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Review

Treatment of *Helicobacter pylori* infections: Mitigating factors and prospective natural remedies

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Helicobacter pylori **is a Gram-negative, microaerophilic spiral or motile rod that infects about half the world's population with a very high prevalence in the developing world. It is an important aetiological factor in the development of gastritis, peptic ulcer disease, gastric atrophy and B cell mucosa associated lymphoid tissue (MALT) lymphoma.** ***H. pylori*** **infection is responsible for a significant cause of morbidity and mortality imposing a major burden on health care systems world wide. The high prevalence of infection in the developing countries has been attributed to poor socioeconomic status and sanitation as well as an increased trend of antibiotic resistance. Antimicrobial chemotherapy (two antibiotics and a proton pump inhibitor) employed for the treatment of** ***H. pylori*** **infections has emerged as the most important means to resolve these infections. However, antimicrobial therapy is fraught with a number of inherent limitations such as resistance, cost of treatment, unavailability of drugs in rural areas and undesirable side effects necessitating the need to search for alternative approaches from natural sources including vegetables, honey and probiotics amongst others. These could form the basis of novel low cost, efficient, large-scale and alternative/complementary solutions with minimal side effects to decrease or eradicate** ***H. pylori*** **infections in the future.**

Key words: *Helicobacter pylori*, treatment regimen, factors affecting treatment, alternative approaches, natural products.

INTRODUCTION

The spiral-shaped, microaerophilic and Gram-negative bacterium, *Helicobacter pylori* exhibiting four to six unipolar sheathed flagella has adapted to thrive in the acid environment (Bury-Moné et al., 2003) of the stomach of humans causing diseases (Módena et al., 2007). *H. pylori* infection is probably one of the most common bacterial infections worldwide (Sherif et al., 2004; Tiwari et al., 2005). It is responsible for a significant cause of morbidity and mortality imposing a major burden on the health care systems worldwide. The prevalence of *H. pylori* infection varies from 20 - 50% in industrialized countries to over 80% in developing countries (Feldman, 2001; Ndip et al., 2004). Childhood appears to be the critical period during which *H. pylori* is acquired, especially in areas of overcrowding and socio-economic deprivation (Feldman, 2001; Ndip et al., 2004; Dube et al., 2009b). Although, the mode of transmission of infection is not completely elucidated, most of the available evidence supports person-to-person transmission by fecal-to-oral, oral-to-oral and gastric-to-oral routes (Hardin and Wright, 2002; Asrat et al., 2004; Dube et al., 2009a). In children, gastric inflammation could cause low gastric secretion which results in impaired "gastric barrier" associated with increased susceptibility to enteric infections, a major public health concern linked to diarrhoea, malnutrition and growth failure in developing countries (Thomas et al., 2004).

Acute infection is most commonly asymptomatic and maybe associated with epigastric pain, abdominal distention or bloating, belching, nausea, flatulence and halitosis (Meurer and Bower, 2002; Ndip et al., 2008a). Prolonged infection and inflammation due to bacterial virulence and host genetic factors will lead to gastritis,

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peptic ulcers (gastric ulcers and duodenal ulcers), gastric atrophy and B cell mucosa associated lymphoid tissue lymphoma (Sherif et al., 2004; Módena et al., 2007). The considerable burden of these *H. pylori*-related sequelae means there is an acute demand for accurate diagnosis of the infection (Nguyen et al., 2009). Several invasive and non- invasive diagnostic tests are available for ascertaining the presence of *H. pylori* infections. Invasive tests require endoscopy and include the biopsy urease test, histology, fluorescent *in situ* hybridization, culture and polymerase chain reaction (PCR). On the other hand, non- invasive tests do not require endoscopy and are more convenient. They include ^{13}C-urea breath tests, serology and stool antigen enzyme immunoassay tests (Gramley et al., 1999; Tanih et al., 2008). Eradication of the bacterium is effective in healing peptic ulcers, preventing ulcer relapse and potentially decreases the risk of progression to gastric carcinoma (Sherif et al., 2004; Tanih et al., 2009a).

The growing resistance of the organism to conventional antimicrobial agents is a source of concern to clinical microbiologists all over the world. Currently, treatment of symptomatic individuals is with a regimen containing two antimicrobial agents along with a proton pump inhibitor (Malekzadeh et al., 2004; Bytzer and O'Morain, 2005; Tanih et al., 2009b). Drug costs and availability, treatment side effects, non compliance, antibiotic inactivation by pH often result in treatment failure (Alarcón et al., 1999; Wong et al., 2002; Ndip et al., 2008a). As a result, efforts are being made to develop new antimicrobial agents from natural sources for better chemotherapeutic effects (Adebolu, 2005). Therefore, a non antibiotic agent which is cheap, readily available, effective and free from side effects might be of utmost importance for the eradication of *H. pylori* infections (Stamatis et al., 2003; Ndip et al., 2007a; Ndip et al., 2008b).

