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Review article

H. pylori-induced Gastric Ulcer: Pathophysiology and Herbal Remedy

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A R T I C L E I N F O

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A B S T R A C T

Background: Gastric ulcer is a common, universal disease. Overall, 50% of gastric ulcers are induced by infection by **Helicobacter pylori (H. pylori)**, a gram-negative spiral-shaped bacillus. *H. pylori* colonization itself is not a disease, but infection causes various clinical disorders in the upper gastrointestinal tract. The treatment for eradication of *H. pylori* is complicated, requiring a minimum of two antibiotics in combination with gastric acid inhibitors. Triple Therapy and Bismuth Quadruple Therapy are well-known therapeutic measures used in eradication of *H. pylori* and *H. pylori*-induced gastrointestinal disorders, but they often cause nausea, antibiotic resistance, recurrence and other side effects. As a result, there is a growing interest in non-toxic, anti-ulcer formulations from medicinal plants to treat *H.pylori*-induced gastric ulcers. Objectives: Review the patho-physiology of *H.pylori* infection and its potential herbal remedy. Methods: Summarize the published literatures collected from Pubmed/Medline, Google Scholar and other online resources. Results: Natural medicines and plant products, such as tea, resveratrol, curcumin, garlic, cinnamon, etc. can heal *H. pylori*-induced gastric ulcers by scavenging the reactive oxygen and nitrogen species, boosting the host immune system, modulating host-pathogen heat shock proteins interactions. They are nontoxic in nature and hence can be used safely. Conclusion: Therefore, it is concluded that inclusion of natural antioxidants in the normal, daily diet may be the best remedial measure for continued protection from *H. pylori* infection.

1. Introduction

The use of herbal medicine can be traced back approximately 5000 years, to China. Extracts of several plants including Camellia sinensis, Phyllanthus emblica, Curcuma longa, and Bacopa monnerii have been used as therapeutic agents for many diseases by virtue of their antioxidant actions. Spices and herbs are recognized sources of natural antioxidants, many of which are phenols and aromatic amines. These can act at different molecular levels, by decreasing local oxygen concentrations, decreasing superoxide formation, and preventing chain initiation, metal-induced free radical generation, and lipid peroxidation. These antioxidants may protect the human body from several diseases [1].

Clinical research has confirmed the efficacy of several medicinal plants for the treatment of gastro-duodenal disease, and basic scientific research has uncovered mechanisms to explain their therapeutic effects [2, 3].

Gastro-duodenal ulcer is a common disease and occurs when the gastric mucosa becomes damaged and perforations lead to bleeding. A report of the Indian Council of Medical Research on the epidemiology of peptic ulcer in India (1972-1975) showed that the overall incidence of the disease ranged from 1 to 6.5 per thousand in the age group of 15 years and above in the selected urban population. Mahadeva and Goh have extensively studied and reported the epidemiology of this disease [4].

A common causative factor for gastric ulceration is an invasion of *Helicobacter pylori,* a micro-aerophilic, gram-negative, flagellated, spiral-shaped bacterium. Half of all gastric ulcer cases are associated with infection by *H. pylori* [5, 6]. The bacterium's spiral shape and high motility allow it to penetrate the deep portions of the mucus gel layer, restrict gastric emptying and survive in the grooves between epithelial cells under the protective gastric mucosal layer of the stomach. There, it causes local damage by inducing inflammatory mediator influx. Prostaglandins are involved in promoting the defense mechanisms

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of the stomach, and *H. pylori* may promote gastric mucosal prostaglandin secretion by up to 50% to maintain its preferred environmental conditions. Because prostaglandin levels in the gastric mucosa are decreased in elderly patients, ageing is associated with a diminished epithelial cell turnover rate and a reduced capacity to repair the gastric mucosa. Advanced age is therefore a major risk factor for complicated peptic ulcer disease. According to an estimate by the World Health Organization (WHO), half of the world's population is infected with *H. pylori*, but the infection has no detectable symptoms in most cases. However, over the past two decades, there has been a decrease in reported *H. pylori*-related peptic ulcer disease. This decrease is due to early detection using several sophisticated diagnostic tools and early treatment of the infection.

