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NATURAL HONEY AND ITS THERAPEUTIC POTENTIAL IN TREATMENT OF *HELICOBACTER PYLORI* INFECTION

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ABSTRACT

Helicobacter pylori (*H. pylori*), a spiral shaped bacteria is one of the potent enemies of our gastrointestinal system. Currently, numerous antibiotic-based therapies are available to treat *H. pylori* infection. However, these therapies have several inherent problems including antibiotic resistance, adverse sideeffects and high cost. Further, long-term therapy with antibiotics can result in pervasive alterations in the gut flora, leading to the susceptibility of infections. Therefore, current antibiotic-based therapy to treat *H. pylori* infection fails in several cases, this situation has demanded the researchers to develop other therapeutic approaches to control *H. pylori* infection. Since, honey is a store of nutrients such as sugars, proteins, amino acids, vitamins, enzymes, organic acids, phenols and volatile organic molecules with therapeutic benefits against various pathogens, natural honey has the potential for treatment of *H. pylori* infection. Honey acts as anti-*H.pylori* agent to treat gastrointestinal disorders. Here, we describe natural honey with its potential role in treatment of *H. pylori* infection.

Key words: *Helicobacter pylori,* honey, antimicrobial, natural therapy, gastric disease.

1. INTRODUCTION

Helicobacter pylori, a spiral shaped bacteria is one of the potent enemies of our gastrointestinal system. Nowadays, various antibiotic-based treatments are available for *H. pylori* infection. But due to the resistance of antibiotics, adverse side effects and the high cost, it's not effective so much.[1] Long-term therapy with antibiotics can result in pervasive alterations in gut flora, leading to the susceptibility of infections.[2,3] Due to antimicrobial resistance and patient non-adherence, current anti-*H. Pylori* therapy fails in several cases. This situation has demanded the researchers to develop other approaches to control *H. pylori* infection.[4]One approach can be to seek for compounds from natural resources with proven antimicrobial activities and test for anti-*H. pylori* function. Such natural compounds serve as important source for the synthesis of new drugs as well as for eradication of *H. pylori* infection.[5]

This god gifted natural sweetest compounds (honey) come medicine have been used for millennia in the treatment of gastric diseases.[6]These two genera of honeybees *Apis* and *Meliponini*is mainly involved for making honey.[7,8]Such honey-related therapy is called apitherapy.[9]Consistently, honey has shown anti-*H. pylori* activity. So it's a upcoming topic for researchers to know the use of honey in the treatment of *H. pylori* infection and gastric cancer. However, additional research and clinical trials remain to be conducted to bring honey-related treatment to the clinic. Therefore, it is important to know natural honey, its composition and

therapeutic values towards developing honey-based therapy.[7] Here, we describe natural honey and its antimicrobial activities on *H. pylori* infection and gastric diseases.

2. NATURAL HONEY

The yellow gel like natural product is storage of essential nutrients.[11]Like carbohydrates (mainly fructose) that is responsible for sweetness of honey. Carbohydrates present in the form of monosaccharide and disaccharide (10-15%) in honey such as fructose and glucose, sucrose, isomaltose, maltose, trehalose and few others.[13,14] The carbohydrates of honey mainly represents the viscosities, hygroscopicity, energy value and granulation.[15,16]

Protein is another nutrient of honey which is only comes from the bee body as *Apis cerana* honey contains 0.1 to 3.3 % and *Apis mellifera* honey contains 0.2 to 1.6% protein.[17-19] Protein present in the form of major royal jelly. Amino acids like proline, arginine, tyrosine and some others present in honey.[20]

Volatile compounds are the flavour indicator of honey which may vary due to different sources and other processing conditions.[21]For example, indicator of lavender honey are hexanal and heptanal.[22]The darker colour of honey is due to the high antioxidant content which is in the form of flavonoids.[23, 24]

According to the study, the average pH of honey is 3.9 which indicate it is acidic in nature.[25] And thus the vitamins in honey like thiamine, riboflavin, nicotinic acid, pantothenic acid, pyridoxine, biotin, folic acid are preserved greatly.[26, 27] But vitamins content of honeyis measure in the range of parts per million that indicate vitamin content of honey is low, which are insignificant to humans.[28] Honey is also rich in minerals like calcium, iron, potassium, sodium and few others.[25] Small fractions of enzymes also present like invertase, catalase, diastase, glucose oxidase etc.[19, 20]

This precious food is low in moisture, with high osmotic pressure which may create a difficult situation for microorganisms to survive in it.[29] Because, it is liquid in nature so, its water content is high such as 15-21g/100g.[25, 30]

The refractive index and viscosity are 1.49 and120 poise (room temperature). Other than it has specific gravity is about 1.4.[18] According to its compositional varieties it provides various types of therapeutic properties as depicted in fig.1.[31-44]

3. HONEY IN GASTROINTESTINAL HEALTH

Honey removed *Salmonella, Shigella* and Enteropathogenic E.coli byits antibacterial activity. Honey coats the bacteria or alters the bacterial electrostatic charge or gives probiotic effect because of its oligosaccharide content.[45-47]In rats all these mechanisms are observed.[48]

Honey used for the treatment of peptic ulcers caused by spiral-shaped microaerophilic bacterium called, *H. pylori*. Due to the presence of hydrogen peroxide in honey at a 20% concentration the growth of *H. pylori* inhibited.[49] We describe below how *H. pylori* is involved in gastrointestinal health and its potential treatment by natural honey.

4. *H. PYLORI* IN GASTROINTESTINAL HEALTH

H. Pylori, evade the immune response and creates gastrointestinal diseases by attaching with epithelial cells. And thus it infects two-thirds of world's population.[50] The *H. pylori*genome codes for 1500 proteins (*Hop* and adhesion proteins).[51] These proteins control the entry of foreign DNA, maintain enzymatic activities, regulate bacterial motility and modify antigenic structure of molecules.*H. pylori* genome was changed by the entry of foreign DNA.[52,53]Another

best-characterized 78-kDa adhesion protein that binds to the fucosylated Lewis B blood group antigen.[54]The genes of *cag-PAI* translocate 120-kDa protein *CagA* into host cell by encoding components of type IV secretion apparatus.[57,58]And in host cell phosphorylation of *CagA* induce cellular response and cytokine production.[59]

The disease causing strains of *H. pylori* (Figure 2) contain cag pathogenicity island *cag-PAI (*37-kb genomic fragment with 29 genes) and cytotoxin *VacA.* Mainly, voltage dependent and hexameric anion-selective channel through which bacteria gets nutrition are formed by *VacA* when it enters itself into the epithelial-cell membrane. [60] *VacA* is responsible for release of *cytochrome c* and also apoptosis. Thus, *VacA* plays important roles in *H. pylori* pathogenicity and bacterial fitness.[61,62]

Pathogenesis of *H.pylori* is depicted in Figure 3. *H. pylori* enter in the human body by ingestion (Figure 3a), evade in the host stomach to induce ulcer infection (Figure 3b). Urea breaks into carbon dioxide and ammonia under the presence of urease enzyme (secreted from *H.pylori*). And thus *H.pylori* survives in the acidic environment of stomach. Subsequently, ammonia reacts with water to produce ammonium hydroxide which neutralizes stomach acidic environment. The whole process occurred in the periplasm of *H. Pylori* (Figure 3c). It moves towards gastric epithelial cells through flagella for the attachment with the host receptor (Figure 3d). Then, *VacA* protein channel allows the entry of the nutrients for their growth. *CagA* stimulates the type IV secretion apparatus. Vesicles are adapted for the multiplication of *H. pylori* in the host body (Figure 3e).