In this paper, an overview of the current treatment regimen for *H. pylori* infection, factors implicated in treatment failure as well as prospective natural remedies which may provide future control/treatment strategies for this notorious pathogen were presented.

CONVENTIONAL ANTIMICROBIAL THERAPY

H. pylori infection is a serious, chronic, progressive and transmissible infection associated with significant morbidity and mortality, which alone emphasizes the priority of developing adequate prophylactic or therapeutic measures (Scarpignato, 2004). Development of a successful treatment for *H. pylori* infection has been fraught with difficulty. Its location within the stomach (that is, the mucus lining the surface epithelium, deep within the mucus-secreting glands of the antrum, attached to cells and even within the cells) provides a challenge for antimicrobial therapy (Ricci et al., 2002; Romano and Cuomo, 2004). In addition, the gastric mucosa is a hostile environment for antimicrobial therapy because drugs must penetrate the thick mucus and may need to be active at pH values below neutral (Malekzadeh et al., 2004; Romano and Cuomo, 2004). Moreover, emerging bacterial resistance presents an added challenge (Hardin and Wright, 2002).

The purpose of treatment of *H. pylori* infection in any clinical situation is the eradication of the bacterium from the fore gut or stomach (Harris and Misiewicz, 2002). Eradication is defined as a negative test for the bacterium four weeks or longer after treatment (Harris and Misiewicz, 2002; Romano and Cuomo, 2004). It results in the effective healing of ulcers (Meurer and Bower, 2002), prevents ulcer relapse (Leodotler et al., 2001; Ables et al., 2007), reduces recurrence of gastric cancer (Steinbach et al., 1999; Lee et al., 2008) and potentially decreases the risk of progression to gastric carcinoma (Bytzer and O'Morain, 2005; Ndip et al., 2008a). For successful eradication of the bacterium, it is imperative that the clinician be aware of the current antimicrobial susceptibility profiles of the isolates within the region (Sherif et al., 2004). Consequently, antibiotic recommended for patients may soon differ across regions of the world because different areas have begun to show resistance to particular antibiotics (Ndip et al., 2005). Such regional variation in resistance patterns probably reflects geographical variation in local antibiotic-prescription practices and antibiotic use and abuse (Ndip et al., 2008a), as drug control is much tighter in some areas than others (Tanih et al., 2009b).

Drugs used for Treatment

H. pylori infections are treated with drugs that kill the bacteria (antibiotics), reduce stomach acid (H_2 blockers and proton pump inhibitor (PPI)) and protect the stomach lining (bismuth compounds).

Bismuth compounds

The discovery of *H. pylori* in 1983 led to renewed interest in bismuth compounds, because these were found to successfully treat the infection in combination with antibiotics (Alarcón et al., 1999; Ford et al., 2008). Bismuth compounds (colloidal bismuth sub citrate and bismuth subsalicylate) may reduce the development of resistance to co-administered antibiotics (Goodwin et al., 1988) and are also effective at treating *H. pylori* strains with established resistance to other antibiotics (Midolo et al., 1999; Andersen et al., 2000).

Bismuth compounds actions include a reduction in intracellular ATP levels (Sox and Olson, 1989) and interference with the activity of urease enzyme, a key enzyme of *H. pylori* (Lee, 1991; Romano and Cuomo, 2004). Also, they induce the formation of an ulcer-specific coagulum

(Sandha et al., 1998), preventing acid back diffusion (Meurer and Bower, 2002) and inhibit protein and cell wall synthesis as well as membrane function (Bland et al., 2004; Meurer and Bower, 2002; Romano and Cuomo, 2004). Furthermore, they cause an increase in the synthesis of prostaglandin E_2 (Sandha et al., 1998), detachment of *H. pylori* from the gastric epithelium and a reduction in capsular polysaccharide production (Meurer and Bower, 2002; Romano and Cuomo, 2004). Therefore, the properties of bismuth compounds are bactericidal for *H. pylori* (Larsen et al., 2003). The bismuth compounds are extremely potent cytotoxic agents when attached to a monoclonal antibody as these can target leukemia, lymphoma and other tumors. Interestingly, *H. pylori* is incriminated in mucosa associated lymphoid tissue lymphoma, thus there is a clear connection between anti-tumor activity and bismuth compounds (Wotherspoon, 1998).

