
A study on the anti-*Helicobacter pylori* activity of three medicinal plant crude extracts from *Cannabis sativa*, *Mitragyna speciosa* and *Phyllanthus emblica*

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Abstract In the present study, medicinal plant crude extracts were prepared from cannabis (*Cannabis sativa*), kratom (*Mitragyna speciosa*) and Indian gooseberry (*Phyllanthus emblica*) using four different solvents including ethanol, methanol, isopropanol, and water. The methanolic crude extracts had the highest weight and percentage yield, whereas the aqueous crude extracts exhibited the lowest values. The antimicrobial activity of these extracts against three *Helicobacter pylori* strains (ATCC 43504, 2888, and BK364) was evaluated using the spot-on-lawn method. The obtained results indicated that all medicinal plant crude extracts had an inhibitory effect against all tested *H. pylori* strains. The methanolic and ethanolic extracts of *Cannabis sativa* inhibited *H. pylori* strains ATCC 43504, 2888, and BK364 at the minimum inhibitory concentration (MIC) values ranging from 0.02-0.05 mg/mL. Additionally, a synergistic effect between *Cannabis sativa*, *Mitragyna speciosa*, and *Phyllanthus emblica* was investigated using the checkerboard assay. The synergistic interaction was observed between the *Cannabis sativa*, *Mitragyna speciosa*, and *Phyllanthus emblica* extracts, with a fractional inhibitory concentration index (FICI) of 2, indicating an indifferent effect when combined. Furthermore, the scanning electron microscopy (SEM) investigation revealed that the *H. pylori* cells were damaged after treatment with methanolic crude extracts of cannabis for 120 minutes.

Keywords: Medicinal plant crude extracts, *Helicobacter pylori*, Synergistic effect, Scanning electron microscopy

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Introduction

Gastric cancer is the fifth most common cancer and the fourth leading cause of cancer deaths worldwide (Pradhan *et al.*, 2025). There were an estimated 770,000 deaths due to gastric cancer in 2020 (Morgan *et al.*, 2022). Infection with *Helicobacter pylori* (*H. pylori*) was recognized as the main risk factor for gastric cancer. *H. pylori* was classified as a Group 1 carcinogen by the International Agency for Research on Cancer (IARC) under the World Health Organization (WHO) in 1994 (IARC, 1994).

The epidemiological data indicate that *H. pylori* is one of the most prevalent global pathogens, colonizing an estimated 50% of the world's population (Thung *et al.*, 2016). In general, the overall prevalence of *H. pylori* infection in developed countries is lower than that in developing countries (Malfertheiner *et al.*, 2022). Although approximately 80% of infected individuals remain asymptomatic and are unaware of the presence of *H. pylori* in their stomachs, the infection always develops into gastric adenocarcinoma (Engelsberger *et al.*, 2024).

The first-line treatment for *H. pylori* infection is typically based on triple therapy, which consists of a proton pump inhibitor (e.g., omeprazole) combined with two antibiotics, commonly clarithromycin and amoxicillin or metronidazole. However, the effectiveness of this treatment has been reported to decline over time due to the increasing prevalence of antibiotic-resistant *H. pylori*, which has become a major global public health concern. Resistance to macrolide antibiotics, particularly clarithromycin, is of particular importance. In response, the WHO has classified clarithromycin-resistant *H. pylori* as a high-priority pathogen for research and the development of new antimicrobial agents (WHO, 2017).

A global rise in *Helicobacter pylori* antibiotic resistance has been reported over the past two decades, resulting in a steady decline in eradication success rates (Thung *et al.*, 2016; Savoldi *et al.*, 2018). Resistance to clarithromycin, metronidazole, and levofloxacin has been reported to exceed 15% in most WHO regions, with some regional variations (Savoldi *et al.*, 2018). In Thailand, clarithromycin resistance rates as high as 36.5% and metronidazole resistance exceeding 50% have been documented (Mahachai *et al.*, 2021). These resistance levels are strongly associated with triple therapy failure, leaving limited options for empirical third-line regimens. Consequently, revisions of treatment guidelines and the development of non-antibiotic therapeutic strategies have been encouraged. Moreover, antibiotic administration has been associated with gut microbiota disruption and adverse effects such as diarrhea, nausea, and dyspepsia, reducing treatment adherence and accelerating resistance.

