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**Overview of the phytomedicine approaches against *Helicobacter pylori***

Vale FF *et al*. Herbal medicine for *H. pylori*

Filipa F Vale, Mónica Oleastro

**Filipa F Vale,** Centro de Estudos do Ambiente e do Mar (CESAM/FCUL), Faculdade de Ciências da Universidade de Lisboa, 1749-016 Campo Grande Lisboa, Portugal

**Mónica Oleastro,** Departamento de Doenças Infeciosas, Instituto Nacional Saúde Dr. Ricardo Jorge, 1649-016 Lisboa, Portugal

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**Correspondence to: Filipa F Vale, PhD,** Centro de Estudos do Ambiente e do Mar (CESAM/FCUL), Faculdade de Ciências da Universidade de Lisboa, Estrada Octávio Pato, 1749-016 Campo Grande Lisboa, Portugal. vale.filipa@gmail.com

**Telephone:** +35-1-214269770 **Fax:** + 35-1-214269800

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**Abstract**

*Helicobacter pylori* (*H. pylori*) successfully colonizes the human stomach of the majority of the human population. This infection always causes chronic gastritis, but may evolve to serious outcomes, such as peptic ulcer, gastric carcinoma or mucosa‑ associated lymphoid tissue lymphoma. *H. pylori* first line therapy recommended by the Maastricht-4 Consensus Report comprises the use of two antibiotics and a proton-pomp inhibitor, but in some regions failure associated with this treatment is already undesirable high. Indeed, treatment failure is one of the major problems associated with *H. pylori* infection and is mainly associated with bacterial antibiotic resistance. In order to counteract this situation, some effort has been allocated during the last years in the investigation of therapeutic alternatives beyond antibiotics. These include vaccines, probiotics, photodynamic inactivation and phage therapy, which are briefly revisited in this review. A particular focus on phytomedicine, also described as herbal therapy and botanical therapy, which consists in the use of plant extracts for medicinal purposes, is specifically addressed, namely considering its history, category of performed studies, tested compounds, active principle and mode of action. The herbs already experienced are highly diverse and usually selected from products with a long history of employment against diseases associated with *H. pylori* infection from each country own folk medicine. The studies demonstrated that many phytomedicine products have an anti-*H. pylori* activity and gastroprotective action. Although the mechanism of action is far from being completely understood, current knowledge correlates the beneficial action of herbs with inhibition of essential *H. pylori* enzymes, modulation of the host immune system and with attenuation of inflammation.

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**Key words:** *Helicobacter pylori*; Alternative treatment; Phytomedicine; Herbal medicine; Phytotherapy; Botanical therapy; Herb medicine; Probiotics; Antibiotic resistance

**Core tip:** Considering the worldwide spread of *Helicobacter pylori* (*H. pylori*) antibiotic resistance, therapeutic alternatives beyond antibiotics have been investigated during the last years, including vaccines, probiotics, photodynamic inactivation, phage therapy and phytomedicine, which are reviewed in the present paper, giving particular attention to phytomedicine. The manuscript offers an extensively referenced text about the effect of herbal medicines on *H. pylori*, describing the first applications of herbal medicine, passing by the category of performed studies, enumerating the tested compounds, identifying the active principle and the mode of action, and concluding with the limitations and promises of this old made new therapy.

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**INTRODUCTION**

*Helicobacter pylori* (*H. pylori*) infects more than half of the human population worldwide. Is the etiologic agent of peptic ulcer disease in 10%-20% of the infected individuals, while 1%-2% are at risk of developing gastric carcinoma or mucosa-associated lymphoid tissue (MALT) lymphoma[1]. On a global scale the burden of disease due to *H. pylori* is huge; elimination of these bacteria would have a major impact on present and future world health.

Currently, the standard first line clarithromycin-based therapy presents undesirable cure rates, and the recent guidelines for *H. pylori* eradication from the Maastricht-4 Consensus Report do not recommend this therapy in regions with high prevalence of clarithromycin resistance[2]. Current treatments are therefore not an effective strategy for worldwide eradication and public health measures improving living conditions may help to reduce the transmission of this infection in selected areas, but will have only a limited effect on infected individuals.

In alternative, infection may be dribbled by the use of new treatment approaches, based on ancient alternative medicines. This paper addresses the problem of *H. pylori* infection, the disease-associated spectrum and the antibiotic resistance against the current treatment regimens, and alternative therapeutic options against resistant strains, with special emphasis on phytotherapy approaches.

***H. PYLORI* BIOLOGY**

The human stomach mucosa is the known ecological niche of *H. pylori*, a pathogenic spiral-shaped, microaerophilic, Gram-negative bacterium, which is unique in its ability to persist and establish a chronic infection. During colonization, propelled by its flagella and resisting to gastric acidity through urease activity, *H. pylori* crosses the gastric mucus layer and adheres to mucins and cells’ surface-receptors of the gastric epithelium. Once here, it delivers its virulence factors into the host cells’ cytoplasm both through the type-IV secretion system and/or by releasing outer membrane vesicles. The cytotoxin-associated gene A (CagA) and the vacuolating cytotoxin (VacA), are among the best studied translocated proteins (reviewed in[3]).

In addition to its set of colonization and virulence factors, *H. pylori* has adapted itself via complex strategies to maintain an inflammation of the gastric epithelium while limiting the extent of the immune response in order to prevent its elimination, through reduced recognition by immune sensors, downregulation of immune cells and escape from immune effectors (reviewed in[4]).

Another unique feature of this bacterium is its tremendous genetic variability, with each strain of these hypermutable bacteria acting as a quasispecies[5,6]. This genome plasticity is mainly due the bacterium natural competence for transformation and for conjugative transfer of genomic islands, resulting in extensive polymorphic genes and in differences in gene content among strains[7]. Moreover, *H. pylori* displays a high frequency of recombination, which in addition to the small size of the recombined fragments results in a mosaic gene structure[8]. Intragenomic recombination has also been reported to occur in *H. pylori*, especially between members of the large family of paralogous outer membrane proteins (OMP) encoding genes or between repetitive sequences, leading to variation even in the absence of mixed colonization[9-11].

Occurrence of point mutations is another mechanism of genetic diversity in *H. pylori*, involved for example in the development of antibiotic resistance[12]. It is likely that the high rate of mutation in *H. pylori* is due to a relative deficiency in DNA repair systems, since many of these systems appear to be absent in this organism[13].

