

Application of traditional Chinese medicine in treatment of *Helicobacter pylori* infection

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Abstract

Helicobacter pylori (*H. pylori*) has a high rate of infection and antibiotic resistance and poses a serious threat to human life. One of the main strategies to overcome drug resistance is to develop new treatment plans. Traditional Chinese medicine (TCM) that is commonly used to treat many diseases in China can reduce drug resistance and increase the eradication rate of *H. pylori*. In this paper, we review the research progress on TCM in the treatment of *H. pylori* infection. The mechanism of action of TCM is reviewed and research and applications of TCM in the treatment of *H. pylori* are demonstrated. Finally, we discuss problems confronting the use of TCM for the treatment of *H. pylori* infection and propose possible solutions. In addition, the plans of TCM in *H. pylori* treatment were also screened: Dampness-heat syndrome in the spleen and stomach, deficiency of spleen and stomach, and cold-heat complicated syndrome, and the effective components therein are studied. The antibacterial effect of TCM is relatively slow; for rapid improvement of the treatment effect of refractory *H. pylori* gastritis, we provide an appropriate treatment regime combining TCM and Western medicine with immune-regulatory and synergistic antibacterial effects.

Key Words: *Helicobacter pylori*; Traditional Chinese medicine; Treatment; Antibacterial effect; Antibiotic resistance

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Core Tip: With the widespread use of antibiotics, *Helicobacter pylori* (*H. pylori*) has a high rate of infection and antibiotic resistance, posing a serious threat to human life. The development of new drugs is difficult. One of the main strategies to overcome drug resistance is to develop new treatment plans. Traditional Chinese medicine (TCM) is commonly used to treat many diseases in China, and it can reduce drug resistance and increase eradication rates of *H. pylori*, which is recognized by most patients. In this paper, the treatment plans of TCM in *H. pylori* treatment are screened out: Dampness-heat syndrome in the spleen and stomach, deficiency spleen and stomach, cold-heat complicated syndrome, and the effective components are analyzed. It is recommended that doctors choose appropriate integrated traditional Chinese and western medicine treatments based on the dialectical type of TCM etiology and the characteristics of *H. pylori* resistance. The program provides new methods and new ideas for the radical cure of *H. pylori* infection.

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INTRODUCTION

Helicobacter pylori (*H. pylori*) infection is an important cause of diseases such as chronic gastritis, peptic ulcer, gastric cancer, and other diseases[1-3]. In addition, *H. pylori* infection is also associated with a variety of parenteral diseases such as periodontitis and secondary immune thrombocytopenic purpura[4]. Currently, *H. pylori* infects more than half of the world's population with the rates of infection higher in developing countries and in some undeveloped areas (> 80%)[5-7]. The prevention and treatment of *H. pylori* infection remain a critical unmet need of major public health significance. Currently, *H. pylori* eradication programs in Western medicine mainly include standard triple, and non-bismuth or bismuth quadruple therapies. However, the drug resistance rate of *H. pylori* is increasing whilst the eradication rate continues to decrease due to the long-term use and abuse of antibiotics[8-10]. Traditional Chinese medicine (TCM) demonstrates a number of potential advantages in the treatment of *H. pylori* infection such as high eradication rates and low levels of toxicity [11]. According to epidemiological statistics, the total effective rate of TCM treatment for *H. pylori* infection can reach 95.45%[12]. This paper reviews the application of TCM in the treatment of *H. pylori* infection and provides a reference for scientists and clinicians regarding the use of TCM in *H. pylori* infection.