Side effects encountered with this drug include darkening of oral cavity and stool (Meurer and Bower, 2002; Ford et al., 2008), nausea and gastrointestinal upset (Stenstrôm et al., 2008). Recently, bismuth containing regimen has been recommended as a potential first line therapy, because there have been concerns that PPI-based triple therapies for *H.pylori* do not lead to a satisfactory eradication rate (Ford et al., 2008).

Acid reducers

Two types of acid-suppressing drugs might be used and these are H_2 blockers and PPI. H_2 blockers work by blocking histamine, which stimulates acid secretion. They include cimetidine, ranitidine, famotidine and nizatidine. On the other hand, PPI suppress acid production by halting the mechanism that pumps the acid into the stomach. They also include omeprazole, lansoprazole, rabeprazole, pantoprazole and esomeprazole (Harris, 1998; Gendull et al., 2003).

H. pylori prefers an acidic environment, so increasing the gastric pH with the use of histamine H_2 receptor antagonist (H_2RA) or PPI has been shown to improve the effectiveness of antibiotic therapy (De Boer et al., 1995). In the presence of ulcer disease, PPI have largely replaced H_2RA because of their ability to provide more rapid pain relief and better control of pH (Meurer and Bower, 2002; Romano and Cuomo, 2004). PPI's also display several pharmacological actions that give them a place in the eradication. These include:

i) They exert an antibacterial action against *H. pylori* (Nakao and Malfertheiner, 1998).
ii) By increasing intra gastric pH, they allow the microorganisms to reach the growth phase and become more sensitive to antibiotics such as Amoxicillin and Clarithromycin (Farthing et al., 1998; Scott et al., 1998; Alarcón et al., 1999).
ii) They increase antibiotic stability (Gustarson et al., 1995) and efficacy (Erah et al., 1997).
iv) By reducing gastric emptying (Parkman et al., 1998) and mucus viscosity (Goddard and Spiller, 1996), they increase the gastric residence time and mucus penetration of antimicrobials (Pedrazzoli et al., 2001).

In addition, some of these anti -ulcer drugs show *in vitro* synergy when tested with some antibiotics (Alarcón et al., 1999). Seemingly, the increased absorption and tissue penetration of antimicrobial agents that occur with elevated gastric mucosal levels caused by omeprazole may contribute to the observed synergy (Calafatti et al., 2000).

Antibiotics

H. pylori is susceptible *in vitro* to commonly used antibiotics such as; amoxicillin (AMOX), tetracycline (TET), metronidazole (MET) and clarithromycin (CLR) (Alarcón et al., 1999). Of the *H. pylori* isolates collected in Cameroon, Ndip et al. (2008a) found 56.1% to be susceptible to TET, 55.3% to CLR, 14.4% to AMOX and only 6.8% to MET. Currently, these antibiotics were administered in combination, with no single agent ever used as monotherapy because of lack of efficacy and the potential development of resistance (Alarcón et al., 1999; Hardin and Wright, 2002).

Metronidazole (prodrug) is highly active against *H. pylori* and requires activation by bacterial nitroreductases (Meurer and Bower, 2002). However, other studies have reported high rates of resistance to this drug (Ndip et al., 2008a; Tanih et al., 2009b). The bacterium possesses a number of enzymes with the potential to reduce MET. The reduced nitroimidazole cause loss of the helical structure of bacterial DNA, break strands and thus, impaired bacterial infection (Romano and Cuomo, 2004). MET can have unpleasant adverse effects (e.g. nausea, a metallic taste, dyspepsia) and a disulfiram-like reaction with alcohol consumption (Hardin and Wright, 2002; Stenström et al., 2008).

Clarithromycin is recognized as the key antibiotic for *H. pylori* treatment because of its powerful bactericidal effect *in vitro* compared with other available molecules (Megraud, 2004; De Francisco et al., 2007). Co-administration with PPI significantly increases the concentration of CLR in the antral mucosa and the mucus layer (Meurer and Bower, 2002). Results of studies showing approximately 90% *H. pylori* eradication with triple therapy regimens using CLR have led to the widespread use of this antibiotics (Romano and Cuomo, 2002), though it is more expensive than other antibiotic agents (Hardin and Wright, 2002). Adverse effects with CLR include a bitter metallic taste (Ables et al., 2007), dysgeusia (Hardin and Wright, 2002), gastrointestinal upset and diarrhea (Stenström et al., 2008).

