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Overview of the phytomedicine approaches against *Helicobacter pylori*

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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-pump 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 revis-

ited 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^[11]. *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 al-

ternative, 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 than 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^[23,26]. 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*, clarithromycin 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 clarithromycin, 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 administered 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*”, “phytotherapy *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 antacid, while the control group just received the herbs. The pains disappear in both groups, but earlier in the group that received the antacid^[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. Aiton var. *nepetifolia* (gastric indisposition), *Solenostemon 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), *Allophylus 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 κB (NF-κB) 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 plated 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,

Table 1 Examples of clinical trials using herbal medicines

Herb	Study design	Sample	Experimental intervention	Control	Outcome	Difference between experimental and control group	Ref.
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 <i>H. pylori</i> 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 <i>H. pylori</i>	10 cloves fresh garlic or 6 jalapeno peppers with 3 meals per test day	Bismuth subsalicylate with 3 meals per	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 cinnamon extract twice a day for 4 wk	test day or no intervention 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 <i>H. pylori</i>	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]
<i>Nigella sativa</i> (<i>N. sativa</i>)	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 <i>N. sativa</i>	Clarithromycin 500 mg twice daily, amoxicillin 1g twice daily, omeprazole 40 mg once daily	2 g/d and TT no statistical difference 1 g/d and 3 g/d significantly less effective than TT by stool antigen test	No Eradication rates with 2 g <i>N. sativa</i> and TT with no statistical difference; eradication rate with 1g or 3 g <i>N. sativa</i> was significantly less than that with TT ($P < 0.05$)	[89]
Green propolis	Non-randomized clinical trial	18 patients infected with <i>H. pylori</i>	20 drops of alcoholic preparation of Brazilian green propolis 3 times a day for 7 d	No	One patient negative for <i>H. pylori</i> 40 d after treatment	Not applicable	[108]
<i>Glycyrrhiza glabra</i>	Randomized double blind placebo controlled trial	107 patients infected with <i>H. pylori</i>	55 patients - 150 mg of GutGard (root extract of <i>G. glabra</i>) once daily for 60 d	52 patients - placebo once daily for 60 d	56% of patients receiving GutGard eradicate <i>H. pylori</i> 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 <i>H. pylori</i>	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 plus wenweishu 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*.

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.

