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Role of *Helicobacter*, An Emerging Zoonotic Pathogen in Gastro-intestinal Diseases

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ABSTRACT

Helicobacter is the organism widely spread in human and all known Helicobacters live in human and animal hosts especially H. pylori, where colonization occurs principally in the gastrointestinal tract and sometime responsible for serious illness such as gastritis, Peptic Ulcer Disease (PUD) and strongly associated with gastric carcinoma, MALT lymphoma. It is considered as a serious problem impairing in public health in both developing and developed countries because it colonises the gastric mucosa of about half of the world population. Although less often Non Helicobacter Pylori Helicobacter (NHPH) are also able to cause disease in humans. Helicobacter naturally infects many poultry birds, some rodent species as well as humans. Helicobacter is a zoonotic bacterium that has also been associated with certain enteric infection in humans. Helicobacter is of zoonotic importance and the animal host remains a natural reservoir for many species. And efforts for Helicobacter's treatment is more difficult due to antibiotic resistance and patient compliance but there are various unani drugs of plants, animals and mineral origin which are being used for the treatment of Helicobacter's infection. The aim of this review is to give a comprehensive knowledge of zoonotic potential of Helicobacters.

1. Introduction

The *Helicobacter* genuses are gram negative bacteria which were originally considered to belong to the *Campylobacter* genus because of resemblance in morphological characters. But, since 1989 they have been classified in a separate genus because of having different biochemical characteristics, more than 35 species having been identified till now and more still being studied (Fox *et al*., 2002; Hua *et al.,* 1999). In this genus, the best known species is *H. pylori*, a specific pathogen of the upper gastrointestinal tract. *Helicobacter pylori* infection is one of the most common infections and nearly about half of the world population is suffering from this carcinogenic organism (Parsonnet *et al*., 1999). It has been reported that *H. pylori* is almost always acquired in childhood (Rowland, 2000). It is the main cause of gasterointestinal diseases like gastritis, peptic ulcers, and gastric carcinoma. In 2005, Barry Marshall and Robin Warren were awarded with the Nobel Prize in Physiology or Medicine "for their discovery of the bacterium *Helicobacter pylori* and its role in gastritis and peptic ulcer disease". The discovery of *H. pylori* increased interest to other spiral bacteria that had been seen in many animal species. Most of these bacteria belong to the genus *Helicobacter* (O'Rourker *et al*., 2001). Other than *H. pylori* that is Non-pylori helicobacters (NPHS) are increasingly being found in human clinical specimens. Thus, their role in human medicine is increasingly reported.

Enterohepatic Helicobacters (EHH) other than *H. pylori* colonize the bowel, biliary tree and liver of animals and human beings with pathogenic potential (Bohr *et al*., 2007) However, although the gastric *Helicobacters* have been the most studied, they only account for one third of the entire genus. The remaining two-thirds correspond to the so-called enterohepatic Helicobacter (EHH) (Schauer *et al.*, 2001).

The organisms are found about 70–90% and 25–50% of the population in developing and developed countries, respectively (Guillermo *et al*., 2004; Sykora *et al*., 2006; Vale and Vitor, 2010). This pathogen is reported as a cohabitant of the host (Cremonini and Gasbarrini, 2003), and it does not always cause illness in infected people and remain