Amoxicillin, a semi synthetic penicillin is an effective

antibiotic for *H. pylori* infection (Meurer and Bower, 2002). Its action against *H. pylori* is pH dependent and therefore requires co-administration with a PPI (Meurer and Bower, 2002; Hardin and Wright, 2002; Romano and Cuomo, 2004). It inhibits the synthesis of bacterial cell wall after absorption into the bloodstream and subsequent delivery into the gastric lumen (Romano and Cuomo, 2004). Side effects include gastrointestinal upset, diarrhea and headache (Stenström et al., 2008).

Tetracycline has demonstrated *in vitro* efficacy against *H. pylori* and is active at low pH (Romano and Cuomo, 2002). It is inexpensive and is a close derivative of the polycyclic naphthacene carboxamides. Therefore, it inhibits protein synthesis and bind specifically to the 30S ribosomal subunit. Tetracycline can cause discoloration of teeth in children, photosensitivity reaction and gastrointestinal upset (Hardin and Wright, 2002).

Furazolidone, a synthetic nitro furan appears to be effective for many *H. pylori* strains which are resistant to MET (Meurer and Bower, 2002). However, it is described as an alternative to MET; patients should be warned against using alcohol or monoamine oxidase inhibitors (Gendull et al., 2003).

Treatment strategy

The treatment of *H. pylori* infection can be likened to the treatment of tuberculosis because it is a multidrug regimens and an adequate length of time is needed to eradicate the organism (Meurer and Bower, 2004). Combination of drug regimens are essential to minimize the risk of promoting antimicrobial (namely to MET and or CLR) resistance (De Boer and Tytgat, 2000; Scarpignato, 2004). The only conditions for which such treatment is strongly recommended on the basis of unequivocal evidence, are peptic ulcer disease and low grade gastric MALT lymphoma (Tanih et al., 2009a). Monotherapy in which antibiotic agents alone were used in the eradication of the bacterium was inefficient, making it imperative to use dual, triple or even quadruple therapy (Alarcón et al., 1999).

Dual therapy regimen refers to the combination of PPI's or Ranitidine bismuth citrate (RBC) and one antibiotic usually AMOX or CLR (Wu and Sung, 1999). The first dual therapy combining omeprazole with AMOX had unpredictable efficacy ranging from 20 to 90% (Bayerdorffer et al., 1995; Laine et al., 1997). The dual therapy is, however, more reproducible when AMOX is replaced with CLR (Wu and Sung, 1999).

Triple therapy regimen is the most popular and standard treatment regimen for the cure of *H. pylori* infection (De Boer and Tytgat, 2000; Hardin and Wright, 2002). It consists of an acid-suppressant (PPI or RBC) and two antimicrobials (Wu and Sung, 1999). The first PPI- based triple therapy was described by Bazzoli et al. (1993) and its good efficacy (eradication rate of more than 80%) has been supported in several studies in Europe (Lind et al., 1999; Malfertheiner et al., 1999) and Canada (Zanten et al., 1999). The choice of antibiotics decides the efficacy of the PPI-based triple therapy, thus CLR being included in the therapy ensures high efficacy and reproducible results (Wu and Sung, 1999).

Because bacterial resistance to MET or CLR results primarily from previous treatment failure, first choice treatment should never combine CLR and MET in the same regimen (Romano and Cuomo, 2004). In fact, even though this combination is highly effective, patients who are not cured will have at least single, and usually double, resistance (Peitz et al., 2002) and no viable empirical treatment remains afterwards.

RBC-triple therapy has proven to be effective in eradicating *H. pylori* with cure rates ranging from 80 to 96% (Laine et al., 1997; Savarino et al., 1997). One week RBC based triple therapy is now increasingly considered as an effective regimen for *H. pylori* eradication (Wu and Sung, 1999).

Quadruple therapy regimen consists of bismuth, a PPI and two antibiotics (Hardin and Wright, 2002; Meurer and Bower, 2002; Malekzadeh et al., 2004). Currently, quadruple therapy is mainly reserved as a second line regimen in cases of treatment failure (Wu and Sung, 1999; De Boer and Tytgat, 2000; Romano and Cuomo, 2002).

