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Dietary Amelioration of *Helicobacter* Infection

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Abstract

We review herein the basis for using dietary components to treat and/or prevent *Helicobacter pylori* infection, with emphasis on: (a) work reported in the last decade, (b) dietary components for which there is mechanism-based plausibility, and (c) components for which clinical results on *H. pylori* amelioration are available. There is evidence that a diet-based treatment may reduce the levels and/or the virulence of *H. pylori* colonization without completely eradicating the organism in treated individuals. This concept was endorsed a decade ago by the participants in a small international consensus conference held in Honolulu, Hawaii, USA, and interest in such a diet-based approach has increased dramatically since then. This approach is attractive in terms of cost, treatment, tolerability and cultural acceptability. This review therefore highlights specific foods, food components, and food products, grouped as follows: bee products (e.g. honey and propolis), probiotics, dairy products, vegetables, fruits, oils, essential oils, and herbs, spices and other plants. A discussion of the small number of clinical studies that are available is supplemented by supportive *in vitro* and animal studies. This very large body of *in vitro* and pre-clinical evidence must now be followed up with rationally designed, unambiguous human trials.

Keywords

anti-inflammatory; broccoli sprouts; cancer; colonization; diet; dietary; food; garlic; gastric; *Helicobacter*; *H. pylori*; infection; stomach; ulcer

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Conflict of Interest

The authors declare no conflict of interest.

1. Introduction

Major cancer burdens in humans, especially cancers of the liver, uterine cervix, and stomach, are caused by infectious agents. Infections of the human gut with the bacterium *Helicobacter pylori* have only been recognized for about three decades and have achieved widespread acceptance only over the past two decades [1]. Clinical studies and basic research on the organism and its close relatives [2] have now so thoroughly validated its discovery and the public health importance of that discovery, for which a Nobel Prize was awarded, that it put the word "Helicobacter" on the tips of tongues worldwide [3]. Alongside a dramatically increased awareness of this infectious agent, there has been a proliferation of strategies for cures, some real, and many imagined, to eradicate *H. pylori* infection.

1.1. Approach, and Scope of Literature Reviewed

We have reviewed herein, the basis for using dietary components or ingredients (food) to treat and/or prevent *H. pylori* infection, with emphasis on work reported since the comprehensive review of Mahady ten years ago [4], and with emphasis on components for which there is mechanism-based plausibility, and there have been published clinical results. For this purpose, the PubMed, Scopus, and ClinicalTrials.gov databases were searched for relevant studies using keywords related to *Helicobacter* through February 2015, without restrictions, and by reviewing the reference lists from retrieved papers. Focusing upon the components illuminated by this strategy resulted in an examination of bee products (eg. honey and propolis), probiotics and dairy products, vegetables, fruits, oils, essential oils, herbs, and spices. We have highlighted the work done with these dietary compounds, following a critical examination of the assumption that the only good *H. pylori* is a dead *H. pylori* (e.g. that complete eradication is necessary) (***Section 2***), and that foods present an alternative to pharmaceuticals for a variety of sound scientific reasons (***Section 3***).

1.2 *Helicobacter* Infection

Helicobacter pylori is recognized by the World Health Organization as a Class I human carcinogen. Infection with *H. pylori* is implicated causally in development of chronic gastritis and in peptic ulcer disease (PUD). The pathophysiology of infection has been exhaustively reviewed by others, notably by Kusters and colleagues [5]. Briefly, this gram-negative, flagellated, spirilliform (rapidly motile) bacterium (order: Campylobacterales), utilizes the enzyme urease, (not present in mammalian tissues), to convert urea in the stomach to carbon dioxide and ammonia, thus elevating the highly acidic pH of the gastric lumen and allowing it to survive an otherwise exceedingly hostile environment. *H. pylori* "tunnels" into the mucus layer covering the gastric epithelium and may persist for decades where it can deliver a highly immunogenic protein dubbed "CagA" and/or a vacuolization inducing protein dubbed "VacA" to epithelial cells (these are strain-dependent) thus activating both immune and inflammatory responses.

H. pylori infection is an important factor leading to a progression through acute or chronic inflammation of the gastric mucosa and peptic ulcer disease (PUD). This gastritis, if persistent, can lead to duodenal ulcers and to mucosa-associated lymphoid tissue (MALT) lymphoma. If atrophic, it can lead to gastric ulcers and to metaplasia, dysplasia, and gastric

cancer. *H. pylori* infection results in a 3- to 6-fold increase in the relative risk for developing gastric adenocarcinoma and MALT lymphoma. Although more than half of the world's population is infected with *H. pylori* (usually in childhood), the vast majority of infected individuals never develop gastric cancer. For those individuals who are infected, attributable risk estimates range from 50 to 73%, such that about half a million new cases of gastric cancer yearly (about 55% of the total number of cases), are directly attributable to infection with *H. pylori* [6]. Societal costs, not only of these cancers, but of gastric and duodenal ulcer, are enormous.