***H. PYLORI* DISEASES AND TREATMENT OPTIONS**

In a similar fashion *H. pylori* is worldwide spread, this bug is implicated in a broad spectrum of diseases, considering its restrict niche. *H. pylori* infection of the human stomach, usually occurring in the childhood, will always elicit an acute immune response. However, if left untreated, infection and inflammation (gastritis) persist. Although often asymptomatic, gastritis may cause dyspeptic symptoms, or it may further progress, causing peptic ulcer disease, distal adenocarcinoma and gastric mucosal lympho‑proliferative diseases such as MALT lymphoma in 10%-15% and 2% of adult patients, respectively[1]. *H. pylori* infection has been linked to diseases localized outside of the stomach as well, with the strongest evidences linking infection with cardiovascular diseases, lung diseases[14], hematologic diseases, such as idiopathic thrombocytopenic purpura[15], neurological diseases[16] and Diabetes Mellitus, although more studies are required to clarify such proposed causal links (reviewed in[17]). In addition, the relationship between bacterial CagA positivity and coronary heart disease has been reportedly emphasized[18,19]. In contrast, the beneficial effects of *H. pylori* concerning allergic diseases[20] and obesity appear clear, while the association with gastroesophageal reflux disease is still controversial[21,22].

*H. pylori* eradication aims mostly to cure functional-associated disease, such as peptic ulcer, but is also a strategy to prevent gastric cancer[23].

In an era in which no anti-*H. pylori* vaccine is yet available, the treatment relies on the use of antimicrobials. Currently, the first-line treatment of *H. pylori* infection consists of two antimicrobials, being the standard combination the use of amoxicillin with clarithromycin or metronidazole, plus a proton-pump inhibitor (PPI). In alternative, levofloxacin can replace clarithromycin in first-line therapy, with apparently higher cure rates[24]. Moreover, an alternative empiric strategy is mandatory when local clarithromycin resistance is higher that 20%[2]. When the triple schemes fail, a quadruple second-line therapy is recommended. The most popular quadruple therapy is still the one containing bismuth, consisting of a combination of bismuth salts, tetracycline and metronidazole, which is now available in 3-in-1 pill, plus a PPI[25,26]. The nonbismuth-based quadruple therapy comprises several combinations of antibiotics, administered in a sequential or concomitant way. An example is the recent combination of levofloxacin, nitazoxanide and doxycycline plus the PPI omeprazole, which showed eradication rates of around 90%[27].

After failure of second-line treatment, treatment should be guided by antimicrobial susceptibility testing whenever possible.

**TREATMENT FAILURE**

Treatment failure is one of the major problems associated with *H. pylori* infection and is mainly associated with bacterial antibiotic resistance but also because bacteria may be in a protective environment like the stomach mucus layer or even inside the epithelial cells[28]. Failure in therapy may also occur because of the lack of patient compliance due to non negligible side effects.

Among the most used antibiotics against *H. pylori*, claritrhomycin is the one that poses higher concerns since resistance to this antibiotic decreases the rate of success of the standard therapy to 20%, against 90% when the strain is susceptible[29]. Currently, *H. pylori* resistance to antibiotics is uneven distributed worldwide, with higher rates reported in developed countries than in developing countries in agreement with prescription frequency. Accordingly, in Europe clarithromycin resistance rate has doubled in a 10 years period, from 9.9% in 1998 to 17.5% in 2008-2009, and it was significantly correlated with the outpatient consumption of long-acting macrolides[30,31]. The consumption varied greatly among European countries and thus the rate of *H. pylori* resistant strains was also highly heterogeneous. Indeed, the rate of resistance strains was found to be significantly higher in Western/Central and Southern Europe (> 20%) than in Northern European countries (< 10%)[31].

Levofloxacin is the other antibiotic for which resistance is also of concern, since success of PPI-amoxicillin-levofloxacin regimen decreases radically if the *H. pylori* strain is resistant to levofloxacin compared with a susceptible strain[32]. Similarly to clartithromycin, the higher the consumption of fluoroquinolones in the community, the higher the *H. pylori* resistance rate to levofloxacin[31].

A high rate of *H. pylori* resistant strains to these two antibiotics has also been reported in other geographies, such as Japan[33], Korea[34], Vietnam[35], China[36] and Iran[37], as well as in South America, such as Mexico[38] and Brazil[39], mostly for levofloxacin, while there are little data concerning US.

Concerning the other antibiotics used to treat *H. pylori* infection, such as amoxicillin, tetracycline and rifampicins, the resistance is still rare, probably because the implicated point mutations have a high biological cost to the bacterium.

As regard to metronidazole, resistance to this antibiotic involves complex mechanisms and although it can contribute to, it is not directly correlated with treatment failure, being overcome in the majority of the situations by changing the associated antibiotics as well as the dosage and length of treatment[40].

**ALTERNATIVE THERAPIES**

In light of the current situation of a worldwide spread of *H. pylori* antibiotic resistance, therapeutic alternatives beyond antibiotics have been investigated during the last years, including vaccines, probiotics, photodynamic inactivation, phage therapy and phytomedicine. This latest further explored below.

Immunization is one of the most cost-effective and successful public health achievements of the 20th century to prevent infectious diseases. Similarly, a prophylactic vaccine against *H. pylori* infection would prevent gastric diseases associated with this infection, in particular gastric cancer. Pioneering work in the early 1990s provided evidence that vaccination against *H. pylori* infection was possible, based on murine models. The feasibility of a preventive vaccination against *H. pylori* infection has since been proven in other animal models, such as dogs, and vaccine candidates against *H. pylori* infection have been tested in humans (reviewed in[41]). The antigens previously used in attempts to develop a vaccine against *H. pylori* infection were mostly secreted proteins (such as urease or VacA) rather than antigens associated with the cell envelope. *H. pylori* possesses an unusual set of OMPs reflecting its adaptation to the unique gastric environment[9]. In this context, effort should be taken in the evaluation of OMPs of *H. pylori* as target antigens for a DNA multivalent vaccine construct.

