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Abstract - Helicobacter pylori is a class 1 carcinogen that requires targeted therapeutic strategy. A number of drugs including proton pump inhibitors, antibiotics and antiprotozoals are available for the treatment of Helicobacter pylori infections like chronic gastric irritation, gastro duodenal ulcers and low grade gastric mucosa associated lymphoid tissue lymphoma. Clinical evaluation of these drugs has shown the incidence of relapses, side effects and drug interactions. Multi drug resistance to Helicobacter pylori has been the main reason for treatment failure. This has been the rationale for the development of new anti- Helicobacter pylori drugs and search for novel molecules has been extended to medicinal herbs that offer better protection, decreased relapse and undevelopment of resistance towards bacteria. The present article reviews the medicinal herbs from global perspective for their anti- Helicobacter pylori activity and active compounds from the plants responsible for this activity. We have highlighted some of the important plants and their active constituents reported for their anti- Helicobacter pylori activity. Ancient system of medicine (Ayurvedic and Unani) supported by modern science is necessary to isolate, characterize and standardize the active constituents from herbal sources for anti-Helicobacter pylori activity.

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Exploring Medicinal Plants for Anti-Helicobacter Pylori Activity

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Abstract - *Helicobacter pylori* is a class 1 carcinogen that requires targeted therapeutic strategy. A number of drugs including proton pump inhibitors, antibiotics and antiprotozoals are available for the treatment of *Helicobacter pylori* infections like chronic gastric irritation, gastro duodenal ulcers and low grade gastric mucosa associated lymphoid tissue lymphoma. Clinical evaluation of these drugs has shown the incidence of relapses, side effects and drug interactions. Multi drug resistance to *Helicobacter pylori* has been the main reason for treatment failure. This has been the rationale for the development of new anti- *Helicobacter pylori* drugs and search for novel molecules has been extended to medicinal herbs that offer better protection, decreased relapse and undevelopment of resistance towards bacteria. The present article reviews the medicinal herbs from global perspective for their anti- *Helicobacter pylori* activity and active compounds from the plants responsible for this activity. We have highlighted some of the important plants and their active constituents reported for their anti- *Helicobacter pylori* activity. Ancient system of medicine (Ayurvedic and Unani) supported by modern science is necessary to isolate, characterize and standardize the active constituents from herbal sources for anti-*Helicobacter pylori* activity.

I. Introduction

Helicobacter pylori (H. pylori), a Gram - negative spiral bacterium which was first detected in 1984 by Marshall et al, is one of the most common chronic bacterial pathogens in humans.[1] Approximately 50% of people in the world are infected with it, and its prevalence is significantly higher in developing countries than in developed countries.[2] Once a person is infected, the organism can live in the stomach indefinitely and may not cause clinical illness. It is still not clear how *H.pylori* are transmitted or why some people infected with bacteria become sick and others do not.[3] *H. pylori* infection is an important etiologic impetus usually leading to chronic gastritis, gastroduodenal ulcer and low grade gastric mucosa associated lymphoid tissue lymphoma. Epidemiological data shows that a high *H. pylori* infection rate is related to the high incidence of gastric cancer and gastric adenocarcinoma.[4] World Health Organization has categorized *H. pylori* as a class 1 carcinogen.[5] Eradication of the organism has been shown to result in ulcer healing, prevention of peptic ulcer reoccurrence and may also reduce the prevalence of gastric cancer in high-risk populations.[6] Many clinical trails involving patients with gastric and duodenal ulcers show that curing the infection is associated with a significant reduction in ulcer reoccurrence rates.[7-8]

II. Current Treatment Regimens

Since 1984 physicians prescribing triple therapy to treat *H. pylori* infections which includes three options. First option includes the combination of proton pump inhibitor (PPI), clarithromycin and ampicillin. Second option includes PPI, clarithromycin and metronidazole. Third option includes bismuth subsalicylate, metronidazole and tetracycline, but the cure rate from standard triple therapy has been low as 50%.[9-10] However, eradication by the triple therapy is not always successful and acquisition by *H. pylori* resistance to antibiotics could present a serious problem that may reduce treatment efficiency.[11] Quadruple therapy, where three antibiotics are taken alongside the PPI, has also been used in cases where triple therapy has not been successful. But the success rate was only 67%.[12]

