Chapter 9

Helicobacter pylori Infection — Challenges of Antimicrobial Chemotherapy and Emergence of Alternative Treatments

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http://dx.doi.org/10.5772/57462

1. Introduction

Classified as a class one carcinogen, *Helicobacter pylori* is a gram-negative coccobacillus (0.5 μm wide by 2 - 4 μm long), microaerophilic, flagellated organism that has chronically infected more than 50% of the world's population [1, 2, 3, 4]. Significant evidence exist that links the bacterium to the pathogenesis and development of certain diseases such as gastric ulcers, chronic gastritis and stomach cancers, although most of the people harboring this organism are asymptomatic [5, 6]. The prevalence of infection caused by this organism increases with advancing age and is reported to be higher in developing countries and among low socio-economic populations, probably owing to conditions that favor the infection such as poor hygiene, crowded living conditions, and inadequate or no sanitation. The prevalence of this infection in human varies with geographical location and socio-demographic characteristics of the population; however does not parallel the incidence of morbidity caused by the infection [7, 8]. Studies have highlighted inconsistencies in the prevalence rates for *Helicobacter* and disease. In industrialized countries there is generally a low prevalence of *H. pylori* infection and yet a relatively high prevalence of gastric cancer. On the other hand, some countries with high *Helicobacter* prevalence rates have low gastric cancer prevalence [9].

Over the years, different treatment regimens have been proposed for eradication of *H. pylori.* Eradication of the organism has proven to be the first therapeutic approach and constitutes a reliable long-term prophylaxis of peptic ulcer relapse, accelerating ulcer healing and reducing the rate of ulcer complications [10]. Successful regimens generally require two or more antibiotics coupled with a proton pump inhibitor [11]. A proton pump inhibitor (PPI) or

bismuth compounds and two antibiotics most commonly clarithromycin and metronidazole and/or amoxicillin [12]. However, problems related to poor patient compliance, undesirable side effect and resistance are presenting with numerous challenges as far as treatment failure is concern. Antibiotic resistance is a growing global concern both in the developing and in developed countries. Resistance to this organism has been delineated worldwide [13]. Many *H. pylori* strains have been reported to show resistance to the limited range of antibiotics used in its treatment *in vitro.* Of particular interest, resistance to metronidazole and clarithromycin has increased recently with more than 90% resistance reported against metronidazole and up to 36% against clarithromycin depending on regions [14, 15]. Emerging resistance of the bacterium to tetracycline, fluoroquinolones, and rifampicins, which are alternative antibiotics with known anti-*H. pylori* activity, have also been reported [14].

The emerging resistance to these antibiotics limits their use in the treatment of these infections [6, 16, 17]. Resistance to the antibiotics commonly used for treatment has been associated with mutations in specific genes which have been shown to be associated with these antibiotics. Clarithromycin resistance for example has been associated with point mutations in the peptidyl transferase-encoding region of 23S *rRNA* which affects the binding of macrolides to the bacterial ribosome, while *rdxA* and *frxA* are genes whose mutation has been associated with metronidazole resistance. Other genes such as the P-glycoprotein (P-gp) as well as mutations of *GyrA, GyrB*, and *16SrRNA* in *H. pylori* have also been associated with resistance fluoroquinolone and tetracycline respectively [18, 19].

With the problem of resistance to currently recommended antibiotics; there is the need to seek alternative compounds from other sources with proven antimicrobial activity to overcome the problem. This has encourage the search of active agents from natural products, with the ultimate aim of discovering potentially useful active ingredients that can serve as template for the synthesis of new antimicrobial drugs [20]. These include medicinal plants, honey and probiotics which have been variously described to be associated with increase success rates in the eradication of *H. pylori* both *in vitro* and *in vivo* [21, 22, 23, 24]. Several plants have been investigated for their anti-*H. pylori* activity. Some of these plants with proven activity include *Combretum molle*, *Calophyllum brasiliense, Sclerocarya birrea*, *Garcinia kola*, *Alepidea amatymbica, Bridelia. Micrantha*, *Peltophorum africanum, Cyrtocarpa procera Kunth* and some *Strychnos species* [25, 26, 27]. The antimicrobial activity of honey is now well documented [28, 29]. Manyi-Loh and co-workers investigated the anti-*H. pylori* activity of three South African honeys; Pure honey, citrus blossom and gold crest and found that all honey varieties demonstrated varying levels of anti-*H. pylori* activity [24]. Evidence exists that probiotics may inhibit growth of *H. pylori*, stimulate an immunological response and reduce inflammatory effect of infection by bacteria increasing the rate of *H. pylori* eradication [21]. Some probiotics that have been tested either singly or in combination include *Lactobacillus acidophilus, Lactobacillus rhamnosus, Lactobacillus bulgaricus, Lactobacillus casei, Streptococcus thermophilus, Bifidobacterium infantis* and *Bifidobacterium breve* [30]. In this communication, we provide information on the prevalence, epidemiology and antimicrobial chemotherapy and challenges in treatment of *H. pylori* in an effort to continuously highlight the clinical and epidemiological significance.

http://dx.doi.org/10.5772/57462

2. *Helicobacter pylori* infections, disease and prevalence

Helicobacter pylori (H. pylori) inhabit various areas of the human stomach [17]. The ability of this organism to convert the stomach acidic environment, a bactericidal barrier with protection against many infections, makes the environment suitable for its survival [4, 31]. Infection starts in the gastric antrum and spreads to the corpus, after extensive mucosal damage. Upon invasion, mucosa damage is caused that is eventually worsened by the acid produced in the stomach and this may lead to complications (ulcers and cancers) [16, 14]. Half of the world's population is infected by this gastric organism [32]. Since its discovery in 1983 by Marshall and Warren, infection with *H. pylori* has been shown to be strongly associated with chronic gastritis, peptic ulcer and gastric cancer using technologies available at the time and others (fibre endoscopy, silver staining of histological sections and culture techniques for microaerophilic bacteria). These authors proved beyond reasonable doubts that made an indisputable link between the bacteria and the diseases mentioned [3, 33].

