REVIEW

Pharmacological ins and outs of medicinal plants against *Helicobacter pylori*: A review

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Abstract: Since *Helicobacter pylori* was discovered in 1980, it has been considered as a major cause in the pathogenesis of gastric ulcer, mucosa-associated lymphoid tissue (MALT) lymphomas, and gastric cancer. Eventually antibiotics were designed to eradicate this bacterium, which not only prevent peptic ulcer recurrence but also decrease the chances of developing gastric cancer. Propitious consequences of these antibiotic regimens and better hygienic conditions, particularly in developed countries, resulted in significant decline in the prevalence of *H. pylori* infection. However, persistent high *H. pylori* infection in developing countries, decreased patience compliance and emerging antibiotic resistance forced researchers to quest for novel candidates. Herbal medicines have always served as a leading source in drug discovery. Since time immemorial, herbs have been used to treat various disorders covering from minor illnesses as pain to life threatening conditions like cancer. Ample amount of studies from different parts of the world have shown promising activities of medicinal herbs not only against *H. pylori* but also associated disorders while employing *in vitro*, *in vivo* and clinical studies. In this review, these multiple pharmacological effects of medicinal plants and their chemical constituents will be discussed in relation to *H. pylori* not only to scientifically evaluate the beneficial effects of these medicinal plants but to also critically analyze their plausible role as chemo preventive agents against *H. pylori*-associated disorders

Keywords: Medicinal plants; anti-*Helicobacter pylori* activity; anti-inflammatory activity; gastric cancer; peptic ulcer.

INTRODUCTION

Around 50% of the world's human population is infected with *Helicobacter pylori*, a class I carcinogen (Suerbaum and Michetti, 2002). Developing countries have been reported to possess higher rate of infections compared to developed countries (Marshal and Gilman, 1999; Muhammad *et al.,* 2012). The intimate correlation of *H. pylori* infection with duodenal or gastric ulcer and gastric carcinoma has been thoroughly investigated (Muhammad *et al.,* 2013). Eradication of *H. pylori* results in healing of gastric ulcer and may also reduce the incidence of gastric carcinoma (Sepulveda and Coelho, 2002).

Various drug regimens have been used for the eradication of *H. pylori* such as triple or quadruple drug therapy (Hentschel *et al.,* 1993). However, alarming increase in the resistance to antibiotics, high cost of combination therapy and undesirable side effects resulted in an emerging surge in alternative approaches such as anti-oxidants, anti-inflammatory agents, probiotics, herbal extracts and phytoceuticals (Lind *et al.,* 1999; Sherif *et al.,* 2004; O'Gara *et al.,* 2000; Lee *et al.,* 2008).

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As prolong interaction of *H. pylori* with gastric mucosa results in release of inflammatory cytokines and reactive oxygen species (ROS) leading to atrophy of the gastric glands and carcinogenic changes like dysplasia and metaplasia (Holian *et al.,* 2002), alternative approaches might modulate these key pathogenic pathways simultaneously to halt and prevent *H. pylori* associated disorders. Extracts from medicinal plants has shown multiple activities against *H. pylori* and associated pathogenesis such as bactericidal, anti-inflammatory, anti-oxidant, anti-adhesion and anti-mitogenic activities.

In this review, we will discuss these potential effects of medicinal plants on the scientific basis and examine underlying molecular mechanisms behind their beneficial and modulatory effects against *H. pylori* related pathogenic sequel.

Molecular mechanism of the herbs against Helicobacter pylori

As mentioned above, several pathogenic pathways can be modulated by medicinal plants but generally most of these effects can be divided into two major categories:

Anti-bacterial activity

Bactericidal or antibacterial activity is one of the most extensively evaluated effects of medicinal herbs or spices against *H. pylori*. Geographically distinct medicinal plants were evaluated in several studies from all around the globe which are summarized in table 1.

From Korea

First study of screening medicinal plants against *H. pylori* was published by Korean researchers who screened several medicinal plants against *H. pylori* and found extracts of *Eugenia caryophyllata* (flower), *Coptidis japonica* (rhizoma), *Magnolia officinalis* (cortex), *Rheum palmatum* (rhizoma) and *Rhus javanica* (galla rhois) had bacteriostatic effect on *H. pylori*. On further isolation of active constituents, the effects of decursinol angelate and decursin on bacterial inhibition were the most potent with minimum inhibitory concentrations (MICs) values of 6-20 mg/ml (Bae *et al.,* 1998).

