

Management of *H. pylori* Induced Peptic ulcer – A Phytotherapeutic Approach

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Abstract

A peptic ulcer is a chronic infectious disease that creates erosion on the epithelial lining of the stomach. It is a commonly encountered problem in the gastrointestinal tract (GI tract). Patients failed multiple regimens due to resistant *H. pylori* infection. *H. pylori* show maximum resistance towards Clarithromycin. Due to the consistent increase in resistance there is urgent need for the development of new drugs. Paying much for the antibiotic treatment one should go for the natural treatments with no side effects. Modern treatment of peptic ulcers emphasizes diet with routinely recommend hospitalization of several weeks. Currently, a lot of medications are coming out of natural products. The phytotherapeutic approach for the resistant *H.pylori* treatment is assessed. The plant produces many secondary metabolic substances which have a lot of beneficial roles in maintaining human health. Administration of plant products would prevent disease and able to eradicate resistant *H.pylori*. This review includes many phytoproducts having a wide range of antimicrobial activity. Reviewed phytoproducts includes Phytoceutical, Caffeic acid, phenethyl ester, Flavonoid, Capsaicin, Carotenoid, etc are effective treatment against *H.pylori*. To see their effect on the resistant *H.pylori* and to manage this resistant bacteria with an application of plant products is the prime concern of this review. The linkage between phytochemical and peptic ulcers will provide a novel framework for the future.

Keywords: *H. pylori*, Peptic Ulcer, Plant Products, Resistant Antibiotics, Phototherapeutic Management, Ethnomedicine

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Citation: Lenka S, Bhuyan R. Management of *H. pylori* Induced Pepticulcer – A Phytotherapeutic Approach. J Pure Appl Microbiol. 2022;16(3):1530-1537. doi: 10.22207/JPAM.16.3.36

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INTRODUCTION

The stomach is a glandular 'J' shaped organ lined with epithelial cells and it has a considerable amount of mucus mass and is constantly influenced by digestive enzymes, hydrochloric acid, microbes, and bile which in turn encounter producing mucus, prostaglandins, and bicarbonate to maintain the integrity of its lining, and this equilibrium is persistently synchronized and called mucosal defense. A peptic ulcer is due to an imbalance between mucosal protective mechanisms against damaging forces.¹ It can be defined as the roughened area or cavity which is found in the stomach. Due to the hypersecretion of acid, it attacks the epithelial lining of the stomach which in turn causes soreness and is termed an ulcer. The ulcer is of two types that is a duodenal ulcer and gastric ulcer and combinedly termed as peptic ulcer.

The human body is exposed to numerous microorganisms in the environment every day. These organisms play important role in both health and diseases. *H. pylori* has been the main focus of study for gastrointestinal tract diseases for a long. It is a Gram-negative, microaerophilic organism that is associated with a variety of diseases like chronic gastritis, peptic ulcer, non-cardio gastric adenocarcinoma, gastric cancer, and gastric mucosa-associated lymphoid tissue lymphoma.^{2,3} However, it's important to understand at the outset that the vast majority of people who were infected with *H. pylori* when they are young are infected for life, and about three-quarters of these people or more have no symptoms in their whole lifetime. They would never know they had *H. pylori* unless somebody either cultures them or does another kind of test. A subset of people who have *H. pylori* develops gastritis. Some of these people go on to develop ulcer disease.

Duodenal ulcers and 70% of gastric ulcers are due to *H. pylori* infection.⁴ *H. pylori*-infected persons develop gastric damage. Among those infected patients, only 17% develop peptic ulcers.⁵ Triple therapy and quadruple therapy are used for the eradication of *H. pylori* but the rate of efficacy varies between 75% - 95% and the main reason for failure is due to antibiotic resistance.⁶

Despite several drug treatments that have been developed for various types of ulcer

diseases, it has pernicious side effects. Emerging more resistant *H. pylori* is a worldwide problem and it demands the replacement of antibiotics with natural products. We believe that a combination of natural plant products that have anti-*H. pylori* activity could give the best result. This review was carried out with the help of bibliographic databases such as Google scholar, web of science, and PubMed.

