

# Traditional Chinese medicine for Helicobacter pylori infection

## A protocol for a systematic review and meta-analysis

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### Abstract

**Background:** Helicobacter pylori (Hp) is the only bacterium in the stomach. It is characterized by its ability to adhere to gastric mucosa and cause a series of pathological changes in the gastric mucosa. Modern research shows that Hp is an important pathogenic factor for chronic gastritis, gastroduodenal ulcer, and gastric cancer. Triple, quadruple, and triple combinations of antibacterial drugs, proton pump inhibitors, and bismuth aluminate preparations have been developed in modern medical research. Sequential therapy is used to treat Hp, but antibiotic resistance and repeated infections still exist. A large number of clinical trials have proved that traditional Chinese medicine has a good therapeutic effect on Hp. In this systematic review, we aim to evaluate the efficacy and safety of traditional Chinese medicine in the treatment of Hp.

**Methods and analysis:** We will search for publications from Web of Science, PubMed, Science Direct, Wan Fang Data Knowledge Service Platform, Chinese Biomedical Literature Database (CBM), Chinese Scientific Journal Database (VIP database), China National Knowledge Infrastructure (CNKI) and EMBASE, which should be published from inception to December 2020. Two researchers will independently perform the selection of the studies, data extraction, and synthesis. The Cochrane Risk of Bias Tool will be used to evaluate the risk of bias in the randomized controlled trials. Statistical analysis will be performed by using the Cochrane Review Manager (RevMan 5.3) software. The  $I^2$  test will be used to identify the extent of heterogeneity. We will use the Egger funnel chart to evaluate possible publication biases, in addition, when possible we will perform a subgroup/meta-regression analysis. The strength of the evidence will be assessed according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE).

**Results and conclusions:** This study will systematically evaluate the efficacy of traditional Chinese medicine in the treatment of Hp infection, and provide evidence for the clinical application of this treatment. The results of the research will be published in a peer-reviewed journal.

**Ethics:** This systematic review will evaluate the efficacy of traditional Chinese medicine for Hp infection. Because all data used in this systematic review and meta-analysis have been published, this review does not require ethical approval.

**Trial registration number:** INPLASY2020120057.

**Abbreviations:** CI = confidence interval, GRADE = Grading of Recommendations Assessment, Development, and Evaluation, Hp = Helicobacter pylori, MD = mean difference, RCT = randomized controlled trial.

**Keywords:** Helicobacter pylori, protocol, systematic review and meta-analysis, Traditional Chinese medicine

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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## 1. Introduction

In 1983, Australian scientists Warren and Marshall found and isolated Helicobacter pylori (Hp) in human gastric mucosa.<sup>[1,2]</sup> Public health studies have shown that Hp, as a pathogen, only spreads from person to person. In addition to mouth-to-mouth, fecal-oral and iatrogenic routes, Hp can also be spread through water. Because of its wide transmission route, it is easy to get sick, highly contagious and spread widely.<sup>[1,3]</sup> The incidence rate in developing countries is higher than that in developed countries. The global population infection rate is as high as 50%, which has been on the rise in recent years.<sup>[4-6]</sup> It has been found in the laboratory that Hp is a Gram-negative bacterium, which can cause damage and degradation of gastric mucosa by adhering to gastric mucosa and urease and its release of cytotoxin, protease and phospholipase.<sup>[7-9]</sup> Etiology and pathology studies have proved that Hp is an important pathogenic factor of chronic gastritis, gastroduodenal ulcer, intestinal metaplasia, and gastric cancer.<sup>[10-14]</sup> Therefore, as early as 1994, the World Health

Organization listed this bacteria as a Class I carcinogen.<sup>[15]</sup> Hp infection develops into chronic gastritis at an early stage and may develop into precancerous lesions and intestinal metaplasia of atrophic gastritis, among which gastric cancer is the most serious result.<sup>[9]</sup> Gastric cancer is a major global health threat and it is also the third leading cause of cancer deaths worldwide. It is estimated that more than 720,000 people die each year worldwide.<sup>[6]</sup>

