Sys Rev Pharm 2021; 12(8): 460-465
A multifaceted review journal in the field of pharmacy
E-ISSN 0976-2779 P-ISSN 0975-8453

Review Article

Prospectives of *Helicobacter pylori*

S Manodhini Elakkiya*, R Sambath Kumar, N Venkateswaramurthy
Department of pharmaceutics, JKK Nattraja College of Pharmacy, Tamil Nadu, India

Article History: *Submitted: 26.04.2021* *Accepted: 10.05.2021* *Published: 17.05.2021*

ABSTRACT

Helicobacter pylori (H. pylori) is a gram negative bacteria whose infection is highly prevalent among the human population and leads to gastrointestinal tract related diseases (gastric and duodenal ulcers, mucosa associated tissue lymphoma and gastric adenocarcinoma). Most people with *H. pylori* infection will never have any signs or symptoms. While this bacterium infects 50% of the world's population, in Africa its prevalence reach as high as 80% as the infection is acquired during childhood. *H. pylori* eradication treatment is becoming more challenging due to increasing antimicrobial resistance. Treatment regimens are expected to overcome the increasing prevalence of resistant strains of *H. pylori* and achieve a >90% eradication rate. Although treatment regimens provide acceptable *H. pylori* eradication rates, the regimens used should contribute to future resistance of *H. pylori* to antimicrobials and other therapies.

Keywords: *Helicobacter pylori*, Route of transmission, Thumb rules, Treatment regimen

***Correspondence:** S Manodhini Elakkiya, Department of Pharmaceutics, JKK Nattraja College of Pharmacy, Tamil Nadu, India, E-mail: manodhinielakkiya@jkkn.ac.in

INTRODUCTION

Helicobacter pylori (H. pylori), previously known as Campylobacter pylori, are a spiral shaped bacteria which is indicated by the term '*Helico*'. They are attached to or located just above the gastric mucosa (Tan VP and Wong BC, 2011). The significance of the *H. pylori* for the human diseases were first acknowledged at 1983. Nearly 60 percent of the world's adult population has been infected. Though they are asymptomatic, they can lead to peptic ulcers and gastritis, an inflammatory condition of the stomach, in some people (Amieva M and Peek Jr RM, 2016). Gastric infections caused by *H. pylori* is one of the most widespread infectious disease worldwide with an estimation of 40%-50% of the population(McNamara D, *et al.*, 2002).Various diagnostic tests are available for the testing the presence of *H. pylori* in patients suffering with ulcer or dyspepsia. The commonly used tests are the evaluation of biopsy specimens during upper Gastrointestinal tract (GI) I endoscopy, the detection of serum anti-*H. pylori* antibodies and breathe tests with 13 C-labeled urea (Howden CW and Hunt RH, 1998; Drumm B, *et al.*, 2000; Graham DY and Qureshi WA, 2001).

H. pylori is adapted to live in harsh acidic environment and so they are well suited to survive in the stomach. These bacteria are capable of changing their surrounding environment and it reduces the acidity of stomach so they could live there. The spiral shape of the bacteria helps in penetrating of the stomach lining, where they are protected by mucus from the body's immune system. These bacteria lead to stomach related problems (McNamara D, *et al.*, 2002).

More than 80% of the people affected do not express any symptoms and it may also play an important role in the natural stomach ecology. Nearly 50%-75% of the worldwide population has been affected by *H. pylori* infection. Over 70% of the people are affected in the developing countries whereas only 25%-50% of the population are affected in the developed countries (Howden CW and Hunt RH, 1998). It is revealed in the annual report that the rate of the infection in Asia is 4.3%-13% greater than the West, where the infection rate is only 0.5%-2.5% (Drumm B, *et al.*, 2000). Studies has shown that in Asia the prevalence is greater in the over populated countries like China(58%), South Korea(60%), Vietnam(75%), India(79%), Bangladesh(92%) than the less populated countries like Singapore(31%), Malaysia(36%), Japan(39%), Taiwan(55%) and Thailand(57%) (Graham DY and Qureshi WA, 2001).

Most of the children are affected by this infection from the parents or siblings and they are also affected due to the transmission of the bacterium to the GI tract by oral cavity, by fecal-oral route or by human to human transmission (Zhao S, *et al.*, 2014; Safavi M, *et al.*, 2016). The *H. pylori* infection is most commonly associated with the lower socioeconomic background, poor diet and hygiene, over-crowding, ethnicity, ages and sex, as well as less educated level and geographic location, which plays a major role in the distribution of the infection (Rana R, *et al.*, 2017).

