EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 3
Issue: 5
214-222
Year: 2016

SYSTEMATIC REVIEW OF *HELICOBACTER PYLORI* INFECTION AND PLANT BASED THERAPY

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Article Received on 27/02/2016 **Article Revised on 18/03/2016** **Article Accepted on 09/04/2016**

ABSTRACT
More than 50% of the world population are infected with *Helicobacter pylori.* The bacterium highly linked to peptic ulcer and duodenal ulcer diseases, further infection causes lifelong chronic gastritis, which can lead to peptic ulcer, mucosa-associated lymphoid tissue (MALT) lymphoma and gastric cancer. The antibiotic therapies have several inherent problems, including the appearance of resistance to the antibiotics used and associated adverse effects, such as the risk of re infection and its high cost. The decision on the therapy of invasive gastric cancer depends on several factors such as environmental factors and the presence or absence of virulent factors such as mainly Cag A, Vac A, and urease action in the gastric environment. The growing problem of antibiotic resistance by the *H. pylori* demands the search for novel candidates from plant-based sources. The alternative therapies have not been effective in eradicating the bacteria but have been shown to maintain the bacterial growth levels. This review summarizes pathogenesis, culture conditions and the most relevant recent studies on new treatments using natural resources such as plants.

KEYWORDS: *Helicobacter pylori*, Gastritis, Culture conditions, Medicinal plants.

1. INTRODUCTION
Helicobacter pylori is a spiral shaped gram-negative flagellate bacterium that colonizes the antral region of the human stomach. Approximately half of the world's population is infected with *H. pylori* and the majority of *H. pylori*-infected patients develop coexisting chronic gastritis. In most infected patients, *H. pylori* colonization does not cause any symptoms such as abdominal pain, which typically occurs when the stomach is empty during night, or a few hours after meals, feeling bloated, feeling sick or vomiting, losing appetite, losing weight and blood or a black color in feces.[1] Various diseases those are closely associated with *H. pylori* infection including gastrointestinal malignancies. Infection with *H. pylori* is the primary cause of gastric cancer. Genetic sequence analysis has indicated that human being has coevolved with *H. pylori* for more than 58,000 years ago.[2] Gastric cancer is the second leading cause of cancer-related infection in worldwide.[1a] *H. pylori* bacterium has been established as the most important risk factor for gastric cancer (GC). The genomic diversity of *H. pylori* parallels that of its host species, consistent with colonization of the earliest humans and co-migration out of East Africa. The major risk factor associated with gastric adenocarcinoma is infection by *H. pylori*. It is a Gram-negative microaerophilic bacterium that colonizes the gastric mucosa of approximatively 45% of the human population; it induces a chronic gastric inflammation, which evolves in approximatively 15% of cases towards more severe forms of gastric diseases, such as peptic ulcer, gastric carcinoma and mucosa-associated lymphoid tissue (MALT) lymphoma. In 2003, an estimated 1.9 million cases, or 18.8% of the worldwide incidence of cancer, were considered to be attributable to infectious diseases, with *H. pylori* infection as the leading cause (5.5% of all type of cancers).[3] *H. pylori* are responsible for about 75% of all noncardiac gastric cancer and 63.4% of all stomach cancers worldwide. *H. pylori* are a highly heterogeneous bacterial species, both genotypically and phenotypically and are highly adapted for survival in the gastric niche.[4] With respect to gastric cancer, the major *H. pylori* candidate virulence factors include the cag pathogencity island (PAI), the CagA protein and the vacuolating toxin VacA, the blood group antigen binding sticking together (BabA) and possibly the duodenal ulcer producing gene (DupA). Medicinal plant is widely distributed in countries with tropical and subtropical climates, especially in coastal regions due to the plant's ability to easily adapt to salinity and winds.[5] In Asian

