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TOPIC HIGHLIGHT

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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-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.



**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 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 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 20$^{th}$ 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 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 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,

**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 *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 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 *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 difference 1 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 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 | *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, | 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 | epigallocatechin, epicatechin gallate, pigallocatechin gallate) 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, 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] |
| *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] |

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| 16 Mexican plants[1] | *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* activity Did not cure Mongolian gerbil, but colonization rate diminish | Mongolian folk medicine | Alkyl methyl quinolone alkaloids *Rhei rhizome* is the most effective component | Inhibited biofilm formation by *H. pylori* partial 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 cells noncompetitive inhibitor of *H. pylori* shikimate dehydrogenase, among others decrease 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 $H_2O_2$, 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, 134-136] |

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| *Anisomeles indica* | *In vitro* test against *H. pylori*<br>*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*<br>*In vitro* using AGS cells<br>*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*<br>*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*<br>*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*<br>*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 Weikang Capsule (Chinese patent drug for peptic ulcer | NA | NA | [145] |
| *Momordica cochinchinensis* Springer (*Cucurbitaceae*) | *In vivo* mice | Gastroprotective effect | | Momordica saponin I | NA | [146] |

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| Sangre de grado (*Croton lecheleri* and *Croton palanostigma*) | *In vitro* test against *H. pylori* *In vivo* C57BL/6 mice | Anti-*H. pylori* activity No 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*.

### 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 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 es-

sential 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.

## REFERENCES


1 **Basso D**, Plebani M, Kusters JG. Pathogenesis of Helicobacter pylori infection. *Helicobacter* 2010; **15** Suppl 1: 14-20 [PMID: 21054648 DOI: 10.1111/j.1523-5378.2010.00781.x]

2 **Malfertheiner P**, Megraud F, O'Morain CA, Atherton J, Axon AT, Bazzoli F, Gensini GF, Gisbert JP, Graham DY, Rokkas T, El-Omar EM, Kuipers EJ. Management of Helicobacter pylori infection--the Maastricht IV/ Florence Consensus Report. *Gut* 2012; **61**: 646-664 [PMID: 22491499 DOI: 10.1136/gutjnl-2012-302084]

3 **Salama NR**, Hartung ML, Müller A. Life in the human stomach: persistence strategies of the bacterial pathogen Helicobacter pylori. *Nat Rev Microbiol* 2013; **11**: 385-399 [PMID: 23652324 DOI: 10.1038/nrmicro3016]

4 **Müller A**, Oertli M, Arnold IC. H. pylori exploits and manipulates innate and adaptive immune cell signaling pathways to establish persistent infection. *Cell Commun Signal* 2011; **9**: 25 [PMID: 22044597 DOI: 10.1186/1478-811X-9-25]

5 **Israel DA**, Salama N, Krishna U, Rieger UM, Atherton JC, Falkow S, Peek RM. Helicobacter pylori genetic diversity within the gastric niche of a single human host. *Proc Natl Acad Sci USA* 2001; **98**: 14625-14630 [PMID: 11724955 DOI: 10.1073/pnas.251551698]

6 **Salama NR**, Gonzalez-Valencia G, Deatherage B, Aviles-Jimenez F, Atherton JC, Graham DY, Torres J. Genetic analysis of Helicobacter pylori strain populations colonizing the stomach at different times postinfection. *J Bacteriol* 2007; **189**: 3834-3845 [PMID: 17337568 DOI: 10.1128/JB.01696-06]

7 **Dorer MS**, Cohen IE, Sessler TH, Fero J, Salama NR. Natural competence promotes Helicobacter pylori chronic infection. *Infect Immun* 2013; **81**: 209-215 [PMID: 23115044 DOI: 10.1128/IAI.01042-12]

8 **Falush D**, Kraft C, Taylor NS, Correa P, Fox JG, Achtman M, Suerbaum S. Recombination and mutation during long-term gastric colonization by Helicobacter pylori: estimates of clock rates, recombination size, and minimal age. *Proc Natl Acad Sci USA* 2001; **98**: 15056-15061 [PMID: 11742075 DOI: 10.1073/pnas.251396098]

9 **Alm RA**, Bina J, Andrews BM, Doig P, Hancock RE, Trust TJ. Comparative genomics of Helicobacter pylori: analysis of the outer membrane protein families. *Infect Immun* 2000; **68**: 4155-4168 [PMID: 10858232 DOI: 10.1128/IAI.68.7.4155-4168.2000]

10 **Pride DT**, Blaser MJ. Concerted evolution between duplicated genetic elements in Helicobacter pylori. *J Mol Biol* 2002; **316**: 629-642 [PMID: 11866522 DOI: 10.1006/jmbi.2001.5311]

11 **Solnick JV**, Hansen LM, Salama NR, Boonjakuakul JK, Syvanen M. Modification of Helicobacter pylori outer membrane protein expression during experimental infection of rhesus macaques. *Proc Natl Acad Sci USA* 2004; **101**: 2106-2111 [PMID: 14762173 DOI: 10.1073/pnas.0308573100]

