Journal of Applied Biomedicine xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Journal of Applied Biomedicine

journal homepage: www.elsevier.com/locate/jab

Review article

Propolis: The future therapy against *Helicobacter pylori*-mediated gastrointestinal diseases

Ummay Mahfuza Shapla[a], Md. Jinat Raihan[a], Md. Asiful Islam[b], Fahmida Alam[b], Md. Solayman[a,c], Siew Hua Gan[b], Md. Sakib Hossen[a,c], Md. Ibrahim Khalil[a,b,*]

[a] *Jahangirnagar University, Department of Biochemistry and Molecular Biology, Laboratory of Preventive and Integrative Biomedicine, Savar, Dhaka, Bangladesh*
[b] *Universiti Sains Malaysia, School of Medical Sciences, Human Genome Centre, Kubang Kerian, Kelantan, Malaysia*
[c] *Primeasia University, Department of Biochemistry, Banani, Dhaka, Bangladesh*

ARTICLE INFO

Article history:
Received 3 November 2016
Received in revised form 10 August 2017
Accepted 16 October 2017
Available online xxx

Keywords:
H. pylori
Propolis
Natural products
Gastrointestinal diseases
Microbial infections

ABSTRACT

Helicobacter pylori (H. pylori), which is found in the stomach of approximately 50% of humans, remains there for almost the entire lifetime of the infected individual, leading to various gastrointestinal tract-associated disorders following full-blown infection. Due to the emergence of antibiotic resistance, recurrence and high cost of therapy, most antibiotic-based treatment strategies are not very effective in eradicating *H. pylori* infections. The quest for an alternative treatment free of these inconveniences is currently in demand. One of the important alternatives is propolis, produced by the honeybee *Apis mellifera,* which has been used to treat different diseases since it possesses a wide range of biochemical properties. Propolis has been reported as a useful therapeutic regimen against *H. pylori,* which is an important cause of gastric inflammation, peptic ulcer, gastric cancer, and lymphomas of mucosa-associated lymphoid tissues. Apart from propolis, various active compounds of other natural products have also been confirmed to be effective. This review compiles the scientific evidence of the role of propolis and other natural products against *H. pylori*-associated gastrointestinal tract-related health complexities by acing as an anti-angiogenic, anti-inflammatory, and antioxidant factor as well as via modulation of enzymatic activities.

Introduction

Approximately 50% of the world population is infected by *Helicobacter pylori* (*H. pylori),* a microaerophilic bacterium (Higashi et al., 2002). It was the first bacterium classified as a group I carcinogen in the report of the International Agency for Research on Cancer (IARC, 1994) based on epidemiologic evidence (Correa and Houghton, 2007; Covacci et al., 1999; Møller et al., 1995; Westblom et al., 1999). *H. pylori* is a unique bacterium because of its ability to colonize the human stomach, where it develops a long-term parasitic relationship (Blaser and Atherton, 2004). Apart from the presence of various virulent factors, its survival mechanisms are the modification of host immune systems such as persistent signalling by IL (interleukin-1β), IL-8, and other cytokines to epithelial cells, as well as infiltration of macrophages, neutrophils and lymphocytes, acid homeostasis by acid-producing parietal cells and somatostatin-producing delta cells (Beales and Calam, 1998; Mekori and Metcalfe, 2000; Peek et al., 1995; Supajatura et al., 2002). It has also high mutation and recombination rates as well as compatibility to DNA uptake from other strains (Falush et al., 2001; Suerbaum et al., 1998). Due to its ability to cause a chronic immune response and cellular proliferative-apoptotic homeostasis, *H. pylori* causes a variety of diseases. The prevalence of *H. pylori* infection ranges from 11% in Sweden to 83.4% in China (Thung et al., 2016). Acute infection caused by *H. pylori* has been rarely diagnosed. The individuals in which *H. pylori* persistently colonize, develop different types of chronic gastritis, such as antral predominant gastritis, non-atrophic pangastritis and corpus predominant atrophic gastritis/multifocal atrophic gastritis, and 90% of cases are asymptomatic. Chronic infection may lead to gastric ulceration (0.05%), duodenal ulceration (0.3%), intestinal metaplasia (0.2%), gastric cancer (0.01%), and mucosa-associated lymphoid tissue (MALT) lymphoma (Blaser and Atherton, 2004;