countries, the leaves of this species are commonly used for the treatment of dermatitis, hepatitis, diarrhea and pyresis.[6] This was also listed in Pharmacopeia vegetables of the Caribbean, where the leaves of this plant are used in a decoction for gastritis and urinary infection.[7] The literature also shows that the polar extract from different parts (leaves, fruits and bark) of have shown the following biological activities: antimicrobial, antifungal[8], previously reported the antisecretory effect of the ethanolic extract from leaves, although the mechanism responsible for this preventive effect remains unknown, thus the use of this specie against gastric bacteria is relevant. Infection caused to *H. pylori* is considered the most prevalent cause of gastric diseases such as ulcers, dyspepsia and stomach cancer.[7a] The drug therapy available for the treatment of diseases caused by this microorganism has limitation such as the high rate of resistance to conventional drugs and inappropriate patient treatment, as presented to numerous side effects.[9] In this sense, the use of natural products as an alternative to control this bacterium has shown to be satisfactory, what drives the improvement of investigations of medicinal plants as adjuvant or new antimicrobial drugs.[10-11] The present review focuses on the concepts of innovative drug discovery rather than on specific pharmaceutical techniques and knowledge.

2. Epidemiology of *H. pylori* infection and gastric cancer

The impact of *H. pylori* infection on gastric malignancies may depend on the anatomic location. Cancer of the proximal stomach (cardiac and gastroesophageal junction) have different epidemiological and pathophysiological characteristics are not commonly found in high *H. pylori* endemic areas.[12] For example, adenocarcinoma derived from gastroesophageal junction may be associated with in either *H. pylori* infection or Barrett's esophagus.[13] It was well established that gastric cancers normally arise in a stomach that was chronically inflamed; it was initially difficult to demonstrate the association of *H. pylori*.

With gastric cancer from histological studies with decreased acid secretion, consequent to loss of specialized acid-secreting cells (parietal cells) from gastric gland atrophy, a gastric luminal environment increasingly hostile to the survival of this acidophilic bacterium. However, in the early 1990s, several prospective observational studies have been studied for a positive association between *H. pylori* infection and non-cardiac gastric cancer. *H. pylori* infection in non-cardiac gastric cancer ranges from as low of 2% and high as 20% with no substantial differences between males or females for gastric cancer of the intestinal subtype of the diffuse histological subtype. Overall, the matched odds ratio in meta-analysis of *H. pylori* infection and gastric cardiac cancer is around 1.0 protective effect of *H. pylori* against cardiac gastric cancer.[14]

3. Non-cardiac gastric cancer

Epidemiologic studies have shown that individuals infected with *H. pylori* have an increased risk of gastric adenocarcinoma.[15] The risk increase appears to be restricted to non-cardiac gastric cancer. For example, in 2001 combined analysis of 12 case-control studies of *H. pylori* and gastric cancer estimated that the risk of non-cardiac gastric cancer was nearly six times higher for *H. pylori*-infected people than for uninfected people. Additional evidence for an association between *H. pylori* infection and the risk of non-cardiac gastric cancer comes from prospective cohort studies such as the Alpha-tocopherol, Beta- Carotene (ATBC). The researchers found that *H. pylori*-infected individuals had nearly eight fold increased risk for non-cardiac gastric cancer.[16]

4. Pathogenesis of *H. pylori*

H. pylori-induced molecular pathogenesis will be critical to understand the basis and origin of gastric cancer and will be provide us with options for future prevention and intervention in combating this deadly disease. Consequently, nowadays, there is no doubt that *H. pylori* infection is responsible for the majority cases of gastritis.[17] The chronic inflammatory state induced by persistent *H. pylori* infection over decades provides a rich milieu of inflammatory cytokines, as well as reactive oxygen and nitrogen species that are capable of inducing cellular damage and mutagenesis. Increased cell turnover in this environment can lead to the emergence of cell lineages not normally found in the stomach (gastric metaplasia) and in a small subset of humans infected chronically by *H. pylori*, the emergence of neoplastic clones under the pressure of accelerated DNA replication. *H. pylori*-infected subjects compared to cells from uninfected individuals, pointing its importance in *H. pylori*-related pathogenesis.[18]