12 **Mégraud F**. Helicobacter pylori resistance to antibiotics: prevalence, mechanism, detection. What's new? *Can J Gastroenterol* 2003; **17** Suppl B: 49B-52B [PMID: 12845352]
13 **Kraft C**, Suerbaum S. Mutation and recombination in Helicobacter pylori: mechanisms and role in generating strain diversity. *Int J Med Microbiol* 2005; **295**: 299-305 [PMID: 16173496 DOI: 10.1016/j.ijmm.2005.06.002]
14 **Deng B**, Li Y, Zhang Y, Bai L, Yang P. Helicobacter pylori infection and lung cancer: a review of an emerging hypothesis. *Carcinogenesis* 2013; **34**: 1189-1195 [PMID: 23568955 DOI: 10.1093/carcin/bgt114]
15 **Papagiannakis P**, Michalopoulos C, Papalexi F, Dalampoura D, Diamantidis MD. The role of Helicobacter pylori infection in hematological disorders. *Eur J Intern Med* 2013; **24**: 685-690 [PMID: 23523153 DOI: 10.1016/j.ejim.2013.02.011]
16 **Roubaud Baudron C**, Letenneur L, Langlais A, Buissonnière A, Mégraud F, Dartigues JF, Salles N. Does Helicobacter pylori infection increase incidence of dementia? The Personnes Agées QUID Study. *J Am Geriatr Soc* 2013; **61**: 74-78 [PMID: 23252507 DOI: 10.1111/jgs.12065]
17 **Figura N**, Franceschi F, Santucci A, Bernardini G, Gasbarrini G, Gasbarrini A. Extragastric manifestations of Helicobacter pylori infection. *Helicobacter* 2010; **15** Suppl 1: 60-68 [PMID: 21054655 DOI: 10.1111/j.1523-5378.2010.00778.x]
18 **Niccoli G**, Franceschi F, Cosentino N, Giupponi B, De Marco G, Merra G, Conte M, Montone RA, Ferrante G, Bacà M, Gasbarrini A, Silveri NG, Crea F. Coronary atherosclerotic burden in patients with infection by CagA-positive strains of Helicobacter pylori. *Coron Artery Dis* 2010; **21**: 217-221 [PMID: 20389238 DOI: 10.1097/MCA.0b013e3283399f36]
19 **De Bastiani R**, Gabrielli M, Ubaldi E, Benedetto E, Sanna G, Cottone C, Candelli M, Zocco MA, Saulnier N, Santoliquido A, Papaleo P, Gasbarrini G, Gasbarrini A. High prevalence of Cag-A positive H. pylori strains in ischemic stroke: a primary care multicenter study. *Helicobacter* 2008; **13**: 274-277 [PMID: 18665936 DOI: 10.1111/j.1523-5378.2008.00610.x]
20 **Oertli M**, Müller A. Helicobacter pylori targets dendritic cells to induce immune tolerance, promote persistence and confer protection against allergic asthma. *Gut Microbes* 2012; **3**: 566-571 [PMID: 22895083 DOI: 10.4161/gmic.21750]
21 **Banić M**, Franceschi F, Babić Z, Gasbarrini A. Extragastric manifestations of Helicobacter pylori infection. *Helicobacter* 2012; **17** Suppl 1: 49-55 [PMID: 22958156 DOI: 10.1111/j.1523-5378.2012.00983.x]
22 **O'Connor A**, O'Moráin C. Helicobacter pylori infection in Europe: current perspectives. *Expert Rev Gastroenterol Hepatol* 2013; **7**: 541-548 [PMID: 23985003 DOI: 10.1586/17474124.2013.824707]
23 **Malfertheiner P**, Sipponen P, Naumann M, Moayyedi P, Mégraud F, Xiao SD, Sugano K, Nyrén O. Helicobacter pylori eradication has the potential to prevent gastric cancer: a state-of-the-art critique. *Am J Gastroenterol* 2005; **100**: 2100-2115 [PMID: 16128957 DOI: 10.1111/j.1572-0241.2005.41688.x]
24 **Molina-Infante J**, Perez-Gallardo B, Fernandez-Bermejo M, Hernandez-Alonso M, Vinagre G, Dueñas C, Mateos-Rodriguez JM, Gonzalez-Garcia G, Abadia EG, Gisbert JP. Clinical trial: clarithromycin vs. levofloxacin in first-line triple and sequential regimens for Helicobacter pylori eradication. *Aliment Pharmacol Ther* 2010; **31**: 1077-1084 [PMID: 20180787 DOI: 10.1111/j.1365-2036.2010.04274.x]
25 **Mégraud F**. The challenge of Helicobacter pylori resistance to antibiotics: the comeback of bismuth-based quadruple therapy. *Therap Adv Gastroenterol* 2012; **5**: 103-109 [PMID: 22423259 DOI: 10.1177/1756283X11432492]
26 **Gisbert JP**. Helicobacter pylori eradication: A new, single-capsule bismuth-containing quadruple therapy. *Nat Rev Gastroenterol Hepatol* 2011; **8**: 307-309 [PMID: 21643037 DOI: 10.1038/nrgastro.2011.84]