Traditional medicinal plants such as cannabis (*Cannabis sativa*), kratom (*Mitragyna speciosa*) and Indian gooseberry (*Phyllanthus emblica*) have been investigated as promising alternatives for the development of

novel antimicrobial agents. These plants have been reported to possess diverse pharmacological properties and to exhibit antibacterial activities, including effectiveness against drug-resistant strains (Appendino *et al.*, 2008; Chin *et al.*, 2016; Singha *et al.*, 2003). Their mechanisms of action are considered multifaceted, thus differing from conventional antibiotics that typically target specific bacterial pathways. Furthermore, plant-derived extracts have been suggested to reduce the risk of resistance development due to the presence of multiple bioactive constituents acting synergistically (Cowan, 1999; Bassolé and Juliani, 2012). Additional advantages include favorable safety profiles, cost-effectiveness, and local availability, making them suitable candidates for further development as complementary or alternative antimicrobial agents (Cragg and Newman, 2005; Fabricant and Farnsworth, 2001). Medicinal plants such as cannabis (*Cannabis sativa*), Indian gooseberry (*Phyllanthus emblica*) and kratom (*Mitragyna speciosa*) have been investigated for their potential to inhibit *H. pylori* both domestically and internationally. Cannabis extracts enriched with cannabinoids such as CBD, CBG, and CBN were reported to exhibit anti-*H. pylori* activity, with MIC values of 0.98 mg/L (Luca *et al.*, 2024). In the case of *P. emblica*, inhibition of was reported by the National Cancer Institute of Thailand, with MIC values ranging from 0.91 to 1.87 mg/mL (National Cancer Institute of Thailand / DRIC, 2020). Although no direct studies on *H. pylori* have been reported for *M. speciosa*, several investigations have demonstrated its antibacterial activity against other Gram-negative bacteria. Ethanolic and methanolic extracts of kratom leaves were shown to effectively inhibit *Staphylococcus aureus* and *Escherichia coli* (Tajuddin *et al.*, 2010).

Therefore, this research aimed to study the extraction and testing of compounds against *H. pylori* from these medicinal plants, determined the minimum inhibitory concentration (MIC), and studied the morphology of *H. pylori* after exposure to medicinal plant crude extracts to assess the potential for future application.

Materials and methods

Preparation of medicinal plant crude extracts

Three medicinal plants, cannabis (*Cannabis sativa*), kratom (*Mitragyna speciosa*) and Indian gooseberry (*Phyllanthus emblica*), were collected as flowers, leaves and fruits, respectively. The extraction method was adapted from Zhang *et al.* (2018). The plant materials were oven-dried at 50°C with forced air for 48 h. The dried samples were extracted using four different solvents including absolute ethanol, absolute methanol, absolute isopropanol, and water, by maceration at a ratio of 1:15 (sample:solvent) for 7 days at room temperature (RT). Subsequently, all

samples were filtered through Johnson No. 1 filter paper to obtain ethanolic, methanolic, isopropanolic, and aqueous extracts, which were then concentrated using a vacuum rotary evaporator (Eppendorf, Germany) and dried by a speed vacuum concentrator (Eppendorf, Germany). For aqueous extracts, freeze-drying was performed using a freeze dryer (Labconco Freezone, USA) to obtain crude extracts. All crude extracts were stored in amber glass bottles at -15°C.

The percentage yield of each crude extract was calculated as follows:

$$\% \text{Yield} = \frac{\text{Weight of dried extract}}{\text{Weight of initial dried plant material}} \times 100$$

Determination of the minimal inhibitory concentration (MIC)

Three strains of *Helicobacter pylori* (ATCC 43504, 2888, and BK 364) were cultured on Columbia blood agar plates (Oxoid, UK) supplemented with 5% (v/v) sheep blood. The plates were incubated under microaerophilic conditions at 37°C for 72 h.

The MIC values were determined using the spot-on-lawn method, as modified from Lim *et al.* (2018). Crude extracts of the medicinal plants were dissolved in dimethyl sulfoxide (DMSO) (Loba, India) to a final concentration of 100 mg/mL and two-fold serially diluted. Five microliters of each diluted extract were spotted on to Columbia blood agar plates containing 5% sheep blood previously inoculated with *H. pylori* adjusted to a turbidity equivalent to 2 McFarland standard. DMSO alone served as a negative control. Plates were incubated under microaerophilic conditions at 37 °C for 72 h, and MIC values were expressed in mg/mL.