Therefore, Hp infection has great influence on society and economy, and eradication of Hp has become the main goal of digestive system diseases. Eradication of Hp can promote the alleviation of gastric inflammation, advance the damage of gastric mucosa, prevent further DNA damage caused by Hp, improve gastric acid secretion and restore the normal microbial population. For Hp infection, modern medicine adopts triple, quadruple and sequential treatment based on antibacterial drugs, proton pump inhibitors and bismuth aluminate preparations. The treatment effect is to direct sterilization, protection of gastric mucosa and neutralization of gastric acid.<sup>[16]</sup> However, with the abuse of antibiotics, pure western medicine treatment is faced with many problems, such as high drug resistance, great toxic and side effects, intestinal flora imbalance, high recurrence rate, etc.<sup>[3,17–22]</sup>

With the wide application of traditional Chinese medicine in the treatment of Hp, a large number of clinical and pharmacological studies of traditional Chinese medicine show that traditional Chinese medicine has a curative effect on Hp and repeated infections.<sup>[1,12,23–25]</sup> Traditional Chinese medicine has a superior curative effect in treating gastropathy, paying attention to protecting the function of the spleen and stomach, and has few adverse reactions. In the history of the development of Chinese medicine, there is no saying that Hp infection. According to the clinical symptoms of patients with Hp infection, Chinese medicine classified it as “stomach pain”, “acid reflux”, “vomiting”, “hiccup”, “noisy”, and “fullness”. As a pathogenic microorganism, Hp can be classified into the category of “damp-heat pathogens” in traditional Chinese medicine, which has the property of “toxicity”.<sup>[23]</sup> On the basis of 4 diagnosis and syndrome differentiation, Chinese medicine believes that Hp infection is related to living habits such as spicy and greasy diet, which is easily affected by healthy qi deficiency and pathogenic factors. The pathogenesis includes weakness of the spleen and stomach, damp-heat block, stagnation of qi and blood stasis, stagnation of liver qi, etc.<sup>[26–29]</sup> Most of the treatment methods are to eliminate pathogenic factors, improve stomach microenvironment, protect the righteousness and create an environment unsuitable for Hp. Traditional Chinese medicine treatment is mainly focuses on clearing away heat and toxic materials, aromatic eliminating dampness, strengthening spleen and benefiting qi. There are also clinical studies that single Chinese medicines have antibacterial effects, such as Coptis, Cortex Phellodendri, and Dandelion have direct antibacterial effects.<sup>[23,30–32]</sup> Chinese medicine has obvious advantages, but it has not been developed and utilized to a greater extent. The main purpose of this study is to make a comprehensive and systematic evaluation and meta-analysis of the treatment of Hp infection by traditional Chinese medicine, so as to determine the curative effect of traditional Chinese medicine on Hp infection and provide clinical evidence.

## 2. Methods and analysis

This protocol is conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocol

(PRISMA-P) statement guidelines and the Cochrane Handbook for Systematic Reviews of Interventions. This systematic review protocol has been registered on INPLASY as INPLASY2020120057 (doi: 10.37766/inplasy2020.12.0057)

### 2.1. Inclusion and exclusion criteria

**2.1.1. Types of studies.** This study only includes human randomized controlled trials, and there are no restrictions on language, dissemination date or publication type. Non-randomized controlled trials, quasi-randomized controlled trials, retrospective studies, retrospective studies, case reports, non-controlled trials and animal mechanism studies will be excluded from the systematic review. For inclusion in the trials, researchers need to accurately report randomized methods, diagnostic criteria, intervention details and efficacy evaluation. The duration of treatment and follow-up is infinite.

**2.1.2. Types of participants.** All patients who have been diagnosed with Hp will be included. There are no restrictions on age, sex, region, race, belief, race, origin and disease course.