* Corresponding author at: Jahangirnagar University, Department of Biochemistry and Molecular Biology, Laboratory of Preventive and Integrative Biomedicine, Savar, Dhaka 1342, Bangladesh.
E-mail address: drmikhalil@gmail.com (M. I. Khalil).

https://doi.org/10.1016/j.jab.2017.10.007
1214-021X/

Conteduca et al., 2013; Correa and Houghton, 2007). *H. pylori* infections occur worldwide and studies have shown that low socioeconomic status is associated with high risk. To overcome *H. pylori* infection, several treatment strategies, including the use of antibiotics and anti-secretory agents like proton pump inhibitors, triple, quadruple, bismuth-based triple, and ranitidine bismuth citrate combination therapy, have failed to completely eradicate *H. pylori* infection, with a mean eradication rate of 65–92% due to the antimicrobial resistance of the bacteria. In addition, the use of these therapeutic methods has undesirable side effects (Beek and De Craen, 1999; Duck et al., 2004). Therefore, an effective treatment regimen for *H. Pylori* is a major clinical concern. Recently, there has been considerable interest in the use of non-antibiotic agents, such as natural products, that are effective and free from side effects.

Natural products have been traditionally used for centuries in the treatment of a wide range of ailments, including gastrointestinal disorders such as dyspepsia, gastritis and peptic ulcer (Borrelli and Izzo, 2000; Thompson Coon and Ernst, 2002). Important constituents, such as different types of polyphenols, phenolic esters, steroid glycosides, and organosulfur compounds, of natural products have the ability to combat *H. pylori*-associated diseases. A unique natural product named propolis (a resinous hive product collected by honey bees from living plants) contains different chemical compounds. Among these compounds are caffeic acid phenethyl ester (CAPE), artepillin C, quercetin, hesperidin, galangin, kaempferide, aromadendrine 4-methyl-ester, 3-prenyl-p coumaric acid, methyl caffeate, phenylethyl caffeate and phenylethyl dimethyl caffeate. These compounds have antibacterial, antifungal, antiviral (Kujumgiev et al., 1999), anti-protozoan (Higashi and De Castro, 1994), and antioxidant (Kanbur et al., 2009) activities. Several studies have also shown that propolis has anti-inflammatory (Borrelli et al., 2002) and anti-tumour (Oršolić and Bašić, 2003) effects. In an *in vitro* study by Banskota et al. (2001) and Boyanova et al. (2003, 2005), it was revealed that propolis had many promising activities against various *H. pylori* strains. In addition to propolis, the common natural products with potent anti-*H. pylori* effects include garlic, ginger, turmeric, citrus fruits, bael, apple, cranberry, broccoli, green tea, celery, potato, virgin olive oil, liquorice, black pepper, sea almond, walnut, pear and many others. They exert their activity via different mechanisms, such as by inhibiting bacterial adhesion and enzymes (urease), neutralizing bacterial toxins, suppressing *H. pylori*-induced pathogenic signal transduction pathways at the transcriptional level, modulating the action of the host's immune repertoire and by direct bacteriocidal as well as cytoprotective action (Bonifácio et al., 2014). The aim of this review is to summarize and shed light on the biomedical applications of propolis and other natural products against *H. pylori*-associated gastrointestinal tract ailments.

Mechanisms of *H. pylori*-induced gastrointestinal tract diseases

The pathogenic strains of *H. pylori* have an extraordinary capability to survive and develop pathologic manifestations in the most hostile environment of the human stomach. It can survive under strong selective pressure due to the presence of special cagA pathogenicity islands, vacuolating toxin A (VacA toxin), the bacterial IV secretion system and other virulent factors encoded by the OipA, HopQ, HopZ (*Helicobacter* outer membrane proinflammatory proteins), IceA (induced by contact with epithelium), and dupA (duodenal ulcer producing) genes (Cover et al., 1990; Kim, 2016; Odenbreit et al., 2000; Wessler, 2016; Yamaoka et al., 2000). Persistent *H. pylori* infection in the stomach causes chronic gastritis, which eventually leads to peptic ulcers, gastric cell carcinoma and MALT lymphoma, as determined by the severity of infection and degree of inflammation (Blaser and Atherton, 2004; Naito and Yoshikawa, 2002). On the basis of the presence or absence of cag pathogenicity islands (a genomic fragment of 40 kb length housing 31 genes), *H. pylori* can be divided into cagPAI positive (more virulent than the latter) and cagPAI negative strains (Tomb et al., 1997). CagPAI encodes the antigenic effector protein CagA and 18 genes required to insert CagA through the bacterial IV secretion system into gastric epithelial cells involved in the development of different pathological conditions (Peek and Blaser, 2002; Viala et al., 2004).