Table 2 Herbal medicines tested against *Helicobacter pylori*

Herb	Study type	Result	Observation	Active principle	Mechanism of action	Ref.
Garlic	<i>In vivo</i> clinical trial	No improved eradication (consult Table 1)	NA	NA	NA	[111,112]
<i>Pelargonium sidoides</i> roots (eps) 7630	<i>In vitro</i> using AGS cells and <i>in situ</i> using biopsies	Inhibit <i>H. pylori</i> growth and cell adhesion	South African herbal remedy	NA	Anti-adhesive activity	[114,115]
Cranberry juice	<i>In vitro</i> using immobilized human mucus and erythrocytes	Inhibit <i>H. pylori</i> cell adhesion	NA	NA	Anti-adhesive activity (sialic acid-specific adhesion)	[116,117]
Oregano and cranberry	<i>In vitro</i> agar diffusion assay	Inhibition zones on agar plate	NA	Phenolic compounds	Urease inhibition; disruption of energy production inhibiting proline dehydrogenase at the plasma membrane	[93]
<i>Magnolia officinalis</i> Rehd. Et Wils. (<i>Magnoliaceae</i>) and <i>Cassia obtusifolia</i> L. (<i>Leguminosae</i>)	Compounds tested against Jack bean urease	Inhibit urease	Chinese medicinal herbs	Hydroxamic acids, phosphoramidates, urea derivatives, quinones, and heterocyclic compounds	Inhibit urease	[118]
<i>Camellia sinensis</i>	<i>In vitro</i> test against <i>H. pylori</i> , urease activity assay	Inhibit urease; reduction of <i>H. pylori</i> population	Tea leaves	Polyphenolic compounds and catechin contents (epicatechin, epigallocatechin, epicatechin gallate, pigallocatechin gallate)	Inhibit urease	[94]
Apple peel polyphenols	Compounds tested against Jack bean urease; <i>in vitro</i> test against <i>H. pylori</i> ; <i>in vitro</i> test using hela cells; <i>in vivo</i> 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]
<i>Calophyllum brasiliense</i> Camb. (<i>Clusiaceae</i>)	<i>In vitro</i> disk diffusion; <i>in vivo</i> using Wistar rats infected with <i>H. pylori</i>	Dose-dependent reduction of ulcerated area; decreased number of urease-positive animals; partial anti- <i>H. pylori</i> 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]
<i>Mouriri elliptica</i> Martius (<i>Melastomataceae</i>)	<i>In vivo</i> Swiss albino mice and male Wistar albino rats animal	Gastric protective action without antisecretory effect; anti- <i>H. pylori</i> 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]
<i>Hancornia speciosa</i> Gomez (Mangaba)	<i>In vivo</i> Swiss albino mice and male Wistar albino rats animal	Antiulcer activity	Medium-sized tree (3–10 m) from central Brazil, known as "mangaba", "mangabeira" or "mangava"	Polymeric proanthocyanidins	Increase pH and decrease acid output of gastric juice, stimulate mucus synthesis and produce antisecretory effect	[120]
<i>Byrsonima fagifolia</i> Nied. (<i>Malpighiaceae</i>)	<i>In vivo</i> Swiss albino mice and male Wistar albino rats animal <i>In vitro</i> disc diffusion technique	Gastric protective action; anti-inflammatory effect; anti- <i>H. pylori</i> action	Brazilian herb known as "murici" or "murici-do-mato"	Phenolic compounds, flavonoids, gallic acid derivatives	Antioxidant properties	[97]
<i>Alchornea triplinervia</i>	<i>In vivo</i> mouse model	Antisecretory property; anti- <i>H. pylori</i> effect; gastroprotective action	Medicinal plant from Brazil	Flavonoids	Antisecretory action, increase of gastric mucosa prostaglandin E(2) levels	[96]
<i>Amphipterygium adstringens</i> (Schltld.) Standl. (<i>Anacardiaceae</i>)	<i>In vitro</i> killing assay	Exhibits potent dose-dependent anti- <i>H. pylori</i> activity	Mexican folk medicine	Anacardic acids mixture	NA	[121]
Extract of Japanese rice also	<i>In vivo</i> Mongolian gerbil model	Anti- <i>H. pylori</i> activity; anti-inflammatory effect	NA	NA	NA	[122]