From Turkey

Yesilada *et al* from Turkey screened seven medicinal plants, against nine *H. pylori* strains, which are used in the traditional medicine for the treatment of gastric ailments and found six of them with anti-*H. pylori* activity. Among the six plants, the bacterial inhibitory properties of *Cistus laurifolius* were found prominent (Yesilda *et al.,* 1999).

From Iran

A study from Iran evaluated anti-*H. pylori* activity of six native plants and found *Trachyspermum copticum* and *Xanthium brasilicum* to be most active extracts with MIC value range of 31.25-250 mg/ml (Nariman *et al.,* 2004).

From Japan

Shin *et al* from Japan reported anti-*H. pylori* activity of wasabi (*Wasabia japonica*) and demonstrated higher bactericidal activity of leaves than root of wasabi (Shin *et al.,* 2004).

From China

Chinese conducted the antibacterial action of thirty herbal medicines, which have been frequently used since ancient times for the treatment of gastritis-like disorders (Li *et al.,* 2005). Among those thirty tested Chinese herbs, the ethanol extracts of *Saussurea lappa* (Asteraceae), *Abrus cantoniensis* (Fabaceae) and *Eugenia caryophyllata* (Myrtaceae) had the most strongly bacteriostatic effect (MICs: approximately 40 mg/ml).

From Malaysia

A study from Malaysia employed culinary spices and plants to evaluate anti-*H. pylori* activity and demonstrated bactericidal activities by turmeric, ginger, cumin, black caraway, chilli, borage, oregano and liquorice (O'Mahony *et al.,* 2005).

From Taiwan

Researchers from Taiwan conducted a large scale study and employed fifty medicinal plants against *H. pylori*. While half of the employed plants showed bactericidal activity, five plants namely *Anisomeles indica* (L.) O. Kuntze, *Bombax malabaricum* DC., *Paederia scandens* (Lour.) Merr., *Plumbago zeylanica* L., and *Alpinia speciosa* (J. C. Wendl.) K. Schum demonstrated strong anti-*H. pylori* activities (MIC: 0.64-10.24 mg/ml) (Wang and Huang, 2005).

From Cameron

Ndip *et al* screened ten medicinal plants from Cameron against 15 clinical isolates by disk diffusion method and determine MIC and minimum bactericidal concentration (MBC) values. All the tested plants showed anti-*H.pylori* activity with inhibition zone diameters of 0-30 mm. Out of these, *Ageratum conyzoides*, *Scleria striatinux* and *Lycopodium cernua* showed potent anti-*H. pylori* activity with the lowest MIC and MBC of 0.032 mg/mL and 0.098 mg/mL respectively (Ndip *et al.,* 2007).

From Pakistan

We have conducted a study of fifty medicinal plants including twenty-five spices that are commonly prescribed for the treatment of gastrointestinal disorders in Unani medical practice in Pakistan (Zaidi *et al.,* 2009a). MBC values determined were at the concentration range of 7.8 to 500 μg/ml using seven *H. pylori* clinical isolates and one ATCC reference *H. pylori* strain (ATCC 43504). It was interesting to note that >50% of herbs at the concentration of 500 μg/ml inhibited the growth of all *H. pylori* strains. Extracts of *Mallotus phillipinesis* (Lam) Muell., *Curcuma amada* Roxb., *Psoralea corylifolia* L. and *Myrisctica fragrans* Houtt showed strong anti-*H. pylori* activity (MBC: 15.6-62.5 μg/ml). The most potent extract (*Mallotus phillipinesis* (Lam) Muell) was further evaluated for active constituents and found rottlerin to possess strong MBC value range of 3.12-6.25 μg/ml even against geographically distinct Japanese strains and antibiotic resistant strains (Zaidi *et al.,* 2009b).