27 **Basu PP**, Rayapudi K, Pacana T, Shah NJ, Krishnaswamy N, Flynn M. A randomized study comparing levofloxacin, omeprazole, nitazoxanide, and doxycycline versus triple therapy for the eradication of Helicobacter pylori. *Am J Gastroenterol* 2011; **106**: 1970-1975 [PMID: 21989146 DOI: 10.1038/ajg.2011.306]
28 **Dubois A**, Borén T. Helicobacter pylori is invasive and it may be a facultative intracellular organism. *Cell Microbiol* 2007; **9**: 1108-1116 [PMID: 17388791 DOI: 10.1111/j.1462-5822.2007.00921.x]
29 **Mégraud F**. H pylori antibiotic resistance: prevalence, importance, and advances in testing. *Gut* 2004; **53**: 1374-1384 [PMID: 15306603 DOI: 10.1136/gut.2003.022111]
30 **Glupczynski Y**, Mégraud F, Lopez-Brea M, Andersen LP. European multicentre survey of in vitro antimicrobial resistance in Helicobacter pylori. *Eur J Clin Microbiol Infect Dis* 2001; **20**: 820-823 [PMID: 11783701 DOI: 10.1007/s100960100611]
31 **Megraud F**, Coenen S, Versporten A, Kist M, Lopez-Brea M, Hirschl AM, Andersen LP, Goossens H, Glupczynski Y. Helicobacter pylori resistance to antibiotics in Europe and its relationship to antibiotic consumption. *Gut* 2013; **62**: 34-42 [PMID: 22580412 DOI: 10.1136/gutjnl-2012-302254]
32 **Perna F**, Zullo A, Ricci C, Hassan C, Morini S, Vaira D. Levofloxacin-based triple therapy for Helicobacter pylori retreatment: role of bacterial resistance. *Dig Liver Dis* 2007; **39**: 1001-1005 [PMID: 17889627 DOI: 10.1016/j.dld.2007.06.016]
33 **Kobayashi I**, Murakami K, Kato M, Kato S, Azuma T, Takahashi S, Uemura N, Katsuyama T, Fukuda Y, Haruma K, Nasu M, Fujioka T. Changing antimicrobial susceptibility epidemiology of Helicobacter pylori strains in Japan between 2002 and 2005. *J Clin Microbiol* 2007; **45**: 4006-4010 [PMID: 17942652 DOI: 10.1128/JCM.00740-07]
34 **Lee JW**, Kim N, Kim JM, Nam RH, Chang H, Kim JY, Shin CM, Park YS, Lee DH, Jung HC. Prevalence of primary and secondary antimicrobial resistance of Helicobacter pylori in Korea from 2003 through 2012. *Helicobacter* 2013; **18**: 206-214 [PMID: 23241101 DOI: 10.1111/hel.12031]
35 **Binh TT**, Shiota S, Nguyen LT, Ho DD, Hoang HH, Ta L, Trinh DT, Fujioka T, Yamaoka Y. The incidence of primary antibiotic resistance of Helicobacter pylori in Vietnam. *J Clin Gastroenterol* 2013; **47**: 233-238 [PMID: 23090037 DOI: 10.1097/MCG.0b013e3182676e2b]
36 **Lu H**, Zhang W, Graham DY. Bismuth-containing quadruple therapy for Helicobacter pylori: lessons from China. *Eur J Gastroenterol Hepatol* 2013; **25**: 1134-1140 [PMID: 23778309 DOI: 10.1097/MEG.0b013e3283633b57]
37 **Shokrzadeh L**, Jafari F, Dabiri H, Baghaei K, Zojaji H, Alizadeh AH, Aslani MM, Zali MR. Antibiotic susceptibility profile of Helicobacter pylori isolated from the dyspepsia patients in Tehran, Iran. *Saudi J Gastroenterol* 2011; **17**: 261-264 [PMID: 21727733 DOI: 10.4103/1319-3767.82581]
38 **Ayala G**, Galván-Portillo M, Chihu L, Fierros G, Sánchez A, Carrillo B, Román A, López-Carrillo L, Silva-Sánchez J. Resistance to antibiotics and characterization of Helicobacter pylori strains isolated from antrum and body from adults in Mexico. *Microb Drug Resist* 2011; **17**: 149-155 [PMID: 21303219 DOI: 10.1089/mdr.2010.0154]
39 **Eisig JN**, Silva FM, Barbuti RC, Navarro-Rodriguez T, Moraes-Filho JP, Pedrazzoli Jr J. Helicobacter pylori antibiotic resistance in Brazil: clarithromycin is still a good option. *Arq Gastroenterol* 2011; **48**: 261-264 [PMID: 22147131 DOI: 10.1590/S0004-28032011000400008]
40 **Fischbach L**, Evans EL. Meta-analysis: the effect of antibiotic resistance status on the efficacy of triple and quadruple first-line therapies for Helicobacter pylori. *Aliment Pharmacol Ther* 2007; **26**: 343-357 [PMID: 17635369 DOI: 10.1111/j.1365-2036.2007.03386.x]
41 **Czinn SJ**, Blanchard T. Vaccinating against Helicobacter pylori infection. *Nat Rev Gastroenterol Hepatol* 2011; **8**: 133-140 [PMID: 21304478 DOI: 10.1038/nrgastro.2011.1]