### 2.1.3. Types of interventions

**2.1.3.1. Experimental intervention.** The experimental group mainly treated Hp infection with traditional Chinese medicine. The use of traditional Chinese medicine is limited to prescription medicines and proprietary Chinese medicines. Prescription drugs need a definite dose, but there are no restrictions on the ingredients, dosage form and doses. For the dosage, such as decoction, granule, pill, powder, etc, other types of traditional Chinese medicine treatment, such as traditional Chinese medicine injections, acupuncture, massage, cupping, etc, will not be included.

**2.1.3.2. Comparison interventions.** The control group was given conventional western medicines combined with antibiotics, proton pump inhibitors and aluminate preparations. There are no restrictions on specific drugs, doses and methods. If the control group is treated with Chinese medicine, the study will be excluded.

**2.1.4. Types of outcome measures.** The DOI value of C<sup>13</sup> and C<sup>14</sup> breath test decreased or was negative, the antibody of Hp in serum, bacterial culture in gastric mucosa and enzyme test in uremia were negative.

## 2.2. Data sources and search strategy

Relevant research will be conducted on the following databases from establishment to December 2020: Science Net, PubMed, Science Direct, Wanfang Data Knowledge Service Platform, China Biomedical Literature Database (CBM), China Science Journal Database (VIP Database), China National Knowledge Infrastructure (CNKI) and EMBASE. Two reviewers (ZM and YJ) will independently search the research. Any discrepancies will be resolved through discussion with the first author (ZM). We will also search the ongoing trial registrations of the National Institutes of Health, the WHO International Clinical Trials Registration Platform, the Chinese Clinical Trial Registry and Google Scholar to find any relevant ongoing or unpublished trials. For a comprehensive search, we will adopt a search strategy that combines MeSH words and free words. Table 1 shows PubMed's search strategy and the modified search strategy will be applied to other databases.

Number	Search terms
1	Traditional Chinese Medicine(MeSH)
2	(Zhong yi xue OR Chinese herbal medicine)
3	(Single medicine OR Compound prescription):ti.ab
4	1 OR 2 OR 3
5	Helicobacter pylori MeSH)
6	(Hp OR Helicobacter pylori infection OR Eradication of Helicobacter pylori):ti.ab
7	5 OR 6
8	(Randomized controlled trial): pt
9	(Randomized OR placebo):ti.ab
10	8 OR 9
11	4 and 7 and 10

**2.3. Data collection and analysis**

**2.3.1. Study selection.** Two researchers will independently evaluate all relevant studies and review the titles and abstracts to select qualified articles that meet the inclusion criteria. The full text of the article will be reviewed for further evaluation. If there are differences between the review authors, an agreement will be reached through discussion with the corresponding author (YJ).

The procedure selected for the study will be summarized through the use of system reviews and preferred reporting items in the Meta-Analytics protocol flow chart (Fig. 1).

**2.3.2. Data extraction and management.** Before data extraction, a standard data extraction table (Excel) containing the specified results will be created based on the included content. Then, 2 reviewers (ZF and ZC) will independently extract data such as first author, publication year, diagnosis information, disease course, sample size, age, intervention measures, control and results, treatment time, follow-up time, and adverse events. If necessary, any differences will be resolved through discussion or negotiation between the 2 reviewers. The final decision of the third reviewer (YJ) will be sought. When the data of the article is insufficient or ambiguous, one of the authors will contact the original author to request detailed information about the research by email or telephone or estimated data.

**2.3.3. Risk of bias assessment.** In order to assess the methodological quality of the included studies, 2 reviewers (ZM and ZF) will independently use the Cochrane risk of bias tool to examine 7 aspects: random sequence generation, allocation hiding, blindness of participants and personnel, blindness of result evaluation, incomplete data Evaluations, selective results reports and other sources of bias.