Probiotics are live organisms or produced substances that are orally administered to promote health[42]. In the case of *H. pylori* infection, their use could be attractive mostly to prevent antibiotic side effects, such as diarrhea, as well as improve eradication rates. Indeed, probiotics can act in several ways in the gut microbiota, for instance by direct antagonism to pathogens through the production of inhibitory substances, competition for adhesion or nutrients, host immune modulation or inhibition of toxins[43,44]. Various probiotics have shown favorable effects in animal models of *H. pylori* infection, by reducing colonization and alleviating the inflammation of the stomach[45,46]. Most of the studies in humans, using combinations of antibiotics and probiotics showed an overall improvement of *H. pylori* gastritis and an increase in *H. pylori* eradication, as well as attenuation of total side effects after administration of probiotics[47,48]. However, no study could demonstrate complete eradication of *H. pylori* infection by probiotic treatment. Finally, long-term intakes of products containing probiotic strains may have a favorable effect on *H. pylori* infection, particularly by reducing the risk of developing gastric inflammation-associated disorders.

More unconventional alternative anti-*H. pylori* treatments have revisited some “old” technologies, such as photodynamic inactivation and phage therapy, both dating long before the golden era of antibiotics. Photodynamic therapy (PDT) uses a photosensitizer and light sources of specific wavelengths to treat malignant tumors or localized infectious diseases. The reactive oxygen species generated by the photodynamic reaction will induce damage to multiple cellular structures, with bactericidal effects[49]. The bactericidal effect of PDT is well known against Gram-positive bacteria but usually inactive against Gram-negative bacteria. However, *H. pylori* displays two characteristics that turn it susceptible to PDA: its natural ability to accumulate photoactive porphyrins and lack of genes to repair phototoxicity-induced DNA damage[50]. Therefore, efficient *H. pylori* killing is possible just by low fluency of broad-spectrum conventional white endoscopic light[51]. Moreover, the localization of the infection in the gastric mucosa facilitates the endoscopic access for light delivery. A recent study showed that the bactericidal activity of PDT against *H. pylori* involved cell membrane injury[52].

Phage therapy consists of the use of lytic bacteriophages to treat infectious diseases[53]. The description of phages in *H. pylori* is still limited, although is a growing field, prompted by the recent description of a temperate phage of *H. pylori*, induced by UV[54], and with the sequences of complete[55-57] and remnant prophages provided by whole genome sequencing of *H. pylori* strains[58]. Nevertheless, there is no information on the nature of the life cycle of the described *H. pylori* phages, and therefore of their potential usage in phage therapy. An alternative would be the use of phage lytic proteins, such as a lysin, which is responsible for the lysis of host bacterial cell wall. However, lysins would have to be modified in order to overcome the limitation of crossing the Gram-negative outer membrane, as it was described for another bacterial species[59].

**PHYTOTHERAPY**

Phytotherapy, also described as herbal therapy or botanical therapy, consists in the use of plants or plant extracts for medicinal purposes[60]. Herbal products include raw or processed parts of plants, such as leaves, stems, flowers, roots, and seeds. According to legislation herbs are considered dietary supplements that can be marketed without previous demonstration of safety and efficacy[61]. Western medicine typically employs an active principal, often of synthetic origin, for therapy proposes. On the opposite, in phytotherapy applications rarely the active principle is either identified or administrated solely. Instead herbs are complex mixtures of organic chemicals. Herbal medicine origins are based on empirical knowledge, and scientific validation of these products is still very limited[60]. This lack of knowledge and evidence indicating the efficacy of herbal medicine makes it suspicious for western physicians and researchers. The risks and benefits of herbal medicine are incomplete, complex, and confusing. There is a need for further controlled clinical trials addressing the potential efficacy of herbal medicine, together with understanding the mode of action and implementation of legislation to maximize their safety and quality[62].

The whole plants and plant extracts used are very diverse and typically belong to the natural flora of a specific world’s area. For this reason the use of search motors can easily miss publications owned to the dispersion of key words selected by authors. Our search was done on Pubmed and ISI web of knowledge, from 1983 to 2013, using the keywords "herbal *H. pylori*", "herbs *H. pylori*", "phytomedicine *H. pylori*", "botanical medicine *H. pylori*", "dietary supplement *H. pylori* not probiotics" and "functional food *H. pylori*" to find any *in vitro* and *in vivo* studies evaluating single or compound herbal preparations in the management of *H. pylori* infection. While the first four keywords correctly identify the use of plants or plant extracts for the eradication of *H. pylori*, the last two terms identify mainly the use of vitamins for eradication or slow of disease progression.

***History: A therapy older than H. pylori discover***

Phytotherapy is as old as human civilization and for that reason telling its early years, that occurred sooner than written history, should always lead to an incomplete report. The ancient use of plants was based on experience, since the cause of illness and the mode of cure was not understood. Until the application of chemistry to medicine in the 16th century, herbs were the source of treatment and prophylaxis. Then the use of herbs gradually diminished being replaced by synthetic drugs. In the last three decades there was another inversion, owing to the increasing of resistance of microorganisms to drugs[63].

Even long before the identification of *H. pylori* in the beginning of the early 1980s[64,65] herbs have been used to deal with diseases that today are known to be associated with *H. pylori* infection[66,67]. This is the case of the use of *Symphitum officinalis* and *Calendula officinalis* to treat a group of patients with duodenal ulcer or gastroduodenitis. In this trial, a group of patients received the herbs and an antiacid, while the control group just received the herbs. The pains disappear in both groups, but earlier in the group that received the antiacid[67]. In fact, the reduction of acid production was central in the therapy of peptic ulcer. Several drugs that act as anticholinergic or antimuscarinic, that reduce gastric acid secretion, were used in an attempt to replace parietal cell vagotomy, in which the resection of the vagus nerve led to the reduction of the production of acid by the parietal cells of the stomach[68], including the use of herbs, such as belladonna (*Atropa belladonna* L. or its variety acuminata Royle ex Lindl)[69].

Presently, three decades after the discovery of *H. pylori*, herbs are still being used for stomach diseases but not all of them have been tested either *in vitro* or *in vivo* for their anti-*H. pylori* activity yet. For instance this is the case of African São Tomé plants, such as *Leonotis nepetifolia* (L.) W. T. Ainton var. *nepetifolia* (gastric indisposition), *Solenostenom monastachyus* (*P*. Beauv.) Briq. subsp. *monostachyus* (stomach pain), *Piper umbellatum* L. (stomach problems), *Bertiera racemosa* (G. Don) K. Shum var. *elephantina* N. Hallé (stomach pain), *Allophyllus grandifolius* (Baker) Radlk (gastric affection), and *Solanum gilo* Raddi (stomach pain)[70].