1.3 Gastric cancer

Stomach cancer, as well as gastritis, gastric ulcers, and duodenal ulcers, are diseases of both the industrialized and the developing world. In many developing countries, over 90% of the population is infected, but not all developing countries have a high incidence of gastric cancer. Many African countries were originally reported to have an extremely low incidence of gastric cancer and very high rates of *H. pylori* infection [7], leading to examination of factors such as bacterial virulence genotype, dietary factors, and host (human) genetic polymorphism, to help explain the gastric cancer incidence in this region [8–11]. Although infection with *H. pylori* is rapidly declining in Western nations, 50–80% of adults in Asia and 70–90% of adults in South and Central America are colonized [12]. Globally, gastric cancer is the third leading cause of cancer mortality of both sexes, with more than 951,000 cases worldwide and approximately 723,000 deaths [13], and it is still a leading cause of cancer death in many countries.

1.4 Treatment of *Helicobacter* infection

The development or identification of ways in which to lower the prevalence of *H. pylori* infection and the consequent risk of cancer is of compelling importance because infection can result in gastritis, gastric and duodenal ulcers and perhaps other sequelae [14,15]. There are currently no vaccines against this infection and expectations for their future development are generally negative [16,17]. Combinations consisting of twice daily treatment for 7 to 14 days, with: (1) a proton pump inhibitor (PPI) such as omeprazole or lansoprazole, and the antibiotics (2) amoxicillin, and (3) clarithromycin or metronidazole (dubbed "triple therapy") [18,19], are generally effective therapies for those who can afford them (e.g. residents of industrialized countries). However, antibiotic therapy for infected individuals in most of the developing world is impractical due to complex economic, social and logistic considerations. There are other problems with antibiotic treatment in that the development of antibiotic resistance is of considerable concern (discussed in more detail later in this review), and eradication rates in many studies are as low as 70%. This bodes poorly for a strategy of treating entire populations with antibiotics.

However, complete eradication of *H. pylori* in symptom-free people might not be prudent due to the intriguing, but not yet proven possibilities of adverse side-effects. These may include such things as an increased risk of lower esophageal adenocarcinoma and an exaggeration of gastroesophageal reflux symptoms [20,21]. The concept that a diet-based treatment could **reduce** levels of *H. pylori* colonization or virulence, mitigate gastritis, inhibit progression of corpus atrophy, and perhaps eventually delay or prevent development

of gastric cancer -- without completely eradicating the organism in treated individuals -- presents alternatives from a number of perspectives including those of cost, treatment tolerability, and cultural acceptability. Evaluation of a number of potential diet-based treatments (e.g. *Lactobacillus* spp., *Saccharomyces boulardii*, broccoli sprouts, honey, cranberries and garlic) have been reported. Scores of other indigenous plants and other foods have been used for many centuries by native and traditional healers as cures for syndromes that are likely to involve *H. pylori* infection [22–31]. The proposed mechanisms of action for these natural products, although beyond the scope of this review, include a direct antimicrobial effect, as well as anti-inflammatory, antioxidant, anti-adhesive, and immune stimulatory effects, and the inhibition of the enzyme urease, one of the bacterial pathogenesis factors (Fig. 1).

Clinical trials to conclusively support or refute the efficacy of such treatments are fraught with difficulties. Numerous endpoints or biomarkers are available – many involve endoscopy and/or gastric biopsy and thus place medical, economic and logistical limits upon the numbers of subjects that can be enrolled. They also place ethical limitations on such studies, which serve to focus scientific attention on individuals with symptoms when, in fact, asymptomatic but infected individuals may be a much more useful and/or appropriate population for study, as well as being the most logical target for preventive strategies [32].

2. Reduction of the Impact, or Elimination of Infection?

A question that underlies much of the dietary strategy to reduce the incidence of gastritis, ulcers, or stomach cancer, can be very simply stated as follows:

Is it necessary to completely prevent or eradicate infection with *H. pylori,* or will reducing the level and/or virulence of colonization (of the gastric mucosae), result in a reduced risk of disease or reduced disease severity? Martin Blaser provides cogent analyses of this issue [20,21,33–36]. Almost two decades ago he concluded that:

> *"Although further research may show that human beings are better off without their long-time companions H. pylori, I maintain that we are at present too ignorant of the diversity of H pylori strains and their interactions with human beings to advocate their total elimination"* [20].

Blaser's earlier predictions (based upon his understanding of *H. pylori* ecology), have provoked much discussion, (see for example: [4,22,37,38]), however the tools of modern microbiology are reinforcing his early insights regarding *H. pylori* and what he now calls the "disappearing microbiota hypothesis" [39]. Further, and addressed by Blaser and many others, is the fact that there are deep, long-lasting, and severe effects of antibiotic therapy on the gut microbiota. It has only been in the past decade or so that the gravity of these effects and their impact on host immunity, metabolism, and even neuropsychiatry have been understood and clinically demonstrated [39,40], but it is the collective effect that mitigates against the frivolous use of antibiotics for treatment of *H. pylori* infection [19]. Suitable endpoints for interventions designed to reduce damage to the human stomach resulting from infection with *H. pylori*, without necessarily eradicating the bacterium, must thus be identified. Several primary non-invasive endpoints for detecting **eradication** of infection

have been used in recent years: (A) the urea breath test (UBT), (B) fecal antigen detection, (C) serum pepsinogen (PG) I and PGII levels and ratios, (D) culture from a “string test”, and (E) markers of inflammation. [N.B. The UBT, (for which patients consume labelled urea and then provide a breath sample that exploits *H. pylori*’s high urease activity to create labelled CO_2 that is measured in exhaled breath), is simple to conduct, is inexpensive, and has high sensitivity and specificity for detection of active *H. pylori* infection]. However, the adaptability of such tests to the accurate measurement of a **reduction** of bacterial levels or bacterial virulence-related genotypes is problematic. Determination of the most appropriate biomarkers to use in these human clinical trials is still far from complete [41,42].