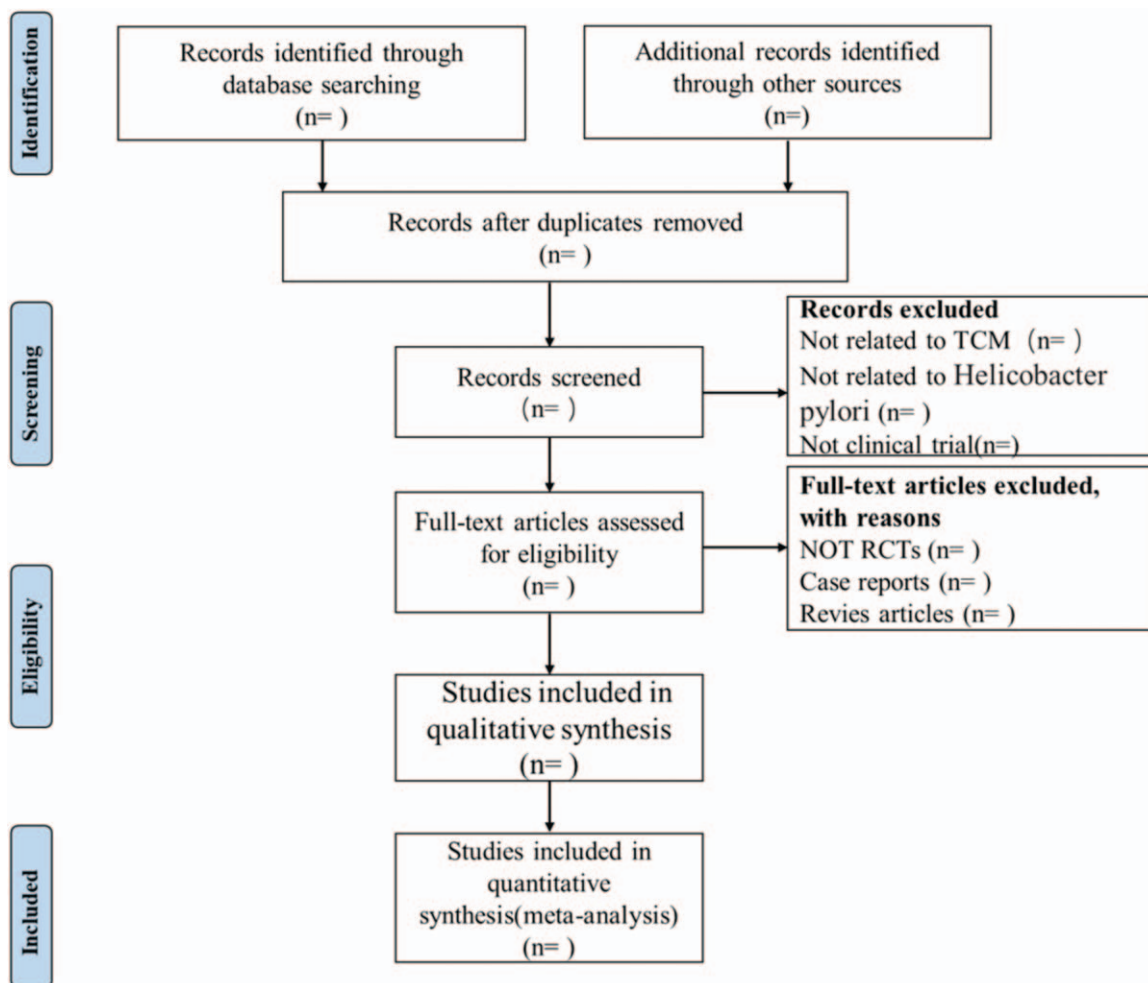


Figure 1. Flow diagram of study selection process.

