

Antibacterial Activity of *Aloe Vera*, Curcumin, Garlic, and Plau-noi Against *Helicobacter pylori*

Duangporn Thong-Ngam*
Thanitta Chatsuwan**

ABSTRACT

Background: *Helicobacter pylori* is a bacterium implicated in the etiology of gastritis and peptic ulcers. Certain herbal agents have been reported to have antibacterial activity against *H. pylori*.

Aim: To assess the in vitro anti-*H. pylori* potential of four herbal substances, namely *Aloe vera*, curcumin, garlic, and plau-noi.

Methods and Materials: A standard strain (NCTC 11637) and 9 clinical isolates of *H. pylori* were used to assess antibacterial activity of *Aloe vera*, curcumin, garlic, and plau-noi, employing an agar dilution and disk diffusion method. The agar dilution was tested by two-fold dilution of various concentrations of herbal substances, ranging 0.016-512 micrograms/mL on Columbia blood agar. The disk diffusion was tested using varying amounts of herbal substance at 20, 50, 100, 200 and 400 micrograms.

Results: The minimum inhibitory concentrations (MICs) of *Aloe vera*, curcumin, garlic, and plaunotol were >512, 64, >512, >512 micrograms/mL, respectively. There were no inhibition zones found when testing with *Aloe vera*, garlic, and plau-noi, although the inhibition zone diameters of 6.5-8 mm and 10-12 mm were detected at 200 and 400 micrograms curcumin disk, respectively.

Conclusion: Curcumin exhibited potential of in vitro antibacterial activity against *H. pylori*, which suggests that it may be useful for the treatment of *H. pylori* infection. *Aloe vera*, garlic, and plau-noi, on the other hand, did not show antibacterial activity against *H. pylori* in this study.

Key words : *Aloe vera*, curcumin, garlic, plau-noi, *H. pylori*

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Address for Correspondence: Duangporn Thong-Ngam, MD, Department of Physiology, Faculty of Medicine, Chulalongkorn University, Bangkok, 10330, Thailand. thongngam007@yahoo.com
Telephone: +662-256-4267, Fax: +662-256-4267

*Department of Physiology, **Department of Microbiology, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand.

INTRODUCTION

Helicobacter pylori is a bacterium implicated in the etiology of gastritis and peptic ulcers. Eradication of *Helicobacter pylori* is reported to be important in preventing relapse and accelerating the healing of duodenal and gastric ulcers⁽¹⁾. Triple therapy with bismuth or a proton pump inhibitor (PPI) plus two antibiotics is highly effective, but patient compliance is the most important factor for predicting successful eradication of *H. pylori*⁽²⁾. Resistance to antibiotics, in particular to metronidazole and clarithromycin, is also an increasing problem. Some herbal agents have been reported to show antibacterial activity against *H. pylori*.

Aloe vera is a kind of herbal medicine that has been widely used in basic health care in many countries. The plant may be separated into two portions, namely *Aloe vera* gel and the latex portion. Aloe vera gel contains many biologically active substances⁽³⁾. It has been reported that a glycoprotein extracted from *Aloe vera* has a strong anti-inflammatory response⁽⁴⁻⁷⁾ and could exhibit anti-inflammatory activity by reducing changes in cutaneous microcirculation such as reduced leukocyte adherence, wound healing promotion and reduction of TNF- α and IL-6 levels^(8,9).

Moreover, *Aloe vera* has been used to treat a variety of gastrointestinal conditions. It is suggested in Thai Pharmacopeia that the latex portion of *Aloe vera* has anthraquinone glycosides that could improve indigestive disease. As for the aloe gel portion, it has been reported that oral administration of the mucilaginous gel from *Aloe vera* has prophylactic and curative effect against gastric lesion induced by hydrochloric acid (0.6 N HCl) and acetic acid (30% and 100%) (Mahattanadul, 1995). Mucopolysaccharide and glycoproteins contents found in aloe gel have been shown to possess a synergistic action responsible for the antagastric ulcer action^(11,12).