Most affected person's are asymptomatic, for which the reason is not very clear, but some person's could be born with more resistant immune system. But when the symptoms occur, the may include:

- An ache or burning pain in your abdomen
- Abdominal pain that's worse when your stomach is empty
- Nausea
- Loss of appetite
- Frequent burping
- Bloating
- Unintentional weight loss

H. pylori can lead to various upper gastrointestinal disorders such as gastric inflammation (gastritis), heartburn, gastro esophageal reflux disease, gastric duodenal ulcer disease, gastric cancer and Mucosa-Associated Lymphoid Tissue (MALT). Several eradication measures are available to treat the infection caused by *H. pylori* and one of the most widely used method is the several combined antibiotics, such as amoxicillin plus clarithromycin or metronidazole with a proton-pump inhibitor. Nowadays, the main problems faced towards *H. pylori* infection is antibiotic resistance, patients compliance and intolerance to therapeutic regimens. Antibiotic resistance is a major concern as the *H. pylori* becomes resistant to drugs and thus the treatment fails (Stollman NH and Graham DY, 2014). This resistance can be caused due to poor drug penetration, low drug concentration, short gastric residence time and also the antibiotic resistance represent a significant health care burden on the society. Patient compliance also becomes a problem due to poor stability of antibiotics in gastric content which requires frequent administration of the antibiotics (Pacifico L, *et al.*, 2010; Carraher S, *et al.*, 2013). The different therapies used for the treatment of *H. pylori* infection are standard, sequential, quadruple, concomitant and levofloxacin therapy. These therapies are best of the treatments and assure high cure rate. Though, recently standard triple therapy has shown reduced efficacy due to antibiotic resistance. Bismuth quadruple, concom-

itant, sequential and levofloxacin therapies are currently better than standard therapy that is providing promoted efficacy (Graham DY B, *et al.*, 2014). The last few decades has been proved that the eradication of this infection has been standardized but the resistance to therapeutic regimen poses as a growing problem. The intention of this paper is to provide an appraisal of the most effective, current treatments that are readily available for *H. pylori*, and also to speculate on the potential for newer approaches in treatment and prophylaxis in the future *(Figure 1)*.

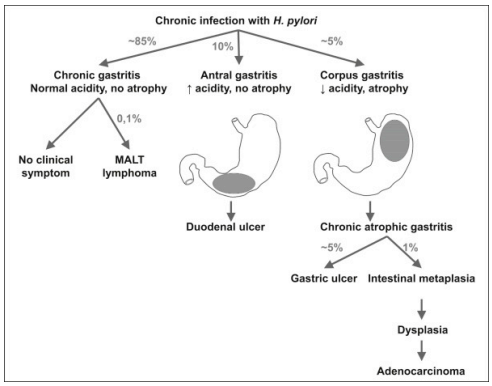

Figure 1: *Helicobacter pylori* infection

ROUTE OF TRANSMISSION

The transmission mechanism of *H. pylori* are still not well defined. The known factor is that the *H. pylori* travels from mouth to esophagus. The most likely modes of transmission are oral-oral and fecal-oral routes. Iatrogenic transmission is a rarely reported route. And then role of insect vectors is yet to be clarified.

Oral-oral transmission

This method has not been confirmed as of yet. *H. pylori* has been identified in dental plaque and has been rarely cultured in the buccal region (Hardo PG, *et al.*, 1995). Even then, the incidence of the infection has not been reported in hygienists and dentists much frequently, despite the fact that they are experiencing occupational exposure to oral aerosols. But on the either hand, gastroenterologists are reported to have higher prevalence than age-matched controls; 52%, compared with 21%. These changes were mostly observed in older gastroenterologists, who did not follow the necessary precautions in their early stages of practice (Mitchell HM, *et al.*, 1989). *H. pylori* was also cultivated from the vomit and saliva from healthy infected volunteers (Parsonnet J, *et al.*, 1999).

Fecal-oral transmission

This method is also possible. In the developing countries, water contamination serves as a source of organism exposure. Polymerase Chain Reaction (PCR) techniques were performed to confirm the presence and growth of *H. pylori* colony in the municipal water supplies and the other studies also suggests that these organism can survive in water for several days (Hulten KR, *et al.*, 1996). These organisms have also been found in the stools of children from Gambia and West Africa, where there is 99% prevalence of infection (Thomas JE, *et al.*, 1992). Intra-familial clustering of infection also supports and enhances person to person spread. The young children who gets affected by the *H. pylori* infection are most likely to have an already affected parent or siblings (Drumm B, *et al.*, 1990). However, the isolates may not be the same within each family member, implying the involvement of other sources.