5. AVAILABLE TREATMENTS OF *H. PYLORI* INFECTION:

To erase the *H. pylori* infection various antibiotics are prescribed but luminal acidity may inter fare with the efficiency of antibiotics, that's why proton pump inhibitor (PPI) should be used with antibiotics. The whole treatment schedule of *H. pylori* infection is described in table 1.[63,64]

First line therapy

In this therapy clarithromycin is used with PPI and also called standard triple therapy. But due to the resistance of clarithromycin it is not applicable for clarithromycin resistance strain. Many researches are focus on the triple therapy resistance theory to solve this problems.[65-67]

Sequential therapy

It is more effective in eradicating *H. pylori* infection instead of standard triple therapy. It is gaining a high eradication rate (91%-93%) for administration either 7 or 10-day triple therapy.[68,69]Sequential therapy is actually second-line treatment, for example, according to triple therapy for 5 days, amoxicillin (1g) PPI is given along with other dose of PPI plus clarithromycin and tinidazole.[70-72]

Quadruple bismuth therapy

It is the best therapy for eradication of *H. pylori* because it is easily released into the gastric mucous layer with a low antibiotics resistance.[73,74] A quadruple therapy consists of bismuth, a PPI, and two antibiotics with a cure rate of 85-92%.[75] Nevertheless, quadruple therapy is recently falling off the *H. pylori* treatment in nearly 20 to 30% patients due to the resistance of clarithromycin and metronidazole.[76,77]Current research reported that PPI with a single capsule containing three antibiotics such as bismuth subcitrate, metronidazole, tetracycline (quadruple therapy) provides a better eradication rate (92-93%).[78,79]

Concomitant therapy

It was providedwith a PPI (esomeprazole) and three antibiotics (amoxicillin, clarithromycin, metronidazole) for 10 days which gives 90% eradication rate .[80-82]

Levofloxacin therapy

It is based on a broad-spectrum of fluoroquinolone antimicrobial agents that inhibit the DNA synthesis and are well-tolerated.[83,84] It has superior efficacy than triple therapy. It is the best treatment for *H. pylori* infected patients with antibiotic resistance, especially metronidazole resistance (76%) and clarithromycin resistance (71%).[85] On the other hands, levofloxacin therapy is used when standard triple and sequential therapies fail. And it provides eradication rate ofmore than 95%.[86-89]

Alternative therapies

Due to the antibiotic resistance, now a days many researches throw an eye on the alternative theories which are plant based or diet based mainly traditional medicines.The alternative therapies of*H. Pylori* treatment is displayed in Figure4.[90-97]

6. HONEY AS A THERAPEUTIC AGENT AGAINST *H. PYLORI*

Studies for the sensitivity of *H. pylori* to honey were conducted in an agar well diffusion assay, using isolates from biopsies of gastric ulcers. Result showed sensitivity to a 20% (v/v) solution of manuka honey whereas no sensitivity to a 40% solution of honey that contained antibacterial agent, hydrogen peroxide.[98] Saudi Arabia and New Zealand honeyshowed anti-*H. pylori*activity at the concentrations of 20% (v/v) via both hydrogen peroxide and non-peroxide-mediated killing mechanisms.[99] Another study observed the antimicrobial activity of four honeys, namely Manuka™, Capillano®, Eco- and Mountain, at different concentrations (10%v/v, 20%v/v, 50%v/v and 75%v/v, respectively) against *H. pylori* in clinical isolates. Importantly, like Clarithromycin Mountain honey showed strongest inhibitory activity (82.22%) followed by Capillano® and Manuka™ honeys (75.56%), and Eco-honey (73.36%) at the same concentration of 75% v/v. The minimum inhibitory concentration and minimum bactericidal concentration of Mountain honey were 0.117 - 0.938ìg/mL and 0.366 - 2.965ìg/mL.[100,101]

Solutions containing 15% (w/v) carbohydrate (simple carbohydrate like glucose, fructose, honey) provides growth inhibition of all isolates of *H.pylori*.[99]Another study suggested that natural ingredients in garlic and capsaicin can also be used for the treatment of the *H.pylori* infection.[102] Consumption of honey for ≥1 day/week and the effect of dietary factors lower the prevalence rate of *H.pylori* is about50.6%($p = 0.013$) Whereas green/black tea consumption for ≥1 day/week show 45.2% positivity rate ($p = 0.028$).[103] Thus, like honey, green/black tea contributes to lower positivity rate of *H. pylori* infection.

Another active factor for prevention of *H.pylori* is osmotic effect of honey.[99] Chemicals/compounds present in honey can also block *H. pylori* infection by inhibiting the urease that promotes the generation of ammonium hydroxide to counteract acidic pH of stomach for survival of *H. pylori*. Honey fractions extracted by both Chloroform and diethyl ether showed 48% and 42% inhibition against urease from *H. pylori* (369C and ATCC43526) is about 48%, 42%, 45%,51%.[104]Thus, honey has the potential to prevent *H. pylori* infection via inhibition of urease.

Another fact related to honey that, honey may suppress *H. pylori*-associated inflammation. To test this, Manuka honey alone and in combination with broccoli sprouts and omega-3 oil were screened to limit *H. pylori*-associated inflammation, using an *in vitro* system. This function of Manuka honey is mediated via the suppression of Nuclear Factor (NF-kB, a key player in inflammation for transcribing cytokines that include interleukines) activation. In agreement, manuka honey has shown reduced IL-8 (Interleukin 8) expression in *H. pylori*-infected gastric epithelial cells. However, the IL-8 levels in Tumor Necrosis Factor (TNF-α)- treated cells were found to be unchanged in the presence of manuka honey. Manuka honey provides its anti-

adhessive function during the adherence of *H. pylori* to Adenocarcinoma Gastric (AGS) cells. Thus, honey appears to have a combination of antibacterial, anti-adhesive, and anti-inflammatory activities.[105,106]

To determine the therapeutic functions of commercial honey, three brands of commercial honey were tested for their inhibitory roles on the growth of *H. pylori.* Irrespective of the brand or country of origin, all commercial honeys showed the growth inhibition of *H. pylori* at a concentration of 20% and above. Thus, commercially available honey retains its antibacterial effects due to the presence of catalase and hydrogen peroxide, and can be used in clinical investigations.[107,108]

When honey (gold crest honey) extracted by solvent and n-hexane, it act s as bactericidal and bacteriostatic as well as gives anti-*H. pylori* activity due to the combined and/or separate actions of volatile compounds such as pyran, aldehyde, furan, ketones, hydrocarbon, aliphatic acids, benzene compounds, alcohols in honey.[109] Both *Nigella sativa* and honey (Dosin) showed a anti *H.pylori* (57%) activity in 19 patients. It is lower than the eradication rate of triple therapy.[110] Importantly, investigation of the effects of honey (5g/kg) on experimentally induced gastric lesions in rats revealed almost full protection against *H.pylori*.About 98% haemorrhagic lesions are cured by honey. [111,112] Moreover, honey can also increase stomach acid content by about 110-703%. It can also use in current therapies as a prophylactic in future.[113]

Ethanol extracted (30%) Bulgarian Propolis against 94 *H. pylori* strains revealed that only 7.2% of the *H. pylori* strains with no inhibition by the agar well diffusion method.[114] Korean acacia honey and its active components showed antibacterial activity against *H. pylori* at a concentration as low as 10% (v/v). The anti *H.pylori* activity is showed by Abscisic acid (potential component of Korean acacia honey).[115] *Lactobacillus rhamnosus* as a probiotic derived by honey similar as clarithromycin in the eradication of *H. pylori* infection (induced gastritis) inmice (C57BL/6).[116]

7. CONCLUSION

The field of natural therapies including honey therapy for *H.pylori* infection is a novel interest for now a days. Investigators on the basis of their findings advocated that natural honey provides therapeutic benefit against *H. pylori* infection as well as gastrointestinal tract diseases. However, further studies are required to replicate these findings and explore the therapeutic mechanisms of action of honey. This article provides a wide description of honey and its role in *H. pylori* infection with potential avenues of new thoughts, new research directions and discoveries, and novel therapies for eradicating *H. pylori* infection and treatment of gastrointestinal disorders.