42 **Food and Agriculture Organization**, World Health Organization. Guidelines for the evaluation of probiotics in food. Report of a joint FAO/WHO working group on drafting guidelines for the evaluation of probiotics in food. London, Ontario, Canada: World Health Organization; 2000
43 **Jonkers D**, Stockbrügger R. Review article: Probiotics in gastrointestinal and liver diseases. *Aliment Pharmacol Ther* 2007; **26** Suppl 2: 133-148 [PMID: 18081657 DOI: 10.1111/j.1365-2036.2007.03480.x]
44 **Lesbros-Pantoflickova D**, Corthésy-Theulaz I, Blum AL. Helicobacter pylori and probiotics. *J Nutr* 2007; **137**: 812S-818S [PMID: 17311980]
45 **Johnson-Henry KC**, Mitchell DJ, Avitzur Y, Galindo-Mata E, Jones NL, Sherman PM. Probiotics reduce bacterial colonization and gastric inflammation in H. pylori-infected mice. *Dig Dis Sci* 2004; **49**: 1095-1102 [PMID: 15387328 DOI: 10.1023/B:DDAS.0000037794.02040.c2]
46 **Sgouras DN**, Panayotopoulou EG, Martinez-Gonzalez B, Petraki K, Michopoulos S, Mentis A. Lactobacillus johnsonii La1 attenuates Helicobacter pylori-associated gastritis and reduces levels of proinflammatory chemokines in C57BL/6 mice. *Clin Diagn Lab Immunol* 2005; **12**: 1378-1386 [PMID: 16339060]
47 **Wang ZH**, Gao QY, Fang JY. Meta-analysis of the efficacy and safety of Lactobacillus-containing and Bifidobacterium-containing probiotic compound preparation in Helicobacter pylori eradication therapy. *J Clin Gastroenterol* 2013; **47**: 25-32 [PMID: 23090045 DOI: 10.1097/MCG.0b013e318266f6cf]
48 **Szajewska H**, Horvath A, Piwowarczyk A. Meta-analysis: the effects of Saccharomyces boulardii supplementation on Helicobacter pylori eradication rates and side effects during treatment. *Aliment Pharmacol Ther* 2010; **32**: 1069-1079 [PMID: 21039671 DOI: 10.1111/j.1365-2036.2010.04457.x]
49 **Wainwright M**. Photodynamic antimicrobial chemotherapy (PACT). *J Antimicrob Chemother* 1998; **42**: 13-28 [PMID: 9700525 DOI: 10.1093/jac/42.1.13]
50 **Hamblin MR**, Viveiros J, Yang C, Ahmadi A, Ganz RA, Tolkoff MJ. Helicobacter pylori accumulates photoactive porphyrins and is killed by visible light. *Antimicrob Agents Chemother* 2005; **49**: 2822-2827 [PMID: 15980355 DOI: 10.1128/AAC.49.7.2822-2827.2005]
51 **Choi SS**, Lee HK, Chae HS. In vitro photodynamic antimicrobial activity of methylene blue and endoscopic white light against Helicobacter pylori 26695. *J Photochem Photobiol B* 2010; **101**: 206-209 [PMID: 20692848]
52 **Choi S**, Lee H, Chae H. Comparison of in vitro photodynamic antimicrobial activity of protoporphyrin IX between endoscopic white light and newly developed narrowband endoscopic light against Helicobacter pylori 26695. *J Photochem Photobiol B* 2012; **117**: 55-60 [PMID: 23079538 DOI: 10.1016/j.jphotobiol.2012.08.015]
53 **Hanlon GW**. Bacteriophages: an appraisal of their role in the treatment of bacterial infections. *Int J Antimicrob Agents* 2007; **30**: 118-128 [PMID: 17566713 DOI: 10.1016/j.ijantimicag.2007.04.006]
54 **Vale FF**, Alves Matos AP, Carvalho P, Vitor JM. Helicobacter pylori phage screening. *Microsc Microanal* 2008; **14** suppl 3: 150-151 [DOI: 10.1017/S1431927608089721]
55 **Lehours P**, Vale FF, Bjursell MK, Melefors O, Advani R, Glavas S, Guegueniat J, Gontier E, Lacomme S, Alves Matos A, Menard A, Mégraud F, Engstrand L, Andersson AF. Genome sequencing reveals a phage in Helicobacter pylori. *MBio* 2011; **2**: pii: e00239-11 [PMID: 22086490 DOI: 10.1128/mBio.00239-11]
56 **Luo CH**, Chiou PY, Yang CY, Lin NT. Genome, integration, and transduction of a novel temperate phage of Helicobacter pylori. *J Virol* 2012; **86**: 8781-8792 [PMID: 22696647 DOI: 10.1128/JVI.00446-12]
57 **Uchiyama J**, Takeuchi H, Kato S, Takemura-Uchiyama I, Ujihara T, Daibata M, Matsuzaki S. Complete genome sequences of two Helicobacter pylori bacteriophages isolated from Japanese patients. *J Virol* 2012; **86**: 11400-11401 [PMID: 22997420 DOI: 10.1128/JVI.01767-12]
58 **Thiberge JM**, Boursaux-Eude C, Lehours P, Dillies MA, Creno S, Coppée JY, Rouy Z, Lajus A, Ma L, Burucoa C, Ruskoné-Foumestraux A, Courillon-Mallet A, De Reuse H, Boneca IG, Lamarque D, Mégraud F, Delchier JC, Médigue C, Bouchier C, Labigne A, Raymond J. From array-based hybridization of Helicobacter pylori isolates to the complete genome sequence of an isolate associated with MALT lymphoma. *BMC Genomics* 2010; **11**: 368 [PMID: 20537153 DOI: 10.1186/1471-2164-11-368]
59 **Lukacik P**, Barnard TJ, Keller PW, Chaturvedi KS, Seddiki N, Fairman JW, Noinaj N, Kirby TL, Henderson JP, Steven AC, Hinnebusch BJ, Buchanan SK. Structural engineering of a phage lysin that targets gram-negative pathogens. *Proc Natl Acad Sci USA* 2012; **109**: 9857-9862 [PMID: 22679291 DOI: 10.1073/pnas.1203472109]
60 **Vítor JM**, Vale FF. Alternative therapies for Helicobacter pylori: probiotics and phytomedicine. *FEMS Immunol Med Microbiol* 2011; **63**: 153-164 [PMID: 22077218 DOI: 10.1111/j.1574-695X.2011.00865.x]
61 **Bent S**. Herbal medicine in the United States: review of efficacy, safety, and regulation: grand rounds at University of California, San Francisco Medical Center. *J Gen Intern Med* 2008; **23**: 854-859 [PMID: 18415652 DOI: 10.1007/s11606-008-0632-y]
62 **Ke F**, Yadav PK, Ju LZ. Herbal medicine in the treatment of ulcerative colitis. *Saudi J Gastroenterol* 2012; **18**: 3-10 [PMID: 22249085 DOI: 10.4103/1319-3767.91726]
63 **Petrovska BB**. Historical review of medicinal plants' usage. *Pharmacogn Rev* 2012; **6**: 1-5 [PMID: 22654398 DOI: 10.4103/0973-7847.95849]
64 Unidentified curved bacilli on gastric epithelium in active chronic gastritis. *Lancet* 1983; **1**: 1273-1275 [PMID: 6134060]
65 **Marshall BJ**, Warren JR. Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration. *Lancet* 1984; **1**: 1311-1315 [PMID: 6145023 DOI: 10.1016/S0140-6736(84)91816-6]
66 **Chin EP**, Chiang my, wang fy, wang kw. the effect of chianchung-tang, a chinese herb recipe, upon shay rat ulceration. *Yaoxue Xuebao* 1965; **12**: 440-445 [PMID: 14342704]
67 **Chakŭrski I**, Matev M, Stefanov G, Koĭchev A, Angelova I. Treanntment of duodenal ulcers and gastroduodenitis with a herbal combination of Symphitum officinalis and Calendula officinalis with and without antacids. *Vutr Boles* 1981; **20**: 44-47 [PMID: 7336704]
68 **Stockbrügger RW**. Antimuscarinic drugs. *Methods Find Exp Clin Pharmacol* 1989; **11** Suppl 1: 79-86 [PMID: 2657292]
69 **Sodeman WA**, Augur NA, Pollard HM. Physiology and pharmacology of belladonna therapy in acid-peptic disease. *Med Clin North Am* 1969; **53**: 1379-1388 [PMID: 4900719]
70 **Madureira MC**, Paiva JM, Fernandes AF, Gonçalves A, Catalão C, Fernandes C. Estudo etnofarmacológico de plantas medicinais de S. Tomé e Príncipe. São Tomé: Ministerío de Saúde da RDSTP, 2008
71 **Zaidi SF**, Yamada K, Kadowaki M, Usmanghani K, Sugiyama T. Bactericidal activity of medicinal plants, employed for the treatment of gastrointestinal ailments, against Helicobacter pylori. *J Ethnopharmacol* 2009; **121**: 286-291 [PMID: 19041711 DOI: 10.1016/j.jep.2008.11.001]
72 **Wang YC**, Huang TL. Screening of anti-Helicobacter pylori herbs deriving from Taiwanese folk medicinal plants. *FEMS Immunol Med Microbiol* 2005; **43**: 295-300 [PMID: 15681161 DOI: 10.1016/j.femsim.2004.09.008]
73 **Stamatis G**, Kyriazopoulos P, Golegou S, Basayiannis A, Skaltsas S, Skaltsa H. In vitro anti-Helicobacter pylori activity of Greek herbal medicines. *J Ethnopharmacol* 2003; **88**: 175-179 [PMID: 12963139 DOI: 10.1016/S0378-8741(03)00217-4]
74 **Lai CH**, Rao YK, Fang SH, Sing YT, Tzeng YM. Identification