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asymptomatic (Santos *et al*., 2009). Several risk factors for *H. pylori* infection have been known and this include poor social and economic development (Lehours and Yilmaz, 2007), low education level, poor hygienic conditions such as poor hygiene practices during childhood, lack of a household bath, absence of sanitary drinking water, absence of a sewage disposal facility during childhood, crowded families (Nouraie *et al*., 2009), and unhygienic food handling (Van Duynhoven and de Jonge, 2001). Most of these factors are a consequence of and associated with socioeconomic development. The prevalence of the infection decreases by the improvement of general hygienic conditions (Fujimoto *et al*., 2007). The transmission pathways of *H. pylori* remain unclear. The most commonly accepted hypothesis is that infection can takes place through fecal–oral route (Vale and Vitor, 2010)and contaminated food and water may play an important role in transmission of this organism to humans (Van Duynhoven and de Jonge, 2001; Gomes and De Martinis, 2004; Vale and Vitro, 2010). Indeed, *H. pylori* have been detected in drinking water (Queralt *et al*., 2005) and foods of animal origin such as milk, and meat (Dore *et al*., 2001; Fujimura *et al*., 2002; Quaglia *et al*., 2008). Due to that, the existence of animal reservoirs of this organism has been hypothesized (Dore *et al*., 2001; Fujimura *et al*., 2002). This hypothesis is further more supported by the demonstration of *H. pylori* in the gastric mucosa of calves, pigs, and horses and its isolation from sheep's gastric tissue and milk (Dore *et al*., 2001), by this it can be suggesting that these animal species may act as reservoirs and are the spreaders of *H. pylori*. *H. pylori* can survives for long period in foodstuffs such as milk and instant foods (Poms and Tatini, 2001; Quaglia *et al*., 2007). Therefore, food may serve as a vehicle for H. pylori infection.

Etiology

H. pylori are a helical or curved shaped Gram-negative bacterium and the name *Helicobacter pylori* is Latin for spiral rod of the lower part of the stomach. It has two to six flagella which varies in different species of *Helicobacters* and they helps in mobility to withstand rhythmic gastric contractions and penetrate the gastric mucosa. The primary reservoir for gastric *Helicobacters* like *H. pylori* (human stomach), *H. canis* (canine stomach), *H. suis* (pig stomach) and in case of NHPH (non-helicobacter pylori helicobacter) the site are others such as *H. pullorum* (poultry intestine), *H.hepaticus* (liver). All gastric *Helicobacters* contains a large amount of urease enzyme that produces urease, which makes the environment alkaline that enables to survive the the bacteria in acidic medium of stomach. On the other hand NHPH does not produce urease enzyme therefore they cannot create alkaline medium in stomach hence do not survive in stomach. *Helicobacters* have number of virulence factors, including VacA and CagA that may have different disease associations (Atherton, 1997). The optimum growth temperature is 35-37°C but some species of *Helicobacters* grow poorly at 42°C and 30°C. *Helicobacter* species are micro-aerophilic and grow best in an atmosphere of 86% N_2, 4% O_2 with 5% CO_2 and 5% H_2 (Goodwin, 1989). All the required growth conditions are met in the gastrointestinal tract of all warm-blooded animals. At temperatures below 30°C, *H. pylori* could survive in some foods, such as fresh fruit and vegetables, fresh poultry or fish, fresh meats, and some dairy products, water and milk (Fan *et al*., 1998).

Routes of Transmission

Numerous epidemiological studies have been carried out to determine the factors affecting of this pathogen's transmission. Socio-economic status is obviously the most significant determinant for the occurance of *Helicobacteriosis* infection, with a significantly higher prevalence of poorer/lower social group (Mitchell, 2001). These factors encompasses conditions such as levels of hygiene, density of living, sanitation, and educational opportunities, which have all been individually identified as markers of the bacterium presence.

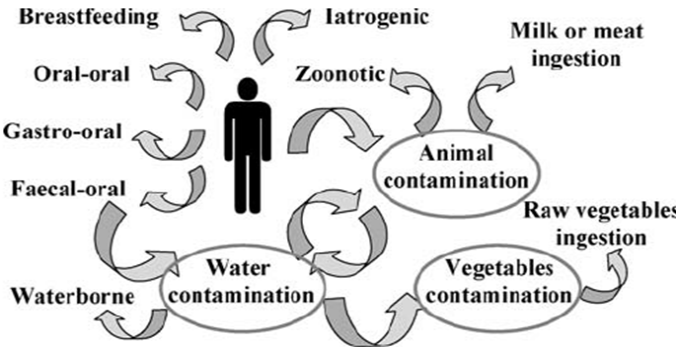

Fig. 1 Suggested transmission routes for *Helicobacters*. Five of the proposed pathways are representative of direct person-to-person transmission (breastfeeding, iatrogenic, oral-oral, gastro-oral, and fecal-oral), whereas the remaining four require an environmental reservoir in between. Possible reservoirs outside the human host are marked with a red circle.

