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Food phytochemicals against *Helicobacter pylori*

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Abstract

H. pylori is a widespread pathogen, being the main culprit behind gastric and peptic ulcers with possible implications in the development of gastric cancers. In vitro studies have shown that ellagic acid and derivatives present in significant amounts in fruits and leaves have moderate bactericidal effects on H. pylori, while resveratrol was noted to inhibit urease enzyme as high as 90% in different strains of H. pylori. Quercetin seems to inhibit pathogen's VacA enzyme and kaempferol may prevent translocation of CagA, both phytochemicals being found in significant amounts in berries. In one clinical study, allicin was found to act synergically with standard antibiotic regimens. Although in vitro results seem promising, in vivo studies did not underline significant clinical benefits of phytochemicals compared to standard therapy. Therefore, further studies are needed to accurately estimate any clinical benefit of dietary phytochemicals in H. pylori infection.

Keywords: *Helicobacter infection, phytochemicals, plant origin*

INTRODUCTION

Research conducted in the past decades suggests that *Helicobacter pylori* has been an important part of the human oral and stomach bacterial flora for at least 58.000 years (1). While being present in the flora of approximately 50% of the world's population, only 20% of those infected develop clinical symptoms (2).

H. pylori plays a significant role in the gastric and peptic ulcers etiology, and it is also a suspect in the later development of gastric lymphoma and cancer (2), the gastric cancer risk in infected people being 2 to 7 times higher compared with the uninfected people. Approximately 1-3% of the patients with active gastric or peptic ulcers progress to cancers and more than half of the gastric cancer patients also have an *H. pylori* infection (3). World Health Organization (WHO) classified *H. pylori* as a group I carcinogen in 1994 (4), with a higer infection rate in the developing countries (70-80%) compared to 13-50% in the developed ones (5).

H. pylori is a Gram-negative bacillus, spirilliform bacteria, that uses flagella to move rapidly and perform a 'tunneling' operation in the mucus covering the gastric epithelium. The complete mechanism by which it infects its host has been described elsewhere (6, 7, 8). Briefly, using urease, an enzyme specific for

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this pathogen, it transforms urea present in the stomach to carbon dioxide and ammonia. As a result, the pH of the gastric environment increases allowing bacteria to use other mechanisms to continue the infectious process. Urease might be a short-term survival solution in the low pH stomach environment and the flagella for movement towards the neutral pH (9, 10, 11). Also, *H. pylori* seems to posses chemotactic motility towards the mucus layer through urea- and bicarbonate-mediated mechanism (6). From there it can deploy highly immunogenic protein (CagA) and/or vacuolization-inducing protein (VacA) to epithelial cells, activating inflammatory and immune responses (7).

Eradication relies on the type and duration of the infectious process, antibiotic resistance and patients' compliance to therapy. Regimens are usually prescribed for 10-14 days, have two or three antibiotics (amoxicillin, clarithromycin and a proton pump inhibitor-PPI- or bismuth) and have 85-90% eradication rates (12). Despite that, there still is a notable increase of antimicrobial resistance to antibiotics, correlated with the standard prescriptions failure to eradicate the pathogen and with their adverse effects (nausea, diarrhea, headaches, skin rash) which have a significant impact on patients' compliance, treatment's success and costs, the treatment being inaccessible to the majority of the population (13, 14, 15, 16). As a result, efforts to find an efficient and low-cost alternative, other than antibiotics, are being made by the scientific community.

In the quest for novel compounds with potential benefits in preventing *H. pylori* infection, phytochemicals have received a considerable attention (17). While they do not eradicate *H. pylori* permanently, they can substantially reduce bacterial colonisation, inflammatory responses and mucosal atrophy and have shown synergistic effects with antibiotics, thus reducing the antibiotic dose and preventing undesirable side effects (17,18).

ELLAGIC ACID

Ellagic acid (EA) and ellagitannins (ETs) occur naturally in foods, usually in walnuts, arctic bramble, strawberries, pomegranates, raspberries and red raspberries (19,20). Currently, there is no consensous over dietary ETs and EA intake estimates as there is limited information on the precise content of the aforementioned phytochemicals in different plant species. Scalbert and Wiliamson (2000) estimate a 1g/day total dietary intake of ETs and EA, although it varies considerably by different geographic regions (21). For example, in France it is estimated to be 0.2-0.3 mg/day (22), while in Finland it is aproximately 12 mg/day (23), in the German region of Bavaria it is estimated to range between 4.9-5.4 mg/day (24) and in Spain between 2590-3016 mg/day (25). However, recent estimates suggest that ETs intake may be much higher than previously estimated, especially if ET-rich foods are consumed daily (26).