3. Why A Food-Based Approach to *H. pylori* Treatment?

Graham and colleagues have shown that many compounds have anti-*H. pylori* activity *in vitro*, but do not eradicate infection *in vivo* in human beings [43,44]. Likewise reductions in *H. pylori* colonization following treatment, without achieving its eradication, have been shown following treatment of animals with dietary/phytochemical agents [45,46]. We have approached the question of diet-based treatment from a slightly different perspective, however: If by following a dietary regimen one can achieve a reduction in indicators of inflammation and of colonization, but not complete resolution of that infection, then is this dietary strategy not worthy of further development, either by itself or in a combinative approach, since complete resolution may be undesirable? We suggest that a number of foods may each have a small but measurable effect on the severity of infection and/or the risk of gastritis, ulcers, or stomach cancer, and that it is therefore worthwhile to utilize the available biomarkers of *H. pylori* colonization in order to evaluate the efficacy of this incremental effect *in vivo*. These questions must of course be considered in the context of rapid development of *H. pylori* strains resistant to synthetic antibiotics, oppressive poverty in many of the areas with very high prevalence of *H. pylori* infection, and the huge monetary cost of any long-term pharmaceutical preventive strategy [19,47].

Compared with the use of synthetic pharmaceuticals, a dietary approach to prevention can be very inexpensive, and may be the only practical or affordable approach to take in areas underserved by healthcare systems [32]. If indigenous plants and/or foods can be identified which are effective in preventing or reducing *H. pylori* infection, these could be introduced in such areas [48]. For example, potent anti-inflammatory activity [49] and rapid uptake by cells and organs [50] has been demonstrated for certain phytochemicals (e.g. sulforaphane from broccoli sprouts). There is also considerable precedent for treating and ameliorating gastritis and digestive disorders with foods (e.g. garlic, honey, *Lactobacillus* spp.). The literature on phytochemical mechanisms and their employment to treat gastric disorders is extensive, and we cite some key reviews, but do not cover the subject exhaustively herein [51–57].

4. Foods and dietary ingredients with activity against *H. pylori*

Phytochemical components of vegetables (and fruits) have been examined in many laboratories for their effects on *H. pylori* infection (Fig. 1). Additionally, many epidemiologists have evaluated the effects of fruit and vegetable consumption on cancer

incidence. They have attempted to draw conclusions that relate to specific phytochemical ingredients of those dietary components.

Clinical studies lag behind both popular and scientific interest in this area: Of the 230 *Helicobacter* studies catalogued in the USA government's ClinicalTrials.gov database, only 6 of them deal with dietary/food ingredients (NCT01028690, *Lactobacillus reuterii*; NCT01593592, *L. reuterii*; NCT01456728, *L. reuterii*; NCT01115296, probiotics; NCT02018328, curcumin; NCT01045408, berries) -- most of the balance are drug or epidemiologic investigations [58]. The 236 clinical trials posted come from the following regions (number of studies in each, in parentheses): China & Korea (102), Europe (44), USA (29), Middle East (21), Japan (10), S.E. Asia (8), Africa (6), India (5), South America (5), Canada (3), Mexico (2), Russian Federation (1).

In Table 1 we highlight primary references, reviews, and meta-analyses of clinical studies. Key recent examples of *in vitro* and animal studies for the best-studied foods are summarized in Table 2, which, along with the remainder of this section, focus on research published since the topic was comprehensively reviewed ten years ago [4], and studies of foods for which no robust clinical trial results have been published.

4.1. Bee products

Honey in general, and a specific honey harvested from the flowers of the manuka bush, (*Leptospermum scoparium)* have activity against *H. pylori* and other bacteria *in vitro* [51,89–92]. However, *in vivo* studies have not been able to demonstrate eradication of the bacterium [59]. A large body of work over the years by Peter Molan and colleagues in New Zealand has demonstrated effects of manuka honey on wound healing and other bacteria-related pathologies [142]. In the case of *Helicobacter* infection, Molan and others have invoked both peroxide and non-peroxide mediated mechanisms [93,95]. Of the non-peroxide effects, (phytochemical content and simple osmotic effects), the osmotic effects appear to best explain the *in vitro* evidence [89] and this may be why *in vivo* activity of honey(s) against *H. pylori* has not been demonstrated [59]. It is impractical to maintain a solution of, for example, 15% honey at the gastric epithelium for sufficient time for it to have direct osmotic effects.

