



Anti-*Helicobacter* activity of medicinal plants and probiotics as alternatives for *Helicobacter pylori* treatment: Review article

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ABSTRACT

Helicobacter pylori, a gram-negative bacterium, known factor for chronic active gastritis, stomach and peptic ulceration, which may progress to gastric cancer. It is also associated with other non-gastric diseases such as stroke, diabetes mellitus and alzheimer's disease. Although conventional treatment achieved a great advancements in controlling *H.pylori* infection nowadays it is not effective thus it's intended to find some other alternative sources that may be used alone or in combination with antibiotics to eradicate the infection. Recently published literature of natural sources such as plant -derived bioactive compounds and probiotics are studied for their reduced side effects and for being safe and inexpensive. However, the mechanism of action by which these herbs and probiotics exert their medicinal properties in *H.pylori* treatment is still not fully clear. In this review, we highlight the potential anti-bacterial mechanisms of some traditionally used bioactive compounds and their possible role on *H.pylori* colonization. On the other hand, we focused on the possible inhibitory role of probiotics in the eradication of *H. pylori* infection through the release of organic acids and their role in the stabilization of the gastric barrier function in order to decrease the mucosal inflammation, modulate *H.pylori* colonization and enhance compliance in infected patients.

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INTRODUCTION

Helicobacter pylori (*H. pylori*) is a gram negative spiral shaped bacterium that is known as the most persistent infection worldwide. According to the previous studies the prevalence of *H.pylori* among developing countries was higher than that in developed countries (50.8%, 34.7%), due to many factors as socio-economic status and hygienic levels (Ernst and Gold, 2000).

H. pylori colonization depends largely on urease

enzyme and needs basic environment in stomach to live, it converts urea into ammonia to neutralize stomach pH thus support its colonization. Among the colonized patients some may develop diseases as gastritis, peptic and duodenal ulcer, gastric MALT lymphoma, gastric adenocarcinoma, and others. On the other hand, *H. pylori* infection may be linked with several chronic diseases, where some studies mentioned that the occurrence of the infection is tightly connected with the type of many chronic diseases such as stroke, Alzheimer's disease (AD), diabetes mellitus (DM) (Garza-González, 2014) and many other extragastric chronic diseases.

The accurate diagnosis of *H. pylori* is essential to eradicate the infection. Different methods are done for the diagnosis of *H. pylori* are classified as invasive (polymerase chain reaction and the rapid urease test), and non-invasive procedures (urea breath test, serology and stool antigen test). The cost, the accessibility and the availability of diagnostic tests may affect the priority for diagnostic test selection and the accuracy of the infection detection (Abadi and Kusters, 2016).

In this review we will discuss the available conventional regimen for *H. pylori* treatment, the bioactive compounds of natural plant sources that have shown an effect on *H. pylori* infection, and the possible positive effect of Probiotics in *H. pylori* treatment and inhibition.

Conventional treatment of *H. pylori* infection

Antibiotic treatment as monotherapy is not effective against *H. pylori* infection because of upcoming resistance for antibiotics, thus the combination of antibiotics with a proton pump inhibitors (PPIs) are required to eradicate the infection. Triple, quadruple and quinolone-based therapies are being used instead.

Triple therapy

This treatment is widely used and considered the standard therapy. The therapy consists of PPI and clarithromycin with amoxicillin as an empirical therapy given for 7 – 14 days. The second line therapy has substituted clarithromycin with metronidazole in combination with amoxicillin and PPI. Both treatments were successful until the resistance of *H. pylori* toward clarithromycin and metronidazole has appeared. On the other hand, amoxicillin shows uncommon *H. pylori* resistance, and no significant change of *H. pylori* response (Abu-Qatouseh et al., 2016). There are many beneficial effects of PPI addition to the eradication therapy, beside stomach protection effect by proton pump (H^+/K^+ ATPase) blockage of gastric parietal cells, it can improve the

eradication effect of other antibiotics toward the bacterium by improving the antibiotics stability in the stomach (Thung et al., 2016).