Significant amounts of EA and ETs can be found in berries of the *Rosaceae* family (raspberry, strawberry, cloudberry), while in *Elaeagnaceae* family the levels are lower (27). On the other hand, grapefruits, peaches, red apples, pears, cherries, elderberries, blue plums, kiwi, navel oranges, peanuts, cashews and Brazil nuts have EA concentrations below the detection limit of HPLC systems (28). Kähkönen et al. (2001) found that ETs were the main phenolics in the genus *Rubus* (cloudberry and raspberry), while in *Fragaria* (strawberry) genus they were placed second after anthocyanins. EA levels showed variation from 47 mg/g in raspberries to 90 mg/g in black raspberries (29, 30). Available data on EA content of fresh raspberries varies by study. Koponen et al. (2007) have found 263.7 mg EA/100g product, Daniel et al. (1991) detected 103.0±3.3 mg EA/100g product and Kähkönen et al. (2001) detected as much as 1794 mg EA/100g product (28, 29, 31). The same quantitative variability applies for strawberries, EA ranging from 31 mg /100g product to as high as 184 mg EA/100g product (29, 32). More estimated EA content in different, commonly encountered fruits and seeds and determined by various authors, are shown in Table 1.

Plant products with a high content of phenolic derivatives, especially EA and ETs have shown promising *in vitro* bacteriostatic effects. A study conducted by Chung (1998) revealed that EA has dose-dependent bactericidal effects on clinical isolates of *H. pylori*, the most potent bactericidal dose being IC50 = 1 mM (33). Martini et al. (2009) showed that *Rubus ulmifolius* leaves extract had a moderate in vitro bactericidal effect on two *H. pylori* strains (MBC = 1200 µg/ml and 1500 µg/ml after 24h exposure and MBC=134 µg/ml and 270 µg/ml after 48h) compared to EA control (34).

TABLE 1. Ellagic acid (EA) content in commonly consumed fruits and seeds

Fruits	EA content (mg/100g fresh product)	Reference
Arctic bramble	390	Määttä-Riihinen et al. (2004)
Blackberries	150.0 ± 12.0	Daniel et al. (1989)
Black raspberries	90	Wada and Ou (2002)
Boysenberries	70	
Cloudberry	315.1 1090 - 1432 360	Koponen et al. (2007) Kähkönen et al. (2001) Määttä-Riihinen et al. (2004
Cranberry	12.0 ± 0.4	Daniel et al. (1989)
Raspberry	263.7 150.0 ± 10.0 1692 - 1794 270 (wild)	Koponen et al. (2007) Daniel et al. (1989) Kähkönen et al. (2001) Määttä-Riihinen et al. (2004)
Raspberry (yellow)	1900	Määttä-Riihinen et al. (2004)
Strawberry	81 - 184 65 - 85 63.0 ± 9.0 31	Kähkönen et al. (2001) Määttä-Riihinen et al. (2004) Daniel et al. (1989) Mattila and Kumpulainen (2002)
Walnuts	59 ± 0.1	Daniel et al. (1989)
Pecans	33 ± 0.3	
Seeds	**EA content (mg/g dried product)**	**Reference**
Marion blackberry	32	Bushman et al. (2004)
Boysenberry	30	
Evergreen blackberry	21	
Red raspberry	8.7	
Black raspberry	6.7	
Longan	1.6	Soong and Barlow (2006)
Mango	1.2	

RESVERATROL

Although resveratrol concentrations in common foods are very low, in wine the content was found to be 0.361-1.972 mg/l (red wine), 0.29 mg/l (rosé wine) and 0-1.089 mg/l (white wine) (35,36, 37). Other concentrations of resveratrol in foods are shown in Table 2.

TABLE 2. Resveratrol content in foods

Food/Drink	Concentration	References
Tomato skin	~19 000 µg/kg	Ragab et al. 2006
Dark chocolate	350 µg/kg	Hurst et al. 2008
Milk chocolate	100 µg/kg	
Itadori tea	68 µg/ 100 ml	Burns et al. 2002
Red grapes	92 - 1604 µg/kg	Okuda and Yokotsuka 1996
White grapes	59 - 1759 µg/kg	
Apples	400 µg/kg	Farneti et al. 2015
Beer	1.34 - 77 µg/L	Chiva-Blanch et al. 2011
Peanuts (no coats)	30-140 µg/kg	Sanders et al. 2000

In the recent years, the interest for phytoalexins such as resveratrol has grown as they might have potential antimicrobial activity against H. pylori by inhibiting IL-8 secretion from *H. pylor*i-infected cells at concentrations of 75-100 µM along with a reduction in reactive oxygen species reduction at concentrations between 1-100 µM (34,38,39,40).