On the basis of epidemiological and microbiological evidence, several routes of transmission have been conjectured as shown in above picture. Transmission from one person to another is widely viewed as the most likely route of infection. In addition, several epidemiological studies have consistently identified domestic overcrowding and infection of family members as a risk factor for its transmission. The most relevant pathways of person-to-person transmission include the gastro-oral, oral-oral, and fecal-oral routes. Iatrogenic and breastfeeding transmission are often used as possible means of transmitting the pathogen. Additionally, there are at least three potential vectors suggested to maintain the bacterium in viable form: water, food, and animals. Most scholar accept the relative importance of these routes in the transmission of the bacterium is likely to vary between developing and developed countries (Perez-Perez, Rothenbacher, and Brenner 2004; Megraud, 2003).

Zoonotic Transmission

An obvious reasoning, including contact with animals as a possible mode of transmission mode, since zoonotic transmission represents one of the leading causes of disease and death from infectious disease worldwide. Many epidemiological studies seem to support the role of animals in the acquisition of *H. pylori*, but the extent of this aid depends on the animals under study. Considered vectors include sheep (Dore *et al*. 2001), cows (Fujimura et al. 2002), domestic pets (Boomkens *et al*. 2004), houseflies (Osato *et al*. 1998) and cockroaches (Imamura *et al*.

2003). Epidemiological data showed a greater prevalence in shepherds and their families compared to the general population (Dore *et al*. 1999; Plonka *et al*. 2006). An epidemiological study has been shown controversial results in respect to the risk of the presence of domestic animals in the household (e.g., Bode *et al*. 1998; Lindo *et al*. 1999; Kearney and Crump 2002). *H. pylori* has not been found in dogs and only very rarely in cats' stomachs (ElZaatari *et al*. 1997; Neiger and Simpson 2000), and it has been suggested that the presence in animals is of human origin (Cittelly *et al*. 2002; ElZaatari *et al*. 1997). Recent studies have identified *H. pylori* by PCR in the bile of cats, thus increasing the chance of this animal being a vector (Boomkens *et al*. 2004). Nearly every animal is now considered to colonize by its own endogenous *Helicobacter* spp. As *H. pylori*, that has co-evolved with humans to be highly specialized in the colonization of the human GI tract (Falush *et al*. 2003), such bacteria have specialized in colonizing their specific natural host's GI tract. In the model where mammal's stomach is colonized by only one strain. *H. pylori* would find tough competition by these other *Helicobacter* spp. in search for essential nutrients and not subsist. With the emergence of a multiple infecting strains and species model for the same host it is more credible that *H. pylori* is a zoonotic agent as well.

Diseases associated with *Helicobacters*

Helicobacter pylori are the main cause of gastric inflammation in nearly all infected subjects (Farinha and Gascoyne, 2005). Most infected people show little to no symptoms, and only a small percentage will develop severe gastric disease (Suerbaum and Josenhans, 2007; Amieva and El-Omar, 2008). The pattern and distribution of chronic gastric inflammation is associated with the type of lesions found. Individuals with body-predominant gastritis and normal or decreased acid production are more likely to develop gastric ulcers, gastric atrophy, gastric intestinal metaplasia and eventually, gastric carcinoma while individuals with antral-predominant gastritis, which is the most common form, show increase acid production and increased risk to develop duodenal ulcers (Kusters *et al.,* 2006; Lochhead and El-Omar, 2007).