Epidemiology and Prevalence of Peptic Ulcer

The rate of prevalence of *H. pylori* in developing countries is very high, that is about 80-90% in the case of adults in comparison with developed countries which is about 10-50% and this is due to low socioeconomic conditions.⁷ *H. pylori* infection is very common and in fact, is one of the most common infections worldwide. The rate of peptic ulcers brings down from before, but it has become more powerful than before and the occurrence of this disease are linked with age, sex, geographic environmental factors, and occupation.^{8,9} the frequency of peptic ulcers is between 19.4 - 57.0 per 100,000 people, with the number increasing every year.¹⁰

According to a study of 1335 peptic ulcer patients in Iran, the prevalence of peptic ulcers differed between male and female patients, with 60% and 30% respectively, and 62% of patients developed peptic ulcers as a result of *H. pylori* colonization and 30% as a result of environmental variables.¹¹

Major Factors

The first most common cause of peptic ulcer is infection with *H. pylori* and the second major cause of peptic ulcer is excessive secretion of hydrochloric acid (HCl). Higher concentration and higher volume of HCl secretion can alter the protective epithelial lining of the stomach and gastric cells because the amount is more than what the body can resist.⁸ The third cause is anti-inflammatory drugs like aspirin [Figure 1]. Studies showed that these drugs irritate the lining of the stomach and impair the barrier properties of the mucosa and increase the suppression of anti-inflammatory gastric prostaglandins, reducing gastric mucosa blood flow which affects the defense and repair of the lining of the stomach.^{12,13}

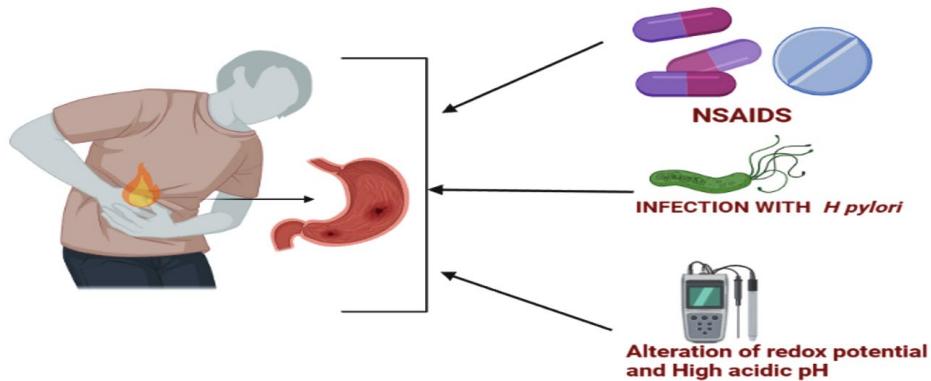


Figure 1. Etiology of peptic ulcer.

***Helicobacter pylori* Pathogenesis**

The most common cause of peptic ulcer is infection with *H. pylori*. It is a gram-negative, spiral-shaped bacteria having flagella that help in motility. The root of transmission is by fecal-oral route or through oral-oral route.¹⁴ The important virulence factor that *H. pylori* possess includes lipopolysaccharide which helps in adhering cells, so it can attach itself to the gastric cells of the stomach by secreting adhesion molecule which is recognized by glycan structure that is expressed on the surface of gastric epithelial cells and the surface of mucus layer lining (Figure 2). Another important virulence factor of *H. pylori* is the enzyme on the surface known as urease and this enzyme protects from acidity as urease converts urea to ammonia and CO₂. Further ammonia helps the bacteria from acidity by increasing pH to neutral as it is alkaline.¹⁵ This bacteria also secrete

some exotoxins such as Vac A and Cag A. Vac A is a fairly potent kind of poison that causes apoptosis of cells and Cag A is responsible for disrupting cellular integrity and structure, and promotes inflammation. Cag A stimulates the production of certain chemokines such as IL-8 within its cells which in turn attracts neutrophils into the area. Neutrophils are highly inflammatory and can damage the stomach tissues (Figure 3). The combination of Cag A and Vac A causes stomach cells to break down, resulting in ulcer formation.¹⁶

According to Khademi et al.²¹ the generality of resistance for clarithromycin is excessive than other antibiotics and that is about 64.9% which has been shown on the graph [Figure 4] [Table 1]. The prevalence of resistance for amoxicillin shows very little [Table 1].¹⁷⁻¹⁹ Our diet is rich in red meat, junk food, sugar, starch, etc. We do not consume the number of vegetables and

