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

Christy E. Manyi-Loh¹, Anna M. Clarke¹, Noxolo F. Mkwetshana¹ and Roland N. Ndip¹,²*

¹Microbial Pathogenicity and Molecular Epidemiology Research Group, Department of Biochemistry and Microbiology, Faculty of Science and Agriculture, University of Fort Hare, P/Bag X1314, Alice 5700, South Africa.  
²Department of Biochemistry and Microbiology, Faculty of Science, University of Buea, Box 63, Buea, Cameroon.

Accepted 26 November, 2009

*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 diarrhea, 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,
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 13C-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 (H2 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
Acid reducers

Two types of acid-suppressing drugs might be used and these are H₂ blockers and PPI. H₂ 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; Bower, 2002; Ford et al., 2008). PPI's also increase gastric pH with the use of histamine H₂ receptor antagonists (H₂RA) 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 H₂RA 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).

iii) 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 3OS 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 regimen and an adequate length of time is needed to eradicate the organism (Meurer and Bower, 2004). Combination of drug regimens are essential to minimize eradicate the organism (Meurer and Bower, 2004). It 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 3OS 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 regimen and an adequate length of time is needed to eradicate the organism (Meurer and Bower, 2004). Combination of drug regimens are essential to minimize eradicate the organism (Meurer and Bower, 2004). It 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 3OS 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 regimen and an adequate length of time is needed to eradicate the organism (Meurer and Bower, 2004). Combination of drug regimens are essential to minimize eradicate the organism (Meurer and Bower, 2004). It 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 3OS 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 regimen and an adequate length of time is needed to eradicate the organism (Meurer and Bower, 2004). Combination of drug regimens are essential to minimize eradicate the organism (Meurer and Bower, 2004). It 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 3OS 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).
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 (Alarçon 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 Weissella confusa and Bacillus subtilis (Pinchuk et al., 2001; Nam et al., 2002). The action of inhibition of H. pylori by probiotics could be nonimmunologically 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 Oğuz (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,
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, 2003). 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 produce their honey.

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

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

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

### ACKNOWLEDGEMENT

We are grateful to the Govan Mbeki Research and Development Centre, University of Fort Hare, South Africa for financial assistance.

### REFERENCES


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

<table>
<thead>
<tr>
<th>Country</th>
<th>Honey concentration (%v/v)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cameroon</td>
<td>≥10</td>
<td>Ndip et al., 2007b</td>
</tr>
<tr>
<td>America</td>
<td>≥15</td>
<td>Osato et al., 1999</td>
</tr>
<tr>
<td>New Zealand</td>
<td>5</td>
<td>Somal et al., 1994; Namias, 2003</td>
</tr>
<tr>
<td>Saudi Arabia</td>
<td>10 and 20</td>
<td>Ali et al., 1991</td>
</tr>
</tbody>
</table>
Helicobacter pylori. Gut. 43: 56-60.