DECLARATION

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There is no conflict of interest.

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Consent for publication
AR confirms the consent for publication

REFERENCES
(1) Camargo, M. C.; García, A.; Riquelme, A.; Otero, W.; Camargo, C.A.; Hernandez-García, T.; Candia, R.; Bruce, M. G.; Rabkin, C. S. The problem of *Helicobacter pylori* resistance to antibiotics: a systematic review in Latin America. *Am. J. Gastroenterol*. 2014, *109*, 485-495.
(2) Gatta, L.; Vakil, N.; Vaira, D.; Scarpignato, C. Global eradication rates for *Helicobacter pylori* infection: systematic review and meta-analysis of sequential therapy. *Bmj*. 2013, *347*, f4587.
(3) Thung, I.; Aramin, H.; Vavinskaya, V.; Gupta, S.; Park, J. Y.; Crowe, S. E.; Valasek, M. A. The global emergence of *Helicobacter pylori* antibiotic resistance. *Aliment. Pharmacol. Ther*.2016, *43*, 514-533.
(4)Talley, N. J.; Lam, S. K.; Wong, B. C.; Xia, H. H. Alternative and rescue treatment regimens for *Helicobacter pylori* eradication. *Expert Opin.Pharmacother*.2002, *3*, 1301-1311.
(5) Vítor, J. M.; Vale, F. F. Alternative therapies for *Helicobacter pylori*: probiotics and phytomedicine. *FEMS Immunol. Med. Microbiol.*2011, *63*, 153-164.
(6) Saxena, M.; Saxena, J.; Nema, R.; Singh, D.; Gupta, A. Phytochemistry of medicinal plants. *J. Pharmacogn. Phytochem.*2013, *1*, 168-182.
(7) Namias, N. Honey in the management of infections. *Surg. Infect*. 2003, *4*, 219-226.
(8) Al-Jabri, A. A. Honey, milk and antibiotics. *Afr. J. Biotechnol*. 2005, *4*.1580-1587.
(9) Ghosh, S.; Playford, R. J. Bioactive natural compounds for the treatment of gastrointestinal disorders. *Clin. Sci.*2003, *104*, 547-556.
(10) Vit, P.; Medina, M.; Eunice Enríquez, M. Quality standards for medicinal uses of Meliponinae honey in Guatemala, Mexico and Venezuela. *Bee world*.2004, *85*, 2-5.
(11) Qiu, P. Y.; Ding, H. B.; Tang, Y. K.; Xu, R. J. Determination of chemical composition of commercial honey by near-infrared spectroscopy. *J. Agr. Food Chem.* 1999, *47*, 2760-2765.
(12) Doner, L. W. The sugars of honey—a review.*J. Sci. Food Agric.*1977, *28*, 443-456.
(13) Guo, W.; Zhu, X.; Liu, Y.; Zhuang, H. Sugar and water contents of honey with dielectric property sensing. *J. Food Eng.*2010, *97*, 275-281.
(14) De La Fuente, E.; Ruiz-Matute, A. I.; Valencia-Barrera, R. M.; Sanz, J.; Castro, I. M. Carbohydrate composition of Spanish unifloral honeys. *Food Chem.*2011, *129*, 1483-1489.

(15) Kamal, M. A.; Klein, P. Determination of sugars in honey by liquid chromatography. *Saudi J. Biol. Sci.*2011, *18*, 17-21.
(16) Anjos, O.; Iglesias, C.; Peres, F.; Martínez, J.; García, Á.; Taboada, J. Neural networks applied to discriminate botanical origin of honeys. *Food Chem*. 2015, *175*, 128-136.
(17) Won, S. R.; Li, C. Y.; Kim, J. W.; Rhee, H. I. Immunological characterization of honey major protein and its application. *Food Chem*. 2009, *113*, 1334-1338.
(18) Azeredo, L. D.; Azeredo, M. A.; De Souza, S. R.; Dutra, V. M. Protein contents and physicochemical properties in honey samples of Apismellifera of different floral origins. *Food Chem*. 2003, *80*, 249-254.
(19) Sak-Bosnar, M.; Sakač, N. Direct potentiometric determination of diastase activity in honey. *Food Chem*. 2012, *135*, 827-831.
(20) Weirich, G. F.;Collins, A. M.; Williams, V. P. Antioxidant enzymes in the honey bee, *ApisMellifera*. *Apidologie* 2002, *33*, 3-14.
(21) Aliferis, K. A.; Tarantilis, P. A.; Harizanis, P. C.; Alissandrakis, E. Botanical discrimination and classification of honey samples applying gas chromatography/mass spectrometry fingerprinting of headspace volatile compounds. *Food Chem.* 2010, *121*, 856-862.
(22) Castro-Vázquez, L.; Díaz-Maroto, M. C.; Pérez-Coello, M. S. Aroma composition and new chemical markers of Spanish citrus honeys. *Food Chem.* 2007, *103*, 601-606.
(23) Abubakar, M. B.; Abdullah, W. Z.; Sulaiman, S. A.; Suen, A. B.A review of molecular mechanisms of the anti-leukemic effects of phenolic compounds in honey.*Int. J. Mol.*2012, *13*, 15054-15073.
(24) Alvarez-Suarez, J. M.; Giampieri, F.; González-Paramás, A. M.; Damiani, E.; Astolfi, P.; Martinez-Sanchez, G.; Bompadre, S.; Quiles, J. L.; Santos-Buelga, C.; Battino, M. Phenolics from monofloral honeys protect human erythrocyte membranes against oxidative damage. *Food Chem. Toxicol.*2012, *50*, 1508-1516.
(25) Ball, D. W. The chemical composition of honey.*J. Chem. Educ.* 2007, *84*, 1643-1647.
(26) Abano, E. E.; Dadzie, R. G. Simultaneous detection of water-soluble vitamins using the High Performance Liquid Chromatography (HPLC)-a review. *Croat. J. Food Sci. Technol.*2014, *6*, 116-123.
(27) Bonté, F.; Desmoulière, A.; Le, miel. Origineet composition. *Actual. Pharm.* 2013, *52*, 18-21.
(28) Hoyle, E. The vitamin content of honey.*Biochem. J.* 1929, *23*, 54-60.
(29)Chirife, J.; Zamora, M. C.; Motto, A. The correlation between water activity and moisture in honey: Fundamental aspects and application to Argentine honeys.*J. Food Eng*. 2006, *72*, 287-292.
(30) Yücel, Y.; Sultanoğlu, P. Characterization of Hatay honeys according to their multi-element analysis using ICP-OES combined with chemometrics. *Food Chem*. 2013, *140*, 231-237.
(31) Valdés-Silverio, L. A.; Iturralde, G.; García-Tenesaca, M.; Paredes-Moreta, J.; Narváez-Narváez, D. A.; Rojas-Carrillo, M.; Tejera, E.; Beltrán-Ayala, P.; Giampieri, F.; Alvarez-Suarez, J. M. Physicochemical parameters, chemical composition, antioxidant capacity, microbial contamination and antimicrobial activity of Eucalyptus honey from the Andean region of Ecuador. *J. Apic. Res.*2018, *57*, 382-394.
(32) Juszczak, L.; Gałkowska, D.; Ostrowska, M.; Socha, R. Antioxidant activity of honey supplemented with bee products. *Nat. Prod. Res.*2016, *30*, 1436-1439.
(33)Krishnasree, V.; Ukkuru, M. P. *In vitro*antidiabetic activity and glycemic index of bee honeys.*Indian J. Tradit. Know.*2017, *16*, 134-140.
(34). Ramli, N. Z.; Chin, K. Y.; Zarkasi, K. A.; Ahmad, F. A review on the protective effects of honey against metabolic syndrome.*Nutrients.*2018,*10*, 1009 (1-21).

