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Evaluating urease inhibition by herbal extracts for peptic ulcer management: A novel approach to combat *Helicobacter Pylori* and antimicrobial resistance

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Abstract
Peptic ulcer disease (PUD) remains a significant global health burden, particularly in India, where the mortality rates from ulcer-related complications are alarmingly high. The major etiological contributors, *Helicobacter pylori* infection and non-steroidal anti-inflammatory drugs (NSAIDs), disrupt gastric mucosal defenses through distinct mechanisms, leading to gastric erosion and ulceration. The treatment of PUD is increasingly challenged by rising antimicrobial resistance (AMR), notably to clarithromycin and metronidazole, reducing the effectiveness of standard therapies. Moreover, proton pump inhibitors (PPIs), the cornerstone of acid suppression, are associated with adverse effects, including hypomagnesemia, microbial imbalance, and fracture risk. In response to these limitations, this study investigated the urease inhibitory potential of 20 traditionally used Indian medicinal plants as alternative or adjunct therapies. Ethanolic extracts were prepared and evaluated using a phenol red-based urease-inhibition assay. Results revealed *Solanum nigrum* (IC_{50}: 1.25 ± 2.07 µg/mL), *Terminalia chebula* (2.44 ± 2.98 µg/mL), and *Phyllanthus niruri* (2.54 ± 3.05 µg/mL) as potent inhibitors, outperforming the reference standard thiourea (4.22 ± 3.44 µg/mL). These herbs demonstrated strong dose-dependent activity, likely because of bioactive compounds such as flavonoids, tannins, and alkaloids. In contrast, several commonly used herbs, such as *Azadirachta indica* and *Eclipta prostrata*, showed comparatively weaker inhibition. This study highlights the promising antiurease activity of selected herbal extracts, supporting their potential integration into PUD management protocols, especially in antibiotic-resistant cases. Further isolation and standardization of the active constituents are warranted to develop consistent and effective herbal formulations. Such alternatives may reduce dependence on synthetic drugs and help address the growing threat of AMR in gastrointestinal infection.

Keywords: Peptic ulcer disease, *Helicobacter Pylori*, urease inhibitory assay, herbal medicine, antimicrobial resistance, nonsteroidal anti-inflammatory drugs

Introduction

1. Peptic ulcer disease: A global and national burden

Peptic ulcer disease (PUD) is a long-term digestive condition marked by the erosion of the mucosal lining in the stomach or duodenum. and continues to pose a significant global health burden. Globally, PUD accounted for approximately 267,000 deaths in 2019, representing approximately 0.5% of all digestive disease-related mortalities (GBD 2019 Collaborators, 2020; WHO, 2021) [16, 50]. India alone contributes to nearly 15% of these deaths, with approximately 40,000 annual fatalities, mainly due to complications such as gastrointestinal bleeding and perforation, particularly in rural regions with poor healthcare infrastructure (GBD 2019 Collaborators, 2020; ICMR, 2022) [16, 20]. Nearly 45% of Indian patients present with severe complications at diagnosis, and states such as Bihar and Uttar Pradesh report mortality rates that are 25% higher than the national average (Sharma *et al.*, 2023; National Health Profile, 2023) [33, 41]. PUD primarily results from *Helicobacter pylori* infection and nonsteroidal anti-inflammatory drug (NSAID) use, with duodenal and gastric ulcers accounting for 70% and 30% of cases, respectively (Malfertheiner, Chan, & McColl, 2024; Zhang *et al.*, 2024) [29, 56]. Risk factors include smoking, alcohol consumption, stress, dietary habits, and genetic predisposition (Kumar *et al.*, 2022; Kim *et al.*, 2023) [23, 25]. The disease emerges from an imbalance between aggressive agents and mucosal defense mechanisms, emphasizing the need for combined microbial eradication and mucosal protection (Takeuchi & Amagase, 2021; Wallace & Granger, 2022) [43, 48].