Propolis (a flavonoid-rich by-product of bees) also manifests anti-*H. pylori* activity *in vitro* [96,97], that has not been confirmed *in vivo*. Propolis also has anti-inflammatory and immune stimulatory activity [97] – both mechanisms clearly being important in the pathophysiology of *H. pylori* infection.

4.2. Probiotics and Dairy Products

Probiotics are introduced-, and frequently transient members of the gastrointestinal flora. They have been defined by the FAO/WHO as "live microorganisms which when administered in adequate amounts confer a health benefit on the host" (143). Prebiotics are ingested fiber that serves as food for our gastrointestinal microflora, but is not directly utilized by our [mammalian] cells. As defined by Gibson and colleagues in 2010 they are "a selectively fermented ingredient that results in specific changes in the composition and/or

activity of the gastrointestinal microbiota, thus conferring benefit(s) on host health" [29]. Probiotics, along with prebiotics, saliva, and gastrointestinal secretions, are all considered important for optimal digestive function. Approximately two-thirds of the immune system is localized in the gastrointestinal tract, and the literature abounds with reports and with controversy over whether prebiotics or probiotics offer protection against- and cure of a variety of endemic and acute diseases, influencing the immune system through several molecular mechanisms.

Many probiotics are composed of mixtures of bacteria that produce lactic acid, and they are thus resistant to acidic conditions found in the stomach. According to Johnson-Henry and colleagues, they may also be able to colonize the stomach at least in a transient fashion, can competitively exclude some pathogens such as *Escherichia coli* 0157:H7 from gastrointestinal niches, may enhance mucin secretion, may act as bactericides, and may enhance epithelial barrier integrity [101]. Thirty-three clinical studies of the effects of probiotics supplements on *H. pylori* colonization were evaluated in a meta-analysis that concluded there was a significantly higher pooled *H. pylori* eradicating effect of the supplemented groups compared to control groups [102].

Various species of *Lactobacillus* (a common constituent of yogurt, and a component of a variety of probiotic commercial products) have *in vitro* activity against *H. pylori* [98,100,103,104], and *in vivo* activity in animals [98,100,103,104] and in humans [62–65,67,98,99]. *Lactobacillus* species also possess anti-inflammatory activity [100] and immune-stimulant activity [98]. A meta analysis concluded that *Lactobacillus* supplementation could be effective in increasing eradication rates of anti-*H. pylori* therapy for first-treated patients, and had a positive impact on some *H. pylori* therapy related side effects [60]. *Saccharomyces boulardii* has also been the subject of intense clinical scrutiny and a recent meta analysis of its use as an adjuvant to triple therapy gave a strong odds ratio for efficacy (OR=0.46)[66].

Colostrum and cow's milk show activity against *H. pylori in vitro* [110,111], as do fermented milk products [68]. A component of cow's milk, as well as human milk, is the iron-binding glycoprotein (and natural antibiotic), lactoferrin. Lactoferrin, which is also found in neutrophils, has an inhibitory effect on the growth of a number of bacteria including *H. pylori*, perhaps due to the high affinity of lactoferrin for iron [105–107]. Dial and colleagues have evaluated the effects of oral lactoferrin on *Helicobacter* in a mouse model, and demonstrated significant effects on *Helicobacter*-induced gastritis [108,109]. The results of clinical trials of the effects on humans of oral lactoferrin have been both negative [72,73] and positive [70,71]. A recent meta analyses of the effects of fermented milk-based probiotic preparations on *H. pylori* eradication shows that they improved eradication rates by 5–15% [69]. Interestingly, this has led to the European gastroenterology community's recent inclusion of a tempered and qualified recommendation in their Consensus Report, that "Certain probiotics show promising results as an adjuvant treatment in reducing side effects" [144].

4.3. Vegetables

4.3.1. Broccoli sprouts—Anecdotal evidence that the consumption of broccoli sprouts may relieve peptic ulcer symptoms has led to the discovery that the isothiocyanate sulforaphane, most abundant in broccoli sprouts and currently under intense investigation for its protective effects against a variety of chronic diseases, is a very potent and selective antibiotic against *H. pylori* [117]. The same team later showed that a few other plant-derived isothiocyanates (e.g. 8-methylthiooctyl- and 4-rhamnopyranosyloxybenzyl-isothiocyanate) had similar activity against *H. pylori*, but many other isothiocyanates were not active [118]. Using a gastric xenograft model in nude mice and both histological and bacteriological evaluation criteria, Lozniewski and colleagues showed that *H. pylori* infections were effectively eliminated in 8 of 11 transplants following *in situ* infusion of 7.5 μmol sulforaphane on five successive days [119]. Other *in vitro* studies have underscored the efficacy of both the phytochemical and the broccoli sprouts from which they come [88,94,112,114], and have demonstrated that in addition to its direct bactericidal activity sulforaphane inactivates *H. pylori* urease, whereas numerous other isothiocyanates do not inactivate it [74].