***Category of performed studies***

The study of phytotherapy products is typically subdivided in two groups, one based on *in vitro* testing using *H. pylori* pure cultures obtained from clinical isolates or reference strains; another based on *in vivo* tests, in which the herbal products are administered to animal models or used in clinical trials involving humans. The first studies are more abundant in the literature namely because of their simplicity, cost, legislation demands and to early years of studding herbal products in a similar way to western medicine products.

Concerning preparation of plants extracts, these are prepared usually by drying and reduce to fine powder which is then dissolved in a solvent, such aqueous ethanol or methanol, sonicated, filtered or centrifuged and the solvent evaporated. The herbal residue is dissolved in dimethyl sulfoxide (DMSO)[71,72]. Different concentration of plant extracts are mixed with a bacterial suspension of *H. pylori* for 1h and plated in standard *H. pylori* medium. The minimum bactericidal concentration corresponds to the test sample at which there was no visible growth[71]. Alternatively, wells can be punched on the plates and the herbal extract introduced; extract embedded paper discs are another option. The inhibitory action is evaluated by determination of the clear zone around each well or disc[72]. For the *in vitro* test, the 96-well micro-titer plates cultured micro-aerobically can also be used[73]. Regarding the negative and the positive control, DMSO may be used as negative control[71,72], while standard antibiotic agents can be applied as positive control[74].

Other *in vitro* assays include the use of gastric epithelial cells, such as AGS cells[75,76] or macrophage cells, like RAW264.7[75,77], or HeLA cells[78]. In this assays eukaryotic cells are treated with herbal extracts followed by infection with *H. pylori* (multiplicity of infection 1:100), for instance during 6h. Then several parameters of infection can be determined to understand if the herbal plants interfere with their concentration. These parameters include nuclear factor ĸB (NF-ĸb) and cytokines, such as interleukin-8, tumor necrosis factor-α, nitric oxide (NO) production and expression levels of inflammation related proteins inducible NO synthase and cyclooxygenase[74]. The effect of the herbal compound on bacterial adhesion and invasion of epithelial cells may also be determined[74,79]. The effect of herbal extracts on cell-adhesion is determined by removing unbound bacteria using a series of washes in phosphate-buffered saline, followed by cell lysis with distilled water. The lysates are then platted on *H. pylori* appropriate medium and colony forming units determined. To verify the effect on the number of viable intracellular bacteria, infected epithelial cells are treated with the membrane impermeable antibiotic gentamicin in order to eliminate external bacteria. Then the same procedure is applied and the colony forming units determined. Appropriate controls without herbal extracts and without gentamicin should be performed, so that these may be considered as total adhesion or invasion[79]. The [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] (MTT) viability assay may be used to measure the cytotoxicity of tested agents[75].

Animal models may also be used to understand the action of herbal medicine on gastric colonization by *H. pylori* and gastric pathology. In those, such as the Mongolian gerbil[80-83], the specific-pathogen-free mice[78,84,85], or the Wistar albino rat[86,87], animals are infected with *H. pylori* strains and treated with different doses of plant extracts. After sacrifice the eradication or decrease in the number of *H. pylori* colonies may be determined. Further histopathological analysis can also be performed in sections of the stomach fixed in formalin and embedded in paraffin.

A summary of clinical trials using different plant extracts is presented in table 1. In these trials a plant extract is tested in opposition to a placebo or, more recently, in addition to conventional triple therapy. In these studies there is no evidence of statistical significant improvement in eradication when herbs are used. Nonetheless these studies are still few, involving a small number of patients and moreover applied as a supplement to antibiotic triple therapy that is known to eradicate *H. pylori* in the great majority of the cases.

From Table 1 only the study of Puram *et al*[88] uses herbal medicine (GutGard) alone against a control group receiving placebo. Although the eradication rate is evident in the group receiving GutGard (56%) against 4% in the placebo group[88], it is still lower to the eradication obtained using triple therapy. Nevertheless, it should be emphasized that the treatment with GutGard was found to be 3.73 times more effective than placebo.

Detail attention should be given to data on clinical trials. For instance in the study of Salem *et al*[89], two recruited patients were positive for *H. pylori* after two consecutive triple therapy courses, but they changed to negative after receiving *N. sativa* treatment in a dose of 3 g/d along with 40 mg omeprazole for four weeks, *H. pylori* status evaluated by stool antigen test.

A systematic review of the use of traditional Chinese medicine against *H. pylori*[90] analyzed 16 randomized clinical trials using several different herbs with proton pump inhibitor or colloidal bismuth subcitrate based triple therapy as controls. The heterogeneity of the studies did not allow a meta-analysis. Overall, conventional triple therapy originated higher eradication rate than Chinese medicine, and the opposite is observed for secondary effects, favoring Chinese medicine.

From the clinical trials analysis it is not possible to completely understand the efficacy of the herbs used, namely because of the poor quality of the trials[90]. Only the extension of the requirements of evidence-based medicine to phytomedicine clinical trials would allow assessing with accuracy the efficacy of the herbal extracts.

***Tested compounds***

There is a high diversity of tested compounds (Table 2) against *H. pylori* using diverse experimental approaches. The era of blind screening of compounds come to an end, the natural resources screening being no exception, so it is rational to use folk medicine plants. The majority of the studies report the use of herbs from China, given that the traditional Chinese medicine is a common practice in this country. Latin American countries come in second place, another continent with a rich history in medicinal plants usage. Usually each country studies its own herbs from folk medicine. So it is understandable the diversity of medicinal plants already tested or currently being tested.

The access to the information is not always an easy task. Effectively, many papers have only the abstract in English language, which difficult the access to information by the global scientific community.

Considering the high diversity of herbal medicines used, finding all papers reporting their use is not straightforward. In fact, the keywords associated with each study not always include general terms, but the name of the species used or its active compound. We suggest that studies analyzing the efficacy of plant extracts include the keywords phytomedicine, phytotherapy, herbal medicine or herb medicine, in order to turn papers' identification easier.

