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TOPIC HIGHLIGHT

2016 *Helicobacter pylori*: Global view

Non-pharmacological treatment of *Helicobacter pylori*

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Abstract

Many food and plant extracts have shown *in vitro* anti-*Helicobacter pylori* (*H. pylori*) activity, but are less effective *in vivo*. The anti-*H. pylori* effects of these extracts are mainly permeabilitization of the membrane, anti-adhesion, inhibition of bacterial enzymes and bacterial grown. We, herein, review treatment effects of cranberry, garlic, curcumin, ginger and pistacia gum against *H. pylori* in both *in vitro*, animal studies and *in vivo* studies.

Key words: *Helicobacter pylori*; Cranberry; Garlic; Curcumin; Ginger; Pistacia gum

Core tip: *Helicobacter pylori* (*H. pylori*) infection is difficult to eradicate and therefore, it is necessary to combine several antibiotics as well as administering a proton-pump inhibitor. Many food and plant extracts have demonstrated *in vitro* antibacterial activity, however, in *in vivo*, they are less effective. The food reviewed, herein, can be effective in preventing and/or reducing *H. pylori* infection. A preventive dietary approach can be very inexpensive in areas with poor health care systems.

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INTRODUCTION

The main cause of peptic ulcers, chronic gastritis and gastric neoplasms is *Helicobacter pylori* (*H. pylori*) infection. The International Agency for Research on Cancer[1,2] first classified this bacterium as a group I carcinogen. Several putative virulence-associated factors contribute to its pathogenesis[3]. Virulence markers of *H. pylori* are intermittently associated with diseases. To effectively treat *H. pylori* associated diseases, the need to eradicate *H. pylori* in infected

individuals remains the best option. This infection is difficult to eradicate and therefore it is necessary to administer a proton-pump inhibitor (PPI)[4] and group several antibiotics together. *H. pylori i*s sensitive to several antibiotics, *i.e.,* clarithromycin, amoxicillin, metronidazole and tetracycline[5], however, alone these antibiotics cannot eradicate the microorganism[6]. The widespread treatment of amoxicillin, clarithromycin and omeprazole at present, is hardly effective due to increasing resistance to antibiotics. The efficacy of a particular therapy may vary due to patient compromise, age, local antibiotic guidelines, food and hygiene[7].

CRANBERRY

Vaccinium macrocarpon, also known as cranberry is a natural fruit. Studies have shown drinking cranberry juice can in part attenuate *H. pylori* infection. Cranberries are indigenous to North America and have been widely developed commercially in states, *i.e.,* Wisconsin, Massachusetts, and New Jersey. Cranberry juice is successful in inhibiting or treating urinary tract infections (UTIs) due to its capability to avoid adhesion to the lining of the UT. This bacteriostatic characteristic is attributable to proanthocyanidins[8]. Cranberries, a resource of vitamin C may also provide a bacteriostatic effect.

A previous study demonstrated that an integral part of elevated molecular weight of cranberry juice can prevent *H. pylori* adhesion *in vitro* to the human gastric mucosa[9,10] and act on specific adhesions. Other adhesions such as BabA, may also be affected[11].

Animal model studies have demonstrated the importance of BabA in associated *H. pylori* diseases, influencing the severity of the disease[12]. A recent study illustrated that when cranberry juice was fed to mice infected with *H. pylori*, 80% were cured 24 h following treatment, with an eradication rate of 20%, 4 wk post-treatment[13]. However, the actual process by which cranberry juice affects the colonization of *H. pylori* and its suppression deserves further exploration.

Several mechanisms have been postulated as causing the inhibitory action of cranberries against *H. pylori*; among them are adhesion, biofilm formation blocking[14], anti-oxidative and anti-carcinogen activity[15], proliferation suppression[16,17] due to high concentrations of proanthocyanidins[17], urease inhibition[18], inhibition of the *H. pylori* adhesion to human gastric mucus[19] and even a cytotoxic effect against the germ[20].

Significant positive results in treating *H. pylori* infections with cranberry juice have been shown in human *in vivo* studies. Almost a decade ago, cranberries were tested in combination with traditional anti-*H. pylori* antibiotics such as metronidazole and clarithromycin[21,22] and proved effective in improving eradication rates and suppressing infections in endemic populations. Nevertheless, very few studies have evaluated the possible beneficial effect of cranberries in healing *H. pylori* infection.