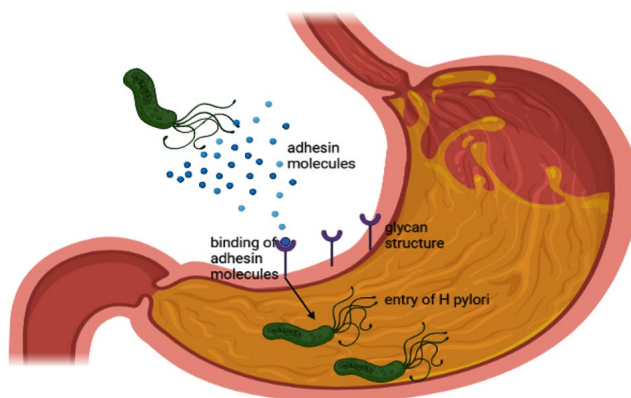


Figure 2. Pathophysiology of *H.pylori* with the lining of the stomach.

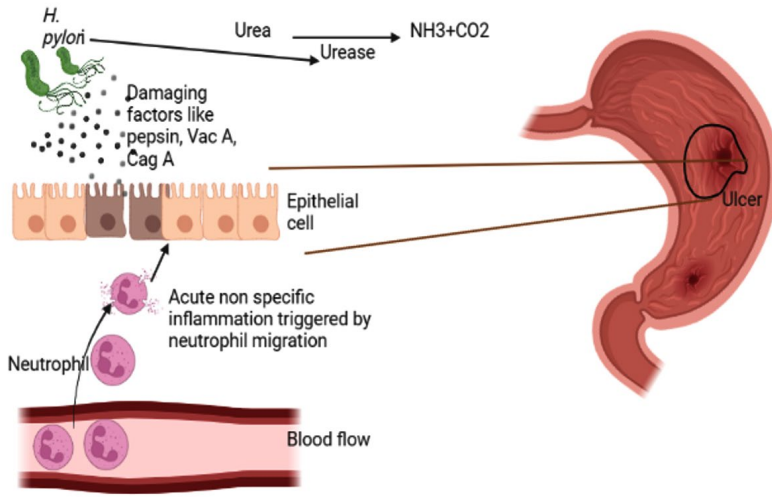


Figure 3. Pathogenesis of *H. pylori*.

fruits that we are supposed to take, and do not intake the right balance of foods that balance out our body systems and therefore end up with a lot of different diseases. A lot of natural supplements do help in regulating our bodies.

Table 1. Illustrates the resistance of different antibiotics in different years.

Polyphenol

Polyphenol is a bioactive secondary metabolic compound, generally obtained from

fruits and vegetables, can suppress the negative effects of *H. pylori* in the GI tract. Traditionally, it is used for prevention of many diseases like cancer, neurodegenerative, osteoporosis, etc. It is potentially involved in inhibiting telomerase, cyclooxygenase enzymes.^{32,33}

Capsaicin

Capsaicin is a natural compound, extracted mostly from chili pepper shows a wide range of significant effects in maintaining the GI-

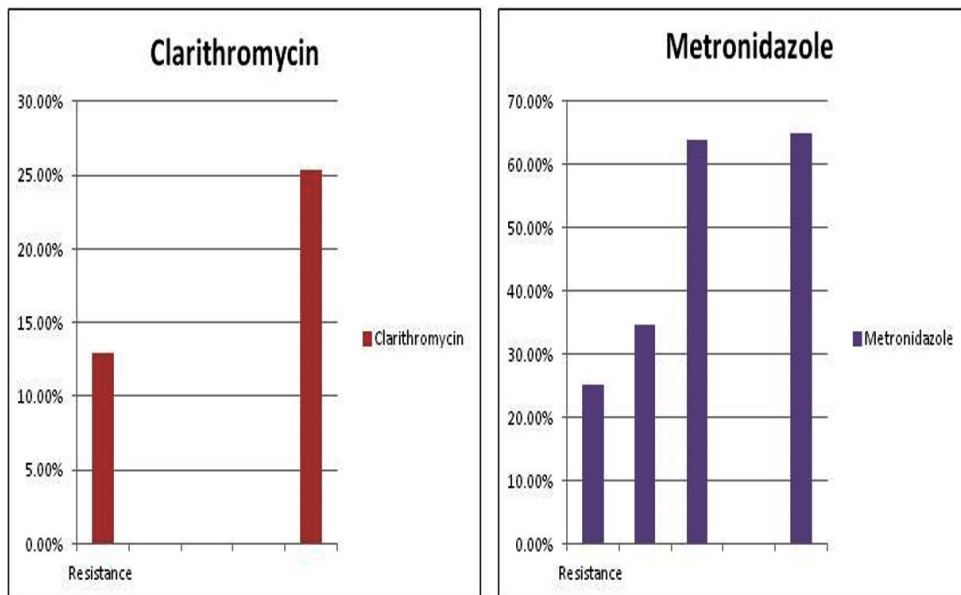


Figure 4. Most resistant antibiotic.

