Management of multi-drug resistant *Helicobacter pylori* infection by supplementary, complementary and alternative medicine; a review

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ABSTRACT

*Helicobacter pylori* is recognized as the most common bacterial pathogen colonizing the gastric epithelium of nearly half of the world’s population. This bacterium is the main etiological cause of gastroduodenal ulcers, and more importantly as the substantial risk factor for development of gastric cancer. The emergence and rapid increase in the prevalence of multi-drug resistant phenotypes have posed major pitfalls in effectiveness of various treatment regimens and eradication strategies against *H. pylori* infections. Several natural products and supplementary food components have been reported to have established anti-*H. pylori* activity. Herein, we review the application and efficacy of some specific natural products and foodstuffs such as milk, bee products (honey and propolis), fish oil, vitamins C and E, and also a nickel free-diet used as anti-*H. pylori* alternative treatment regimens.

Keywords: *Helicobacter pylori*, Drug resistance, Dietary supplementation, Anti-inflammatory, Eradication therapy

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Introduction

*Helicobacter pylori* is a spiral bacterium that colonize in the human gastric epithelium. The bacterium causes different precancerous lesions like gastritis, atrophy, intestinal metaplasia and dysplasia, and is the strongest known risk factor for gastric cancer (GC) (1-3). *H. pylori* infects more than half of the people globally, and the prevalence of *H. pylori* infection is highly variable across different countries; for example, high prevalence is observed in developing countries (~80%) in comparison to developed countries with about 30-50% of the population (4). The bacterium usually is acquired in childhood and can persist for lifetime in the host stomach. *H. pylori* pathogenesis is mediated by a complex interplay between various bacterial virulence factors, host genetic predisposition, and environmental factors (5-7). *H. pylori* is also known as one of the most genetically diverse bacterial species that presents various virulence genotypes responsible for different gastric diseases (8-10). The emergence and more importantly the increasing prevalence of multi-drug resistant strains of *H. pylori* has led to reduced success in different treatment regimens (11-17). Several natural products and supplementary nutrients have been reported to have established antimicrobial activity against *H. pylori* infection (Table 1). Here, we tried to have a short
overview on the application and efficacy of some natural products and supplementary compounds used as anti-*H. pylori* alternative treatments.

**Dairy, bee products and fish oil, Vitamins, Nickel free-diet**

**Milk**

Milk, especially the human milk, has long been identified as one of the natural products encompassing high nutritional values as well as antimicrobial effects against a variety of infections. Before the discovery of antibiotics, a non-specific therapy named protein therapy, used the antibacterial properties of milk protein contents (18). Moreover, nutrient fortification of human milk with medium-chain triglycerides (MCT) and iron has been also applied as an acceptable supplement therapy for feeding preterm infants (19).

Lactoferrin is a multifunctional iron-binding glycoprotein with potent antibacterial and immunomodulatory properties against several bacterial pathogens (20, 21). It is released in the human colostrums with highest concentration in comparison with human milk and cow milk (20). It is also present in saliva, tears, seminal fluid and immune cells like neutrophils (20, 22). Lactoferrin has been shown to have inhibitory effects on growth of a number of bacterial pathogens including Streptococcus mutans, Streptococcus pneumoniae, Haemophilus influenza, Neisseria meningitidis, Escherichia coli and *H. pylori* (21, 23). The antimicrobial activity of lactoferrin is well studied and is likely attributed to its high affinity for iron, functioning as an iron chelator that sequesters iron elements from bacterial access (22, 24).

There are some in vivo studies showing that lactoferrin can improve *H. pylori* eradication rate in humans and mouse models (25-28). In another in vitro study, Akedo et al. showed anti-*H. pylori* property of cow’s milk (29). Moreover, in a survey on 482 children aged 0-12-years-old, Okuda and et al. assessed the relation between breast feeding and *H. pylori* infection, and proposed breast feeding can be a natural way to protect children from infection due to anti-adhesive property of lactoferrin, sialyllactose and oligosaccharides present in breast milk (30). In 2013, a review study suggested that fermented milk-based probiotic preparations and bovine lactoferrin can be effective for *H. pylori* eradication (31).