From South Africa

Njume *et al* employed five South African plants against thirty strains of *H. pylori* along with a reference strain (NCTC 11638). According to their results, all the plant extracts showed anti-*H. pylori* activity with inhibition zone diameters of 0 to 38 mm and 50% MIC (MIC50) values ranging from 0.06-5.0 mg/ml. Interestingly, *Combretum molle* and *Sclerocarya birrea* acetone extracts revealed extraordinary anti-*H. pylori* activity killing >50% of the strains within 18 hours at 4 times the MIC and their anti-*H. pylori* activity was comparable with Metronidazole and amoxicillin (Njume *et al.,* 2011). Manyi-Loh *et al* evaluated the anti-*H. pylori* activity of six varieties of South African honeys at different concentrations by the Hole Plate diffusion method. All the honey varieties as well as their solvent extracts

demonstrated varying levels of antibacterial activity, the most potent bactericidal effect against the test isolates was obtained with chloroform extract of pure honey (Manyi-Loh *et al.*, 2013).

From Mexico

A study from Northwestern part of Mexico evaluated the anti-*H. pylori* activity of seventeen plant extracts prescribed mainly in the northwestern part of Mexico (Sonora) for the empirical treatment of gastrointestinal disorders. Among the plant extracts *Amphipterygium adstringens, Ambrosia confertiflora, Couterea latiflora, Castella tortuosa, Ibervillea sonorae, Krameria erecta, Marrubium vulgare, Pscalium decompositum, Pimpinella anisum and Selaginella lepidophylla* exhibited 50% MIC of less than 200 to 400 µg/mL (Robles-Zepeda *et al.*, 2011). This study not only provides potential candidates for future drug discovery but also justify the clinical use of these plants in gastrointestinal disorders related to *H. pylori*.

The above-mentioned *in vitro* studies have presented strong anti-bacterial activities of medicinal plants and some of them have compared the activity with current conventional antibiotics against *H. pylori*. These promising *in vitro* results prompted researchers to validate these results in *in vivo* and clinical settings. Few studies have demonstrated *in vivo* evidence of medicinal plants against *H. pylori*. Paraschos *et al* has reported the effect of mastic gum extract in reducing *H. pylori* colonization in *H. pylori* SS1-infected mice and posed that the major triterpenic acids in the acid extract may be responsible for such an activity (Paraschos *et al.*, 2007).

Curcumin has also been documented to eradicate *H. pylori* in C57BL/6 infected mice and in reducing the gastric damage (De *et al.*, 2009). Some clinical trials of medicinal plants have also been conducted to evaluate the eradication of *H. pylori* but seem to reveal some arguable data when compared to *in vitro* and *in vivo* studies. A curcumin-based one-week triple therapy was designed to evaluate the potential of curcumin in the eradication of *H. pylori* but the results demonstrated eradication in only 3 out of 25 patients (Mario *et al.*, 2007). Another clinical study by Graham *et al* employed garlic and jalapeños peppers to examine the inhibitory effect against *H. pylori* in humans. Data revealed from twelve patients indicate that neither garlic nor peppers had any effect on *H. pylori* in clinical settings (Graham *et al.*, 1999). Number of *in vivo* and clinical studies are quite few with less number of tested groups, which demands for large scale studies specially randomized double blind trials.

Anti-inflammatory activity

The attractiveness of phytoceuticals is in their multiple modes of actions in combating any disease. This useful element of nature was verified by several scientists via evaluating anti-inflammatory potential of medicinal plants against *H. pylori*-associated pathogenic processes. The term anti-inflammatory activity refers to wide variety of pharmacological actions, which ultimately inhibit the pathways leading to inflammation. This infers that medicinal plants not only possess direct bactericidal activity but also module various pathogenic pathways induced by *H. pylori* (fig. 1).

