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**Exploring alternative treatments for *Helicobacter pylori* infection**

Ayala G *et al*. Alternative treatments for *H. pylori* infection

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**Abstract**

*Helicobacter pylori* (*H. pylori*) is a successful pathogen that can persist in the stomach of an infected person for their entire life. It provokes chronic gastric inflammation that leads to the development of serious gastric diseases such as peptic ulcers, gastric cancer and MALT lymphoma. It is known that these ailments can be avoided if the infection by the bacteria can be prevented or eradicated. Currently, numerous antibiotic-based therapies are available. However, these therapies have several inherent problems, including the appearance of resistance to the antibiotics used and associated adverse effects, the risk of re-infection and the high cost of antibiotic therapy. The delay in developing a vaccine to prevent or eradicate the infection has furthered research into new therapeutic approaches. This review summarises the most relevant recent studies on vaccine development and new treatments using natural resources such as plants, probiotics and nutraceuticals. In addition, novel alternatives based on microorganisms, peptides, polysaccharides, and intragastric violet light irradiation are presented. Alternative therapies have not been effective in eradicating the bacteria but have been shown to maintain low bacterial levels. Nevertheless, some of them are useful in preventing the adverse effects of antibiotics, modulating the immune response, gastroprotection, and the general promotion of health. Therefore, those agents can be used as adjuvants of allopathic anti-*H. pylori* eradication therapy.

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**Key words:** *Helicobacter pylori*; Treatment; Natural products; Probiotics; Nutraceuticals

**Core tip:** *Helicobacter pylori* (*H. pylori*) plays a role in several gastric diseases. Current anti-*H. pylori* therapy fails in more than 20% of cases, primarily due to antimicrobial resistance and patient non-adherence. This situation has encouraged the search for other approaches to control *H. pylori* infection. This review discusses advances in the development of an *H. pylori* vaccine and new treatments based on plants, probiotics, nutraceuticals, microorganisms, peptides and intragastric violet light irradiation. Alternative therapies have not been effective in eradicating the bacteria *in vivo* but are promising as complementary treatments diseases associated with *H. pylori* infection.

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**INTRODUCTION**

*Helicobacter pylori* (*H. pylori*) infection is an important public health problem in several parts of the world. Because this pathogen is associated with various gastric diseases, ranging from mild discomfort, such as superficial gastritis, to severe ailments, such as chronic atrophic gastritis, gastric cancer or peptic (gastric or duodenal) ulcer, there is much interest in understanding how infection with *H. pylori* could be prevented.

***Virulence factors of H. pylori***

*H. pylori* has virulence factors that are necessary to colonise the acid environment of the stomach and to survive in it; these factors are expressed in all isolates[1]. Of these, the most remarkable are urease and the adhesins. Urease metabolises urea into ammonia and carbon dioxide, and it contributes to the neutralisation of gastric acid[2]. In addition, urease is strongly immunogenic and chemotactic for phagocytes[3], and it promotes the production of the proinflammatory cytokines interleukin (IL)-1β, IL-6, and IL-8, as well as tumoural necrosis factor-alpha (TNF-α)[4,5]. *H. pylori* adheres specifically to the epithelial cells of the gastric mucosa by means of the adhesins. Of these, the most studied are BabA and SabA, which are external membrane proteins that link to the blood group antigens Lewis-b and Lewis-x, respectively[6,7]. The gene *babA* is polymorphic, occurring as *babA1* and *babA2*[8]. Strains containing *babA2* are associated with a higher risk of peptic ulcer, intestinal metaplasia and gastric cancer. Moreover, *babA2*+ strains generally display the most cytotoxic *vacA* genotype (s1/m1) and they are *cagA+*, which further increases the risk of peptic ulcer, intestinal metaplasia and gastric cancer[9,10]. Other membrane proteins that function as adhesins have been reported, including AlpA, AlpB, HopZ and HopH, also called outer inflammatory protein A (OipA) due to its association with the increased secretion of IL-8 by epithelial cells *in vitro* and with intense gastric inflammation *in vivo*[11-14]. Nevertheless, only approximately 20% of the *H. pylori* population in the stomach adheres to the epithelial cells, whereas the rest is found in the mucosal layer[15].

The neutrophil-activating protein of *H. pylori* (HP-NAP allows the bacteria to capture iron, which is essential for its growth[16]. HP-NAP it is particularly important in the pathogenesis of the infection because it induces adhesion and chemotaxis of mononuclear (MN) and polymorphonuclear (PMN) phagocytes[17]. HP-NAP activates the NADPH oxidase enzyme, which is involved in the production of reactive species of oxygen (ROS)[18]. It also stimulates the production of IL-12 and IL-23 by neutrophils and monocytes; these cytokines promote inflammation[19]. Because of its properties, HP-NAP increases the degree of gastric mucosa inflammation and the continuous harm to gastric cells caused by ROS.

There are other important enzymes that protect *H. pylori* against the ROS produced through internal metabolic processes as well as by neutrophils and macrophages during inflammation[20]. Among these are superoxide dismutase (Hp-SOD), which catalyses the dismutation of the superoxide radical into hydrogen peroxide and molecular oxygen, and catalase (KatA), which converts hydrogen peroxide into water and oxygen. Another important anti-ROS enzyme is alkyl hydroperoxidase (AhpC), which is a highly abundant and conserved protein in *H. pylori*[21]. This enzyme is a member of the peroxiredoxin family that has been shown to be capable of reducing different peroxides, but its major function under physiological conditions is to reduce organic hydroperoxides into non-toxic alcohols[22].

Several *H. pylori* virulence factors have been associated with gastric carcinogenesis. The most important of these include vacuolating cytotoxin (VacA) and the CagA protein. Both are especially relevant for the pathology of the infection by *H. pylori* infection because strains that produce them have been more frequently isolated from patients with gastric cancer[23,24].

VacA is one of the most important factors determining the virulence of the pathogenic strains of *H. pylori*. It was first characterised by its ability to cause cell vacuolisation in tissue culture cells. VacA creates pores in the membrane of the host cells, allowing the exit of chlorine and bicarbonate ions, pyruvate and urea[25,26]. VacA causes the release of iron, nickel, sugars and amino acids through the tight junctions of the gastric epithelium without affecting their integrity[27]. It has been reported that VacA interferes with the process of antigen presentation *in vitro*[28], induces apoptosis in epithelial cells[29] and inhibits the activation and proliferation of T and B cells *in vitro*[30,31]. The functions of VacA suggest that its initial activity consists in providing nutrients for the establishment of the infection. Afterwards, it contributes to the persistence and chronicity of the infection by inhibiting immune cells and altering the balance of cellular turnover; it also increases cellular proliferation and allows the persistence of mutation-carrying cells, thus contributing to the carcinogenic process.