(35) Zakaria, N. H.; Ahmad, N. Z.; Hashim, S. N.; Adnan, L. H.; Halim, M.; Shariff, M.; Mohamad, N.; Mat, K. C.; Bakar, N. H. Analgesic effect of honey bioactive compounds and its role in reducing morphine tolerance. *J. Appl. Pharm. Sci.* 2015, *5*, 146-150.
(36) Oinaala, D.; Lehesvaara, M.; Lyhs, U.; Tikkanen-Kaukanen, C. Antimicrobial activity of organic honeys against food pathogenic bacterium *Clostridium Perfringens*. *Org. Agri.*2015, *5*, 153-159.
(37) Pathare, S.; Ravikumar, P.; Mistry, A. Promising pharmaceutical applications of honey. *J. Pharm. Sci*. 2015, *4*, 377-392.
(38) Goharshenasan, P.; Amini, S.; Atria, A.; Abtahi, H.; Khorasani, G. Topical application of honey on surgical wounds: a randomized clinical trial.*Complement. Med. Res*. 2016, *23*, 12-15.
(39) Safitri, E.; Utama, S.; Widiyatno, T. V.; Sandhika, W.; Prasetyo, R. H. Auto-regeneration of mice testicle seminiferous tubules due to malnutrition based on stem cells mobilization using honey. *Asian Pac. J. Reprod*.2016, *5*, 31-35.
(40) Banihani, S. A. Mechanisms of honey on testosterone levels. *Heliyon*2019, *5*, e02029.
(41)Barry, J. P.; Metz, M. S.; Hughey, J.; Quirk, A.; Bochman, M. L. Two novel strains of *Torulasporadelbrueckii* isolated from the honey bee microbiome and their use in honey fermentation. *Fermentation.*2018, *4*, 22 (1-11).
(42) Pai, S.; Shivappa, C. B.; Surendra, A. Anti-obesity and Anti-hyperlipidemic activity of Processed Honey-A Randomised, Open labeled, Controlled Clinical Study. *JRTM*.2018, *4*, 40-48.
(43) Afroz, R.; Tanvir, E.; Little, P. J. Honey-derived flavonoids: natural products for the prevention of atherosclerosis and cardiovascular diseases. *Clin. Exp. Pharmacol. Physiol.*2016, *6*, 208 (1-4).
(44) Asaduzzaman, M.; SohanurRahman, M.; Munira, S.; MuedurRahman, M.; Hasan, M.; Siddique, M. A.; Biswas, S.; Belal, M. H.; Khatun, M.; Khan, M. M.; Rahman, M. M. Effects of honey supplementation on hepatic and cardiovascular disease (CVD) marker in streptozotocin-induced diabetic rats. *J. Diabetes Metab*. 2015, *6*, 2.
(45) Pasupuleti, V. R.; Sammugam, L.; Ramesh, N.; Gan, S. H. Honey, propolis, and royal jelly: a comprehensive review of their biological actions and health benefits.*Oxidative Med. Cell Longev.*2017, *2017*, 1-21.
(46) Samarghandian, S.; Farkhondeh, T.; Samini, F. Honey and health: A review of recent clinical research.*Pharmacognosy Res.*2017, *9*, 121-127.
(47) Alnaqdy, A.; Al-Jabri, A.; Al Mahrooqi, Z.; Nzeako, B.; Nsanze, H. Inhibition effect of honey on the adherence of *Salmonella* to intestinal epithelial cells *in vitro*.*Int. J. Food Microbiol.*2005, *103*, 347-51.
(48) Almasaudi, S. B.; El-Shitany, N. A.; Abbas, A. T.; Abdel-dayem, U. A.; Ali, S. S.; Al Jaouni, S. K.; Harakeh, S. Antioxidant, anti-inflammatory, and antiulcer potential of manuka honey against gastric ulcer in rats. *Oxidative Med. Cell Longev*.2016, *2016*, 1-10.
(49)Abdellah, F.; Abderrahim, L. A. Honey for gastrointestinal disorders. Honey in Traditional and Modern Medicine. *CRC Press Taylor and Francis Group*.2010, 160-86.
(50) Blaser, M. J. An endangered species in the stomach.*Sci. Am.*2005, *292*, 38-45.
(51) Tomb, J. F.; White, O.; Kerlavage, A. R.; Clayton, R. A.; Sutton, G. G.; Fleischmann, R. D.; Ketchum, K. A.; Klenk, H. P.; Gill, S.; Dougherty, B. A.; Nelson, K. The complete genome sequence of the gastric pathogen *Helicobacter pylori*.*Nature* 1997, *388*, 539-547.
(52) Falush, D.; Kraft, C.; Taylor, N. S.; Correa, P.; Fox, J. G.; Achtman, M.; Suerbaum, S. Recombination and mutation during long-term gastric colonization by *Helicobacter pylori*: estimates of clock rates, recombination size, and minimal age.*Proc. Natl. Acad. Sci.*2001, *98*, 15056-15061.
(53) Suerbaum, S. Genetic variability within *Helicobacter pylori*. *Int. J. Med. Microbiol*. 2000, *290*, 175-181.