Confirmed is the fact that this organism causes of 90% of all duodenal ulcers, 75% of all gastric ulcers and two forms of stomach cancer; adenocarcinoma and mucosa-associated lymphoid tissue (MALT) lymphoma [34]. The evidence of its association with gastric cancer, led to its classification as a class 1 carcinogen by the International Agency for Research on Cancer and the World Health Organization [35]. *H. pylori* is the first bacterium, and the second infectious organism after hepatitis B virus to be classified a carcinogen. A majority of *H. pylori*-infected individuals of (80–90%) have clinically asymptomatic gastritis, 10–15% develop peptic ulcer, and 1–2% gastric malignancies [36, 37]. Until the discovery of Marshall and Warren, diet, stress and life-style factors were considered major causes of gastritis and peptic ulcer, and the stomach, a sterile environment [38, 39].

Clinical outcome of long-term infection is variable and is considered to relate to bacterial virulence factors along with host genotype, physiology and environmental factors [40, 41, 42, 43]. The cytotoxin-associated gene, *cagA*, a marker for the cag pathogenicity island (PAI), is present in many but not all *H. pylori* strains. Its presence is associated with more severe clinical outcomes [44, 45]. *H. pylori* infection confers around a two-fold increase in the risk of developing gastric cancer particularly with strains expressing the cytotoxin-associated gene A antigen (*cagA*) [46]. The *vacA* gene is far from the cag PAI. At least some forms of *vacA* protein generate vacuoles in epithelial cells, disrupt tight junctions between epithelial tissues, interfere with antigen processing, etc. [47]. The *vacA* gene is present in all *H. pylori* strains and contains two importantly variable regions, s and m [40].

Geographic differences in predominant *H. pylori* genotypes, based either on virulence associated genes such as *vacA* and *cagA* or "housekeeping genes" have been delineated [40, 48]. Several other *H. pylori* genes that are related to the risk of disease have been identified some of which include, *iceA* and several other housekeeping genes" such as *ureA, ureC, ureAB, flaA, flaB, atpA, efp, mutY, ppa, trpC, ureI, yphC* etc, which may not be directly linked to disease [49, 50]. The cytotoxin-associated gene, *cagA*, a marker for the cag pathogenicity island (PAI), is present in many but not all *H. pylori* strains. Its presence is associated with more severe clinical outcomes [44, 45].

H. pylori is the principal species of the genus *Helicobacter* and a common human pathogen that is responsible for a variety of gastro–duodenal pathologies with high prevalence reported both in the developed and developing world since its discovery in 1983 by Marshall and Warren [51, 52]. Different studies worldwide have demonstrated the presence of this organism in their population. Substantial morbidity and mortality have been reported to be associated with *H. pylori* infection [15, 17, 42]. Fallen prevalence values has been observed in most developed countries; with rates from 25–50% in developed countries to 70–90% in the second and third world countries, this however varies [2, 7, 16, 53]. With improvements in treatments modalities, gastrointestinal pathology related to *H. pylori* is still ever present and remains a major burden on Western health systems. Populations like African American, Hispanic, Asian and Native American have experienced increased prevalence and infection rates are similar in males and females [54].

Rate of acquisition, rate of loss of infection and the length of persistence period all seem to determine the prevalence of this highly inflicting pathogen [7]. The prevalence of *H. pylori* infection has also been reported to vary widely by geographic area, age, socioeconomic status and even between ethnic groups of the same region [8, 15]. All these factors including environmental factors all play a role in the acquisition and transmission of *H. pylori* and further influence the wide variation in prevalence observed in the different population [55]. For example, variation exist the prevalence between more affluent urban populations and rural population. A lack of proper sensitization, drinking water and basic hygiene as well as poor diet and overcrowding all play a role in determining the overall prevalence of infection [2]. Although there is geographical and socio–demographic variation in the prevalence of human infection, prevalence does not parallel the incidence of morbidity caused by the infection [2, 16, 56]. Astoundingly high prevalence of *H. pylori* infection is observed in developing countries which does not commensurate the low prevalence of gastric cancer compared to the developed nations with a relatively low prevalence and yet a high prevalence of gastric cancer. For example, in Africa, the prevalence of infection is very high but the incidence of gastric carcinoma and other *H. pylori*-associated morbidities is relatively low. An anomality termed the African enigma' [6, 42]. Apparently, coinfection with other organisms is known to modulate the *H. pylori* immune reaction and has been proposed to explain the "African enigma" [57]. The organism is ubiquitous with childhood acquisition seemingly being the role and may last for years or decades however, it is difficult to ascertain when infection occurs clinically hence seroprevalence data are the source of information of *H. pylori* rates both in geographically and demographically diverse populations [2, 52, 58, 59, 60]. Retrospective sero-epidemiological studies have shown a cohort effect consistent with the hypothesis that infection is mainly acquired in early childhood [59, 61]. Seroprevalence values of (61%–100%) have been described from various studies conducted in Africa and these values vary among countries and between different racial groups present within each country [2, 42, 53]. Seroprevalence studies in the western world have depicted rates not as high as those elaborated in Africa. Most individuals harbour specific antibodies for most of their lives especially in Africa [42].

http://dx.doi.org/10.5772/57462

In a rural village of Linqu Country, Shandong Province, China, a study of 98 children found that nearly 70 percent of those aged 5-6 years were infected with *H. pylori*, a rate equivalent to that reported for adults in that area, suggesting that most infection takes place early in childhood [61]. Generally, 50% of all children are infected by the age of 10 years, with prevalence rising to 80% in adults [7]. In their study of Kenyan school children, Nabwera and coworkers observed high prevalence among their subjects who were only aged 3–5 years, indicating that most children in the study area were infected before they reached their third birthday [62]. The highest rates of *H. pylori* prevalence have been reported in Eastern Europe, Asia, and many developing countries and developing populations in developed countries (for example, Native Americans) [63].

3. Repository of infection and transmission

Accurately assessing the incidence or route of transmission of *H. pylori* has been difficult because of the inaccuracy and cost of detecting (non-invasively) *H. pylori* [59]. Studies with regards to environmental factors and animal reservoirs as possible sources of infection have been examined. DNA has been extracted from food, animals and water sources suggesting they could be reservoirs of this organism [37]. However, there is no definitive evidence that they are natural or primary vehicles of transmission. Various studies have remarked a variety of factors such as bacterial host, genetic and environmental factors to determine the causative links to *H. pylori* infection, but knowledge of reservoirs and transmission still remains elusive [61]. Some routes of transmission have been described this include iatrogenic, oral-oral or faecal-oral routes [64, 65].

