7th International Conference on Agricultural Sciences Medicinal Plants and Traditional Medicine
September 17, 2024 Tbilisi - Georgia

A review of the treatment of some medicinal plants against *Helicobacter pylori*

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Abstract
Helicobacter pylori is a type of bacteria that infects the stomach. It can damage the tissue of the stomach and the duodenum, the first part of the small intestine. Known as *H. pylori*, this bacterium can cause inflammation, leading to redness and pain. In some cases, it results in painful ulcers in the upper digestive tract. *H. pylori* is very common and affects many people. Most individuals with this infection do not experience symptoms or harm. However, it is important to know that *H. pylori* is the primary cause of stomach ulcers. Globally, *H. pylori* is recognized as the primary cause of peptic ulcers and gastric cancer. It is estimated that around 50 percent of the global population is infected with *H. pylori*. However, treatments aimed at eradicating the bacteria have often failed due to various factors, including the development of antibiotic resistance. This has led to a pressing need for new medications targeting *H. pylori*, prompting a search for alternative, more effective, and safer inhibitors. In contemporary drug development, medicinal plants are being proposed as sources of new synthetic compounds. These plants are considered environmentally friendly, straightforward, safer, quick, and less toxic compared to traditional treatments. This review aims to emphasize the anti-*H. pylori* properties of medicinal plants, their secondary metabolites, and their mechanisms of action, with the goal of documenting these plants before they are lost to changing cultures and traditions. In this review study, the effects of some medicinal plants and compounds within plants on *H. pylori* have been investigated until 2024.
Keywords: *Helicobacter pylori*, antibiotic resistance, medicinal plants.

Introduction

H. pylori is a gram-negative bacterium that cannot survive independently, relying on a host for its survival. It primarily inhabits the mammalian digestive system, particularly the stomach. Its polar flagella and curved shape allow it to navigate and penetrate the stomach mucus. The bacterium initially uses receptor molecules (ligands) on its surface to bind to molecular receptors on the gastric epithelial cells. This interaction, along with other factors, contributes to its pathogenicity and facilitates its spread within the host. Unfortunately, antibiotic resistance has increased in this bacterium in recent years. Studies conducted in Iran have shown a high resistance to metronidazole, approximately 57%, which aligns with findings from other Asian countries. The average rate of resistance to ciprofloxacin in Iran, based on limited studies, is around 18%. In Europe, resistance rates vary, with France reporting 13.2% and Italy 47.39% [1, 2].

In addition, *H. pylori* is one of the main causes of stomach cancer in the long run. As a result, finding alternative treatment solutions to antibiotics is of great interest to researchers. In recent years, the use of medicinal plants has been on the rise due to their proven beneficial effects, affordability, lack of side effects, and environmental compatibility. Antibacterial compounds found in plant extracts and essential oils can disrupt bacterial membranes and increase the permeability of both cytoplasmic and external membranes due to their hydrophobic properties. This allows these substances to penetrate the lipids of the bacterial cell membrane and mitochondria, turning into ions. Some of these compounds not only inhibit the growth of bacterial cells but also prevent toxin production by bacteria [3].

There are two theories explaining this phenomenon. One theory suggests that interference with ATP production results in insufficient ATP to expel the toxin from the cell, an active and energy-dependent process. The other theory proposes that as the specific growth rate decreases, the cell uses all its energy for survival. Generally, the higher the concentration of phenolic substances in an extract or essential oil, the stronger its antibacterial properties against food pathogens. Essential compounds include carvacrol, eugenol, and thymol. The mechanism of action of these compounds likely involves disrupting the cytoplasmic membrane, disrupting the proton motive force and electric current, and coagulating cell contents. The chemical structure of an essential oil also influences its mechanism; for instance, the presence of a hydroxyl group in phenolic compounds like carvacrol and thymol is crucial. Using certain medicinal plants may be effective in combating *H. pylori* [4, 5]

***Helicobacter pylori* and pathogenicity**

Upon entering the stomach, *H. pylori* begin synthesizing urea using the urease enzyme. This process not only helps the bacterium withstand the stomach's acidic conditions but is also essential for its metabolism. This rod-shaped, spiral bacterium can colonize the lower layers of the human stomach. By adapting to its environment, it ensures its survival and reproductive cycle within the host's stomach for an extended period [6].