2. Diagnosis and treatment

H. pylori infection is diagnosed using both noninvasive and invasive methods. Non-invasive tests include the urea breath test, which detects labeled CO_2 after urease activity, stool antigen tests, and serology for anti-*H. pylori* antibodies (Katelaris *et al.*, 2023; Gatta *et al.*, 2022) [14, 21]. Invasive methods typically employed during upper GI endoscopy include histological examination, rapid urease testing, and culture from biopsy specimens (Sugano *et al.*, 2023) [42]. The treatment methods, drugs used, duration, and adverse effects are shown in Table 1.

Table 1: Modern treatment methods for peptic ulcer disease caused by *Helicobacter pylori, including* drugs, duration, and adverse effects

S.No.	Method	Drugs	Duration	Adverse Effects	Reference(s)
1	Triple Therapy	PPI (e.g., omeprazole 20 mg BID) + Amoxicillin 1 g BID + Clarithromycin 500 mg BID	10–14 days	Diarrhea, taste disturbances, nausea, allergic reactions, antibiotic resistance	Khosravi & Nassaji 2023 [24], Chey *et al.* 2024 [8],
2	Bismuth	PPI BID + Bismuth subsalicylate 300	10–14 days	Dark stools, metallic taste,	Graham *et al.* 2023 [18],

	Quadruple Therapy	mg QID + Tetracycline 500 mg QID + Metronidazole 500 mg TID		nausea, constipation, dizziness	Malfertheiner *et al*. 2023 [30].
3	Non-Bismuth Quadruple Therapy	PPI BID + Amoxicillin 1 g BID + Clarithromycin 500 mg BID + Metronidazole 500 mg BID	10–14 days	GI upset, diarrhea, antibiotic-associated colitis	Aghaizu *et al*. 2022 [1].
4	High-Dose Dual Therapy	Vonoprazan 20 mg BID + Amoxicillin 1 g TID	14 days	Mild GI symptoms (lower than quadruple therapy)	Chey *et al*. 2024[8].
5	Rifabutin-Based Therapy	PPI BID + Amoxicillin 1 g BID + Rifabutin 150 mg BID	14 days	Myelotoxicity (rare), elevated liver enzymes	USFDA Talicia Approval 2023 [47], Tshibangu-Kabamba *et al*. 2024
6	Hybrid Therapy	PPI + Amoxicillin (7 days), then PPI + Amoxicillin + Clarithromycin + Metronidazole (7 days)	14 days	Similar to concomitant therapy but lower adverse events	Georgopoulos *et al*. 2024[15].

3. *Helicobacter pylori* and Non-steroidal anti-inflammatory drugs (NSAIDs)

Helicobacter pylori, a gram-negative, helical bacterium with multiple flagella, colonizes the gastric mucosa by surviving in acidic environments through urease production, which neutralizes gastric acid (Ashraf *et al*., 2024; Malfertheiner *et al*., 2024) [4, 29]. H. pylori is transmitted mainly via the fecal–oral route and less commonly through oral–oral contact. *H. pylori* adheres to gastric epithelial cells using adhesins, such as BabA and SabA (Okuda *et al*., 2022; Yamaoka, 2023) [37, 53]. Its virulence factors, CagA and VacA, disrupt epithelial integrity, induce apoptosis, and provoke inflammation, thereby promoting ulcer and gastric cancer development (Cover & Blanke, 2023; Hatakeyama, 2022) [10, 19]. This bacterium evades immune detection, enabling chronic infection (Arpaia *et al*., 2023) [3]. In a similar vein, nonsteroidal anti-inflammatory drugs (NSAIDs), which are frequently utilized for alleviating pain and reducing inflammation, can lead to gastrointestinal issues by blocking COX-1, an enzyme that safeguards the stomach lining. (FitzGerald & Patrono, 2021; Lanas *et al*., 2023) [12, 26]. NSAID-related ulcers can be mitigated using proton pump inhibitors and selective COX-2 inhibitors, albeit with cardiovascular caution (Bally *et al*., 2022; Whelton & Zhang, 2022) [6, 49, 55].