2. OVERVIEW OF LITERATURE

2.1. Pathogenesis of *Helicobacter pylori*

H. pylori is a gram-negative, short (0.2 to 0.5 m long), spiral-shaped, micro-aerophilic bacillus which invariably causes chronic active gastritis. *H. pylori,* identified in 1982, is now recognized as the primary etiological factor associated with the development of gastritis and peptic ulcer disease. *H. pylori* infections are also associated with chronic gastritis, gastric carcinoma and primary gastric B-cell lymphoma. Upon gastric colonization, *H. pylori* is found primarily in the deep portions of the mucus gel layer (that coats the gastric mucosa) and in between the mucus gel layer and the apical surfaces of the gastric mucosal epithelial cells. *H. pylori* sometimes adhere to the luminal surfaces of gastric epithelial cells but do not invade the gastric mucosa.

H. pylori colonization itself is not a disease, but an infection can lead to various clinical disorders in the upper gastrointestinal tract. In most cases, *H. pylori* colonization induces histological gastritis, but pronounced clinical signs seldom develop. It is estimated that *H. pylori*-positive patients have a 10% to 20% lifetime risk of developing ulcer disease and a 1% to 2% risk of developing distal gastric cancer [7, 8, 9]. This infection depends on different factors that relate primarily to the pattern and severity of gastritis (10). *H. pylori* bacteria mainly adhere to gastric epithelial cells and release cytotoxins causing duodenal ulcer. Several infection-associated factors of *H. pylori*, such as urease, catalase, lipase, adhesion molecules, cytotoxin-associated gene protein (CagA), a homologue of the Bordetella pertussis toxin secretion protein (picB) [11] and vacuolating cytotoxin (VacA), contribute to gastric ulceration.

H. pylori produces a variety of enzymes and is characterized by high urease activity. Urease breaks urea into bicarbonate and ammonia, which help to neutralize gastric hydrochloric acid (HCl) and protect the bacterium in the acidic environment of the stomach. Hydroxide ions generated by the equilibration of water and ammonia may contribute to gastric mucosal epithelium damage. Conversely, *H. pylori* infection reduces epithelial cell bicarbonate secretion, which leads to excessive diffusion of HCl into the mucosa, causing damage of the gastro-duodenal lining and leading to ulcer formation. It appears that *H. pylori* infection activates the vago-vagal reflexes (gut-brain axis) in the gastro-duodenal mucosa that damage the mucosal cells directly and enhance the secretion of gastric HCl, which ultimately leads to ulcerogenesis [12, 13]. Two other types of enzymes produced by *H. pylori*, proteases and phospholipases, also participate in the breakdown of the glycoprotein lipid complex of the mucous gel layer; this can cause severe gastric ulceration. In elderly persons, the integrity of the gastric mucosal surface becomes impaired and progressively susceptible to damage by factors that can overwhelm the protective barriers of the stomach.

Another class of proteins, termed heat shock proteins (HSPs), also plays a crucial role in *H. pylori*-induced gastric ulceration. HSPs are a class of functionally-related proteins whose expression is increased when exposed to elevated temperatures or other stress [14]. *H. pylori* appears to bind gastric epithelial cells and mucin via HSP 60. Adaptive immunity targeting HSP60 was found to be induced in *H. pylori*-infected patients. Interestingly, in contrast to their aforementioned protective roles, HSPs can also facilitate cell damage and promote carcinogenesis [15, 16]. Moreover, increasing evidence demonstrates that mammalian cells are not the only possessors of HSPs: bacteria such as *H. pylori* have HSPs, either to aid in survival against hostile host offense systems or to disrupt host defense systems.

A 62K urease-associated protein belonging to the HSP60 family of stress proteins participates in extracellular assembly and/or protection of urease inactivation in the hostile environment of the stomach [17].