tract. It shows cytoprotective effect, antioxidant property, anti-inflammatory, anti-proliferative effects, and inhibitory effect at 50ug/ml. Cancer cell line like MKN-45 in the stomach induces the production of IL-8, which is ultimately suppressed by administration of capsaicin. It can suppress the activation of NF-κB, whose activation is induced by *H. pylori* infection.^{34,35}

Caffeic Acid Phenethyl Ester

Caffeic acid phenethyl ester are extracted products of propolis, have antioxidant, anti-carcinogenic, immunomodulatory, anti-inflammatory properties.²³

Flavonoids

Flavonoids are the main constituents of most herbal products. According to Toshio Fukui et al. Flavonoids (licoricone, gancaonol, vestitol and 1-methoxyphaseollidin) extracted from

Glycyrrhiza glabra is a potential herbal medicine against resistance *H. pylori* as it shows inhibitory effect on both amoxicillin and clarithromycin resistance strain.³⁶ In stress condition, flavonoids are released from plants as secondary metabolic polyphenolic substances and protect the plant from a pathogen.³⁷

Quercetin

Quercetin is found broadly in most vegetables and fruits and has strong antioxidant properties. The skeletal structure of Quercetin is quite similar to flavone. According to Xin-Ting et al. gastroprotective mechanism has been observed with the application of Quercetin. When Quercetin is applied on gastro epithelial cells, it is observed that loss of cell viability due to hydrogen peroxide, reduces drastically. It is also found that it suppresses Calcium ion influx and reactive oxygen species activity.³⁸

Table 1. Antibiotics preferred for the management of *H. pylori*

| Antibiotics | Metronidazole | Clarithromycin | Amoxicillin | Tetracycline | levofloxacin | Reference |
|-------------|---------------|----------------|-------------|--------------|--------------|-----------|
| Resistance | 25.1% | 12.9% | 0.9% | 0% | | [17] |
| | 34.7% | 16.7% | 11.8% | | | 18 |
| | 63.9% | 37.2% | 0.3% | 1.2% | 50.3% | 19 |
| | 30%-40% | 65%-75% | | | 37.5% | 20 |
| | 64.9% | 25.3% | 20.7% | 16.1% | 21.9% | 21 |