III. Multidrug Resistance to H.Pylori

Many strains of *H. pylori* are now developing resistance to commonly used antibiotics. *H. pylory* acquires resistance by mutations to all the antibiotics used in the treatment regimens. The mechanism of resistance involves point mutations which are transmitted vertically, however transformation may be possible if two strains are present simultaneously in the stomach. Drug efflux proteins also can contribute to natural insensitivity to antibiotics and to emerging antibiotic resistance. Efflux pump gene hef A of *H. pylori* play an important role in multidrug resistance. Global resistance of *H. pylori* to metronidazole, clarithromycin, amoxicillin and tetracycline was also reported. One person may have more than one strain of *H. pylori*. Here the antibiotics may kill one strain, but not the other.[13-14] Furthermore, undesirable side effects of the drugs and the significant cost of combination therapy require the

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exclusive need to search alternative approaches of eradicating or preventing infection.

As phytomedicine has proved to be an untapped treasure for the discovery of lead compounds to cure gastrointestinal disorders. Hence several studies have been aimed to evaluate the anti-helicobacter pylori activity of medicinal herbs.[15] To the best of our knowledge, there is no extensive global view on exploring medicinal plants for anti-helicobacter pylori activity. List of medicinal herbs with anti-Helicobacter pylori activity including their source and active extracts are given in table 1.

IV. Solvents Employed in the Study of Plant Extracts Against H.Pylori

The insolubility of non-polar extracts makes it very difficult for the investigators to be used in an aqueous medium during the study of anti-*Helicobacter pylori* activity.[26] Water or alcohol (methanol/ethanol) are used mainly for a large number of crude extract preparations.[27] The type of solvent used may have an effect on the nature of the compounds extracted and the resulting bioactivity of the extract.[28] To estimate the value of each extract therefore, several factors, including the rate of extraction, the quantity extracted (yield), the diversity of compounds extracted, the diversity of inhibitory compounds extracted, the ease of subsequent handling of the extracts, toxicity of the solvent in the bioassays and the potential health hazards of the extractants have to be evaluated. In many research works, methanol/ethanol is used for alkaloid extraction; acetone for flavonoids and steroids; hexane, diethyl ether and chloroform for fat soluble oils, wax, lipids and esters. Dichloromethane for terpenoids, ethylacetate for esters, ethanol may be used for sterols, poly phenols, tannins and water for water soluble components like glycosides, polysaccharides, polypeptides and lectins.[29] Hundreds of plants with antimicrobial compounds have been reported. However, very few of these studies have reported the *in vivo* anti-*Helicobacter pylori* activity of these compounds. It is very important to know whether these compounds will still maintain their maximum activity in the gastric mucus niche of *H. pylori.* Anti-*Helicobacter pylori* compounds from plants and their mechanism of action are given in table 2.

Curcumin, biologically active poly phenolic from *Curcuma longa* has recently been shown to arrest *H. pylori* growth. The anti-*Helicobacter pylori* activity of curcumin against 65 clinical isolates of *H. pylori in vitro* was examined. Minimum inhibitory concentration ranging from 5-50 μg/ml, showing its effectiveness against *H. pylori* growth *in vitro* irrespective of genetic makeup of strains. Curcumin showed immense therapeutic potential against *H.pylori* infection as it was highly effective in eradication of *H.pylori* from infected mice as well as restoration of *H.pylori* induced gastric damage.

Curcuma longa extract was the most efficient in killing the seven strains of H.pylori within 15 minutes followed by chilli and ginger.[46-48] *Mallotus phillipinesis* is (Lam) Muell. Exhibited the most potent bactericidal activity against *H.pylori* which completely killed the bacteria at the concentration of 15.6-31.2 μg/ml.[16] There is no evidence of *in vivo* effectiveness of this plant. Antibacterial activity of *Allium sativum* L(garlic) against *H.pylori* is well documented (40 μg/ml) and resistance has not been reported.The synergistic action of garlic and omeprazole against *H.pylori* was also reported. Thiosulfinates play an important role in the antibiotic activity of garlic. Further clinical evaluation seems warranted.[49-51] A mixture of tannic acid and n-propyl gallate can limit the gastric mucosa deterioration induced by *H.pylori* infection and vac A administration, suggest that vac A inhibition plays a role in this protective activity. So, polyphenols from plant sources may contribute to limit the pathological outcomes of *H.pylori* infection.[52] Successive extracts of *Sapindus mukorossi* and *Rheum emodi* inhibited the growth of 30 resistant clinical isolates of *H.pylori in vitro* and *in vivo* studies and there was no acquired resistance against these herbal extracts even after ten consecutive passages.[53]