Iatrogenic transmission

This type of spread can be documented. A contaminated pH probe can affect 17/34 consecutive patients (Ramsey EJ, *et al.*, 1979). In another study, it is known that a volunteer was infected with a contaminated endoscope. The risk of this transmission has been estimated at 4/1000 endoscopies in the developed world.

Vector transmission

Non human vectors plays an important role. Recent studies has also suggested that the domestic cats may also act as a carrier of *H. pylori* but it remains as a controversial fact (Handt LK, *et al.*, 1995). Though isolation of organisms in cat saliva suggests transmission of *H. pylori* studies have also shown that house flies can not only carry the bacterium but also harbor them (Grübel P, *et al.*, 1997). Evidence of *H. pylori* has been gathered in the house flies in the developing countries as well as in the United States, but it may also be due to environmental contamination rather than mode of transmission (Grubel P and Huang L, 1998).

Reinfection

Reinfection after cure is unusual in developed countries, and is estimated to be less than 1% per year (Parsonnet J, 1995). Recurrence of infection most likely represents recrudescence. Reinfection rates are higher in developing countries and are approximately 8%-15% (Rollan A, *et al.*, 2000). However, it is not yet clear whether it is due to inadequate monitoring. In developed countries it has become an uncommon occurrence in children and it may be due to improved sanitary and hygiene conditions.

Diseases associated with H. pylori

The *H. pylori* condition is associated with gastritis, Non-Ulcer Dyspepsia (NUD), duodenal ulcer, gastric ulcer, gastric cancer, gastric lymphoma of Mucosa Associated Lymphoid Tissue (MALT) and even coronary heart disease. It is also proved that they are also the cause of almost all Duodenal Ulcers (DU) and chronic benign Gastric Ulcers (GU) which are not associated with Nonsteroidal Anti-Inflammatory Drugs (NSAID). More than 95% of DU and 90% of GU are associated with *H. pylori* infection and there is a dramatic decrease in their relapse rate after the *H. pylori* eradication. As for now there in no reliable evidence that NUD symptoms are due to *H. pylori* infection. The prevalence of this disease can be compared between a healthy individual and the patients who shows symptoms of NUD. Further studies are necessary to eradicate the *H. pylori* completely in NUD (Rogha M, *et al.*, 2012; Rogha M, *et al.*, 2012).

Rules of thumb for optimizing Helicobacter pylori treatment

1. Use four drugs
2. Use maximal acid inhibition
3. Treat for 2 weeks
4. Do not repeat antibiotics after treatment failure
5. If your treatment works locally, keep using it.

Rule of thumb 1: Use four drugs: Overall, three main groups of quadruple therapies have been assessed in the literature:

(a) adding metronidazole to classical clarithromycin-containing triple therapy,

(b) classical PPI-bismuth-metronidazole-tetracycline quadruple therapy, and

(c) adding bismuth to triple therapy.

Rule of thumb 2: Use maximal acid inhibition: *H. pylori* needs an acidic medium to survive due to its production of NH3 which needs to be neutralized by acid. High gastric pH allows the replication of the bacterium. Higher PPI doses to adequately control gastric pH Many meta-analyses have shown that increasing acid inhibition raises cure rates with *H. pylori* triple therapy.

Rule of thumb 3: Treat for 2 weeks: Since the first meta-analysis was published (Hwang JJ, *et al.*, 2015), it has been clearly established that increasing the length of triple therapy from 7 to 14 days increases cure rates. 14-day concomitant therapies consistently achieved cure rates of around 90%, whereas 10-day therapies were somewhat less reliable.

Rule of thumb 4: Do not repeat antibiotics after treatment failure: Repeating of certain antibiotics only when it is indispensable and in the setting of 14-day quadruple therapies. Thus, it helps in the forming of reduced resistance against the antibiotics and so the antibiotic can be used repeatedly without decrease in the efficacy. Therefore, certain antibiotics like bismuth, amoxicillin and tetracycline can be used in the same patients despite the fact that the previous treatment has failed. These data should be taken into consideration when choosing a rescue therapy among the various consensus recommendations.

Rule of thumb 5: If your treatment works locally, keep using it: There is no defined worldwide gold standard treatment. Most of the studies have been using combinations of the drugs mentioned above. However, recommendations should be locally adapted. As long as monitoring of cure rates confirm high effectiveness, there is no reason to change to more complicated schedules (Saad R, *et al.*, 2005; McCarthy C, *et al.*, 1995).

TREATMENT

First-line therapy

The current first-line treatment for *H. pylori* includes a PPI in combination with the antibiotics clarithromycin, metronidazole or amoxicillin for a duration of 7, 10 or 14 days (Hwang JJ, *et al.*, 2015; Dos Santos AA and Carvalho AA, 2015). Due to high resistence of antibiotics gastroenterologists proposed a novel regimen, called 'sequential therapy', for regions with high rates of clarithromycin resistance (>20%) (Zullo A, *et al.*, 2003).