In vivo studies in a *Helicobacter*-infected mouse model have shown a dramatic protective effect of broccoli sprouts against salt-induced gastritis. The bactericidal effectiveness of sulforaphane against *H. pylori* appears to be at least in part systemic, since it inhibited colonization, inflammation, and gastric mucosal atrophy in an *H. pylori*-infected, high salt diet mouse model [45]. The protective effects were much less pronounced in n*rf2* gene knockout mice [113]. An initial study with *H. pylori*-colonized human subjects in Japan was unable to demonstrate an effect of broccoli sprouts owing to the use of a single biomarker (UBT; the ^{13}C Urea Breath Test) and an insufficient sample size [145].

A pilot study in *H. pylori*-infected subjects also reported loss of *H. pylori* colonization following broccoli sprout treatment in four of nine subjects [120]. A small study of five subjects, in which very low levels of market stage broccoli were mixed with Tibetan yogurt, failed to show an effect of the treatment on UBT [76]. This is not surprising given the presumed very low levels of active ingredient (actual levels not reported), and the fact that for technical reasons, the homogenization and food processing used would be expected to have destroyed most of any sulforaphane released, prior to ingestion. Yanaka and colleagues in Japan reported a significant reduction in markers of inflammation, *H. pylori* levels, and UBT scores in colonized adults following daily consumption of broccoli sprouts containing ca. 420 μmol of the sulforaphane precursor, glucoraphanin, for 2 months, and these effects disappeared at the end of the intervention [45,115,116]. More recently, using similar metrics and outcomes to the Yanaka study, a group in Iran showed substantial effects of a 4 week dietary supplementation (86 Type 2 diabetes patients) with 6 g/d of high sulforaphane broccoli sprouts (about 135 μmol/d)[75].

4.3.2. Crucifers and other Vegetables—Numerous epidemiological studies have examined the association between cruciferous vegetable consumption and gastric cancer (see, for example [77,146,147]). These studies point to an inverse relationship, but whether this might be due to an anti-*H. pylori* effect, or a more general, systemic induction of cancer

protective defenses is not clear at this time. Cabbage juice has historically been used to treat stomach ulcers [148], and has significant inhibitory effects on *H. pylori*-induced gastritis in a Mongolian gerbil model [114]. Leaves of the tree *Moringa oleifera*, widely consumed in some tropical regions, also have anti-ulcer activity (reviewed in [149]), and certain glucosinolates/isothiocyanates from Moringa have strong antibacterial activity *in vitro* against *H. pylori* and a variety of other human pathogens [118,149]. Okra also has anti-*H. pylori* activity *in vitro*, thought to be an anti-adhesive effect of okra polysaccharides [150], and it is reported to provide some protection against duodenal ulcer [154]. Even a seaweed, the brown alga *Cladosiphon fucoidan*, has anti-*H. pylori* activity *in vitro* and in gerbils [136], also speculated to be due to the anti-adhesive effect of the alga's glucuronic acid-rich polysaccharide (fucoidan).

4.3.3. Garlic—A number of studies have demonstrated the anti-*H. pylori* activity of garlic *in vitro* [43,78], but the results of *in vivo* studies in humans have not been encouraging [43,44,78,152]. Garlic has antimicrobial activity against other bacteria [121] and possesses antioxidant activity [153]. This work has stimulated considerable debate in the literature on the efficacy of dietary treatment of *H. pylori* infection.

4.4. Fruits

A number of fruits, their juices and their extracts, inhibit growth of *H. pylori in vitro*. Among them, blueberry, bilberry, elderberry, cranberry, raspberry, and strawberry inhibit *H. pylori*, and enhance the susceptibility of *H. pylori* to clarithromycin, one of the synthetic antibiotics most commonly used to eradicate human infections with this microbe [125]. Cranberry juice has been the focus of particular attention for its ability to inhibit the growth of *H. pylori* and other bacteria (*E. coli* and *Streptococcus*) *in vitro* [51,122,123] and for its anti-adhesion activity against *H. pylori* [124]. There are at least two published studies in which the effects of cranberry juice was evaluated in colonized human beings. In the first, a double-blind, randomized, placebo-controlled trial sponsored by a cranberry juice company, the authors concluded that there was a significant effect of regular consumption of cranberry juice on a Chinese cohort of 189 subjects with positive urea breath test (UBT) results [81]. The second study, by Gottland and colleagues in Chile, showed that administration of cranberry juice for three weeks inhibited *H. pylori* about 15% of asymptomatic, colonized children, and that in most subjects who became negative (as measured by UBT), the clearing effect did not persist following cessation of consumption [80]. Furthermore, grape skin/seed extracts and wine preparations [128], (recently reviewed by Friedman [127]), pomegranate fruit and ellagic acid-rich juice (recently reviewed by Colombo [52]), apple [126], and *Rubus idaeus* and *R. occicentalis* fruit [154], have all been shown to have antimicrobial activity against *H. pylori in vitro*. Whereas animal models have been used to demonstrate efficacy of some of these fruit products, no trials currently listed on the USA government website ClinicalTrials.gov, propose to evaluate effects on *H. pylori* colonization.