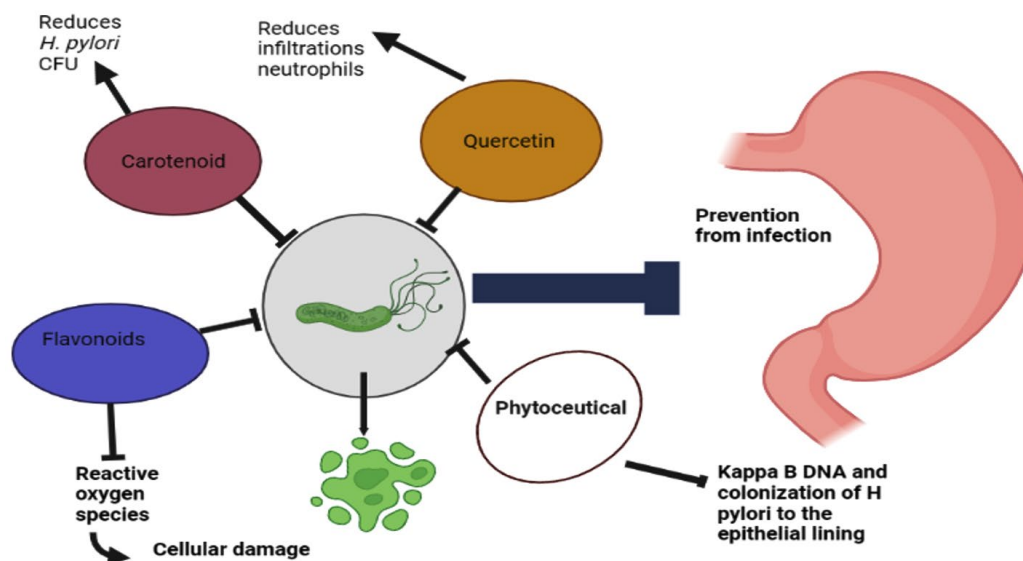


Figure 5. *H. pylori* prevention Mechanism using plant products

Table 2. List of plant products having anti-*H. pylori* activity

| No. | Plant products | Source | Role | Ref. |
|-----|----------------------------------|--|--|------------|
| 1. | Capsaicin | Chilies | Decreases IL-8 production Suppresses | 22 |
| 2. | Caffeic acid phenethyl ester | Propolis | inflammation and also decreases the density of <i>H.pylori</i> | 23 |
| 3. | Flavonoid | Sideritis mugronensis | Increases prostaglandins which in turn boosts defense mechanism in the stomach | 24 (Fig.5) |
| 4. | Acacetin and luteolin | Chamomile tea, broccoli, carrots, apple skin | Reduces ulcer which happens due to histamine induction. | 24 |
| 5. | Phytoceutical | Probiotics, Green tea, broccoli sprouts, red wine, flavonoids, garlic, | It prevents the colonization of <i>H. pylori</i> to the epithelial lining It also halts cancer by Suppressing the activity of kappa B DNA | 25 (Fig.5) |
| 6. | Flavonoids and proanthocyanidins | Citrus fruits, berries, onions, and legumes | Due to antioxidant properties, it prevents reactive oxygen species which causes cellular damage | 26 (Fig.5) |
| 7. | Quercetin | Vegetables and fruits | Reduces neutrophils | 27 (Fig.5) |
| 8. | polyphenol | Apple peel | Anti-inflammatory and reduces colonization of <i>H.pylori</i> | 28 |
| 9. | Ethanol extract | Garlic | Reduces erosion on the stomach | 29 |
| 10. | Curcumin | Turmeric plant | Plays vital role in the eradication of <i>H.pylori</i> | 30 |
| 11. | Carotenoid | Apple peel | Reduces <i>H.pylori</i> CFU | 31 (Fig.5) |

Curcumin

It has anti-oxidant, anti-inflammatory, anticarcinogenic, and antimicrobial properties. It inhibits iNOS, COX-2, LOX, mediated signaling pathways. It reduces the inflammation which is caused by certain cytokines like TNF- α , IL-6, and IL-1 β .^{39,40}

Carotenoids

Carotenoids can act more efficiently than metronidazole. The minimum inhibitory concentration of carotenoids is considerably high than the amoxicillin and clarithromycin but Carotenoids can act more efficiently than metronidazole. Carotenoids like neoxanthin and luteoxanthin show more effective results than other carotenoids.³¹

Ethanol Extract

It is observed that the application of garlic can give a significant result. About 1-4% of garlic intake can suppress the gastric lesion in *H. pylori*-infected individuals.

It can be used for various pharmacological functions like wound healing, anti-cancer, anti-

oxidant, immunomodulatory potential, anti-inflammatory, etc. It inhibits the growth of different strains of bacteria and fungi. Allicin and ethanol bioactive chemicals present in garlic make it more potent against various kinds of diseases.⁴¹

Table 2 Emphasizes the plant products having a wide range of antimicrobial properties. Phytoceutical which is obtained from broccoli, garlic, green tea, etc. And polyphenol from apple peel can be used in the management of *H.pylori* products.

CONCLUSION

Many plants having anti-ulcer and other medicinal properties were used as ethnomedicine worldwide. It is obtained from the data that Phytoproducts like Phytoceutical, flavonoids, and carotenoids, protect the lining of the stomach by preventing colonization of *H. pylori* and also has erosion healing activity. Its antioxidant property provides defense towards reactive oxygen species. Further, more clinical trial is needed concerning the following points-

1. Standardization of plant products is necessary

to deal with peptic ulcers.

2. We can normalize Eh and the pH of the stomach using Phytoproducts.

A comparative study should be carried out with a large sample size on different populations with different diets to rule out the efficacy of plant products in the management of *H. Pylori* induced peptic ulcers.

ACKNOWLEDGMENTS

The authors would like to thank President of Siksha 'O' Anusandhan deemed to be University, India for providing necessary facilities to carry out this study.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORS' CONTRIBUTION

RB conceptualized and designed the work. SL perform the literature survey and wrote the manuscript. RB reviewed and edited the manuscript. Both authors read and approved the final manuscript for publication.

FUNDING

None.

DATA AVAILABILITY

All datasets generated or analyzed during this study are included in the manuscript.

ETHICS STATEMENT

Not applicable.

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