IMPACT OF TCM ON ETIOLOGY AND PATHOGENESIS OF *H. PYLORI* INFECTION

TCM treats diseases mainly according to the theory of human body balance (Yin and Yang). *H. pylori* infection belongs to the category of "damp-heat pathogenic Qi" or "toxins from pathogenic bacteria". People who have deficiency of spleen and stomach are exposed to external moisture and heat coupled with unclean foods and are more susceptible to pathogenic toxins which in this case refer to *H. pylori*[13]. According to TCM syndrome differentiation and types, *H. pylori* infection can be divided into five types: Deficiency of spleen and stomach, dampness-heat syndrome in spleen and stomach, stomach-Yin deficiency, liver-stomach disharmony, and blood stasis in the stomach collaterals. Deficiency of spleen and stomach, and stomach-Yin deficiency were classified into the group with spleen Qi and stomach-Yin deficiency (SQSYD), and the group of other three types have no SQSYD[14].

Although *H. pylori* infection occurs in the stomach, disease occurs in the spleen. The external invasion of pathogenic Qi, deficiency of vital Qi, and dysregulation of the Qi machinery are the causes of onset. Dampness-heat syndrome in spleen and stomach is an important inducing factor as the humid and hot environment in the stomach

provides favorable conditions for the growth of bacteria. In addition, the damaged gastric mucosa and the damaged normal physiological structure in the stomach increase susceptibility to *H. pylori* infection[15]. Deficiency of spleen and stomach is often the root cause of related stomach diseases induced by *H. pylori* infection. These stomach diseases are commonly characterized by damp-heat and blood stasis[16]. *H. pylori* infection-related gastritis belongs to "root deficiency and branch excess". The deficiency of spleen and stomach often causes humans being susceptible to *H. pylori* infection due to a series of pathological changes such as damp-heat and blood stasis. These changes result in diseases such as chronic atrophic gastritis and intestinal metaplasia[17,18]. In recent years, most TCMs for treating *H. pylori* infection are spleen-invigorating and Qi-invigorating, which can also support spleen Qi deficiency and stomach weakness as a basic mechanism of pathogenesis in *H. pylori* infection[19].

RESEARCH AND APPLICATION OF TCM IN TREATMENT OF *H. PYLORI* INFECTION

TCM treatment involves the use of medicines with Chinese characteristics. Some monomer compositions containing mucosal protective agents have high eradication rates of *H. pylori* and show low drug resistance, reduced adverse reactions, and low toxicity, and even kill drug-resistant *H. pylori*[20]. The treatment of *H. pylori* infection with TCM emphasizes overall regulation of adult health[21]. In addition to the principle of drug selection to enhance the resistance to infection and eliminate pathogenic factors, TCM aims to replenish Qi, invigorate Qi, promote blood circulation, and remove blood stasis as well as detoxify and dissipate heat[22].

According to TCM syndrome differentiation and types of *H. pylori* infection, an appropriate treatment plan should be selected specifically based on the principle of considering syndrome differentiation and combination of diseases and syndromes. This should enable the development of individualized treatments according to the specific conditions of each patient and allows different TCM formulae to be given according to different symptoms. Cold-natured herbs supplemented with a moderate amount of hot-natured drugs are often used as the main TCM treatment for *H. pylori* infection. Drugs that impact circulation and blood stasis can be added according to specific syndromes to eliminate *H. pylori* and prevent recurrence[23]. TCM treatment for *H. pylori* infection also considers the ingredient addition and reduction method which means that, based on the use of several kinds of TCMs for invigorating the spleen and Qi replenishing, reasonable addition and decrease of ingredients in TCM can be made aiming at different symptoms. For example, more medicines for warming kidney and invigorating spleen can be prescribed for those with Yang deficiency, and more medicines for strengthening the spleen and Qi for those with Qi (a vital energy that circulates through the body at all time) deficiency may be used. Medicines that tonify Qi with a sweet taste and gentle smell should be selected for damp-heat constitution[24]. Based on the "National Consensus for the Treatment of *H. pylori* and Related Symptoms based on Integrative Traditional Chinese and Western Medicine" [25], and research of different syndrome types and TCM at home and abroad[26-34], the recommended treatment scheme of TCM is displayed in Table 1.