of 3′,4′,5′-trimethoxychalcone analogues as potent inhibitors of Helicobacter pylori-induced inflammation in human gastric epithelial cells. *Bioorg Med Chem Lett* 2010; **20**: 5462-5465 [PMID: 20705463 DOI: 10.1016/j.bmcl.2010.07.094]

75 **Lien HM**, Wang CY, Chang HY, Huang CL, Peng MT, Sing YT, Chen CC, Lai CH. Bioevaluation of Anisomeles indica extracts and their inhibitory effects on Helicobacter pylori-mediated inflammation. *J Ethnopharmacol* 2013; **145**: 397-401 [PMID: 23178270 DOI: 10.1016/j.jep.2012.11.015]

76 **Kundu P**, De R, Pal I, Mukhopadhyay AK, Saha DR, Swarnakar S. Curcumin alleviates matrix metalloproteinase-3 and -9 activities during eradication of Helicobacter pylori infection in cultured cells and mice. *PLoS One* 2011; **6**: e16306 [PMID: 21283694 DOI: 10.1371/journal.pone.0016306]

77 **Lai CH**, Wang HJ, Chang YC, Hsieh WC, Lin HJ, Tang CH, Sheu JJ, Lin CJ, Yang MS, Tseng SF, Wang WC. Helicobacter pylori CagA-mediated IL-8 induction in gastric epithelial cells is cholesterol-dependent and requires the C-terminal tyrosine phosphorylation-containing domain. *FEMS Microbiol Lett* 2011; **323**: 155-163 [PMID: 22092715 DOI: 10.1111/j.1574-6968.2011.02372.x]

78 **Pastene E**, Speisky H, García A, Moreno J, Troncoso M, Figueroa G. In vitro and in vivo effects of apple peel polyphenols against Helicobacter pylori. *J Agric Food Chem* 2010; **58**: 7172-7179 [PMID: 20486708 DOI: 10.1021/jf100274g]

79 **Geethangili M**, Fang SH, Lai CH, Rao YK, Lien HM, Tzeng YM. Inhibitory effect of Antrodia camphorata constituents on the Helicobacter pylori-associated gastric inflammation. *Food Chem* 2010; **119**: 149-153 [DOI: 10.1016/j.foodchem.2009.06.006]

80 **Kataoka M**, Hirata K, Kunikata T, Ushio S, Iwaki K, Ohashi K, Ikeda M, Kurimoto M. Antibacterial action of tryptanthrin and kaempferol, isolated from the indigo plant (Polygonum tinctorium Lour.), against Helicobacter pylori-infected Mongolian gerbils. *J Gastroenterol* 2001; **36**: 5-9 [PMID: 11211212 DOI: 10.1007/s005350170147]

81 **Takabayashi F**, Nakamura Y, Harada N. Effect of black tea aqueous non-dialysate onHelicobacter pylori infection in Mongolian gerbils. *Environ Health Prev Med* 2004; **9**: 176-180 [PMID: 21432329 DOI: 10.1007/BF02898098]

82 **Takabayashi F**, Harada N, Yamada M, Murohisa B, Oguni I. Inhibitory effect of green tea catechins in combination with sucralfate on Helicobacter pylori infection in Mongolian gerbils. *J Gastroenterol* 2004; **39**: 61-63 [PMID: 14767736 DOI: 10.1007/s00535-003-1246-0]

83 **Matsubara S**, Shibata H, Ishikawa F, Yokokura T, Takahashi M, Sugimura T, Wakabayashi K. Suppression of Helicobacter pylori-induced gastritis by green tea extract in Mongolian gerbils. *Biochem Biophys Res Commun* 2003; **310**: 715-719 [PMID: 14550260 DOI: 10.1016/j.bbrc.2003.09.066]

84 **Ruggiero P**, Rossi G, Tombola F, Pancotto L, Lauretti L, Del Giudice G, Zoratti M. Red wine and green tea reduce H pylori- or VacA-induced gastritis in a mouse model. *World J Gastroenterol* 2007; **13**: 349-354 [PMID: 17230601]

85 **Ruggiero P**, Tombola F, Rossi G, Pancotto L, Lauretti L, Del Giudice G, Zoratti M. Polyphenols reduce gastritis induced by Helicobacter pylori infection or VacA toxin administration in mice. *Antimicrob Agents Chemother* 2006; **50**: 2550-2552 [PMID: 16801443 DOI: 10.1128/AAC.01042-05]

86 **Souza Mdo C**, Beserra AM, Martins DC, Real VV, Santos RA, Rao VS, Silva RM, Martins DT. In vitro and in vivo anti-Helicobacter pylori activity of Calophyllum brasiliense Camb. *J Ethnopharmacol* 2009; **123**: 452-458 [PMID: 19501278 DOI: 10.1016/j.jep.2009.03.030]

87 **Lemos LM**, Martins TB, Tanajura GH, Gazoni VF, Bonaldo J, Strada CL, Silva MG, Dall'oglio EL, de Sousa Júnior PT, Martins DT. Evaluation of antiulcer activity of chromanone fraction from Calophyllum brasiliesnse Camb. *J Ethnopharmacol* 2012; **141**: 432-439 [PMID: 22425905 DOI: 10.1016/j.jep.2012.03.006]

88 **Puram S**, Suh HC, Kim SU, Bethapudi B, Joseph JA, Agarwal A, Kudiganti V. Effect of GutGard in the Management of Helicobacter pylori: A Randomized Double Blind Placebo Controlled Study. *Evid Based Complement Alternat Med* 2013; **2013**: 263805 [PMID: 23606875 DOI: 10.1155/2013/263805]

89 **Salem EM**, Yar T, Bamosa AO, Al-Quorain A, Yasawy MI, Alsulaiman RM, Randhawa MA. Comparative study of Nigella Sativa and triple therapy in eradication of Helicobacter Pylori in patients with non-ulcer dyspepsia. *Saudi J Gastroenterol* 2010; **16**: 207-214 [PMID: 20616418 DOI: 10.4103/1319-3767.65201]

90 **Lin J**, Huang WW. A systematic review of treating Helicobacter pylori infection with Traditional Chinese Medicine. *World J Gastroenterol* 2009; **15**: 4715-4719 [PMID: 19787835 DOI: 10.3748/wjg.15.4715]

91 **Xie JH**, Chen YL, Wu QH, Wu J, Su JY, Cao HY, Li YC, Li YS, Liao JB, Lai XP, Huang P, Su ZR. Gastroprotective and anti-Helicobacter pylori potential of herbal formula HZJW: safety and efficacy assessment. *BMC Complement Altern Med* 2013; **13**: 119 [PMID: 23721522 DOI: 10.1186/1472-6882-13-119]

92 **Middleton E**, Kandaswami C, Theoharides TC. The effects of plant flavonoids on mammalian cells: implications for inflammation, heart disease, and cancer. *Pharmacol Rev* 2000; **52**: 673-751 [PMID: 11121513]

93 **Lin YT**, Kwon YI, Labbe RG, Shetty K. Inhibition of Helicobacter pylori and associated urease by oregano and cranberry phytochemical synergies. *Appl Environ Microbiol* 2005; **71**: 8558-8564 [PMID: 16332847 DOI: 10.1128/AEM.71.12.8558-8564.2005]

94 **Hassani AR**, Ordouzadeh N, Ghaemi A, Amirmozafari N, Hamdi K, Nazari R. In vitro inhibition of Helicobacter pylori urease with non and semi fermented Camellia sinensis. *Indian J Med Microbiol* 2009; **27**: 30-34 [PMID: 19172056]

