

# Treatment of *helicobacter pylori* infection by herbal drugs; a review on current data

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## Abstract

*Helicobacter pylori* (*H. pylori*) is a very common pathogenic microorganism that colonizes the stomach of about half of all populations. It plays an important role in the gastroduodenal diseases like gastric lymphoma, peptic ulcers, and acute chronic gastritis. Some common antibiotics used for the treatment of *H. pylori* infection are metronidazole (MTZ), clarithromycin (CLA), amoxicillin and tetracycline. However, recently much attention had been directed toward administration of medicinal plants for the treatment of *H. pylori*. The use of herbal medicines as a source for new drugs as well as relief from diseases can be traced back over the early civilization. Considering the potentiality of medicinal plants as a source for antimicrobial drugs, the present study was based on the review of such plants to review the published papers about the effects of herbal medicines and medicinal plants against *H. pylori* infection.

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## Introduction

*Helicobacter pylori* (*H. pylori*) is a very common pathogenic microorganism that colonizes the stomach of about half of all populations. It plays an important role in the gastroduodenal diseases like gastric lymphoma, peptic ulcers, and acute chronic gastritis (1). It was estimated by World Health Organization (WHO) in 1994 that around half of the world's population was infected with *H. pylori*, in spite of the fact that most infections are silent. Around 550 000 new cases a year of gastric cancer were credited to *H. pylori* and it was foretold that by 2020 to enter the top 10 of leading causes of death worldwide (2). Some common antibiotics used for the treatment of *H. pylori* infection are metronidazole (MTZ), clarithromycin (CLA), amoxicillin and tetracycline. However, resistance to antibiotics, especially to CLA and MTZ can emerge due to point mutations. Therapies can be ineffective and unfavorable side effects may occur. So, the investigation for new drugs for the improvement of alternative therapies is pretty important (3).

## Materials and Methods

This review article discusses the pathophysiological mechanism accountable for cisplatin nephrotoxicity. For this review, we used a variety of sources by searching through Web of Science, PubMed, Scopus, directory

## Core tip

The use of herbal medicines as a source for new drugs as well as relief from diseases can be traced back over the early civilization. Considering the potentiality of medicinal plants as a source for antimicrobial drugs, the present study was based on the review of such plants to review the published papers about the effects of herbal medicines and medicinal plants against *Helicobacter pylori* infection.

of open access journals (DOAJ), EMBASE and Google Scholar. The research was performed using combinations of the following key words and or their equivalents such as *H. pylori*, medicinal plants, alternative therapy and gastric lymphoma

About 80% of the world people rely on traditional medicine, particularly medicinal plants for their health care. Medicinal plants have a long history of usage with low side effects (4).

## *H. pylori* infection

Colonization by *H. pylori* is known to trigger chronic gastritis and leads to the development of severe gastroduodenal diseases such as lymphoma of the mucosa associated lymphoid tissue (MALT), peptic ulcer or gastric adenocarcinoma. *H. pylori* infection is related to gastritis and considerable infiltration of



neutrophils, lymphocytes and monocytes into the gastric mucosa, which give to maintaining and expanding local inflammation (5).

### Virulence factor of *H. pylori*

*H. pylori* has virulence factors which are essential to colonize the acid environment of the stomach and to endure in it. The most considerable are urease and the adhesins. Urease stimulates the production of the pro-inflammatory cytokines interleukin (IL)-1 $\beta$ , IL-6 and IL-8, also tumor necrosis factor-alpha (TNF- $\alpha$ ) (6). *H. pylori* adheres specially to the epithelial cells of the gastric mucosa with using the adhesions. Of these, the most searched are SabA and BabA, which are external membrane proteins which link to the blood group antigens Lewis-b and Lewis-x, respectively (7,8). Other membrane proteins which act as adhesions have been described as AlpA, AlpB, HopH and HopZ, which is called outer inflammatory protein A (OipA) due to its relation to the increased secretion of IL-8 by epithelial cells *in vitro* and with intense gastric inflammation *in vivo* (9,10).

Some *H. pylori* virulence factors have been related to gastric carcinogenesis. The most important of these comprise vacuolating cytotoxin (VacA) and the cytotoxin-associated gen A (CagA) protein. Both of them are relevant for the pathology of the *H. pylori* infection because the strains which produce them have been more often isolated from patients with gastric cancer (11). A gene related to the increase of duodenal ulcer (dupA) has been described. The dupA gene is the most common gene in strains isolated from patients with duodenal ulcer. It is related to the increase of duodenal ulcers, in addition to with neutrophil infiltration in the antrum and higher levels IL-8 (12).

### Herbal drugs against *H. pylori* infections

The use of natural products and investigation for drugs came from plants with therapeutic properties is as old as human civilization and mineral and plant products were the main source of drugs (13). Considerable attention has been given to the searching and screening of medicinal plants all over the world as a means to identify inexpensive sources of new drugs against *H. pylori* (14). Due to increasing appearance of drug-resistance in *H. pylori* isolates traditional plants are valuable sources of novel *anti-H. pylori* agents (15). Some useful plants or herbal products against *H. pylori* would be discussed in the following paragraphs.