The *H. pylori* CagA protein is a 120- to 140-kDa protein produced by approximately 60% of clinical isolates. The *cagA* gene is located at the end of the cytotoxin-associated genes pathogenicity island (*cag*PAI)[32]. This region contains 32 genes, some of which encode for multiple structural components of the type IV secretion system (T4SS). The T4SS is an external structure that can be visualised microscopically as pilus-like structures protruding from the bacterial membrane[33]. In addition to CagA, there are other *cag*PAI products that are equally important in the pathogenesis processes associated with *H. pylori*. Among these is the CagL protein, which is found at the tip of the pilus and serves as an adhesine, which binds to host cell integrin[34] to trigger the translocation of CagA into the cell[35]. Additionally, CagL interacts with the α5β1 integrin to induce IL‑8 production and the nucleotide-binding oligomerisation domain-containing 1 (NOD1) signalling[36] independently of CagA translocation. Once CagA is translocated into gastric epithelial cells, it carries out functions that depend on both the phosphorylated and the non-phosphorylated forms of CagA[37]. Phosphorylation-dependent functions include the dispersion and elongation of cells, affecting their proliferation and adhesion, as well as the organisation of the cytoskeleton[38-40]. Phosphorylation-independent functions include: interruption of the tight adhesive junctions, loss of cellular polarity, proinflammatory and mitogenic responses, degradation of the extracellular matrix, and induction of cell cycle progression[41-45]. The result of these processes is the destabilisation of the gastric epithelium, which potentially contributes to the pathogenesis of *H. pylori in vivo*. Moreover, these findings point to the preferential survival of *H. pylori*-infected cells and to the oncogenic role of the bacteria.

A gene associated with the development of duodenal ulcer (*dupA*) has been reported. The *dupA* gene is the most frequent gene in strains isolated from patients with duodenal ulcer. It is associated with the development of duodenal ulcers, as well as with neutrophil infiltration in the antrum and higher levels IL-8[46]. However, other investigations have not found these associations, so more research work is needed to confirm this finding[47,48].

***Immune response and disease***

The development of innate immunity depends on the host’s recognition of microbial pathogens through pathogen-associated molecular patterns (PAMPs), such as lipopolysaccharide (LPS), peptidoglycan, lipoproteins, flagellins or double-stranded RNA[49]. These PAMPs are highly conserved molecular structures that are recognised by Toll-like receptors (TLRs)[50] or by nucleotide oligomerisation domain (NOD)-like receptors (NLRs)[51]. *H. pylori* LPS and flagellin are poor activators of TLR-4 and TLR-5, respectively. *H. pylori* LPS has a weak endotoxic activity compared to *Salmonella typhimurium* LPS[52] and is a weaker inducer of pro-inflammatory cytokines than *Escherichia coli* LPS[53]. *H. pylori* flagellin is weakly recognised by TLR-5 and it is not pro-inflammatory[54,55]. *H. pylori* evades an initial innate response by preventing intense immune activation; thus, it can colonise the gastric mucosa. The *H. pylori* peptidoglycan is delivered into cells through the T4SS[56] and the outer membrane vesicles (OMVs)[57]. Once translocated, the peptidoglycan is recognised by NLR NOD-1, resulting in the translocation of NF-kB to the nucleus and the activation of the immune response genes[56,58].

The hallmark of the interaction between *H. pylori* and the host’s immune system is the persistence of the infection for years, leading to a chronic inflammation of the gastric mucosa. Once the *H. pylori* infection is established, both cellular and humoural adaptive immunities are developed: naive T helper (Th) CD4+ cells differentiate into Th effector cells (cellular response), and B cells that produce specific antibodies are activated (humoural response)[59]. However, there is evidence indicating that B cells and antibodies are dispensable for *H. pylori* control[60,61], whereas Th1 and Th17 effector T cell subsets and their cytokines are essential for the control of the infection[62-64]. Th1 cells produce the pro-inflammatory cytokines gamma interferon (IFN-γ) and tumour necrosis factor α and β that stimulate innate and T-cell immune responses[65]. Th17 cells are a recently identified class of effector T cells that produce pro-inflammatory cytokine IL-17. This interleukin stimulates fibroblasts, endothelial and epithelial cells, and gastric and lamina propria mononuclear cells to produce a diversity of cytokines and chemokines; this process results in neutrophil infiltration that contributes to *H. pylori*-associated inflammation[66]. Despite the local and systemic response against the infection, *H. pylori* can subvert and/or modulate the adaptive immunity perpetuating the infection and chronic inflammation[67]. In a small proportion of infected individuals, this chronic inflammation leads to the development of gastric cancer.

Regulatory T cells (Treg cells) are CD4 + CD25 + FOXP3 + T cells that contribute to peripheral immunologic tolerance by suppressing activated T cells, natural killer cells, B cells and dendritic cells[68]. Treg cells are induced by IL-18 in response to *H. pylori*; they regulate the effector T cells to prevent excessive activation and promote a persistent infection[69]. Treg cells from the gastric mucosa of *H*. *pylori*-associated gastric cancer patients could down-modulate the T cell response against *H. pylori* *in vitro*[70]. Furthermore, high levels of suppressive cytokine IL-10[71] and a Treg cell-mediated reduction of T cell transendothelial migration[72] from *H. pylori*-associated gastric cancer patients has been detected. Anti-tumour responses are characterised by cell-mediated immunity. In the mouse model, Treg cells can suppress an effective immune response against tumours[73,74]. It seems that the suppressive functions of the Treg cells may contribute to the reduced anti-tumour responses and thus to tumour progression in *H. pylori*-associated gastric cancer patients.

In some *H. pylori*-infected individuals, acid secretion is higher than normal. The acid flows into the duodenum, leading to gastric metaplasia. *H. pylori* cannot colonise a normal duodenum; it preferentially colonises areas of duodenal gastric metaplasia[75]. The numbers of CD4 + FOXP3 + T cells are increased in areas of gastric metaplasia in the duodenum of *H. pylori*-infected ulcer patients[76]. Interestingly, there is evidence showing reduced cytokine production in the duodenal epithelium of duodenal ulcer patients[77]. These findings suggest that a down-regulation of the immune response, possibly by Treg cells, allows a higher bacterial density in the duodenum that, together with the high secretion of acid, plays a role in the development of *H. pylori*-associated duodenal ulcer[78].

***H. PYLORI* TREATMENT**

In most individuals, the *H. pylori* infection can continue throughout life as an asymptomatic condition. Unfortunately, its persistence in the stomach causes chronic gastric inflammation and tissue damage, leading to alterations that could evolve to severe gastric diseases such as peptic ulcers, gastric cancer, or MALT lymphoma. Therefore, eradication appears to offer the most direct approach to reducing the enormous human and economic consequences of *H. pylori* infection[79,80].

In general, several international guidelines for treating patients diagnosed with *H. pylori* infections are consistent with the use of triple therapy as the first-line treatment. This treatment consists of the administration of a proton pump inhibitor (PPI), clarithromycin, and amoxicillin during for 7–14 d[81-83]. However, *H. pylori* eradication treatments following this regimen produce cure rates lower than 80%, mainly due to an increase in clarithromycin resistance[84,85]. As a result, other regimens (second-line therapies) have been proposed[85]. These treatments usually consist of a PPI in combination with two or three antibiotics, among which amoxicillin, clarithromycin, metronidazole, and tetracycline are included. To overcome the antimicrobial resistance problem and to increase the cure rates of initial treatments, new drug combinations are being developed from existing formulas. The use of a four-drug treatment *(i.e.*, either sequential, concomitant or bismuth-containing) has been recommended. Sequential treatment consists of a dual therapy (a PPI plus amoxicillin) for 5 d, followed by a 5-d triple therapy with a PPI plus clarithromycin and tinidazole or metronidazole to complete a 10-d treatment. Concomitant therapyconsists of four drugs (a PPI, clarithromycin, metronidazole/tinidazole and amoxicillin) given twice a day for 3–7 d. Bismuth-containing quadruple therapy consists of a bismuth salt, tetracycline HCl, metronidazole/tinidazole, and a PPI given three or four times a day for 7–14 d[86].