Most studies report the *in vitro* efficacy of the herbal therapy against *H. pylori*, but this isn't always followed by an effective eradication of the bacteriumin animal models and/or clinical trials (Table 2). The clearance of H. pylori from the stomach of infected patients occurs by direct topical activity of the ingested drugs at the gastric mucosal epithelium, and specially by the systemic therapeutic activity, which result from the back secretion and re-entry of the absorbed active principle from the basal to the apical side of the gastric epithelium[91]. The inefficiency of the herbal product in an *in vivo* test after proved efficient in an *in vitro* test against *H. pylori* may be due to the inability of the compound to resist to the acidic medium of the stomach, inability to reach the bacteria trough the mucus layer secreted by the gastric mucosa epithelial cells (the thickness of the mucus layer or its impermeability to herbs at the site of infection), use of insufficient dose or to its inability to reach the bacteria via systemic circulation.

***Active principle and mode of action***

The active ingredient is not always identified; sometimes the group of compounds, but not the exact formula, is identified. The most common active principle identified belong to the group of flavonoids (Table 2). Flavonoids are widely distributed in plants and are recognized as the pigments responsible for the colours of leaves, especially in autumn (yellow). Flavonoids have low molecular weight and are composed of a three-ring structure with various substitutions. The flavonoids are recognized to possess anti-inflammatory, antioxidant, antiallergic, hepatoprotective, antithrombotic, antiviral, and anticarcinogenic activities. The flavonoids are phenolic compounds and, therefore, act as potent metal chelators and free radical scavengers[92]. These properties are again evidenced in the studies present in Table 2.

The mode of action of the herbs can be through the inhibition of essential bacterial enzymes. Some examples are given. Considering *H. pylori*, some flavonoids have also demonstrated inhibitory effects on bacterium growth[78,80,88,93-100], on *H. pylori* DNA gyrase[88,100] and urease[78,93,95,99], and vacuolation activity[99]. H. pylori induces gastric epithelial cell apoptosis via secreted mediators such as the VacA cytotoxin and lipopolysacccharides, damaging epithelial acid-secreting parietal cells[101]. Several flavonoids may inhibit the apoptotic signaling induced by H. pylori VacA toxin[99]. Since urease of *H. pylori* is essential for its colonization, the inhibition of this enzyme explains partly the anti-*H. pylori* activity[83]. Resveratrol, which inhibits *H. pylori in vitro* and is present in grapes and red wine[102], inhibits urease enzyme as well[103]. Resveratrol also targets bacterial ATPases, which protect *H. pylori* from low pH levels by maintaining a proton gradient across membranes[104]. These results suggest that the consumption of grape extracts and wine constituents, in addition to triple therapy, might be useful in the treatment of *H. pylori* infection[105].

The *H. pylori* shikimate dehydrogenase, present in the shikimate pathway is essential for the synthesis of important metabolites, such as aromatic amino acids, folic acid, and ubiquinone. Curcumin is a competitive inhibitor of shikimate dehydrogenase[76]. Besides this action, it was shown that curcumin administration diminish the expression of NF-κB p65 in *H. pylori*-infected mice. Gastric inflammation is associated with increased NF-κB activation, which appears to be attenuated by curcumin[106]. Curcumin also suppresses the expression of, the matrix metalloproteinase-3 and -9 inflammatory molecules associated to the pathogenesis of *H. pylori* infection[76].

Some compounds with a known mechanism of action[107], like propolis (Table 2) are active *in vitro* but a not randomized clinical trial (Table 1) show that propolis was not efficient in eradicating *H. pylori*, which might be related to an insufficient dosage[108]. Briefly, caffeic acid phenethyl ester, the propolis active compound, is a competitive inhibitor of *H. pylori* peptide deformylase that catalyzes the removal of formyl group from the N-terminus of nascent polypeptide chains, which is essential for *H. pylori* survival[107]. Nevertheless, for the majority of the compounds the active component and the molecular mechanism of action (inhibition) against *H. pylori* remain unknown.

***Limitations and promises***

Adverse effects are typically minor than the ones that patients taking antibiotics have. The comparative study of *Nigella sativa* (*N. sativa*) and triple therapy revealed that adverse effects in patients taking *N. sativa* were minor than in patients taking antibiotics[89]. Side effects using cinnamon[109] and GutGard[110] were minor as well. Also, adverse reactions to flavonoids in humans appear to be rare[92].

Even considering that herbs are commonly perceived as natural products and thus safe, there is a need to test the biological active constituents of herbs, side effects caused by contaminants and drug-herb interactions. The safety of herbs could be obtained by requiring manufacturers to register with the FDA (or similar), to proceed with mandatory safety tests similar to those required for drugs, to require registering all health claims, and to assure that product labels provide an accurate list of all ingredients[61].

**CONCLUSION**

There is a huge multiplicity of phytotherapy studies; the majority of them done *in vitro* by exposing *H. pylori* cultures to the herbs. Some of these herbs appear very promising for fighting *H. pylori* antibiotic resistant strains. However, the mode of action, the active principle and the design of accurate clinical trials of promising herbal products should be addressed in future studies. Most of these phytotherapy approaches uses folk medicine products, especially from Asia (China) and Latin America, although other herbs are being tested from countries all over the world. For the herbs for which the mechanism of action is known, the anti-*H. pylori* activity appears to include inhibition of essential bacterial enzymes, while the gastroprotective action appears to be related with the modulation of the host immune system and/or attenuation of inflammation.