Curcumin is a polyphenolic chemical constituent derived from turmeric (*Curcuma longa*). Curcumin has been shown to possess a wide range of pharmacological activities including anti-inflammatory^(13,14), anti-cancer⁽⁵⁾, anti-oxidant⁽¹⁶⁾, wound healing⁽¹⁷⁾ and anti-microbial effects⁽¹⁸⁾.

Garlic (*Allium sativum*), has been used for medicinal purposes for over 3000 years, and has bactericidal⁽¹⁹⁾ and fungicidal⁽²⁰⁾ properties. There is substantial evidence of the tumor-inhibitory effects of garlic, based on works in various experimental systems⁽²¹⁾.

Epidemiological studies have provided evidence that significant garlic consumption is correlated with a reduced cancer risk⁽²²⁾.

Plaunotol, an acyclic diterpene alcohol extracted from the leaves of the plau-noi tree found in Thailand, was reported to be effective in the treatment of ulcers, of IL-8 secretion induced by *H. pylori* and of the inhibitory adhesion activity of the bacterium to gastric epithelial cells⁽²³⁾. It has also been used in combination therapies against *H. pylori* associated diseases because of its strong bactericidal effect against *H. pylori*. Furthermore, the combination of plaunotol, clarithromycin and a PPI is reported to eradicate *H. pylori* better than the combination of clarithromycin and PPI alone (Kobayashi *et al.*, 1987), (Koga *et al.*, 1996).

This study was designed to assess the in vitro anti-*H. pylori* potential of four herbal substances, namely *Aloe vera*, curcumin, garlic, and plau-noi, using the agar dilution and disk diffusion method.

MATERIALS AND METHODS

Preparation of herbal substances

Aloe vera, Aloe vera gel spray dried power, supplied by Concentrated Aloe Corporation (CAC), Florida, USA, was dissolved in sterile distilled water before use.

Curcumin, the product of Cayman Chemical Company, Michigan, USA, was dissolved in 0.1N NaOH before use.

Garlic, the commercial garlic tablet (Khao-La - Or Lab. Ltd. Samutprakarn, Thailand, was dissolved in dimethylsulphoxide (DMSO) before use.

Plau-noi, the commercial plau-noi tablet (One Tambon One Product (OTOP), Petchaburi, Thailand) was dissolved in dimethylsulphoxide (DMSO) before use.

Determination of the antimicrobial effect of herbal medicines

We used one standard strain (NCTC 11637) and 9 clinical isolates from Thai dyspeptic patients of *H. pylori*. These strains were grown on Columbia agar (Oxoid, Basingstoke, UK) containing 7% sheep blood and 7% horse serum. Plates were incubated at 37 °C under microaerophilic conditions (10% CO₂, 5% O₂ and 85% N₂) produced by a gas generating system, CampyGen (Oxoid, Basingstoke, UK), in anaerobic jar

(Oxoid, Basingstoke, UK) for 72 h (Figure 1).

The agar dilution method

Inocula were prepared by suspending growth from Columbia blood agar plates in Brain heart infusion broth (Oxoid, Basingstoke, UK) and adjusted to a no.3

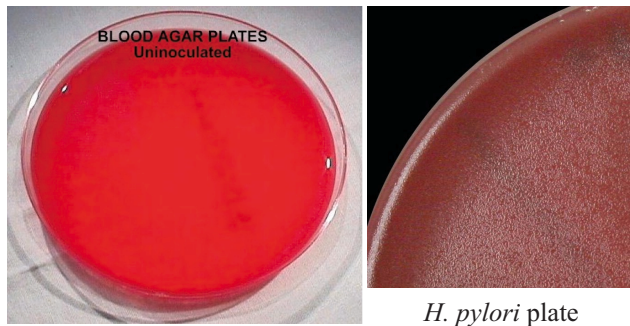


Figure 1 Show the *H. pylori* colonies on blood agar plate



Figure 2 Show the agar dilution method

McFarland standard (109 CFU/ml). A final inoculum of 5×10^6 cfu/spot was applied using a multi-inoculator. Experiments were performed in duplicate, and all plates were incubated for 3 days at 37°C under microaerophilic conditions. The agar dilution was tested by two-fold dilution of various concentration of herbal substances including *Aloe vera*, curcumin, garlic, and plau-noi, ranging 0.016-512 micrograms/mL (Figure 2). The MIC was investigated as the lowest concentration of herbal substances preventing visible growth.