**Honey**

In the traditional medicine, honey was used as an antimicrobial substance for treatment of infectious diseases, and also gastrointestinal disorders like dyspepsia, gastritis, peptic ulcer disease, and liver disease (27-29). Additionally, it is reported that honey can accelerate wound healing process and was used to dress wounds and burns (32). The antibacterial property of honey varies due to its color and floral sources. Red honeys have shown more potent antibacterial properties than white honeys, which this property depends on different phenolic acid contents of various kinds of honeys (33, 34). The bactericidal and bacteriostatic potency of honey is broad-spectrum, and is effective against several bacterial agents such as *Staphylococcus aureus*, *Pseudomonas aerugiosa*, *E. coli* and *Streptococcus pyogenes* (34). It has been proposed that antibacterial activity of honey is mainly due to its high osmotic and acidity, hydrogen peroxide production, flavonoids and over-mentioned phenolic acids content (35-38).

Some studies revealed that high osmotic and high acidity effects of honey can inhibit the urease activity of *H. pylori* (37, 38). Abdel-Latif and colleagues investigated the molecular mechanisms by which natural honey may inhibit *H. pylori* infection. They reported that Manuka honey can inhibit *H. pylori* by suppression of *H. pylori* induced NF-kB and AP-1 activation, and down regulation of COX-2 expression in gastric epithelial cells (35). Another in vivo study in Bulgaria showed the anti-*H. pylori* effect of honey via its high osmotic and acidity effect (36).

**Propolis**

Propolis is a resinous bee product that contains plant resin, bee enzymes and wax (39, 40). It is reported to be an antioxidant, antibacterial, antifungal, anti-inflammatory, antiproliferative and anti-diabetic substance. The natural composition of propolis varies due to its original floral sources, and contains different amounts of phenolic compounds (39-41). The anti-*H. pylori* properties of propolis may be due to its phenolic substances such as flavonoids, phenolic acids and their esters like caffeic acid phenethyl ester (CAPE) and chrysirin (40-42). Baltas and colleagues studied the anti-*H. pylori* effect of 15 ethanol extracts of propolis and reported that all extracts inhibited *H. pylori* J99 strain by urease inhibition (41). In 2013, Cui et al. assayed
different propolis phenolic compounds for _H. pylori_ peptide deformylase (HpPDF) inhibition, which is necessary for _H. pylori_ perpetuity and persistence (40).

**Fish oil**

From many years ago, essential oils were among the most useful components in traditional medicine around the world and their activity against _H. pylori_ have been delineated (43, 44). Fish oil (Eicosapen) includes 33.5% omega-3-fatty acids with a variety of immunomodulating effects, which has bacteriostatic effect on _H. pylori_ (45-49). Moreover, it has been reported that omega-3-fatty acids declined the secretion of gastric acid in healthy volunteers (50). It has been proposed that the inhibitory effects of fish oil on _H. pylori_ may be due to: 1) direct inhibition or killing the bacteria (49), 2) inhibition of bacterial adhesion to gastric epithelium, and 3) inhibition of the _H. pylori_-induced inflammatory pathways (51, 52).

**Vitamins**

Vitamin C, an acidic molecule, is one of the most important component of living tissues. Two forms of vitamin C including: AA (ascorbic acid) and DHA (dehydroascorbic acid), the reduced and oxidized form, respectively, which can convert to each other. Inside the cell, DHA is immediately converted to AA in presence of glutathione or other thiols as electron donors via the specific enzyme systems like DHA reductase, glutaredoxins and protein disulfide isomerase (53, 54). Unfortunately, stability of AA and DHA are low and have a rapid wild irreversible hydrolysis particularly at a pH > 4 (55). Vitamins C and E have been studied to show their antioxidant effect for eradication of _H. pylori_ infection (56, 57). It seems vitamins C and E break the microenvironment created by _H. pylori_ or directly inhibit bacteria. Additionally, the detriment of antioxidants on colonization and proliferation of _H. pylori_ have been shown (58-60).

In a study by Sezikli et al., they showed that under the oxidative stress vitamins C and E were effective in eradication of _H. pylori_ infection (56). In another work, administration of high dose vitamin C treatment had inhibitory effects on _H. pylori_ growth (61). In a study by Demirci and coworkers, the effect of vitamins C and E supplementation along with triple and quadruple eradication regimens was assessed using 400 _H. pylori_ infected patients. They showed that _H. pylori_ eradication rate was 56% for smokers and 94% for non-smokers. The success rate of _H. pylori_ eradication for smokers was lower than non-smokers (62). Zojaji et al., also reported that addition of vitamin C to _H. pylori_ treatment regimen including amoxicillin, metronidazole, and bismuth increased the eradication rate among the infected patients (63).