5. The origin of gastric cancer cells

Epithelial cells that line the gastric mucosa are formed by four major cell types pit include chief cells, parietal cells, G cells and enterochromaffin-like cells (ECLs) etc. Studies of the transcript of gastric epithelial cells from the stomach of *H. pylori*-infected mice demonstrated that gastric pit cells or mucus-producing cells are the major targets of *H. pylori*[19], which are recognized by *H. pylori* adhesions and interaction with and resides within a subset of these progenitor cells. The damages that originate from genetic and epigenetic processes are progressively accumulated during aging and directly contribute to cell transformation.[20] *H. pylori* have been shown to invade epithelial cells, intracellular and interstitially with gastric progenitor cells, therefore introducing the molecular damage to these cells *H. pylori* infection is able to activate several oncogenic pathways. All stages of cancer development and progression, deregulation of a few relevant pathways may initiate transformation, while activation of other genes may contribute to progression or metastasis.

6. Virulence Factors of *H. pylori*

Several possible disease-specific virulence factors have been suggested to be associated with *H. pylori* infection[21-23], the virulence factors are usually involved in the development of diseases. In *H. pylori* major virulence factors such as Cag A, Vac A and Bab A, are believed to correlate with the development and severity of gastritis, gastric ulcer and a newly identified virulence factor, Oip A, in particular its relationship to *H. pylori*-related disease is also extensive studied. The Cag A gene codes for one of the major *H. pylori* virulence proteins. The bacterial strains that have the Cag A gene are associated with an ability to cause ulcers (**Table.1**).

Table 1: Virulence Factors of *H. Pylori.*

Factor	Function	Distribution	Reference
Urease	Buffers stomach acid	All strains	Feldberg et al. [38]
Flagella	Motility	All strains	Feldberg et al. [38a]
BabA	Adhesin for Le^b	Prevalent on type I strains	Mazari-Hiriart *et al*. [39]
VacA	Cytotoxicity (two alleles)	All strains	Graham *et al*.[40]
Cag PAI	31 genes coding for type IV secretion system	Type I strains	Manyi-Loh *et al*.[41]
CagA	Immunodominant antigen (part of *cag* PAI)	Type I strains	Lee [42]
PicB	Equivalent to CagE	Type I	Schmidt *et al*.[43]

The *H. pylori* requires special features to overcome host defense mechanisms and be successful as a pathogen have to survive in the acidic gastric juice for at least a short period of time, need to enter the highly viscous gastric mucus gel, to reach and adhere to epithelial cells, to acquire sufficient nutrients to multiply and to evade the host immune response. Whereas these events are essential for the maintenance of chronic infection, major tissue damage is probably not a prerequisite for infection. Indeed, although all infected individuals have gastritis, only a minority develop more severe lesions. Nevertheless, the bacterial factors that cause tissue damage are obviously of great medical interest; because of this, they will be discussed here, although their potential to be included as components of a vaccine appears limits. In addition to potential virulence factors and adhesion molecules with a direct effect on host cells, mostly explained above, there are some further metabolic mechanisms that are not per set considered as virulence factors. Adhering and colonizing of gastric epithelial cells is the initial and indispensable step for *H. pylori* to induce cancer, although this step is not sufficient to cause cancer. Adaptation of *H. pylori* to the hostile environment of the host's stomach relies on a set of proteins including secreted extracellular enzymes and outer membrane adhesions like urease, Bab A (blood-group antigen binding adhesion), and Sab A (sialic acid-binding adhesion) are the most prominent pathogenic city factors with known receptors in the host gastric epithelium (Fig.1).