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**Table 1 Examples of clinical trials using herbal medicines**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Herb**  | **Study design** | **Sample** | **Experimental intervention** | **Control** | **Outcome** | **Difference between experimental and control group** | **Reference** |
| Garlic oil | Blind non-randomized trial | 20 dyspeptic patients | 275 mg garlic oil 3 times a day for 14 d | Same plus 20 mg omeprazole | Negative for histology and urease test | No | Symptom score (8.7 ± 1.70 *vs* 8.5 ± 1.51) and *H. pylori* density (2.0 ± 0.82 *vs* 2.1 ± 0.74) did not significantly changed | [111] |
| Fresh garlic or jalapeno peppers  | Open non-randomized trial | 12 healthy patients with *H. pylori* | 10 cloves freshgarlic or 6 jalapeno peppers with 3 mealsper test day | Bismuth subsalicylatewith 3 meals pertest day or no intervention | Reduction in urea breath test counts |  | Garlic and jalapeno add no effect (*P* > 0.8), but significant reduction after bismuth (*P* < 0.001) | [112] |
| Cinnamon | Blinding placebo-controlled | 23 patients undergoing gastroscopy | 40 mg cinnamonextract twice a dayfor 4 wk | Placebo | Reduction in urea breath test counts | No | Mean urea breath test reading (23.9 *vs* 25.9) did not significantly changed | [109] |
| Lycopene | Quasi-control trial | 54 patients with *H. pylori* | Metronidazole 500 mg/*bd*, amoxicillin 1g/*bd*, omeprazole 20 mg/*bd*, bismuth 240 mg/*bd*, and lycopene 30 mg/daily | Metronidazole 500 mg/*bd*, Amoxicillin 1 g/*bd*, Omeprazole 20 mg/*bd*, Bismuth 240 mg/*bd* | Slight increased eradication rate with lycopene (no statistical difference) evaluated by urease rapid test | No statistical difference |  | [113] |
| *Nigella sativa* (*N. sativa*) | Randomized trial | 88 dyspeptic patients | Triple therapy (TT: clarithromycin 500 mg twice daily, amoxicillin 1g twice daily, omeprazole 40 mg once daily) and 1, 2 or 3 g *N. sativa* | Clarithromycin 500 mg twice daily, amoxicillin 1g twice daily, omeprazole 40 mg once daily | 2 g/d and TT no statistical difference1 g/d and 3 g/d significantly less effective than TT by stool antigen test | No | Eradication rates with 2 g *N. sativa* and TT with no statistical difference; eradication rate with 1g or 3 g *N. sativa* was significantly less than that with TT (*P* < 0.05) | [89] |
| Green propolis | Non-randomized clinical trial | 18 patients infected with *H. pylori* | 20 drops of alcoholic preparation of Brazilian green propolis 3 times a day for 7 d | No | One patient negative for *H. pylori* 40 d after treatment | Not applicable |  | [108] |
| *Glycyrrhiza glabra* | Randomized double blind placebo controlled trial | 107 patients infected with *H. pylori* | 55 patients – 150 mg of GutGard (root extract of *G. glabra*) once daily for 60 d | 52 patients - placebo once daily for 60 d | 56% of patients receiving GutGard eradicate *H. pylori* *vs* 4% on placebo | Yes | Asignificant interaction effect between group and time (*P* = 0.00) | [88] |
| Chinese patent medicine wenweishu /yangweishu | Randomized, controlled and multicenter trial | 642 patients infected with *H. pylori* | PCM plus wenweishu group (*n* = 196); and PCM plus yangweishu group (*n* = 224) | PCM group (*n* = 222, pantoprazole 40 mg twice a day, clarithromycin 500 mg twice a day, metronidazole 400 mg twice a day, for 7 d) | Higher healing rate in PCM plus wenweishu;Higher rates of symptom relief in PCM plus wenweishu and PCM plus yangweishu; Eradication rate between PMC group and PMC plus wenweishu or PMC plus yangweishu group was not significantly different (*P* = 0.108, 0.532, respectively) | Yes | Healing rate in PCM pluswenweishu groups was significantly higher than the rate in PCM group (*P* = 0.004)Symptom relief rates in PCM plus wenweishu groups and PCM plus yangweishu were significantly higher than the rate in PCM group (both *P* < 0.01) | [110] |

PCM: Pantoprazole, clarithromycin, metronidazole; *H. pylori*: *Helicobacter pylori.*