**Nickel free-diet**

Nickel is a metallic element that is widely found in almost all kinds of diets (64). It is abundant in fruits and vegetables like apricots, figs, pears, plums, raisins, pineapples, cabbage, onions, beans, lentils, potatoes, peas, tomatoes, spinach, cauliflower, asparagus, corn and margarine. This element is also present in different kinds of nuts including almonds, peanuts, walnuts, hazelnuts, and cocoa as well as some sea foods like lobster, mussels, oysters and plaice (65, 66). However, it seems that nickel is not essential for humans, but it is necessary for _H. pylori_ colonization because of its important role in activation of _H. pylori_ urease and hydrogenase enzymes. So, there is no competition between _H. pylori_ and human body for nickel access (64). According to these facts, Campanale and colleagues in 2014 designed a pilot study to investigate the effect of a nickel free-diet on the eradication of _H. pylori_ infection. In their in vivo study, 52 participants with _H. pylori_ infection were divided into two groups: standard triple therapy and standard triple therapy with nickel free-diet. In the second group, the participants were prohibited to consume foods with high quantity of nickel for 4 weeks. They found that addition of nickel free-diet to standard triple therapy can significantly promote _H. pylori_ eradication rate (64).

**Discussion**

Currently, the treatment of all symptomatic _H. pylori_-infected patients is less probable, and could rapidly increase the emergence and prevalence of multi-drug resistant strains in the community. Moreover, despite the availability of several therapeutic strategies for _H. pylori_-induced gastric diseases, the bacterial eradication is very challenging and none of the treatment regimens appear to be ideal. Therefore, the application of relatively low-cost natural products and foodstuffs with established anti- _H. pylori_ activity seems to be promising as alternative medicine and adjuvant.
| Food types | Active components | Putative anti- \( H. \text{pylori} \) properties | Testing methods | Year/country | Ref. |
|------------|-------------------|---------------------------------|----------------|--------------|------|
| Milk       | Lactoferrin, sialyllactose, oligosaccharides | Inhibition of \( H. \text{pylori} \) attachment | \( H. \text{pylori} \) stool antigen assay (HpSA) | 2001/Japan | 30   |
| Lactoferrin adsorbed into biomimetic hydroxyapatite nanocrystals | Iron chelating and sequestration | Inhibition zone assay and the bacterial load were measured in orally \( H. \text{pylori} \)-infected BALB/c mice using SYBR Green I quantitative real-time PCR assay | Italy/2016 | 67   |
| Bovine milk glycoproteins and glycoconjugates and lactoferrin | Iron deprivation, decreasing gastric colonization of \( H. \text{pylori} \) and inflammation score | Growth inhibition assay, haemagglutination inhibition assay and adherence assay | Sweden/2001 | 28   |
| Hydrogen peroxide and phytochemicals (flavonoids and phenolic acids) | High osmotic effect, pH (high acidity) | | Bulgaria/2015 | 36   |
| Flavonoids and phenolic acids | Inhibition of bacterial urease activity | Urease activity assay by spectrophotometry | South Africa/2014 | 38   |
| Honey      | High osmotic effect, pH (high acidity) | Hole plate diffusion method and microbroth dilution method | Cameroon/2013 | 37   |
| Hydrogen peroxide and phytochemicals (flavonoids and phenolic acids) | Inhibition of \( H. \text{pylori} \)-induced NF-\( \kappa \)B and AP-1 activation and downregulation of COX-2 expression, growth inhibition | Electrophoretic mobility shift assay (EMSA), cell viability assay and cytotoxicity assay | Egypt/2016 | 35   |
| Propolis   | Flavonoids, Phenolic compounds, Caffeic acid phenethyl ester and chrysin | Urease inhibition | Agar-well diffusion method and urease inhibition assay | Turkey/2016 | 41   |
| Fish oil   | Phenolic compounds, Caffeic acid phenethyl ester | Inhibition of \( H. \text{pylori} \) peptide deformylase | Enzymatic activity of \( HpPDF \) was evaluated using a FDH coupled assay | China/2013 | 40   |
| Vitamin C  | Ascorbic acid | Direct inhibition of bacteria, antiadhesive activity, anti-inflammatory effect | Agar diffusion test (Kirby-Bauer method) | Italy/1999 | 52   |
| Vitamin C and E | Ascorbic acid, tocopherols and tocotrienols | Inhibition of \( H. \text{pylori} \) colonization, antioxidant effects | Urease test and histological examination (Giemsa staining) | Poland/1998 | 61   |
| Ascorbic acid, tocopherols and tocotrienols | Rapid urease test, histopathological evaluation and UBT | | Turkey/2015 | 62   |
| Ascorbic acid, tocopherols and tocotrienols | Antioxidant effects | Histologic examination, rapid urease test, 14C-urea breath test, HpSA and Measurement of Total Antioxidant Capacity (TAC) | Turkey/2009 | 56   |