There are many examples of remarkable therapeutic effects achieved with TCM, which are also supported by some experimental evidence. Yang used Coptis and Official Magnolia Bark Beverage and Banxia Xiexin Decoction to treat 20 *H. pylori*-infected patients as the observation group. The total effective rate after treatment reached 95.0%, which was much higher than that of the control group that was treated with Western medicine alone (60.0%). Also, TCM symptom complex score improved significantly with a low recurrence rate[35]. Lin *et al*[36] randomly divided 60 *H. pylori*-infected rats into control group, model group, and groups of medium-concentration and high-concentration of Liujunzi decoction according to their curative effect. The study showed decreased levels of inducible nitric oxide synthase activity and nitric oxide in the gastric mucosa of the high concentration Liujunzi decoction group (1.195 ± 0.026 mmol/g). In addition, serum tumor necrosis factors- α and interleukin (IL)-6 levels were also significantly down-regulated, effectively improving the pathological changes in the gastric mucosa and demonstrating the effectiveness and safety of this decoction[36]. Liang[37] used Xiaoyou Fuwei decoction to treat patients with *H. pylori* infection, with a total effective rate of 94.7% achieved. This decoction could inhibit the activity of arylamine acetyltransferase and multidrug-resistant strains *in vitro* to remove *H. pylori*. Also, the study showed improvements in the clinical symptoms of patients who had protected gastric mucosa by promoting the expression of villi

Table 1 Recommended scheme for traditional Chinese medicine syndrome differentiation and typing

Syndrome	Treatment	Main prescription	Medicament
Dampness-heat syndrome in spleen and stomach (heat)	Clearing heat and dampness, and regulating and neutralizing Qi	Coptis and Official Magnolia Bark Beverage	Magnolia officinalis, Coptis chinensis, Acorus tatarinowii, Rhizoma Pinelliae, Sojao Semen Praeparatum, Gardenia jasminoides Ellis, Phragmitis Rhizoma
		Xiaoyou Fuwei Decoction	Radix scutellariae, Coptis chinensis, Astragalus membranaceus, Atractylodes macrocephala, Rheum palmatum, Pinellia ternata, Wolfiporia cocos, Tetradium ruticarpum, Cynanchum otophyllum, Glycyrrhizae
		Jiawei Pingwei powder	Bupleurum chinense, Atractylodes macrocephala, Atractylodes Lancea, Magnolia officinalis, Coptis chinensis, Costusroot, Rhizoma corydalis, Sepia esculenta
		Yiwei Zhitong Kangyou decoction	Taraxacum mongolicum, Gardenia jasminoides Ellis, Coptis chinensis, Liliumbrownii var. viridulum, Aurantii Fructus, Lindera aggregata, Melia toosendan Sieb, Pogostemon cablin, Finger Citron, Faeces Trogopterpri, Rhizoma Cyperi, Typhae Pollen, Amomum
		Zuojin Decoction	Concha Arcae, Radix Astragali preparata, Coptis chinensis, Evodia, Calcined oyster, Rhizoma Cyperi, Bupleurum, curcuma, ginseng, Glycyrrhizae, pseudo-ginseng
Deficiency spleen and stomach (cold)	Strengthening spleen and replenishing qi, and easing stomach	Curative effect of Sijunzi decoction	Costusroot, Amomi fructus, Citrus, Rhizoma Pinelliae Preparatu, Radix codonopsis, Rhizoma Atractylodes, Poria cocos, Glycyrrhizae
		Shenqi Yangwei decoction	Radix Astragali, Semen Coicis, Codonopsis pilosula, Paeonia lactiflora Pall, Pinellia ternata, Scutellaria baicalensis, Bletilla striata, CassiaTwig, Atractylodes, rhizoma corydalis, Bupleurum, Curcuma zedoaria, Glycyrrhizae, Rheum palmatum L
		Zishengtang	Codonopsis pilosula, Atractylodes macrocephala, Wolfiporia cocos, Alisma plantago-aquatica, Dioscorea oppositifolia L, Semen Nelumbinis, Orange peel, Hordeum vulgare L, Massa Medicata Fermentata, Semen Coicis, Euryale ferox Salisb, Amomum villosum Lour, DolichoslablabL, Crataegus pinnatifida, Platycodon grandiflorus, Agastache rugosa, Alpinia tonkinensis Gagnep, Coptis chinensis, Glycyrrhizae
Cold-heat complicated syndrome	Opening with acidity and decreasing bitter, and regulating stomach Qi and removing painful abdominal mass	Banxia Xiexin Decoction	Rhizoma Pinelliae, Scutellaria baicalensis Georgi, Coptis chinensis, Zingiber officinale Rosc, Glycyrrhizae, Codonopsis pilosula, Ziziphus jujuba Mill
		Zhishi Xiaopi decoction	Vaccaria segetalis, Hirudo, Rhizoma corydalis, Curcuma zedoaria, Citrus aurantium L, Sepia esculenta, Radix Aucklandiae, Atractylodes macrocephala, Cynanchum paniculatum, Hedyotisdiffusa, Magnolia officinalis, Pseudostellaria, Astragalus membranaceus

