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Review Article

Anti-Bacterial Properties of Herbs against *Helicobacter Pylori* Infection: A Review

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ABSTRACT

Helicobacter pylori is a gram-negative bacterium that lives in human stomach. This bacterium is the most important cause of chronic gastritis, peptic and duodenal ulcers and gastric cancer. The therapies include the use of antibiotics and a proton pump inhibitor, but unfortunately, these therapeutic methods are not always responsive due to resistance to antibiotics. In recent years, use of alternative treatment, including medicinal herbs was shown to have anti-*H. Pylori* properties. So, in this review, anti-*H. Pylori* features of herbals were investigated including ginger, garlic, cranberry, curcumin, green tea and broccoli sprouts derived through the search in Google Scholar search engine, and PubMed scientific database using English keywords such as *Helicobacter pylori*, anti-*H. pylori*, ginger, garlic, cranberry, curcumin, broccoli and green tea, between 1984 -2016. Results showed that ginger, garlic, cranberry, curcumin, broccoli and green tea have antibacterial, antioxidant and anti-inflammatory potential properties, and because of their role in protecting the stomach against *H. pylori* infection, it seems, they can be an appropriate treatment option for patients with this infection.

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Introduction

Gastritis is the inflammation of the gastric mucosa and is associated with diseases such as peptic ulcer, pernicious anemia and gastric cancer (1). Worldwide, the most common cause of chronic gastritis, is *Helicobacter pylori* infection. This infection caused a progressive damage to mucosal tissue of the stomach and currently has a decisive role in the development of duodenal ulcer and is associated with diseases such as peptic ulcer, stomach adenocarcinoma and malignancies associated with lymphoid tissue (MALT) (2-4).

*H. pylori*is a gram negative spiral-shaped bacteria and is one of the most common bacteria that lives in the human body, generally in the stomach and has also infected more than half of the world's population. About 10-20% of affected people with *H. pylori*suffer from peptic ulcer and 1-2% are exposed to risk of

gastric cancers (5). In fact, this bacterium has been classified as carcinogen class 1 by the WHO (6). In Iran, the prevalence of this infection is high and reaches to 50.7%. The highest and lowest incidence of this infection is related to Tehran (74.27%) and Mazandaran province (19.2%), respectively (7).

The Pathogenesis Mechanisms of Helicobacter Pylori

This bacterium is connected to mucin layer and surface receptors of gastric epithelial cells through the passage from mucosal layer by its spiral shape and the forward movement of its flagella. It is resistant to gastric acid using its urease activity and the bacteria release some toxic factors (cagA: cytotoxin associated gene A), vacA (vacuolating cytotoxin A) and LPS (lipopolysaccharides) into cytoplasm of host cells and causes chronic infection and inflammation. In addition, *H. pylor*i adapts itself to the environment through maintaining inflammation in gastric epithelial cells and reducing the immune response and enhancing its own survival (5).

Oxidative stress caused by this infection plays an important role in changing the proliferation of epithelial cells, increasing apoptosis (8, 9) and DNA damage (9, 10). On the other hand, the reduced levels of ascorbic acid resulting from infection is associated with the creation of a pro-oxidative status (11). *H. pylori* activates a number of transcription factors such as NF-KB through its toxic factors in gastric epithelial cells or inflammatory cells such as macrophages and T-cells. These activated transcription factors, induce the expression of inflammatory cytokines (IL6, IL8), chemokines and inflammatory regulators (ROS, COX2) and by creating an inflammatory environment facilitate the transformation of gastric epithelial cells (12).

Treatment Methods

H. pylori infection in humans usually occurs in childhood and is often asymptomatic, but induced gastritis can cause the symptoms to be associated with indigestion and if it does not treated, it may progress and cause peptic and duodenal ulcers and/or formation of two types of gastric cancers (5). The most common treating methods of this infection are triple and quadruple therapies. Triple therapy that uses two antibiotics (amoxicillin, clarithromycin or metronidazole) and a proton pump inhibitor is considered as an effective treatment for *H. pylori* infection (13). However, the infection in more than 20% of patients do not disappear completely. Quadruple therapy involves use of a proton pump inhibitor, bismuth, tetracycline and metronidazole, but unfortunately this kind of treatment is not responding in 20-30% of patients too (14).