(54)Ilver, D.; Arnqvist, A.; Ögren, J.; Frick, I. M.; Kersulyte, D.; Incecik, E. T.; Berg, D. E.; Covacci, A.; Engstrand, L.; Borén, T. *Helicobacter pylori* adhesion binding fucosylatedhisto-blood group antigens revealed by retagging. *Science*1998, *279*, 373-7.
(55) Guruge, J. L.; Falk, P. G.; Lorenz, R. G.; Dans, M.; Wirth, H. P.; Blaser, M. J.; Berg, D. E.; Gordon, J. I. Epithelial attachment alters the outcome of *Helicobacter pylori* infection.*Proc. Natl. Acad. Sci.* 1998, *95*, 3925-2930.
(56) Censini, S.; Lange, C.; Xiang, Z.; Crabtree, J. E.; Ghiara, P.; Borodovsky, M.; Rappuoli, R.; Covacci, A. *Cag, a* pathogenicity island of *Helicobacter pylori*, encodes type I-specific and disease-associated virulence factors. *Proc. Natl. Acad. Sci*. 1996, *93*, 14648-14653.
(57)Odenbreit, S.; Püls, J.; Sedlmaier, B.; Gerland, E.; Fischer, W.; Haas, R. Translocation of *Helicobacter pylori CagA* into gastric epithelial cells by type IV secretion. *Science* 2000, *287*, 1497-1500.
(58)Segal, I.; Ally, R.; Mitchell, H. *Helicobacter pylori*—an African perspective. *Qjm*. 2001, *94*, 561-565.
(59) Higashi, H.; Tsutsumi, R.; Muto, S.; Sugiyama, T.; Azuma, T.; Asaka, M.; Hatakeyama, M. SHP-2 tyrosine phosphatase as an intracellular target of *Helicobacter pyloriCagA* protein. *Science*2002, *295*, 683-686.
(60) Montecucco, C.; Rappuoli, R. Living dangerously: how *Helicobacter pylori* survives in the human stomach.*Nat. Rev. Mol. Cell Biol.*2001,*2*, 457-466.
(61)Szabò, I.; Brutsche, S.; Tombola, F.; Moschioni, M.; Satin, B.; Telford, J. L.; Rappuoli, R.; Montecucco, C.; Papini, E.; Zoratti, M. Formation of anion-selective channels in the cell plasma membrane by the toxin *VacA* of *Helicobacter pylori* is required for its biological activity. *EMBO J*. 1999, *18*, 5517-5527.
(62) Galmiche, A.; Rassow, J.; Doye, A.; Cagnol, S.; Chambard, J. C.; Contamin, S.; De Thillot, V.; Just, I.; Ricci, V.; Solcia, E.; Van Obberghen, E. The N-terminal 34 kDa fragment of *Helicobacter pylori*vacuolatingcytotoxin targets mitochondria and induces *cytochrome c* release. *EMBO J*. 2000, *19*, 6361-6370.
(63) Vakil, N. *Helicobacter pylori* treatment: a practical approach.*Am. J. Gastroenterol.* 2006, 497-499.
(64)Ables, A. Z.; Simon, I.; Melton, E. R. Update on *Helicobacter pylori* treatment.*Am. Fam. Physician*2007, *75*, 351-358.
(65) Kwon, S. B.; Lee, K. L.; Kim, J. S.; Lee, J. K.; Kim, W.; Jung, Y. J.; Jeong, J. B.; Kim, J. W.; Kim, B. G. Antibiotics-associated diarrhea and other gastrointestinal abnormal responses regarding *Helicobacter pylori* eradication. *Korean J. Gastroenterol*.2010, *56*, 229-235.
(66)McNicholl, A. G.; Linares, P. M.; Nyssen, O. P.; Calvet, X.; Gisbert, J. P. Meta-analysis: esomeprazole or rabeprazole vs. first-generation pump inhibitors in the treatment of *Helicobacter pylori* infection.*Aliment.Pharmacol.Ther.*2012, *36*, 414-425.
(67)Fischbach, L.; Evans, E. L. Meta-analysis: the effect of antibiotic resistance status on the efficacy of triple and quadruple first-line therapies for *Helicobacter pylori*. *Aliment.Pharmacol.Ther.*2007, *26*, 343-357.
(68)Jafri, N. S.; Hornung, C. A.; Howden, C. W. Meta-analysis: sequential therapy appears superior to standard therapy for *Helicobacter pylori* infection in patients naive to treatment.*Ann. Intern. Med*. 2008, *148*, 923-931.
(69) Wu, D. C.; Hsu, P. I.; Wu, J. Y.; Opekun, A. R.; Kuo, C. H.; Wu, I. C.; Wang, S. S.; Chen, A.; Hung, W. C.; Graham, D. Y. Sequential and concomitant therapy with four drugs is equally effective for eradication of *H. pylori* infection.*Clin.Gastroenterol.Hepatol.*2010, *8*, 36-41.
(70)Vaira, D.; Zullo, A.; Vakil, N.; Gatta, L.; Ricci, C.; Perna, F.; Hassan, C.; Bernabucci, V.; Tampieri, A.; Morini, S. Sequential therapy versus standard triple-drug therapy for *Helicobacter pylori* eradication: a randomized trial. *Ann. Intern. Med*. 2007, *146*, 556-563.
(71)Zullo, A.; Vaira. D.; Vakil.N.; Hassan, C.; Gatta, L.; Ricci, C.; De Francesco, V.; Menegatti, M.; Tampieri, A.; Perna, F.; Rinaldi, V. High eradication rates of *Helicobacter pylori* with a new sequential treatment.*Aliment.Pharmacol.Ther.*2003, *17*, 719-726.

(72) Sánchez-Delgado, J.; Calvet, X.; Bujanda, L.; Gisbert, J. P.; Titó, L.; Castro, M. Ten-day sequential treatment for *Helicobacter pylori* eradication in clinical practice. *Am. J. Gastroenterol*. 2008, *103*, 2220-2223.
(73)Molina–Infante, J.; Romano, M.; Fernandez–Bermejo, M.; Federico, A.; Gravina, A. G.; Pozzati, L.; Garcia–Abadia, E.; Vinagre–Rodriguez, G.; Martinez–Alcala, C.; Hernandez–Alonso, M.; Miranda, A. Optimized nonbismuth quadruple therapies cure most patients with *Helicobacter pylori* infection in populations with high rates of antibiotic resistance. *Gastroenterol.*2013, *145*, 121-128.
(74)Uygun, A.; Kadayifci, A.; Safali, M.; Ilgan, S.; Bagci, S. The efficacy of bismuth containing quadruple therapy as a first-line treatment option for *Helicobacter pylori*.*J. Dig. Dis.*2007, *8*, 211-215.
(75)Chuah, S. K.; Tsay, F. W.; Hsu, P. I.; Wu, D. C. A new look at anti-*Helicobacter pylori* therapy. *WJG*2011, *17*, 3971-3975.
(76)Malfertheiner, P. Bismuth improves PPI-based triple therapy for *H. pylori* eradication. *Nat. Rev. Gastroenterol. Hepatol*. 2010, *7*, 538-539.
(77)Gisbert, J. P. Rescue therapy for *Helicobacter pylori* infection 2012. *Gastroenterol. Res. Pract.*2012, *2012*, 1-12.
(78) Franceschi, F.; Gasbarrini, A.; Polyzos, S. A.; Kountouras, J. Extragastric diseases and *Helicobacter pylori*. *Helicobacter*2015, *20*, 40-46.
(79)Liu, C.; Zhang, Y.; Zhan, J.; Zhao, Y.; Wan, Q.; Peng, H.; Zhu, W. Interleukin-23A is associated with tumor growth in *Helicobacter-pylori*-related human gastric cancer. *Cancer Cell Int*. 2014, *14*, 104 (1-9).
(80)Federico, A.; Gravina, A. G.; Miranda, A.; Loguercio, C.; Romano, M. Eradication of *Helicobacter pylori* infection: which regimen first? *WJG*2014, *20*, 665-672.
(81)Gisbert, J. P.; Calvet, X. Non-bismuth quadruple (concomitant) therapy for eradication of *Helicobater pylori*.*Aliment.Pharmacol.Ther.*2011, *34*, 604-617.
(82)Tong, J. L.; Ran, Z. H.; Shen, J.; Xiao, S. D. Sequential therapy vs. standard triple therapies for *Helicobacter pylori* infection: a meta-analysis. *J. Clin. Pharm. Ther.*2009, *34*, 41-53.
(83)Gisbert, J. P.; De La Morena, F. Systematic review and meta-analysis: levofloxacin-based rescue regimens after *Helicobacter pylori* treatment failure. *Aliment.Pharmacol.Ther.*2006, *23*, 35-44.
(84)Federico, A.; Nardone, G.; Gravina, A. G.; Iovene, M. R.; Miranda, A.; Compare, D.; Pilloni, P. A.; Rocco, A.; Ricciardiello, L.; Marmo, R.; Loguercio, C. Efficacy of 5-day levofloxacin-containing concomitant therapy in eradication of *Helicobacter pylori* infection. *Gastroenterol.*2012, *143*, 55-61.
(85)Saad, R. J.; Schoenfeld, P.; Kim, H. M.; Chey, W. D. Levofloxacin-Based Triple Therapy versus Bismuth-Based Quadruple Therapy for Persistent *Helicobacter pylori* Infection: A Meta-Analysis: CME. *Am. J. Gastroenterol*. 2006, *101*, 488-496.
(86) Lai, K. C.; Lam, S. K.; Chu, K. M.; Hui, W. M.; Kwok, K. F.; Wong, B. C.; Hu, H. C.; Wong, W. M.; Chan, O. O.; Chan, C. K. Lansoprazole reduces ulcer relapse after eradication of *Helicobacter pylori* in nonsteroidal anti-inflammatory drug users–a randomized trial. *Aliment.Pharmacol.Ther.*2003, *18*, 829-836.
(87)Polat, Z.; Kadayifci, A.; Kantarcioglu, M.; Ozcan, A.; Emer, O.; Uygun, A. Comparison of levofloxacin-containing sequential and standard triple therapies for the eradication of *Helicobacter pylori*.*Eur. J. Intern. Med.* 2012, *23*, 165-168.
(88)Romano, M.; Cuomo, A.; Gravina, A. G.; Miranda, A.; Iovene, M. R.; Tiso, A.; Sica, M.; Rocco, A.; Salerno, R.; Marmo, R.; Federico, A. Empirical levofloxacin-containing versus clarithromycin-containing sequential therapy for *Helicobacter pylori* eradication: a randomised trial. *Gut.*2010, *59*, 1465-1470.