4.5. Oils

Considerable work on naturally occurring *H. pylori* therapeutics has focused upon the truly lipoidal oils which include the short-, medium-, and long-chain fatty acids, monoglycerides, and the polyunsaturated fatty acids (commonly referred to as PUFAs). Fish oil [129], garlic

oil [121], and blackcurrant seed oil (rich in ω-3 and ω-6 unsaturated fatty acids) [82,94], all have *in vitro* antibiotic activity against *H. pylori*. Fish oil [83] shows activity against *Helicobacter* in humans. Evening primrose oil (rich in the ω-6 unsaturated linoleic acid) heals ulcers in rats [155] and consumption of fish oil is inversely associated with the prevalence of duodenal ulcer [129]. Numerous investigators have reported *in vitro* effects of specific PUFAs against *H. pylori* [156–158] but studies in humans have been mixed, with some studies showing anti *H. pylori* activity [82,83] and others showing none [156,159]. Anti-inflammatory activity has been reported [160], as has protection against ulcer formation [151], reduced risk of atrophic gastritis [161], and suppression of gastric acid secretion [83,162]. Shorter chain fatty acid activity against *H. pylori* has only been demonstrated *in vitro* [163,164].

4.6. Essential oils, herbs, spices, and food components

There has been considerable interest over the past decade or more in the utility of a variety of essential oils to eradicate or reduce *H. pylori* infection, and to ameliorate the symptoms of infection. The term “essential oils” refers to the mixture of low molecular weight compounds, typically rich in terpenes, aldehydes, ketones, or phenols, which is usually obtained from plants by steam extraction and distillation. The essential oils of a variety of herbs have antimicrobial, antioxidant, anti-inflammatory, and immune stimulatory activity, and the anti-*H. pylori* properties of a variety of these extracts have been comprehensively reviewed [53]. The essential oils from carrot seed, cloves, manuka, and lemon verbena have *in vitro* anti-*H. pylori* activity and the activity of lemongrass essential oil was demonstrated in an *in vivo* mouse model [54]. Peppermint oil has anti-inflammatory activity and reduces symptoms of dyspepsia in combination with caraway oil [55]. Lack of *in vivo* results from essential oils and other herb and spice extracts has led the authors of a recent review on the subject of their antibiotic activity to comment:

Perhaps the most striking result of this review is the extreme paucity of controlled clinical trials testing herbal antibiotics. In light of the long history and present popularity of their use, it is surprising that so few trials have tested the efficacy of herbal antibiotics. One obvious reason is the lack of patent rights on herbal medicines. Another reason could be that traditionally, herbal medicine has been hesitant to embrace modern methods for efficacy testing [56].

Other essential oils have shown efficacy against *H. pylori*, including that from the fungus, *Hericium*, in a randomized trial [84], and from chili peppers [79]. A green tea extract (*Camillia sinensis*) rich in 3′-sialyllactose had anti-*H. pylori* adhesion effects in a very small trial with Rhesus monkeys [165].

Extracts of cinnamon [56,87], rosemary, turmeric, fingerroot, nutmeg, ginger, [133] and licorice [23], all inhibit *H. pylori* growth *in vitro*, as does mastic gum (from the Mediterranean shrub *Pistacia lentiscus*) [134], vitamin C [166–168], a variety of flavonoids [169–171], berberine (from the barberry bush and goldenseal), a fermented rice extract, numerous traditional Chinese medicine (TCM) components [138,139], and a sulphated polysaccharide from brown seaweed. A few of these have additional activities such as improvement in gastritis or ulcer healing, but by and large there have been no notable

successes in *in vivo* eradication of *H. pylori* or in eradication of its symptoms with these compounds, preparations, herbs or extracts. On the other hand, anti-inflammatory activity has been reported with ginger, turmeric, licorice [131,132], and nutmeg [133], but the connection between this response and modulation of the sequelae of *H. pylori* infection has not been adequately probed. Inhibition of urease activity was reported from green tea extracts [137]. The sole reported clinical trial of a spice against *H. pylori* used cinnamon [87], and although there was no effect overall on UBT, the authors of this study point out that in patients whose initial UBT was exceptionally high, there was a decline in UBT following cinnamon ingestion [87].

Mastic gum (an inexpensive exudate obtained from the food plant *Pistacia lentiscus*) previously documented in the in the clinical trial literature in the mid-1980's for its effect on treatment of duodenal and gastric ulcers, was shown to kill *H. pylori* in 1998 [133]. It has since been the subject of clinical trials with both negative [86] and positive [85] outcomes.

Recent studies reported by Keenan and colleagues in New Zealand show significant synergy or enhanced effects of multiple foods (e.g. blackcurrant oil and broccoli sprouts) on a number of metrics of colonization and inflammation (see Fig. 2) [88,94]. When these studies are examined in the context of the theses discussed in ***Sections 2 and 3***, a more concerted search for truly synergistic effects of food components may be warranted.