European guidelines recommend culture before the selection of a third-line treatment based on the microbial antibiotic sensitivity. After two eradication failures, *H. pylori* isolates are often resistant to both metronidazole and clarithromycin. The alternative candidates for third-line therapy are quinolones, tetracycline, rifabutin and furazolidone; high-dose PPI/amoxicillin therapy might also be promising[87].

The main reasons for treatment failure are antimicrobial resistance and patient non-adherence. The lack of treatment compliance by the patient is a basic factor that explains the low rates of bacterial eradication. The cause is the complexity of the therapy, which involves at least three drugs, administered in repeated doses for a long time. Consequently, there are side effects, which, coupled with a lack of immediate improvement, discourage the patient to continue with the therapy. The high cost of anti-*H. pylori* treatments is another drawback. Finally, the recurrence of *H. pylori* infection after successful eradication also represents a problem in terms of the efficiency of therapies, especially in developing countries.

Taking into account the problems inherent to anti-*H. pylori* therapies in clinical practice, new therapeutic approaches to obtain a vaccine against the bacteria and to find new molecules with antibiotic activity or adjuvants that help patients to comply with the therapies have emerged. In this review we summarise the most relevant recent research on alternative treatments to the current therapy against *H. pylori* (Figure 1).

**VACCINES**

The need for a vaccine is especially evident in those countries with a high prevalence of the infection; with increased resistance to the antibiotics used to treat it, which might increase the recurrence rate of the infection; and with high morbidity and mortality rates caused by *H. pylori* infection-associated pathologies[85]. The high cost of treatment for diseases associated with thisinfection (*i.e.*, gastric cancer and peptic ulcer) make vaccine development a cost-effective alternative. Thus, effective vaccines that could prevent and/or cure the infection or at least modify the host-pathogen interactions in a manner that prevents disease progression are desirable.

The continued efforts to obtain a vaccine against *H. pylori* have been focused on finding the best delivery route, as well as adjuvants and antigens that favour the induction of protective immunity. Because *H. pylori* is an extracellular mucosal pathogen, most of the vaccines that have been developed are based on mucosal immunisation. Several routes of mucosal vaccination and different antigens in combination with mucosal immune adjuvants, such as the cholera toxin (CT) or the *E. coli* heat-labile toxin (LT), have been tested[88]. In animal models, both CT and LT are strong adjuvants that induce protection, defined as a significant reduction in the bacterial load; they also induce protection against a challenge with *H. pylori*. However, these adjuvants have adverse effects in humans, which prevent their clinical application. The best alternative for human studies is aluminium hydroxide, which is already approved by the United States Food and Drug Administration (FDA)[89]. The introduction of live attenuated S*almonella* expressing *H. pylori* urease A and B subunits[90,91] is an alternative strategy that does not require adjuvants, but studies in humans[92,93] did not produce satisfactory results.

Different antigens have been shown to be effective in inducing the immune response to the infection. Urease (UreA and UreB), CagA, VacA, NapA and catalase are recognised by antibodies[94,95]; therefore, these antigens are the best candidates for vaccine formulations. Among these antigens, urease is highly expressed by all *H. pylori* strains, which makes it a good candidate for a vaccine formulation. Although the initial results were disappointing, the combination of urease with other antigens such as HpaA (essential surface protein) conferred better protection[96]. The search for novel antigens has led to an interesting new development: a vaccine comprising genetically fused HspA, UreB and HpaA to create a multivalent vaccine[97]. When this trivalent fusion vaccine was tested in BALB/c mice, it showed significant protection against *H. pylori* infection, which was associated with *H. pylori*-specific antibody production and the Th1/Th2-type immune responses. Another innovative development consists of a system where the measles virus (MV) is used as a vector for the expression of the *H. pylori* neutrophil-activating protein (NapA). It was demonstrated that attenuated MV strains expressing the NAP antigen induce a significant humoural and cellular immune response against both the MV and the NAP antigen[98]. Other novel antigens include antioxidant enzymes, superoxide dismutase[99] and alkyl hydroperoxide reductase[100], which are essential for *H. pylori*’s survival *in vivo*. When they are used as vaccines, the immune response generated against them could also have an impact on bacterial survival and thus favour elimination. Recent research reports from human studies show that a vaccine formulation comprising CagA, VacA and NapA, in combination with aluminium hydroxide as an adjuvant and delivered by intramuscular injection, elicits antigen-specific humoural and cellular responses against CagA and VacA; specific T cells against CagA and VacA were observed, and they were detectable 24 mo after the primary vaccination, suggesting T cell memory[89].

There is evidence that cellular immunity is required for *H. pylori* clearance and that an initial humoural response fails to prevent infection and colonisation[60,101]. Studies in animal models have found that certain antigens and adjuvant combinations for immunisation can induce protective immunity[102-104], although the protective mechanism remains unclear. From these studies, it has also been revealed that the immune response induced by *H. pylori* contains a significant component of Treg cells that may limit both the inflammatory and the immune mechanisms in the gastric mucosa, which might play an important role in clearing the infection. These immunomodulatory mechanisms used by *H. pylori* to persist in its gastric niche are crucial to prevent sterilising immunity[61]. Therefore, successful vaccine formulations and vaccination strategies must overcome the immunomodulatory response induced by *H. pylori*[105,106].

Although some promising results have been obtained in animal models, pointing to the feasibility of developing a secure and effective vaccine for human use[107], more clinical trials are needed to establish whether the positive results obtained in animal models can be reproduced in humans. In addition, other aspects require investigation, to provide clues regarding vaccine formulations, antigens, adjuvants, and delivery systems.

**PLANTS AS THERAPY**

Plants and spices have been used since ancient times as therapeutic agents, and their uses have been passed down from generation to generation. Today, traditional medicine systems based on the use of plants are especially recognised in developing countries, where the availability of medical services and the accessibility to allopathic treatments is limited. Natural products, specifically those of plant origin, are potential sources for the discovery and development of new effective agents against infections[108].

There are hundreds of scientific publications worldwide that describe specifically the antibiotic activity of herbal products against *H. pylori*. A search (plant anti *H. pylori*) in the PubMed database from 1991 to August 31, 2013, lists over 300 entries, including plant extracts, plant compounds, and plant processed products. In 1991, the anti-*H. pylori* effect of 13 Malagasy medicinal plants was reported[109]. Since then, several investigations of medicinal plants of a specific region or country have been undertaken. Examples include studies of the anti-*H. pylori* activity of Chinese[110], Mexican[111-113], Iranian[114,115], Taiwanese[116], African[117,118], and Greek[119] herbal medicines. The largest group of reports refers to the activity of an individual plant, either for medicinal or dietary use.

In addition to screening for active regional medicinal plants, research efforts have also focused on the bioguided isolation and identification of pure compounds, as well as on chemical modification of lead compounds in order to obtain more active molecules against *H. pylori*. From these phytochemical studies, many compounds with remarkable anti-*H. pylori* effect *in vitro* have been identified[120,121]. However, very few of them retain their *in vivo* activity. Examples include catechins, particularly epigallocatechin gallate[122], the terpene plaunotol[123], 1-methyl-2-[(Z)-8-tridecenyl]-4-(1H)-quinolone and 1-methyl-2-[(Z)-7-tridecenyl]-4-(1H)-quinolone[124], the flavonoid kaempferol, the alkaloid tryptanthrin[125], sulphoraphane[126,127], 4-vinyl-2,6-dimethoxyphenol, canolol[128], and β-artecyclopropylmether, an artemisinin derivative[129].