The disk diffusion method

To determine the inhibitory effect of various herbal medicines on *H. pylori* growth, the disk diffusion was tested using disks with varying amounts of *Aloe vera*, curcumin, garlic, and plau-noi at 20, 50, 100, 200 and 400 micrograms. *H. pylori* suspensions equivalent to a 3 McFarland standard were spread onto Columbia blood agar, and herbal disks were placed on the surface of the agar. The plates were incubated for 3 days at 37°C under microaerophilic conditions. The inhibition zone was recorded based on the contents of *Aloe vera*, curcumin, garlic, and plau-noi concentration. The disk size was 6 mm.

RESULTS

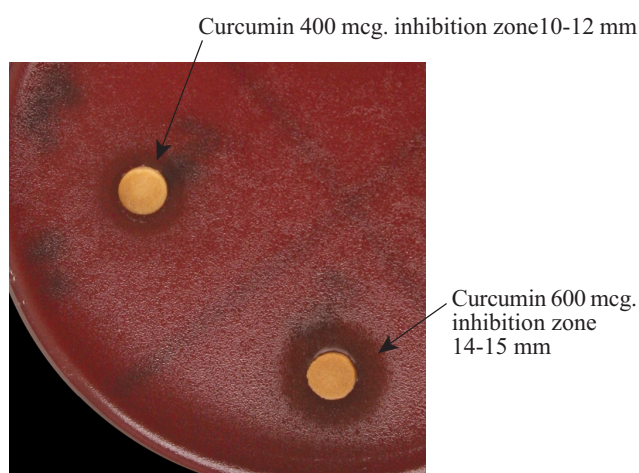
The minimum inhibitory concentrations (MICs) of *Aloe vera*, curcumin, garlic, and plau-noi were >512, 64, >512, >512 micrograms/mL, respectively (Table 1). No inhibition zones were found when testing with *Aloe vera*, garlic, and plau-noi, although the inhibition zone diameter of 6.5-8 mm was detected at 200 micrograms curcumin disk (Table 2). The inhibition zone diameter of 10-12 mm was noted at 400 micrograms curcumin disk. We further tested for 600 micrograms curcumin disk and found the inhibition zone diameter of 14-15 mm (Figure 3).

Table 1 The results of agar dilution method

Agar dilution	Minimum inhibitory concentrations (MICs) micrograms/mL
<i>Aloe vera</i>	>512
Curcumin	64
Garlic	>512
Plau-noi	>512

Table 2 The results of disk diffusion method

Disk diffusion	Inhibition zone diameter (mm.)				
	20	50	100	200	400
<i>Aloe vera</i>	0	0	0	0	0
Curcumin	0	0	0	6.5-8	10-12
Garlic	0	0	0	0	0
Plau-noi	0	0	0	0	0

**Figure 3** Show the inhibition zone of curcumin disk

DISCUSSION

H. pylori infection is the most common gastrointestinal bacterial disease worldwide. It is the principle cause of chronic gastritis, and many of the diseases associated with gastritis are also associated with *H. pylori*. From epidemiological data, it has been shown that in developing countries there is a high incidence of *H. pylori* infection in people ranging from 13% to 70% in the under 20 age group and from 70% to 94% in the over 30 group⁽²⁶⁾. Infection by this bacterium may lead to gastric ulcer, duodenal ulcer, or chronic gastritis.