Evaluation of synergism among medicinal plant crude extracts

The interaction between crude extracts of *C. sativa*, *M. speciosa*, and *P. emblica* were evaluated using the checkerboard antimicrobial synergy assay, following the method modified from Ahmad *et al.* (2019). The fractional inhibitory concentration index (FICI) was calculated as:

$$\text{FICI} = \text{FIC(A)} + \text{FIC(B)}$$

where FIC(A) = MIC of A in combination / MIC of A alone, and FIC(B) = MIC of B in combination / MIC of B alone. The interpretation was as follows: synergy (FICI < 0.5), additive effect (0.5 ≤ FICI < 1), indifference (1 ≤ FICI ≤ 4), and antagonism (FICI > 4).

The observation of H. pylori morphology by scanning electron microscopy (SEM)

The morphological alterations of *H. pylori* after treatment with medicinal plant crude extracts were examined by SEM. The *H. pylori* strain

BK 364 was adjusted to a turbidity of 1 McFarland standard in phosphate-buffered saline (PBS) at pH 7.2 and exposed to crude extracts at 32-fold the MIC. The bacterium suspension which was untreated with any medicinal plant crude extract was used as a negative control. The samples were incubated under microaerophilic conditions at 37°C for 2 h, followed by centrifugation at 8,000 rpm and washing twice with PBS. The bacterial pellets were placed on aluminum foil, air-dried, and fixed with 2.5% glutaraldehyde for 18 h at 4°C. The samples were dehydrated through a graded ethanol series (25%, 50%, 75%, and 100%), sputter-coated with gold, and examined using a scanning electron microscope (Hitachi, Japan).

Results

Effect of extraction solvent on the yield of medicinal plant extracts

The extraction of medicinal plant was prepared from cannabis (*Cannabis sativa*), kratom (*Mitragyna speciosa*), and Indian gooseberry (*Phyllanthus emblica*), using four different solvents including ethanol (EtOH), methanol (MeOH), isopropanol (IPA), and water. The methanol extraction of all plants yielded the highest weight of the crude extract, whereas the aqueous extraction of all plants yielded the lowest values, as shown in Table 1.

Table 1. Weight and %yield of medicinal plant crude extracts

Name of medicinal plants	Weight of crude extracts (g)				Yield (%)			
	IPA ¹	MeOH ²	EtOH ³	Water	IPA ¹	MeOH ²	EtOH ³	Water
Cannabis (<i>Cannabis sativa</i>)	2.61	5.55	4.57	2.1	17.4	37	30.47	14
Kratom (<i>Mitragyna speciosa</i>)	0.61	2.5	1.14	0.92	6.1	25	11.4	9.2
Indian gooseberry (<i>Phyllanthus emblica</i>)	4.07	5.88	4.81	2.79	27.1	39.23	32.08	18.57

¹/ Isopropanol

²/ Methanol

³/ Ethanol

Determination of the minimal inhibitory concentration (MIC)

The minimum inhibitory concentration (MIC) of medicinal plant crude extracts against *H. pylori* was determined. It was observed that the type of solvent had a significant effect on the antibacterial activity of the crude extracts. For cannabis, the methanolic and ethanolic extracts were found to exhibit the strongest inhibitory effect, with MIC values of 0.02 mg/mL. In the case of kratom leaves, the methanolic extract showed the strongest activity, with an MIC value of 0.10 mg/mL. Similarly, the methanolic extract of Indian gooseberry demonstrated the best activity, with an MIC value of 3.13 mg/mL. When the methanolic extracts of the three

medicinal plants were compared, the cannabis extract was demonstrated to possess the strongest anti-*H. pylori* effect. In contrast, the aqueous extracts showed weaker inhibitory activity than the alcohol-based extracts. Nevertheless, among the aqueous extracts, cannabis still exhibited the strongest inhibition, with MIC values ranging from 1.56 mg/mL, whereas Indian gooseberry and kratom aqueous extracts exhibited MIC values of 50 mg/mL and 100 mg/mL, respectively, as shown in Table 2.