The host range of *H. pylori* is narrow and is found almost exclusively in humans and some non-human primates [66]. Humans been the only known reservoir of infection, hence the possibility of picking the infection from siblings, parents predominates via gastro-oral route [67]. Using specific culture approaches the organism has been isolated from vomitus [68, 69]. Perhaps the most important transmission route is faecal-oral transmission. Typically, isolation of this organism from faeces is not common though its isolation from faeces is established [61]. Sexual transmission of these organisms has not been observed [70].

Oral-oral transmission is regarded as a plausible route [39]. It has been shown to be potentiated by specific eating habits, such as the premastication of food by mothers before feeding children in some African countries. In Burkina Faso, premastication of food was common amongst families with high sero-positivity *H. pylori* status for both mother and child [71]. The importance of this cannot be over emphasized considering that childhood appears to be the critical period during which *H. pylori* is acquired, especially in areas of over-crowding and socio-economic deprivation [3, 24]. Possibility of dental plaque been a route of transmission has been proposed but this has failed in other studies though [72, 73]. In a recent study in South Africa, it was deduced that the oral cavity is unlikely to contribute to the spread of this organism as oral cavities were found not to favour prolonged colonization by the organism [53, 74]. Repeated use of gastric tubes from one patient to another by enodoscopists without proper

sterilization may be a possible means of transmission. *H. pylori* infection has been shown to follow socio- other studies [73]. Gastroenterologists are occupationally at risk, however has proven the least common form of transmission [75].

4. *Helicobacter pylori* treatment

The need for an adequate prophylactic or therapeutic measures for *H. pylori* is very important being a serious, chronic, progressive and transmissible infection associated with significant morbidity and mortality especially in the developing world [76]. Over the years, several treatment regimens have been proposed for the eradication of *H. pylori*. However, development of a successful treatment for *H. pylori* infection has been fraught with difficulties; owing to 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) providing a great challenge to therapeutic measures [77]. The hostile environment in the gastric mucosa poses additional challenges reasons being the antibiotic therapy need to be active at pH values below neutral [24]. In addition, the ever existing presence of emerging resistant strains presents a formidable challenge which is at the verge of frustrating every attempt to a solution provision [78]. Infection with *H. pylori* will persist for life and may result in severe gastro duodenal complications without the intervention of antimicrobial therapy (treatment) [52, 79]. Complete eradication of the organism from the gut or stomach is the ultimate goal to treatment. A negative test for the bacterium four weeks or longer after treatment defines eradication [80].

There has been evolution with regards to treatment regimen for *H. pylori* infection since the early 1990s, when monotherapy was first recommended. However, employment of single agent is unacceptable because of extremely low eradication rates. *H. pylori* infections are treated with antibiotics, H2 blockers which reduces stomach acidicity and a proton pump inhibitor (PPI) that protects the stomach lining (bismuth compounds). This triple drug regimen involving; two antibiotics, bismuth salt and a proton pump inhibitor (PPI) or H2 blockers has been used as a standard treatment [13, 77, 81]. Bismuth compounds (colloidal bismuth sub citrate and bismuth subsalicylate) act by reducing intracellular ATP levels and interfere with the activity of urease enzyme, a key enzyme of *H. pylori* [77]. They also induce the formation of an ulcer-specific coagulum, preventing acid back diffusion and inhibit protein and cell wall synthesis as well as membrane function [82, 83]. Detachment of *H. pylori* from the gastric epithelium and a reduction in capsular polysaccharide production is the enabling function of bismuth compounds [77]. Typically, two types of acid reducers exist and include a proton pump inhibitor (PPI) and H2 blockers. H2 blockers include cimetidine, ranitidine, famotidine and nizatidine and this function by blocking histamine, which stimulates acid secretion. The PPI (omeprazole, lansoprazole, rabeprazole, pantoprazole and esomeprazole) on its part suppresses acid production by halting the mechanism that pumps the acid into the stomach [84]. PPI also increases antibiotic stability and efficacy [85].

The most commonly used antibiotics include metronidazole (MET), clarithromycin (CLR), amoxicillin (AMOX) and tetracycline (TET) all of which *H. pylori* is susceptible too except in

http://dx.doi.org/10.5772/57462

cases of drug resistance [13, 86, 87]. Clarithromycin (500 mg twice a day [b.i.d.]) and amoxicillin (1 g b.i.d.) plus PPI for 7 days (treatment 1) are the most commonly used treatment combination the world over. Other regimens employed for 7-day include clarithromycin (500 mg b.i.d.) and metronidazole (500 mg b.i.d.) (treatment 2) and a double dose of PPI plus or amoxicillin (1 g b.i.d.) and metronidazole (500 mg b.i.d.) (treatment 3) a double dose of PPI plus [88]. Efficacy of the agents range from 85% - 95%. Susceptibility of *H. pylori* to these drugs has been reported to change with time, ethnicity, ulcer status, geographical location and test method [14]. Consequently, antibiotic recommended for patients may soon differ across regions of the world because different areas have begun to show resistance to particular antibiotics. These factors therefore have to be considered in making a prescription for the eradication of the infection.

5. Challenges to *Helibacter pylori* treatment regimens

The recommended regimens for *H. pylori* treatment and eradication pose a number of difficulties to patients such as poor compliance; coping with unpleasant adverse effects do little to encourage patient cooperation [15, 78]. Apart from patient non-compliance, antibiotic resistance is the major cause of treatment failure leaving clinicians with a limited list of drugs to choose from [14, 15, 89]. This can seriously affect attempts to eradicate the bacterium. Bacterial resistance to antimicrobials could be either primary (that is, present before therapy) or secondary (that is, develop as the result of failed therapy [77]. In different countries primary resistance in *H. pylori* has been reported in MET (6-95%), CLR (0-17%), and TET (0-6%) [90, 91]. Fairly recently, resistance to amoxicillin has been reported in many countries across the globe especially countries in Africa like Cameroon, Nigeria and South Africa where stringent control of drugs is lacking [17]. On the other hand metronidazole-containing regimens have recently been shown to have limited effectiveness owing to the alarming increase in the prevalence of resistance to this drug. Resistance to this antibiotic varies from 10% to 90% in different countries [92]. For example, Studies by Boyanova and colleagues reported a resistance rate of 28.6% for metronidazole against clinical isolates of *H. pylori* circulating in Sofia, Bulgaria [17, 90]. In our study in South Africa we reported a rate of 95.5% resistant. In Cameroon, studies have documented a very high resistance to metronidazole. Studies in Australia showed a resistance level of 36% of *H. pylori* isolates against metronidazole [93]. High resistance to metronidazole is attributed to the frequent and uncontrolled use of nitroimidazole derivatives for the treatment of protozoan infections and gynecological problems [17]. Clarithromycin resistance is referred to as the corner stone for treatment failure and is increasing worldwide [94]. A prevalence rate of 12.9% was recorded for Clarithromycin resistance in the U.S and rates as high as 24% were some European countries [91]. Resistance to clarithromycin frequently develops after treatment failure and more recently due to its increasing use in the treatment of upper respiratory tract infection [92]. Increasing prevalence of resistance to antimicrobial jeopardizes the success of therapeutic regimens aimed at the eradication of the infection making it sensitivity testing imperative prior to appropriate antibiotic selection [95].