### Garlic

Garlic, *Allium sativum*, is invaluable not only as an indispensable flavoring element in food but also for its therapeutic properties. Garlic has specific oil- and water-soluble organosulfur compounds including thiosulfates, which are accountable for the flavor and odour of garlic. The interest matter is about the relationship between garlic consumption and gastric cancer because it is proved the therapeutic properties of garlic on *H. pylori* infection (16,17). Sivam (18) investigated the antimicrobial activity of garlic on *H. pylori*. In this research an aqueous extract

of a kind of garlic (Oswego white) was applied. The extract was standardized for thiosulfate concentration. The MIC was 40  $\mu$ g/mL. In this research *Staphylococcus aureus*, which was control, was not inhibited by the garlic extract at this concentration. Thus, *H. pylori* is more vulnerable to garlic extract. Another research by Cellini et al was tested 16 clinical isolates of *H. pylori*. They proved 90% of inhibition of the separates with aqueous garlic extract at 5mg/ml. The concentration used in this research was the total weight of garlic per milliliter. However, computation show that the MIC reported in the two searches are comparable. It is reasonable that the sensitivity of *H. pylori* to garlic extract at low concentration can be associated with the recorded lower risk of stomach cancer in those with a high allium vegetable consumption. The inhibitory concentration of garlic in the two researches above is attainable in the stomach by using a medium size clove of garlic or equal amount of garlic complements. Therefore, this finding can identify a strategy for inexpensive interference for stomach cancer with few side effects at high risk populations, especially in the case of high resistance to antibiotics (18).

### Broccoli

The traditional medicinal value of broccoli is up to its antibacterial, antiviral and anticancer properties. A study was done by Galan et al on *H. pylori* infected human volunteers. *H. pylori* positive patients were screened. Patients consumed broccoli sprouts twice daily for 7 days. They found that consumption of oral broccoli sprouts was related to eradication of *H. pylori* infection in patients (19).

### Green tea

Green tea is one of the most generally consumed beverages in the world. It has been shown antibiotic activity to inhibit the growth of *Helicobacter* spp. Such as *H. pylori* and *H. felis* at Stoicov et al study. Their results clearly showed growth effects of green tea against *Helicobacter* and significantly showed that green tea consumption could prevent gastric mucosal inflammation if consumed prior to contact to *H. pylori* infection. Thus, components within natural remedies including green tea could be used for prevention and treatment of *Helicobacter* infection in human (20). A research was done by Ruggiero et al about red wine and green tea which reduce *H. pylori*- or VacA-induced gastritis in a mouse model. They proved In *H. pylori*-infected mice, the green tea and red wine mixture significantly could prevent gastritis and limit the localization of bacteria and VacA to the surface of the gastric epithelium (21).

### Thyme

Thyme is a popular herbal medication in ancient Egypt, Rome and Greece which was generally used for digestive problems, headaches, respiratory illness and as a mood-enhancer. Smith-Palmer et al researched the antimicrobial properties of 21 essential oils and essences against 5 important food-borne pathogens such as *Escherichia coli* noticed that thyme was pretty effective at in-

hibiting the bacteria. Thyme extract was associated with many antibacterials, it had an important inhibitory effect on *H. pylori* (22).

### Turmeric

Curcumin is a polyphenolic chemical component developed from turmeric (*curcuma longa*), has been proved to prevent gastric and colon cancers in rodents. Several mechanisms have been offered for the chemo-preventative effects, even though the effect of curcumin against the growth of *H. pylori* has not been reported (23). *H. pylori* is a group 1 carcinogen and is related to the development of colon and gastric cancer. In a study curcumin and a methanol extract of the dehydrated powdered turmeric rhizome were experienced against 19 strains of *H. pylori*, containing 5 CagA-positive strains. Both the curcumin and methanol extract inhibited the growth of all strains of *H. pylori* in vitro. The MIC range was 6.25-50 µg/mL. these data showed that curcumin could inhibit the growth of *H. pylori* CagA-positive strains in vitro and this could be one of the mechanisms by which curcumin used its chemo-preventative effects (24,25).

### Ginger

Ginger root has been consumed for the treatment of gastrointestinal illness including motion sickness, dyspepsia and hyperemesis gravidarum. Since *H. pylori* is the most etiological agent associated with peptic ulcer diseases, dyspepsia and the development of gastric and colon cancer. So, study of Mahady et al demonstrated that ginger root-extracts including the gingerols inhibit the growth of *H. pylori* (2,26).