95 **Pastene E**, Troncoso M, Figueroa G, Alarcón J, Speisky H. Association between polymerization degree of apple peel polyphenols and inhibition of Helicobacter pylori urease. *J Agric Food Chem* 2009; **57**: 416-424 [PMID: 19128009 DOI: 10.1021/jf8025698]

96 **Lima ZP**, Calvo TR, Silva EF, Pellizzon CH, Vilegas W, Brito AR, Bauab TM, Hiruma-Lima CA. Brazilian medicinal plant acts on prostaglandin level and Helicobacter pylori. *J Med Food* 2008; **11**: 701-708 [PMID: 19053863 DOI: 10.1089/jmf.2007.0676]

97 **Lima ZP**, dos Santos Rde C, Torres TU, Sannomiya M, Rodrigues CM, dos Santos LC, Pellizzon CH, Rocha LR, Vilegas W, Souza Brito AR, Cardoso CR, Varanda EA, de Moraes HP, Bauab TM, Carli C, Carlos IZ, Hiruma-Lima CA. Byrsonima fagifolia: an integrative study to validate the gastroprotective, healing, antidiarrheal, antimicrobial and mutagenic action. *J Ethnopharmacol* 2008; **120**: 149-160 [PMID: 18761075 DOI: 10.1016/j.jep.2008.07.047]

98 **Shin JE**, Kim JM, Bae EA, Hyun YJ, Kim DH. In vitro inhibitory effect of flavonoids on growth, infection and vacuolation of Helicobacter pylori. *Planta Med* 2005; **71**: 197-201 [PMID: 15770537 DOI: 10.1055/s-2005-837816]

99 **Quílez A**, Berenguer B, Gilardoni G, Souccar C, de Mendonça S, Oliveira LF, Martín-Calero MJ, Vidari G. Anti-secretory, anti-inflammatory and anti-Helicobacter pylori activities of several fractions isolated from Piper carpunya Ruiz & amp; Pav. *J Ethnopharmacol* 2010; **128**: 583-589 [PMID: 20152892 DOI: 10.1016/j.jep.2010.01.060]

100 **Asha MK**, Debraj D, Prashanth D, Edwin JR, Srikanth HS, Muruganantham N, Dethe SM, Anirban B, Jaya B, Deepak M, Agarwal A. In vitro anti-Helicobacter pylori activity of a flavonoid rich extract of Glycyrrhiza glabra and its probable mechanisms of action. *J Ethnopharmacol* 2013; **145**: 581-586 [PMID: 23220194 DOI: 10.1016/j.jep.2012.11.033]

101 **Boquet P**, Ricci V, Galmiche A, Gauthier NC. Gastric cell apoptosis and H. pylori: has the main function of VacA finally been identified? *Trends Microbiol* 2003; **11**: 410-413 [PMID:

