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 antioxidants, anti-inflammatory agents, probiotics, herbal extracts and phytocuticals (Lind et al., 1999; Sherif et al., 2004; O’Gara et al., 2000; Lee et al., 2008).

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, antioxidant, 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 anagela 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 coticum* and *Xanthium brasiliicum* to be most active extracts with MIC value range of 31.25-250 µg/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 µg/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 *Antisomes 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 Cameroon
Ndip et al. screened ten medicinal plants from Cameroon 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 striatirnux* 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 phillipinensis* (Lam) Muell., *Curcuma amada* Roxb., *Psoralea corylifolia* L. and *Myristica fragrans* Hoult showed strong anti-*H. pylori* activity (MBC: 15.6-62.5 µg/ml). The most potent extract (*Mallotus phillipinensis* (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-\textit{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 \textit{Amphipterygium adstringens}, \textit{Ambrosia confertiflora}, \textit{Couterea latiflora}, \textit{Castella tortuosa}, \textit{Ibervillea sonorae}, \textit{Krameria erecta}, \textit{Marrubium vulgare}, \textit{Pascalium decompositum}, \textit{Pimpinella anisum} and \textit{Selaginella lepidophylla} exhibited 50\% MIC of less than 200 to 400 \(\mu\)g/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 \textit{H. pylori}.

The above-mentioned \textit{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 \textit{H. pylori}. These promising \textit{in vitro} results prompted researchers to validate these results in \textit{in vivo} and clinical settings. Few studies have demonstrated \textit{in vivo} evidence of medicinal plants against \textit{H. pylori}. Paraschos et al has reported the effect of mastic gum extract in reducing \textit{H. pylori} colonization in \textit{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 \textit{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 \textit{H. pylori} but seem to reveal some arguable data when compared to \textit{in vitro} and \textit{in vivo} studies. A curcumin-based one-week triple therapy was designed to evaluate the potential of curcumin in the eradication of \textit{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 \textit{H. pylori} in humans. Data revealed from twelve patients indicate that neither garlic nor peppers had any effect on \textit{H. pylori} in clinical settings (Graham et al., 1999). Number of \textit{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.

\textbf{Anti-inflammatory activity}
The attractiveness of phytocauticals 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 \textit{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 \textit{H. pylori} (fig. 1).

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{Fig1.png}
\caption{Diverse mechanism of actions of medicinal plants against \textit{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).}
\end{figure}

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

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|}
\hline
1 & Anti-bacterial activity & 2 & Anti-adhesion activity \\
\hline
3 & Inhibition of inflammatory molecules expression & 4 & Inhibition of hummingbird morphology or motogenic response \\
\hline
5 & Inhibition of ROS or oxidative stress &  \\
\hline
\end{tabular}
\caption{Diverse mechanism of actions of medicinal plants against \textit{H. pylori} associated pathogenesis.}
\end{table}
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Table 1: Anti-H. pylori activity of various phytomedicine-based studies from different parts of the world.

<table>
<thead>
<tr>
<th>Location</th>
<th>Method</th>
<th>Number of herbs</th>
<th>Most Active herbs</th>
<th>Reference published</th>
</tr>
</thead>
<tbody>
<tr>
<td>Korea</td>
<td>MIC</td>
<td>Five</td>
<td>Coptidis japonica, Eugenia caryophyllata, Rheum palmatum, Magnolia officinalis, Rhus javanica</td>
<td>Bae et al (1998)</td>
</tr>
<tr>
<td>Turkey</td>
<td>MIC</td>
<td>Seven</td>
<td>Cistus laurifolius</td>
<td>Yesilada et al (1999)</td>
</tr>
<tr>
<td>China</td>
<td>MIC</td>
<td>Thirty</td>
<td>Abrus cantoniensis, Saussurea lappa, Eugenia caryophyllata</td>
<td>Li et al (2005)</td>
</tr>
<tr>
<td>Malaysia</td>
<td>MBC</td>
<td>Twenty five</td>
<td>Curcuma longa, Cuminum cymimum, Zingiber officinale, Capsicum annuum, Borago officinalis, Nigella sativa, Origanum vulgare, Glycyrrhiza glabra apofosa</td>
<td>O’Mahony et al (2005)</td>
</tr>
<tr>
<td>Taiwan</td>
<td>MIC</td>
<td>Fifty</td>
<td>Paederia scandens, Plumbago zeylanica, Anisomeles indica, Bombax malabaricum, Alpinia speciosa</td>
<td>Wang et al (2005)</td>
</tr>
<tr>
<td>Pakistan</td>
<td>MBC</td>
<td>Fifty</td>
<td>Curcuma amada, Mallotus philipinesis, Myrsictica fragrans, Psoralea corylifolia</td>
<td>Zaidi et al (2009)</td>
</tr>
<tr>
<td>South Africa</td>
<td>MIC</td>
<td>Five</td>
<td>Combretum molle, Sclerocarya birrea, Garcinia kola, Alepidea amatymbica and a single Strychnos species</td>
<td>Njume et al (2011)</td>
</tr>
</tbody>
</table>

MIC: Minimum inhibitory concentration; MBC: Minimum bactericidal concentration

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 signify 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).

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 pathogenicity 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.

**REFERENCES**


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