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Medicinal plants possessed anti- *Helicobacter pylori* activity, as promising future gastroprotective therapies

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Abstract

Peptic ulcer disease is one of the main sources of morbidity and mortality worldwide. Many medicinal plants showed gastroprotective activity by many mechanisms, some medicinal plants possessed anti *Helicobacter pylori* activity. This review will discuss the medicinal plants with anti- *Helicobacter pylori* activity.

Keywords: Medicinal Plants; Peptic Ulcer; Gastroprotective; *Helicobacter Pylori*

1. Introduction

Peptic ulcer disease is one of the main sources of morbidity and mortality worldwide. It is characterized by erosions in mucosal linings of stomach and duodenum. It is the most common gastrointestinal disorder caused by the alteration in balance between offensive (pepsin, gastric acid and *Helicobacter pylori*) and defensive factors (prostaglandins, bicarbonate ions, mucin, growth factors and nitric oxide) (1). *Helicobacter pylori* is a gram-negative organism that has been identified as a potential causative agent in the pathogenesis of peptic ulcer disease. The exact mechanism by which it contributes to mucosal damage is unknown. It is thought that the organism may disrupt the protective mucous layer, allowing the underlying epithelium to be injured by gastric acid. *Helicobacter pylori* cause an inflammatory response with neutrophils, lymphocytes, plasma cells, and macrophages within the mucosal layer and causes epithelial cell degeneration and injury. More than 50% of the world population is infected with *Helicobacter pylori*. The bacterium highly links to peptic ulcer diseases and duodenal ulcer. The pathogenesis of *Helicobacter pylori* is contributed by its virulence factors including urease, flagella, vacuolating cytotoxin A (VacA), cytotoxin-associated gene antigen (Cag A), and others. Of those virulence factors, VacA and CagA play the key roles. Infection with *Helicobacter pylori* vacA -positive strains can lead to vacuolation and apoptosis, whereas infection with cagA-positive strains might result in severe gastric inflammation and gastric cancer (2). Plants based remedies were tested for anti-*Helicobacter pylori* activity and were prescribed as gastroprotective mechanisms (3-4). This review will discuss the medicinal plants possessed anti-*Helicobacter pylori* activity.

1.1. *Allium sativum*

Garlic extracts can also prevent the formation of *Staphylococcus* enterotoxins A, B, and C1 and thermonuclease. Garlic extracts are also effective against *Helicobacter pylori* (5-6).

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1.2. *Aloe vera*

Aloe-emodin inhibited growth of *Helicobacter pylori* in a dose-dependent fashion. *Aloe vera* inhibited gastric acid secretion in mice and rats and has protective effects against gastric mucosal damage in rats. Pretreatment with *Aloe vera* extract reduced aspirin-induced gastric mucosal injury by 70% in experimental rats. *Aloe vera* extracts also suppressed the ulcerogenic effects of stress in experimental rats. Intraperitoneal injection of ethanol extract exerted a gastroprotective effect in acute gastric mucosal lesions induced by 0.6 M HCl in rats. A clinical study showed that *Aloe vera* gel might be helpful in treating patients with duodenal ulcers (7-13).

1.3. *Anethum graveolens*

Anethum graveolens seed extracts have also been reported to possess anti-ulcer activity, and have shown moderate activity against *Helicobacter pylori*. Aqueous and organic extracts of seeds have exhibited potent antibacterial activity (14-16).

1.4. *Bacopa monnieri*

Fresh *Bacopa monniera* juice exerted significant antiulcerogenic activity. *Bacopa monniera* have a protective and curative effect for gastric ulcers. In rats, *Bacopa monniera* extract standardized for bacoside-A was evaluated for its prophylactic and healing effects in five models of gastric ulcers. At a dose of 20 mg/kg for 10 days, Bacopa extract significantly healed penetrating ulcers induced by acetic acid, significantly strengthened the mucosal barrier, and decreased mucosal exfoliation. The extract also alleviated stress-induced ulcers as observed by significant reduction in lipid peroxidation in rat gastric mucosa. It was also exerted anti *Helicobacter pylori* effect (17-18).

1.5. *Betula alba*

Betulinic acid possessed considerable antibacterial effects, and also showed a strong inhibition of the urease activity of *Helicobacter pylori* (19-20).

1.6. *Calendula officinalis*

The influence of *Calendula officinalis* on heparin-binding epidermal growth factor (HB-EGF)-like growth factor gene expression in KATO-III cells under the stimulation of *Helicobacter pylori* strain N6 using real-time PCR was investigated with and without addition of and *Calendula officinalis*. Addition of *Calendula officinalis* led to a significant reduction of *Helicobacter pylori* induced increase in gene expression of HB-EGF (reduced to 75.32±1.16% vs. control; $p<0.05$) (21-22).