Abbreviations: UBT, urease breath test; \( HpPDF \), \( H. \text{pylori} \) peptide deformylase; FDH, formate dehydrogenase; PCR, Polymerase chain reaction; PH, potential of hydrogen; NF-\( \kappa \)B, nuclear factor kappa-light-chain-enhancer of activated B cells; AP-1, Activator protein 1; COX-2, Prostaglandin-endoperoxide synthase 2 (cyclooxygenase-2); EPA, Eicosapentaenoic acid; DHA, docosahexaenoic acid
therapy to manage the infections caused by antibiotic-resistant *H. pylori* strains. However, it is very important to evaluate the antibacterial effectiveness of different natural products and food components by both *in vitro* and *in vivo* experiments, especially in the clinical trials, to propose a potentially effective diet-based treatment regimen (68). Finally, further studies are needed to explore novel, local and natural therapeutics to be co-administrated with conventional antimicrobial agents as adjunctive therapy against *H. pylori* infections.

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**Conflict of interests**

The authors declare that they have no conflict of interest.

**References**

1. Shokrzadeh L, Baghaei K, Yamaoka Y, Dabiri H, Jafari F, Sahebekhtiari N, et al. Analysis of 3'-end variable region of the cagA gene in Helicobacter pylori isolated from Iranian population. J Gastroenterol Hepatol 2010;25:172-77.
2. Baghaei K, Shokrzadeh L, Jafari F, Dabiri H, Yamaoka Y, Bolfion M, et al. Determination of Helicobacter pylori virulence by analysis of the cag pathogenicity island isolated from Iranian patients. Dig Liver Dis 2009;41:634-38.
3. Kao CY, Chen JW, Huang YT, Sheu SM, Sheu BS, Wu JJ. Genome sequence and annotation of Helicobacter pylori strain Hp238, isolated from a Taiwanese patient with mucosa-associated lymphoid tissue lymphoma. Genome Announc 2015;3:00006-15.
4. Sahebekhtiari N, Nochi Z, Eslampour MA, Dabiri H, Bolfion M, Taherikalani M, et al. Characterization of Staphylococcus aureus strains isolated from raw milk of bovine subclinical mastitis in Tehran and Mashhad. Acta Microbiol Immunol Hung 2011;58:113-21.
5. Taremi M, Mehdi Soltan Dallal M, Gachkar L, MoezArdalan S, Zolfagharian K, Reza Zali M. Prevalence and antimicrobial resistance of Campylobacter isolated from retail raw chicken and beef meat, Tehran, Iran. Int J Food Microbiol 2006;108:401-403.
6. Yadegar A, Alebouyeh M, Lawson AJ, Mirzaei T, Nazemalhosseini Mojaref E, Zali MR. Differentiation of non-panpilori Helicobacter bacteria based on PCR-restriction fragment length polymorphism of the 23S rRNA gene. World J Microbiol Biotechnol 2014;30:1909-17.
7. Yadegar A, Alebouyeh M, Zali MR. Analysis of the intactness of Helicobacter pylori cag pathogenicity island in Iranian strains by a new PCR-based strategy and its relationship with virulence genotypes and EPIYA motifs. Infect Genet Evol 2015;35:19-26.
8. Cover TL. Helicobacter pylori diversity and gastric cancer risk. MBio 2016;7:01869-15.
9. Gunaletchumy SP, Seesavan I, Tan MH, Croft LJ, Mitchell HM, Goh KL, et al. Helicobacter pylori genetic diversity and gastro-duodenal diseases in Malaysia. Sci Rep 2014;4:7431.
10. Farzi N, Malekian T, Alebouyeh M, Vaziri F, Zali MR. Genotype diversity and quasispecies development of Helicobacter pylori in a single host. Jpn J Infect Dis 2015;68:176-80.
11. Sugimoto M, Yamaoka Y. Virulence factor genotypes of Helicobacter pylori affect cure rates of eradication therapy. Arch Immunol Ther Exp (Warsz) 2009;57:45-56.
12. Bohnke KF, Valdivieso M, Bussalleu A, Sexton R, Thompson KC, Osorio S, et al. Antibiotic resistance among Helicobacter pylori clinical isolates in Lima, Peru. Infect Drug Resist 2017;10:85-90.
13. Megraud F. *H pylori* antibiotic resistance: prevalence, importance, and advances in testing. Gut 2004;53:1374-84.
14. Vianna JS, Ramis IB, Ramos DF, VON GROLL A, Silva PEAd. Drug resistance in Helicobacter pylori. Arq Gastroenterol 2016;53:215-23.
15. Thung I, Aramin H, Vavinskaya V, Gupta S, Park J, Crowe S, et al. Review article: the global emergence of Helicobacter pylori antibiotic resistance. Aliment Pharmacol Ther 2016;43:514-33.
16. Shokrzadeh L, Alebouyeh M, Mirzaei T, Farzi N, Zali MR. Prevalence of multiple drug-resistant Helicobacter pylori strains among patients with different gastric disorders in Iran. Microb Drug Resist 2015;21:105-10.
17. Alebouyeh M, Yadegar A, Farzi N, Mirm M, Zojahi H, Gharibi S, et al. Impacts of *H. pylori* mixed-infection and heteroresistance on clinical outcomes. Gastroenterol Hepatol Bed Bench 2015;8:S1-5.
18. Lahov E, Regelson W. Antibacterial and immunostimulating casein-derived substances from milk: casecidin, isracidin peptides. Food Chem Toxicol 1996;34:131-45.
19. Chan GM. Effects of powdered human milk fortifiers on the antibacterial actions of human milk. J Perinatol 2003;23:620-3.
20. Farnaud S, Evans RW. Lactoferrin--a multifunctional protein with antimicrobial properties. Mol Immunol 2003;40:395-405.
21. Jenssen H, Hancock RE. Antimicrobial properties of lactoferrin. Biochimie 2009;91:19-29.
22. Fahey JW, Stephenson KK, Wallace AJ. Dietary amelioration of Helicobacter infection. Nutr Res 2015;35:461-73.