protein in LEC-6 cell[37]. Zhang[38] utilized Zhishi Xiaopi decoction to treat 52 *H. pylori*-infected patients and showed an eradication rate of 94.23%, which was significantly higher than that of the control group (78.85%). The TCM syndrome complex score decreased significantly ($P < 0.01$) in the treated group which also indicated a significant decrease in adverse reactions ($P < 0.01$)[38]. Taken together, these studies showed the potential importance of TCM in *H. pylori* treatment, but the question remains as to which TCM ingredients are active therein.

Many experiments have proved that a variety of single Chinese herbal medicines, herbal medicine prescriptions, and patent medicine preparations all have significant effects in inhibiting or killing *H. pylori*[39]. These can also be used as drug-resistant inhibitors, drug-resistant sensitizers, or synergists to achieve the effect of reversing drug resistance. Chinese medicines can act to destroy biofilms[40], reduce the virulence[41] and adhesion ability of *H. pylori*[42], change the living environment of *H. pylori*, improve human immunity[43], reduce damage to the gastric mucosa, remove oxygen free radicals, and inhibit the release of inflammatory factors[44]. For example, Chinese medicine Angelica can protect the gastric mucosa of patients infected with *H. pylori* by decreasing the inflammatory response through the nuclear factor kappa B-mediated inflammatory response signaling pathway, decreasing the production of peroxide, and enhancing peroxidase activity to effectively prevent *H. pylori*-induced gastritis and other diseases[45]. The pathogenicity of a series of diseases (such as peptic ulcers) after *H. pylori* infection is mediated by bacterial urease, which is the main virulence factor. Bacterial urease hydrolyzes urea to produce carbon dioxide and ammonia, which increases pH in the stomach. As a result, *H. pylori* can effectively colonize acidic environments. The active ingredient of honey can inhibit *H. pylori* urease with an inhibition rate of about 45%[42]. These ingredients of TCM have been widely applied in Chinese medicine preparations for eradicating *H. pylori*[46].