In fact, failure of treatment is one of the important problems that is associated with *H. pylori* infection and mostly happens due to resistance to antibiotics, especially to clarithromycin and metronidazole. In addition, the penetration of bacteria in an environment that protects it like mucosal layer and epithelial cells and also individual intolerance to side effects of antibiotics and high cost of treatment can be considered as other reasons (5). Considering the development of resistance to antibiotics in the treatment of *H. pylori* infection, use of alternative treatment or complementing the treatment process in recent years has been highly evaluated. Phytotherapy is one method of alternative treatment (5). This type of alternative therapy has been highly regarded especially due to its naturality, low toxicity, least side effects, and low cost when compared to pharmacological therapy. The aim of this study is review of anti-*H. Pylori* features of some herbs including ginger, garlic, cranberry, curcumin exist in turmeric, broccoli sprouts and green tea.

Ginger Anti-H. Pylori Property

The root of ginger plant (*Zingiber officinale*) historically had been used for digestive disorders such as severe vomiting, dyspepsia, peptic ulcer and inflammatory diseases (15). Ginger has numerous biological features, including antioxidant, anti-ulcer (16), anti-inflammatory, anti-tumor (17), anti-bloating properties and digestion of food (18). Phenolic compounds of ginger include 6-gingerol, 8-gingerol, 10-gingerol, 6-shogaol, phenolic acids and their derivatives have anti-*H. pylori* features (19). In a study, oral administration of 100 milligrams per kilogram of body weight ginger extract during 3 weeks prior to induction of *H. pylori* infection in laboratory animals was shown to reduce the risk of infection to bacteria. The ginger extract could also reduce significantly the rate of acute and chronic inflammation, ulcers and corrosion of stomach tissue and deterioration of epithelial cells (20).

Ginger extract also inhibited the in vitro COX2 gene expression that is increased in acute phase of inflammation. It also resulted into inhibition of NF-KB and inflammatory cytokines such as IL6, IL8 and IL1β and prevented the development of acute and chronic inflammation caused by *H. pylori* (20). It was shown that the methanol extract of ginger root leads to inhibition of 19 species of *H. pylori* with minimum inhibitory concentration between 6.25-50 micrograms per ml (21). It is observed that the water and ethanol extracts of ginger, suppress the growth of the *H. pylori* that are resistant to antibiotics *in vitro* (19) and aqueous extract of ginger prevented ulcers in gastric mucosal

tissue caused by stress and also inhibited gastric acid secretion through blocking the activity of H-K ATPase, while the thereby limited the growth of *H. pylori* (22). Some studies suggested that consumption of ginger is related to a reduced risk of stomach and colon cancers and play a protective role against *H. pylori* (21, 23). It also purged free radicals, and prevented damage to DNA and lipid peroxidation (24, 25).

Garlic Anti-H. Pylori Property

It was demonstrated that garlic (*Allium sativum* L.) has antibiotic, anti-cancer, anti-inflammatory and antioxidant properties and play a role in blood sugar reduction and protect the cardiovascular system (26). Garlic in comparison with garlic family (allium vegetables) include a wide range of tiosulfinat, such as allicin, which has anti-bacterial activity against a broad spectrum of gram-positive and gram-negative bacteria, particularly *H. pylori*. So inactivation of allicin by alliinase, prevents its antibacterial activity (27, 28). Allicin does not exist naturally in garlic, but it is produced after hydrolysis and oxidation of the substance called allyn (29). Allicin increases the efficacy of proton pump inhibitor drugs and omeprazole in the treatment of *H. pylori* infection *in vitro* (30). The effect of raw garlic extract or garlic pills has been seen against *H. pylori* in some studies (31, 32).

The increments in consumption of garlic family vegetables also have a positive effect in reducing stomach cancer against the *H. pylori* (33). In one study, the effectiveness of anti-*H. pylori* properties of pure garlic oil, garlic powder and allyl sulfur dioxide compounds were investigated and were shown that all three compounds have potential effects as anti-*H. pylori* (34). However, in a pilot study, daily intake of four capsules containing 4 milligrams of garlic oil for 2 weeks had no effect on the eradication of *H. pylori* infection and symptoms improvement that this could be due to the small size of population and short duration of the intervention (35). Garlic anti-inflammatory mechanism is related to preventing the activation of NF-KB that plays a role in increase of the expression of inflammatory cytokines resulting into inflammation and cancer (35).