(89)Di Caro, S.; Zocco, M. A.; Cremonini, F.; Candelli, M.; Nista, E. C.; Bartolozzi, F.; Armuzzi, A.; Cammarota, G.; Santarelli, L.; Gasbarrini, A. Levofloxacin based regimens for the eradication of *Helicobacter pylori*.*Eur. J. Gastroenterol. Hepatol.*2002, *14*, 1309-1312.
(90)Gotteland, M.; Brunser, O.; Cruchet, S. Systematic review: are probiotics useful in controlling gastric colonization by *Helicobacter pylori*?.*Aliment Pharmacol. Ther.*2006, *23*, 1077-1086.
(91)Maisch, T. Anti-microbial photodynamic therapy: useful in the future? *Lasers Med. Sci.*2007, *22*, 83-91.
(92)Goderska, K.; Pena, S. A.; Alarcon, T. *Helicobacter pylori* treatment: antibiotics or probiotics. *Appl. Microbiol. Biotechnol.*2018, *102*, 1-7.
(93) Abadi, A. T.; Kusters, J. G. Management of *Helicobacter pylori* infections. *BMC Gastroenterol.*2016, *16*, 94 (1-4).
(94)Pourakbari, B.; Mahmoudi, S.; Parhiz, J.; Sadeghi, R. H.; Monajemzadeh, M.; Mamishi, S. High frequency of metronidazole and clarithromycin-resistant *Helicobacter pylori* in formalin-fixed, paraffin-embedded gastric biopsies. *Br. J. Biomed. Sci.* 2018, *75*, 61-65.
(95)Parreira, P.; Seabra, C. L.; Lopes-de-Campos, D.; Martins, M. C. Nonantibiotic-Based Therapeutics Targeting *Helicobacter pylori*: From Nature to the Lab. *In Helicobacter Pylori-New Approaches of an Old Human Microorganism.*2018, IntechOpen.
(96)Namkin, K.; Zardast, M.; Basirinejad, F. *Saccharomyces boulardii* in *Helicobacter Pylori* eradication in children: a randomized trial from Iran.*Iran. J. Pediatr.* 2016, *26*,e3768.
(97)Zamani, M.; Zamani, V.; Shokri-Shirvani, J. *Helicobacter pylori* Antibiotic Resistance: What is the Future of Treatment?.*Iran. J. Pediatr.*2016, *26*, 105-106.
(98)Al Somal, N.; Coley, K. E.; Molan, P. C.; Hancock, B. M. Susceptibility of *Helicobacter pylori* to the antibacterial activity of manuka honey.*J. R. Soc. Med.*1994, *87*, 9-12.
(99)Osato, M. S.; Reddy, S. G.; Graham, D. Y. Osmotic effect of honey on growth and viability of *Helicobacter pylori*. *Dig. Dis. Sci*. 1999, *44*, 462-464.
(100)Ndip, R. N.; Takang, A. E.; Echakachi, C. M.; Malongue, A.; Akoachere, J. F.; Ndip, L. M.; Luma, H. N. In-vitro antimicrobial activity of selected honeys on clinical isolates of Helicobacter pylori. *Afr. Health Sci.* 2007, *7*.
(101)French, V. M.; Cooper, R. A.; Molan, P. C.The antibacterial activity of honey against coagulase-negative staphylococci. *J. Antimicrob. Chemother.* 2005, *56*, 228-231.
(102) Graham, D. Y.; Anderson, S. Y.; Lang, T. Garlic or jalapeno peppers for treatment of *Helicobacter pylori* infection. *Am. J. Gastroenterol.*1999, *94*, 1200-1202.
(103)Boyanova, L.; Ilieva, J.; Gergova, G.; Vladimirov, B.; Nikolov, R.; Mitov, I. Honey and green/black tea consumption may reduce the risk of *Helicobacter pylori* infection. *Diagn.Microbiol. Infect. Dis.*2015, *82*, 85-86.
(104) Matongo, F.; Nwodo, U. U.*In vitro* assessment of *Helicobacter pylori* ureases inhibition by honey fractions.*Arch. Med. Res.* 2014, *45*, 540-546.
(105) Keenan, J. I.; Salm, N.; Wallace, A. J.; Hampton, M. B. Using food to reduce *H. pylori*- associated inflammation. *Phytother. Res.*2012, *26*, 1620-1625.
(106) Abdel-Latif, M. M.; Windle, H. J.; Homasany, B. S.; Sabra, K.; Kelleher, D. Caffeic acid phenethyl ester modulates *Helicobacter pylori*-induced nuclear factor-*kappa B* and activator protein-1 expression in gastric epithelial cells.*Br. J. Pharmacol.*2005, *146*, 1139-1147.
(107) Moosa, A.; Kadri, M. Inhibition of *Helicobacter pylori* by commercial honey.*Med. Princ. Pract.*1994, *4*, 114-116.
(108) Weston, R. J. The contribution of catalase and other natural products to the antibacterial activity of honey: a review. *Food Chem.*2000, *71*, 235-239.
(109)Manyi-Loh, C. E.; Clarke, A. M.; Ndip, R. N. Detection of phytoconstituents in column fractions of n-hexane extract of Goldcrest honey exhibiting anti-*Helicobacter pylori* activity. *Arch. Med. Res.*2012, *43*, 197-204.

(110) Hashem-Dabaghian, F.; Agah, S.; Taghavi-Shirazi, M.; Ghobadi, A. Combination of *Nigella sativa* and honey in eradication of gastric *Helicobacter pylori* infection.*Iran. Red Crescent Med. J*. 2016, *18*, e23771.
(111)Ali, A. T.; Al-Humayyd, M. S.; Madan, B. R. Natural honey prevents indomethacin-and ethanol-induced gastric lesions in rats. *Saudi Med. J.* 1990, *11*, 275-279.
(112) Ali, A. T. Prevention of ethanol-induced gastric lesions in rats by natural honey, and its possible mechanism of action.*Scand. J. Gastroenterol.* 1991, *26*, 281-288.
(113) Maddocks, S. E.; Jenkins, R. E. Honey: a sweet solution to the growing problem of antimicrobial resistance?*Future Microbiol.*2013, *8*, 1419-1429.
(114) Boyanova, L.; Gergova, G.; Nikolov, R.; Derejian, S.; Lazarova, E.; Katsarov, N.; Mitov, I.; Krastev, Z. Activity of Bulgarian propolis against 94 *Helicobacter pylori* strains *in vitro* by agar-well diffusion, agar dilution and disc diffusion methods. *J. Med. Microbiol.* 2005, *54*, 481-3.
(115) QURAISIAH, A.; Fazalda, A.; Alfizah, H.; Azlina, M. F. N. In vitro Study of Anti-Helicobacter pylori Activity of Honey: A Systematic Review. *Sains Malays*.2020, *49*, 411-420.
(116)Asgari, B.; Kermanian, F.; Derakhshan, N.; Asna-ashari, M.; Sadat, Z. R.; Yaslianifard, S. Honey-derived *Lactobacillus rhamnosus* alleviates *Helicobacter pylori*-induced gastro-intestinal infection and gastric inflammation in C57BL/6 Mice: an immuno-histologic study. *Arq.Neuropsiquiatr*. 2018, *55*, 279-282.