The next phase of human *H. pylori* infection is regulated by changes of the epithelial cell cycle, particularly increased rates of apoptosis and cell proliferation. These alteration may be responsible for the multifocal atrophy which characterizes the type of gastritis associated with the increased risk of cancer. During this advanced phase nuclear and architectural abnormalities become apparent, which can reflect progressive mutational events as expected in classical molecular models of carcinogenesis (Correa, 2004).Inspite of hereditary and other known factors *H. pylori* infection is one of the major risk factor for developing cancer in human (Gonzalez *et al*., 2012; Wadhwa *et al*., 2013). Nearly about 1–3% of people infected with *H. pylori* develop gastric cancer. Even though only a small proportion of patients with *H. pylori* will ultimate develop malignant disease, the widespread high prevalence of this bacterium explains that gastric cancer remains the fifth most common cancer in the world (Globocan, 2012). It is also documented as the third common cause of cancer-related death in men and fifth in women (Torre *et al*., 2015; Chmiela *et al.,* 2017). In 1994 the International Agency for Research on Cancer classified *H. pylori* as a class I carcinogen on the basis of epidemiological evidences (IARC, 1994; Chmiela *et al.,* 2017). In fact, *H. pylori* infection plays a key role in the development of two different gastric malignancies: gastric adenocarcinoma and gastric MALT lymphoma (Parsonnet, 1994; Stolte *et al.,* 2002; Farinha and Gascoyne, 2005; Suerbaum and Josenhans, 2007; Patel *et al.*, 2014).

Nearly 60% of the intestinal type gastric cancer is due to *H. pylori* infection. Chronic *H. pylori* infection causes genetic instability in gastric epithelial cells and affects the DNA damage repair systems. Consequently, *H. pylori* infection should always be treated as pro-cancerous factor (Chmiela *et al.*, 2017**)**. In 1991, The association between MALT-lymphoma and *H. pylori* was firstly reported in 1991(Wotherspoon *et al.,* 1991) and it is responsible for 92 to 98% of gastric MALT-lymphomas (Mbulaiteye *et al.,* 2009) throughout the world.

The occurrence of NHPH infection in human patients is lower in comparison to *H. pylori,* but it is probably an underestimation of the real infections because NHPH screening is not frequent (Kawakubo *et al*., 2018). Until now, 5 gastric NHPH species have been reported in human patients suffering from gastric disorders. In Belgium, Germany and China, it has been revealed that *H. suis* is the most common NHPH species in human patients suffering from gastric disorders, followed by *H. salomonis, H. felis, H. heilmannii* and *H. bizzozzeronii*.(Van den Bulck *et al*., 2005**;** Liu *et al*., 2014) . Although less commonly, gastric NHPH may also able to cause disease in humans. NHPH infections in human stomach may be accompanied by acute gastritis (Lavelle *et al.,* 1994; Yoshimura *et al.,* 2002), active chronic gastritis (Haesebrouck *et al.,* 2009), erosions mainly located in the antrum (Debongnie *et al.,* 1998; Seo *et al.,* 2003) and duodenal ulcers (Jhala *et al.,* 1999; Iwanczak *et al.,* 2012). Moreover, some species (*H. mustelae, H. hepaticus* and *H. bilis*) exhibit carcinogenic potential in animals and harbor several virulence genes and may cause diseases not only in animals, but also in humans. The presence of NHPH was significantly associated with large intestinal carcinoma (68%) and mucinous adeno-carcinoma (92%) in man and animal (Swennes *et al*., 2016).Glandular atrophy and intestinal metaplasia of the fundic gastric mucosa were also reported. Still, these lesions appear to be less common and less severe than those which are associated with *H. pylori* (Yoshimura *et al.,* 2002). Infection of Human NHPH such as *H. heilmannii*, have also been associated with low-grade MALT lymphoma of the stomach as well as other type of gastric cancer and the risk of developing this disease is higher for NHPH than *H. pylori* (Haesebrouck *et al*. 2009; Joosten *et al*., 2015). They have been reported to determine after clearance of the NHPH, therefore, emphasizing a causal relationship (Morgner *et al.,* 2000; Thomas-Marques *et al.,* 2005). Many human patients infected with NHPH species are asymptomatic (Mazzucchelli *et al.,* 1993) while others have atypical complaints like acute or chronic epigastric pain and nausea, hematemesis, recurrent dyspepsia, irregular defecation frequency and consistency, vomiting, heartburn, dysphagia and loss of appetite (Dieterich *et al.,* 1998; Mention *et al.,* 1999; Kaklikkaya *et al.,* 2002; Seo *et al.,* 2003). Most human isolates are cultured rarely *in vitro*; therefore NHPHs associated with human chronic gastritis have been poorly characterized (Kawakubo *et al.,* 2018). Thus, the clinical outcome of *Helicobacter* infection is diverse and dependent on the strain, virulence characteristics, host genetic susceptibility, environmental factors and their interactions. *Helicobacter*-like organisms are often found in canine stomachs including healthy