Zhang et al. (2015) noted similar results in a mouse model of *H. pylori* infection. Orally administration of resveratrol (100 mg/kg/day) for six weeks determined a reduction in *H. pylori*- induced mRNA transcription and protein expression levels of inducible nitric oxide synthase (iNOS) and interleukin 8 (IL-8). It was also observed an increased activity of the potent antioxidant enzyme heme oxygenase-1 (HO-1) and for the nuclear factor-erythroid 2 related factor 2 (Nrf2) which upregulates the antioxidant response. Cumulated with the effect of supression H. pylori-induced phosphorylation of nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor (IκBα), resveratrol showed significant activities against oxidative stress and inflammation (41). Paulo et al. (2011) noted that resveratrol, at a concentration of

400 µg/ml, seems to decrease urease activity by 90% in some strains of *H. pylori* (42).

ALLICIN AND ALLIXIN

Allicin is an oxygenated sulfur-containing volatile compound present in *Allium species,* mainly in *Allium sativum* (garlic). It accounts for aproximately 70% (w/w) of the total garlic thiosulfinates. In one fresh crushed garlic clove there is aproximately 4-5 mg of allicin. Allicin is an unstable compound and it is rapidly degraded under the influence of temperature and pH (43, 44). Acidic solutions (e.g. vinegar) seem to increase allicin's lifespan to 10-17 days, by lowering the pH (45, 46).

Allixin is also a non-sulfur compound and it was the first phytoalexin isolated from *Allium sativum.* It is a secondary metabolite released by plants during stressful conditions and seems to possess some antimicrobial activities. However, bioavailability of allixin alone was noted to be very low (47, 48).

Both allicin and allixin are very reactive and unstable, thus, it is questionable if there are any therapeutical benefits when administered orally as they have low bioavailability, are quickly decomposed to other organosulfur, antimicrobial-inactive compounds and quickly react with thiol groups from aminoacids (49, 50).

Despite the drawbacks, *in vitro* studies using simulated gastric environment have shown that garlic inhibits colonization and bacterial growth, including *H. pylori* (51). Also, Cellini et al. (1996) found that a cold aqueous extract from garlic cloves has anti-*H. pylori* properties at concentrations ranging from 2 to 5 mg/ml in an agar plate assay (52). Koçkar et al. (2001) evaluated the potential benefits of allicin, ascorbic acid and beta-carotene in treating *H. pylori* infection in a randomized, controled trial (210 patients) compared to the standard regimen and whether there was synergy with the standard treatment. Infection eradication has been achieved in approximately 27 patients (90%) from the group treated with standard regimen and allicin 4200 µg/day. Still, only seven patients (23.3%) from the group treated with allicin only (1200 µg/day) had the infection eradicated, while ascorbic acid and beta carotene had no effect. The study noted the effectiveness of allicin as an add-on therapy to the standard regimen (53).

In a prospective, crossover study conducted on 27 *H. pylori*-infected adults, Graham et al. (1999) compared the administration of fresh garlic and capsaicin-cantaining peppers (jalapenos) with a bismuth subsalicylate positive control group and a negative control group using 13C-urea breath test. They found that neither garlic nor jalapenos had any in vivo effect on *H. pylori* compared to bismuth subsalicylate (54).

The aforementioned studies show contrasting results. *In vitro* studies have shown some inhibitory effect of garlic and/or allicin on *H. pylori* (51, 52), while in vivo studies have shown no benefit from associating garlic with standard treatment or garlic alone (53, 54).

EPIGALLOCATECHIN GALLATE AND DERIVATIVES

Epigallocatechin (EGCG) and its derivatives are the most abundant in green tea (*Camelia sinensis)*, constitute aproximately 40% of the total polyphenol content and posessess various health benefits through their potent antiinflammatory and antioxidant activities (55). In *H. pylori* infections, EGCG seems to inhibit glycosylation of *H. pylori*-induced toll-like receptor 4 (TLR-4) signaling pathway induced by the pathogen alongside with the inhibition of urease enzyme and diminishing DNA damage and gastric mucosa cytotoxicity of epithelial cells induced by H. pylori (56). Also, green tea inhibited the *in vitro* growth of *H. pylori* at a MIC90 of 0.25 - 0.5% (w/w), while pure EGCG and epicatechin inhibited its growth at a MIC90 of 50-100 µg/ml and 800-1600 µg/ml, respectively (57). Nonetheless, caution is required when extrapolating in vitro results to in vivo recommendations.