Zhang *et al*[23]'s 90 d trial of cranberry juice compared to placebo in 189 patients, exhibited an increase in eradication rates of *H. pylori*. Shmuely *et al*[24] suggested, following a double-blind randomized clinical study of several hundreds of subjects, that the inclusion of cranberry juice into a standard therapy protocol of amoxicillin, clarithromycin and omeprazole, may improve eradication rates of *H. pylori* in females. A recent *in vivo* study[17] showed that the consumption of cranberry juice may assist in managing colonization among asymptomatic children. Further *in vivo* studies are needed to advance our knowledge of these mechanisms.

GARLIC

The action of oxidation of fresh *Allium sativum L*. (garlic) has been established. It is mainly due to unpredictable and irritating organosulphur compounds. Fresh garlic kept for a protracted period (until 20 mo) yields an odorless aged garlic extract comprised of unchanging water soluble organosulphur compounds that deter oxidative damage by scavenging free radicals. Garlic, comparable to allium vegetables, includes a wide range of thiosulphinates, *i.e.,* allicin believed to be accountable for antibacterial activity[25]. It has been shown that the discriminate elimination of thiosulphinates or the avoidance of their creation by obstructing alliinase, destroys the garlic's antibacterial activity[25].

Several studies have revealed that extracts from raw garlic[26] or garlic powder tablets[27] maintains *in vitro* activity against *H. pylori*, *i.e.*, steam-distilled garlic oil.

In Cañizares *et al*[28]'s study of allium sativum extracts; the authors used purple garlic of the "Las Pedroñeras" variety. By using the solvents ethanol and acetone in a stirred tank, it was shown that garlic extracts inhibit *H. pylori* comparable to commercial materials. The extracted material can be directly applied thus, necessitating an extraction procedure which is simple and economical.

Allicin, associated with Allium sativum is believed accountable for garlic's bacteriostatic properties. The existence or lack of allicin is critical in inhibiting *in-vitro* growth of *H. pylori*[27].

Several studies have proven a diminished gastric cancer risk with a rise in the intake of allium vegetables[29], perhaps producing a positive influence on *H. pylori.* You *et al*[30] in a randomized trial of 3365 subjects randomly selected from villages in the Shandong Province of China, a district with high gastric cancer death rates and an occurrence of approximately 67% in individuals infected with *H. pylori,* tested the outcomes of short-term (once) *H. pylori* treatment and continuous vitamin or garlic supplements (long-term) in the incidence of progressive precancerous gastric lesions. Individuals aged 35-64 years were randomly assigned to three interventions or placebos: Amoxicillin

and omeprazole for 14 d (*H. pylori* treatment); vitamin C, vitamin E, and selenium for 7.3 years (vitamin supplement); and aged garlic extract and steam-distilled garlic oil for 7.3 years (garlic supplement)[30]. The patients endured an esophagogastroduodenoscopy and biopsy. The frequency of the appearance of precancerous gastric lesions was established by a histopathologic examination of seven biopsy sites[30]. Treatment for *H. pylori* did not diminish the occurrence of dysplasia or gastric cancer. However, a smaller number of patients receiving treatment for *H. pylori* rather than a placebo developed gastric cancer. There were no significant favorable disparities when garlic or vitamin supplements were consumed.

In a recent study[31], permanent residents of West China underwent a ^{14}C-urea breath test (^{14}C-UBT) used to diagnose *H. pylori* infection. Of the 8365 participants, 53.1% were diagnosed with *H. pylori* infection. Those who ate raw garlic had a statistically significant lower level of *H. pylori* infection than those who did not eat the raw garlic. In this region, raw garlic seemed to reduce the infection.

Salih *et al*[32] reported that in a Turkish population, consumption of garlic for long periods of time did not affect the occurrence of *H. pylori* infection. Those ingesting garlic demonstrated a significantly lower antibody titer than the non-garlic groups, suggesting an unintended inhibitory effect on the generation of *H. pylori* and a possible advancement to more acute diseases. McNulty *et al*[33]'s *in vivo* pilot study, failed to show that steam distilled garlic oil, inhibits *H. pylori* based on *in vitro* activity. In this study, 20 dyspeptic patients aged 18-75 years, exhibiting *H. pylori* positive serology, verified by a ^{13}C urea breath test, were treated with a 4 mg garlic oil capsule taken with meals, 4 times a day for two weeks.