TCMs for treating *H. pylori* infection are mainly cold-natured herbs supplemented by warm and hot herbs which aim to treat heat, Qi stagnation and blood stasis, and Qi deficiency. Heat-clearing drugs include Scutellaria, Coptis chinensis, and rhubarb; dehumidifying drugs include Wrinkled Glanthyssop, atractylodes, and Magnolia officinalis; tonifying medicines are glycyrrhiza, ginseng, and white peony root; drugs for relieving exterior disorders include ginger, mint, and chrysanthemum; and mild medicines are Evodia rutaecarpa and clove. The aforementioned drugs have all been widely used in Chinese medicine decoctions and preparations for *H. pylori* eradication. The most bitter drugs can effectively relieve fever, remove dampness, promote blood circulation, and replenish Qi. These act to greatly improve the *H. pylori* eradication rate and reduce adverse reactions. Of the medicines mentioned above, Coptis chinensis is a single Chinese herb which has the highest efficacy for eradicating *H. pylori*. The main component of Coptis chinensis that inhibits *H. pylori* is berberine. The bactericidal mechanism of berberine may be elucidated through inhibition of oxidation of bacterial glucose and metabolic intermediates of glucose which act to kill *H. pylori*[47]. Some of the quinolone alkaloid components in the Chinese medicine Evodia can inhibit the growth of *H. pylori* without eradicating other intestinal flora[48]. Based on the prescriptions mentioned in Table 1, the effective ingredients of the main anti-*H. pylori* monomers of TCM in these prescriptions are summarized by combining with current research results[49-61]. As shown in Table 2, the effective ingredients of these drugs may provide a basis for understanding the mechanism of action of Chinese medicines and provide ideas for novel research directions.

PROBLEMS AND SOLUTIONS ENCOUNTERED BY TCM IN TREATMENT OF *H. PYLORI* INFECTION

Although the treatment of *H. pylori* with TCM can achieve a high eradication rate with low drug resistance and toxicity, problems towards its widespread clinical use remain. Specifically, these include: (1) The extraction of active ingredients of TCM has not yet been performed; (2) pharmacological research on single Chinese herbs and compound preparations remains to be performed; (3) the mechanism of *H. pylori* eradication has not been fully revealed; (4) studies relating to TCM are largely based on small sample sizes which fail to establish a complete *H. pylori* eradication treatment plan; (5) some medicines do not meet the requirements of finished medicines; and (6) diverse lifestyles and diets from different regions may affect responses. The corresponding solutions to these problems are illustrated in Figure 1[62-67], yet there remain many obstacles towards completely resolving these problems.

COMBINATION OF TCM AND WESTERN MEDICINE IS IDEAL SOLUTION FOR TREATMENT OF *H. PYLORI* INFECTION

Compared to simple Western medicine and TCM treatments, the combination of these approaches may provide the ideal solution for the treatment of *H. pylori* infection. Antibiotics have advantages and disadvantages characterized by fast onset, broad antibacterial spectrum, being prone to drug resistance, adverse reactions, severe side effects, and difficulty in completely eradicating *H. pylori*. TCM also exhibits advantages and disadvantages including slow immune-regulation and onset, reduced drug resistance, low toxicity, complex mechanisms of action, and few side effects[68]. Therefore, the combination of the two treatment strategies may be used to effectively cure *H. pylori* infection. Recently, the combination of Chinese and Western medicine has been shown to effectively alleviate *H. pylori* drug resistance, shorten the course of antibiotics, reduce the use of antibiotics, and also improve clinical adverse reactions and toxic side effects[69].

Currently, the theory of combination of TCM and Western medicine for *H. pylori* treatment should be used to select a reasonable treatment plan according to the different stages of diseases and different syndromes. TCM is used for *H. pylori* prevention when patients are not infected. During infection treatment, combined treatments of TCM and Western medicine, such as TCM combined with triple or quadruple treatment for 14 d, can improve the eradication rate. After failure to eradication of infection when the strain has developed drug resistance[70], TCM can be used for conditioning of organism. Refractory gastritis is classified as a type of warm and cold complex regional pain syndrome during treatment of a long course of

Table 2 Anti-*Helicobacter pylori* active ingredients in the recommended classification scheme

