to the accumulation of pathogenic factors that is not resolved." It is believed that the toxin is a type

of pathogenic factor, which can be either internal or external, and both can damage the body's functions. For the symptoms such as Hp-related chronic gastritis, dyspepsia, peptic ulcers, and gastric cancer, they can be classified under the categories of "gastric pain", "stuffiness and fullness", "acid regurgitation", and "gastric discomfort with a burning or upset sensation" in TCM. The Huangdi Neijing classifies the causes of diseases mainly as invasion of external pathogens, internal injury due to overstrain and fatigue, improper diet, emotional disturbance, and changes in other internal organs. The Hp infection and related diseases fall under the category of disorders within the spleen and stomach system in TCM. The spleen and stomach are internally-externally related and are regarded as the foundation of postnatal constitution. The spleen functions well when it ascends properly, and the stomach is harmonious when it descends appropriately. Hp-related diseases are closely related to the spleen, stomach and liver. Their pathological nature is mostly characterized by deficiency in root and excess in branch, or intermingling of deficiency and excess. The deficiency aspect mainly involves spleen and stomach weakness, qi deficiency, yin deficiency or yang deficiency. The excess aspect mainly consists of dampness-heat, qi stagnation and blood stasis. The treatment mainly follows the principles of invigorating the spleen and replenishing qi, clearing heat and resolving dampness, regulating qi to relieve pain, promoting blood circulation to dissolve blood stasis, nourishing yin and moistening dryness, warming the center and harmonizing the stomach, etc. The TCM diagnostic types for Hp infection are: damp-heat syndrome, liver-stomach disharmony syndrome, spleen-stomach deficiency syndrome, and syndrome of static blood blocking the stomach collaterals [14].

### 3.1. Single herbs

Both in vivo and in vitro experiments have shown that single TCMs and their active components demonstrate significant potential in inhibiting the growth of Hp and the expression of its virulence factors. Lin Yishan et al [15] used the TCM inheritance assistance system to conduct data mining on the medication patterns of clinical prescriptions over the past decade. They found that the core drugs for treating Hp infection were mainly those with clearing heat and removing toxicity (such as *Coptis chinensis* and *Scutellaria baicalensis*) and those with invigorating the spleen and replenishing qi (such as *Astragalus membranaceus* and *Codonopsis pilosula*). The combination patterns of these drugs conformed to the traditional Chinese medical principle of 'strengthening the healthy qi and eliminating the pathogenic', suggesting that the TCM compound prescriptions may exert dual effects of antibacterial and immune regulation through the synergistic action of multiple components. Specifically, the alkaloids such as berberine in *Coptis chinensis* can damage the integrity of bacterial cell walls, inhibit DNA/RNA synthesis, and still have significant antibacterial activity against multi-drug resistant strains; the baicalin and baicalein in *Scutellaria baicalensis* not only can inhibit the activity of Hp urease and the expression of virulence genes, but also can block the NF- $\kappa$ B inflammatory pathway and reduce the risk of recurrence of drug-resistant bacterial infections [16]. The medicinal serum of *Astragalus membranaceus* inhibits the activity of VacA vacuolar toxin in a concentration-dependent manner. Its polysaccharides and saponin components possess the functions of promoting gastric mucosal repair and regulating the host's immune response; The limonin from *Evodia rutaecarpa* directly inhibits the translocation of the CagA carcinogenic protein and alleviates the inflammatory damage of the gastric mucosa [17]. These single herbs achieve this by jointly disrupting the bacterial structure, neutralizing the toxic factors, and regulating the immune-inflammatory network, thereby providing a crucial pharmacological basis for the design of the compound formula.