In addition to *H. pylori* eradication therapy, patient's education about the need for effective eradication therapy and the necessity of completing the initial drug regimen is critical. Also, they should be counseled to avoid other factors that increase their risk of dyspepsia and peptic ulcer disease (Meurer and Bower, 2002). Confirmation of the eradication of the bacterium from the fore gut is necessary after treatment. This could be done using ^{13}C-UBT which is the first line post-treatment diagnostic test (Malfertheiner et al., 2002). The stool antigen test would be an alternative, if UBT is not available (Vaira et al., 2000). These tests should be performed four weeks after therapy (Stenström *et al*., 2008). Confirmation of cure reassures the patients and provides confidence that the risk of complications is removed provided the eradication is successful. In addition, it facilitates the direction of any further management on individual basis, be it re-treatment following treatment failure, or a switch to symptommatic therapy (Malekzadeh et al., 2004).

FACTORS AFFECTING THE EFFECTIVENESS OF TREATMENT REGIMENS

Factors implicated in treatment failure include drug costs and availability, treatment side effects (Alarcón et al.,1999), lack of penetration of antibiotics into the depth of gastric mucosa (Wong et al., 2002), antibiotic inactivation by pH , lack of compliance by patients (Bytzer and O'Morain, 2005), lack of correlation between *in vitro* susceptibility test and *in vivo* efficacy and the presence of

H. pylori strains with primary or secondary resistance to the antimicrobial agents used (Bytzer and O'morain, 2005), duration of treatment and antibiotics dosage (Gendull et al., 2003). Antimicrobial resistance is increasing and regional variations in susceptibility and resistance patterns maybe ascribed to differences in local antibiotic prescription practices, antibiotic usage in the community and mass eradication programmes for *H. pylori* (Destura et al., 2004; Ndip et al., 2008a).

Until recently, the recommended duration of therapy for *H. pylori* eradication was 10 to 14 days (Ables et al., 2007). Potential benefits for shorter regimens include better compliance, fewer adverse drug effects, and reduced cost to the patient (Meurer and Bower, 2002).

Low gastric pH seems to affect the activity of antibiotics since most are active at neutral pH. The minimal bactericidal concentrations (MBC) and minimal inhibitory concentrations (MIC) of most antibiotics against *H. pylori* (except MET and TET), are dependent on the pH of the environment (Megraud and Lamouiatte, 2003). At pH values lower than 7 or 7.4, the MIC increases. This is why PPI's are used in therapy so as to increase the pH of the stomach, to allow better antimicrobial activity (Farthing et al., 1998; Alarcón et al., 1999). In patients who are acid hyper secretors, the pH remains low. Consequently, antimicrobial activity may be insufficient to eradicate the bacteria. As a result, increasing the dosage of PPI in the treatment regimen may have beneficial effects (Malekzadeh et al., 2004).

The most important causes of treatment failure are poor compliance on the part of the patients and the development of bacterial resistance to antimicrobial agents (Wu and Sung, 1999; Huynh et al., 2004; Ndip et al., 2007a). Patient compliance can only be improved by choosing a simple and well tolerated treatment regimen. Also, patients should be educated on the significance of eradication therapy (Stenström et al., 2008).

Antimicrobial resistance

Resistance of *H. pylori* to the limited range of antibiotics that have efficacy in its treatment can severely affect attempts to eradicate the bacteria. The prevalence of bacterial resistance in certain geographical areas can influence the selection of first line eradication regimen in those regions (Malekzadeh et al., 2004). Bacterial resistance to antimicrobials, however, could be either primary (that is, present before therapy) or secondary (that is, develop as the result of failed therapy (Romano and Cuomo, 2004). Primary resistance in *H. pylori* has been reported in MET (6 - 95%), CLR (0 - 17%), and TET (0-6%) in different countries (Boyanova et al., 2000; Huynh et al., 2004). The issue of resistance primarily concerns MET and CLR, however, acquired resistances to AMOX and TET have also been reported (Kim et al., 2003), although they are extremely rare (Kwon et al., 2000; Romano and Cuomo, 2004).

Metronidazole-containing regimens have recently been shown to have limited effectiveness because of the increasing prevalence of resistance to this drug (Wang et al., 2000; Tanih et al., 2009b). Its prevalence varies from 10 to 90% in different countries (Wu and Sung, 1999). For example, a resistance rate of 28.6% for MET was reported by Boyanova et al. (2000) in their attempt to assess the primary resistance of four antimicrobials against clinical isolates of *H. pylori* circulating in Sofia, Bulgaria. Furthermore in Cameroon, Ndip et al. (2008a) documented a very high resistance for MET while Tanih et al. (2009b) reported a rate of 95.5% in South Africa. Seemingly, Mollison et al. (2000) in their study in Australia, registered a resistance of 36% of *H. pylori* isolates against MET. Increasing the dosage of MET administered generally improves the result of the therapy when treating MET-resistant *H. pylori* strains (Romano and Cuomo, 2004; Stenström et al., 2008). The generally high prevalence of metronidazole resistance, for example, is probably as the result of the frequent, uncontrolled use of nitroimidazole derivatives for the treatment of protozoan infections and gynecological problems (Alarcón et al., 1999; Ndip et al., 2008a).