Figure 1. Therapeutic Benefits of Honey

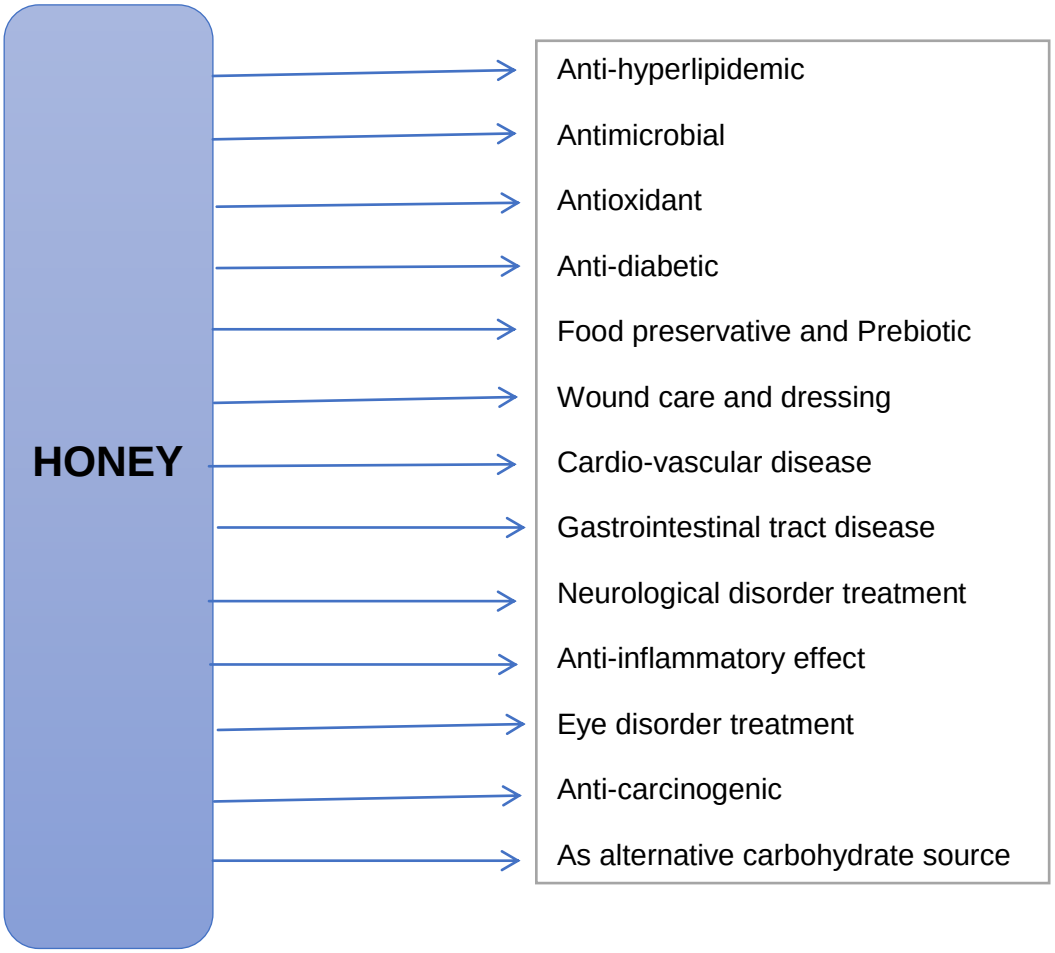
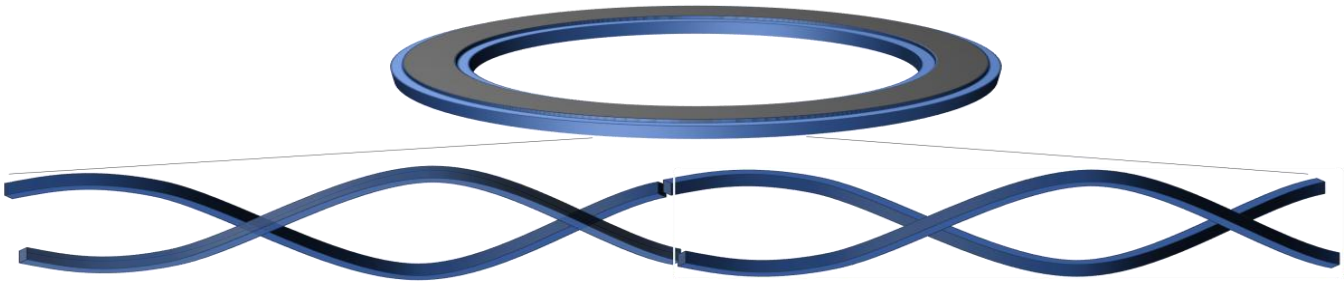
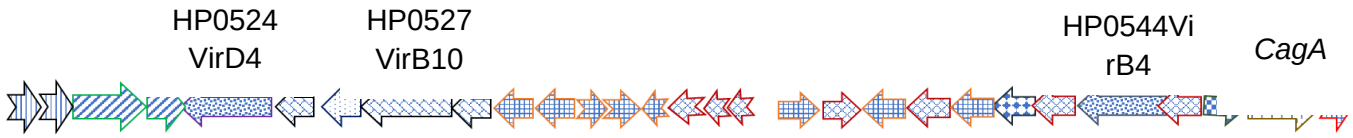


Figure 2. Cag Pathogenicity Island of *H. Pylori*.

H. pylori strain 26695 genome (1,667,867 base pair)



Cag Pathogenicity Island (37,000 base pair, 29 genes)



HP0525
VirB11

HP0528
VirB9

The proteins encoded by this gene assemble to form a complex type IV secretion apparatus capable of delivering *cagA* from the bacterium into host cells.

Translocation of *cagA* into gastric epithelial

Phosphorylation of *cagA* by host-cell kinases c-Src & Lyn

Binding to & activation of cellular phosphatase SHP-2

Growth factor like response in host cell, cytoskeletal rearrangements

Figure 3. Pathogenesis of *H. pylori*.