Chronic gastritis associated with *H. pylori* is characterized by infiltration of the lamina propria with inflammatory cells, enhanced release of proinflammatory cytokines such as interleukins (IL e.g. IL-1 β and IL-8) and tumor necrosis factor- α (TNF- α) as well as the generation of reactive oxygen species⁽²⁷⁾. TNF- α and IL-1 β are potent inducers of IL-8 production and up regulation of neutrophil expression of CD11b/CD18. The latter enhances ICAM-1-dependent neutrophil adherence⁽²⁸⁾. These are responsible for a positive feed-

back loop through the stimulatory actions of chemical mediators on neutrophil chemotaxis and activation⁽²⁹⁾. Many kinds of herbal medicines are supposed to have anti-inflammatory or antimicrobial effect against *H. pylori*.

Aloe vera gel has been used to treat a variety of gastrointestinal conditions. *Aloe vera* gel was attributed to inhibition of hydrochloric acid secretion and a general detoxifying effect in the treatment of patients with peptic ulcers⁽¹²⁾. Mucopolysaccharide and glycoproteins content found in aloe gel exhibit a synergistic action that is responsible for the antigastric ulcer activity, rather like gastric mucin which protects the gastric mucosa from damage. The antithromboxane B2 effect of the gel causes reduction of vasoconstriction and results in improved perfusion of gastric mucosal capillaries, which and the glycoproteins, namely Alectin-A or Lectin P-2 have a healing effect on the ulcer⁽¹⁰⁾. A recent study evaluated the prophylactic and curative effects of *Aloe vera* on gastric ulcer induced by cytodestructing agents, 0.6 NHCl and acetic acid (30% and 100%) in rats⁽¹⁰⁾. *Aloe vera* was prepared in different forms. freshly gel. fresh freeze-dried powder (a change from gel by a freeze dry method using lyophilizer) and two-month prestored freeze-dried powder. All three forms had similar antigastric ulcer effects. The results showed that *Aloe vera* 400 mg/kg/day given orally was efficacious both in protecting gastric mucosa against the injuries caused by necrotizing agent, 0.6 NHCl, and in healing ulcers already induced by acetic acid (30% and 100%). Comparing the efficacy effect of *Aloe vera* with that of a standard cytoprotective agent, sucralfate, using the same treatment at the same dosages, all three preparations of *Aloe vera* gel were shown to be as efficacious as sucralfate on acetic gastric ulcer and induced healing. The findings suggested that *Aloe vera* gel exerts an antigastric ulcer action by directly protecting the gastric mucosa and by exerting cytoprotective activity resulting in an enhancement of local healing process⁽¹⁰⁾. *Aloe* prophylactically protects gastric mucosa against injuries caused by necrotizing agents. The effects of ethanol extract of *Aloe vera* (Liliaceae) on acute mucosal lesions induced by 0.6M HCl and on acid output in pylorus ligated and lumen perfused rats has recently been reported. It was found that *Aloe vera* could protect the gastric mucosa and possessed the authors gastric acid anti-secretory activity in a dose dependent pattern⁽⁶⁾.

In our previous study, we found the antiinflammatory effects of *Aloe vera* on leukocyte-endothelium interaction in the gastric microcirculation of *H. pylori* infected rats⁽³⁰⁾. Although in this study, we found no inhibition zone even with a high dose of *Aloe vera*, the MIC of *Aloe vera* being >512 micrograms/mL suggesting no antibacterial effect of *Aloe vera* against *H. pylori*.