Second-and third-line therapy

Several reports have confirmed that the first-line therapy. Accordingly, after several reports of failures in first-line therapy, 10 days of bismuth-containing quadruple therapy or levofloxacin-containing triple therapy as second-line treatment was increasingly recommended (Song Z, *et al.*, 2016). It has been observed that there is a limit for prescribed antibiotics in second- and third-line therapies. It has been shown that extending the duration from 1 week to 2 weeks in second-line therapy can increase the efficacy of treatment (Chuah SK, *et al.*, 2012; Miehlke S, *et al.*, 2011; Tai WC, *et al.*, 2013). It was logical to redesign the regimens with different antibiotics such as levofloxacin or rifabutin due to *H. pylori* resistence to antibiotics (metronidazole and clarithromycin) (Chuah SK, *et al.*, 2011).

Probiotics

A living microbe that may have a positive effect towards eradicating pathogens is called probiotics. The main explanations for this theory are: decreasing side effects following therapy; and (ii) increasing eradication rate. However, a long list of examinations is required to accurately identify which probiotic strains, delivery route and administered dose can provide the best probiotic panel in the clinical setting (Lesbros-Pantoflickova D, *et al.*, 2007; Schrezenmeir J and de Vrese M, 2001). Mostly it is suggested that the probiotics should be given as an adjuvant along with the regularly prescribed antibiotic therapy to provide better therapeutic effectiveness. At the least, they reduce the side effects which occur followed by chemotherapy (Rostami N, *et al.*, 2008; Fallone CA, *et al.*, 2016; Gatta L, *et al.*, 2018).

A number of mechanisms have been anticipated for probiotic efficacy against *H. pylori*. Probiotic bacteria can modulate *H. pylori* activity by either immunological (e.g., increment of serum IgA and reduction in cytokine profiles such as IL-6) or non-immunological mechanisms (antagonism and competition with potential pathogen (Ayala G, *et al.*, 2014; Patel A, *et al.*, 2014; Yang YJ and Sheu BS, 2012; Ljungh A and Wadstrom T, 2006). The use of probiotics, as adjuvant therapy, appears promising for the current *H. pylori* eradication treatment, in order to reduce the frequency of antibiotic induced side-effects, though it still requires optimization (Zojaji H, *et al.*, 2013; Khodadad A, *et al.*, 2013). Briefly, we are still in the early stages of using probiotics against *H. pylori* infection *(Table 1)*.

Table 1: Evidence based treatment regimens (Fallone CA, et al., 2016; Gatta L, et al., 2018; Ayala G, et al., 2014)

Treatment	Drugs used	Duration of use	No of days used
Clarithromycin based therapy	PPI, clarithromycin, and amoxicillin	Twice daily (for all antibiotics)	14
Bismuth based therapy	PPI, bismuth, tetracycline, and nitroimidazole	Four times daily for all antibiotics	10 to 14
Concomitant therapy	PPI, clarithromycin, amoxicillin, and nitroimidazole	Once daily for all antibiotics	10 to 14
Sequential therapy	PPI and amoxicillin; then PPI, clarithromycin, and nitroimidazole	Twice daily for all antibiotics	7; 7
Hybrid therapy	PPI and amoxicillin; then PPI, amoxicillin, clarithromycin, and nitroimidazole	Twice daily for all antibiotics	7; 7
Levofloxacin based therapy	PPI, levofloxacin and amoxicillin	Once daily Twice daily	10-14
Fluoroquinolone based sequential therapy	PPI and amoxicillin; then PPI, levofloxacin, and Nitroimidazole	Twice daily for all antibiotics	5-7;5-7

Herbal therapy

Recently a phytomedicine has a complementary function for *Helicobacter pylori*. Many plant extracts, partially purified reactions and natural compounds with the anti-*H. pylori* activity has been reported (Safavi M, *et al.*, 2015; Shahani S, *et al.*, 2012; Wang YC, 2014; Falsafi T, *et al.*, 2015). Some bioactive compounds from medicinal plants with anti-*H. pylori* activity include carvacrol (Takabayashi F, *et al.*, 2004), polyphenolic catechins (Ali SM, *et al.*, 2005), tannins (Ramadan MA and Safwat NA, 2009), cinnamaldehyde, eugenol (Fukai T, *et al.*, 2002), quercetin (Mahady GB, *et al.*, 2003), licoricidin, licoisoflavone B (Dabos KJ, *et al.*, 2010), Berberine, sanguinarine, chelerythrine, protopine, β-hydrastine (Paraschos S, *et al.*, 2007), mastic (Wang YC and Huang TL, 2005), plumbagin (Bisignano C, *et al.*, 2012), protocatechuic acid. This may be more beneficial if the medicinal plants in combination with present antibiotic regimens are used to develop more effective eradication regimens (Tadjrobehkar O and Abdollahi H, 2014). However, mode of action, potential cytotoxicity and benefits of herbal medicine are complex, incomplete and confusing (Vale FF and Oleastro M, 2014).