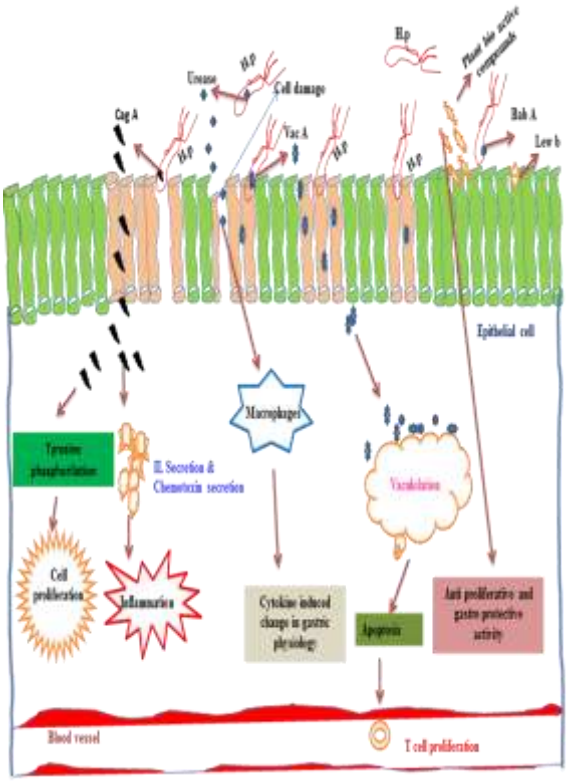

Fig 1. Interaction between *H. Pylori* Virulence Factors and Gastric Epithelial Cell in the Adherence and Colonization Step.

7. Culture conditions

H. pylori is a microaerophilic organism that requires a small amount of oxygen (3 to 7%) for its metabolic activities. It cannot be grown at higher oxygen concentrations like fully aerobic microorganisms.[24] Through whole genome sequencing of *H. pylori* in experimental studies of the bacterial metabolism, it has been inferred that several pathways are missing for the biosynthesis of essential amino acids, lipids and nucleotides in comparison to other microorganisms like *E. coli*. While its amino acids and lipids can also be

potential sources of carbon and energy[25], glucose appears to be the only source of carbohydrate utilized by the bacterium.[26] It has been reported that *H. pylori* exploits not only oxidative phosphorylation but also fermentation processes. Out of many extensive investigations regarding urea and urease, it is important to point out that the presence of large amounts of urease in the cytoplasm and also in the extracellular milieu of *H. pylori* is unique. Urease is constitutively expressed by *H. pylori* and comprises more than 10% of the whole protein content produced by *H. pylori*.[27] This highly active enzyme is the main responsible factor for the production of ammonia, which beside involvement in biosynthesis also acts in acid resistance. It has been clearly showed that urease is a critical virulence factor essential for the colonization of stomach. These specific properties have designated an exclusive position for urease in vaccine research[28-29] and must inform successful diagnostic approaches for *H. pylori*.[30-31]

8. Environmental factor in gastric cancer

H. pylori have been classified as low-potential carcinogens (cancer-causing substances) and it thrives in an aerobic environment at 35-37^{o}C which cause the production of excess stomach acid. Colonies may be visible after 3-5 days of incubation but may take longer to appear on primary isolation. The existence of environmental *H. pylori* reservoirs has been suggested and epidemiological studies indicate that water can be a source of *H. pylori* infection. Environmental factors also to be important factors for increased cancer risk. They are examined the relationship of household characteristics, smoking, alcohol drinking, dietary consumption and plasma nutrient levels with the prevalence of two different stages gastric precancerous lesions, chronic atrophic gastritis. It is highly prevalent and mortality due to gastric cancer in the Japanese population are well recognized, but there are geographic differences for gastric cancer *H. pylori* strains and differences in the host genetic background in various ethnic groups, including gastric acid secretion and genetic polymorphisms in pro inflammatory cytokines. *H. pylori* are a significant and certainly initiating factor in chronic gastritis and later development of gastric cancer.[32-33] Apart from the above-discussed mechanisms, some host and environmental factors are also believed to affect the course and progression of *H. pylori*-induced gastric carcinogenesis. *H. pylori* are able to sense the pH gradient in the mucus and move towards the less acidic region. This also keeps the bacteria from being swept away into the lumen with the bacteria mucus environment, which is constantly moving from its site of creation at the epithelium to its dissolution at the lumen interface[34], *H. pylori* is found in the mucus, on the inner surface of the epithelium and occasionally inside the epithelial cells themselves.[35] It adheres to the epithelial cells by producing adhesions, which bind to lipids and carbohydrates in the epithelial cell membrane. The colonization of *H. pylori* and its effect on resident gastric microbiota is relatively unknown. The ability of *H. pylori* to transform from a highly virulent, spiral shaped bacteria to a less virulent, non-culture able coccid state, presents difficulties in the successful detection of this bacterium in both an environmental and clinical examination. It has been known for over a decade now that motility is essential for the survival and successful colonization of *H. pylori*.