**2.3.4. Measures of therapeutic effect.** If the studies can be combined, we will conduct a meta-analysis. For dichotomous data, a risk ratio (RR) with a 95% confidence interval (CI) will be calculated. For continuous data, a standardized mean (SMD) with 95% CI will be calculated. If meta-analysis is not possible, we will provide a narrative synthesis of the findings and results.

**2.3.5. Unit of analysis issue.** Only the date of the first experimental period is considered in the randomized crossover trial. For studies with multiple intervention groups, this review will combine the experimental intervention group and the control intervention group into a single group to avoid analysis problems.

**2.3.6. Assessment of heterogeneity.** According to the guidelines of the Cochrane Intervention System Evaluation Manual, we will select the  $I^2$  statistic and the chi-square test with a significance level of  $P < .1$  to measure the heterogeneity of the study in each analysis. When the  $I^2$  value is less than 50%, the study will not be considered as statistically heterogeneous. When the  $I^2$  value exceeds 50%, there is significant statistical heterogeneity between trials, so meta-analysis will not be performed. And perform subgroup analysis to determine the cause

**2.3.7. Assessment of reporting bias.** If our review includes enough meta-analyses to be included in the analysis, funnel plots and statistical tests will be generated to analyze potential reporting bias and smaller research effects.

**2.3.8. Data synthesis and analysis.** When  $I^2 < 50\%$  is considered to have no evidence of significant statistical heterogeneity, the fixed effects model will be used to merge the data. When  $I^2 \geq 50\%$  is regarded as substantial statistical heterogeneity, random effects models will be used to synthesize the data and draw conclusions more cautiously. If the data is not suitable for combining quantitative synthesis, in this case, a narrative description of the system and the information provided in this article will be provided to summarize and explain the characteristics and findings of each study.

**2.3.9. Subgroup analysis.** To identify substantial heterogeneity, subgroup analysis will be implemented according to characteristics of patients, type of intervention and outcome measures.

**2.3.10. Sensitivity analysis.** When studies are adequate, sensitivity analysis will be adopted for primary outcomes to explore the robustness of conclusions if feasible, and assess the impact of methodological quality, sample size and missing data. Sensitivity analysis will be conducted by removing lower quality studies if heterogeneity remains after subgroup analysis or studies with incomplete results according to the STRICTA checklist. The meta-analysis will be carried out again after trials of lower quality have been excluded. The results of these meta-analyses then will be compared and discussed according to their sample size, the strength of evidence and influence on the pooled effect size. However, if all included studies have a high risk of bias, we will not carry out sensitivity analyses.

**2.3.11. Grading the quality of evidence.** The GRADE system will be used for evaluating the quality of evidence in systematic reviews. The evaluation included bias risk; heterogeneity; indirectness; imprecision; publication bias. And each level of

evidence will be made “very low,” “low,” “moderate,” or “high” judgment.

### 3. Discussion

*Helicobacter pylori* (Hp) is a slightly aerobic Gram-negative bacteria, which adheres to the gastric mucosa and damages it, resulting in chronic gastritis, gastroduodenal ulcer, intestinal metaplasia and gastric cancer. The conventional treatment methods for Hp infection include antibiotics, proton pump inhibitors and aluminum bismuth preparations, but they are resistant to drug and re-positive. In recent years, traditional Chinese medicine has been widely used in Hp infection. The purpose of this systematic analysis is to evaluate the efficacy of traditional Chinese medicine in eradicating Hp infection, explore the application of traditional Chinese medicine in improving gastric mucosal environment combined with traditional Chinese medicine antibacterial drugs in patients with Hp infection, and screen out traditional Chinese medicines with antibacterial effects. Research and development of new drugs. The results of the report will be circulated after peer review and publication.

### Author contributions

**Conceptualization:** Mao Zhao, Yong Jiang.  
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**Software:** Zhipeng Fan.  
**Supervision:** Yong Jiang.  
**Writing – original draft:** Mao Zhao.  
**Writing – review & editing:** Zhipeng Fan, Yong Jiang.

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