Negative UBT indicated *H. pylori* eradication. A 50% fall in ^{13}C excess between baseline and follow-up was defined as suppression. There was no verification that by ingesting garlic oil, *H. pylori* was either eradicated, suppressed or improvement of symptoms.

Aydin *et al*[34] also reported negative results in a trial using "Ortis" brand "garlic oil" produced by mixing ground garlic cloves with vegetable oil. These negative *in vivo* results show that garlic oil at these doses does not inhibit *H. pylori*. Further exploration of the possible beneficial outcomes of garlic oil against *H. pylori,* is necessary.

CURCUMIN

Curcumin (diferuloylmethane) was first chemically classified in 1910 and is generally considered the most active component of the Curcuma longa herb (turmeric). Due to its distinguishing flavor and yellow color similar to curry, it is used as a spice[35]. Its anti-inflammatory, antimutagen, antioxidant, and anti- infectious properties have been previously studied[36-41]. The significance of curcumin has been established in *in vitro* and *in vivo* studies. Curcumin has been used in healing peptic ulcers as well as preventing *H. pylori* growth[42-44].

Kundu *et al*[45] demonstrated that curcumin is capable of eradicating *H. pylori* in mice. In *H. pylori* infected human gastric epithelial cells, a dose of curcumin suppressed MMP-3 and -9 expression. Eliminating *H. pylori* using curcumin, entails significant down regulation of MMP-3 and -9 activities in addition to expression in the cytotoxic associated gene (*cag*) positive and cag-negative *H. pylori*-infected gastric tissues. These data indicate that curcumin healing of *H. pylori* infection includes regulating MMP-3 and -9 activities.

Han *et al*[46] confirmed that the growth inhibitory activity of curcumin *via H. pylori* infection is a result of inhibition of the shikimate pathway essential for the production of aromatic amino acids in bacteria, but not in humans. The shikimate pathway is vital for the production of metabolites in bacteria, *i.e.,* aromatic amino acids, folic acid and ubiquinone[47]. The enzymes affected include shikimate dehydrogenase which are innovative drug targets in the development of nontoxic antimicrobial agents[48].

Recently, the effect of curcumin on the formulation of interleukin (IL)-8, IL-1β, tumor necrosis factor (TNF)-α and cyclooxygenase (COX)-2 in gastric mucosa taken from *H. pylori*-infected gastritis subjects, was investigated by Koosirirat *et al*[49]. Patients were assigned at random to either a treatment course of Omeprazole, Amoxicillin and Metronidazole (OAM) or curcumin. Gastric biopsies were collected pre and post-treatment. In addition, the level of inflammatory cytokines mRNA were measured using semi-quantitative reverse transcription polymerase chain reaction.

Patients who received OAM treatment found that the eradication rate was significantly higher in these patients than those who ingested curcumin (78.9% *vs* 5.9%). In the OAM group, the levels of IL-8 mRNA expression significantly worsened after treatment, however, no alterations of other cytokines were found. Thus, only curcumin may have a reduced *in-vivo* anti-bactericidal effect on *H. pylori* and on the generation of inflammatory cytokines.

Prucksunand *et al*[50]'s phase Ⅱ clinical trial reporting on the results of healing peptic ulcers with long turmeric (Curcuma longa Linn), examined patients with peptic ulcer symptoms. While performing an endoscopy, ulcers measuring 0.5 to 1.5 cm in diameter were found in the duodenal bulb and stomach. An oral dose of 300 mg, 5 times daily of capsule-filled turmeric was given. Treatment after 4 wk, revealed no ulcers in 48% and after another 12 wk of treatment, 76% had no ulcers. Abdominal pain and discomfort sufficiently lessened during the first and second week. The subjects were able to ingest normal foods instead of soft meals. New insights as to the therapeutic effect of curcumin in the treatment of peptic ulcers, encourages the use of curcumin as an alternative therapy. Yet *in-vivo* evidence

that curcumin is active against *H. pylori* infection is still lacking.

GINGER

Ginger root (Zingiber officinale) is traditionally designed for treating gastrointestinal ailments, *i.e.,* hyperemesis gravidarum, dyspepsia, peptic ulcer, motion sickness and inflammatory disorders[51]. The proximate chemical composition of ginger contains volatile oils (1%-4%), medically active elements of ginger.