dogs and those showing signs of gastrointestinal disease, but the relationship between such organisms and gastric pathology has not been well-known. Some of such organisms have zoonotic importance (Asl *et al*., 2010). The predominant gastric NHPH spp. found in dogs are *H. bizzozeronii*, *H. felis* and *H. heilmannii (s.s.),* whereas *H. salomonis* has not often been detected. *H. cynogastricus* was recently isolated from the stomach of a dog (Haesebrouck et al., 2009). *Helicobacter canis* has been associated with hepatobiliary and gastrointestinal disease in dogs, cats and humans (Hristova *et al*., 2017). Though less frequent, the role of *H. canis* in the etiology of gastric cancer was also observed where in a recent Norwegian survey, canine GC accounts for 0.16% of all reported canine cancer cases (Seim-Wikse *et al*., 2013). Similarly, *Helicobacter suis* mainly colonizes from the porcine stomach and seems to be the most important among the NHPH. It is mostly associated with gastric pathologies in animals (Haesebrouck *et al*., 2009) and also the most commonly detected NHPH species in humans (De Groote *et al*., 2005; Van den Bulck *et al*., 2005; Liu *et al*., 2014) where it may cause gastritis, peptic ulcer disease and gastric mucosa-associated lymphoid tissue (MALT) lymphoma (Flahou *et al*., 2012; Matsui *et al*., 2014). Infections with this bacterium have also been associated with decreased daily weight gain in pigs from 5 to 10 % (Haesebrouck *et al*., 2009; Kumar *et al*., 2010). Pigs are the main reservoir of *H. suis* (De Bruyne *et al*., 2012) Therefore, this organism has also been found in the stomach of rhesus and crab-eating macaques (Bosschem *et al*., 2016). In human, histologic analysis of biopsies from a patient with asymptomatic nodular gastritis also discovered the presence of spiral-shaped bacteria in the gastric mucosa, indicative for a NHPH infection. Besides this, it has also been detected in 27% of patients with Parkinson's disease (Blaecher *et al*., 2013 and 2017). Likewise, the presence of co-infections in human patients and an increased prevalence of peptic ulceration during co-infection have been reported **(**Liu *et al*., 2014; Overby *et al*., 2017).

H. pullorum infection has been linked to vibrionic hepatitis and enteritis in chickens (Stanely *et al*., 1994). It is also associated with gastroenteritis and hepatobiliary disease in humans (Ceelen *et al*., 2006; Turk *et al*., 2012**)**. Moreover, *H. pullorum* has been detected in humans with gastroenteritis, women suffering from chronic cholecystitis and a patients suffering from cirrhosis and/or hepato-cellular carcinoma. The species reportedly has also been isolated from a diarrheic psittacine bird, suggesting that pet birds may be a zoonotic risk for humans (Ceelan *et al*., 2006; Turk *et al*., 2012**)**.

Diagnosis

For clinical purposes, several methods can be used to diagnose *Helicobacter* infection, which are divided into two main methods that is invasive and non-invasive methods which are based on the use of endoscopy (Kamboj *et al*., 2017). Histopathology, culture and rapid urease test (RUT) which is widely available and employed worldwide are considered as the invasive tests. Fecal antigen test, urea breathe test (UBT) and serology are known as the non-invasive tests (Guarner *et al.,* 2010; McColl *et al.,* 2010).