4. Limitations and challenges of current PUD Therapies

Hip fracture risk is heightened by the use of proton pump inhibitors (PPIs). by up to 20–24% (Chubineh & Kumar, 2023) [9], hypomagnesemia (affecting up to 50% of long-term users, particularly those with renal impairment) (Zhou *et al*., 2023), and gut microbiome alterations that elevate susceptibility to Clostridioides difficile and enteric infections (Freedberg *et al*., 2023) [13]. Rebound acid hypersecretion occurs in 44% of patients after abrupt discontinuation, complicating the withdrawal of therapy (Tack *et al*., 2024) [44]. *Helicobacter pylori* treatment is increasingly hindered by antibiotic resistance, with clarithromycin resistance at 27–34%, metronidazole at 69–70%, and levofloxacin at 24–34%, reducing the efficacy of standard triple therapy to below 70% and necessitating costly, side-effect-prone alternatives, such as bismuth-based quadruple therapy (Savoldi *et al*., 2023; Fallone *et al*., 2023) [11, 40].

5. Antimicrobial resistance and the role of herbal medicines

Antimicrobial resistance (AMR) is a mounting global health crisis, with estimates projecting up to 10 million deaths annually by 2050 if not addressed (O'Neill 2016) [36]. Alarming resistance levels have been observed in pathogens such as *Klebsiella pneumoniae*, with 40–60% carbapenem resistance in ICU settings and emerging pan-resistant strains (Nordmann *et al*., 2022) [35]. Methicillin- and vancomycin-resistant *Staphylococcus aureus* (MRSA and VRSA) is implicated in nearly 100,000 deaths annually (Turner *et al*., 2023) [46]. Extensively drug-resistant tuberculosis constitutes 6.2% of MDR cases, with cure rates below 40% (WHO, 2023) [51]. Resistance arises from mechanisms such as drug inactivation, targ*et al*teration, and efflux pumps (Bush & Bradford, 2020; Redgrave *et al*., 2014; Li *et al*., 2022) [7, 27, 39]. Herbal medicines, supported by WHO (2023) [51], offer multi-targeted, resistance-limiting effects through bioactive compounds like curcumin and berberine (Tariq *et al*., 2021; Yuan *et al*., 2023) [45, 54]. These treatments are not only cost-effective—reducing expenses by up to 70% but also enhance mucosal healing in gastrointestinal conditions, often outperforming conventional therapies (Zhang *et al*., 2022; Willcox *et al*., 2020; Marx *et al*., 2017) [31, 52, 55].

6. Urease and urease inhibitory assay

Urease, a metalloenzyme that relies on nickel, facilitates the breakdown of urea into ammonia and carbamate., enabling *Helicobacter pylori* to survive acidic gastric conditions (Mobley & Hausinger, 2021) [32]. Urease inhibition assays are crucial for identifying compounds that impair this function and reduce *H. pylori* colonization. They also help address urease-related issues, such as struvite kidney stones in UTIs and excessive urea breakdown in agriculture (Khan *et al*., 2023) [22]. Methods such as the Berthelot and phenol red assays allow high-throughput screening of inhibitors, including acetohydroxamic acid and thiol-based natural products (Gonçalves *et al*., 2022) [17]. These assays support both therapeutic development and enzymatic mechanism research.

Materials and methods

1. Selection, collection, and extraction of drugs

Of the 100 medicinal plants from the list prepared with known antibacterial properties, 20 were selected for this study. These were: Babool (*Acacia arabica*, bark), Bael (*Aegle marmelos*, leaves/bark/fruits), Garlic (*Allium sativum*, bulbs), Aloe Vera (*Aloe barbadensis*, leaves), Neem (*Azadirachta indica*, leaves), Indian Barberry (*Berberis aristata*, stem), Beetroot (*Beta vulgaris*, roots), Papaya (*Carica papaya*, leaves), False Daisy (*Eclipta alba*, aerial parts), Sacred Fig (*Ficus religiosa*, latex), China Rose (*Hibiscus rosa-sinensis*, flowers), Mango (*Mangifera indica*, stem bark), Wild Mint (*Mentha arvensis*, leaves),