CHLOROGENIC ACID

Coffee and green tea are the most abundant sources of chlorogenic acid (CGA). In literature data, CGA concentrations in green coffee seeds vary from 4 to 8.4 g/100 g dried product. In contrast, in roasted beans, they range from 0.3 to 3.5 g/100 g, including lactones formed during roasting (58). Daily intake doses of CGA may vary between 100 and 1000 mg. There are no daily recommended doses as there are no studies that directly link doses to various pharmacological effects (22).

CGA has been reported to inhibit urease in *H-pylori* (59). *H. pylori* growth is inhibited by CGA isolated from Anthemis altissima extracts at a MIC = 312.5 µg/ml and 1250 µg/ml, respectively (60). Studies conducted by Paun et al (2014) on Geranium robertianum, *Hyssopus officinale* and *Helleborus purpurascens* extracts having CGA in composition (1.5 mg/L herbal extract) reported urease inhibitory effects. CGA isolated from apricot fruits extract (*Prunus armeniaca L.*) has antimicrobial activity against *H. pylori* at a MIC 20.313 µg/ml, while the mechanism of action remains to be uncovered (61, 62).

QUERCETIN AND KAEMPFEROL

Quercetin is a flavonoid present in various fruits and vegetables, thus being a common element in the human diet. It is estimated that the daily intake in humans is approximately 5-40 mg quercetin (63). Berries have the highest content of quercetin per kg of fresh product, bog whortleberry, lingoberry and cranberry leading with concentrations up to 158 mg/kg, 74- 146 mg/kg and 83-121 mg/kg, respectively. Other berries are located at the lower end of the spectrum, such as rowanberry (63 mg/kg), sea buckthorn berry (62 mg/kg) and crowberry (53 and 56 mg/kg) (19). Quercetin is also present in spring onion leaves (841 ± 8 mg/kg dry product) and white onion bulls (50 ± 9 mg/kg dry product). Apples and especially apple peels have reasonable amounts of quercetin (250 ± 4 mg/kg dry product). At the same time, *Hyperici herba* (*Hypericum perforatum)* contains 13.3 ± 1.2 mg/kg dry product, whereas *Sambuci flos* (*Sambucus nigra*) have the lowest content in quercetin, about 7.9 ± 0.7 mg/kg dry product (64).

Along with its potent free radical scavenging, cardioprotective, hypotensive, anti-atherosclerotic, antidiabetic and antitumor activities, quercetin has also been reported to possess anti-*H. pylori* activity by inhibiting the vacuolating enzyme VacA at an IC50= 19 µM (63, 65, 66). However, in a mouse model of H. pylori infection, quercetin did not eradicate the infection, but it lowered the bacterial numbers in the quercetin treated group compared with the infected control (67). Regarding the daily flavonoid intake in humans, Hollman et al. (1996) reported aproximately 23 mg/day, of which quercetin makes up for aproximately 16 mg/day (68).

Kaempferol showed a significant inhibitory effect on two H. pylori strains, as a 15 mm diameter of inhibition was noted for a concentration of 1 mg/ml. Moreover, In association with 50 µg/ml (-)-epicatechin, 150 µg/ml kaempferol seemed to produce a synergistic effect against *H. pylori,* inhibiting the growth of *H. pylori* strains in liquid culture medium with CFU/ml = 1.4 × 103 (69). *In vitro* studies carried on gastric adenocarcinoma cell line showed that kaempferol reduced the expression of pro-inflammatory cytokines TNF-α, IL-1β and production of IL-8, thus exhibiting antiinflammatory effects in *H. pylori*-induced inflammation. Additionally, it suppressed translocation of cytotoxin-associated gene A (CagA) and vacuolating cytotoxin A (VacA), both virulence factors generated by *H. pylori* (70). Similarly to quercetin, there are no dietary guidelines regarding kaempferol intake. The highest kaempferol content is in onion leaves (832.0 mg/kg product) while in berries it had been detected only in gooseberries (16 and 19 mg/kg) and strawberries (5 and 8 mg/kg) (19,71).

CONCLUSIONS

Although *in vitro* studies suggest that some phytochemicals present in the diet might possess a potential antimicrobial activity in *H. pylori* infection, findings from *in vitro* studies cannot be extrapolated to *in vivo* studies, as results are conflicting. Further research is needed to determine whether phytochemicals may represent a viable alternative as an add-on therapy to standard regimens used to treat infection with *H. pylori.*

Author contributions

Alexandru Mandici - conceptualization, original draft preparation, editing; Alina-Alexandra Covrig - data collection; Irina Macovei - review, editing.

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