Invasive tests

Invasive methods are endoscopic biopsy based procedures and include brush cytology, urease test, histological examination, electron microscopy, culture, the polymerase chain reaction techniques (PCR). There has been a suggestion that some factors capable of affecting the performance of all biopsy-based tests, such as site, number and dimension of biopsies or a previous eradication attempt, which can significantly decrease the diagnostic accuracy. Culture methods have the advantages of allowing antimicrobial susceptibility testing and detailed characterization of the cultured organism. However, the culture of *H. pylori* from gastric biopsy specimen is the gold standard methods for diagnosis of infection, the culture of this bacterium typically take 3-5 days and hence are very slow. Endoscopy samples can also be assessed by histological methods. *H. pylori* can be visualized with hematoxylin and eosin (H&E) staining of tissue sections. There is a possibility of false identification with this stain. Hence, a sensitive staining technique consisting of a combination of H&E staining, Steiner silver staining and alcian blue staining is used for more accurate results (Genta *et al.,* 1994). Another application of endoscopy samples is in the tissue urease tests. However, these tests are dependent on the bacterial load in the stomach. Biopsy samples obtained by endoscopy can also be used for PCR analysis.

Non-invasive tests

As the invasive procedure are expensive, unpleasant to patients and carries a small but definite risk of complications the non-endoscopic tests to assess *Helicobacters* infection have been welcomed. The more widely available non-invasive procedures for diagnosing *Helicobacters* infection are the urea breath test, serological assays and detection of bacteria, as well as bacterial DNA and antigens in stool. A recently developed stool assay has been shown to be a reliable diagnostic tool and is becoming increasingly available and employed.

Unani approach for the treatment of *Helicobacter*

WHO has classified *Helicobacter pylori* as a class I carcinogen and the eradication of this silent killer with antibiotics (triple therapy) combinations has been reported to be beneficial in preventing gastric ailments especially cancer (IARC, 1994). However, increasing dilemma of antibiotic resistance, adverse effects and high costing has lead researchers to explore natural resources especially plant materials as an alternative source of antimicrobials.

Unani physicians listed a broad range of care for this disease based on the causes, clinical presentations, locations, environments, age, acuteness or chronicity, and dietary habits with primary concern for the correction of patients' Mizaj (temperament) and Akhlat (humours).

In Unani,medicinal plants, animals as well as drugs of mineral origin are being used for the treatment of chronic gastritis which is mainly due to *H. pylori* without any repoted side effects e.g some of widely used single drugs (adviya mufrida) are *Aloe barbedensis* Mill *(Elva), Alpinia galangal* Willd (khulanjan)*, Althaea rosea* Linn (khatami), *Anchusa strigosa* Labill (Gaozaban), *Glycyrrhiza glabra* Linn (Asl-us-soos), *Withania somnifera* Linn (Asgandh), *Andrographis paniculata* Wall (Bhuineem), *Zingiber officinale* Rosc (Adrak), *Picrorhiza kurroa Royle* (Kutki), *Emblica officinale* (Amla), *Nigella sativa* Linn (kalonji), *Momordica charantia* Linn (Karela), *Curcuma longa* Linn (Haldi), *Asparagus racemosus* Willd (satawar), *Aegle marmelos* Correa (Bael), *Myristica fragrans* Houtt (jaiphal) etc and in the form of compound drugs (Adviya murakkaba) are Majoon Dabidul Ward, Jawarish Anarain, Sharbat Anar, Majoon Zanjbil,