Touch-Me-Not (*Mimosa pudica*, whole plant), Drumstick Tree (*Moringa oleifera*, leaves/bark/seeds), Holy Basil (*Ocimum sanctum*, leaves), Stonebreaker (*Phyllanthus niruri*, leaves), Black Nightshade (*Solanum nigrum*, whole plant), Tamarind (*Tamarindus indica*, stem/bark/leaves), and Chebulic Myrobalan (*Terminalia chebula*, leaves). All plant parts were purchased from verified local markets, cleaned to remove any dirt, and dried at ambient temperature. The dried samples were coarsely powdered and subjected to ethanol extraction by maceration. The extracts were filtered, concentrated, and dried to obtain a dry powder for subsequent antibacterial evaluation.

2. Urease inhibition assay procedure

A 0.1 M phosphate buffer (pH 6.8) was prepared as the assay medium. Urea was dissolved in this buffer to make a 100 mM stock solution. A 0.01% (w/v) phenol red solution was freshly prepared in distilled water and used as a pH indicator. Urease enzyme (from *Jack bean*, Sigma-grade or equivalent) was reconstituted in phosphate buffer to yield an activity of 1.0 U/mL. The herbal test extracts were dissolved in buffer to prepare a series of concentrations (5, 10, 20, 40, and 80 µg/mL).

For each assay, 50 µL of urease solution, 50 µL of test extract, 50 µL of urea solution, and 50 µL of phenol red were combined in the test tubes. The positive control used a known urease inhibitor instead of the test extract, while the negative control replaced the extract with buffer. The reaction mixtures were kept at 37°C for 30 minutes during incubation. Post incubation, urease activity was assessed by color change (from yellow to pink due to ammonia-induced alkalization) and quantified by pH measurement. Urease inhibition (%) was calculated using the following formula

$$\text{Inhibition } (\%) = \left[1 - \frac{\text{pH of sample - pH of blank}}{\text{pH of control - pH of blank}}\right] \times 100$$

IC_{50} values (concentration causing 50% inhibition) were calculated from dose–response curves plotted using non-linear regression analysis (Fig 1) (Nath *et al.*, 2021; Azhar *et al.*, 2022) [5, 34].