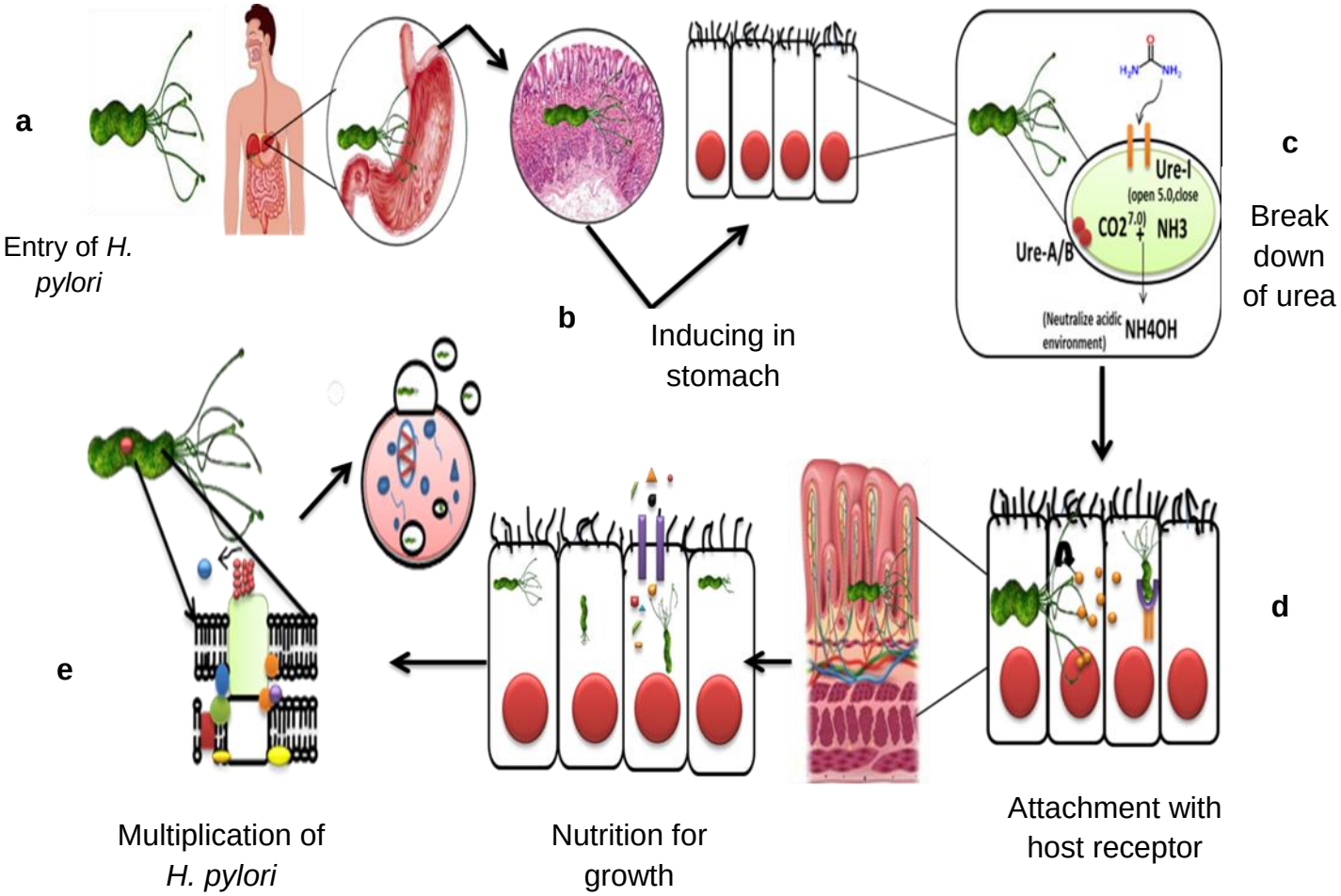


Figure 4. Alternative Approaches to the Current Allopathic Therapy against *H. Pylori*.

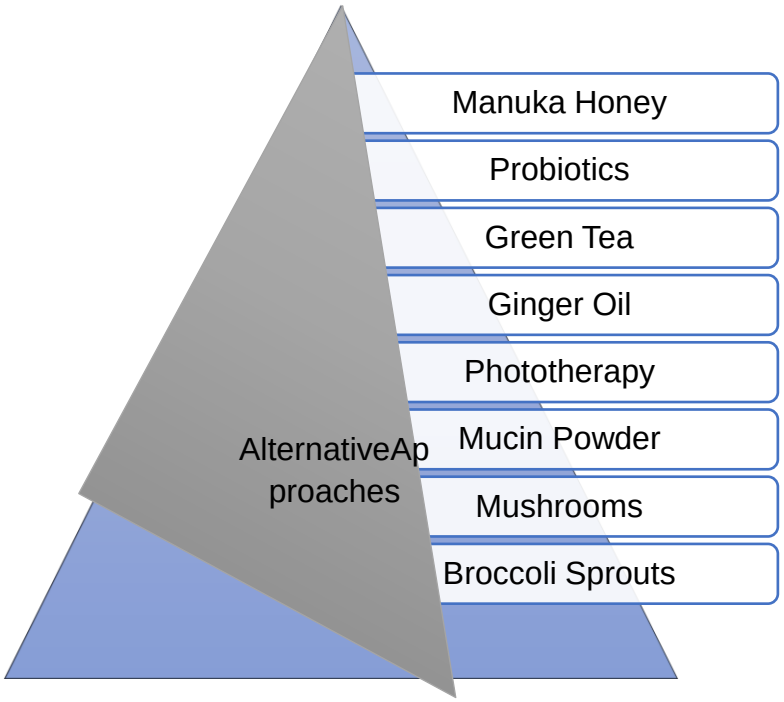


TABLE 1: Treatment Schedule of *H. pylori*.

Therapy	Eradication rate	Antibiotic resistance	Side effects	Patients compliance	Notes
Standard regimen/triple therapy (7-14 d) - A PPI (standard dose, bid) + amoxicillin (1 g, bid) + clarithromycin (500 mg, bid). - A PPI (standard dose, bid) + metronidazole (400mg, bid) + clarithromycin (500 mg, bid). - A PPI (standard dose, bid) + amoxicillin (1 g, bid) + metronidazole (400 mg, bid). - PPI (standard dose, bid) + amoxicillin (1 g, bid) + furazolidone (200 mg, bid).	80-90%	More	Low	High	First line therapy
Sequential regimen (5 d) - A PPI (standard dose, bid) + amoxicillin (1 g, bid). - A PPI (standard dose, bid) + amoxicillin (1 g, bid) followed by PPI + clarithromycin (500 mg) + metronidazole (500 mg). - PPI (standard dose, bid) + amoxicillin (1 g, bid) followed by PPI + clarithromycin (500 mg) + tinidazole (500 mg).	63-90%	Low	More than Standard therapy.	High	First line therapy
Quadruple bismuth regimen (7, 10-14 d) - A PPI (standard dose, bid) + bismuth (240 mg, bid) +amoxicillin (1 g, bid) + furazolidone (20 mg, bid). - A PPI (standard dose, bid) + bismuth (240 mg, bid) +amoxicillin (1 g, bid) + metronidazole (400 mg, bid). - A PPI (standard dose, bid) + bismuth (240 mg,qid) + Tetracycline (500 mg, qid) + Metronidazole (500 mg, tid). - A PPI (standard dose, bid) + bismuth subsalicylate (525 mg, qid) + metronidazole (250 mg, qid) + tetracycline (500 mg, qid). - Rabeprazole (40 mg, bid) + bismuth potassium citrate (220 mg, bid) + metronidazole (500 mg, tid) + tetracycline (500 mg, tid).	90%	Lower than standard and sequential.	Low	High	First line or second line therapy
Concomitant regimen (7-10 d). - A PPI (standard dose, bid) + Clarithromycin (500 mg, bid) + Amoxicillin (1 g, bid) + Metronidazole (500 mg, bid) +tinidazole (500 mg, bid). - Sitafloxacin therapy (7-d). - A PPI (standard dose, bid) + amoxicillin (750 mg, bid) + sitafloxacin (100 mg, bid).	89-93%	More	Low	High	First line therapy

Hybrid regimen (14 d). -PPI (standard dose) and amoxicillin 1 g bid(7d) + PPI (standard dose), amoxicillin 1 g, metronidazole 0.5 g and clarithromycin 0.5 g bid (7 d)					First line therapy
Levofloxacin regimen (5-7-d) - A PPI (standard dose, bid) + levofloxacin (500 mg, bid)+ either amoxicillin (1000 mg or tinidazole 500 mg, bid). - Esomeprazole (40 mg, bid + amoxicillin (1 g, bid) followed by esomeprazole (40 mg, bid) + levofloxacin (240 mg, bid) + metronidazole (500 mg, bid). - Esomeprazole (20 mg, bid) + amoxicillin (1 g, bid) + levofloxacin (250 mg, bid) - Esomeprazole (40 mg, bid) + amoxicillin (1000 mg, bid) + levofloxacin (500 mg, bid)	90-96%	Lower than other therapies.	Lower than other therapies.	Higher than other therapies.	Second line/ third line therapy.
Culture-guided therapy (10d) -PPI (standard dose) bid, bismuth standard dose qid, levofloxacin 0.5 g qid and amoxicillin 1 g bid.					Third line therapy
High-dose dual PPI therapy (14 d) -A PPI (high dose) qid and amoxicillin 0.5 g qid					Third line therapy
Rifabutin triple therapy (14d) -A PPI (standard dose) bid, rifabutin 0.15 g bid and amoxicillin 1 g bid.					Third line therapy

Abbreviation: PPI, Proton pump inhibitor; bid, Twice daily; qid, Four times daily; tid, Three times daily; and d, days.