Ginger employs anti-oxidant and anti-ulcer[52], anti-inflammatory, anti-tumor[53], carminative, diaphonic and digestive, expectorant actions[54]. The phenols found in solvent extracts of ginger are mainly gingerol and zingerone.

Siddaraju *et al*[55] found that an aqueous extract of ginger can protect the gastric mucosa from stress-induced mucosal lesions and inhibit gastric acid secretion, which can be done by blocking H^+, K^+-ATPase action, thus restricting H. *pylori* growth. Ginger produces anti-oxidant protection against oxidative stress-induced gastric damage, thus, exhibiting anti-oxidative properties *in vitro*.

Li *et al*[56] validated and strengthened the association between hyperemesis gravidarum (HG) and *H. pylori* infection in normal pregnant control subjects and pregnant women with HG. They found positive *H. pylori* in 1289 (69.6%) HG cases and 1045 (46.2%) *H. pylori*-positive in the control group. The infection rate of *H. pylori* was considerably higher in pregnant women with HG compared to the non-HG normal pregnant controls. Analysis of a subgroup revealed that *H. pylori* infection was a risk factor of HG in other countries, *i.e.*, Oceania, Asia and especially Africa. Karaca *et al*[57] stated that lower socio-economic status was an important risk factor for *H. pylori* infected pregnant women with an HG factor.

Other studies have found that certain agents active against *H. pylori* are very effective in the treatment of hyperemesis[58,59]. The human Chorionic Gonadotropin (hCG) when elevated in pregnancy, concurrently alters the pH in pregnancy. hCG was found to induce gastrointestinal dysmotility, altered humoral as well as cell mediated immunity in pregnancy believed to be the basis for infection.

Several preclinical studies suggest that ginger, an agent linked to gastric and colon carcinogenesis, generates a protective effect against *H. pylori*[57,58]. Ginger phenolic fractions provide inhibitory effects on the growth of *H. pylori,* scavenge free radicals, reduce power abilities, protect DNA and inhibit lipid peroxidation[59,60].

Mahady *et al*[58] reported on the chemo-preventative effects of ginger which directly impede *H. pylori* growth, particularly CagA+ strains. The authors showed that gingerols and ginger extracts inhibit the development of *H. pylori in vitro* of 19 clinical strains. In addition, the fraction comprising the gingerols and 6-shogoal was very successful in inhibiting the growth of *H. pylori* CagA+ strains. This documentation suggests that specific ginger extracts containing gingerols may assist in treating or preventing *H. pylori* CagA and strains *in vivo*.

Researchers studying Mongolian gerbils noted that ginger extract prevented and treated *H. pylori*-induced infection and inflammation[61]. Moreover, additional research was implemented to clarify the *in vitro* mechanism of the ginger extract. These results confirm the medicinal properties of ginger in Ayurveda and folklore medicines and further advocate that ginger be considered a new therapeutic approach in the treatment of gastric disorders.

PISTACIA GUM

A resin called Chios mastic gum (CMG), produced by the Pistacia lentiscus var. chia. plant, is nurtured predominantly in the southern part of the Greek island of Chios and other Mediterranean countries. However, this plant can be planted or re-planted in other locations around the world, including the northern part of Chios, however, it will not produce resin.

The first mention of mastic was noted by Herodotus in the 5th century BC. Since 3000 BC, CMG has been used by the Greeks in cooking, cosmetics, and treating gastric illnesses.

In the 1980s, CMG was found to be a potential agent in treating duodenal ulcers in humans[62]. The antibacterial action of CMG was assessed and compared to clinical isolates of *H. pylori*[63]. Transmission electron microscopy determined CMG's influence on *H. pylori* morphology. CMG presents with anti-*H. pylori* activity due its inducement of protrusions, morphological abnormalities and cellular fragmentation in *H. pylori* cells[64].

A 2011 study presented proof that CMG prevents *H. pylori* inflammation by inhibiting neutrophil activation *in vitro*[65]. Dabos *et al*[66] confirmed these observations by examining the influence of CMG on *H. pylori* eradication in *H. pylori* patients. Mastic gum was well tolerated and the mild side effects were reversible.

It was determined that CMG has bactericidal action against *H. pylori in vivo*[66]. Paraschos *et al*[67] found that extracts and elements of CMG were active against *H. pylori*. After the insoluble polymer was removed, a total mastic extract without polymer was prepared, thus improving solubility and enhancing *in vivo* activity. The acid fraction generated major triterpenic acids after chromatographic separation, while the neutral fraction generated several triterpenic alcohols and aldehydes.