Table 2. The minimum inhibitory concentration (MIC) of medicinal plants crude extracts obtained using various solvents against *H. pylori*

Name of medicinal plants	Solvent used for extraction	Minimum Inhibitory Concentration (mg/mL)		
		ATCC 43540	2888	BK 364
Cannabis (<i>Cannabis sativa</i>)	Isopropanol	0.05	0.05	0.05
	Methanol	0.05	0.02	0.05
	Ethanol	0.05	0.02	0.05
	Water	12.50	1.56	12.50
Kratom (<i>Mitragyna speciosa</i>)	Isopropanol	25.00	0.20	50.00
	Methanol	25.00	0.10	50.00
	Ethanol	25.00	0.20	50.00
	Water	100	100	100
Indian gooseberry (<i>Phyllanthus emblica</i>)	Isopropanol	6.25	3.13	6.25
	Methanol	6.25	3.13	3.13
	Ethanol	12.50	12.5	12.50
	Water	50	50	50
10% DMSO (Control)		No inhibition		

Antimicrobial synergy testing of medicinal plant crude extracts

The synergistic interactions between the methanolic extracts of cannabis (*Cannabis sativa*), kratom (*Mitragyna speciosa*), and Indian gooseberry (*Phyllanthus emblica*) against *H. pylori* strain 2888 were determined with a fractional inhibitory concentration index (FICI) of 2, indicating no synergistic antibacterial effect, as shown in Table 3.

Effect of methanolic extract of cannabis on H. pylori morphology

The morphological characteristics of *H. pylori* were observed under scanning electron microscopy (SEM) before and after exposure to methanolic extract of cannabis. Prior to exposure to medicinal plant crude extracts, *H. pylori* cells exhibited their characteristic morphology, appearing as curved or spiral-shaped rods resembling an “S” form. The cell surface

appeared smooth and intact, with no visible damage to the cell wall, and flagella were clearly observed protruding from the cell poles, consistent with the morphology of viable *H. pylori* as shown in Figures 1(A) and 1(B). Following exposure to cannabis crude extract for 120 minutes, obvious morphological alterations were observed. Some bacterial cells appeared swollen with irregular surfaces, showing bleb formation and localized membrane disruption accompanied by cytoplasmic leakage. These features indicate membrane damage and the initiation of cell lysis, as shown in Figures 1(C) and 1(D).

Table 3. The synergistic capacity of medicinal plant crude extracts against *H. pylori*

Name of medicinal plants	MIC Alone (mg/mL)	MIC in Combination (mg/mL)	FIC	FICI*	Interaction
<i>C. sativa</i>	0.024	0.024	1	2	No synergistic antibacterial effect
<i>M. speciosa</i>	0.097	0.097	1		
<i>C. sativa</i>	0.024	0.024	1	2	No synergistic antibacterial effect
<i>P. emblica</i>	3.125	3.125	1		
<i>M. speciosa</i>	0.097	0.097	1	2	No synergistic antibacterial effect
<i>P. emblica</i>	3.125	3.125	1		

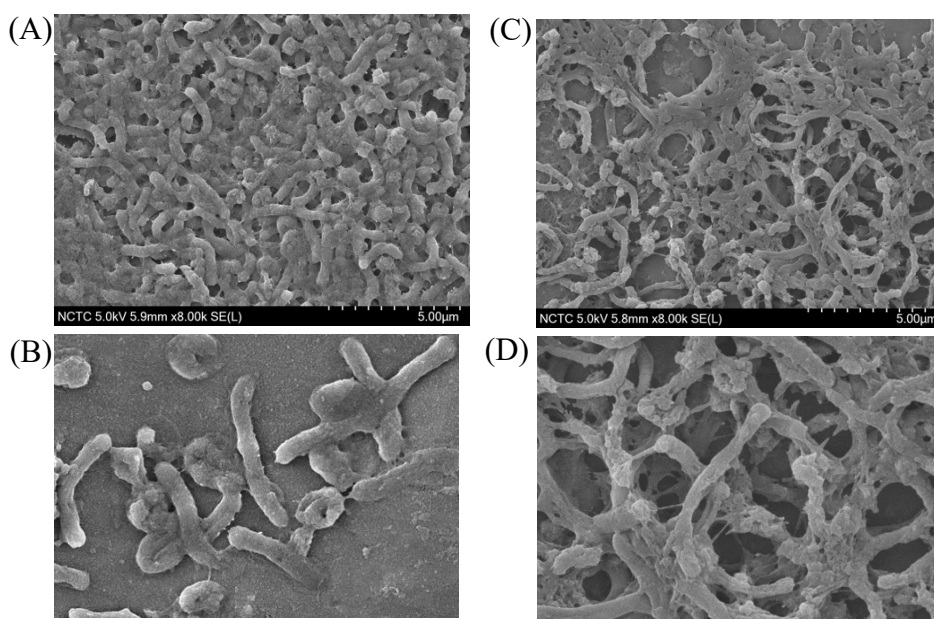


Figure 1. The morphological characteristics of *H. pylori* observed under SEM: (A) and (B): morphology of *H. pylori* before exposure to methanolic crude extracts of cannabis (C) and (D): morphology of *H. pylori* after exposure to cannabis crude extracts