23. Roseanu A, Damian M, Evans RW. Mechanisms of the antibacterial activity of lactoferrin and lactoferrin-derived peptides. Rom J Biochem 2010;47:203-9.

24. Holubiuk L, Imiela J. Diet and Helicobacter pylori infection. Gastroenterol Rev 2016;11:150-4.

25. Moosavi A, Haghighi A, Mojarad EN, Zayeri F, Alebouyeh M, Khazan H, et al. Genetic variability of Blastocystis sp. isolated from symptomatic and asymptomatic individuals in Iran. Parasitol Res 2012;111:2311-15.

26. Dial E, Romero J, Headon D, Lichtenberger L. Recombinant human lactoferrin is effective in the treatment of Helicobacter felis-infected mice. J Pharm Pharmacol 2000;52:1541-6.

27. Okuda M, Nakazawa T, Yamauchi K, Miyashiro E, Koizumi R, Booka M, et al. Bovine lactoferrin is effective to suppress Helicobacter pylori colonization in the human stomach: a randomized, double-blind, placebo-controlled study. J Infect Chemother 2005;11:265-9.

28. Wang X, Himno S, Willen R, Wadström T. Inhibition of Helicobacter pylori infection by bovine milk glycoconjugates in a BALB/cA mouse model. J Med Microbiol 2001;50:430-5.

29. Akedo I, Tatsuta M, Narahara H, Iishi H, Uedo N, Yano H, et al. Prevention by bovine milk against Helicobacter pylori-associated atrophic gastritis through its adherence inhibition. Hepatogastroenterology 2003;51:277-81.

30. Okuda M, Miyashiro E, Koike M, Okuda S, Minami K, Yoshikawa N. Breast-feeding prevents Helicobacter pylori infection in early childhood. Pediatr Int 2001;43:714-5.

31. Sachdeva A, Rawat S, Nagpal J. Efficacy of fermented milk and whey proteins in Helicobacter pylori eradication: a review. World J Gastroenterol 2014;20:724-37.