This nuclear factor activation is carried out through signaling the receptors called TLR4 (36). Allicin inhibits the NF-KB activation by this inhibition of this signaling (37). Several studies have found that *H. pylori* produced inflammatory factors such as TNFα, IL8 and the CRP through the production of antigenic materials such as heat shock proteins and lipopolysaccharides and absorption of these materials by the stomach epithelial cells (38, 39). Thiosulfinate compounds in garlic react with these antigenic compounds and inhibit them, so reduces the bacterial colonization (40). On the other hand, *H. pylori* increases gastric pH, provide situations for activity of manufacturer microbes of nitroso compounds that are potentially carcinogen, while allicin reduces infection caused by *H. pylori* and cancers through inhibition of nitrous production and nitric acid and free radicals purging (41).

Cranberries Anti-H. Pylori Property

Cranberries are a good source of bioactive compounds such as flavonoids (Prosianidin and flavonols) and phenolic acid derivatives. Its anti-bacterial properties have been reported in some studies (42, 43). These studies showed that drinking cranberry juices leads to improvement of *H. pylori* infection. High levels of vitamin C and bioflavonoids in cranberries lead to antibacterial properties and high levels of proanthocyanidins prevented the connection of *H. pylori* to human gastric mucosal surface (44-46). In addition, anti-inflammatory and antioxidant activity of polyphenols contained in it, reduces inflammation caused by bacterial colonization (47). In one study, oral administration of cranberry juice to mice infected with *H. pylori* lead to treatment of 80% of them within 24 hours after intervention (48). There are several mechanisms to explain the anti-*H. pylori* propertyof cranberries including anti-adhesion feature (49), antioxidant and anti-cancer activities (50), suppressing the proliferation of cells due to high levels of proanthocyanidins contents (51, 52), inhibition of urease activity in the bacterium (53) and cytotoxic property to the bacteria (54).

In last decade, cranberry combination with antibiotics which was used to treat infections has been able to increase the effectiveness of drugs and caused an increase in the destruction of the infection and suppression of bacterial population (55, 56). In a 90-day study on 189 patients who consumed cranberry juice versus placebo, the eradication rate of *H. pylori* infection showed an increasing trend in intervention group (57). Also, a clinical trial revealed a synergistic effect for combined use of cranberry juice and standard drug treatment, including amoxicillin, clarithromycin and omeprazole in improving eradication of bacteria in women (58). It has been observed that consumption of cranberry juice helped to control colonization of this bacteria among children with no symptoms (52). However, more *in vivo* studies are needed to understand the mechanisms.

Curcumin Anti-H. Pylori Property

Curcumin is known for its active compound as turmeric that has anti-inflammatory, anti-mutagenic, antioxidant and antiseptic properties (59-62). This material is used to treat peptic ulcer and prevention

of *H. pylori* growth too (63-65). In fact, in animal study, it was shown that curcumin can eradicate *H. pylori* infection. Also in gastric epithelial cells of individuals with this infection in a dose-dependent manner, it causes suppression of matrix metalloproteinase-3, and 9 in the bacteria. These metalloproteinases are associated with pathogenesis as inflammatory molecules. Curcumin also decreases expression of genes associated with cell toxicity (cag) and treats the *H. pylori*infection (66).

In a study, it was found that curcumin had anti-*H. pylori* features due to inhibition of the shikimate path that plays an important role in the production of vital metabolites such as amino acids, aromatics, folic acid and ubiquinone in bacteria. Shikimate dehydrogenase enzyme was demonstrated to be affected in this pathway (67-69). However, in a clinical trial, the effect of curcumin on IL8, TNFα and COX2 Il1B on stomach mucosa was studied in patients with *H. pylori* infection. Patients were randomly assigned into two groups of consumers of omeprazole, amoxicillin and metronidazole (OAM) or as curcumin consumer group. Finally, the infection rate in patients of OAM group was significantly higher than the group receiving the curcumin. IL8 expression level in OAM group after treatment significantly decreased and no changes were observed in other cytokines. In the group receiving curcumin, no reduction was seen in levels of these cytokines that this could be due to low bioavailability of curcumin in *in vivo* enviroment (70).