9. Treatment of *Helicobacter pylori*

H. pylori infection adding to the severity of the disease sustainable efforts and constant research in the area lead to the development of several drugs that can act at multi steps during ulcer pathogenicity such as proton pump blockers (Lansoprazole, Omeprazole), histamine receptor blockers (Ranitidine, Cimitidine, Famotidine) and *H. pylori* inhibitors (Amoxicillin, Erythromycin, Metronidazole). However, majority of attribution have been documented to pose problems of adverse effects. Eradication rates depend on several factors: drug regimen, resistance rate to the antibiotic used, compliance with the drug, duration of therapy and genetic variations in drug-metabolizing enzymes. Therefore triple therapy containing combination of two antibiotics and proton pump *H. pylori* infection is the major factor in most cases of ulcer disease. As with any established microbial disease, we need to understand the epidemiology and mechanisms of pathogenesis, but the major focus should be towards improving therapies and defining the long-term outcome of *H. pylori* eradication. To devise novel therapeutic agents effectively, there should be knowledge of the basic physiology of *H. pylori* and its ecology in the stomach.[78] The quadruple therapy containing bismuth in addition to triple therapy are recommended for successful eradication of *H. pylori*. The Maastricht Consensus Report provides recommendations on management of *H. pylori* infection historically, natural products have provided an endless source of medicine and despite the diversification of drug discovery technology and reduced funding for natural product–based drug discovery, natural products from plants and other biological sources remain an undiminished source of new pharmaceuticals. Indeed, even though industrial funding specifically allocated for natural product–based drug discovery declined from 1984 to 2003, the percentage of natural product–derived, small-molecule patents has remained relatively unchanged. A comprehensive review of human drugs introduced since 1981 suggests that, out of 847 small-molecule drugs, 5% were natural products, 27% were derived from natural products (usually semi synthetically) and the remaining 572 were synthetic molecules. However, 262 of the synthetic molecules had a natural product–inspired pharmacophore or could be considered natural-product analogs.

10. Natural Medicinal Plants *H. pylori* treatment

Natural compounds from dietary or plant sources with discrete bio-activities towards animal biochemistry and metabolism are being widely examined for their ability to provide health benefits. It is important to establish the