Resistance of the bacterium toward antibiotics differs from country to another. According to previous studies, the rate of clarithromycin resistance is increasing worldwide because of the extensive use of macrolide antibiotics and due to bacterium point mutations of the 23S rRNA gene, mutations that have been mentioned were the replacement of adenine residues at positions 2143 and 2144 with cytosine A2143C or guanine (A2143G and A2144G) (Gibson et al., 1999).

Metronidazole resistance could be referred to the over consumption of nitroimidazoles in many other infections, and for the genetic alterations of nitroreductase encoding genes of *H. pylori*. Thus, both clarithromycin and metronidazole have extreme resistance due to genetic mutations of *H. pylori* but the priority for which one to be combined with amoxicillin to be used as first line therapy depends on geographical reasons, because the resistance rate of each antibiotic differs from one country to another, so it could be useful to make genotypic resistance test to give the most effective treatment to eradicate the infection (Liou et al., 2018).

Quadruple regimen therapy

The quadruple regimen with bismuth salt combined is used for 10 days and showed more effect especially in regions with increased clarithromycin resistance.

It is not yet known how bismuth improves the eradication of *H. pylori* infection. One of the possible mechanisms is that bismuth salt could be deposited into the periplasmic space of bacterium to form complexes that inhibit different types of *H. pylori* enzymes such as urease, alcohol dehydrogenase, formase and phospholipase (Alkim et al., 2017).

Although bismuth quadruple regimen was successful in improving eradication rates of *H. pylori* infection, the frequently administered doses and the side effects of bismuth lead to the development of other therapies (Saad et al., 2006).

Quinolone containing triple regimen therapy

Quinolone containing therapy is considered as a rescue therapy for clarithromycin resistant populations when administered for 7 to 14 days. Levofloxacin based therapy has been reported with high prevalence of resistance, thus, fourth generation quinolones (moxifloxacin, sitafloxacin, gemifloxacin and gatifloxacin) were included in *H. pylori* eradication therapy, because of their broad-spectrum activity against gram positive and gram-negative bacte-

ria. These drugs can inhibit DNA replication and enhance antibacterial activity. But there was conflict on results of eradication, some studies show high eradication results (Abu-Sini *et al.*, 2017) and others show no satisfactory effects with fourth generation quinolone eradication therapy. Mainly this group should be preserved as third- or fourth-line therapy to prevent the possible occurrence of resistance.

Plant source alternative treatment of *H. pylori* infection

Alternative, effective plant source compounds are being thoroughly studied to overcome the drawbacks of conventional regimens mainly antibiotic resistance.

Here, we will discuss the most commonly studied plants and their important bioactive compounds that were reported to inhibit the growth of *H. pylori* bacterium.

Garlic (*Allium sativum* L.)

Garlic has extensively been studied for its antimicrobial and antioxidant effects. Many studies have stated that *A. sativum* exhibits broad spectrum activity against gram negative and gram positive bacteria, also it lacks any possible microbial resistance, thus, makes garlic a good choice for synergistic effect with other antimicrobials to treat infections (Sivam, 2001). Antimicrobial activity is achieved by the thiosulfate component that directly inhibits RNA synthesis and for a lesser instant DNA and protein synthesis. Studies revealed that the extracted materials of garlic as allicin has bacteriostatic properties. Commercially available extracts of ethanol and acetone have been reported the highest activity against *H. pylori* (Guercio *et al.*, 2014).

Ethnopharmacological studies showed that individuals with high garlic intake are less susceptible for gastric cancer. Since because *H. pylori* infection is one of the risk factors of gastric cancer, garlic may have countable effect on preventing the occurrence of gastric carcinoma that results from *H. pylori* colonization (Kim *et al.*, 2018).

It's important to mention that one of the draw backs of garlic as complementary drug that thiosulfate can interact with the conventional treatment and make chemical interactions that inhibits the activity of the structure, on the other hand some variables may play a major role in the activity of garlic as the degree of milling and extraction, storage conditions and storage time (Ali *et al.*, 2000).