Also, current antimicrobial susceptibility profiles of the isolates within the region should be known as this will act as a guide to clinician [96].

Resistance mechanisms to the commonly used antibiotics have been elaborated. Selection pressure may progressively increase resistance with the use of these antibiotics [88]. Plasmid associated resistance is rare. Drug efflux proteins can contribute to natural insensitivity to antibiotics and to emerging antibiotic resistance as is the case of many bacteria [97].

5.1. Metronidazole resistance mechanisms

Resistance to metronidazole (Mtz) has shown to limit the effectiveness of Mtz containing regimens [98, 99]. Mtz, a synthetic nitroimidazole is a prodrug and becomes active when reduced in the cytosol of the microorganism to a toxic metabolite. Unstable Mtz radicals react rapidly with proteins, RNA and DNA, eventually resulting in cell death [88, 99, 100]. Most Mtz sensitivity in *H. pylori* accounted for by NADPH nitroreductase a non-oxygen sensitive encoded by the *rdxA* gene reduces Mtz by a two-electron transfer step into a toxic metabolite that cannot be retransformed to its parent by molecular oxygen [99]. Resistance to Mtz is associated with mutation somewhere in the *rdxA* coding sequence [101]. Mutation of a second reductase NAD (P) H flavin oxidoreductase encoded by *frxA* could also confer low-level Mtz sensitivity in some strains [102]. Such resistance has been linked mostly to genetic mutations in the *rdxA* and *frxA* genes of the bacterium [100]. Based on gene sequencing and other reports concluded that most Mtz resistance in *H. pylori* depend on *rdxA* inactivation, of which mutations in *frxA* can enhance resistance, and that genes conferring Mtz resistance without *rdxA* inactivation are rare or nonexistent in *H. pylori* populations [100].

5.2. Resistance mechanisms to clarithromycin

Clarithromycin is part of the combination therapy used as the first-line therapy against *H. pylori*. Resistance to clarithromycin therefore is important ingredient for treatment failure. Clarithromycin acts by binding to the peptidyl transferase region of *23SrRNA* and inhibits bacterial protein synthesis just like other macrolides Clarithromycin resistance has been linked to mutation in the *23S rRNA* gene [103]. Several reports have demonstrated that more than 90% of macrolide resistance in *H. pylori* is mediated by either of two transition mutations Adenine to Guanine (A→G) at adjacent positions 2142 and 2143 in the bacterium's 23SrRNA gene [103]. A transversion mutation (A→C) at position 2143 has been reported to be the cause of resistance in 7% of the resistant isolates. Other mutation observed in clarithromycin resistant *H. pylori* isolates include A2515G and T2717C, A2116G, G2141A, A2144T, T2182C, G2224A, C2245T

5.3. Amoxicillin resistance mechanisms

H. pylori resistance to amoxicillin is not common. Deloney and schiller, showed that amoxicillin resistance in *H. pylori* could develop because of amino acid substitutions in the penicillin binding proteins (pbp) leading to structural alterations in the protein or interference with peptidoglycan synthesis [104]. Resistance to amoxicillin and related drugs is usually as a result

http://dx.doi.org/10.5772/57462

of decreased permeability to the drug; increased efflux of the drug from the bacterial cell, modification of the PBPs that diminish the affinity of the drug for the protein, and the presence of β-lactamases that inactivate the antibiotic by hydrolyzing its ring structure [105]. Amoxicillin-resistant *H. pylori* strains harbour mutations on the pbp-1a gene with amino acid substitution Ser-414→Arg appears to be involved, leading to a blockage of penicillin transport. Resistance to amoxicillin may also result from the production of β -lactamases by the bacterium [106]. Colonization of the stomach with β -lactam- resistant bacteria of other species may lead to the transfer of amoxicillin resistance to *H. pylori* [17]. Mutations in *hopB* and *hopC* genes of the outer membrane have also been associated with resistance in amoxicillin [107].

5.4. Tetracycline resistance mechanism

Tetracyclines are often used as a second line therapy when *H. pylori* infections are not cured by the first line drug regimen. Tetracycline is a protein synthesis inhibitor. This is achieved by disrupting codon-anticodon interaction on the ribosome. It binds to the 30S ribosomal subunit, preventing attachment of aminoacyl-tRNA to the acceptor site [108]. Thus bacterial peptide synthesis is stopped leading to cell death. Resistance to tetracycline has been linked to mutation in 16SrRNA-encoding genes that affect the binding site of tetracycline. The change in a nucleotide triplet (AGA-926 to 928→TTC), cognate of the positions 965 to 967 in *Escherichia coli*, has been associated with resistance to these compounds maybe because of the absence of the h1 loop; the binding site of tetracyclines. Strains resistant to tetracycline and no mutation in position 926 to 928 have also been described [14, 86, 109].

5.5. Resistant Mechanism to Fluoroquinolone

Fluoroquinolones have proven their worth in the treatment of most infections. In the management of *H. pylori* infection, they are used as salvage therapy when all other therapies cannot help (Chisholm and Owen, 2009). Their mode of action is based on inhibition of A and B subunits of the gene encoding DNA gyrase (*gyrA* or *gyrB)* in the bacterial cell [110], automatically interfering with DNA replication. Resistance to quinolones is associated mutations in *gyrA* at positions 87 and 91 [105, 111].