H. pylori can cause various digestive diseases, including chronic gastritis, gastric ulcers, and duodenal ulcers (the initial part of the small intestine). In some cases, it can lead to stomach cancer and lymphoid-mucous tissue lymphoma. These latter diseases, particularly stomach cancer and lymphoid-mucous tissue lymphoma, are especially significant due to the numerous challenges they present for treatment. The disease caused by *H. pylori* is one of the most prevalent digestive system disorders. It was first identified through culture in 1984, and since then, extensive information has

been gathered using various diagnostic methods and research conducted by different scientific communities [7]. The rate of *H.pylori* infection and prevalence is less than 10% in developed countries with high economic and social standards. However, in developing countries or those experiencing economic hardship, the prevalence rate can reach up to 60%. This bacteri has a complex mechanism in the occurrence of stomach cancer. The first step for *H. pylori* to penetrate and infect cells and spread within the epithelial tissue of the digestive tract is its attachment to cell surface receptors. This interaction between the bacteria and the host's epithelial cells not only establishes the bacteria within the target structure but also initiates certain intracellular signaling pathways. *H. pylori* initially binds to type IV collagen, allowing it to invade the lamina propria tissue. It then interacts with laminin, another critical component of the basement membrane, which facilitates its attachment to host tissue. This connection stabilizes the bacteria in the damaged areas, enabling *H. pylori* to transmit itself to cells through surface receptors such as LPS and 67 kDa proteins, leading to peptic ulcers. This process can ultimately influence pathways leading to cancer. As a result of this interaction, other pathogenic factors are activated, playing a significant role in the bacterium's pathogenicity.Additionally, the bacteria utilize a system to inject the critical CagA protein, produced by the type IV secretion system, directly into the cell. Once inside, CagA is phosphorylated, leading to increased cell proliferation and enhanced binding between adjacent cells, which plays a significant role in cancer metastasis. The presence of CagA increases the risk of developing peptic ulcers, gastritis, or stomach cancer by 50-70% [8, 9].

Antibiotic treatment and antibiotic resistance in *Helicobacter pylori*

Many people believe that; If the bacterium is detected in the early stages of infection, it can be eradicated through antibiotics. But with the progress of the disease and the persistence of *H. pylori* in the digestive tract, treatment with antibiotics can only reduce the severity of the disease. Because the long-term acidic environment of the stomach reduces the use of antibiotics. For this reason, PPI or gastric acid controllers and bismuth salt should be used along with antibiotics. There are clinically acceptable treatments; which can at least reduce about 85% of the complications of the disease and also have little drug resistance. Currently, many drugs with different brand names are used for partial treatment of this infection. According to reports, *H. pylori* is sensitive to several antibiotics, including cephalosporins, penicillins, tetracyclines, and macrolides such as erythromycin, clarithromycin, and quinolones. On the other hand, metronidazole has a more limited application because it has an average performance level and some *H. pylori* strains are resistant to it. Additionally, lansoprazole has the same efficacy as omeprazole, showing significant effects on this bacterium by creating active basic metabolites [10, 11].

Three profiles of resistance in *H.pylori*—single drug resistance, multidrug resistance, and heteroresistance—appear to occur, likely due to overlapping fundamental mechanisms and clinical implications. The most studied mechanisms involve chromosomally encoded mutational changes that disrupt the cellular activity of antibiotics through target-mediated mechanisms. Other biological factors contributing to drug resistance in *H. pylori* have been less explored, suggesting more complex physiological changes, such as impaired regulation of drug uptake and/or efflux, or biofilm and coccoid formation, that remain largely unknown. These resistance-related attributes cause treatment failures, diagnostic difficulties, and ambiguity in interpreting therapeutic outcomes. Due to increasing antibiotic resistance, there has been a significant global decline in the efficacy of *H. pylori* treatments. In the absence of an effective vaccine, there is a need for enhanced efforts to develop new treatment strategies, improve our understanding of the emergence and

spread of drug-resistant bacteria, and advance diagnostic tools that can help optimize current antimicrobial regimens [12, 13].

Medicinal plants

Medicinal plants have played a crucial role in the development of human culture. They have been a primary source of medicine in virtually all civilizations throughout history. These plants are rich resources of traditional medicines, and many modern medicines have been derived from them. For thousands of years, medicinal plants have been used to treat health disorders, enhance the flavor and preservation of food, and prevent disease epidemics. The secondary metabolites produced by these plants are typically responsible for their biological characteristics and therapeutic properties. Plant-derived products are also effective in controlling microbial growth in various situations. Phytochemicals or nutritional plants derive their name from "phyto," meaning "plant," and "chemical," meaning "chemical substance." These naturally occurring chemical compounds in plants are typically medicinal rather than nutritional. They contribute to the color and organoleptic characteristics of plants, such as the vibrant color of fruits or the aroma of garlic. Phytochemicals like carotenoids and flavonoids have significant biological importance and may be highly valuable. There are over 4,000 different types of phytochemicals in nature. Medicinal plant materials consist of chemical compounds that are produced and stored in various parts of the plants and are typically used as pharmaceutical raw materials. Through a series of technological processes, these medicinal plants are transformed into herbal medicines containing substances that predominantly affect the human body. There are two main types of substances found in medicinal plants. The first group includes materials resulting from primary metabolism, which are mainly saccharides and are essential for the plant's survival [14].