32. Lusby P, Coombes A, Wilkinson J. Honey: a potent agent for wound healing? J Wound Ostomy Continence Nurs 2002;29:295-300.

33. Hegazi AG, Guthami FM, Gethami AF, Allah FM, Saleh AA, Fouad EA. Potential antibacterial activity of some Saudi Arabia honey. Vet World 2017;10:233-7.

34. Wasihun AG, Kasa BG. Evaluation of antibacterial activity of honey against multidrug resistant bacteria in Ayder Referral and Teaching Hospital, Northern Ethiopia. SpringerPlus 2016;5:842.

35. Abdel-Latif MM, Abouzied MM. Molecular mechanisms of natural honey against H. pylori infection via suppression of NF-kB and AP-1 activation in gastric epithelial cells. Arch Med Res 2016;47:340-8.

36. 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;82:85-6.

37. Manyi-Loh CE, Clarke AM, Green E, Ndip RN. Inhibitory and bactericidal activity of selected South African honeys and their solvent extracts against clinical isolates of Helicobacter pylori. Pak J Pharm Sci 2013;26:897-906.

38. Matongo F, Nwodo UU. In vitro assessment of Helicobacter pylori ureases inhibition by honey fractions. Arch Med Res 2014;45:540-6.

39. Boonsai P, Phuwapraisirisan P, Chancho C. Antibacterial activity of a cardanol from Thai Apis mellifera propolis. Int J Med Sci 2014;11:327-36.

40. Cui K, Lu W, Zhu L, Shen X, Huang J. Caffeic acid phenethyl ester (CAPE), an active component of propolis, inhibits Helicobacter pylori peptide deformylase activity. Biochem Biophys Res Commun 2013;435:289-94.

41. Baltas N, Karaoglu SA, Tarakci C, Kolayli S. Effect of propolis in gastric distorders: inhibition studies on the growth of Helicobacter pylori and production of its urease. J Enzyme Inhib Med Chem 2016;31:46-50.

42. Villanueva M, Gonzalez M, Fernandez H, Wilson M, Manquín N, Otth C, et al. In vitro antibacterial activity of Chilean propolis against Helicobacter pylori. Rev Chilena Infectol 2015;32:530-5.

43. Bergonzelli G, Donniciola D, Porta N, Corthesy-Theulaz I. Essential oils as components of a diet-based approach to management of Helicobacter infection. Antimicrob Agents Chemother 2003;47:3240-6.

44. Chun SS, Vattem DA, Lin YT, Shetty K. Phenolic antioxidants from clonal oregano (Origanum vulgare) with antimicrobial activity against Helicobacter pylori. Process Biochem 2005;40:809-16.

45. Hawthorne A, Daneshmend T, Hawkey C, Belluzzi A, Everitt S, Holmes G, et al. Treatment of ulcerative colitis with fish oil supplementation: a prospective 12 month randomised controlled trial. Gut 1992;33:922-8.

46. Kemen M, Senkal M, Homann HH, Mummke A, Dauphin AK, Baier J, et al. Early postoperative enteral nutrition with arginine-omega-3 fatty acids and ribonucleic acid-supplemented diet versus placebo in cancer patients: An immunologic evaluation of Impact Registered Trademark. Crit Care Med 1995;23:652-9.

47. Nordøy A. Is there a rational use for n-3 fatty acids (fish oils) in clinical medicine? Drugs 1991;42:331-42.

48. Senkal M, Kemen M, Homann H, Eckhoff U, Baier J, Zumtobel V. Modulation of postoperative immune response by enteral nutrition with a diet enriched with arginine, RNA, and omega-3 fatty acids in patients with upper gastrointestinal cancer. Eur J Surg 1995;161:115-22.

49. Thompson L, Cockayne A, Spiller R. Inhibitory effect of polysaturated fatty acids on the growth of Helicobacter pylori: a possible explanation of the effect of diet on peptic ulceration. Gut 1994;35:1557-61.

50. Riber C, Wojdemann M, Bisaard T, Ingels H, Rehfell J, Olsen O. Fish oil reduces gastric acid secretion. Scand J Gastroenterol 1999;34:845-8.
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51. Zurier R. Fatty acids, inflammation and immune responses. Prostaglandins Leukot Essent Fatty Acids 1993;48:57-62.