Main anti- <i>H. pylori</i> drugs	Active ingredients in anti- <i>H. pylori</i> drugs	Drug-resistant inhibitors	Drug-resistant Sensitizer	Synergies agent
Magnolia officinalis	Magnolol, honokiol	+	-	-
Coptis chinensis	Berberine, rhizome, epiberberine, palmatine, coptisine	+	+	+
Gardenia	geniposide	-	-	-
Radix scutellariae	Baicalin, baicalein, neobaicalein, norwogonin, skullcap flavone, acacetin, wogonin	+	+	+
Radix Astragalus	astragalus saponin	+	-	-
Rhubarb	Rhein, emodin	+	+	+
Evodia	Limonin, rutecarpine	+	-	-
Bupleurum	saikosaponin-d	+	-	-
Rhizoma corydalis	Quinolone alkaloids	-	-	-
Pogostemon cablin	Patchouli alcohol	+	-	-
Curcuma longa	Diterpenoid C extracted from radix curcumae, curcumin	+	-	-
Ginseng	Panaxatriol, ginsenoside	-	-	-
Pseudo-ginseng	Sanchinoside	-	-	-

+: Existing literature has shown this effect; -: No previous research reporting this effect; *H. pylori*: *Helicobacter pylori*.

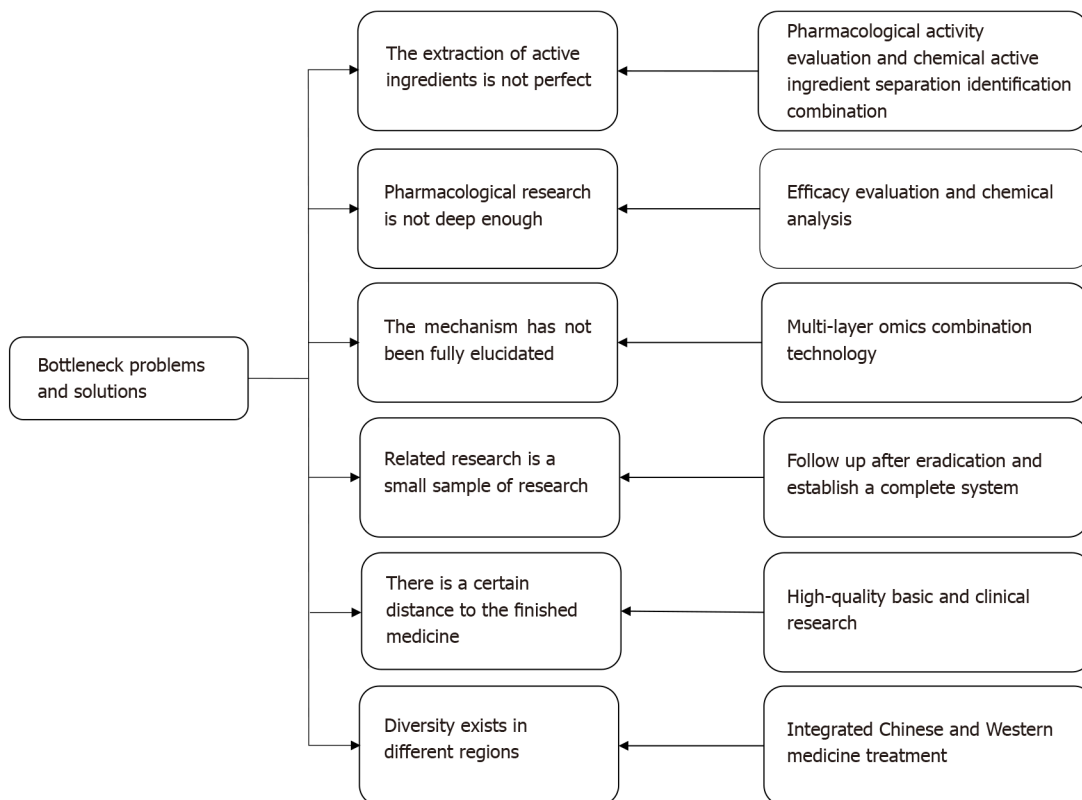


Figure 1 Bottleneck problems encountered by traditional Chinese medicine in treatment of *Helicobacter pylori* and their solutions.

disease in patients with spleen Qi deficiency and stomach weakness, and warm and cold complex regional pain syndrome[71]. Many trials have been conducted in combination with antibiotics or proton pump inhibitors based on the recommended scheme of TCM syndrome differentiation. The total effective rate of *H. pylori* eradication, adverse reactions, *H. pylori*-induced treatment rate of related diseases, and