Discussion

Analysis of the extracts of medicinal plants showed that the methanolic extracts had the highest weight and percentage yield, whereas the aqueous crude extracts exhibited the lowest values, which is consistent with the theory of “like dissolves like,” which explains that compounds with similar polarity are more effectively dissolved in solvents of comparable polarity (Sasidharan *et al.*, 2011; Azwanida, 2015). Three medicinal plants examined contained major compounds such as cannabinoids in *C. sativa*, mitragynine in *M. speciosa*, and flavonoids in *P. emblica*, which are weakly polar or amphipathic molecules. These compounds dissolve more efficiently in solvents of intermediate polarity, such as methanol. However, they are poorly soluble in water.

Consequently, methanol proved to be the most effective solvent for extracting the major compounds from the three medicinal plants. The antimicrobial findings further confirm this outcome. The methanolic extracts of *C. sativa*, *M. speciosa*, and *P. emblica* exhibited the greatest inhibitory activity against *H. pylori*, corresponding to their higher concentrations of major compounds. The methanolic extract of *C. sativa* exhibited the lowest MIC values, indicating the potent chemical properties and antimicrobial mechanisms of cannabinoids. These compounds are highly lipophilic and amphipathic due to the presence of hydroxyl groups attached to large hydrophobic structures (Zengin *et al.*, 2018). Such properties are critical for effective penetration of the outer membrane of Gram-negative bacteria, which is composed of a phospholipid bilayer with hydrophobic regions (Epanand *et al.*, 2016; Bakkali *et al.*, 2008). Once inside the cell, cannabinoids can directly disrupt the bacterial membrane, increasing permeability, compromising membrane integrity, and causing cytoplasmic leakage that ultimately leads to cell death (Blaskovich, 2021). Importantly, these mechanisms act independently of protein-receptor binding, offering an advantage in reducing the risk of antibiotic resistance (Blaskovich, 2021). In contrast, the major compounds of *M. speciosa* and *P. emblica* crude extract are mitragynine and flavonoids, respectively. Although these molecules contain hydroxyl (-OH) or methoxy (-OCH₃) groups that provide some polarity, they are generally less lipophilic than cannabinoids, which may explain their comparatively weaker activity against *H. pylori* (Cushnie and Lamb, 2014).

However, *C. sativa*, *M. speciosa*, and *P. emblica* crude extracts demonstrate notable antimicrobial activity, with cannabis being more potent. Additionally, the chemical complexity of cannabis extracts included cannabinoids, flavonoids, and terpenes, which may contribute to synergistic interactions among constituents, an effect often described as the “entourage effect” (Russo *et al.*, 2011; Zengin *et al.*, 2018). This mechanism could further enhance the overall inhibitory activity against *H. pylori*, surpassing

the anticipated effects of specific compounds alone. However, it is important to note that hydrophobicity alone is not sufficient to account for antimicrobial activity.

Effective inhibition requires not only membrane penetration but also disruption of essential cellular processes, such as metabolism or induction of reactive oxygen species (ROS) (Bakkali *et al.*, 2008). Compounds that are excessively hydrophobic may also face solubility challenges, potentially reducing their bioactivity. Therefore, amphipathic molecules, which balance hydrophilic and hydrophobic characteristics, generally display superior antimicrobial activity by effectively interacting with bacterial membranes (Epanand *et al.*, 2016). Taken together, these findings highlight the significance of solvent selection in extracting major compounds and demonstrate that methanolic cannabis crude extracts, rich in cannabinoids, exhibit the most effective antibacterial activity against *H. pylori*. The synergistic interaction between the methanolic extracts of *C. sativa*, *M. speciosa*, and *P. emblica* may be explained by the differences in the mechanisms of action of their active constituents against *H. pylori* (Cushnie and Lamb, 2014). If certain compounds from one plant interfere with, or competitively inhibit, the activity of bioactive molecules from another plant or bind to the same cellular target with lower inhibitory efficacy, the overall antimicrobial effect can be attenuated, preventing the more potent compound from exerting its full activity.

Moreover, the combination of extracts with markedly different solubility and dispersion characteristics may affect the stability of the mixture and limit the accessibility of active compounds to bacterial cells when present in the same solution (Bakkali *et al.*, 2008).

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Conflicts of interest

The authors declare no conflict of interest.

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