Antibacterial and antioxidant properties of medicinal plants

Antibacterial compounds in plant extracts and essential oils can disrupt bacterial membranes and increase the permeability of both cytoplasmic and external membranes due to their hydrophobic properties. This allows these substances to penetrate the lipids of the bacterial cell membrane and mitochondria, where they become ions. These compounds not only inhibit bacterial growth but also prevent toxin production by bacteria. There are two theories to explain this phenomenon. One theory suggests that interference with ATP production results in insufficient ATP to expel the toxin from the cell, an active and energy-dependent process. The other theory posits that as the specific growth rate decreases, the cell uses all its energy for survival. Generally, higher amounts of phenolic substances in extracts and essential oils enhance their antibacterial properties against food pathogens. Compounds such as carvacrol, eugenol, and thymol are particularly effective. The mechanism of action of these compounds likely involves disruption of the cytoplasmic membrane, interference with the proton motive force and electric current, and coagulation of cell contents [15]. The chemical structure of an essential oil also influences its mechanism; for instance, the presence of a hydroxyl group in phenolic compounds like carvacrol and thymol is crucial for their antibacterial activity. Phenolic compounds and antioxidant substances found in plants are an integral part of the human diet, providing significant benefits, primarily due to their anti-cancer and antioxidant activities. Flavonoids and other plant phenolic compounds, such as phenolic acids, tannins, and lignins, play crucial roles in the natural growth of plants and their resistance to infection and injury [16].

Mechanisms of medicinal plants against *H. pylori*

Medicinal plants have been used for centuries to treat various ailments, and many have shown potential against *H. pylori*, a bacterium associated with peptic ulcers and gastric cancer. The mechanisms by which these plants act against *H. pylori* include:

1. **Antibacterial Activity**: Many medicinal plants contain compounds that have direct antibacterial effects, which can inhibit the growth of *H. pylori*. These compounds include alkaloids, flavonoids, tannins, and essential oils [17].
2. **Inhibition of Urease Activity**: *H. pylori* produces urease, an enzyme that neutralizes stomach acid, allowing the bacterium to survive in the acidic environment of the stomach. Certain plant extracts can inhibit urease activity, making it difficult for the bacteria to survive [18].
3. **Disruption of Biofilm Formation**: *H. pylori* forms biofilms to protect itself from the hostile environment of the stomach and from antibiotics. Some plant extracts can disrupt these biofilms, making the bacteria more susceptible to treatment [19].
4. **Anti-Adhesion Properties**: *H. pylori* adheres to the gastric mucosa to colonize the stomach. Certain plant compounds can prevent the bacteria from adhering to the stomach lining, thereby reducing colonization and infection [20].
5. **Antioxidant Properties**: Oxidative stress plays a role in the inflammation and damage caused by *H. pylori* infection. Plants rich in antioxidants can help reduce oxidative stress, thereby alleviating the symptoms of infection and promoting healing [21].
6. **Modulation of Immune Response**: Some medicinal plants can modulate the immune system, enhancing the body's ability to fight off *H. pylori* infection. They can boost the production of antibodies or enhance the activity of immune cells that target the bacteria [22].

Herbal compounds against *H. pylori*

Several herbal compounds have shown significant activity against *H. pylori.* These compounds, derived from various medicinal plants, exhibit a range of antibacterial properties and mechanisms (Table 1). These compounds work through various mechanisms such as direct bacterial inhibition, disruption of bacterial biofilms, inhibition of bacterial enzymes like urease, and modulation of the host's immune response. This multifaceted approach enhances their effectiveness against *H. pylori* and reduces the likelihood of the bacteria developing resistance.