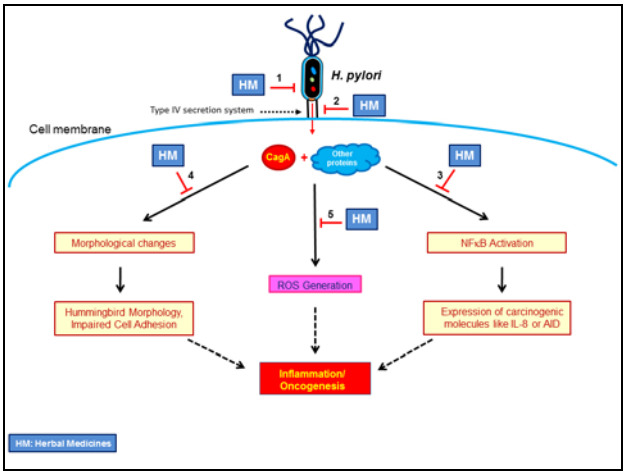

Fig. 1: Diverse mechanism of actions of medicinal plants against *H. pylori* associated pathogenesis. 1: Anti-bacterial activity, 2: Anti-adhesion activity, 3: Inhibition of inflammatory molecules expression, 4: Inhibition of hummingbird morphology or motogenic response, 5: Inhibition of ROS or oxidative stress. (CagA: Cytotoxin associated gene-A, NFkB: Nuclear factor kappa B, IL-8: Interleukin-8, AID: Activation-induced cytidine deaminase, ROS: Reactive oxygen species).

From bench to bedside, various studies have demonstrated the beneficial role of medicinal plants or spices in alleviating *H. pylori*-induced inflammatory/carcinogenic molecules like nuclear factor kappa B (NFκB), interleukin-8 (IL-8), tumor necrosis factor-alpha (TNF-a), and ROS. One of the extensively investigated herb or spice in this regard is turmeric or its active constituent, curcumin. Foryst-Ludwig *et al* documented that *H. pylori*-induced NFκB activation and the subsequent release of IL-8 are inhibited by curcumin (80 µM), a yellow pigment in turmeric (*Curcuma longa* L.) (Foryst-Ludwig *et al.*, 2004). They further showed that *H. pylori*-induced motogenic response was also blocked by curcumin. Later, we demonstrated that curcumin (at very low concentration of 10 µM) not only blocked NFκB activation but also suppressed the subsequent anomalous over expression of activation-induced cytidine deaminase (AID), an enzyme highly linked with the pathogenesis of *H. pylori*-induced gastric carcinogenesis (Zaidi *et al.*, 2009c). A group from Thailand later conducted *in vivo* study of curcumin in Sprague-Dawley rats and exhibited that *H. pylori* induced gastric inflammation is associated with increased activation of NFκB leading macromolecular leakage which can be reduced by supplementation of curcumin in

Table 1: Anti-*H. pylori* activity of various phytomedicine-based studies from different parts of the world.

Location	Method	Number herbs	Most Active herbs	Reference published
Korea	MIC	Five	*Coptidis japonica, Eugenia caryophyllata, Rheum palmatum, Magnolia officinalis, Rhus javanica*	Bae *et al* (1998)
Turkey	MIC	Seven	*Cistus laurifolius*	Yesilada *et al* (1999)
Iran	MIC	Six	*Trachyspermum copticum* and *Xanthium brasilicum*	Nariman *et al* (2004)
Japan	MBC	One	*Wasabia japonica*	Shin *et al* (2004)
China	MIC	Thirty	*Abrus cantoniensis, Saussurea lappa, Eugenia caryophyllata*	Li *et al* (2005)
Malaysia	MBC	Twenty five	*Curcuma longa, Cuminum cyminum, Zingiber officinale, Capsicum anunum, Borago officinalis, Nigella sativa, Origanum vulgare, Glycyrrhiza glabra apofosa*	O′ Mahony *et al* (2005)
Taiwan	MIC	Fifty	*Paederia scandens, Plumbago zeylanica, Anisomeles indica, Bombax malabaricum, Alpinia speciosa*	Wang *et al* (2005)
Cameron	MIC, MBC	Ten	*Ageratum conyzoides, Scleria striatinux, Lycopodium cernua*	Ndip *et al* (2007)
Pakistan	MBC	Fifty	*Curcuma amada, Mallotus phillipinesis, Myrisctica fragrans, Psoralea corylifolia*	Zaidi *et al* (2009)
South Africa	MIC	Five	*Combretum molle, Sclerocarya birrea, Garcinia kola, Alepidea amatymbica and a single Strychnos species*	*Njume et al (2011)*
Mexico	MIC	Seventeen	*Castella tortuosa, Amphipterygium adstringens, Ibervillea sonorae, Pscalium decompositum, Krameria erecta, Selaginella lepidophylla, Pimpinella anisum, Marrubium vulgare, Ambrosia confertiflora, Couterea latiflora*	*Robles-Zepeda et al (2011)*

MIC: Minimum inhibitory concentration; MBC: Minimum bactericidal concentration

rats diet (Sintara *et al.,* 2010). A clinical study has also demonstrated that curcumin based triple therapy significantly improved dyspeptic symptoms and reduced serologic signs of gastric inflammation even 2 months after the therapy (Mario *et al.,* 2007). These studies overall signifies the potential role of curcumin or turmeric as a novel non-antibiotic chemo preventing agent against *H. pylori*-associated disorders.