H. pylori infection activates both epithelial and immunomodulatory cells, including monocytes and mononuclear phagocytes, which in turn secrete a number of pro-inflammatory cytokines, including TNF-α, IL-1/, IL-6, interferon (IFN)- and granulocyte-macrophage colony stimulating factor (18). Activated monocytes overexpress interleukin-2 receptors on their surfaces and produce superoxides and other inflammatory factors that ultimately damage mucus epithelial cells [19].

The *H. pylori* genome study is centered on attempts to understand pathogenesis. Approximately 29% of the loci in the genome database are categorized as pathogenic. A specific region of the bacterial genome encodes the virulence factor CagA. The cagA gene codes for one of the major *H. pylori* virulence proteins. The bacterium physically interacts with gastric epithelial cells and introduces CagA protein into the host cells. Bacterial strains that possess the cagA gene are associated with an ability to cause ulcers through inhibition of mucin synthesis [20]. This finding may suggest that cooperation among different *H. pylori* proteins is necessary to induce cell-cycle alterations in infected cells [21]. *H. pylori* induces mitogenic signals and proto-oncogene expression in gastric epithelial cells. The consequent hyperproliferation may trigger the development of cancer. An accumulation of intracellular reactive oxygen metabolites (ROMs) can induce point mutations in the DNA, thus disrupting the expression and function of several genes (such as p53); this is believed to contribute to the pathogenesis of gastric cancer. However, early eradication of *H. pylori* may be helpful to achieve complete reversal of oxidative damage of this highly-proliferating compartment, thus preventing the cellular DNA damage, which could trigger carcinogenesis [22].

This DNA damage could explain the increased risk of gastric cancer in *H. pylori*-infected patients. Interestingly, oxidative damage to DNA is not easily repaired and the damage becomes partially irreversible after *H. pylori* eradication.

2.2.Treatment of *H. pylori*

To date, the most effective therapies of *H. pylori* infection require a minimum of two antibiotics in combination with a gastric acid inhibitor. Both Triple Therapy (levofloxacin / Clarithromycin + amoxicillin + proton pump inhibitor) and Bismuth Quadruple Therapy (bismuth + tetracycline + metronidazole + proton pump inhibitor) are well known for *H. pylori* eradication as well as for *H. pylori*-induced gastropathy prevention. Complete eradication of *H. pylori* infection improves symptoms, including dyspepsia, gastritis and peptic ulcers, and may prevent gastric cancer. However, these treatments may cause nausea, drug resistance [23], infection recurrence [24], stomach upset and diarrhea [25]. Rising levels of acquired antimicrobial resistance necessitate the search for an effective *H. pylori* infection prevention strategy [23].

Extensive vaccine studies in mouse models have shown promising results [26]. Researchers are studying different adjuvants, antigens, and routes of immunization to ascertain the most appropriate system of immune protection; most of the research has only recently moved from animal studies to human trials [27].

Alternatively, there is a growing interest in and need to find non-toxic, safe and inexpensive anti-ulcer formulations from medicinal plants.

2.3.*H. pylori* and natural medicines

For centuries, herbals have been used in traditional medicine to treat a wide range of ailments, including gastrointestinal (GI) disorders, such as dyspepsia, gastritis and peptic ulcer disease (PUD) [28]. Natural antioxidants are usually considered safe by most consumers, and safety tests are not typically required by legislation because natural products are generally recognized as safe (GRAS). The medicinal properties of folk plants are attributed mainly to the presence of natural antioxidants (mainly polyphenols and flavonoids).

Flavonoids and other polyphenols present in the plant materials are beneficial for human health. Several mechanisms may account for their antioxidant activity. Flavonoids and polyphenols are efficient in trapping superoxide anion (O2-), hydroxyl (OH·), peroxyl (ROO·) and alcohoxyl (RO·) radicals, decreasing acid mucosal secretion, inhibiting the production of pepsinogen, promoting gastric mucosa formation and decreasing ulcerogenic lesions [29]. In addition, they have membrane-stabilizing properties, inhibit lipid peroxidation in different systems and affect some processes of intermediary metabolism. Any clinical trial of a putative herbal drug should be accompanied by a measurement of oxidative damage to show whether any benefit of that drug is correlated with its antioxidant activity.