13678854 DOI: 10.1016/S0966-842X(03)00211-7]
102 **Mahady GB**, Pendland SL. Resveratrol inhibits the growth of Helicobacter pylori in vitro. *Am J Gastroenterol* 2000; **95**: 1849 [PMID: 10926010]
103 **Paulo L**, Oleastro M, Gallardo E, Queiroz JA, Domigues F. Anti-Helicobacter pylori and urease inhibitory activities of resveratrol and red wine. *Food Res Int* 2011; **44**: 964-969 [DOI: 10.1016/j.foodres.2011.02.017]
104 **Martini S**, Bonechi C, Rossi C, Figura N. Increased susceptibility to resveratrol of Helicobacter pylori strains isolated from patients with gastric carcinoma. *J Nat Prod* 2011; **74**: 2257-2260 [PMID: 21936484 DOI: 10.1021/np100761u]
105 **Martini S**, D'Addario C, Braconi D, Bernardini G, Salvini L, Bonechi C, Figura N, Santucci A, Rossi C. Antibacterial activity of grape extracts on cagA-positive and -negative Helicobacter pylori clinical isolates. *J Chemother* 2009; **21**: 507-513 [PMID: 19933041]
106 **Sintara K**, Thong-Ngam D, Patumraj S, Klaikeaw N, Chatsuwan T. Curcumin suppresses gastric NF-kappaB activation and macromolecular leakage in Helicobacter pylori-infected rats. *World J Gastroenterol* 2010; **16**: 4039-4046 [PMID: 20731017 DOI: 10.3748/wjg.v16.i32.4039]
107 **Cui K**, Lu W, Zhu L, Shen X, Huang J. Caffeic acid phenethyl ester (CAPE), an active component of propolis, inhibits Helicobacter pylori peptide deformylase activity. *Biochem Biophys Res Commun* 2013; **435**: 289-294 [PMID: 23611786 DOI: 10.1016/j.bbrc.2013.04.026]
108 **Coelho LG**, Bastos EM, Resende CC, Paula e Silva CM, Sanches BS, de Castro FJ, Moretzsohn LD, Vieira WL, Trindade OR. Brazilian green propolis on Helicobacter pylori infection. a pilot clinical study. *Helicobacter* 2007; **12**: 572-574 [PMID: 17760728 DOI: 10.1111/j.1523-5378.2007.00525.x]
109 **Nir Y**, Potasman I, Stermer E, Tabak M, Neeman I. Controlled trial of the effect of cinnamon extract on Helicobacter pylori. *Helicobacter* 2000; **5**: 94-97 [PMID: 10849058 DOI: 10.1046/j.1523-5378.2000.00014.x]
110 **Hu FL**. [A multicenter study of Chinese patent medicine wenweishu/yangweishu in the treatment of Helicobacter pylori positive patients with chronic gastritis and peptic ulcer]. *Zhonghua Yi Xue Za Zhi* 2010; **90**: 75-78 [PMID: 20356485]
111 **Aydin A**, Ersöz G, Tekesin O, Akçiçek E, Tuncyürek M. Garlic oil and Helicobacter pylori infection. *Am J Gastroenterol* 2000; **95**: 563-564 [PMID: 10685782]
112 **Graham DY**, Anderson SY, Lang T. Garlic or jalapeño peppers for treatment of Helicobacter pylori infection. *Am J Gastroenterol* 1999; **94**: 1200-1202 [PMID: 10235193]
113 **Shidfar F**, Agah S, Ekhlasi G, Salehpour A, Ghourchian S. Lycopene an adjunctive therapy for Helicobacter pylori eradication: a quasi-control trial. *J Complement Integr Med* 2012; **9**: Article 14 [PMID: 22850072 DOI: 10.1515/1553-3840.1588]
114 **Beil W**, Kilian P. EPs 7630, an extract from Pelargonium sidoides roots inhibits adherence of Helicobacter pylori to gastric epithelial cells. *Phytomedicine* 2007; **14** Suppl 6: 5-8 [PMID: 17188478 DOI: 10.1016/j.phymed.2006.11.024]
115 **Wittschier N**, Faller G, Hensel A. An extract of Pelargonium sidoides (EPs 7630) inhibits in situ adhesion of Helicobacter pylori to human stomach. *Phytomedicine* 2007; **14**: 285-288 [PMID: 17350240 DOI: 10.1016/j.phymed.2006.12.008]
116 **Burger O**, Ofek I, Tabak M, Weiss EI, Sharon N, Neeman I. A high molecular mass constituent of cranberry juice inhibits helicobacter pylori adhesion to human gastric mucus. *FEMS Immunol Med Microbiol* 2000; **29**: 295-301 [PMID: 11118911 DOI: 10.1111/j.1574-695X.2000.tb01537.x]
117 **Shmuely H**, Burger O, Neeman I, Yahav J, Samra Z, Niv Y, Sharon N, Weiss E, Athamna A, Tabak M, Ofek I. Susceptibility of Helicobacter pylori isolates to the antiadhesion activity of a high-molecular-weight constituent of cranberry. *Diagn Microbiol Infect Dis* 2004; **50**: 231-235 [PMID: 15582295 DOI: 10.1016/j.diagmicrobio.2004.08.011]
118 **Shi DH**, Liu YW, Liu WW, Gu ZF. Inhibition of urease by extracts derived from 15 Chinese medicinal herbs. *Pharm Biol* 2011; **49**: 752-755 [PMID: 21639688 DOI: 10.3109/13880209.2010.547205]
119 **Moleiro FC**, Andreo MA, Santos Rde C, Moraes Tde M, Rodrigues CM, Carli CB, Lopes FC, Pellizzon CH, Carlos IZ, Bauab TM, Vilegas W, Hiruma-Lima CA. Mouririelliptica: validation of gastroprotective, healing and anti-Helicobacter pylori effects. *J Ethnopharmacol* 2009; **123**: 359-368 [PMID: 19501267 DOI: 10.1016/j.jep.2009.03.040]
120 **Moraes Tde M**, Rodrigues CM, Kushima H, Bauab TM, Villegas W, Pellizzon CH, Brito AR, Hiruma-Lima CA. Hancornia speciosa: indications of gastroprotective, healing and anti-Helicobacter pylori actions. *J Ethnopharmacol* 2008; **120**: 161-168 [PMID: 18761076 DOI: 10.1016/j.jep.2008.08.001]
121 **Castillo-Juárez I**, Rivero-Cruz F, Celis H, Romero I. Anti-Helicobacter pylori activity of anacardic acids from Amphipterygium adstringens. *J Ethnopharmacol* 2007; **114**: 72-77 [PMID: 17768020 DOI: 10.1016/j.jep.2007.07.022]
122 **Ishizone S**, Maruta F, Suzuki K, Miyagawa S, Takeuchi M, Kanaya K, Oana K, Hayama M, Kawakami Y, Ota H. In vivo bactericidal activities of Japanese rice-fluid against H. pylori in a Mongolian gerbil model. *Int J Med Sci* 2007; **4**: 203-208 [PMID: 17717596 DOI: 10.7150/ijms.4.203]
123 **Robles-Zepeda RE**, Velázquez-Contreras CA, Garibay-Escobar A, Gálvez-Ruiz JC, Ruiz-Bustos E. Antimicrobial activity of Northwestern Mexican plants against Helicobacter pylori. *J Med Food* 2011; **14**: 1280-1283 [PMID: 21663492 DOI: 10.1089/jmf.2010.0263]
124 **Goel RK**, Sairam K, Babu MD, Tavares IA, Raman A. In vitro evaluation of Bacopa monniera on anti-Helicobacter pylori activity and accumulation of prostaglandins. *Phytomedicine* 2003; **10**: 523-527 [PMID: 13678238 DOI: 10.1078/094471103322331494]
125 **Banskota AH**, Tezuka Y, Adnyana IK, Ishii E, Midorikawa K, Matsushige K, Kadota S. Hepatoprotective and anti-Helicobacter pylori activities of constituents from Brazilian propolis. *Phytomedicine* 2001; **8**: 16-23 [PMID: 11292234 DOI: 10.1078/0944-7113-00004]
126 **Zhang BL**, Fan CQ, Dong L, Wang FD, Yue JM. Structural modification of a specific antimicrobial lead against Helicobacter pylori discovered from traditional Chinese medicine and a structure-activity relationship study. *Eur J Med Chem* 2010; **45**: 5258-5264 [PMID: 20832915 DOI: 10.1016/j.ejmech.2010.08.045]
127 **Bai CL**, Osaki T, Yonezawa H, Hanawa T, Zaman C, Kurata S, Kamiya S, Tanaka H. In vitro and in vivo effects of the Mongolian drug Amu-ru 7 on Helicobacter pylori growth and viability. *Microbiol Immunol* 2010; **54**: 508-515 [PMID: 20840149 DOI: 10.1111/j.1348-0421.2010.00246.x]
128 **Cwikla C**, Schmidt K, Matthias A, Bone KM, Lehmann R, Tiralongo E. Investigations into the antibacterial activities of phytotherapeutics against Helicobacter pylori and Campylobacter jejuni. *Phytother Res* 2010; **24**: 649-656 [PMID: 19653313 DOI: 10.1002/ptr.2933]
129 **De R**, Kundu P, Swarnakar S, Ramamurthy T, Chowdhury A, Nair GB, Mukhopadhyay AK. Antimicrobial activity of curcumin against Helicobacter pylori isolates from India and during infections in mice. *Antimicrob Agents Chemother* 2009; **53**: 1592-1597 [PMID: 19204190 DOI: 10.1128/AAC.01242-08]
130 **Adeniyi BA**, Anyiam FM. In vitro anti-Helicobacter pylori potential of methanol extract of Allium ascalonicum Linn. (Liliaceae) leaf: susceptibility and effect on urease activity. *Phytother Res* 2004; **18**: 358-361 [PMID: 15173992 DOI: 10.1002/ptr.1265]
131 **Zhou Y**, Taylor B, Smith TJ, Liu ZP, Clench M, Davies NW, Rainsford KD. A novel compound from celery seed with a bactericidal effect against Helicobacter pylori. *J Pharm Pharmacol* 2009; **61**: 1067-1077 [PMID: 19703351 DOI: 10.1211/