1.7. *Calotropis procera*

The methanol and acetone extract from *Calotropis procera* exhibited strong anti- *Helicobacter pylori* activity, almost comparable activity with tetracycline, but were found to be less potent than amoxicillin and clarithromycin (23-24).

1.8. *Carthamus tinctorius*

The antibacterial activity of methanol extract of *Carthamus tinctorius* was evaluated against *Helicobacter pylori*. The inhibition zone of methanol extract of *Carthamus tinctorius* at concentration 2 mg/disc against *Helicobacter pylori* clinical isolates was 18.77±0.56mm, while, MIC and MBC for the same extract were 691.25 µg/ml respectively (25-26).

1.9. *Carum carvi*

The *in vitro* susceptibility of 15 *Helicobacter pylori* strains to *Carum carvi* seed methanolic extract was studied. Methanol extracts of *Carum carvi* showed anti *Helicobacter pylori* effect with MIC of 100 microg/ml (27-28).

1.10. *Casuarina equisetifolia*

The anti-*Helicobacter pylori* and urease inhibition activities of extracts of *Casuarina equisetifolia* were investigated. The extracts exhibited lower activity than the standard antibiotics (29-30).

1.11. *Cydonia oblonga*

The *in vitro* anti-*Helicobacter pylori* activity of 33 substances, juices and plant extracts and 35 of their combinations were tested using an agar diffusion method on Columbia blood agar. Quince (*Cydonia oblonga*) juice demonstrated the strongest anti- *Helicobacter pylori* activity followed by cranberry juice (31-32).

1.12. *Coriandrum sativum*

The effect of selected indigenous medicinal plants of Pakistan was evaluated on the secretion of interleukin-8 (IL-8) and generation of reactive oxygen species (ROS) to rationalize their medicinal use and to examine the anti-inflammatory and cytoprotective effects in gastric epithelial cells. AGS cells and clinically isolated *Helicobacter pylori* strain (193C) were employed for co-culture experiments. *Coriandrum sativum*, demonstrated significant suppression of ROS from *Helicobacter pylori*- infected cells ($p<0.01$) (33-34).

1.13. *Dianthus caryophyllus*

Aqueous and methanolic extracts of aerial parts of *Dianthus caryophyllus* showed anti-*Helicobacter pylori* activity with MIC >1000 and >500 µg/ml respectively (35-36).

1.14. *Eucalyptus camaldulensis*

The *in vitro* anti- *Helicobacter pylori* of *Eucalyptus camaldulensis* was investigated in six strains of *Helicobacter pylori* (ATCC 4504, ATCC 47619, A2, TI8984, 019A, and A6). The minimum inhibitory concentrations of the crude extracts against all the tested strains ranged from 12.5 to 400 mug/ml (37-38).

1.15. *Glycyrrhiza glabra*

The *in vitro* activity of glycyrrhizic acid, glycyrrhetinic acid and a novel lipophilic derivative of glycyrrhetinic acid monoglucuronide acetylated GAMG was investigated against 29 *Helicobacter pylori* strains. Glycyrrhetinic acid was the most potent compound ($MIC_{50/90}$, 50/100 mg/l), inhibiting 79.3% of the strains at MIC <50 mg/l (39-40).

1.16. *Hibiscus sabdariffa*

The antimicrobial combinatory effect of the aqueous extract of *Hibiscus sabdariffa* with antibiotics (clarithromycin, amoxicillin, metronidazole) were evaluated against *Helicobacter pylori* strains. AEHS exerted remarkable bacteriostatic effect against all *Helicobacter pylori* tested strains with MICs values ranging from 9.18 to 16.68 µg/ml. Synergy effect of aqueous extract of *Hibiscus sabdariffa* with clarithromycin or metronidazole was obtained against four of seven *Helicobacter pylori* strains tested with ∑FIC ranging from 0.21 to 0.39. The additive effect of aqueous extract of *Hibiscus sabdariffa* with amoxicillin was obtained against five of seven *Helicobacter pylori* strains tested with ∑FIC ranging from 0.61 to 0.91 (41-42).

1.17. *Juglans regia*

Juglone potently inhibited the three key enzymes from *Helicobacter pylori,* cystathionine γ-synthase (HpCGS), malonyl-CoAacyl carrier protein transacylase (HpFabD), and β-hydroxyacyl-ACP dehydratase (HpFabZ) with IC_{50} values of 7.0±0.7, 20±1, and 30±4 µmol/L, respectively (43).