Green tea (*Camellia sinensis* T.)

Green tea is one of the widely consumed beverages in Asia, it contains compounds as polyphenols,

polysaccharides, aminoacids and vitamins.

Epigallocatechin gallate, a polyphenolic compound that is found in tea extract, has shown an antioxidant, antibacterial, antitumor and immunomodulatory effects, and it can inhibit tumor necrosis factor alpha (TNF- α) gene expression, which is the central mediator of tumor promoter. Urease enzyme is required for *H. pylori* colonization; thus, the inhibition of this enzyme may lead to disruption in bacterial colonization. Hence, polyphenols of green tea can prevent or treat gastric diseases associated with *H.pylori* (Ruggiero *et al.*, 2007).

Oral administration of green tea with antimicrobials may improve the reveal of *H. pylori* colonization and suppress gastric diseases, but it has some side effects as dizziness, diarrhea, headache, insomnia and iron deficiency (Safavi *et al.*, 2015).

Cinnamon (*Cinnamomum zeylanicum* L.)

Cinnamon is a widely used remedy to relief respiratory and digestive problems. One of the major components of cinnamon is the essential oil cinnamaldehyde that possesses activity against bacteria, fungi and virus infections. It can also inhibit protein synthesis that is essential for bacterial survival. One other major component is eugenol, that acts as antioxidant and reduces oxidative stress (Hamidpour *et al.*, 2015).

Methanol extracts of cinnamon leaves and stem bark show antioxidant and antibacterial activity. The anti *H. pylori* effect of cinnamon extract was studied both *invitro* and *invivo*. Results have shown that cinnamon can reduce *H. pylori* colonization as in single drug therapy. However, the use of cinnamon extract as monotherapy was not effective where bacteria can gain resistance against its bioactive ingredients (Nir *et al.*, 2000).

Saffron (*Crocus sativus* L.)

Saffron is a food additive that has been used in the treatment of cardiovascular diseases, fever and bronchitis. Moreover, it has shown some other activities such as anticancer, antimicrobial and antifungal. The potential anti *H. pylori* effect of saffron was studied on the two major bioactive compounds of *C.sativus*, which is crocin, and safranal.

Extracts of crocin and safranal decreased gastric secretions and ulcer occurrence in *invivo* studies, it was suggested that *C.sativus* can have beneficial effect against *H. pylori* by inhibiting *H.pylori* peptide deformylase (HpPDF) which catalyzes the removal of the formyl group from the N-terminal of the nascent polypeptide chains, this chain is essential for the survival of *H. pylori* bacterium. On the other hand, saffron extracts can prevent the formation of

tumor cells by inhibiting the DNA and RNA synthesis in gastric cancer in mouse (Tavakkol-Afshari *et al.*, 2008).

Curcumin (*Curcuma longa* Z.)

Curcumin, the major component of *Curcuma longa*, has been widely used and prescribed for its beneficial effect in the treatment of Alzheimer's disease, inflammatory bowel disease and for its antimicrobial, anti-oxidant and antimutagenic activity.

In 2002, (Mahady *et al.*, 2002), showed that curcumin can inhibit the growth of *H. pylori* in *in vitro* studies along with chemopreventative effects (Mahady *et al.*, 2002). Another study that was conducted by (Mario *et al.*, 2007) showed that administered curcumin daily for one week as an antimicrobial treatment regimen for patients with *H. pylori* infection and found that curcumin has no effect and can only decrease the symptoms of mucosal inflammation (Mario *et al.*, 2007).

The possible explanation for the curcumin activity against *H. pylori* infection is curcumin ability to inhibit the shikimate pathway in the bacteria which is needed to synthesize the aromatic amino acids (Voravuthikunchai and Mitchell, 2008). Another study suggested that curcumin activity against *H. pylori* infection is related to its antioxidant capacity, its ability to inhibit IL-6 secretion and its ability to prevent apoptosis in a dose dependent manner (Mario *et al.*, 2007).

