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 higher 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
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 possess 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 consensus 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 Williamson (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 approximately 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                          |                                         |
| Pecans               | 33 ± 0.3                          |                                         |

**Seeds**

- Marion blackberry 32
- Boysenberry 30
- Evergreen blackberry 21
- Red raspberry 8.7
- Black raspberry 6.7
- Longan 1.6
- Mango 1.2

**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    | Chiava-Blanch et al. 2011         |
| Peanuts (no coats)| 30-140 μg/kg | Sanders et al. 2000 |

**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.

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. pylori-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 suppression 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**

Alllicin is an oxygenated sulfur-containing volatile compound present in *Allium species*, mainly in *Allium sativum* (garlic). It accounts for approximately 70% (w/w) of the total garlic thiosulfinates. In one fresh crushed garlic clove there is approximately 4-5 mg of allicin. Alllicin 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-containing 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 alllicin on *H. pylori* (51, 52), while in vivo studies have shown no benefit from associating garlic with standard treatment or garlic alone (53, 54).

**EPICALLOCATECHIN GALLATE AND DERIVATIVES**

Epigallocatechin (EGCG) and its derivatives are the most abundant in green tea (*Camelia sinensis*), constitute approximately 40% of the total polyphenol content and possesess 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 officinalis* 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 bulbs (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 approximately 23 mg/day, of which quercetin makes up for approximately 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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