Photodynamic therapy

Photodynamic inactivation of microorganisms is on the basis of the combination of a sensitizer or photo sensitiser and harmless visible light of an appropriate wavelength. Recently, some *in vitro*(Choi SS, *et al.*, 2010; Simon C, *et al.*, 2014; Hamblin MR, *et al.*, 2005) and *in vivo* (Lembo AJ, *et al.*, 2009; Ganz RA, *et al.*, 2005) studies to develop anti-*H. pylori* photodynamic therapy for the eradication of *H. pylori* were

successful (Maisch T, *et al.*, 2007). It is necessary to perform *in vivo* photodynamic therapy and indicate the limitations and effectiveness of this novel technique with less cost, side effects and ease of administration (Calvino-Fernández M, *et al.*, 2013; Choi SS, *et al.*, 2010).

CONCLUSION

Although oral delivery is considered to be the most promising administration route due to its specific advantages, it faces substantial challenges that need to be addressed before oral systems can be commercially available for the delivery of biopharmaceuticals. Fabrication protocols of the carriers should adequately avoid any destructive on the drug molecules, especially for biopharmaceutical encapsulation/delivery. Concurrently, the delivery material, design, size and polydispersity must be accurately controlled, due to their significant influence on treatment efficacy. Oral carriers deal with various biological barriers to successfully deliver drugs. Sustained delivery, microencapsulation have also been major focuses in oral delivery studies. Nonetheless, the most significant issue against the commercialization of the oral systems is their low throughput. This review introduced the most promising solutions recently proposed for each barrier, which point to a positive progress in the field of oral drug delivery. Considering the recent achievements in the case of technological challenges, we believe that future research in this field will mainly target biological barriers, especially the barriers associated with tissues. The main advantages of oral delivery systems, include sustained delivery, interaction with mucus and the capability for solid formulations that preserve pharmaceuticals, still making this the most attractive administration route for pharmaceuticals.