16 Mexican plants ¹	<i>In vitro</i> broth microdilution method	Anti- <i>H. pylori</i> activity	Mexican folk medicine	NA	NA	[123]
<i>Bacopa monniera</i>	<i>In vitro</i> broth microdilution method	Anti- <i>H. pylori</i> activity	In Ayurveda, (ancient medicine of India) known as <i>medhya rasayana</i> or "brahmi"	NA	Augmentation of defensive mucosal: mucin secretion, life span of mucosal cells, and gastric antioxidant	[124]
Propolis	<i>In vitro</i> test against <i>H. pylori</i> Test against Recombinant protein (peptide deformylase)	Anti- <i>H. pylori</i> activity	Resinous hive product collected by honeybees	Phenolic compounds, mainly Caffeic acid phenethyl ester (CAPE)	CAPE is a competitive inhibitor of <i>H. pylori</i> peptide deformylase	[107,125]
Gosyuyu (Wu-Chu-Yu) and Psoralen (extract from <i>Psoralea corylifolia</i>)	<i>In vitro</i> test against <i>H. pylori</i>	Anti- <i>H. pylori</i> activity	Chinese herbal medicine, namely "buguzhi"	Alkyl methyl quinolone alkaloids	NA	[126]
Amu-ru 7, a	<i>In vitro</i> test against <i>H. pylori</i> <i>In vivo</i> Mongolian gerbil	Anti- <i>H. pylori</i> activity Did not cure Mongolian gerbil, but colonization rate diminish	Mongolian folk medicine	Alkyl methyl quinolone alkaloids <i>Rhei rhizome</i> is the most effective component	Inhibited biofilm formation by <i>H. pylori</i> partial inhibition of urease	[127]
<i>Agrimonia eupatoria</i> , <i>Hydrastis canadensis</i> , <i>Filipendula ulmaria</i> , and <i>Salvia officinalis</i>	<i>In vitro</i> test against <i>H. pylori</i>	Anti- <i>H. pylori</i> activity	Western herbal medicine	NA	NA	[128]
Curcumin diferuloylmethane	<i>In vitro</i> test against <i>H. pylori</i> <i>In vitro</i> using AGS cells <i>In vivo</i> C57BL/6 mice and Male Sprague-Dawley rats	<i>In vitro</i> anti- <i>H. pylori</i> activity; effective in eradication of <i>H. pylori</i> from infected mice and in restoration of <i>H. pylori</i> -induced gastric damage	The major yellow pigment present in the rhizome of turmeric (the perennial herb <i>Curcuma longa</i>)	Diferuloylmethane	Suppressing secretion of metalloproteinases 3 and 9 by gastric cells noncompetitive inhibitor of <i>H. pylori</i> shikimate dehydrogenase, among others decrease nuclear factor-κB (NF-κB) p65	[76,106,129]
<i>Nigella sativa</i> (Ranunculaceae)	<i>In vivo</i> 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 <i>Allium ascalonicum</i>	<i>In vitro</i> test against <i>H. pylori</i>	Anti- <i>H. pylori</i> activity	Known as garlic	Alkaloids, cardiac glycosides and saponins	Decrease urease activity	[130]
Leaves of <i>Piper carpunya</i> Ruiz and Pav. (syn <i>Piper lenticellosum</i> C.D.C.) (Piperaceae)	<i>In vitro</i> test against <i>H. pylori</i> <i>In vitro</i> 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]
<i>Apium graveolens</i> seeds	<i>In vitro</i> test against <i>H. pylori</i>	Anti- <i>H. pylori</i> activity	Used in Ayurvedic medicine	Compound with anti- <i>Helicobacter</i> activity, an asymmetric phthalide dimer	Induces morphologic changes in <i>H. pylori</i> and inhibits protein and DNA synthesis	[131]
<i>Davilla elliptica</i> and <i>Davilla nitida</i>	<i>In vivo</i> Swiss albino mice and male Wistar albino rats animal <i>In vitro</i> disc diffusion technique	Anti- <i>H. pylori</i> activity; gastric protection action	Brazil folk medicine	Phenolic acid derivatives, acylglycoflavonoids, and condensed tannins	Stimulates moderate levels of H ₂ O ₂ , trigger moderation of the oxidative burst and consequently the immune response	[132]
Resveratrol	<i>In vitro</i> test against <i>H. pylori</i> <i>In vitro</i> 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 <i>H. pylori</i> -induced IL-8 secretion, reactive oxygen species production, and morphological changes	[102,103,133, 134-136]