More integral investigations include other pharmacological aspects of the plants and extracts in addition to their anti-*H. pylori* activity; for instance, anti-secretory, antioxidant, gastroprotective, anti-inflammatory, anti-haemorrhagic, and gastric ulcer resolution activities[130-133].

Studies that have attempted to elucidate the mechanism of action of the plant extracts or compounds on *H. pylori* are available. For example, some of these studies have examined their effect of various compounds on bacterial virulence factors such as urease[134], adherence[135-138], motility, vacuolisation[139,140] or on some key metabolic enzymes[135,141].

Below, we describe examples of the research conducted on plants or plant products, emphasising those in which its anti-*H. pylori* effectiveness *in vivo* was studied.

***Garlic***

Garlic, Allium sativum, is invaluable not only as an essential flavouring element in food but also for its therapeutic properties. These effects are attributable to specific oil- and water-soluble organosulphur compounds such as thiosulphinates, which are responsible for the typical odour and flavour of garlic. The interest in studying the therapeutic properties of garlic on *H. pylori*-related diseases arose when an inverse relationship between garlic consumption and the incidence of gastric cancer was reported[142].

The *in vitro* anti-*H. pylori* activity of extracts and compounds obtained from garlic[143-147] has been extensively documented, although a few studies reported negative results[138,148]. An aqueous garlic extract, standardised for its thiosulphinate concentration, had a minimum inhibitory concentration (MIC) of 40 μg/mL, and for other garlic compounds (allicin, ajoenes, vinyldithiins, thiosulphinates), the MIC values were approximately 10 to 25 μg/mL[144,147,149]. However, in the few *in vivo* studies that have been carried out, the viability of the bacterium was not affected. For example, the inclusion of sliced garlic in the diet of patients did not result in a reduction of the infection as assessed by measuring *H. pylori* infection by the urease breath test[150]. Treatment with a 4 mg garlic oil capsule, administered four times a day for 14 d, also gave negative results[151]. Similar results were obtained when a 4% garlic extract was administered daily for 6 wk to Mongolian gerbils with *H. pylori*-induced gastritis, but in this case, a reduction in gastritis was observed[152].

The Shandong Intervention Trial began in Linqu County, Shandong, China (a rural region with a high incidence of gastric cancer) in 1995, with the aim of assessing interventions to reduce the prevalence of advanced precancerous gastric lesions. The individuals selected (3365 subjects) were randomly assigned to three interventions or placebos. The 3 interventions included a 2-wk course of amoxicillin and omeprazole (*H. pylori* treatment); the second group was treated for 7 years with an oral supplementation of a mixture of garlic extract and steam-distilled garlic oil, and the third group was treated for 7 years with vitamin supplementation. The trial demonstrated that amoxicillin and omeprazole significantly reduced the prevalence and the average of the histological severity of precancerous gastric lesions, whereas no statistically significant favourable effects were observed for garlic or vitamin supplements[153].

The results of a 14.7-year follow-up for gastric cancer incidence and cause-specific mortality among the subjects in the Shandong trial showed that the treatment with amoxicillin and omeprazole resulted in a statistically significant 39% reduction in gastric cancer incidence. A similar but non-statistically significant decline was observed for gastric cancer mortality. Neither garlic nor vitamin long-term supplementation was associated with a statistically significant decrease in gastric cancer incidence and mortality[154].

In another case-control study conducted to evaluate the effects of dietary and life-style habits of patients diagnosed with gastric cancer in Turkey, it was found that frequent consumption of garlic did not result in a lower gastric cancer risk[155].

***Broccoli***

The traditional medicinal value of broccoli is due to its anticancer, antiviral and antibacterial properties. Two pilot trials were conducted to evaluate the effect of short-term broccoli consumption (alone or in combination with yoghurt) on *H. pylori* eradication in infected volunteers. In one group, a temporally associated eradication of *H. pylori* infection was observed[156]; in the other group, the treatment was ineffective[157].

An epidemiological investigation of the relationship between broccoli consumption and chronic atrophic gastritis was conducted in 438 male employees, aged 39 to 60, at a Japanese steel company. Chronic atrophic gastritis was serologically determined by measuring pepsinogen I and the pepsinogen I/pepsinogen II ratio (biomarkers of gastric inflammation). Broccoli consumption (weekly frequency) in the diet was monitored by using a 31-item food frequency questionnaire. Unexpectedly, the results showed that broccoli consumption once or more weekly significantly increased the risk for chronic atrophic gastritis[158].

Isothiocyanate sulphoraphane (SF), an abundant compound in broccoli sprouts, has been identified as a potent bacteriostatic agent against *H. pylori* (in 48 tested strains, MIC media = 2μg/mL); moreover, brief exposure to SF eliminated intracellular *H. pylori* from a human epithelial cell line (HEp-2). SF was effective in eradicating *H. pylori* from human gastric xenografts in nude mice[159].

Another *in vivo* approach was used to evaluate the efficacy of fresh broccoli sprouts in reducing *H. pylori* infection and its sequelae in an *H. pylori*–infected mouse model, as well as in infected human volunteers[127]. Oral treatment with SF-rich broccoli sprouts of C57BL mice infected with *H. pylori* and maintained on a high-salt diet (7.5% NaCl has been shown to exaggerate *H. pylori*–induced gastritis in mice) reduced gastric bacterial colonizationcolonisation, attenuated mucosal expression of tumour necrosis factor-α and interleukin-1β, mitigated corpus inflammation, and prevented the expression of high salt-induced gastric corpus atrophy.

In the human trial, 48 *H. pylori*–infected volunteers were instructed to consume broccoli sprouts (70 g/d; containing 420 μmol of SF precursor) for 8 wk. The treatment decreased urease levels as measured by the urea breath test, *H. pylori* stool antigens, and serum pepsinogens I and II. Nevertheless, all values recovered to their original levels 2 mo after treatment discontinuation, indicating that broccoli sprout treatment does reduce *H. pylori* colonisation but does not completely eradicate it. In summary, evidence from mice and humans suggests that SF may have two mechanisms: a direct effect on *H. pylori* (bacteriostatic), leading to a reduction in gastritis, and an indirect effect by inducing the host cytoprotective response.

***Green tea***

Green tea is one of the most widely consumed beverages worldwide, and it has been shown to inhibit the growth of *Helicobacter* spp. Remarkable antibiotic activity of green tea against *H. pylori* and *H. felis* has been demonstrated *in vitro*[160]*.* In *in vivo* models, green tea administration also gave encouraging results. In one case, green tea decreased the number of bacteria and the inflammatory score of *H. pylori*-infected C57BL/6J mice, but the greatest impact on these two parameters was obtained when mice received green tea prior to infection[160]*.* In another assay, infected Mongolian gerbils received green tea extract in drinking water (500, 1000, and 2000 ppm) for 6 wk; interestingly, gastritis and the prevalence of *H. pylori*-infected animals were suppressed in a dose-dependent manner[161].