Pomegranate (*Punica granatum* L.)

P. granatum is a plant that belongs to *Punicaceae* family which is rich in tannins. It has been used as a herbal remedy for many years for the treatment of diarrhea, dysentery, and stomachache and in wound healing remedy. Recent studies have focused on the antimicrobial activity of *P. granatum* extracts against Gram positive and Gram-negative bacteria.

It was found that *P. granatum* has a remarkable activity against *H. pylori* which was explained by the increase in cell surface hydrophobicity of the microorganism which in turn inhibits the attachment of *H. pylori* to the gastric mucosa (Gharzouli *et al.*, 1999). The other possible explanation for *P. granatum* activity against *H. pylori* is its protective and anti ulcerogenic activity because of the presence of saponins, tannins and flavonoids which acts as antioxidants, anti-secretory and cytoprotective agents (Schubert *et al.*, 1999).

Ginger (*Zingiber officinalis* Z.)

Ginger (*Zingiber officinalis*) belongs to Zingiberaceae family and is being used as dietary component and spice in different cultures. Ginger is considered

as a powerful medicinal plant that exerts antioxidant, anti-ulcer, anti-emetic, anti-inflammatory, anti-tumor, and gastro protective effects. Many studies showed that ginger may be beneficial in inhibiting ulcerogenic effects of *H. pylori*. The possible mechanism of inhibition was explained by (Siddaraju and Dharmesh, 2007), where he mentioned that ginger is effective in inhibiting H⁺, K⁺-ATPase activity which in turn inhibits the colonization of *H. pylori* (Siddaraju and Dharmesh, 2007). On the other hand, (Nostro *et al.*, 2006) in his study couldn't explain the possible inhibition mechanism of ginger on the *H. pylori* but he reported that ginger can potentiate the activity of clarithromycin by enhancing its influx of clarithromycin (Nostro *et al.*, 2006).

Probiotic supplements in the treatment of *Helicobacter pylori* infection

Probiotics are living microorganisms that can interact with gut microflora to relieve diseases and give beneficial effects. The best studied Probiotics are *Lactobacillus* sp., *Bifidobacterium* sp., *Escherichia coli*, *Streptococcus* sp., *Enterococcus* sp., *Bacteroids* sp., *Bacillus* sp., *Propionibacterium* sp. and different types of fungi (Johnson-Henry *et al.*, 2004).

Many studies reported that the use of Probiotics for *H. pylori* treatment with or without conventional therapy may have an inhibitory role in the eradication of *H. pylori*. The mechanism of action for *H. pylori* growth inhibition is the secretion of lactic acid and by reducing IL-8 secretion via TNF- α -independent *H. pylori* death. Lactic acid acts as antimicrobial and as a permeabilizer of gram negative bacteria outer membrane and potentiates the antimicrobial activity of other substances (Alakomi *et al.*, 2000). The other suggested mechanism is that Probiotics can strongly adhere to the human gut which in turn activates biological pathways and releases cytokines and chemokines which potentiates the immune system in humans (Hemaiswarya *et al.*, 2013).

However, *in vitro* and *in vivo* studies have so far failed to give solid evidence on the effect of probiotics on the inhibition of the adhesion of *H. pylori* to the gastric mucosal and thus prevention of the bacterium colonization (Penner *et al.*, 2005).

CONCLUSIONS

Although treatment of *H. pylori* is still a challenge, the triple therapy of clarithromycin, amoxicillin and PPI remains the first line regimen to treat and eradicate the bacterium. It is important to give a multi drug therapy with low cost and less side effects to achieve best results with more compliance. Plant

sources can be of promising results as a new regimen that can eradicate the infection without resistance problems especially in areas where conventional therapy has failed. None the less, further studies should be done on plant source bioactive compounds and on Probiotics to provide an alternative safe and effective regimen.

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Conflict of Interest

None

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