REFERENCES

1. Tan VP, Wong BC. *Helicobacter pylori* and gastritis: Untangling a complex relationship 27 years on. J Gastroenterol Hepatol. 2011; 26: 42-45.
2. Amieva M, Peek Jr RM. Pathobiology of *Helicobacter pylori*-induced gastric cancer. Gastroenterology. 2016; 150(1): 64-78.
3. McNamara D, Buckley M, Gilvarry J, O'morain C. Does *Helicobacter pylori* eradication affect symptoms in nonulcer dyspepsia: A 5-year follow-up study. Helicobacter. 2002; 7(5): 317-321.
4. Howden CW, Hunt RH. Guidelines for the management of *Helicobacter pylori* infection. Am J Gastroenterol. 1998; 93(12): 2330-2338.
5. Drumm B, Koletzko S, Oderda G, European paediatric task force on *Helicobacter pylori. Helicobacter pylori* infection in children: A consensus statement. J Pediatr Gastroenterol Nutr. 2000; 30(2): 207-213.
6. Graham DY, Qureshi WA. Markers of infection. *Helicobacter pylori*: Physiology and genetics. 2001; 499-510.
7. Zhao S, Lv Y, Zhang JB, Wang B, Lv GJ, Ma XJ. Gastroretentive drug delivery systems for the treatment of *Helicobacter pylori*. World J Gastroenterol. 2014; 20(28): 9321.
8. Safavi M, Sabourian R, Foroumadi A. Treatment of *Helicobacter pylori* infection: Current and future insights. World J Clin Cases. 2016; 4(1): 5.
9. Rana R, Wang SL, Li J, Wang YX, Rao QW, Yang CQ. *Helicobacter pylori* infection: A recent approach to diagnosis and management. J Biomed. 2017; 2(1): 45-56.
10. Stollman NH, Graham DY. Rallying community health care providers to close the gap between *H pylori* guidelines and the challenges of eradication. Gastroenterol Hepatol. 2014; 10(12): 811.
11. Pacifico L, Anania C, Osborn JF, Ferraro F, Chiesa C. Consequences of *Helicobacter pylori* infection in children. World J Gastroenterol. 2010; 16(41): 5181.
12. Carraher S, Chang HJ, Munday R, Goodman KJ, CANHelp Working Group. *Helicobacter pylori* incidence and re-infection in the Aklavik *H. pylori* Project. Int J Circumpolar Health. 2013; 72(1): 21594.
13. Graham DY, Lee YC, Wu MS. Rational *Helicobacter pylori* therapy: Evidence-based medicine rather than medicine-based evidence. Clin Gastroenterol Hepatol. 2014; 12(2): 177-186.
14. Hardo PG, Tugnait A, Hassan F, Lynch DA, West AP, Mapstone NY, *et al. Helicobacter pylori* infection and dental care. Gut. 1995; 37(1): 44-46.
15. Mitchell HM, Lee A, Carrick J. Increased incidence of *Campylobacter pylori* infection in gastroenterologists: Further evidence to support person-to-person transmission of *C. pylori*. Scand J Gastroenterol. 1989; 24(4): 396-400.
16. Parsonnet J, Shmuely H, Haggerty T. Fecal and oral shedding of *Helicobacter pylori* from healthy infected adults. JAMA. 1999; 282(23): 2240-2245.
17. Hulten KR, Han SW, Enroth HE, Klein PD, Opekun AR, Gilman RH, *et al. Helicobacter pylori* in the drinking water in Peru. Gastroenterology. 1996; 110(4): 1031-1035.
18. Thomas JE, Gibson GR, Darboe MK, Weaver LT, Dale A. Isolation of *Helicobacter pylori* from human faeces. Lancet. 1992; 340(8829): 1194-1195.
19. Drumm B, Perez-Perez GI, Blaser MJ, Sherman PM. Intrafamilial clustering of *Helicobacter pylori* infection. N Engl J Med. 1990; 322(6): 359-363.
20. Ramsey EJ, Carey KV, Peterson WL, Jackson JJ, Murphy FK, Read NW, *et al.* Epidemic gastritis with hypochlorhydria. Gastroenterology. 1979; 76(6): 1449-1457.
21. Handt LK, Fox JG, Stalis IH, Rufo R, Lee G, Linn J, *et al.* Characterization of feline *Helicobacter pylori* strains and associated gastritis in a colony of domestic cats. J Clin Microbiol. 1995; 33(9): 2280-2289.
22. Grübel P, Hoffman JS, Chong FK, Burstein NA, MePani C, Cave DR. Vector potential of houseflies (Musca domestica) for *Helicobacter pylori*. J Clin Microbiol. 1997; 35(6): 1300-1303.
23. Grubel P, Huang L. Detection of *Helicobacter pylori* DNA in houseflies (Musca domestica) on three continents. Lancet. 1998; 352(9130): 788-789.
24. Parsonnet J. The incidence of *Helicobacter pylori* infection. Aliment Pharmacol Ther. 1995; 9: 45-51.
25. Rollan A, Giancaspero R, Fuster F, Acevedo C, Figueroa C, Hola K, *et al.* The long-term reinfection rate and the course of duodenal ulcer disease after eradication of *Helicobacter pylori* in a developing country. Am J Gastroenterol. 2000; 95(1): 50-56.
26. Rogha M, Nikvarz M, Pourmoghaddas Z, Shirneshan K, Dadkhah D, Pourmoghaddas M. Is *Helicobacter pylori* infection a risk factor for coronary heart disease? ARYA Atheroscler. 2012; 8(1): 5.
27. Rogha M, Dadkhah D, Pourmoghaddas Z, Shirneshan K, Nikvarz M, Pourmoghaddas M. Association of *Helicobacter pylori* infection with severity of coronary heart disease. ARYA Atheroscler. 2012; 7(4): 138.
28. Saad R, Chey WD. A clinician's guide to managing *Helicobacter pylori* infection. Cleve Clin J Med. 2005; 72(2): 109-110.