H. pylori-*associated gastric inflammation*

H. pylori may cause gastric inflammation by two pathways. First, it inhabits the area under the mucosa layer in close proximity to gastric epithelial cells. It interacts with epithelial cells via its different surface components and causes cellular damage. Second, it inserts different virulent factors into epithelial cells. Both mechanisms trigger specific and nonspecific immune responses along with the secretion of a vast array of immunologic messenger molecules known as cytokines (Bodger and Crabtree, 1998). A number of proinflammatory chemokines orchestrate their functions in *H. pylori*-mediated gastritis: growth related oncogene alpha (Gro-α), a monokine induced by IFN-c (CXCL11), IFN-c inducible protein-10 (CXCL-10), regulated on activation normal T cell expressed and secreted (RANTES), CCL20 (MIP-3a/LARC/exodus), and IL-8 (Eck et al., 2000; Wen et al., 2004; Wu et al., 2007; Yamaoka et al., 1998). *H. pylori* inserts peptidoglycan into gastric epithelial cells through the bacterial IV secretion system encoded by cagPAI, which upregulates the expression of IL-8 by stimulating intracellular pathogen recognition receptor Nod1 and thus activating NFκB (nuclear factor kappa B) and AP-1 (activator protein-1) (Allison et al., 2009; Viala et al., 2004). IL-8 is a potent chemoattractant and activator of neutrophils (Hommes et al., 1992). *H. pylori* activates monocytes and macrophages (resident of lamia propia) through lipopolysaccharide (LPS)-dependent and independent pathways. It also increases the expression of HLA-DR (human leukocyte antigen), IL-2R (interleukin 2 receptor), surface receptors, increased synthesis of IL-1, TNF (tumour necrosis factor) mRNA, different peptides, and ROS (reactive oxygen species) (Mai et al., 1991). IL-1β is a potent inhibitor of the proton pump inducer and recruiter of IL-8 and neutrophils (Dinarello, 1984; March et al., 1985; Noach et al., 1994; Yoshimura et al., 1987). In addition, the neutrophil activating protein of *H. pylori* (HP-NAP) gains entrance into the lamina propria and stimulates the synthesis of chemokines, such as CXCL8, CCL3 and CCL4, to recruit leukocytes at the site of infection (Polenghi et al., 2007). Recruited mast cells are also stimulated in this way by HP-NAP to degranulate different inflammatory molecules (Montemurro et al., 2002). The infiltrating neutrophils significantly damage mucosal cells (Suzuki et al., 1992). Neutrophils secrete different ROS, such as singlet oxygen, superoxide anion, hydroxyl radical, hydrogen peroxide, and hypochlorous, and hence exert oxidative stress on the surrounding tissues and cause damage (Kehrer, 2008). Myeloperoxidase reacts with different ROS that produce hypochlorous acid; then, it reacts with ammonium (produced by urease from *H. pylori*) and forms monochloroamines that cause DNA fragmentation (Bhattacharjee et al., 2002; Mizuki et al., 2000; Roe et al., 2002). It has been reported that VacA, γ-glutamyltranspeptidase and cholesteryl α-glucosides of *H. pylori* cause Th1, Th17 and Treg–subpopulations of T-lymphocytes to come into play, which intensify the chronicity of inflammation (Beigier-Bompadre et al., 2011).

Peptic ulcers caused by H. pylori

Peptic ulcers consist of gastric ulcers (accounting for one-third of peptic ulcers) and duodenal ulcers (accounting for the rest)

Please cite this article in press as: U.M. Shapla, et al., Propolis: The future therapy against *Helicobacter pylori*-mediated gastrointestinal diseases, J. Appl. Biomed. (2017), https://doi.org/10.1016/j.jab.2017.10.007