Turmeric, *Curcuma longa* L. (Zingiberaceae family) rhizomes, has been widely used for centuries as an indigenous medicine for the treatment of a variety of inflammatory conditions and other diseases⁽³¹⁾. Its medicinal properties have been attributed mainly to the curcuminoids and the main component present in the rhizome includes curcumin (diferuloylmethane)-(1,7-bis (4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione). Curcumin has been shown to down regulate the production of pro-inflammatory cytokines tumor necrosis factor- α (TNF- α), IL-1 β and inhibit the activation of transcription factors nuclear factor- κ B (NF- κ B) and activator protein-1 (AP-1), which regulate the genes for pro-inflammatory mediators and protective antioxidant genes^(32,33). Curcumin inhibited NF- κ B activation by blocking phosphorylation of I- κ B⁽³⁴⁾ through inactivation of I- κ B kinase complex⁽³⁵⁾. Suppression of AP-1 was due to a direct interaction of curcumin with AP-1 binding to its DNA binding motif⁽³⁶⁾ and also due to inhibition of c-Jun and c-fos, components of AP-1⁽³⁷⁾. It is also reported to suppress the activity of a number of enzymes such as cytochrome P450 and COX-2⁽³⁸⁾. In another study of ours, we found that curcumin blocks VEGF synthesis and NF- κ B activation on the prevention of gastric microcirculatory albumin leakage in *H. pylori* infected rats (unpublished data). In this study, we showed the inhibition zone with the curcumin concentration of ≥ 200 micrograms/mL. Moreover the diameter of the inhibition zone correlated with the curcumin concentration. The MIC of curcumin was 64 micrograms/mL, therefore, curcumin has the antibacterial effect against *H. pylori*.

Fresh garlic bulb, dried and powdered or oil extracts from the bulb, have been used for medicinal purposes. The active constituents of garlic include alliin, allinase, diallyl disulphide, ajoens and others. Alliin is enzymatically converted to allicin which is responsible for the characteristic, sulphur like odour. The pharmacologic actions of garlic are multifold: antibacterial, antiviral, antifungal antihypertensive, blood glucose lowering antithrombotic, antimutagenic and anti-

platelet^(39,40). The antibacterial effect of a home made raw garlic extract and commercial garlic tablets alone and in combination with antibiotics or omeprazole was determined against clinical isolates of *H. pylori*. The MIC values of raw garlic extract and three types of commercial garlic tablets ranged from 10,000 to 17,500 mg/L. The MIC values of the commercial tablets were based on the allicin content (O'Gara *et al.*, 2000). In this study, we used the garlic in the form of commercial garlic tablet, and found no inhibition zone even with the high dose of garlic. The MIC of garlic was >512 micrograms/mL meaning no antibacterial effect of garlic against *H. pylori*.

Plaunotol, extracted from the leaves of the plau-noi tree, has been used in Japan as an anti-ulcer agent for treatment of peptic ulcers. Thiourea derivatives 2-4 were synthesized regions selectively using effective synthetic route for plaunotol, and diol derivatives 6-10 were also synthesized. Their antibacterial activities against *H. pylori* were determined and C1-thiourea derivative 2c was found to be the most potent antibacterial agent⁽⁴²⁾. Plaunotol has been shown to have a cytoprotective effect via prostaglandin synthesis, and an inhibitory effect on hypergastrinemia induced by omeprazole^(43,44). As plaunotol is hypothesized to cause a change in membrane fluidity, with an associated increased membrane permeability, plaunotol might potentiate the anti-*H. pylori* activity of clarithromycin and amoxicillin by increased permeability of the membranes. Plaunotol inhibited *H. pylori* growth, suppressed IL-8 secretion from gastric epithelial cells and improved gastritis in *H. pylori*-infected mice⁽²³⁾. In this study, we used plau-noi in form of commercial tablet. We found no inhibition zone even with the high dose of plau-noi, and the MIC of plau-noi was >512 micrograms/mL meaning no antibacterial effect against *H. pylori*.

CONCLUSIONS

Herbal medicine has become popular for healthcare. Although many differences exist between herbal and conventional pharmacologic treatments, herbal medicine can be tested for efficacy using conventional trial methodology. Several specific herbal extracts have been demonstrated to be efficacious for specific conditions. This study was designed to assess the *in vitro* anti-*H. pylori* potential of four herbal substances, namely *Aloe vera*, curcumin, garlic, and

plau-noi. It was found that curcumin has potential of *in vitro* antibacterial activity against *H. pylori*, suggesting that it may be useful for the treatment of *H. pylori* infection, while, *Aloe vera*, garlic, and plau-noi have no antibacterial activity against *H. pylori*.

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