### 3.2. Formula

In recent years, the research on Hp treatment has shown two major trends: one is the expansion of research subjects from single Chinese herbs to compound preparations and classic prescriptions; the other is the deepening of mechanism research from clinical efficacy observation to the molecular biological level. Taking the Banxia Xiexin Decoction in the "Shanghan Zabing Lun" by the Eastern Han medical sage Zhang Zhongjing as an example, this decoction significantly reduces the release of pro-inflammatory factors such as IL-8 and TNF- $\alpha$  by inhibiting the expression of key proteins in the TLRs/NF- $\kappa$ B pathway. The overall efficacy of the full formula is superior to that of the individual components of the decoction, highlighting the therapeutic advantages of the "cold and heat combined" compatibility in eradicating Hp and treating cold-heat intermingling type gastritis [18]. The Zuojin Formula, which combines *Coptis chinensis* and *Evodia rutaecarpa* (in a ratio of 6:1), can effectively inhibit the growth of Hp at a concentration of 200  $\mu\text{g}\cdot\text{ml}^{-1}$ . At the same time, it promotes ulcer healing by reducing gastric acid secretion, enhancing the mucosal barrier, and regulating the EGF/PI3K pathway, significantly improving symptoms of acid reflux and stomach pain [19]. Anwei Decoction inhibits lipid peroxidation and reactive oxygen species (ROS) production by activating the AMPK/SREBP1 signaling axis, and downregulates the expression of IL-6 and COX-2 to block the inflammatory cascade, thereby reversing the pathological progression of the gastric mucosa in Hp-positive atrophic gastritis [20]. Data mining further confirms that the compound prescription pattern of "clearing heat and removing toxicity combined with invigorating the spleen and replenishing qi" (such as *Coptis chinensis* – *Astragalus membranaceus*, *Scutellaria baicalensis* – *Codonopsis pilosula*) can synergistically regulate the microbiota-immune-inflammation axis, providing an innovative solution for dealing with antibiotic resistance.

### 4. Issues and future prospects

At present, there are three major challenges in the treatment of Hp infection with TCM. These include the lack of standardization, which leads to fluctuations in the effective components of *Coptis chinensis* exceeding 30%, and the absence of unified quality control standards. The weak mechanism research results in 80% of the compound targets remaining unclear, and the lack of validation through organoid or single-cell sequencing technologies. Additionally, the clinical evidence is insufficient, manifested by a median sample size of only 82 in randomized controlled trials (RCTs), and the absence of long-term follow-up data. These issues limit the standardized application and efficacy evaluation of TCM. To address these challenges, in the short term, Hp-related TCM quality control standards should be established, such as ensuring that the content of Baicalin is not less than 12% and the content of *Coptis chinensis* berberine is not less than 5%, etc. At the same time, 'high antibacterial - low resistance' TCM compound preparations should be developed to enhance the effect. In the long term, an 'disease-condition combination' individualized plan should be constructed to fully utilize the advantages of TCM. TCM provides innovative solutions for clinical problems such as antibiotic resistance and dysbiosis through the multi-target synergy of 'antibacterial - immune regulation - mucosal repair'. Future research should focus on promoting the construction of a standardized system for TCM, deepening the analysis of the mechanism of compound drugs, and constructing an evaluation system that integrates multiple dimensions such as eradication rate, micro-ecological protection, and symptom improvement, to provide scientific support for the early intervention of precancerous gastric lesions.

## 5. Conclusion

This article systematically sorts out the etiology and pathogenesis of *H. pylori* (Hp) infection, analyzes its pathogenic mechanism from three stages: colonization, action of virulence factors, and host immune dysregulation, summarizes the limitations in modern medical treatment such as antibiotic resistance and intestinal flora imbalance, and focuses on expounding the advantages of TCM in prevention and treatment. Single herbs (such as *Coptis chinensis*, *Scutellaria baicalensis*, *Astragalus membranaceus*, etc.) and classic compound prescriptions (such as Banxia Xiexin Decoction, Zuojin Formula, etc.) can improve the Hp eradication rate, relieve symptoms, alleviate drug resistance and maintain intestinal microecological balance through the multi-target synergistic mechanism of "bacteriostasis-repair-regulation". Meanwhile, it summarizes their potential mechanisms of action, such as inhibiting virulence factors, regulating inflammatory pathways, and repairing mucous membranes. The above research echoes the background in the introduction that Hp infection is a major global public health problem, and provides new ideas for addressing antibiotic resistance and reducing the risk of gastric cancer. The integrated intervention model of TCM, which "strengthens the body resistance and eliminates pathogenic factors", can make up for the deficiencies of single-target treatment in modern medicine, and provide a multi-dimensional solution for the prevention and treatment of Hp infection and related diseases.

The current research still has limitations, such as the imperfect standardization system for TCM, insufficient depth in explaining the mechanism of compound prescriptions, and a lack of high-quality long-term clinical evidence. In the future, efforts should be made to accelerate the construction of quality control standards for TCM, utilize technologies like single-cell sequencing to deepen the research on the mechanism of compound prescriptions, and establish a multi-dimensional evaluation system that integrates eradication rate, micro-ecological protection, and symptom improvement. This will promote the standardized application of TCM and provide more solid scientific support for the early intervention of precancerous gastric lesions.

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