Table 1- Herbal compounds against *H. pylori* and the mechanisms of action of these compounds [23, 24]

Compounds	Mechanism
Allicin	Exhibits broad-spectrum antibacterial activity, including inhibition of *H. pylori* growth and urease activity
Catechins	Particularly epigallocatechin gallate (EGCG) inhibits *H. pylori* growth, disrupts biofilms, and interferes with urease activity
Curcumin	Possesses antibacterial, antioxidant, and anti-inflammatory properties, directly inhibiting *H. pylori* and reducing gastric inflammation

Sulforaphane	Has been shown to kill *H. pylori* and reduce gastritis through its potent antibacterial properties
Berberine	Exhibits strong antibacterial activity, including against *H. pylori*, and inhibits urease
Epicatechin	Inhibits *H. pylori* growth and disrupts bacterial biofilms
Resveratrol	Exhibits antibacterial properties and can inhibit the growth of *H. pylori*
Quercetin	Shows antibacterial activity against *H. pylori* and can inhibit urease
Carnosol	Demonstrates antibacterial activity, including against *H. pylori*
Mastic Gum	Directly inhibits *H. pylori* and has been traditionally used to treat stomach ulcers
Gingerol	Exhibits antibacterial properties and can reduce *H. pylori* colonization
Linalool	antibacterial properties against *H. pylori*
Saponins	Exhibit antibacterial activity, including against *H. pylori*, and can enhance the mucosal barrier
Caffeic Acid	Shows antibacterial properties and can inhibit *H. pylori* growth
Thymol	Demonstrates antibacterial activity, including against *H. pylori*

Some studies on the effects of medicinal plants on *H. pylori*

Since Helicobacter pylori has infected at least half of the world's population at some point in their lives, and unfortunately, antibiotic resistance to this organism is increasing, researchers are conducting extensive studies on medicinal plants effective in destroying Helicobacter pylori. Some of the latest research in this field is presented in Table 2.

Table2- Some studies conducted on medicinal plants against *H.pylori*

Plant	Result	Reference
Allium sativum+ Allium cepa+ Cuminum cyminum L+ T. foenum-graecum L (Mixture of methanolic extract)	*H.pylori* was inhibited by all combinations of extracts and probiotics with varying results. The highest anti-H. pylori activities were observed in the combinations of *fenugreek/B. breve* (29 mm), *cumin/B. breve* (26 mm), *garlic/B. breve* (23 mm), and *onion/B. breve* (25 mm). Probiotics inhibited *H. pylori* due to lactic acid, bacteriocins, and phenolic compounds like gallic acid, caffeic acid, quercetin, and vanillic acid in the plants. Fenugreek extract showed a concentration-dependent inhibition of *H. pylori*. In *H. pylori*-infected rats, *B. breve* significantly reduced the infection rate, and the combination of *B. breve* and fenugreek extract effectively inhibited *H. pylori* and significantly reduced gastritis.	[25]

Spathodea campanulate (bark)	Among the sub-fractions obtained, SB2 showed the capacity to inhibit *H. pylori* urease in a heterologous bacterial model. One additional sub-fraction (SE3) was able to simultaneously modulate the expression of two adhesins (HopZ and BabA) and one cytotoxin (CagA)	[26]
Bryophyllum pinnutum (Dried leaves)	Methanol extract showed a significant anti-Helicobacter activity with MIC and MBC values of 32 and 256 µg/mL, respectively. Bryophyllum pinnatum and ciprofloxacin reduced *H. pylori* colonization of mouse gastric tissue from 100% to 17%. *Bryophyllum pinnatum* extract (85.91 ± 52.91 CFU) and standard (25.74 ± 16.15 CFU) also reduced significantly ($p < 0.05$) bacterial load of gastric mucosa as compared to untreated infected mice (11883 ± 1831 CFU). DPPH radical, hydroxyl radical and reducing power assays showed IC50 values of 25.31 ± 0.34, 55.94 ± 0.68 and 11.18 ± 0.74 µg/mL, respectively.	[27]
Parthenium hysterophorus	Organic extracts inhibited the growth of H. pylori, with the dichloromethane extract from roots showing the strongest effect (MIC of 15.6 µg/ml). There was a direct correlation between antibacterial activity and motility inhibition. Urease activity was partially inhibited by organic extracts, with the roots' dichloromethane extract achieving 74% inhibition at 500 µg/ml (IC50=136.4 µg/ml). Plant extracts also inhibited adherence to varying degrees, with dichloromethane–methanol extracts showing the highest effect (70% inhibition at 1 mg/ml).	[28]
Acacia nilotica + *Calotropis procera*	In the H. pylori urease inhibitory assay, methanol and acetone extracts of *Acacia nilotica* and *Calotropis procera* showed significant inhibition.	[29]
Bridelia (stem bark)	Complete killing of strain PE430C by the ethyl acetate extract was observed at 0.1 mg/mL (2 × MIC) and 0.2 mg/mL (4 × MIC) at 66 and 72 h. For strain PE369C, 100% killing was observed at 0.1 mg/mL (2 × MIC) in 66 and 72 h. The ethyl acetate extract could thus be a potential source of lead molecules for the design of new anti-*Helicobacter pylori* .	[30]
Curcuma amada Roxb and *Mallotus phillipinesis* (aqueous-ethanol extracts)	The most potent bactericidal activity was exhibited by *Mallotus phillipinesis* (Lam) Muell. which completely killed the bacteria at the concentration of 15.6-31.2 µg/ml.	[31]