Primary clarithromycin resistance is increasing worldwide and it has been regarded as the main factor reducing the efficacy of eradication therapy (De Francisco et al., 2007). However, the prevalence rate of CLR resistance is 12.9% in the U.S and it is as high as 24% in some European countries (Huynh et al., 2004). Acquired resistance to CLR frequently develops in individuals after initial treatment failure (Wu and Sung, 1999). These CLR-resistant strains of *H. pylori* can be treated using a regimen containing levofloxacin (Hsu et al., 2008). Nevertheless, there is a trend of rising resistance due to widespread use of CLR in the treatment of upper respiratory tract infections.

The increasing prevalence of antimicrobial resistance jeopardizes the success of therapeutic regimens aimed at the eradication of infection (Deltenre, 1997). Therefore, clinicians should choose the appropriate combination of drugs based on sensitivity patterns provided by a local reference centre (Meurer and Bower, 2002). Ideally, in cases of treatment failure, the antibiotic sensitivity pattern of the organism should be established before the second line therapy is chosen (Destura et al., 2004).

PROSPECTIVE NATURAL REMEDIES

The current increasing prevalence of antimicrobial resistance and its negative impact on the eradication treatment regimens has brought forth the quest for novel therapeutic approaches. *H. pylori* infection is determined by several factors, including the type of *H. pylori* strain, the extent of inflammation and the density of *H. pylori* colonization (Ernst and Gold, 2000). It has been reported

that the risk of the development of peptic ulcer disease and gastric cancer increases with an increasing level of infection (Tokunaga et al., 2000). On the other hand infection could be beneficial for example, by protecting the host from the reflux esophagitis and its complications (Richter, 2001). Therefore permanent or long-term suppression of *H. pylori* may at least in some patients, be desirable alternatives to eradication treatment as well as it could decrease the risk of developing *H. pylori*-related diseases (Blaser, 1999). A non-antibiotic agent, which is readily available, inexpensive, and effective and free from side effects, might be of utmost importance for the eradication of *H. pylori* (Stamatis et al., 2003; Ndip et al., 2007b). Natural foods can be attractive as an alternative treatment for *H. pylori* (Calvet et al., 2000).

Diet

Dietary approaches that would keep *H. pylori* density and infection-mediated inflammation on a low level could be of considerable interest in developing low-cost, large-scale alternative solutions to prevent or decrease *H. pylori* colonization. In this respect; probiotics may close the therapeutic gap. A probiotic is defined as a living microbial species that, on administration, may have a positive effect on bowel micro-ecology and improve health conditions (Fuller, 1991). Probiotics have been proven to be useful in the treatment of several gastrointestinal diseases and can be beneficial in *H. pylori*-infected subjects for several reasons. At present, the most studied probiotics are lactic acid-producing bacteria, particularly *Lactobacillus and Bifidobacterium species* (Rolfe, 2000; Gottenland et al., 2006), but others include *Weissela confusa* and *Bacillus subtilis* (Pinchuk et al., 2001; Nam et al., 2002). The action of inhibition of *H. pylori* by probiotics could be nonimmuologically and immunologically mediated (Lesbros-Pantoflickova et al., 2007).

Nonimmunological barriers such as acidity of the stomach and the gastric mucosal represent a first line defence against pathogenic bacteria. It has been suggested that the intake of probiotics strengthens this barrier by producing antimicrobial substances, competing with *H. pylori* for adhesion receptors, stimulating mucin production and stabilizing the gut mucosal barrier (Lesbros-Pantoflickova et al., 2007). Certain lactobacilli synthesize antimicrobial compounds related to the bacteriocin family and also end products of lactic acid fermentation such as lactic acid, acetic acid and hydrogen peroxide (Sgouras et al., 2004). Lactic acid, in addition to its antimicrobial effect resulting from the lowering of pH, could inhibit the urease enzyme of *H. pylori* (Lesbros-Pantoflickova et al., 2007).