Catechins, the main antioxidant compounds of green tea, also showed antibacterial activity against *H. pylori in vitro* and *in vivo*. Epigallocatechin gallate had the strongest activity, with an MIC = 8 μg/mL for 50% of the tested strains[122]. In infected Mongolian gerbils, the effect of catechins in the diet (2%) for 2 wk was associated with a low rate of bacterial eradication (36%), but with significant decreases in mucosal haemorrhage and erosion[122]. The authors suggest that combining catechins with a proton pump inhibitor and the inclusion of a drug delivery system that prolongs the gastric-transit time would improve the efficacy of catechins.

Green tea extract greatly inhibited *H. pylori* urease, with an IC50 value of 13 μg/mL. Catechins were identiﬁed as the active compounds, and the hydroxyl group at the 5´-position appeared to be important for urease inhibition[161]. Moreover, polyphenols present in green tea inhibited the vacuolisation effect induced by *H. pylori* VacA toxin[140].

***Red wine***

The antibacterial activity of red wine against *H. pylori* has been tested. It has been proposed that resveratrol is, at least in part, the compound responsible for the activity (MIC range of 6.25–25 μg/mL)[162,163]. Moreover, resveratrol and red wine showed an inhibitory effect on *H. pylori* urease activity[163].

Red wine inhibits ion and urea conduction *in vitro,* as well as cell vacuolisation induced by VacA. These inhibitory effects were attributed to its polyphenol content, because these compounds inhibit the VacA channel[140].

It has been shown that administration of a red wine and green tea mixture, or a polyphenol mixture (tannic acid and n-propyl gallate) to *H. pylori* infected mice, or to mice treated with VacA toxin, limited gastric epithelium damage but did not significantly affect bacterial colonisation. These results suggest that VacA inhibition plays a role in this protective effect[139,164].

These data indicate that polyphenols or polyphenol-rich foods or beverages, such as green tea and red wine, may limit some of the symptomatology related to *H. pylori* infection.

***Liquorice***

Glycyrrhiza glabra Linn, commonly known as liquorice, is thought to be a useful treatment for peptic ulcers in traditional systems such as Indian, Chinese and Kampo medicine. Several studies have evaluated *in vitro* the antibiotic effect of liquorice and some of its metabolites on *H. pylori*[138,165,166]. Recently, a flavonoid rich extract of G. glabra, GutGard®, was studied to determine its anti-*H. pylori* activity and to elucidate its possible mechanism of action on the bacteria[135]. GutGard® had an MIC = 32-64 μg/mL, and glabridin, the major flavonoid present in the extract, had a more potent activity against *H. pylori*. The mechanism by which GutGard® exerts its antibiotic action could include inhibition of protein synthesis, DNA gyrase or dihydrofolate reductase. However, the adhesion of *H. pylori* to the human gastric adenocarcinoma cell line (AGS) was not significantly affected by GutGard®.

To assess the *in vivo* effect of GutGard on *H. pylori* colonisation, its effect was evaluated in two animal models[167]. After treating infected Mongolian gerbils (once daily 6 times/wk, for 8 wk) with 15, 30 and 60 mg/kg of the extract, a decrease in bacterial load was observed and the gastric mucosa of the animals did not present significant signs of inflammation. These results were more evident at the higher doses, with an 83% decrement on *H. pylori* infection. To test the efficiency of the extract for suppressing *H. pylori* colonisation in the early stages, C57BL/6 mice were infected and treated in the same way as the gerbils but with a 25 mg/kg GutGard dose for 3 wk. The results showed that GutGard treatment significantly reduced the ability of *H. pylori* to colonise the gastric mucosa. In conclusion, GutGard possesses significant *in vivo* anti-*H. pylori* properties and could be a natural resource to control bacterial associated gastric diseases. Clinical trials are required to test its effectiveness.

**HONEY AND PROPOLIS**

Honey is widely known for its antibacterial properties. The attributed antibacterial mechanisms are: an osmotic effect due to its sugar content, its hydrogen peroxide content (produced by the glucose oxidase added by the bee), its acidity, and other substances derived from flowers. Honey has been studied for its anti-*H. pylori* activity *in vitro*[168-171].

Manuka honey comes from one flower source. This honey has been shown to possess bacteriostatic properties against *H. pylori* at a 50 mL/L concentration[172].

Osato *et al*[169], in an effort to determine the role of osmotic effects and hydrogen peroxide in the inhibitory activity of honey *in vitro*, used control solutions containing glucose, fructose, combined glucose/fructose, and catalase. It was concluded that the anti-*H. pylori* activity was not related to the presence of hydrogen peroxide in the honey samples. However, the osmotic effect was shown to be the most important parameter for killing *H. pylori* at concentrations ≥ 150 mL/L.

In an *in vitro* assay, 8 commercial honey brands sold in Muscat, Oman, were tested for anti-*H. pylori* activity by a surface diffusion method and in combination with amoxicillin or clarithromycin. The results demonstrated that all of them had anti-*H. pylori* activity, but no synergy was observed, either with honey and clarithromycin or honey and amoxicillin[170]. These data suggest that a triple regimen with these honeys could help to eliminate the bacteria.

Recently, in an effort to find the active compounds of honey, two studies were performed. In the first one, 3 honeys from different regions of South Africa were tested for anti-*H. pylori* activity. “Pure Honey” presented the maximal inhibitory effect (73.3%) at 750 mL/L, so it was extracted with different organic solvents (n-hexane, diethyl ether, chloroform or ethyl acetate). All extracts demonstrated anti-*H. pylori* activity at concentrations ≥ 10%, but the chloroform extract had the lowest MIC95 value, ranging from 0.156-500 mL/L depending on the strain[173]. This suggests that all extracts could contain compounds that are inhibitory for the bacteria.

In the second work, a bioguided fractionation of a hexane extract from Golden Crest Honey was undertaken. The highest antibacterial activity was exhibited by fraction GCF3, with an MIC = 5 mg/mL[174]. This value is very high compared to commercial antibiotics (for amoxicillin, the MIC = 0.015 to 0.12 μg/mL for ATCC 43504, according to Clinical and Laboratory Standards Institute guidelines).

Finally, in the only clinical trial made with honey, 12 non-diabetic patients, positive for rapid urease and 14C urea breath tests, but with normal gastroscopies, were recruited. Six of them were treated with a tablespoon of Manuka honey four times a day for 2 wk and 6 were treated with honey and omeprazole (20 mg) twice a day for the same period. Four weeks after the completion of treatment, the twelve patients remained positive for *H. pylori* as demonstrated by 14C urea breath tests[175].

Honey has demonstrated anti-*H. pylori* activity, but more research must be conducted using animal models and in clinical trials to assess its efficiency as an alternative or complementary *H. pylori* therapy.

Propolis is a resinous mixture collected by honeybees from various plant sources to reinforce the structural stability of the hive and is thought to be a natural antibiotic. The exact composition of propolis depends on its botanical origin, but it has a high content of phenolic compounds. It has been reported that 30% ethanolic extracts of propolis have considerable *in vitro* inhibitory effect on the growth of several *H. pylori* clinical isolates, as assessed by agar-well diffusion, agar dilution, and disc diffusion methods[176]. A collection of phenolic compounds derived from propolis were evaluated for enzyme inhibition against *H. pylori* peptide deformylase (HpPDF). This enzyme catalyses the removal of formyl groups from the N-terminus of nascent polypeptide chains, which is essential for *H. pylori* survival, and is considered as a promising drug target for anti-*H. pylori* therapy. The results showed that caffeic acid phenethyl ester (CAPE), one of the main medicinal components of propolis, is a competitive inhibitor of HpPDF, with an IC50 = 4.02 μM. Furthermore, absorption spectra and crystal structure characterisation revealed that is different from most well-known PDF inhibitors. CAPE blocks the substrate entrance to the active site, but has neither a chelative interaction with HpPDF, nor does it disturb metal-dependent catalysis[177].