29. McCarthy C, Patchett S, Collins RM, Beattie S, Keane C, O'Morain C. Long-term prospective study of *Helicobacter pylori* in nonulcer dyspepsia. Dig Dis Sci. 1995; 40(1): 114-119.
30. Hwang JJ, Lee DH, Lee AR, Yoon H, Shin CM, Park YS, *et al.* Efficacy of 14-d vs. 7-d moxifloxacin-based triple regimens for second-line *Helicobacter pylori* eradication. World J Gastroenterol. 2015; 21(18): 5568.
31. Dos Santos AA, Carvalho AA. Pharmacological therapy used in the elimination of *Helicobacter pylori* infection: A review. World J Gastroenterol. 2015; 21(1): 139.
32. Zullo A, Vaira D, Vakil N, Hassan C, Gatta L, Ricci C, *et al.* High eradication rates of *Helicobacter pylori* with a new sequential treatment. Aliment Pharmacol Ther. 2003; 17(5): 719-726.
33. Song Z, Zhou L, Zhang J, He L, Bai P, Xue Y. Levofloxacin, bismuth, amoxicillin and esomeprazole as second-line *Helicobacter pylori* therapy after failure of non-bismuth quadruple therapy. Dig Liver Dis. 2016; 48(5): 506-511.
34. Chuah SK, Tai WC, Hsu PI, Wu DC, Wu KL, Kuo CM, *et al.* The efficacy of second-line anti-*Helicobacter pylori* therapy using an extended 14-day levofloxacin/amoxicillin/proton-pump inhibitor treatment-a pilot study. Helicobacter. 2012; 17(5): 374-381.
35. Miehlke S, Krasz S, Schneider-Brachert W, Kuhlisch E, Berning M, Madisch A, *et al.* Randomized trial on 14 versus 7 days of Esomeprazole, Moxifloxacin, and Amoxicillin for Second-line or Rescue treatment of *Helicobacter pylori* infection. Helicobacter. 2011; 16(6): 420-426.
36. Tai WC, Chiu CH, Liang CM, Chang KC, Kuo CM, Chiu YC, *et al.* Ten-day versus 14-day levofloxacin-containing triple therapy for second-line anti-*Helicobacter pylori* Eradication in Taiwan. Gastroenterol Res Pract. 2013; 2013.
37. Chuah SK, Tsay FW, Hsu PI, Wu DC. A new look at anti-*Helicobacter pylori* therapy. World J Gastroenterol. 2011; 17(35): 3971.
38. Lesbros-Pantoflickova D, Corthesy-Theulaz I, Blum AL. *Helicobacter pylori* and probiotics. J Nutr. 2007; 137(3): 812S-818S.
39. Schrezenmeir J, de Vrese M. Probiotics, prebiotics, and synbiotics-approaching a definition. Am J Clin Nutr. 2001; 73(2): 361s-364s.
40. Rostami N, Keshtkar-Jahromi M, Rahnavardi M, Keshtkar-Jahromi M, Soghra Esfahani F. Effect of eradication of *Helicobacter pylori* on platelet recovery in patients with chronic idiopathic thrombocytopenic purpura: A controlled trial. Am J Hematol. 2008; 83(5): 376-381.
41. Fallone CA, Chiba N, van Zanten SV, Fischbach L, Gisbert JP, Hunt RH, *et al.* The Toronto consensus for the treatment of *Helicobacter pylori* infection in adults. Gastroenterology. 2016; 151(1): 51-69.
42. Gatta L, Scarpignato C, Fiorini G, Belsey J, Saracino IM, Ricci C, *et al.* Impact of primary antibiotic resistance on the effectiveness of sequential therapy for *Helicobacter pylori* infection: Lessons from a 5-year study on a large number of strains. Aliment Pharmacol Ther. 2018; 47(9): 1261-1269.
43. Ayala G, Escobedo-Hinojosa WI, de la Cruz-Herrera CF, Romero I. Exploring alternative treatments for *Helicobacter pylori* infection. World J Gastroenterol. 2014; 20(6): 1450.
44. Patel A, Shah N, Prajapati JB. Clinical application of probiotics in the treatment of *Helicobacter pylori* infection-a brief review. J Microbiol Immunol Infect. 2014; 47(5): 429-437.
45. Yang YJ, Sheu BS. Probiotics-containing yogurts suppress *Helicobacter pylori* load and modify immune response and intestinal microbiota in the *Helicobacter pylori*-infected children. Helicobacter. 2012; 17(4): 297-304.
46. Ljungh A, Wadstrom T. Lactic acid bacteria as probiotics. Curr Issues Intest Microbiol. 2006; 7(2): 73-90.
47. Zojaji H, Ghobakhlou M, Rajabalinia H, Ataei E, Sherafat SJ, Moghimi-Dehkordi B, *et al.* The efficacy and safety of adding the probiotic Saccharomyces boulardiito standard triple therapy for eradication of *H. pylori*: A randomized controlled trial. Gastroenterol Hepatol Bed Bench. 2013; 6(1): S99.
48. Khodadad A, Farahmand F, Najafi M, Shoaran M. Probiotics for the treatment of pediatric *Helicobacter pylori* infection: A randomized double blind clinical trial. Iran J Pediatr. 2013; 23(1): 79.
49. Safavi M, Shams-Ardakani M, Foroumadi A. Medicinal plants in the treatment of *Helicobacter pylori* infections. Pharm Biol. 2015; 53(7): 939-960.
50. Shahani S, Monsef-Esfahani HR, Saeidnia S, Saniee P, Siavoshi F, Foroumadi A, *et al.* Anti-*Helicobacter pylori* activity of the methanolic extract of Geum iranicum and its main compounds. Z Naturforsch C. 2012; 67(3-4): 172-180.
51. Wang YC. Medicinal plant activity on *Helicobacter pylori* related diseases. World J Gastroenterol. 2014; 20(30): 10368.
52. Falsafi T, Moradi P, Mahboubi M, Rahimi E, Momtaz H, Hamedi B. Chemical composition and anti-*Helicobacter pylori* effect of Satureja bachtiarica Bunge essential oil. Phytomedicine. 2015; 22(1): 173-177.
53. 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(1): 61-63.
54. Ali SM, Khan AA, Ahmed I, Musaddiq M, Ahmed KS, Polasa H, *et al.* Antimicrobial activities of Eugenol and Cinnamaldehyde against the human gastric pathogen *Helicobacter pylori*. Ann Clin Microbiol Antimicrob. 2005; 4(1): 1-7.
55. Ramadan MA, Safwat NA. Antihelicobacter activity of a flavonoid compound isolated from Desmostachya bipinnata. Aust J Basic Appl Sci. 2009; 3(3): 2270-2277.
56. Fukai T, Marumo A, Kaitou K, Kanda T, Terada S, Nomura T. Anti-*Helicobacter pylori* flavonoids from licorice extract. Life Sci. 2002; 71(12): 1449-1463.
57. Mahady GB, Pendland SL, Stoia A, Chadwick LR. *In vitro* susceptibility of *Helicobacter pylori* to isoquinoline alkaloids from Sanguinaria canadensis and Hydrastis canadensis. Phytother Res. 2003; 17(3): 217-221.
58. Dabos KJ, Sfika E, Vlatta LJ, Giannikopoulos G. The effect of mastic gum on *Helicobacter pylori*: A randomized pilot study. Phytomedicine. 2010; 17(3-4): 296-299.
59. Paraschos S, Magiatis P, Mitakou S, Petraki K, Kalliaropoulos A, Maragkoudakis P, *et al. In vitro* and *in vivo* activities of Chios mastic gum extracts and constituents against *Helicobacter pylori*. Antimicrob Agents Chemother. 2007; 51(2): 551-559.
60. Wang YC, Huang TL. High-performance liquid chromatography for quantification of plumbagin, an anti-*Helicobacter pylori* compound of Plumbago zeylanica L. J Chromatogr A. 2005; 1094(1-2): 99-104.