On the other hand, probiotics could modify the immunologic response of the host by interacting with epithelial cells and modulating the secretion of anti inflammatory cytokines, which would result in a reduction of gastric activity and inflammation (Gill, 2003). In addition, it has been shown to strengthen the mucosal barrier by stimulating local Ig A responses, thus leading to a mucosa-stabilizing effect (Vitini et al., 2000). However, distinct probiotic strains may generate divergent immune responses, which, in turn, depend on the host's immune status (Haller et al., 2000). The above-mentioned mechanisms have been demonstrated by some studies (Lesbros-Pantoflickova et al., 2007) as shown in Table 1. Moreover, implementation of these agents in standard anti–*H. pylori* treatment regimen can increase the potential of the therapy to have an antimicrobial effect (Ushiyama et al., 2003; Franceschi et al., 2005). In addition, it can improve patients' compliance to therapy, as a result of reducing the occurrence of antibiotic-related adverse effects such as headache, nausea and gastrointestinal upset (Bergonzelli et al., 2005; Gottenland et al., 2006). Other aspects that are considered are the contribution of probiotics to the healing of the gastric mucosa linked to their antioxidant and anti-inflammatory properties (Gottenland et al., 2006).

Allium vegetables, particularly garlic (*Allium sativum* L.) exhibit a broad antibiotic spectrum against both Gram–positive and Gram negative bacteria. It has been demonstrated *in vitro* that *H. pylori* is susceptible to garlic extract at a fairly moderate concentration. Even *H. pylori* resistant strains are susceptible to garlic (Mahady and Pendland, 2000; Sivam, 2001).

Capsaicin (hot pepper) consumed as a flavoring spice, has pharmacological, physiological and antimicrobial effects (Molina-Torres, 1999). Jones et al. (1997) showed the effect of capsaicin on *H. pylori*. Similarly, Zeyrek and Oguz (2005) demonstrated *in vitro* anti-*H. pylori* activity of capsaicin at a concentration of 50 µg/ml against metronidazole-resistant and metronidazole-susceptible clinical isolates. There is lower ulcer prevalence in people consuming higher amount of pepper compared to controls (Kang et al., 1995). It may be advisable to consume raw pepper, since it is known that cooking can alter some chemical features of *Capsicum* species and by this way, their antibacterial effects may decrease (Cichewicz and Thorpe, 1996). For people who do not like hot pepper, capsules containing capsaicin may be helpful in prevention and treatment of *H. pylori*.

Cranberry (*Vaccinium macrocarpon*) is a natural fruit, native to North America. It is cultivated extensively for commercial use in certain states, including Wisconsin, Massachusetts, New Jersey, Oregon and Washington (Ma et al., 1998). It is a good source of vitamin C, fructose and bioflavonoids with anti-oxidant properties, which may contribute to the bacteriostatic effect of its juice. In a study, Burger et al. (2000) demonstrated that a high molecular weight constituent of cranberry juice inhibited *H. pylori* adhesion to immobilized human gastric mucosa *in vitro*. In addition, Zhang et al. (2005) in their preliminary study in Linqu County of Shandong province,

Table 1. Mechanisms of Inhibition of *H. pylori* by probiotics *in vitro.*

Probiotic	Mechanism of inhibition	Reference
L. acidophilus 4356,	Lactic acid; lowers pH	Aiba et al., 1998
L. casei 393	Lactic acid; lowers pH	Aiba et al., 1998
L. salivarius WB1040	Lactic acid; inhibits urease enzyme	Aiba et al., 1998
L. casei strain Shirota	Heat-labile substance; affects biosynthesis of DNA and proteins	Cats et al., 2003
L. acidophilus LB	Heat-stable protein; induces membrane pore formation	Coconnier et al., 1998
L. lactis BH5	Bacteriocin; dissipates membrane potential	Kim et al., 2003
L. acidophilus	CRL639 autolysins; induces release of proteinaceous compounds	Lorca et al., 2001
W. confusa PL9001	Class II bacteriocin; induces membrane permeability	Nam et al., 2002
L. johnsonii La 1	Heat-stable substance; causes efflux of intracellular ions	Michetti et al., 1999
L. acidophilus	Lactic acid; lowers pH	Midolo et al., 1995
L. casei subsp. Rhamnosus	Lactic acid; inhibits urease activity	Midolo et al., 1995
L. reuteri TM 105	Glycolipid-binding proteins; prevents adhesion to target sites	Mukai et al., 2002
B. subtilis 3	Anticoumacin A, B, C; inhibit cytochrome P	Pinchulk et al., 2001
L. casei strain Shirota	Lactic acid; inhibit urease enzyme	Sgouras et al., 2004

China, suggested that dietary consumption of cranberry juice may reduce *H. pylori* infections in adults, which remains an important public health issue worldwide.