**Table 2 Herbal medicines tested against *Helicobacter pylori***

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Herb** | **Study type** | **Result** | **Observation** | **Active principle** | **Mechanism of action** | **Reference** |
| Garlic | *In vivo* clinical trial | No improved eradication (consult Table 1) | NA | NA | NA | [111,112] |
| *Pelargonium sidoides* roots (eps) 7630 | *In vitro* using AGS cells and in situ using biopsies | Inhibit *H. pylori* growth and cell adhesion | South African herbal remedy | NA | Anti-adhesive activity | [114,115] |
| Cranberry juice | *In vitro* using immobilized human mucus and erythrocytes | Inhibit *H. pylori* cell adhesion | NA | NA | Anti-adhesive activity(sialic acid-specific adhesion) | [116,117] |
| Oregano and cranberry | *In vitro* agar difusion assay | Inhibition zones on agar plate | NA | Phenolic compounds | Urease inhibition; disruption of energy production inhibiting proline dehydrogenase at the plasma membrane | [93] |
| *Magnolia officinalis* Rehd. Et Wils. (*Magnoliaceae*) and *Cassia obtusifolia* L. (*Leguminosae*)  | Compounds tested against *Jack bean* urease | Inhibit urease | Chinese medicinal herbs | Hydroxamic acids, phosphoramidates, urea derivatives, quinones, and heterocyclic compounds | Inhibit urease | [118] |
| *Camellia sinensis* | *In* *vitro* test against *H. pylori*, urease activity assay | Inhibit urease; reduction of *H. pylori* population | Tea leaves | Polyphenolic compounds and catechin contents (epicatechin,epigallocatechin, epicatechin gallate, pigallocatechingallate) | Inhibit urease | [94] |
| Apple peel polyphenols  | Compounds tested against *Jack bean* urease; *in vitro* test against *H. pylori*; in vitro test using hela cells; in vivo test using C57BL6/J mice | Inhibit urease; prevented vacuolation in hela cells; antiadhesive effect; anti-inflammatory effect | NA | Polyphenols | Inhibit urease; anti-adhesive activity | [78,95] |
| *Calophyllum brasiliense* Camb. (*Clusiaceae*) | *In vitro* disk diffusion; *in vivo* using Wistar rats infected with *H. pylori* | Dose-dependent reduction of ulcerated area; decreased number of urease-positive animals; partial anti-*H. pylori* inhibition | Large tree widely distributed in Latin America known in Brazil as "guanandi" | Mixture of chromanone acids | Inhibit urease; modulation of endogenous antioxidant systems | [86,87] |
| *Mouriri elliptica* Martius (*Melastomataceae*) | *In vivo* Swiss albino mice and male Wistar albino rats animal | Gastric protective action without antisecretory effect; anti-*H. pylori* action | Brazilian fruit-bearing plant of known as “coroa-de-frade” | Acid derivatives, acylglycoflavonoids and condensed tannins | Inhibit NO production by macrophages; stimulating proliferation factors (PCNA), COX-2 | [119] |
| *Hancornia speciosa* Gomez (Mangaba) | *In vivo* Swiss albino mice and male Wistar albino rats animal | Antiulcer activity | Medium-sized tree (3–10 m) from central Brazil, knownas “mangaba”, “mangabeira” or “mangava” | Polymeric proanthocyanidins | Increase pH and decrease acid output of gastric juice, stimulate mucus synthesis and produce antisecretory effect | [120] |
| *Byrsonima fagifolia* Nied. (*Malpighiaceae*)  | *In vivo* Swiss albino mice and male Wistar albino rats animal*In vitro* disc diffusion technique | Gastric protective action; anti-inflammatory effect; anti-*H. pylori* action | Brazilian herb known as "murici" or "murici-do-mato" | Phenolic compounds, flavonoids, gallic acid derivatives | Antioxidant properties | [97] |
| *Alchornea triplinervia*  | *In vivo* mouse model | Antisecretory property; anti-*H. pylori* effect; gastroprotective action | Medicinal plant from Brazil | Flavonoids | Antisecretory action, increase of gastric mucosa prostaglandin E(2) levels | [96] |
| *Amphipterygium adstringens* (Schltdl.) Standl. (*Anacardiaceae*) | In vitro killing assay | Exhibits potent dose-dependent anti-*H. pylori* activity | Mexican folk medicine | Anacardic acids mixture | NA | [121] |
| Extract of Japanese rice also | *In vivo* Mongolian gerbil model | Anti-*H. pylori* activity;anti-inflammatory effect | NA | NA | NA | [122] |
| 16 Mexican plants1 | *In vitro* broth microdilution method | Anti-*H. pylori* activity | Mexican folk medicine | NA | NA | [123] |
| *Bacopa monniera*  | *In vitro* broth microdilution method | Anti-*H. pylori* activity | In Ayurveda,(ancient medicine of India) known as *medhya rasayana or "*Brahmi" | NA | Augmentation of defensive mucosal: mucin secretion, life span of mucosal cells, and gastric antioxidant | [124] |
| Propolis  | *In vitro* test against *H. pylori*Test against Recombinant protein (peptide deformylase) | Anti-*H. pylori* activity | Resinous hive product collected by honeybees | Phenolic compounds, mainly Caffeic acid phenethyl ester (CAPE) | CAPE is a competitive inhibitor of *H. pylori* peptide deformylase | [107,125] |
| Gosyuyu (Wu-Chu-Yu) and Psoralen (extract from *Psoralea corylifolia*) | *In vitro* test against *H. pylori* | Anti-*H. pylori* activity | Chinese herbal medicine, namely “buguzhi” | Alkyl methyl quinolone alkaloids | NA | [126] |
| Amu-ru 7, a  | *In vitro* test against *H. pylori**In vivo* Mongolian gerbil | Anti-*H. pylori* activityDid not cure Mongolian gerbil, but colonization rate diminish | Mongolian folk medicine | Alkyl methyl quinolone alkaloidsRhei rhizome is the most effective component | Inhibited biofilm formation by H. pyloripartial inhibition of urease | [127] |
| *Agrimonia eupatoria*, *Hydrastis canadensis*, *Filipendula ulmaria*, and *Salvia officinalis* | *In vitro* test against *H. pylori* | Anti-*H. pylori* activity | Western herbal medicine | NA | NA | [128] |
| Curcumin diferuloylmethane | *In vitro* test against *H. pylori**In vitro* using AGS cells*In vivo* C57BL/6 mice and Male Sprague-Dawley rats | *In vitro* anti-*H. pylori* activity;effective in eradication of *H. pylori* from infected mice and in restoration of *H. pylori*-induced gastric damage | The major yellow pigment present in the rhizome of turmeric (the perennial herb *Curcuma longa*) | Diferuloylmethane | Suppressing secretion of metalloproteinases 3 and 9 by gastric cellsnoncompetitive inhibitor of *H. pylori* shikimate dehydrogenase, among othersdecrease nuclear factor-kB (NF-κB) p65 | [76,106,129] |
| *Nigella sativa* (*Ranunculaceae*)  | *In vivo* adult patients | Administrated with omeprazole had a eradication rate similar to triple therapy (consult Table 1) | Grows in the Middle East, Eastern Europe, and Eastern and Middle Asia | Thymoquinone, dihydrothymoquinone and terpenes | Disrupting the lipid structure of the cell membrane | [89] |