In another *in vitro* study, 25 identified constituents of Brazilian propolis were tested for anti-*H. pylori* activity; 50% of them were active. The labdane type diterpenes and some prenylated phenolic compounds were the most active, with an MIC = 0.13 mg/mL[178]. A clinical trial evaluating a twenty drops/day therapy of a 4% alcoholic preparation of Brazilian propolis in 18 *H. pylori* positive patients showed that the use of green propolis preparation did not succeed in suppressing or eradicating *H. pylori,* as determined by a urea breath test at 3 and 40 d after the end of therapy[179].

**PROBIOTICS**

According to the Food and Agriculture Organization (FAO) and the World Health Organization (WHO)[180], probiotics are “live microorganisms that, when administered in adequate amounts, confer a health benefit on the host”. Interest in probiotic activity against *H. pylori* and its possible inclusion in the eradication therapy has increased because it represents a low-cost, large-scale alternative solution to prevent or decrease *H. pylori* colonisation.

There are numerous studies on probiotics; the scope of these investigations includes evaluations *in vitro* and *in vivo* in animal models, as well as in clinical trials. In fact, the knowledge that has been generated about probiotics and *H. pylori* deserves a separate review. We only report here a brief note about probiotics, highlighting some important findings.

Among probiotics, *Bifidobacterium* is one of the favourite genera used for the prevention of gastrointestinal infection, and it is commonly incorporated in fermented dairy products or food supplements. *Bifidobacterium* exerts an *in vitro* anti-*H. pylori* effect and inhibits adhesion to the mucosa by competition[181]. Several studies have demonstrated a direct relationship between the addition of potential probiotic strains and the *in vitro* inhibition of *H. pylori* growth. *Lactobacillus acidophilus*[182], *Lactobacillus casei* strain Shirota[183], *Bacillus subtilis*[184], and *Weissella confusa*[185], among others, have an antagonistic effect on *H. pylori*.

Several mechanisms have been hypothesised based on *in vitro* studies of host intestinal epithelial or immune cell responses to probiotic strains. Probiotic bacteria can inhibit *H. pylori* by either immunological or non-immunological mechanisms. In addition, distinct probiotic strains may generate divergent immune responses, depending on the host´s immune status[186]. Various probiotics have been shown to exert favourable effects in animal models of *H. pylori* infection. The main outcomes were a prophylactic effect against *H. pylori*, a reduction in bacterial colonisation, and alleviation of *H. pylori*-associated gastric inflammation[187]. The direct role of probiotics in the treatment of gastrointestinal infections is increasingly being documented as an alternative or a complement to antibiotics, with the potential to decrease the use of antibiotics or reduce their side effects. Patel *et al*[188] recently reviewed the *in vivo* clinical trials studying the effect of probiotics on *H. pylori* infection. They reported 12 human studies investigating the efficacy of antibiotic and probiotic combinations, and 16 studies using probiotics alone as an alternative to antibiotics for the infection treatment. The results indicated that in the majority of the cases, an improvement in *H. pylori* gastritis and a reduction in bacterial colonisation were associated with probiotics administration, and in any case, eradication could be completely attained. It also appeared that the use of probiotics was helpful to reduce the adverse effects associated with antibiotics. Long-term intakes of products containing probiotic strains may be beneficial in reducing the risk of *H. pylori*-associated complications.

**FUNGI**

Very potent compounds against *H. pylori* have been isolated from the actinomycete *Pseudonocardia* sp. CL38489 and from the basidiomycete *Phanerochaete velutina* CL6387. In *Pseudonocardia* sp. CL38489, 8 novel quinolones have been obtained with MIC values up to 0.1 ng/mL[189]. Phthalide compounds isolated from *P. velutina* were active against *H. pylori*. One of the most potent was CJ-12,954, with an MIC and a MBC value of 5 ng/mL[190]. Both types of compounds appear to be specific for *H. pylori* because they did not show antimicrobial activity when tested against a panel of other bacteria. Unfortunately, no more research on *H. pylori* and these compounds has been performed.

Recently, the anti-*H. pylori* activity of 14 basidiomycetes used in traditional Chinese medicine was screened by the agar diffusion method. The MIC values of 12 mushroom ethanol extracts were < 3 mg/mL. The best results were obtained for ethyl acetate fractions of *Hericium erinaceus* against 9 clinical isolates of *H. pylori,* with MIC values ranging between 62.5-250 μg/mL, and a MBC value of 200 μg/mL for the strain ATCC 43504[191].

In another finding, the triterpenoid methylantcinate B (MAB) isolated from the medicinal Chinese mushroom Antrodia camphorata displayed anti-*H. pylori* activity and inhibited *H. pylori*-associated inflammation in human gastric epithelial AGS cells by inhibiting adhesion, invasion, (NF)-кB activation, and release of IL-8[192]. The mechanism by which MAB inhibits *H. pylori*-induced inflammation in AGS cells may rely on attenuating CagA function. It is known that CagA interacts with membrane cholesterol provoking inflammation and that MAB competes with this interaction[193]. These reports suggest that it is possible that the pharmaceutical mechanism of secondary metabolites from mushrooms could be directly exerted on the bacteria and by immunomodulation.

Finally, a clinical study was performed using Tremella mesenterica*,* which reportedly has immunomodulatory activities. Fifty-two patients diagnosed with *H. pylori* infection were treated with 2 g/daily of submerged cultivated *T. mesenterica* mycelium for 10 d. The treatment was not effective at eradicating *H. pylori,* as determined by the urea breath test, whether it was administered in the presence or absence of omeprazole. Nevertheless, fewer adverse effects and a significant symptomatic relief were found among treated patients, so the authors suggest that studies should be conducted with a different administration scheme to obtain better results[194].

**MICROORGANISMS**

A promising substance in the fermentation broth of *Streptomyces* sp. strain HC-21 was isolated and identified as indolmycin (TAK-083). This antibiotic inhibits bacterial tryptophanyl-tRNA synthetase, but because it did not have enough activity against other common pathogenic bacteria, its study was abandoned. Nevertheless, indolmycin has a highly selective and potent anti-*H. pylori* activity, with an MIC90 ≤ 0.031 μg/mL, four-fold more potent than the currently available anti-*H. pylori* agents[195]. Additionally, indolmycin completely cleared *H. pylori* in experimentally infected Mongolian gerbils at a dose of 10 mg/kg. Therefore, this antibiotic was considered as a candidate for the treatment of *H. pylori* infection. Nevertheless, Vecchione and Sello[196] found a gene encoding an indolmycin-resistant isoform of tryptophanyl-tRNA synthetase. Overexpression of this gene in an indolmycin-sensitive strain increased the indolmycin MIC 60-fold. The authors speculated that homologs of this antibiotic-resistant gene could be found in other bacteria.