scientific rationale to defend their use in pharmaceuticals. The nutraceuticals or phytochemicals could provide health benefits, substrates for biochemical reactions, cofactors of enzymatic reactions, inhibitors of enzymatic reactions, absorbents sequestrants that bind to and eliminate undesirable constituents in the intestine, ligands that agonize or antagonize cell surface or intracellular receptors, scavengers of reactive or toxic chemicals, compounds that enhance the absorption and or stability of essential nutrients. Plants and phytoconstituents are better choice to treat diseases than the allopathic drugs. Most of the drugs used in primitive medicine were originated from plants and are the earliest and principal natural source of medicines. The drugs from plants are fairly innocuous and relatively free from toxic effects. The nature has provided us various medicinal plants which became the storehouse of remedies to cure all ailments of mankind.[48] In modern era many plant-derived compounds have been used as drugs, either in their original or semisynthetic form research supporting beneficial roles for phytochemicals against cancers, coronary heart disease, diabetes, high blood pressure, inflammation, microbial, viral and parasitic infections, psychotic diseases, spasmodic conditions, ulcers, etc is based on chemical mechanisms using *in vitro* and cell culture systems, various disease states in animals and epidemiology of humans. The fruits and vegetables are rich sources of bioactive compounds including carotenoids, beta-carotene, lutein, lycopene, zeaxanthin, flavonoids, anthocyanins, quercetins and phenolic exhibiting various health beneficial effects and reduce the risk of many diseases including ulcer. Various medicinal plants are used traditionally in the treatment of peptic ulcer and they exhibit their action by various mechanisms like antioxidant, cytoprotective, antisecretory, mucoprotective, anti-inflammatory and antibacterial properties. *Hippocratea celastroides* has the strong potential as a new option for the treatment of ulcers and gastric disorders because of its broad spectrum of activities, including *anti-Helicobacter pylori*, gastroprotective and anti-inflammatory activities, which work together to address the same problem. Plants compounds have been screened in the search for the potential Anti-*H. pylori* activity Garlic (*Allium sativum L*) particularly allium vegetables have been shown exhibit a broad range of antibiotic spectrum against Gram– negative bacteria. Medicinal plants serve as a useful source of novel drugs.[36] On the natural flora of a specific region or country. Many studies have in the past focused on activity against *H. pylori*[37], as well as activity against multi-drug resistant bacteria such as found to exhibit anti-*H. pylori* activity (**Table. 2**).

TABLE 2: *ANTI-HELICOBACTER PYLORI* ACTIVITY OF MEDICINAL PLANTS.

Plants Name	References
Impatiens balsamina L.	Wang *et al*.[49]
Persea americana, Annona cherimola, Guaiacum coulteri, Moussonia deppeana	Castillo-Juárez *et al*.[50]
Myristica fragrans (seed), Rosmarinus officinalis (rosemary leaf)	Mahady *et al*.[51]
Curcuma amada Roxb., Mallotus phillipinesis (Lam) Muell Myrisctica fragrans Houtt Psoralea corylifolia L.	Zaidi *et al*.[52]
Abrus cantoniensis, Saussurea lappa, Eugenia caryophyllata	Li *et al*.[53]
Hippophae rhamnoides, Fritillaria thunbergii, Magnolia officinalis, Schisandra chinensis, Corydalis yanhusuo, Citrus reticulata, Bupleurum chinense, Ligusticum chuanxiong	Li *et al*.[53]
Myroxylon peruiferum	Ohsaki *et al*.[54]
Aristolochia paucine6is	Gadhi *et al*.[55]
Cistus laurifolius, Spartium junceum, Cedrus libani, solstitialis, Momordica charantia, Sambucus ebulus, Hypericum perforatum Solvent extract and hexanefraction MIC: 1.95-250 µg/mL Yeşilada et al Larrea divaricate Cav (leaves and tender branches	Yeşilada *et al*.[56]
Larrea divaricate Cav (leaves and tender branches)	Stege *et al*.[57]
Acacia nilotica (L.) Delile, Calotropis procera (Aiton)	Amin *et al*.[58]
Zingiber officinale	Nostro *et al*.[59]
Tephrosia purpurea (Linn.) Pers.	Chinniah *et al*.[60]
Terminalia macroptera (root)	Silva *et al*.[61]
Black myrobalan (Teminalia chebula Retz)	Malekzadeh *et al*.[62]
Rubus ulmifolius leaves	Martinia *et al*.[63]
Amphipterygium adstringens	Castillo-Juárez *et al*.[64]
Lycopodium cernuum	Ndip *et al*.[65]
Ageratum conyzoides, Scleria striatinux, Lycopodium cernua	Ndip *et al*.[65]
Sclerocarya birrea	Njume *et al*.[66]
Artemisia ludoviciana subsp. mexicana plants	Castillo-Juárez *et al*.[67]
Pteleopsis suberosa	Germanò *et al*.[68]
Ageratum conyzoides, Scleria striatinux, Lycopodium cernua	Ndip *et al*.[65]
Cuminum cyminum L., Cynara scolymus L., Origanum vulgare L. plants	Nostro *et al*.[69]
Allium sativum	Cellini *et al*.[70]
Mentha × piperita, Peppermint Oil, Origanum vulgare, Pimpinella anisum, Aniseed Oil,	Cwikla *et al*.[71]