52. Drago L, Mombelli B, Ciardo G, Vecchi ED, Gismondo M. Effects of three different fish Oil formulations on Helicobacter pylori growth and viability: in vitro study. J Chemother 1999;11:207-10.

53. Nualart FJ, Rivas CI, Montecinos VP, Godoy AS, Guaquill VH, Golde DW, et al. Recycling of vitamin C by a bystander effect. J Biol Chem 2003;278:10128-33.

54. Tsao C. An overview of ascorbic acid chemistry and biochemistry. In: Packer L, FuchsJ, eds. Vitamin C in Health and Disease. New York: Marcel Dekker 1997;25-58.

55. Deutsch JC. Spontaneous hydrolysis and dehydration of dehydroascorbic acid in aqueous solution. Anal Biochem 1998;260:223-9.

56. Sezikli M, Çetinkaya ZA, Sezikli H, Güzelbulut F, Tiftikçi A, Tüzün İnce A, et al. Oxidative stress in Helicobacter pylori infection: does supplementation with vitamins C and E increase the eradication rate? Helicobacter 2009;14:280-5.

57. Sezikli M, Çetinkaya Z, Güzelbulut F, Yeşil A, Coşgun S, Kuruç O. Supplememting Vitamins C and E to standard triple therapy for the eradication of Helicobacter pylori. J Clin Pharm and Ther 2012;37:282-5.

58. Sjunnesson H, Sturegård E, Willén R, Wadström T. High intake of selenium, beta-carotene, and vitamins A, C, and E reduces growth of Helicobacter pylori in the guinea Pig. Comp Med 2001;51:418-23.

59. Sun YQ, Girgensone I, Leanderson P, Petersson F, Borch K. Effects of antioxidant vitamin supplements on Helicobacter pylori-induced gastritis in Mongolian gerbils. Helicobacter 2005;10:33-42.

60. Zhang Z, Patchett S, Perrett D, Katelaris P, Domizio P, Farthing M. The relation between gastric vitamin C concentrations, mucosal histology, and CagA seropositivity in the human stomach. Gut 1998;43:322-6.

61. Jarosz M, Dziemiszewski J, Dabrowska-Ufniarz E, Wartanowicz M, Ziemiłska S, Reed P. Effects of high dose vitamin C treatment on Helicobacter pylori infection and total vitamin C concentration in gastric juice. Eur J Cancer Prev 1998;7:449-54.

62. Demirci H, Uygun İlkihn S, Öztürk K, Üstündag Y, Kurt Ö, Bilici M, et al. Influence of vitamin C and E supplementation on the eradication rates of triple and quadruple eradication regimens for Helicobacter pylori infection. Turk J Gastroenterol 2015;26:456-60.

63. Zojaji H, Talaie R, Mirmartati D, Haghazali M, Molaei M, Mohsenian N, et al. The efficacy of Helicobacter pylori eradication regimen with and without vitamin C supplementation. Dig Liver Dis 2009;41:644-7.

64. Campanale M, Nucera E, Ojeti V, Cesario V, Di Rienzo T, D'Angelo G, et al. Nickel free-diet enhances the Helicobacter pylori eradication rate: a pilot study. Dig Dis Sci 2014;59:1851-5.

65. Rostami Nejad M, Rostami K, Yamaoka Y, Mashayekhi R, Molaei M, Dabiri H, et al. Clinical and histological presentation of Helicobacter pylori and gluten related gastroenteropathy. Arch Iran Med 2011;14:115-18.

66. Minelli M, Schiavino D, Musca F, Bruno M, Falagian P, Mistrello G, et al. Oral hyposensitization to nickel induces clinical improvement and a decrease in TH1 and TH2 cytokines in patients with systemic nickel allergy syndrome. Int J Immunopathol Pharmacol 2010;23:193-201.

67. Fulgione A, Nocerino N, Iannaccone M, Roperto S, Capuano F, Roveri N, et al. Lactoferrin adsorbed onto biomimetic hydroxyapatite nanocrystals controlling-in vivo-the Helicobacter pylori infection. PLoS One 2016;11:e0158646.

68. Nazemalhosseini-Mojarrad E, Haghhighi A, Taghipour N, Keshavarz A, Mohei SR, Zali MR, et al. Subtype analysis of Cryptosporidium parvum and Cryptosporidium hominis isolates from humans and cattle in Iran. Vet Parasitol 2011;179:250-52.