Table 3 Anti-*Helicobacter pylori* program of combination of traditional Chinese and Western medicines

TCM syndrome-type	Treatment	Course of treatment and dose	Efficient rate
Dampness-heat syndrome in the spleen and stomach (heat)	Jiawei Pingwei powder combined with triple therapy (Rabeprazole + Clarithromycin + Amoxicillin)	Jiawei Pingwei powder (2 times/d) + Rabeprazole (10 mg, 2 times/d) + Clarithromycin (0.25 g, 2 times/d) + Amoxicillin (0.25 g, 2 times/d). Course of treatment: 14 d	The combined treatment: 93.48%; Western medicine alone: 77.55%
Deficiency spleen and stomach (cold)	Xiangsha Liu junzi decoction combined with antibiotic (Rabeprazole)	Xiangsha Liu junzi decoction (1 time /d) + Rabeprazole (10 mg, 2 times/d). Course: 14-28 d	The combined treatment: 96.67%; Western medicine alone: 80.00%
Cold-heat complicated syndrome	Banxia Xiexin decoction combined with antibiotics (Omeprazole + aluminum magnesium carbonate)	Banxia Xiexin decoction (2 times/d) + Omeprazole (10 mg, 2 times/d) + aluminum magnesium carbonate (0.5 g, 3 times/d). Course: 14-28 d	The combined treatment: 96.00%; Western medicine alone: 76.00%

TCM: Traditional Chinese medicine.

the amount of antibiotics used were compared and investigated for a variety of programs. The combinations of Chinese and Western medicines are summarized in Table 3[72-74]. However, due to the small sample size of individual experiments, the efficiency remains uncertain.

Due to the individual differences of the patients, a reasonable adjustment to treatment can be made based on local drug resistance situation and the medication history of each patient. For example, other antibiotics can be used when the patient is resistant to clarithromycin. In addition, ingredients in the TCM can be added or subtracted according to the actual situation of the patient. For example, in the curative effect of Sijunzi Decoction, if the patient is afflicted with stomach pain, extra *Rhizoma corydalis* and *salvia* can be added, or if a patient has stomach Yin deficiency, extra *charles abraham* and *liriope* can be added to improve the patient compliance and tolerance.

It is been hypothesized that TCM is complex in its decoction and ingredients, with an unclear mechanism with persistent safety concerns about the medication. The effective ingredients of TCM with clear efficacy can be used to replace TCM decoction when combined with Western medicine. For example, Liu *et al*[75] combined pantoprazole with berberine to treat 40 *H. pylori*-infected patients as the observation group, achieving a total effective treatment rate of 92.5%, which was much higher than that of the control group that was treated with triple therapy (75.0%). In addition, the levels of inflammatory cytokines such as IL-2 and IL-6 were significantly lower in the observation group after treatment than in the control group[75]. The discovery of the active ingredients in anti-*H. pylori* TCM, and transformation of its derivatives may not only improve the efficiency of treatment, but also facilitate the exploration of the underlying mechanism of action to promote the development of TCM and Western medicine combinations.

CONCLUSION

There is an urgent need for the development of novel *H. pylori* treatment and prevention strategies due to high rates of infection and drug resistance. As the development of new drugs remains challenging, the formulation of new treatment programs is currently the main measure to cure or alleviate drug resistance. TCM has achieved some promising results in the treatment of *H. pylori* infection. Some natural Chinese medicine monomers such as Chinese herbal compounds and TCM preparations have been shown to exert inhibitory effects in the treatment of *H. pylori* infection. These agents provide an important reference for curing *H. pylori* infection or intractable gastritis. In the long-term exploration, TCM has been proven to be beneficial as it is reliable, safe, and effective for the treatment of *H. pylori* infection. It has significant potential for popularization and wider application.

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