V. Conclusion

The evidence summarized above tentatively suggests possible benefits from some herbal sources with anti- *Helicobacter pylori* activity. Herbal science, Ayurvedic knowledge supported by modern science is required to standardize the plant extracts and to isolate, characterize and standardize the active constituents from plant sources for anti- *Helicobacter pylori* activity. Extensive investigations and large scale well designed clinical trails are required to provide more conclusive proof to explore medicinal herbs for anti-*Helicobacter pylori* activity.

Table1 : Medicinal herbs having anti-*Helicobacter pylori* activity (global perspective).

Botanical name	Source	Part used	Extract	Reference
South Asian Herbs				
Mallotus phillipinesis	Pakistan	covering fruit	Aqueous ethanol (70%)	16,17,18
Curcuma amada Roxb.	Pakistan	rhizome		
Myristica fragrans Houtt.	Pakistan	seed		
Psoralea corylifolia	Pakistan	seed		
Glycyrrhiza glabra L	India,Srilanka	root		
Terminalia chebula	Pakistan	fruit		
Curcuma longa L	India	rhizome		
Cuminum cyminum	Srilanka	seed		
Coccinia grandis	India	leaves	Ethanol	
Terminalia arjuna	India	bark	Methanol	
East Asian Herbs				
Rhizoma coptidis	China	rhizome	Aqueous	19,20
Radix scutellariae	China	root		
Radix isatidis	China	root		
Asasarum sieboldi	Korea	root	Methanol	
Lindera strychifolia	Korea	root		
Angelica tenuissima	Korea	root		
Alpinia oxyphylla	Korea	fruit		
American Herbs				
Zingiber officinale	USA	rhizome	Methanol	21
Rosmarinus officinalis	USA	rosemary leaf		
Foeniculum vulgare	USA	seed		
Nigella sativa	USA	seed		
African Herbs				
Terminalia spinosa	East Africa	young branches	Aqueous	22
Harrisonia abyssinica	East Africa	root		
Ximenia caffra	East Africa	root		
Azadirachta indica	East Africa	leaves, stem bark		
Combretum molle	South Africa	stem bark	Acetone	23
Sclerocarya birrea	South Africa	stem bark		
Carica papaya	Nigeria	leaf	Aqueous& ethanol	24
Morinda lucida	Nigeria	leaf		
Octimum gratissimum	Nigeria	leaf		
Phyllanthus amarus	Nigeria	leaf		
Brazelian Herbs				
Bixa orellana L	Brazil	seed	Aqueous ethanol (96%)	25
Chamonilla recutita L	Brazil	inflorescence		
Ilex paraguariensis A	Brazil	green leaves		
Malva sylvestris L	Brazil	inflorescence & leaves		

Table 2 : Anti-*Helicobacter pylori* compounds from plants.

Compound name	Examples	Mechanism of action	reference
Quinones	Quinones,idebenone,duroquinone, menadione,juglone,coenzyme Q_1	inhibition of respiration and cellular ATP level	30-32
Flavones, flavonoids and flavonols	Quercetin, catechins, myristin, rutin	Ability to complex with extracellular and cellular proteins	33-34
Phenolics and polyphenols	Catechol, pyrogallol, curcumin	Enzyme inhibition by the oxidized compounds possibly through reaction sulfhydryl or nn-specific interaction with proteins	35-36
Tannins	Polymeric phenols, hydrolysable tannins	Ability to inactivate microbial adhesins, enzymes, cellenvelop transport proteins	37-39
Coumarins	7-hydroxy-4-methyl coumarin, 6,7-hydroxy-4-methyl coumarin, 6-hydroxy-7-methoxy-4-methyl coumarin and 5,7-dihydroxy cyclopentano coumarin	Not known	40-42
Terpenoids and essential oils	Di, tri, tetra and hemi terpenes Quinoline alkaloids, alkylmethyl quinoline	Decrease the risk of associated pathologies	43
Alkaloids	Not explored	Selective against *H.pylori* Without affecting the intestinal flora	44
Lectins and poly peptides		May be formation of ion channels in the microbial membrane or competitive inhibition of adhesion of microbial proteins to host polysaccharide receptors	45

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