| Methanol extract of the leaf of *Allium ascalonicum*  | *In vitro* test against *H. pylori* | Anti-*H. pylori* activity | Known as garlic | Alkaloids, cardiac glycosides and saponins | Decrease urease activity | [130] |
| Leaves of *Piper carpunya* Ruiz and Pav. (syn *Piper lenticellosum* C.D.C.) (*Piperaceae*),  | *In vitro* test against *H. pylori**In vitro* against rat peritoneal leukocytes | Anti-inflammatory; anti-ulcer action | Widely used in folk medicine in tropical and subtropical South American | Flavonoids | Inhibition of H+, K+-ATPase activity | [98,99] |
| *Apium graveolens* seeds  | *In vitro* test against *H. pylori* | Anti-*H. pylori* activity | Used in Ayurvedic medicine | Compound with anti-*Helicobacter* activity, an asymmetric phthalide dimer | Induces morphologic changes in *H. pylori* and inhibits protein and DNA synthesis | [131] |
| *Davilla elliptica* and *Davilla nitida*  | *In vivo* Swiss albino mice and male Wistar albino rats animal*In vitro* disc diffusion technique | Anti-*H. pylori* activity;gastric protection action | Brazil folk medicine | Phenolic acid derivatives, acylglycoflavonoids, and condensed tannins | Stimulats moderate levels of H2O2, trigger moderation of the oxidative burst and consequently the immune response | [132] |
| Resveratrol | *In vitro* test against *H. pylori**In vitro* using MKN-45 cells | Inhibit urease,anti-inflammatory and anti-cancer activity cardioprotective and neuroprotective properties | highly abundant in red grapes | Polyphenol | Modulation of interleukin (IL)-6, NF-κB, and mitogen-activated protein kinases; modulatory effects on *H. pylori*-induced IL-8 secretion, reactive oxygen species production, and morphological changes | [102,103,133,134,134-136] |
| *Anisomeles indica* | *In vitro* test against *H. pylori**In vitro* using AGS cells | Anti-*H. pylori* activity;anti-inflammatory properties | From Southeast Asia and Australia | Ovatodiolide | Attenuated the inflammatory response by decreasing NF-κB activation and IL-8 secretion, inhibit lipopolysaccharide-induced inflammation in macrophages (including the secretion of the pro-inflammatory cytokine tumor necrosis factor-α, and nitric oxide (NO) production, and protein expressions of inducible NO synthase and cyclooxygenase-2 (COX-2) | [75] |
| *Glycyrrhiza glabra* | *In vitro* test against *H. pylori**In vitro* using AGS cells*In vivo* adult patients | Anti-*H. pylori* activity;anti-inflammatory properties (consult Table 1) | Legume known as licorice from southern Europe and parts of Asia | Flavenoid, main component glycyrrhetinic acid | Inhibition *H. pylori* of DNA gyrase, protein synthesis and dihydrofolate reductase enzyme;anti-inflammatory activity likely through inhibition of COX and lipoxygenase pathways | [88,100] |
| Cistus laurifolius | *In vitro* test against *H. pylori* | Anti-*H. pylori* activity | Folk medicine in Anatolia | Flavenoid, most active is quercetin 3-methyl ether (isorhamnetin) | NA | [137] |
| Sclerocarya birrea | *In vitro* test against *H. pylori* | Anti-*H. pylori* activity | Medicinal plant used by Zulus, Vhavendas, Xhosas and Sothos of South Africa | Essential oils: terpinen-4-ol (35.83%), pyrrolidine (32.15%), aromadendrene (13.63%) and α-gurjunene (8.77%) | NA | [138] |
| Phyllanthus urinaria | *In vitro* test against *H. pylori**In vitro* using AGS cells | Anti-*H. pylori* activity;anti-inflammatory properties | Tropical and subtropical countries (Taiwan) | Phyllanthin, phyltetralin, trimethyl-3,4-dehydrochebulate, methylgallate, rhamnocitrin, methyl brevifolincarboxylate, β-sitosterol-3-*O*-β-d-glucopyranoside, quercitrin and rutin | Inhibits AGS cells adhesion and invasion; decreases NF-κB activation and IL-8 secretion | [139,140] |
| Artemisia douglasiana Besser (Asteraceae) | *In vitro* test against *H. pylori* | Anti-*H. pylori* activity | Folk medicine in Argentina known as "matico" | Dehydroleucodine, a sesquiterpene lactone of the guiainolide type | Potent inhibitors of the transcription factor NF-κB | [141,142] |
| Geranium wilfordii | *In vitro* test against *H. pylori* | Anti-*H. pylori* activity | Herb from China | Corilagin (1), and 1,2,3,6-tetra-*O*-galloyl-β-*D*-glucose | NA | [143] |
| HZJW, composed of 12 medicinal herbs | *In vitro* test against *H. pylori**In vivo* Balb/c mice | Anti-*H. pylori* activity;reduction of ulcerative lesion; eradicate *H. pylori* in mice | Chinese herbal formula composed of 12 herbs listed in (91) | Protoberberine alkaloids palmatine, coptisine and aporphinoid alkaloid of magnoflorine | NA | [91] |
| Cratoxylum arborescens (Vahl) Blume | *In vitro* test against *H. pylori**In vivo* Balb/c mice | Anti-*H. pylori* activity, anti-inflammatory activity;reduced ulcer area, higher mucus content | Asian herbal medicine | α-mangostin (AM), is a prenylated xanthone | Anti-COX-2 and anti-NO activities | [144] |
|  *Chenopodium ambrosioides* L. And *Adina pilulifera.**Chenopodium ambrosioides* L. | *In vitro* test against *H. pylori* | Anti-*H. pylori* activity | Jinghua WeikangCapsule (Chinese patent drug forpeptic ulcer | NA | NA | [145] |
| Momordica cochinchinensis Springer (Cucurbitaceae) | *In vivo* mice | Gastroprotective effect |  | Momordica saponin I | NA | [146] |
| Sangre de grado (Croton lecheleri and Croton palanostigma) | *In vitro* test against *H. pylori**In vivo* C57BL/6 mice | Anti-*H. pylori* activityNo bactericidal effect in mice | Sangre de grado is a red, viscous latex from the cortex of trees used in Peruvian medicine | NA | Mice with higher hepatic metallothionein levels | [147] |
| Polygonum tinctorium Lour | *In vitro* test against *H. pylori**In vivo* Mongolian gerbil | Anti-*H. pylori* activity;anti-inflammatory effect; decreased bacterial load in Mongolian gerbil | Known as indigo | Tryptanthrin and kaempferol (flavenoid) | Inhibition of nitric oxide production, and the transcription of cyclooxygenase | [80] |
| Artocarpus obtusus Jarret | *In vitro* test against *H. pylori**In vivo* Mongolian gerbil | Anti-*H. pylori* activity;gastroprotective effect;increased mucus content | Endemic species of Borneo known as “pala tupai” | Pyranocycloartobiloxanthone A, a xanthone | Free radical scavenging effect, induction of HSP70, via anti-apoptotic property (down regulate *bax* gene), inhibits Cox-2 enzyme | [148] |
| Punica granatum and Juglans regia | *In vitro* test against *H. pylori* | Anti-*H. pylori* activity | Iranian plants | NA | NA | [149] |

1*Castella tortuosa, Amphipterygium adstringens, Ibervillea sonorae, Pscalium decompositum, Krameria erecta, Selaginella lepidophylla, Pimpinella anisum, Marrubium vulgare, Ambrosia confertiflora, Couterea latiflora, Byophyllum pinnatum, Tecoma stans linnaeus, Kohleria deppena, Jatropha cuneata, Chenopodium ambrosoides,* and *Taxodium macronatum*. NA: Not applicable; *H. pylori*: *Helicobacter pylori.*