jpp/61.08.0011]
132 **Kushima H**, Nishijima CM, Rodrigues CM, Rinaldo D, Sassá MF, Bauab TM, Stasi LC, Carlos IZ, Brito AR, Vilegas W, Hiruma-Lima CA. Davilla elliptica and Davilla nitida: gastroprotective, anti-inflammatory immunomodulatory and anti-Helicobacter pylori action. *J Ethnopharmacol* 2009; **123**: 430-438 [PMID: 19501275 DOI: 10.1016/j.jep.2009.03.031]
133 **Daroch F**, Hoeneisen M, González CL, Kawaguchi F, Salgado F, Solar H, García A. In vitro antibacterial activity of Chilean red wines against Helicobacter pylori. *Microbios* 2001; **104**: 79-85 [PMID: 11297014]
134 **Zaidi SF**, Ahmed K, Yamamoto T, Kondo T, Usmanghani K, Kadowaki M, Sugiyama T. Effect of resveratrol on Helicobacter pylori-induced interleukin-8 secretion, reactive oxygen species generation and morphological changes in human gastric epithelial cells. *Biol Pharm Bull* 2009; **32**: 1931-1935 [PMID: 19881312 DOI: 10.1248/bpb.32.1931]
135 **Goswami SK**, Das DK. Resveratrol and chemoprevention. *Cancer Lett* 2009; **284**: 1-6 [PMID: 19261378 DOI: 10.1016/j.canlet.2009.01.041]
136 **Brown JC**, Jiang X. Activities of muscadine grape skin and polyphenolic constituents against Helicobacter pylori. *J Appl Microbiol* 2013; **114**: 982-991 [PMID: 23294280 DOI: 10.1111/jam.12129]
137 **Ustün O**, Ozçelik B, Akyön Y, Abbasoglu U, Yesilada E. Flavonoids with anti-Helicobacter pylori activity from Cistus laurifolius leaves. *J Ethnopharmacol* 2006; **108**: 457-461 [PMID: 16870372 DOI: 10.1016/j.jep.2006.06.001]
138 **Njume C**, Afolayan AJ, Green E, Ndip RN. Volatile compounds in the stem bark of Sclerocarya birrea (Anacardiaceae) possess antimicrobial activity against drug-resistant strains of Helicobacter pylori. *Int J Antimicrob Agents* 2011; **38**: 319-324 [PMID: 21752604 DOI: 10.1016/j.ijantimicag.2011.05.002]
139 **Lai CH**, Fang SH, Rao YK, Geethangili M, Tang CH, Lin YJ, Hung CH, Wang WC, Tzeng YM. Inhibition of Helicobacter pylori-induced inflammation in human gastric epithelial AGS cells by Phyllanthus urinaria extracts. *J Ethnopharmacol* 2008; **118**: 522-526 [PMID: 18602230 DOI: 10.1016/j.jep.2008.05.022]
140 **Fang SH**, Rao YK, Tzeng YM. Anti-oxidant and inflammatory mediator's growth inhibitory effects of compounds isolated from Phyllanthus urinaria. *J Ethnopharmacol* 2008; **116**: 333-340 [PMID: 18187278 DOI: 10.1016/j.jep.2007.11.040]
141 **Vega AE**, Wendel GH, Maria AO, Pelzer L. Antimicrobial activity of Artemisia douglasiana and dehydroleucodine against Helicobacter pylori. *J Ethnopharmacol* 2009; **124**: 653-655 [PMID: 19422904 DOI: 10.1016/j.jep.2009.04.051]
142 **Bork PM**, Schmitz ML, Kuhnt M, Escher C, Heinrich M. Sesquiterpene lactone containing Mexican Indian medicinal plants and pure sesquiterpene lactones as potent inhibitors of transcription factor NF-kappaB. *FEBS Lett* 1997; **402**: 85-90 [PMID: 9013864 DOI: 10.1016/S0014-5793(96)01502-5]
143 **Zhang XQ**, Gu HM, Li XZ, Xu ZN, Chen YS, Li Y. Anti-Helicobacter pylori compounds from the ethanol extracts of Geranium wilfordii. *J Ethnopharmacol* 2013; **147**: 204-207 [PMID: 23500884 DOI: 10.1016/j.jep.2013.02.032]
144 **Sidahmed HM**, Abdelwahab SI, Mohan S, Abdulla MA, Mohamed Elhassan Taha M, Hashim NM, Hadi AH, Vadivelu J, Loke Fai M, Rahmani M, Yahayu M. α -Mangostin from Cratoxylum arborescens (Vahl) Blume Demonstrates Anti-Ulcerogenic Property: A Mechanistic Study. *Evid Based Complement Alternat Med* 2013; **2013**: 450840 [PMID: 23634169 DOI: 10.1155/2013/450840]
145 **Liu W**, Liu Y, Zhang XZ, Li N, Cheng H. In vitro bactericidal activity of Jinghua Weikang Capsule and its individual herb Chenopodium ambrosioides L. against antibiotic-resistant Helicobacter pylori. *Chin J Integr Med* 2013; **19**: 54-57 [PMID: 23275015 DOI: 10.1007/s11655-012-1248-y]
146 **Jung K**, Chin YW, Chung YH, Park YH, Yoo H, Min DS, Lee B, Kim J. Anti-gastritis and wound healing effects of Momordicae Semen extract and its active component. *Immunopharmacol Immunotoxicol* 2013; **35**: 126-132 [PMID: 22889079 DOI: 10.3109/08923973.2012.712139]
147 **Tran CD**, Butler RN, Miller MJ. The role of Amazonian herbal medicine Sangre de Grado in Helicobacter pylori infection and its association with metallothionein expression. *Helicobacter* 2006; **11**: 134-135 [PMID: 16579844 DOI: 10.1111/j.1523-5378.2006.00388.x]
148 **Sidahmed HM**, Hashim NM, Amir J, Abdulla MA, Hadi AH, Abdelwahab SI, Taha MM, Hassandarvish P, Teh X, Loke MF, Vadivelu J, Rahmani M, Mohan S. Pyranocycloartobiloxanthone A, a novel gastroprotective compound from Artocarpus obtusus Jarret, against ethanol-induced acute gastric ulcer in vivo. *Phytomedicine* 2013; **20**: 834-843 [PMID: 23570997 DOI: 10.1016/j.phymed.2013.03.002]
149 **Hajimahmoodi M**, Shams-Ardakani M, Saniee P, Siavoshi F, Mehrabani M, Hosseinzadeh H, Foroumadi P, Safavi M, Khanavi M, Akbarzadeh T, Shafiee A, Foroumadi A. In vitro antibacterial activity of some Iranian medicinal plant extracts against Helicobacter pylori. *Nat Prod Res* 2011; **25**: 1059-1066 [PMID: 21726128 DOI: 10.1080/14786419.2010.501763]

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