5.6. Resistance associated to plasmid and Efflux mechanisms

Approximately half of *H. pylori* strains possess a plasmid with size ranging 1.8-63 kbp though the standard strain NCTC 11637 is plasmid free [112]. Plasmid size and number may vary appreciably amongst strains with a gross majority of strains possessing just one plasmid. *H. pylori* plasmids have also been associated with drug resistance though in their study indicated resistance was unlikely to be attributed to plasmid coded determinants [52, 113]. Drug efflux mechanism could be responsible for the observed resistance in *H. pylori* as well. Organisms get protected from possible toxic effects of metabolite accumulation or external compounds using the efflux mechanism. Compound efflux which is mediated through specific pumps could result in decreased susceptibility for a variety of antibiotic [114, 115]. Some families of multidrug efflux transporters have been described these include small multidrug resistance

(SMR) proteins, multidrug and toxic compound extrusion (MATE) proteins, the major facilitator superfamily (MFS), the ATP-binding cassette (ABC) superfamilies, and the resistance-nodulation-cell division (RND) family (helfF, hefC, and hefI) [116]. These active multidrug efflux mechanism and therefore compound efflux needs to be taken into account when determining resistance mechanisms in this organism. The therapy used for salvage of *H. pylori* has as one of its medications rifampicin and rifabutin [105]. Due to their irreversible blockage of DNA-dependent RNA polymerase; they are bactericidal. The β-subunit of the polymerase encoded by *rpoB* gene is inhibited by these medications and annuls protein synthesis of the bacteria [35, 117]. Resistance of *H. pylori* to these medications has been attributed to point mutations in the *rpoB* gene at positions 530, 540 and 545 [118].

6. Substitutes to circumvent challenges to treatment regimens

Due to the shortcoming presented by antibiotics with regards to treatment of *H. pylori*; Research towards development of new antimicrobial agents/ in a bid to scavenge for possible alternatives to overcome the problem of antibiotic resistance in this bacterial pathogen has been encouraged, such as research with plant extract and other natural products that possess antimicrobial potential like honey and probiotics with or without antibiotic both *in-vitro* and *in-vivo* to test for the antimicrobial activity [22, 24, 29, 119, 120].

6.1. Plants as a potential source of *H. pylori* treatment

Plant and plant products have repeated shown awesome hope in the treatment of recalcitrant infection. Medicinal plants usage all over the world preface the introduction of antibiotics and other modern drugs. It is estimated that plant materials are present in or have provided the models for about 50% of Western drugs [121]. Herbal medicines remain a normal part of life for most people worldwide especially amongst Africans and Asians and remains a component of healthcare in most countries worldwide especially Africa [121, 122]. WHO (World Health Organization) estimates 3.5 million people in developing countries rely on plant-based medicine for their primary healthcare and their usage has offered great benefit [122, 123, 124]. Research on herbal product has great significance for plants components could provide lead products for the development of new drugs hence leading to improvement of therapeutic results [124].

The demand to use natural products such as plants based products for the management of intractable infections has increased over the years [22]. Great attention has been directed to the screening of medicinal plants all over the world as a means to identify cheap sources of new drugs against *H. pylori,* a human gastric pathogen with high morbidity rate [2]. Scientific literature is rich on plant based studies on anti-*H. pylori* activity. A number of plants belonging to various families as well as compounds have been screened in the search for their anti-*H. pylori* potential worldwide. For example, Garlic (*Allium sativum L*) particularly allium vegetables have been shown exhibit a broad range of antibiotic spectrum against both Gram–positive

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and Gram negative bacteria including susceptibility to *H. pylori* antibiotic resistant strains [125]. Zeyrek and Oguz demonstrated *in vitro* anti-*H. pylori* activity of capsaicin at a concentration of 50μg/ml against metronidazole resistant and metronidazole-susceptible clinical isolates [126]. This plant also known as hot pepper is consumed as a flavoring spice and is reputed for its pharmacological, physiological and antimicrobial effects [127]. There is lower ulcer prevalence in people consuming higher amount of pepper compared to controls [128]. Studies by Zhang and colleagues in the Linqu County of Shandong Province, China, suggested that dietary consumption of cranberry (*Vaccitnium macrocarpon)* juice may reduce *H. pylori* infections in adults, which remains an important public health issue worldwide [129]. More plants which have been tested and proven to exhibit anti- *H. pylori* activity from their different continents in the world are listed (Table 1).

Analysis of tested plant extract revealed the presence of varying numbers of components depending on different solvent combination used for extraction. For example, 52 compounds were identified from acetone extract of *S. birrea* (which has been reported with anti- *H. pylori* activity) with n-octacosane being the most abundant (41.68%). Other compounds such as pyrrolidine, terpinen-4-ol, n-eicosane, cyclopentane, n-triacontane, aromadendrene and α-gujunene were delineated in *S. birrea*. Terpinen-4-ol and pyrrolidine however demonstrated strong antimicrobial activity against *H. pylori* at all concentrations tested. The identified compounds Terpinen-4-ol could be considered for further evaluation as therapeutic or prophylactic agents in the treatment of *H. pylori*-related infections [130]. Other compounds including quinones, flavones, flavonoid, flavonols, tannins, coumarins, traces of alkaloid, gallotannins, steroids (including β-sitosterol), phenolics and polyphenols, Terpenoids and essential oils Alkaloids, lectins and polypeptides have been isolated from most plants and found to exhibit profound antimicrobial activities in-vitro against an array of organisms although most of these compounds have not been tested against *H. pylori* [131].

The stem bark of the South American trumpet tree (*Tecoma ipe* Mart) has been reported as an important source of active quinone compound against *H. pylori* furanonaphthoquinone was isolated from this plant and has proven activity against *H. pylori* with (MIC 0.1μg/mL). idebenone, duroquinone, menadione, juglone and coenzyme Q1 are other quinines that have been reported with anti- *H. pylori* at low concentration of 0.8 to 3.2 μg /mL [132]. Anti-*H. pylori* activity of a number of flavonoids has been reported. In Turkey for example, *Cistus laurifolius* flower buds which is used traditionally in folk medicine to treat gastric ailments have been shown to possess significant anti-*H. pylori* activity with the flavonoid; quercetin 3-methyl ether (isorhamnetin) as the active component [133]. Inhibition of urease is recorded as the mechanism of action of some flavonoids as hesperidin [134]. Antimicrobial activity of coumarins isolated from the roots of *Ferulago campestris* against *H. pylori* isolates in Italy [135]. Kawase and others, found that a number of hydroxycoumarins;7- hydroxy-4-methylcoumarin, 6, 7-dihydroxy-4-methylcoumarin, 6-hydroxy-7-methoxy-4-methylcoumarin and 5, 7- dihydroxycyclopentanocoumarin showed comparable anti-*H. pylori* activity with metronidazole [136]. Generally, data about specific antibiotic properties of coumarins against *H. pylori* are scarce.