Recent studies have suggested that *H. pylori* infection can be suppressed through the use of medicinal plants. Some important, widely-used medicinal plants and antioxidants for treatment of *H. pylori*-induced gastric ulcers are discussed below.

2.3.1 Berberine: Berberine is an alkaloid isolated from the roots and bark of several plants, including *Hydrastis canadensis, Berberis vulgaris, Berberis aristata and Anemopsis californica.* It has pronounced effect on prevention of *H. pylori* infection [30].

2.3.2. Black myrobalan (*Terminalia Chebula Retz*):

This plant is regarded as a universal panacea in Ayurvedic medicine and in traditional Tibetan medicine. The antibacterial activity of aqueous extracts of black myrobalan against *H. pylori* was significantly higher than that of ether and alcoholic extracts. Water extracts of black myrobalan (Haritaki) showed significant antibacterial activity and had a minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) of 125 and 150 mg/L, respectively [31].

2.3.3. Broccoli sprouts: Broccoli is a plant that evolved from wild cabbage (*Brassica oleracea*) and is a modulator of the immune system. It has great medicinal value, including anticancer, antiviral, and antibacterial activities. It is used extensively for prevention of *H. pylori* infection. A number of reports have demonstrated that 70 g of broccoli sprouts consumed daily for two months reduces the number of colonies of *H. pylori* in the stomach. Previous infection returned within two months if broccoli sprouts were removed from the diet. This treatment also enhances the protection of gastric mucosa against *H. pylori* but is relatively ineffective on related gastric cancers [32].

3. Cinnamon (*Cinnamomum verum* J.S. Presl, *Cinnamomum cassia Blume*, *Cinnamomum zeylanicum* Nees, *Cinnamomum loureirii Nees*): Cinnamon is a spice obtained from the inner bark of several trees from the genus Cinnamomum. These trees are native to South East Asia. A 1998 study from Israel demonstrated that extracts of cinnamon helped the stomach in its fight against *H. pylori* by inhibiting bacterial urease enzymes. The cinnamon was found to work as well as a common antibiotic. The primary constituents of the essential oil of cinnamon are 65% to 80% cinnamaldehyde and lesser percentages of other phenols and terpenes, including eugenol, trans-cinnamic acid, hydroxycinnamaldehyde, o-methoxycinnamaldehyde, cinnamyl alcohol and its acetate, limonene, alpha-terpineol, tannins, mucilage, oligomeric procyanidins, and trace amounts of coumarin [33].

4. Curcumin: Curcumin is a major yellow pigment of turmeric (*Curcuma longa*). In Ayurvedic practices, it is known for its many medicinal properties. In South Asia, it is used as an antiseptic and anti-inflammatory agent. Curcumin also prevents the growth of CagA+ strains of *H. pylori* in vitro and blocks NF-kB activation and the motogenic response in *H.pylori*-infected epithelial cells [34].

5. Garlic (Allium sativum): Garlic has had an important dietary and medicinal role for centuries. Louis Pasteur was the first to describe the antibacterial effect of garlic juices. Historically, garlic has been used worldwide to fight bacterial infections. Thiosulfinates and other secondary metabolites of garlic, including γ-glutamyl peptides, scordinins, steroids, terpenoids, flavonoids and other phenols, may be responsible for the range of therapeutic effects reported for garlic. Hughes and Lawson (1991) showed that the antimicrobial activity of garlic is completely abolished when the thiosulfinates (e.g., allicin) are removed from the extract [35]. It was observed that gram-negative *H. pylori* is susceptible to 40 μg/mL garlic extract [36].

6. Ginger:

Ginger (*Zinger officinale*) has been used as a traditional source of protection against gastric disturbances throughout history. Active components found in ginger rhizome extract are gingerols, which are structurally related polyphenolic compounds. Crude extract containing the gingerols was found to be active and inhibited the growth of CagA+ strains of *H. pylori* with an MIC range of 0.78 to 12.5 μg/mL [37,38].