Broccoli Sprouts Anti-H. Pylori Property

Broccoli is introduced as another option for the treatment of *H. pylori* infection. This plant contains isothiocyanate sulforaphane which is a potent stimulus to induce enzymes of phase 2 detoxification such as glutathione s-transferase and quinone reductase and also has antioxidant, anti-inflammatory, and anti-cancer effects (71-73) and has strong anti-bacterial potential effects against *H. pylori* in human and mouse epithelial cells (74). In a study, it was shown that temporary oral administration of broccoli sprouts was in association with eradication of *H. pylori* in 3 persons of 9 patients with active gastritis (75). Sulforaphane has strong antibacterial activity against a large number of clinical strains of *H. pylori* that most of them are resistant to antibiotics such as metronidazole and clarithromycin. Recently, it was seen that daily intake of broccoli sprouts fortified with sulforaphane for 2 months, reduced bacterial colonization in mice and improved the infection in mice and humans (76).

This treatment can be due to increased gastric mucosal protection against oxidative stress caused by *H. pylori* through antioxidant and anti-inflammatory effects of broccoli sprouts. Also, in a clinical trial for 48 patients with *H. pylori* infection, daily intake of 70 grams of broccoli sprouts for 8 weeks significantly caused reduction in urea breath test and stool antigen test (diagnostic tests for *H. pylori* infection in humans) (76). However, in another study, consumption of broccoli extract containing 2000 mcg of sulforaphane daily for 4 weeks, did not show any significant change in urea breath test at the end of the study. Also, the level of malondialdehyde in the group of receiving the extract did not significantly decrease and gastric mucosal glutathione in groups were not significantly different at the end of the study. However, consumption of extract could prevent lipid peroxidation in the gastric mucous (77).

Green tea Anti-H. Pylori Property

Green tea is used in prevention and treatment of various diseases. Green tea has antioxidant, anti-cancer, anti-inflammatory, anti-bacterial, anti-obesity and anti-peptic ulcers properties (78). These health benefits are attributed to its chemical compounds, including polyphenols (catechins, flavonoids and proanthocyanidins), alkaloids, terpenoids, and etc (78). About 50-80% of the content of catechins in green tea is epigallo catechin gallate (EGCG). In a study, the influence of EGCG consumption on prevention of induced *H. pylori* infection in laboratory animals was examined and found that EGCG reduced the severity of gastritis and inflammation caused by *H.pylori* infection in gastric tissue. EGCG anti-inflammatory function is related to its ability to suppress the expression of TLR4, NF-KB and iNOS genes and reducing the release of inflammatory cytokines of IL1β, IL6 and TNFα (79).

Among the catechins content in tea, EGCG, gallo catechins gallate (GCG) and gallo catechins (GC) were shown to have strong effects against *H. pylori* (80). These effects are primarily related to anti-bacterial properties and inhibition of urease activity in these bacteria. Also, catechin destruct the bacteria by damaging the cell membrane of bacteria. However, its antioxidant and anti-inflammatory properties and or inhibition of gastric acid secretion by catechin can also affect (81). According to the results of one study, *H. pylori* infection was found to be associated with chronic atrophic gastritis and gastric cancer, while consumption of green tea may reduce the atrophic gastritis (82). Also, it has been observed that the prevalence of *H. pylori* infection in patients that consume green or black tea more than once per week, than others were lower (45.2% vs. 64.8% respectively), showing that consumption of tea had protective effects against *H. pylori* infection (83).

Conclusion

Because of the importance of controlling *H. pylori* infection as a serious problem that threatens global health, due to its high prevalence and increased resistance to antibiotics, considering an alternative treatment seems necessary. Some herbs were noted to be appropriate treatment options against *H. pylori* infection due to their role in protecting the gastric mucosa. Alternative therapy that uses natural compounds, has low toxicity and side effects, and is costeffective in comparison to pharmacological therapies. However, their application in human needs more clinical studies.

Conflict of Interest

None declared.

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