Continent and Species		Parts Used	Reference
Africa	Country		
Combretum molle (*Combretaceae*)	South Africa	Stem bark	[172]
*Bridelia micrantha (*Hochst, Baill., *Euphorbiaceae*).	South Africa	Stem bark	[173]
Lippia javanica	South Africa	Leaves	[174]
Hydonora africana	South Africa	check	[175]
Sclerocarya birrea (Anacardiaceae)	South Africa	Stem bark	[130]
Garcinia kola Heckel (Guttiferae)	South Africa	Seeds	[176]
Peltophorum africanum (Sond, Fabaceae)	South Africa	Stem bark	[23]
Ageratum conyzoides (Linn)	Cameroon	Whole plant	[176]
Lycopodium cernuum (Linn) Pic. Serm	Cameroon	check	[17]
Enantia chlorantha Oliver (Annonaceae)	Cameroon	Stem bark	[177] [178]
Eucalyptus camaldulensis Dehnh.	Nigeria	Leaves	[179]
Eucalyptus torelliana F. Muell. (Myrtaceae),	Nigeria	Stem bark	[179]
Europe			
South America/ North America			
*Byrsonima intermedia A. Juss. (Malpighiaceae**)***	Brazil	Leaves	[180]
Croton cajucara Benth. (Euphorbiaceae)	Brazil	Stem bark	[181]
Piper carpunya *Ruiz & Pav. (syn Piper lenticellosum C.D.C.) (Piperaceae)*	Ecuador	Leaves	[182]
Calophyllum brasiliense (Camb.)	Brazil	Stem bark	[25]
Artemisia douglasiana Besser (Asteraceae)	Argentina	Leaves	[183]
Alchornea triplinervia	Brazil	Leaves	[184]
Hancornia speciosa Gomez (Apocynaceae).	Brazil	Bark	[185]
Olea europaea L. (Oleaceae)	Mexico	Leaves/stem	[186]
Tagetes lucida Cav. (Asteraceae)	Mexico	Leaf/stem	[186]
Amphipterygium adstringens (Schltdl.) Standl. (Anacardiaceae)	Mexico	Bark	[186]
Priva grandiflora (Ortega) Moldenke (Verbenaceae)	Mexico	Aerial parts	[186]
Eupatorium petiolare Moc. ex DC. (Asteraceae)	Mexico	Aerial parts	[186]
Monarda austromontana Epling (Lamiaceae)	Mexico	Aerial parts	[186]
Gnaphalium canescens DC. (Asteraceae)	Mexico	Aerial parts	[186]
Larrea tridentata (Sessé & Moc. ex DC.) Coville (Zygophyllaceae)	Mexico	Aerial parts	[186]

Continent and Species		Parts Used	Reference
Tithonia diversifolia (Hemsl.) A.G. Asteraceae)	Mexico	Aerial parts	[186]
Grindelia inuloides Willd. (Asteraceae)	Mexico	Aerial parts	[186]
Buddleja perfoliata Kunth (Loganiaceae)	Mexico	Aerial parts	[186]
Heterotheca inuloides Cass. (Asteraceae)	Mexico	Aerial parts	[186]
Mirabilis jalapa L. (Nyctaginaceae)	Mexico	Aerial parts	[186]
Cyrtocarpa procera Kunth (Anacardiaceae)	Mexico	Bark	[186]
Teloxys graveolens (Willd.)W.A.Weber (Chenopodiaceae)	Mexico	Aerial parts	[186]
Annona cherimola Mill. (Annonaceae)	Mexico	Leaf/stem	[186]
Menthaxpiperita L. (Lamiaceae)	Mexico	Leaf/stem	[186]
Cuphea aequipetala Cav. (Lythraceae)	Mexico	Aerial parts	[186]
Ludwigia repens J. R. Forst. (Onagraceae)	Mexico	Aerial parts	[186]
Artemisia ludoviciana Nutt. subsp. *mexicana* (Willd. Ex Spreng.) Fernald (Asteraceae)	Mexico	Leaf/stem	[186]
Qualea parviflora Mart.	Brazil	bark	[187]
Calophyllum brasiliense	Brazil	stem bark	[25]
North America			
Cyrtocarpa procera Kunth (*Anacardiaceae*)	Mexico	Bark	[27]
Amphipterygium adstringens (Schltdl.) Standl. (Anacardiaceae)	Mexico	Bark	[186]
Casimiroa tetrameria		Leaves	[188]
ASIA			
Wasabia japonica	Japan	Leaves	[189]
Impatiens balsamina L	Asia	Root/stem/leaf, seed, and pod	[190]
Rhizopus oligosporus	Asia	fenugreek extracts	[191]
Plumbago zeylanica L	China	Leaves	[192]
Glycyrrhiza aspera	Iran	n/a	[193]
Juglans regia	Iran	n/a	[193]
Ligustrum vulgare	Iran	n/a	[193]
Thymus kotschyanus	Iran	n/a	[193]
Trachyspermum copticum	Iran	n/a	[193]
Xanthium brasilicum	Iran	n/a	[193]

Continent and Species		Parts Used	Reference
Bacopa monniera			[194]
Carthamus tinctorous L.(Asteraceae)	Khorasan	Flowers	[195]
Satureja hortensis L.(Lamiaceae)	Mashhad-Khorasan	Leaves	[195]
Artemisia dracunculus L. (Asteraceae)	Mashhad-Khorasan	Leaves	[195]
Citrus sinensis L (Rutaceae)	North of Iran	Peel of fruit	[195]
Punica granatum L. (Punicaceae)	Saveh- Markazi	Peel of fruit	[195]
Apium petroselinum L (Apiaceae)	Neishabur-Khorasan	Seeds	[195]
Carum bulbocastanum	Iran	Fruit	[196]
Carum carvi	Iran	Fruit	[196]
Mentha longifolia	Iran	Aerial	[196]
Saliva limbata	Iran	Aerial	[196]
Saliva sclarea	Iran	Aerial	[196]
Ziziphora clinopodioides	Iran	Aerial	[196]
Glycyrrhiza glabra	Iran	Root	[196]
Thymus caramanicus	Iran	Aerial	[196]
Xanthium brasilicum	Iran	Aerial	[196]
Trachyspermum copticum	Iran	Fruits	[196]
Acacia nilotica (L.)) (Fabaceae)	Pakistan	Leaves, flowers	[197]
*Calotropis procera (*Aiton*)(* Apocynaceae)	Pakistan	Leaves, flowers	[197]
Adhatoda vasica Nees (Zygophyllaceae)	Pakistan	Whole plant	[197]
Fagoniaar abica L(Acanthaceae	Pakistan	Whole plant	[197]
Casuarina equisetifolia L. (Casuarinaceae)	Pakistan	fruits	[197]
AUSTRALIA			
Pistacia (Mastic, Kurdica, Mutica and Cabolica)	Sydney	gums	[198]
Others			
Allium sativum L	USA	Leaves	[125]
Capsaicin		Pepper fruits	[126]
Vaccitnium macrocarpon, C		Cranberry	[129]
Prunus mume	Japan	Juice	[199]