7. Kimchi (fermented cabbage): Kimchi is a traditional fermented Korean dish, prepared by fermenting cabbage. Use of kimchi has been documented even as long as 2600 to 3000 years ago. It contains a bacterium strain "showing strong antagonistic activity against *H. pylori*" [39]. The bacterium strain isolated from kimchi, designated Lb. plantarum NO1, was found to reduce the urease activity of *H. pylori* by 40-60% and suppress the bacteria's binding to a human gastric cancer cell line by more than 33% [39].

8. Raspberries (*Rubus idaeus*): Raspberries, an effective natural combatant of the microorganism, have one of the highest concentrations of ellagic acid, a powerful disease-fighting substance. It was demonstrated that the ellagic acid present in raspberries could destroy several *H. pylori* strains. Ellagic acid was found to be a stable substance that does not degrade during storage or cooking and can be taken for eradication of H. pylori .

9. Resveratrol: Resveratrol (3,5,4'-trihydroxy-trans-stilbene) is a polyphenol that acts as a phytoalexin; it is produced naturally in several plants, such as grape (*Vitis vinifera*), peanut (A*rachis hypogaea*), and itadori (*Fallopia japonica*) root, when attacked by pathogens such as bacteria or fungi. Resveratrol has great remedial value. Many reports have suggested that this polyphenol has protective properties against *H. pylori*-induced ulcers [40]. Resveratrol inhibited the growth of CagA+ Strains of *H. pylori* in vitro [41] and induced interleukin-8 secretion, reactive oxygen species generation and morphological changes in human gastric epithelial cells [42].

10. Tea (Camellia sinensis): Tea, perhaps the most well-known neutraceutical, is widely employed as a digestive remedy throughout Europe, and its therapeutic use is well documented [43]. Tea, particularly green tea and black tea, are most important in herbal medicine. Among all of these medicinal plants, tea (*Camellia sinensis*) has provided new hope in the treatment of peptic ulcer and gastric malignancies. Its protective capacity against cancer and cardiovascular disease are of contemporary significance. Many of these medicinal values of tea are attributed to its antioxidant properties. Catechins, epigallocatechin, epicatechin gallate, epigallocatechin gallate and their oxidized forms, such as theaflavins and thearubigins, are the compounds primarily responsible for the antioxidative properties of green and black teas [44-47]. The use of tea in the prevention of *H. pylori* infection will be a major finding and great homage to herbal medicine.

Besides the above-mentioned plants and antioxidants, extracts of *Myristica fragrans* (seed) (MIC of 12.5 μg/mL), *Rosmarinus officinalis* (rosemary leaf) (MIC of 25 μg/mL), *Achillea millefolium* (MIC of 50 μg/mL), *Foeniculum vulgare* (seed) (MIC of 50 μg/mL), Passiflora incarnata (herb) (MIC of 50 μg/mL), *Origanum majorana* (herb) (MIC of 50 μg/mL) and a (1:1) combination of *Curcuma longa* (root) and ginger rhizome have been found to be effective in *H. pylori* eradication and in the healing of gastric ulcers. Botanical extracts included *Carum carvi* (seed), *Elettaria cardamomum* (seed), *Gentiana lutea* (roots), *Juniper communis* (berry), *Lavandula angustifolia* (flowers), *Melissa officinalis* (leaves), *Mentha piperita* (leaves) and *Pimpinella anisum* (seed) have also found to be effective in *H. pylori* eradication (MIC = 100 μg/mL). Methanolic extracts of Matricaria recutita (flowers) and Ginkgo biloba (leaves) (MIC > 100 μg/mL) have also been studied for anti-*H. pylori* properties [48].

Therefore, it is concluded that inclusion of natural antioxidants in the normal, daily diet may be the best remedial measure for continued protection from *H. pylori* infection.

11.Conclusion

Several natural antioxidants are able to promote healing of *H. pylori*-induced gastric ulcers. The beneficial effects of these natural antioxidants are due to their ability to scavenge free radicals, inhibiting lipid peroxidation and the generation of reactive oxygen species and reactive nitrogen species. Our present report states that daily intake of natural antioxidants might be help to reduce *H. pylori*-induced gastric ulceration.

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