Jawarish Mastagi, Qurs Satawari, Itrifal Aftimoon, Sharbat Unnab and Khameera Sandal have been indicated by Unani physicians for the treatment of chronic gastritis(*H. pylori*) and their efficacy against gastritis has also been tested by in vivo and in viro studies.(Aziz ., Jurjani., al., Qurrah., Marwan., Mohd *et al*., 2011). Those drugs mode of action is both systemic and local. Such medicines, apart from the correction of altered mizaj (temperament), have a claiming effect on the inflamed mucosa, provide ground material for healing, eliminate inflammatory factors and also have antiseptic or antibacterial impact. Inspite of that physicians have recommended different seasons, regions and mizaj. Some researchers demonstrate the effect of Unani compound drug containing " *Glycyrrhiza glabra* (*Asl-us-soos), Plantago ovate* (*Aspghol musallam*), *Acacia arabica* (*samagh -arabi*) and *Pistacia lenticus* (*Mastagi*)" for the treatment of gastric anomalies and eradicating *H.pylori* bacteria from the stomach (Rahida *et al*.,2017). *Asl-us-soos* (*Glycirrhiza glabra*)/ *licorice* reduces stomach secretion and produces thick mucus that protects the lining of stomach from inflammation, gastritis and peptic ulceration, it contains flavonoids, therefore an anti-inflammatory and anti-bacterial effect(Khare *et al*.,2004; Kakka *et al*.,1998) *Mastagi* (*Pistacia lenticus*) is cytoprotective and has a moderate anti-secretory effect and beneficial for gastric and duodenal ulcer healing.(Said *et al*.,1986; Huwez *et al*.,1986; Al-Habbal *et al*.,1984). *Samagh-e-arabi(Acacia arabica*) contains tannins, saponins, glycosides, phenols terpenoids and flavonoids that can be easily hydrolyzed, this property of *samagh-arabi* has anti-bacterial and anti-inflammatory attributes.(Sultana *et al*., 2007). It has been reported that licorice extract showed potent eradicative effect against *H. pylori* strain (Kakka *et al*., 1998; Krausse *et al*., 2004; Marjan *et al*., 2013). Other researchers found anti *H. pylori* activity of *Plantago* ovate (Nabati *et al*., 2012). Furthermore Omayma K.H. and M. Amin *et al* conducted in vitro studies and found anti-bacterial and anti-*H. Pylori* activity of *acacia arabica*.(Nabati *et al*., 2012; Omayma *et al*; 2011) *Mastagi* showed anti- *H. Pylori* effect not only in vitro but in clinical trial as well.(Ghani *et al*., 2005; Farhad *et al*.,1998). In 1999 ,Gharzouli K *et al* found gastro-protective effect of tannic acid and the aqueous extract of from *Quercus ilex* L. root bark, *Punica granatum* L. fruit peel and *Artemisia herba-alba* Asso leaves in rats against ethanol-induced gastric damage and suggested that monomeric and polymeric polyphenols can strengthen the gastric mucosal barrier.(Gharzouli *et al*., 1999) On the other hand, In 2005 Ajai Kumar K.B., *et al* conducted in vivo research on the inhibition of gastric mucosal injury by *Punica granatum* methanolic extract and they revealed the gastroprotective effect of the extract through antioxidant mechanism.(Ajai *et al*., 2005) Additionally Jamal et al suggested that *Tabasheer* and other unani mufrad advia/ single drugs are safe and cost effective in gastric ulceration. (Jamal *et al*, 2006) In 2010, an experimental study conducted on Anti-ulcer effect of hydroalcoholic extract of *Tukhme Kishneez (Coriandrum sativum* Linn.) in stress induced gastric ulceration in albino rats with Ranitidine as the standard drug and demonstrated that *Tukhm Kishneez* possesses anti-ulcer effect against stress induced gastric ulcer.(Shagufta *et al*., 2010)Nearly, all Unani physicians have contributed to awareness on the health and disease of Meda/stomach.

Conclusion

This review concluded that *Helicobacter* infection affects more than 50% population world widely. The infection of *Helicobacteriosis* is mostly asymptomatic which make the infection chronic due to which diagnosis become too difficult. Helicobacter having a zoonotic potentials also and having various other species such as *H.canis*, *H.suis*, *H. pullorum* which are transmitted from animals and foods of animal origin (meat and milk).In this era, in where antibiotic resistance is more, we can overcome this situation with the help of Unani drugs.

Conflict of Interest

The authors declared no conflict of Interest

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