Honey

Honey-derived remedies constitute a potential source of new compounds that may be useful in the management of *H. pylori* infections. Honey has been recognised for medicinal properties since antiquity (Namias, 2003). It is a natural substance of very high nutritive value and is made, when the nectar and sweet deposits from plants are gathered, modified and stored in the honeycombs by honeybees of the genera *Apis* and *Meliponinae* (Namias, 2003; Al-jabri, 2005). It contains approximately, 35% glucose, 40% fructose, 5% sucrose, 20% water (Sato and Miyata, 2000), enzymes, amino acids, organic acids, polyphenols (flavonoids and phenolic acids) and carotenoid-like substances, Maillard reaction products, vitamins, ascorbic acids, α-tocopherol and minerals (Gheldof et al., 2002). The actual composition of honey varies depending on many factors such as pollen source, environmental conditions and the processing (Gheldof et al., 2002). Therefore, not all have the same antibacterial components and this could explain the different antibacterial activity for each honey type (Baltrušaitytė et al., 2007).

The anti-*H. pylori* activity of honey has been attributed to its anti-microbial properties with regards to its high osmolarity, acidity and content of hydrogen peroxide and non-peroxide components (Weston, 2000). The major antibacterial activity has been found to be due to hydrogen peroxide (Temaru et al., 2007), produced by the oxidation of glucose by the enzyme glucose-oxidase, which is activated by successive dilutions of honey (Iurlina and Fritz, 2005). The absolute level of hydrogen peroxide in any honey is determined by the respective levels of glucose oxidase and catalase (Weston, 2000). The non-peroxide activity of honey is usually attributed to its phytochemicals (flavonoids and phenolic acids), which are derived from plant origin (Yao et al., 2004). Flavonoids and phenolic acids are natural anti-oxidants and can be extractable by organic solvents (Aljadi and Yusoff, 2003). The amount of these components may be small or diluted in the honey but when extracted, they become concentrated and therefore exhibit activity. Almost all organisms possess antioxidant defence and repair systems that have evolved to protect them against oxidative damage but insufficient to protect them entirely (Oboh, 2005). However, honey contains these natural anti-oxidants which exhibit a wide range of biological effects, including antibacterial, anti-inflammatory, anti-allergic, antithrombotic and vasodilatory actions (Gómez-Caravaca et al., 2006). They are reported to scavenge for free superoxide and other reactive oxygen metabolites liberated during respiratory burst in *H. pylori* induced mucosal damage (Phull et al., 1995; Li et al., 2001).

Honeys from different countries and regions have a wide variability in their antimicrobial activity (Basson and Grobler, 2008). This is evidenced in the study carried out by Ndip et al. (2007b) to evaluate the *in vitro* activity of some selected honeys used by the population to treat gastrointestinal complaints symptomatic of *H. pylori* infection. In this study, it was demonstrated that four honey varieties from different geographical locations exhibited antibacterial activity against *H. pylori*. The strongest inhibitory activity (82.22%) was demonstrated by Mountain honey (from Cameroon) at 75% v/v, followed by Capillano® and Manuka™ honeys (from New Zealand) (75.56%) and Eco-honey (from Kenya) (73.36%) at the same concentration. This is as a result of climatic variation which affects the distribution of flowers and plant species, from which honey bees gather nectar and

Table 2. Regional variation in honey concentrations against *H. pylori* isolates.

Country	Honey concentration (%v/v)	Reference
Cameroon	≥ 10	Ndip et al., 2007b
America	≥ 15	Osato et al., 1999
New Zealand	5	Somal et al., 1994; Namias, 2003
Saudi Arabia	10 and 20	Ali et al., 1991

sweet plant deposits (Osato et al., 1999; Ndip et al., 2007b). As a result of profound heterogeneity exhibited by *H. pylori*, in combination with the regional variation in the antimicrobial components present in honey, there is a difference in the concentration of honey that would inhibit *H. pylori* in specific locations (Table 2).

CONCLUSION

H. pylori infection is a serious, chronic, progressive and transmissible bacterial infection associated with significant morbidity and mortality, which alone emphasizes the priority of developing adequate prophylactic or therapeutic measures (Scarpignato, 2004). The prevalence of antimicrobial resistance is high especially in developing countries (Ndip et al., 2004). Antimicrobial therapy for the treatment of these infections has emerged as the most important means to resolve such infections. There is therefore justification to look for alternative or complementary eradication therapy. These could provide low-cost, large-scale alternative solutions to prevent or decrease *H. pylori* colonization, although much attention has to be drawn on research pertaining to these alternatives.

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