<i>Anisomeles indica</i>	<i>In vitro</i> test against <i>H. pylori</i> <i>In vitro</i> using AGS cells	Anti- <i>H. pylori</i> activity; anti-inflammatory properties	From Southeast Asia and Australia	Ovatodioliide	Attenuated the inflammatory response by decreasing NF- κ B 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]
<i>Glycyrrhiza glabra</i>	<i>In vitro</i> test against <i>H. pylori</i> <i>In vitro</i> using AGS cells <i>In vivo</i> adult patients	Anti- <i>H. pylori</i> activity; anti-inflammatory properties (consult Table 1)	Legume known as licorice from southern Europe and parts of Asia	Flavenoid, main component glycyrrhetic acid	Inhibition <i>H. pylori</i> of DNA gyrase, protein synthesis and dihydrofolate reductase enzyme; anti-inflammatory activity likely through inhibition of COX and lipoxygenase pathways	[88,100]
<i>Cistus laurifolius</i>	<i>In vitro</i> test against <i>H. pylori</i>	Anti- <i>H. pylori</i> activity	Folk medicine in Anatolia	Flavenoid, most active is quercetin 3-methyl ether (isorhamnetin)	NA	[137]
<i>Sclerocarya birrea</i>	<i>In vitro</i> test against <i>H. pylori</i>	Anti- <i>H. pylori</i> 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]
<i>Phyllanthus urinaria</i>	<i>In vitro</i> test against <i>H. pylori</i> <i>In vitro</i> using AGS cells	Anti- <i>H. pylori</i> activity; anti-inflammatory properties	Tropical and subtropical countries (Taiwan)	Phyllanthin, phylltetralin, 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- κ B activation and IL-8 secretion	[139,140]
<i>Artemisia douglasiana Besser (Asteraceae)</i>	<i>In vitro</i> test against <i>H. pylori</i>	Anti- <i>H. pylori</i> activity	Folk medicine in Argentina known as "matico"	Dehydroleucodine, a sesquiterpene lactone of the guainolide type	Potent inhibitors of the transcription factor NF- κ B	[141,142]
<i>Geranium wilfordii</i>	<i>In vitro</i> test against <i>H. pylori</i>	Anti- <i>H. pylori</i> 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	<i>In vitro</i> test against <i>H. pylori</i> <i>In vivo</i> Balb/c mice	Anti- <i>H. pylori</i> activity; reduction of ulcerative lesion; eradicate <i>H. pylori</i> in mice	Chinese herbal formula composed of 12 herbs listed in (91)	Protoberberine alkaloids palmatine, coptisine and aporphinoid alkaloid of magnoflorine	NA	[91]
<i>Cratoxylum arborescens</i> (Vahl) Blume	<i>In vitro</i> test against <i>H. pylori</i> <i>In vivo</i> Balb/c mice	Anti- <i>H. pylori</i> 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]
<i>Chenopodium ambrosioides</i> L. And <i>Adina pilulifera</i> . <i>Chenopodium ambrosioides</i> L.	<i>In vitro</i> test against <i>H. pylori</i>	Anti- <i>H. pylori</i> activity	Jinghua Weikang Capsule (Chinese patent drug for peptic ulcer)	NA	NA	[145]
<i>Momordica cochinchinensis</i> Springer (Cucurbitaceae)	<i>In vivo</i> mice	Gastroprotective effect		Momordica saponin I	NA	[146]

Sangre de grado (Croton lecheleri and Croton palanostigma)	<i>In vitro</i> test against <i>H. pylori</i> <i>In vivo</i> C57BL/6 mice	Anti- <i>H. pylori</i> activity No bactericidal effect in mice	Sangre de grado is a red, viscous latex from the cortex of trees used in Peruvian medicine Known as indigo	NA Tryptanthrin and kaempferol (flavenoid)	Mice with higher hepatic metallothionein levels Inhibition of nitric oxide production, and the transcription of cyclooxygenase	[147] [80]
<i>Polygonum tinctorium</i> Lour	<i>In vitro</i> test against <i>H. pylori</i> <i>In vivo</i> Mongolian gerbil	Anti- <i>H. pylori</i> activity; anti-inflammatory effect; decreased bacterial load in Mongolian gerbil	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]
<i>Artocarpus obtusus</i> Jarret	<i>In vitro</i> test against <i>H. pylori</i> <i>In vivo</i> Mongolian gerbil	Anti- <i>H. pylori</i> activity; gastroprotective effect; increased mucus content	Iranian plants	NA	NA	[149]
<i>Punica granatum</i> and <i>Juglans regia</i>	<i>In vitro</i> test against <i>H. pylori</i>	Anti- <i>H. pylori</i> activity				

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

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 bacterium in 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 ineffi-

ciency 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 lipopolysaccharides, 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 es-

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- κ B p65 in *H. pylori*-infected mice. Gastric inflammation is associated with increased NF- κ B 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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