Table 1. Anti-*H. pylori* medicinal plants occurring in more than one country worldwide

http://dx.doi.org/10.5772/57462

6.2. Honey as a control measure of *H. Pylori* infections

Honey has been used in folk-medicine in many countries since antiquity [137]. It is mentioned for healing purposes in the Bible, the Koran, and the Torah. Research related to honey has revealed the promising effects of honey as an alternative source of *H. pylori* treatment [138]. Its beneficial qualities have been endorsed to its antimicrobial, antioxidant, anti-inflammatory properties added to its phytocomponents [139]. Documentations now exist with proven ability of Honey to inhibit microbial growth, and honey has been successfully used on infections that do not respond to standard antiseptic and antibiotic therapy [28, 137]. In addition, In New Zealand and Saudi Arabia it was observed that concentrations of honey at approximating 20% v/v can inhibit the growth of *H. pylori* in vitro, grounded with the fact that Medihoney™ and manuka honeys have *in vivo* activity against ulcers, infected wounds and burns are significant findings which merits further and extensive investigations [138]. Honey obtained from different floral sources and different geographical region seem to vary in their antimicrobial potency due to inherent differences in their chemical composition which is greatly influenced by the prevailing climatic conditions and soil characteristics in the different geographical areas influencing the plants as well the type of honey composition produced by the foraging bees [140, 141]. Undoubtedly, several factors like floral source used to collect nectar, seasonal and environmental factors, as well as processing and storage conditions might influence the chemical composition of honey [142].

Honey is becoming acceptable as a reputable and effective therapeutic agent by practitioners of conventional medicine and by the general public [139] Honey can be used as an antiseptic for wounds, burns and ulcers, improving the assimilation of calcium and magnesium and decreasing acidity [29, 143]. Stimulation of inflammatory- cytokine production by monocytes and hydrogen peroxide produced as a result of injury or infection is likely the mechanism by which wounds are healed with the use of honey [137, 144]. Motivated by these findings, scientist sought out to investigate the activities of honeys further. Previously, the activity of honey has been reported to differ with types [145]. The presence of hydrogen peroxide, osmotic effect of honey, its naturally low pH, phenolic acids, lysosomes and flavanoids in honey are all thought to help inhibit bacterial growth when honey is applied to a wound. Its low content of water facilitates wound healing by hygroscopic absorption of water molecules on wound surfaces and by soothing of the wound [137]. Honey does not only contain sugars but also an abundance of minerals, vitamins, enzymes and amino acids [6, 137].

Anti- *H. pylori* activities of honey have been investigated with various honey types in different parts of the world. Honey with proven anti- *H. pylori* activity is listed on (Table 2). Different variety of honeys (crude) and solvent extracted honey have been shown to possess potential compounds with therapeutic activity which could be exploited further as lead molecules in the treatment of *H. pylori* infections [24]. Chemical analysis of the chloroform extract of the pure honey led to the identification of 24 volatile compounds belonging to known chemical families present in honey. Astoundingly, thiophene and N-methyl-D3-aziridine were identified as novel compounds [146].

Honey type	Country	References
Goldcrest honey	South Africa	[146]
Pure honey	South Africa	[146]
Citrus blossom	South Africa	[146]
Goldcrest	South Africa	[146]
Black forest	Germany	[137]
Langnese	Germany	[137]
Langnese Natural Bee Honey	Germany	[137]
Blossom Bee Honey	Switzerland	[137]
Al-Shifa Natural Honey	Iran	[137]
Al-Nada Clove Honey	Oman	[137]
Al-Nada Chestnut Honey	Oman	[137]
Manuka honey	Zealand,	[137]
Capillano	Australia	[137]

Table 2. Honey with Anti-*H. pylori* activity worldwide.

6.3. Use of probiotics in the treatment and management of *H. pylori* infections

According to an expert consultation conducted by the Food and Agriculture Organization and the World Health Organization, probiotics are "live microorganisms which when administered in adequate amounts confer a health benefit to the host." The regular intake of probiotic microorganisms has been demonstrated to prevent several disorders including diarrhea and inflammatory bowel disease [147]. Other advantages of the use of probiotics include the inhibition of enteric pathogens such as *Salmonella*, *Shigella* and *Citrobacter*, the decreasing of the luminal pH through the production of lactic acid or through competition with gut pathogens for host surface receptors [148]. The usefulness of probiotics on the eradication of *H. pylori* remains controversial. It has been suggested that the use of probiotic might have a positive impact on *Helicobacter* eradication. However, some studies have demonstrated that there was no change while some have shown an increase in the eradication rate of the bacteria from about 60% to 83% [21, 149]. *In vivo* models demonstrated that pre-treatment with a probiotic can prevent *H. pylori* infection and/or that administration of probiotics markedly reduced an existing infection [150]. Probiotics are often administered as supplemental treatment for the eradication of *H. pylori*. In this regard, a meta-analysis of 14randomized clinical trials was conducted by [151]. This study evaluated the role of supplemental probiotics in *H. pylori* eradication therapy and showed that the cure rates for standard antibiotic treatment when used alone and eradication co-therapy with probiotics, were 74.8% and 83.6%, respectively. The analysis further showed that the combined treatment, had not only increased the eradication rate, but had also decreased the occurrence of adverse effects due to antibiotics, like diarrhea. Several probiotics have been shown to have a beneficial effect on *H. pylori*

infection [150, 151]. However, the exact mechanisms of action have not been clearly elucidated yet [152].