Calophyllum Brasiliense (hydroethanolic extract (HEECb)	In the in vivo assays, rats ulcerated by acetic acid, and inoculated with *H. pylori* showed a marked delay in ulcer healing. Treatment with HEECb (50, 100 and 200 mg/kg) and DCMF (100 and 200 mg/kg) reduced the ulcerated area in a dose-dependent manner. While DCMF, at 200 mg/kg, increased the prostaglandin E2 (PGE2) level, both HEECb and DCMF decreased the number of urease-positive animals, as confirmed by the reduction of *H. pylori* presence in histopathological analysis.	[32]
Cistus laurifolius	The chloroform extract was fractionated by using various chromatography techniques, i.e., Sephadex LH-20 column chromatography and preparative thin layer chromatography and six compounds were isolated (1–6). Each of these six compounds' anti-*H. pylori* activity was tested in vitro and was measured as minimum inhibition concentration (MIC) values by using agar dilution method. The compound 2 had the highest activity against *H. pylori* (MIC 3.9 µg/mL).	[33]
Ginger (*Zingiber officinale*) (root)	The methanol extract of *ginger* rhizome inhibited the growth of all 19 strains in vitro with a minimum inhibitory concentration range of 6.25-50 µg/ml. One fraction of the crude extract, containing the gingerols, was active and inhibited the growth of all *H.Pylori* strains with an MIC range of 0.78 to 12.5 µg/ml and with significant activity against the CagA+ strains.	[34]
Glycyrrhiza glabra (*Liquorice*)	Three new isoflavonoids with a pyran ring, named gancaonols A–C, were isolated along with 15 known flavonoids. Among these, vestitol, licoricone, 1-methoxyphaseollidin, and gancaonol C demonstrated activity against H. pylori, including both CLAR and AMOX-resistant strains, as well as four CLAR (AMOX)-sensitive strains. Other compounds, including glycyrin, formononetin, and several others, showed weaker anti-*H. pylori* activity.	[35]
Teminalia chebula Retz (alcoholic and water extracts)	Water extracts of the black myrobalan at a concentration of 1–2.5 mg/ml inhibited urease activity of *H. pylori*	[36]

According to the research conducted, some medicinal plants contain compounds such as allicin, catechins, curcumin, and sulforaphane, which exhibit mechanisms like antibacterial activities, inhibition of urease activity, and prevention of biofilm formation in the treatment of *H. pylori.*

Challenges

Using medicinal plants to combat *H. pylori* presents several challenges. These include issues with standardization and quality control due to variations in active compounds influenced by geographic and cultivation factors, and ensuring consistent quality without stringent measures. Efficacy and potency vary, with some plants not providing strong antibacterial effects and complex interactions among compounds being poorly understood. Scientific validation is limited by a lack of rigorous clinical trials and standardized research, leading to difficulties in drawing definitive conclusions. Safety concerns include potential side effects, toxicities, and interactions with conventional drugs. Regulatory issues involve stringent approval processes and a lack of standardized guidelines. There's also the potential for resistance development in H. pylori and challenges with patient compliance due to complex treatment regimens and skepticism towards efficacy. Addressing these challenges requires a multidisciplinary approach involving robust scientific research, stringent quality control, and clear regulatory guidelines [37].

Conclusions

Numerous medicinal plant products, including plant extracts, partially purified fractions, and isolated compounds, have been reported for their anti-*H. pylori* activity. Some of these products demonstrated strong anti-*H. pylori* effects, comparable to clinical antibiotics. In animal studies, certain plant products effectively reduced *H. pylori* colonization in the stomach. *H. pylori*-induced atrophic gastritis is a critical precursor to gastric cancer. Various plant products, including isolated compounds and plant formulas, significantly reduce gastric inflammation and injury, even inhibiting the progression of gastric cancer.The use of antibiotic regimens to eradicate *H. pylori* faces limitations, primarily due to antibiotic resistance. Medicinal plant compounds and other natural products offer an alternative method to eradicate *H. pylori* infection. These compounds may also effectively reduce *H. pylori*-induced gastric inflammation and potentially prevent gastric cancer. However, there is a risk of cytotoxicity and adverse side effects from these medicinal plant products. Therefore, further studies on cytotoxicity, both in vitro and in vivo, are necessary. Additionally, further evaluation of the pharmacokinetics of these products in animals is required.

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