5. Conclusions, Gaps in Knowledge and Future Research Needs

The concept of dietary treatment of *H. pylori* infections both for prophylactic and therapeutic purposes has been the subject of considerable discussion and debate in recent years. By the year 2005, a comprehensive review of the subject had been published [4], a Consensus Conference (13–14 February, 2005, Honolulu, HI, USA) was organized by two of the authors (JWF and AJW), and a variety of foods and dietary ingredients were evaluated for their potential to ameliorate infection with *Helicobacter pylori*. The value of amelioration compared to complete eradication were discussed by the conferees, who then agreed to a draft consensus stating that "*the concept that a diet-based treatment could reduce levels of H. pylori colonization without completely eradicating the organism in treated individuals is attractive in terms of cost, treatment, tolerability and cultural acceptability*". In light of the ongoing and voluminous research into this organism-disease complex, and into the clearly overwhelming effects that modification of our gastrointestinal microflora (in particular its diversity) has on health and wellness, there is now evidence that reducing colonization and its sequelae can be achieved with certain, perhaps many dietary ingredients. At this time the dietary components for treatment of *H. pylori* infection that have the greatest evidence to support them are broccoli sprouts, cranberry juice, essential oils of a number of spices (e.g. cloves, and blackcurrant), and some probiotic formulations. Based upon the current state of the science, a dietary approach to reduce the inflammatory response to *H. pylori* infection appears plausible.

Nonetheless, the huge body of *in vitro* and pre-clinical evidence has not received sufficient follow-up attention with rationally designed, unambiguous human trials.

Given the suggestion that complete eradication may even be detrimental, a food based approach may provide a useful adjunct or alternative to conventional drug treatments, and should be explored in colonized human subjects. These food-based approaches operate at levels of intake consistent with levels of consumption in the general population. They might require shifts in food consumption patterns but these would be consistent with adequate nutrition and good health. Moreover, avoidance of excessive antibiotic use could have profound long-term human health effects ranging from reduced development of antibiotic resistance, to maintenance of existing levels of human microbiome diversity, reduction of the risk of pathogen outbreaks, and reduced risk for a variety of non-communicable (chronic) diseases that may ultimately be proven to be influenced by the human microbiome.

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Abbreviations

OR	odds ratio
PPI	proton pump inhibitor
PUD	peptic ulcer disease
PUFA	poly unsaturated fatty acid
UBT	urea breath test

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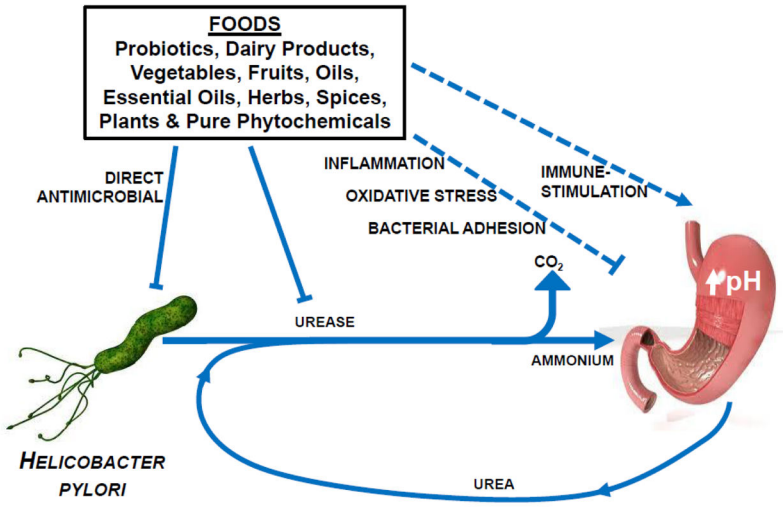

Figure 1.

A large number of foods have been evaluated for their ability to inhibit *Helicobacter pylori, in vitro*. Some of these, and other food components reduce colonization of the stomach and the sequelae of colonization, in animal models and small human trials. Primary mechanisms of action are not in all cases focused on the direct antimicrobial effects, but include inhibition of the urease produced by *H. pylori* as a pathogenic factor, anti-inflammatory antioxidant, anti-adhesive, and immune-stimulatory properties of these foods.

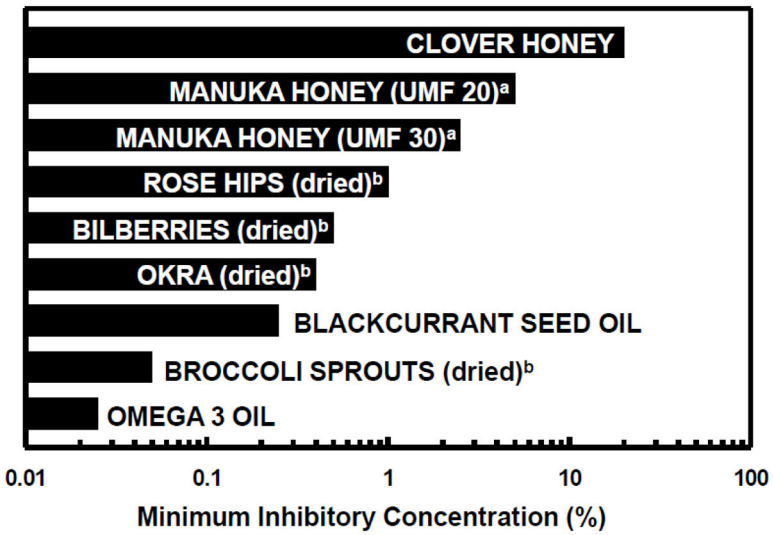

Figure 2.