Over 45% of clinical isolates of *Helicobacter pylori* strain were inhibited by *Juglans regia* aqueous and equal mixture of methanol, diethyl ether and petroleum benzene extract (44-45).

1.18. *Lantana camara*

The antiulcerogenic activity of methanolic extract of *Lantana camara* leaves (250 and 500 mg/kg, orally) was evaluated in aspirin induced gastric ulcerogenesis in pyloric ligated rats, ethanol induced gastric ulcer, and cysteamine induced duodenal ulcer models. The lipid peroxidation, reduced glutathione levels of ethanol induced gastric ulcer model and anti-*Helicobacter pylori* activity was also determined. The inhibition zone in diameter of extract against *Helicobacter pylori* was 20 mm (46-47).

1.19. *Lepidium sativum*

Clinical isolates of *Helicobacter pylori* were tested *in vitro* for susceptibility to ethanol extract of Lepidium *sativum*. The ethanol extracts exerted cytotoxiciy against *Helicobacter pylori* isolates. MIC value was 15-29 mm for concentrations of 100 000, 50 000 and 25 000µg/ml respectively (48-49).

1.20. *Lithospermum officinale*

Shikonin showed broad antibacterial activity including Helicobacter *pylori*. It also inhibited biofilm formation (50-51).

1.21. *Lythrum salicaria*

The anti-*Helicobacter pylori* activity of the *Lythrum salicaria* extract was assessed against clinically isolated strain using disc diffusion method. Clinically isolated *Helicobacter pylori* strain was inhibited at concentration of 500 mg/ml (zone of inhibition: 17 ± 0.08 mm) (52-53).

1.22. *Pimpinella anisum*

Pimpinella anisum extract showed antibacterial activity against *Helicobacter pylori* which suggested an important role in the treatment of gastrointestinal disorders caused by *Helicobacter pylori* (54-55).

1.23. *Plantago psyllium*

The antimicrobial effects of aqueous and hydro-alcoholic of *Plantago psyllium* leaf extracts was investigated in experimental *Helicobacter pylori* infection in rats in comparison with amoxicillin. The results showed that *Plantago psyllium* hydro-alcoholic extract can be applied as effective treatment for *Helicobacter pylori* infection. Antigen was decreased in all groups treated with amoxicillin (p=0.0004), aqueous, and hydro-alcoholic extracts (p<0.05). Antigen decrease in the stool was observed in all groups, which indicated that treatment with the herbal extract was beneficial in the infected rats (56).

1.24. *Punica granatum*

The antimicrobial activity of pomegranate juice was dependent on the test organism, it was highly effective against four Gram-positive species and two Gram-negative species (*Helicobacter pylori* and *Vibrio parahemolyticus*), but it showed no activity against *Salmonella* and *Escherichia coli*. No synergistic antimicrobial activity was seen between pomegranate and either barberry, oregano, or cranberry (57).

1.25. *Quercus brantii*

The activity of the aqueous extract of Quercus *brantii* var. *persica* seed coat extracts against 25 *Helicobacter pylori* isolates was assessed by well diffusion method, microdilution assay, and a disk diffusion assay *in vitro*. Aqueous extract possessed antimicrobial activity with diameters of inhibition ranged from 0 mm to 40 mm. Its inhibitory activity increased simultaneously with increasing extract concentration. The lowest MIC and MBC were 2 µg/ml. Anti-*Helicobacter pylori* activity of the extract was approximately close to tetracycline and metronidazole and less than amoxicillin (58).

1.26. *Sambucus ebulus*

The aqueous extract demonstrated a dose-dependent anti-ulcerogenic activity, resulting in 42.3 to 71.3% inhibitions, while methanol extract was found inactive. *Sambucus ebulus* also possessed anti-*Helicobacter pylori* activity (59-61).

1.27. *Trigonella foenum-graecum*

High antimicrobial activity against *Helicobacter pylori* was exerted by fenugreek sprout extract. However, the *Helicobacter pylori* inhibitory activity was improved with the using of fenugreek seeds extract derived via solid-state bioconversion using *Rhizopus oligosporus* (62-63).

2. Conclusion

Helicobacter pylori have been identified as a potential causative agent in the pathogenesis of peptic ulcer disease. The exact mechanism by which it contributes to mucosal damage is unknown. *Helicobacter pylori* eradication with antibiotic regimens has a limitation mostly due to antibiotic resistance and the high incidence of side effect of triple and quadruple therapy. Numerous medicinal plants were reported with anti- *Helicobacter pylori* activity. However, clinical trials, pharmacokinetic studies and side effect monitoring are required.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict-of-interest to be disclsoed.

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