Syzygium aromaticum	
Chamomila recutita L., Ilex paraguariensis A. St.-Hil	Cogo *et al.*[72]
Sclerocarya birrea	Njume *et al.*[73]
Punica granatum, Quercus infectoria	Voravuthikunchai *et al.* [74]
Mentha × piperita, Peppermint Oil, Origanum vulgare, Pimpinella anisum, Aniseed Oil, Syzygium aromaticum	Cwikla *et al.*[71]
Anthemis melanolepis plants	Stamatis *et al.*[75]
Plumbago zeylanica L.	Wang and Huang.[76]
Allium sativum	Cellini *et al.*[70]
Cymbopogon citratus (lemongrass) plants	Ohno *et al.*[77]

Indeed, some bacteria, which showed resistance to certain antibiotics, were sensitive to medicinal plants extract of both garlic and clove. In this regard, medicinal plants can be a source of new drugs with antibacterial activity or even as resistance modifiers acting as bacterial efflux pump inhibitors.[79] *Decalepis hamiltonii*, have more anti-*H. pylori* activity studied the SRPP[44], with defined sugar composition and phenolics, exhibited multi-potent free radical scavenging, antioxidant inhibition of H+, K+-ATPase and gastric mucosal protective activities is due to the presence of phenol bound pectic polysaccharide.[45] The two pilot trials were conducted to evaluate the effect of short term broccoli consumption (alone or in combination with yoghurt) on *H. pylori* eradication in infected volunteers the eradication of *H. pylori* infection was observed in one group. Isothiocyanate sulphoraphane, an abundant compound in broccoli sprouts, has been identified as a potent bacteriostatic agent against *H. pylori* (in 48 tested strains, MIC media= 2 μg/mL); moreover, brief exposure to SF eliminated intracellular *H. pylori* from a human epithelial cell line (HEp-2). SF was effective in eradicating *H. pylori* from human gastric xenografts in nude mice have been reported.[46] Studied the antibacterial activity of Black myrobalan (*Terminalia Chebula Retz*)[47] aqueous extracts of black myrobalan against *H. pylori* was significantly higher than that of ether and alcoholic extracts. Water extracts showed significant antibacterial activity and had a minimum inhibitory concentration (MIC) 125 mg/ml and minimum bactericidal concentration (MBC) of 150 mg/ml, respectively. The understanding the medicinal activity of plants used in folk medicine in different parts of the world, but it is much more random than an ethno pharmacological criterion, the specific studies of the activity of a plants or principle against a concrete pathological microorganism.

11. CONCLUSION

H. pylori treatment has evolved tremendously over the past decade. The use of different antibiotics has resulted to antibiotic resistance which is leds 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 studied. Clinical trials for the use of medicinal plants for the control of *H. pylori* infections are still awaited. The application of 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. Several mechanisms are likely to account for this protection. Medicinal plant compounds may also provide effective way to reduce *H. pylori*-induced gastric inflammation and even gastric cancer. Furthermore, herbs like plants might become a trail as future chemo preventive candidates against gastric cancer, although, extensive *in vitro, in vivo* and clinical studies are directly required before counting them as chemo preventive agents.

ACKNOWLEDGMENTS

The authors gratefully acknowledge the Department of Science and Technology, New Delhi for providing financial supports under DST-WOS-A start of grant for (DST/SR/WOS-A/LS-629/2012(G), Scheme.

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