Employing a panel of 11 *H. pylori* clinical strains, CMG extracts and isolated pure triterpenic acids were tested for *in vitro* action. The authors demonstrated that

Table 1 Suggested anti-*Helicobacter pylori* mechanisms of the foods and plant extracts

Agent administered	Major mechanisms	Ref.
Cranberry	Bacteriostatic properties of proanthocyanidins	Howell[8], Gotteland *et al*[17]
	Inhibition of adhesion to the human gastric mucosa *in vitro*	Burger *et al*[9], Parente *et al*[10], Burger *et al*[19]
	Inhibition of adhesion and biofilm formation blocking	Shmuely *et al*[14]
	Anti-oxidative and anti-carcinogen activity	Côté *et al*[15]
	Proliferation suppression	Matsushima *et al*[16], Gotteland *et al*[17]
	Urease inhibition	Lin *et al*[18]
	Cytotoxic effect	Zafra-Stone *et al*[20]
Garlic	Antibacterial activity by thiosulphinates	Farbman *et al*[25]
Curcumin	Suppression of Matrix Metalloproteinase-3 and -9 expression in *H. pylori* infected human gastric epithelial cells	Kundu *et al*[45]
	Inhibition of the shikimate pathway, necessary for synthesis of aromatic amino acids	Han *et al*[46]
	Effect upon the production of IL-8, IL-1β, tumor necrosis factor-α and cyclooxygenase-2 in gastric mucosa	Koosirirat *et al*[49]
Ginger	Anti-oxidant and anti-ulcer activity	Yoshikawa *et al*[52]
	Anti-inflammatory and anti-tumor activity	Kim *et al*[53]
	Blocking H^+, K^+-ATPase action, inhibitory effects on the growth of *H. pylori*, DNA protection and inhibition of lipid peroxidation	Siddaraju *et al*[55]
	6-gingerol enhances the tumor necrosis factor-related apoptosis by inhibiting nuclear factor kappa B	Ishiguro *et al*[60]
	Directly inhibiting the growth of *H. pylori*, particularly the CagA+ strains	Mahady *et al*[58]
Pistacia Gum	Induction of protrusions, morphological abnormalities, and cellular fragmentation in *H. pylori* cells	Marone *et al*[64]
	Inhibition of neutrophil activation	Choli-Papadopoulou *et al*[65]
	Triterpenic acids present in the acid extract	Paraschos *et al*[67]

H. pylori: *Helicobacter pylori*; IL: Interleukin.

administration of CMG may reduce *H. pylori* settlement. In addition, the major triterpenic acids found in the acid extract may be responsible for this activity[68].

Other animal studies reported that CMG has no effect on *H. pylori*[68,69]. Monotherapy of CMG was administered to prove its ability to eliminate *H. pylori* infection in mice. The results showed that CMG was unable to eradicate *H. pylori* infection in mice. Also, Loughlin *et al*[69] reported that CMG failed to suppress or destroy *H. pylori* infection in humans. Patients with *H. pylori* infection were treated with 1g of CMG, 4 times daily for 14 d. CMG was found to have no effect on *H. pylori* status; they all remained *H. pylori*-positive. It was resolved that despite the anti-*H. pylori* action *in vitro*, there seems to be no effect on *H. pylori* in humans due to CMG[69].

All *H. pylori*-positive patients, treated with mastic capsules for 7 d remained *H. pylori* positive[70]. Miyamoto *et al*[70] and Huwez *et al*[71] observed that no "antibiotic-like" activity should be anticipated from crude mastic.

It has been shown that mastic has definite antibacterial action *via H. pylori.* This may partially explain the anti-peptic-ulcer mastic's properties[62,71]. By examining the effect of anti-*H. pylori* of the various elements of mastic, researchers may in the future, identify the participating ingredient.

Mastic is inexpensive and widely accessible in third world countries, hence, more *in-vivo* studies should be performed in developing countries.

CONCLUSION

Compared with the use of antibiotic and PPI treatment, a preventive dietary approach can be very inexpensive in areas with poor health care systems. The food reviewed can be effective in preventing and/or reducing *H. pylori* infection due to their potent anti-inflammatory activity. The rapid uptake by cells (Table 1) provides the suggested anti-*H. pylori* mechanisms of the foods and plant extracts.

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