It is believed that probiotics may play an important role in the eradication and possibly the prevention of *H. pylori* infection and could serve as adjunctive treatment. Several probiotics have been shown to have beneficial effects on the treatment and eradication of *H. pylori* the majority of these probiotics known as the lactic acid-producing bacteria. Among these *Bifidobacterium* is one of the favorite genera, particularly in studies focused on the prevention of gastrointestinal infection and is often used in fermented dairy products or food supplements [153]. Some studies have been done in vitro (in test tubes or petri dishes) showing bifidobacterial activity against *H. pylori*. Examples include *Bifidobacterium lactis* which has been demonstrated to have an enhancing activity on the phagocytic capacity of polymorpho-nuclear cells [154]. *Bifidobacterium* spp have been shown to have positive effects of *H. pylori* infections. These are generally administered in dairy products such as yogurt and milk. Clinical trial studies have shown that probiotics-containing yogurt can offer benefits to restore *Bifidobacterium* spp/*E. coli* ratio in children and suppress the *H. pylori* load with increment of serum IgA but with reduction in IL-6 in *H. pylori*-infected children [155]. The Lactobacillus group constitutes an important source of probiotics that have been demonstrated to have a positive effect on *H. pylori* treatment. Strains with this ability include *Lactobacillus acidophilus, L. casei*, *L. johnsonii*, *L. salivarius* some of which are used as dairy starters [156]. Most studies have shown that lactobacilli or their cell-free cultures can inhibit or even kill *H. pylori* by preventing its adhesion to mammalian epithelial cells and preventing interleukin-8 release [157].

Fungal organisms particularly some strains of yeast have been used as probiotic as well.The best studied example is S. boulardii which is a live yeast that has been used extensively as a probiotic and often marketed as a dietary supplement [158]. It is a non-pathogenic yeast that has been prescribed for prophylaxis and treatment of diarrheal diseases caused by bacteria (Reference). Several clinical trials and experimental studies strongly suggest that *Saccharomyces boulardii* has a biotherapeutic capacity for the prevention and treatment of several gastrointestinal diseases including *H. pylori* infections [159]. *S. boulardii* mediates responses resembling the protective effects of the normal healthy gut flora. In a study conducted in Turkey, *S. boulardii* improved anti-*H. pylori* antibiotherapy-associated diarrhea, epigastric discomfort, and treatment tolerability. However, *S. boulardii* had no significant effect on the rate of *H. pylori* eradication in that study [160]. Importantly, *S. boulardii* has demonstrated clinical and experimental effectiveness in gastrointestinal diseases with a predominant inflammatory component, indicating that this probiotic might interfere with cellular signaling pathways common in many inflammatory conditions [161]. In another study by Cremonini probiotic supplementation significantly lowered the incidence of diarrhea and taste disturbance during *H. pylori* eradication compared to the placebo group.

Generally, probiotics can be administered as single microbial species. However, in some cases a combination of several types of probiotic species might yield a much more satisfactory result. In a study by Dylag and colleagues, the combination of *Lactobacillus*, *Bifidobacterium*, *Saccharomyces boulardi* and the treatment with *Escherichia coli* Nissle were found to be beneficial in inducing and maintaining remission of disease activity of gut inflammation and moderately

severe ulcerative colitis [162]. Preparations containing certain Lactobacillus, Bifidobacterium strains or Saccaromyces boulardii could enhance by 5-10% the rate of successful eradication of *H. pylori* and reduce the incidence and severity of the side effects [163]. Instead of considering the probiotics alone, they have been considered in some studies as a safe adjuvant when added to triple eradication therapy against the symptoms induced by the major gastric pathogen, *Helicobacter pylori*.

Several mechanisms by which probiotic bacteria inhibit *H. pylori* have been proposed and include immunological mechanisms, antimicrobial substances, competition for adhesion, and the production of mucosal barrier [164]. Proposed mechanisms underlying the beneficial interaction between probiotics and *H. pylori*, and the modulation of the colonization of the gastric mucosa by this pathogen, include the production of lactic acid with *H. pylori* inhibition because of decreasing gastric pH; the direct killing of *H. pylori* through secreted metabolites with antimicrobial properties, including bacteriocins, autolysins, and organic acids; the interference with *H. pylori* adhesion to epithelial cells, both through the secretion of antimicrobial molecules and through direct competition for adhesion; and the ability to reduce *H. pylori*-induced gastritis through the stabilization of the mucosal barrier, the secretion of mucins, and the modulation of the host immune response to the infection [149]. Infection by *H. pylori*, often induce and inflammatory response which in turn exacerbate the disease through the increase production of inflammatory cytokines such as IL8 and TNF alpha. The subsequent inflammatory processes as well as the bacterial infection generally persist for decades resulting in mucosal damage, gastritis, and finally gastric neoplasm further potentiated by the failure of macrophages to eliminate *H. pylori* [165, 166]. One of the mechanisms by which, probiotics reduce *H. pylori* infections is through the production of conjugated linoleic acids. Conjugated linoleic acids (CLA) produced by *Lactobacillus acidophilus* for example was reported to decrease the activation of nuclear factor-kappa B. In fact strains of probiotic bacteria are known to convert linoleic acid to conjugated linoleic acid which has an immunomodulatory activity [167]. A study conducted by Hwang and colleagues showed that conjugated linoleic acid decreased the expressions of IL-8mRNA/protein as well as that of TNF-a mRNA [168]. This in turn, reduces the inflammation and therefore increases the cure rate of *H. pylori* infection. Some probiotics such as *L. acidophilus* induce a Th1-polarizing response characterized by high expression of interferon beta (IFN-β) and interleukin 12 (IL-12) [169]. This anti-inflammatory effect is contrary to the inflammatory response induced by *H. pylori* and therefore might reduce the effect of the infection on the host and increase the eradication of the pathogen although *H. pylori* contain a pathogenic feature known as vac A which can block the effect of the probiotic [170]. Studies by Yang and colleagues showed that higher doses of *L. acidophilus* pre-treatment reduced *H. pylori*-induced inflammation through the inactivation of the Smad7 and NFκB pathways by reversing the effect of *H. pylori* infection which often induces Smad7, NFκB, IL-8, and TNF-a production [171].

Helicobacter pylori treatment has evolved tremendously over the past decade. The use of different antibiotics has resulted to antibiotic resistance which has led to the adaptation of new ways of controlling the organism. The use of medicinal plants has proven its worth. However, much still need to be done, while very few clinical trials have been conducted over the last

http://dx.doi.org/10.5772/57462

decade. Clinical trials for the use of medicinal plants for the control of *H. pylori* infections are still awaited. The application of probiotics remains controversial although the tendency would be that these organisms are helpful in increasing the eradication rate as well as the reduction of the side effects of the infection.

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