**PEPTIDES**

Antimicrobial peptides are cationic molecules. Although their precise mechanism of action is not yet defined, it is thought that they interact and lyse bacterial membranes. Many organisms produce peptides as part of their defence systems against invasive microorganisms. Amphibian skin glands are rich resources for antimicrobial peptides. Magainin 2[197] and odorranain-HP[198], obtained from Xenopus laevis and Odorrana graham*,* respectively, are antimicrobial peptides with a good anti-*H. pylori* activity. The antibacterial activities of normal and reversed magainin 2 synthetic analogues have been tested against two strains of *H. pylori*. Analogue MSI-78A had the strongest activity against *H. pylori*, with an MIC = 8 and 16 μg/mL for ATCC 43526 and ATCC 43579, respectively. The MIC values were similar to those against *E. coli* and *S. aureus*[197]. Later, the same group reported a new derivative of (±)-6 benzyl-1-(3-carboxylpropyl) indane that is more selective for *H. pylori* (MIC = 32 μg/mL) than for *E. coli* and *S. aureus*[199]. These results showed that with chemical modifications, it could be possible to obtain novel agents with more selective and stronger activity against the bacteria.

In another study, two peptides (S3, S5) obtained by enzymatic hydrolysis of seed proteins from pea (Pisum sativum*)* showed anti-adhesive properties. These peptides have their effect by interacting with *H. pylori* adhesin BabA, one of the outer membrane proteins involved in the adhesion of the bacteria to gastric epithelial cells[136]. This means that bioactive peptides from pea protein could be used in prophylaxis against *H. pylori* infection.

Antimicrobial peptides produced in the gastrointestinal tract are recognised as components of innate immunity against microorganisms. One family of antimicrobial peptides, the defensins, is produced by mucosal epithelial cells and by neutrophils. The cathelicidins comprise another group of mammalian antimicrobial proteins. The single known human cathelicidin is a cationic antibacterial protein of 18 kDa (hCAP18), whose C-terminal 37 amino acid peptide is termed LL-37.

Bajaj-Elliott *et al*[200] evaluated the role of β-defensins in the innate immune response of the gastric epithelium to *H. pylori* infection by measuring mRNA expression and regulation of human β-defensins 1 and 2 (hBD1, hBD2) in AGS and MKN7 cell lines, as well as in biopsies obtained from patients with histologically proven active gastritis (*H. pylori* positive). They found an increased expression of both defensins *in vitro* and *in vivo* in the presence of the bacteria.

A similar study examined the role of LL-37/hCAP18 and found that infection with *H. pylori* up-regulated the production of LL-37/hCAP18 by the gastric epithelium and increased LL-37 concentrations in gastric secretions from infected patients[201]. Unlike the previous study, they did not find a change in hBD1 mRNA levels when chronic mucosal inflammation was observed. They also determined the bactericidal activity of the peptides. LL-37 killed *H. pylori* strains SD4 and SD14 with an EC50 = 1.4 μmol/L in 3 h. On the other hand, hBD1 was capable of killing *H. pylori* SD4 and SD14 at 16 μmol/L, whereas hBD2 was not, and the combination of defensins had synergistic activity to kill bacteria. The difference in the bactericidal activity suggests that other factors besides the cationic nature of the peptides (*e.g.,* differences in the membrane composition or structure of *H. pylori*) are involved in the bioactivity of these antimicrobial peptides.

Although these pilot studies require confirmation, the modulation of human antimicrobial peptide expression may be useful to improve control of the infection. It has been demonstrated that tomato defensins exert a broad antimicrobial spectrum. Based on a representative member of the tomato defensins family, the γ-motif of the peptide was chemically synthesised. It exhibited potent antibacterial activity against Gram-positive (MIC = 40 μg/mL) and Gram-negative bacteria, including *H. pylori* (MIC = 15 μg/mL)[202]. This activity could be due to a strong electrostatic interaction between the cationic nature of the peptide and the anionic bacterial membranes. In addition, the peptide down-regulated the level of proinflammatory cytokines and this effect was comparable with well-known anti-inflammatory drugs. Thus, the peptide displays 2 roles, acting against pathogens and reducing inflammation. These findings represent an alternative source for a new treatment of *H. pylori* illnesses.

**GASTRIC MUCIN**

The progression of diseases such as peptic ulcer or gastric carcinoma is restricted by secreted mucins in the deeper portion of the gastric mucosa. This effect is partly due to the expression of 1,4-N-acetylglucosamine residues attached to the mucin (MUC6). 1,4-N-acetylglucosamine residues inhibit cholesterol α-glucosyltransferase, the enzyme responsible for the first step in the biosynthesis of the unusual *H. pylori* major cell wall component, cholesteryl-α-D-glucopyranoside. This inhibitory activity is thus regarded as a natural antibiotic. Because cholesterol α-glucosyltransferase is unique to *Helicobacter* species[203], it is feasible that by inhibiting the enzyme, *H. pylori* could be eradicated without causing diarrhoea or other symptoms that arise due to adverse effects exerted on the local microbiota of the digestive tract. Moreover, cholesterol α-glucosyltransferase represents an entirely new target for drug development.

**POLYSACCHARIDES**

*H. pylori* is mainly found within the gastric mucus layer and attached to the epithelial cell surface. The carbohydrate structures present on the gastric mucosal surface include secreted and membrane bound mucins. It is known that *H. pylori* interacts with the secreted gel-forming mucin MUC5AC[204],but to establish the infection, adherence to gastric epithelial cells is required. Both interactions (with mucin and cells) occur via lectin-like molecules and specific carbohydrate structure recognition. Therefore, an approach using polysaccharides to block the interaction between *H. pylori* and the host might prevent infection. Under this principle, the likelihood of developing bacterial resistance is unlikely.

Several crude and purified polysaccharides from different sources have been isolated, analysed and examined for their effects against *H. pylori*. Because algae and microalgae possess high concentrations of polysaccharides with several biological activities, their anti-adhesive properties have been explored.Fucoidan, a sulphated polysaccharide mainly found in the edible brown algae Cladosiphon okamuranusTokida, had an inhibitory effect on *H. pylori* attachment to porcine gastric mucin *in vitro*, and reduced *H. pylori*-induced gastritis and the prevalence of infection in Mongolian gerbils[205]. In another *in vitro* study, polysaccharides derived from Spirulina and Chlorella (two commercially available dietary microalgae), prevented *H. pylori* from binding to porcine gastric mucin at low pH without killing the bacteria and AGS cells. Moreover, Spirulina polysaccharides administered 3 times per week for 4 wk before infection with *H. pylori* reduced by > 90% the bacterial density in mice, demonstrating its effectiveness as a carbohydrate-based anti-adhesive treatment[206].

Plant polysaccharides have also been studied for their anti-adhesive properties. An acidic pectin-type polysaccharide from green tea (Camellia sinensis) had a selective inhibitory activity on the adhesion of *H. pylori* to AGS cells, without effects against commensal bacteria. The anti-adhesive activity obtained with *C. sinensis* was better than the that of Artemisia capillaris and Panax ginseng acidic polysaccharides[207]. Liquorice root is another plant that may act against *H. pylori*. An aqueous extract, and a derived polysaccharide fraction, inhibited the adhesion of *H. pylori* to human gastric tissue by interacting with bacterial adhesines and not with binding sites on the epithelial cells[208]. Black currant (*Ribes nigrum L*.) seeds also possess acidic polysaccharides with anti-adhesive properties. High molecular weight galactans are responsible for the activity, by interacting with *H. pylori* adhesins[209].

In general, polysaccharides do not inhibit bacterial growth *in vitro*, but their anti-adhesive properties could be very valuable to prevent or to treat *H. pylori* infection, or even to prevent reinfection after antibiotic eradication therapy. Because the sources of these compounds are easily available, carbohydrate-based anti-adhesive treatment could represent a low cost and safe alternative.