61. Bisignano C, Filocamo A, La Camera E, Zummo S, Fera MT, Mandalari G. Antibacterial activities of almond skins on cagA-positive and-negative clinical isolates of *Helicobacter pylori*. BMC Microbiol. 2013; 13(1): 1-6.
62. Tadjrobehkar O, Abdollahi H. A novel reduction strategy of clarithromycin resistance in *Helicobacter pylori*. Jundishapur J Microbiol. 2014; 7(12).
63. Vale FF, Oleastro M. Overview of the phytomedicine approaches against *Helicobacter pylori*. World J Gastroenterol. 2014; 20(19): 5594.
64. 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(3): 206-209.
65. Simon C, Mohrbacher C, Hüttenberger D, Bauer-Marschall I, Krickhahn C, Stachon A, *et al. In vitro* studies of different irradiation conditions for photodynamic inactivation of *Helicobacter pylori*. J Photochem Photobiol B. 2014; 141: 113-118.
66. 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(7): 2822-2827.
67. Lembo AJ, Ganz RA, Sheth S, Cave D, Kelly C, Levin P, *et al.* Treatment of *Helicobacter pylori* infection with intra-gastric violet light phototherapy: A pilot clinical trial. Lasers Surg Med. 2009; 41(5): 337-344.
68. Ganz RA, Viveiros J, Ahmad A, Ahmadi A, Khalil A, Tolkoff MJ, *et al. Helicobacter pylori* in patients can be killed by visible light. Lasers Surg Med. 2005; 36(4): 260-265.
69. Maisch T. Anti-microbial photodynamic therapy: Useful in the future?. Lasers Med Sci. 2007; 22(2): 83-91.
70. Calvino-Fernández M, García-Fresnadillo D, Benito-Martínez S, McNicholl AG, Calvet X, Gisbert JP, *et al. Helicobacter pylori* inactivation and virulence gene damage using a supported sensitiser for photodynamic therapy. Eur J Med Chem. 2013; 68: 284-290.