Another highly evaluated herb against *H. pylori*-induced inflammation is Korean red ginseng (KRG). It has been reported by Korean researchers that KRG showed significant protective rescuing effect against *H. pylori*-induced cytotoxicity, gastric inflammation, NFκB activation and DNA damage, both by *in vitro* and clinical studies (Park *et al.,* 2005; Kim *et al.,* 2007). Green tea from *Camellia sinensis* leaves has also shown protective effects against *H. pylori* and *in vivo* study by Stoicov *et al* demonstrated profound growth inhibitory effects of green tea against *H. pylori* and also showed that green tea consumption can prevent gastric inflammation if ingested prior to *H. pylori* exposure (Stoicov *et al.,* 2009).

A famous cuisine spice, garlic, has demonstrated promising activities against *H. pylori*-induced gastritis model of Mongolian gerbils by decreasing hemorrhagic spots in the stomach glands and the degree of gastritis, which might be useful in reducing the risk of gastric cancer (Iimuro *et al.,* 2002). However, the same study demonstrated that the number of viable *H. pylori* was not changed by the garlic extract treatment. This was also confirmed by a clinical study showing no effect of garlic on *H. pylori* eradication (De *et al.,* 2009), pointing on the fact that garlic might only be helpful in attenuating *H. pylori*-induced pathological pathways while not killing bacteria itself in *in vivo* settings.

A noteworthy study by Lai *et al*, employing *Phyllanthus urinaria* (PU) chloroform and methanolic extracts, documented not only the potential anti-*H. pylori* activity of PU extract but also the suppressive effect on *H. pylori*-induced NFκB and IL-8 production in AGS cells (Lai *et al.,* 2008). We recently conducted studyusing extracts from twenty-four Pakistani medicinal plants/spices and analyzed their effect on *H. pylori*-induced IL-8 secretion (Zaidi *et al.,* 2012). Out of twenty four, more than half of them inhibited IL-8 secretion at the concentration of 100 μg/ml from infected AGS cells and among them *Cinnamomum cassia* demonstrated significant inhibition of IL-8 at even 3.12 μg/ml (Zaidi *et al.,* 2015). Recently, we confirmed the role of cinnamaldehyde, major constituent of *C. cassia*, at suppressing the inflammation

by down regulation of *H. pylori*-induced IL-8 expressions via inhibition of NF-κB activation in gastric epithelial cells (Muhammad *et al.,* 2015). Similarly, resveratrol found in red grapes, demonstrated strong anti-inflammatory activity by suppressing IL-8 and ROS in *H. pylori*-infected cells (Zaidi *et al.,* 2009d). A recent study on *Morinda citrifolia* fruit extracts in *H. pylori*-infected cells (Huang *et al.,* 2014) revealed the down-regulation of inflammatory responses on *H. pylori* infection and phenolic compounds exhibited the anti-adhesion activity of noni fruit extracts. These anti-inflammatory studies pointed out the fact that medicinal plants can act simultaneously in multiple directions which might help in not only reducing the colonization of bacteria but also suppressing the inflammatory pathogenic sequel.

CONCLUSION

In this review, we have discussed antibacterial and anti-inflammatory activities of medicinal plants from various parts of the world reflecting the potential of indigenous phytoceuticals in alleviating *H. pylori* associated disorders. Although, eradication of *H. pylori* by dietary ingestion of these medicinal plants is yet quite inconclusive but it is probable that their intake may curb the pathogenecity of *H. pylori* by various other mechanisms discussed here in. Although extensive *in vitro* studies have demonstrated potential of medicinal plants or spices, still there is a dire need to explore and authenticate the molecular mechanisms via *in vivo* and large scale clinical studies in order to verify and pose these phytoceuticals as promising agents of chemo prevention against *H. pylori* associated disorders.

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