### Aloe vera

Aloe vera (*A. vera*) gel has mucoprotective consequence is reported to have antiulcer activity as well. Antiulcer activity is dependent to its cytoprotective, anti-inflammatory, and healing and also mucus stimulatory consequence (27). *A. vera* gel showed concentration-dependent inhibition of gastric acid secretion. It has been shown to protect rats and human beings against gastric ulceration (28). *A. vera* showed gastroprotective activity at lower concentrations because of the attendance of lectins. Lectins are proteins/glycoproteins which are able of recognizing and binding to carbohydrate moieties. It had been shown that lectins inhibit aminopyrine uptake using parietal cells. Hence, the ability of gel powder to inhibit gastric acid output mayhap as a result of direct action on the acid producing cells. Retention of *A. vera* gel and amoxicillin in the stomach would result in better action in contradiction of peptic ulcer using maintaining the effective drug concentration. Ranade et al demonstrated the effect of combining *A. vera* gel powder and amoxicillin in the form of a bilayer tablet which could work as an alternative to triple therapy where proton pump inhibitor is substituted by a herbal component which could help in showing better reaction of amoxicillin against *H. pylori* by doing as a cytoprotective agent (27).

### Cranberry juice

Cranberry juice has been studied for its bacterial anti-adhesive properties. In 2 studies were examined the inhibitory effect of cranberry juice against *H. pylori*. They proved that the use of a high molecular mass constituent of cranberry juice could inhibit *H. pylori* adhesion to human gastric mucus. Thus, they suggested that a mixture of antibiotics and a cranberry preparation might improve *H. pylori* eradication (29,30).

### Honey

Honey has been used as a remedy since ancient times in the majority of countries. Its use is noted in Sumerian clay tablets approximated to be 4000 years old and in Egyptian papyri from 1900 to 1250 BC. The expose in the Holy Koran and documentation in the *Hadith* obviously referenced to the effectiveness of honey in the healing of diseases for human. Honey is extensively known for its antibacterial properties. Honey has been examined for its *anti-H. pylori* activity in vitro (31). Abu Taib et al demonstrated that *H. pylori* growth was inhibited by 20% concentration of honey (32). Osato et al, in an attempt to show the role of osmotic effects and hydrogen peroxide in the inhibitory effect of honey in vitro, used control solutions including fructose, glucose, combined fructose/glucose, and catalase. It was accomplished that the *anti-H. pylori* activity was not associated with the attendance of hydrogen peroxide in the honey samples. Although, the osmotic effect was demonstrated to be the most significant parameter against *H. pylori* at concentrations  $\geq 150$  ml/L (33). In an in vitro examine, 13 commercial honey brands sold in Muscat area of Oman, were examined for *anti-H. pylori* activity by a surface diffusion procedure and in combination with CLA or amoxicillin. The results showed that all of them had *anti-H. pylori* activity, but no synergy was detected, either with honey and CLA or honey and amoxicillin. These data recommend that a triple regimen with these honeys could help to eradicate the bacteria (31). Newly, in an attempt to discover the active compounds of honey, 2 studies were done. In the first study, Manyi-loh et al screened 3 locally produced honeys from different areas in South Africa for *anti-H. pylori* activity. Pure honey was extracted by n-hexane, chloroform, ethyl acetate and diethyl ether. All extracts tested for anti *H. pylori* activity and showed *anti-H. pylori* activity at concentrations  $\geq 10\%$ . Chloroform extract demonstrated the lowest MIC<sub>95</sub> values which ranged from 0.156-500 ml/L depending on the strain. This suggests that all honeys and solvent extracts have potential compounds with therapeutic activity which could be used for treatment of *H. pylori* infections (34). In other study, Manyi-loh et al undertook the antibacterial activity of n-hexane extract from Golden crest honey. The best antibacterial activity was shown by fraction GCF3 with MIC equal 5 mg/ml that was composed of some compounds with known antioxidant and antimicrobial properties. This study demonstrated that n-hexane extract could provide new lead molecules which could serve as discerning agents for *H. pylori* chemotherapy and control (35).

## Black myrobalan

The aqueous extract of black myrobalan had been shown to have uniform antibacterial activity in contradiction of ten clinical strains of *H. pylori* (36,37). It was reported that some extracts of this plant such as ethyl gallate, ethanol and gallic acid have antibacterial activity against methicillin resistance and sensitive *Staphylococcus aureus* and other bacteria. The aqueous extracts antibacterial activity of black myrobalan in contradiction of *H. pylori* was considerably higher than that of ether and alcoholic extracts (38).

## Conclusion

The herbal drugs defined here have applications for treatment of *H. pylori* infection although more development is needed for each to be considered as effective drug in human. So, important point of this research is the possibility that alternating herbal components might produce synthetic or chemical drugs effective in *H. pylori* infections. Finally, it should remember that, in the conditions of liver or renal insufficiency and also in hemodialysis patients, the use of herbal drugs should be with caution and requires further investigations.

## Authors' contribution

SN prepared the primary draft. SSBM searched the data and conducted primary editing. Editing the final manuscript done by MRK. All authors read and signed the final manuscript.

## Conflicts of interest

The authors declare no conflict of interest.

## Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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