Effects of foods, and food components/ingredients on the growth of *H. pylori* were determined by the minimum inhibitory concentration (MIC) of that component, expressed as a weight per volume percentage. [a]UMF ("unique manuka factor") is an index of potency that is used in the manuka honey trade. [b]"Dried" foods were lyophilized. Redrawn from Keenan et al. (2010) [94]

Table 1

Clinical studies evaluating effects of selected foods and food components on *H. pylori* and gastric symptoms.

	PRIMARY REFERENCE			
	EFFECT[2]			
FOOD PRODUCTS[1]	POSITIVE	NEGATIVE	REVIEW[3]	META-ANALYSIS[4]
Bee (*Apis mellifera*) Products				
Manuka honey		59		
Probiotics				
(general)	60	61	62	61
Lactobacilli		63	64	
Bifidobacterium bifidum		65		
Saccharomyces boulardii	66			66
Fermented milk based-	67		68	69
Dairy Products				
Lactoferrin	70,71	72,73		
Vegetables				
Broccoli sprouts	46,75,120			
Broccoli		76	77	
Garlic		78		
Pepper (red; capsaicin)		78,79		
Fruits				
Cranberry	80		81	
Oils				
Blackcurrant Seed-	82			
Fish-	82	83		
Essential Oils				
Hericium erinaceus (fungus)	84			
Herbs, Spices, and Other Plants				
Mastic Gum & Resin	85	86		
Cinnamon		87	4,56	

[1] Foods, food products, or extracts of foods or plants used for food;

[2] Outcome of clinical trial, as reported;

[3] Reviews;

[4] Meta-analyses of multiple clinical trials.

Table 2

Effects of selected foods and food components on *H. pylori* and gastric symptoms.

FOOD PRODUCTS[1]	BIOLOGICAL ACTIVITY MEASURED[2]				
	ADH	AOX	IMM	INF	MIC
Bee (*Apis mellifera*) Products					
Honey (general)				88	31,51,89–94
Manuka Honey				88	59,94,95
Propolis		46		96	91,96,97
Probiotics					
(general)			64,98,99	64,99,100	98,100–104
Dairy Products					
Lactoferrin				105	105–109
Colostrum					110,111
Cow's Milk					110,111
Vegetables					
Broccoli sprouts		112,113		45,46,88,114–116	75,94,114,117–121
Garlic					44,121
Cabbage-radish (hybrid)				114	114
Okra					94
Fruits					
Pomegranate				52	
Cranberry	122–124				
Berries (blue-, bil-, rasp-, straw-, elder-)					94,125
Apple				126	126
Grapes (incl. skin/seed extracts, wine, winery byproducts & resveratrol)	127	127	127	127	127,128
Oils					
Blackcurrant Seed-					94
Fish-	129			88	94,129
Essential Oils					
Many, including: cinnamon, lemon verbena, manuka, carrotseed, N. African thyme, rosegum, and fool's watercress					53,54
Wild oregano	130				

FOOD PRODUCTS[1]	BIOLOGICAL ACTIVITY MEASURED[2]				
	ADH	AOX	IMM	INF	MIC
Peppermint				55	53,54
Caraway				55	
Ginger, turmeric, licorice				131,132	
Nutmeg				133	
Chili pepper					79
Herbs, Spices, and Other Plants					
Mastic Gum & Resin					134
Cinnamon					56,87
Licorice	135				23
Oregano	130				130
Lotus					136
Many, including: catmint, Chinese goldenthread, fingerroot, forsythia, ginger, goldenseal, great burdock, green tea, hops, mango ginger, meadowsweet, monkey-face tree, nutmeg, red ginseng, sage, sticklewort, tea, turmeric, wormwood		26		137	26,137–140
Algae: *Cladosiphon fucoida* (seaweed) & sulphated polysachharides	141				136

[1] Foods, food products, or extracts of foods or plants used for food;

[2] Primary reports or reviews of anti-*H.pylori* activity. Column headings indicate general types of activities measured and descriptions in parentheses outline general approaches used for these determinations: **ADH** - antiadhesion (enumeration of *H. pylori* cells in culture, adhered to cultured gastric epithelial cells); **AOX** - antioxidant (determination of antioxidant capacity or reactive oxygen species, ROS, neutralization capacity of the food [e.g. ORAC] and/or total antioxidant capacity of plasma before and after treatment [TEAC]); **IMM** -immuno-stimulatory (measurement of stimulation of macrophage recruitment and release of cytokines [IL-2] and interferon-γ); **INFL** - anti-inflammatory (measurement of inflammatory cytokines, of nitric oxide release [e.g. indicative of an induction of the NfkB pro-inflammatory pathway, and inducible nitric oxide synthase, iNOS]; **MICRO** – direct antimicrobial (plate counts or other enumeration of *H. pylori* cells to determine minimum inhibitory concentration, MIC; or zone of inhibition).