**PHOTOTHERAPY**

*H. pylori* accumulates photoactive porphyrins, making the organism susceptible to inactivation by light. A controlled, prospective pilot trial of eighteen adults with *H. pylori* infection was conducted using a novel light source consisting of laser diodes and diffusing fibres to deliver 408-nm illumination to the whole stomach at escalating total fluences. The results showed an important reduction in bacterial load in the antrum (> 97%), followed by the body (> 95%) and the fundus (> 86%). There was a correlation between logarithmic reduction and initial bacterial load in the antrum. No dose response was observed with increasing illumination times. Nevertheless, the urea breath test results indicated that the bacteria repopulated within a few days after illumination. Although none of the patients achieved complete and sustained eradication of *H. pylori* with this therapy, the results of this study are promising. Intra-gastric ultraviolet light phototherapy is feasible and safe and may represent a novel approach for the eradication of *H. pylori*, particularly in patients who have failed standard antibiotic treatment[210].

**CONCLUSION**

The serious gastric diseases associated with *H. pylori* infection still constitute a public health threat in different parts of the world. Since the difficulties created by standard therapies (*i.e.,* triple, quadruple) to treat *H. pylori*-associated diseases have been recognised, several alternative options that focus on prevention and eradication have been proposed. Because the transmission route is not well defined, prevention can be achieved by blocking the colonisation pathways or through prophylactic vaccination. Antibiotics are the only existing choice for eradication, so efforts should be directed toward finding novel anti-*H. pylori* agents. The current state of research in terms of alternative methods is focused on vaccines, phytotherapy, probiotic-based diets, and nutraceutical agents. The mechanisms and targets used in these alternatives strategies are summarised in Figure 2.

Although large number of studies have been carried out, to date, neither a prophylactic nor a therapeutic vaccine to prevent or clear the infection in humans has been described. Three factors that have delayed the development of an effective vaccine have been identified: (1) type of antigen; (2) need for an adjuvant; and (3) inappropriate host immune response. (1) Of the new developments, the use of multivalent antigens has shown promise. They can target different elements: the enzyme pathways that are vital for bacterial survival and that are common to all strains, the bacterial determinants of pathogenesis, or the factors involved in the induction of the inflammatory immune response; (2) Regarding adjuvants, native or attenuated bacterial toxins are the most commonly used; however, their use in humans has been restricted due to their side effects. To date, the only FDA-approved human adjuvant for parenteral vaccines is aluminium hydroxide. A promising alternative for human use could be to employ live attenuated *Salmonella* bacteria expressing multiple *H. pylori* antigens, since as these bacteria do not require an adjuvant. Some data have shown that the combination of mucosal and systemic immunisation can enhance long-term protection against the *H. pylori* infection; and (3) The failure of the human host response to eliminate the *H. pylori* infection is determined by several factors. First, failure can be explained by poor activation of Toll-like receptors during the innate response. Some bacterial factors, such as VacA, inhibit the adaptive response by blocking antigen presentation and inhibiting T-cell proliferation. Additionally, the induction of Treg cells, which suppress the Th17-cell response, enables the persistence of bacteria.

On the other hand, the few clinical trials that have been carried out have succeeded in terms of neither immunisation nor bacterial clearance. Phase I/II clinical studies are needed before a safe and effective vaccine against *H. pylori* can be obtained. In conclusion, to date, no commercial vaccine is available, and substantial work is required to develop a promising one.

In view of this lack of effective treatment and prevention options, other alternatives, including natural products, such as probiotics and nutraceuticals, have been studied, due to their low cost and relative safety (people have consumed them for a long time). However, the research that has focused primarily on bacterial eradication has had an important limitation, *i.e.,* the lack of correlation between *in vitro* susceptibility and *in vivo* efficacy; only a few studies have also demonstrated *in vivo* efficacy. On the other hand, in those cases where the *in vivo* treatments were successful, either the number of individuals (animals or patients) involved was not statistically significant or only a specific population was analysed. All in all, the results are not completely satisfactory because in most cases *H. pylori* eradication is not achieved. Nevertheless, a reduction in the pathological outcome of the illness and a good resolution of the symptomatology is accomplished. In addition, when alternative treatments are combined with allopathic ones, side effects are reduced and the success rate is increased.

There is an inverse relationship between the low rates of *H. pylori* eradication and the appearance of side effects associated with the current therapies. The most common adverse effects observed in patients treated for *H. pylori* eradication include abdominal discomfort, diarrhoea, nausea, vomiting, headache and weakness; furthermore, these symptoms have an impact on treatment compliance. The inclusion of alternative treatments in the anti-*H. pylori* scheme would enhance both the effectiveness of the therapy and the resolution of the pathology. Moreover, eradication rates would increase, and the development of bacterial resistance could be avoided.

Although some of the treatments based on natural products include instructions for their use, there are no precise indications as to how these products could be integrated into a structured health program. It is clear that further efforts are required to generate more information for the establishment of new options for the treatment of *H. pylori*-related diseases.

A high percentage of *H. pylori*-infected individuals remain asymptomatic, but they are still at risk of developing the pathologies associated with *H. pylori*. However, the eradication of *H. pylori* in the case of asymptomatic patients is not recommended. Alternative therapies have proved to be useful in maintaining low bacterial levels, controlling inflammation, modulating the immune response, inhibiting adherence to the gastric epithelium, and neutralising some of the bacterial virulence factors such as the urease enzyme and the vacuolating toxin. Based on these results, the inclusion of natural products in the diet of asymptomatic patients could reduce the risk, as well as the development, of an unfavourable outcome of the infection.

In conclusion, there are no results indicating that any alternative treatment can truly eradicate *H. pylori*. In contrast, most of the findings have demonstrated that some agents exhibit good anti-inflammatory, immunomodulatory and gastro-protective activities, which as a whole favour the resolution of gastric damage despite the fact that *H. pylori* is not completely eliminated. Therefore, those agents can be used as adjuvants of allopathic anti-*H. pylori* eradication therapy, but not as a monotherapy. As long as a vaccine or new antibiotics remain unavailable, the synergism of allopathic and alternative treatments is most likely the best choice.

Another option would be to combine alternative treatments with no or few adverse effects: using one with high anti-*H. pylori* activity and another offering resolution of gastric damage. Finally, in coming years, the development of new proposals for the eradication of *H. pylori*, such as phototherapy and the use of antimicrobial peptides and mucins, will be followed with great interest.

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**Figure 1 Alternative approaches to the current allopathic therapy against *Helicobacter pylori*.** Different preventive, healing, and adjuvant strategies proposed for anti-*H. pylori* therapy are shown. *H. pylori*:*Helicobacter pylori.*

**Figure 2 Mechanism used in the alternative strategies described here for the treatment of *Helicobacter pylori.*** Three levels are considered as targets for the different alternative treatments. The first involves the host, where vaccines and immune response modulators could act. The second is the stomach, where many mechanisms could have different types of action to restore homeostasis (*i.e.,* gastroprotection, anti-inflammatory). Finally, *H. pylori* is the central target; in this case, alternative treatments are intended to eradicate or prevent the infection, acting upon growth or colonisation factors. In the case of growth inhibitors, many bacterial targets could be used as key enzymes and pathways. *H. pylori*:*Helicobacter pylori.*