Results & discussion

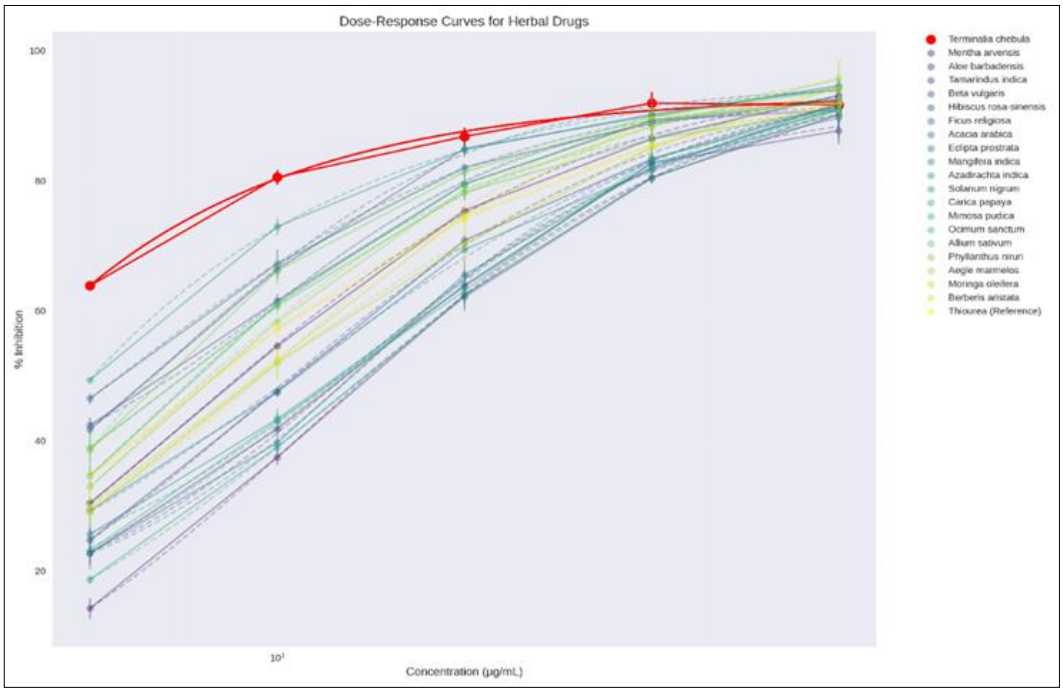

Fig 1: Dose-response curve for all herbal drugs and thiourea, plotting % inhibition (Mean ± SD) against the $\log_{10}$ of concentration (µg/mL). Each curve shows how the percentage inhibition increased with concentration. *Terminalia chebula* is highlighted in red to emphasize its potency compared to the other drugs

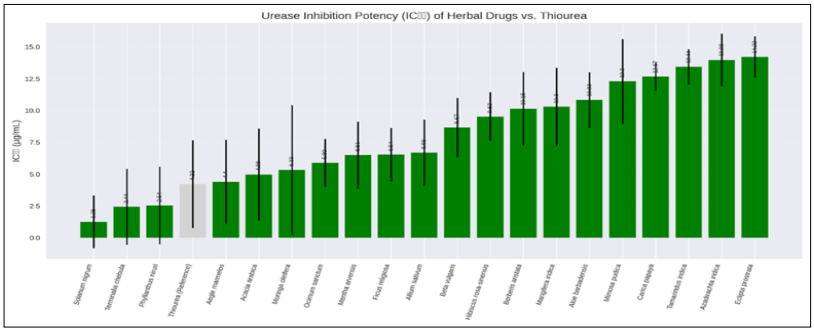

Fig 2: Bar graph comparing the urease inhibition potency (IC_{50} values) of all 20 herbal drugs with that of the reference compound, thiourea. In this plot, thiourea is highlighted in light gray, while all herbal drugs are shown in green.

The IC_{50} values (Fig 2), representing the concentration required for 50% inhibition, revealed significant variability in potency among the tested herbal extracts. Solanum nigrum emerged as the most potent inhibitor, with an exceptionally low IC50 of 1.25 ± 2.07 µg/mL. Similar findings were reported by Singh *et al*. (2020), who identified
Solanum nigrum as a significant source of alkaloids and flavonoids that contribute to strong anti-urease activity. This was followed closely by *Terminalia chebula* (2.44 ± 2.98 µg/mL) and *Phyllanthus niruri* (2.54 ± 3.05 µg/mL), all of which outperformed the reference compound thiourea (4.22 ± 3.44 µg/mL). *Terminalia chebula* and *Phyllanthus niruri* exhibited potent inhibition, consistent with previous studies that highlight their tannin-rich profiles and anti-H. pylori properties (Patel *et al*., 2019; Lin *et al*., 2021) [28, 38]. Moderate activity was observed in *Aegle marmelos* (4.40 ± 3.30 µg/mL) and *Acacia arabica* (4.98 ± 3.60 µg/mL), whereas common medicinal plants such as Ocimum *sanctum* (5.89 ± 1.88 µg/mL) and *Allium sativum* (6.69 ± 2.60 µg/mL) showed intermediate potency. Notably, several traditionally used plants, including *Azadirachta indica* (13.98 ± 2.07 µg/mL) and *Eclipta prostrata* (14.22 ± 1.62 µg/mL), demonstrated relatively weak inhibitory effects. Weaker activity in *Azadirachta indica* and *Eclipta prostrata* aligns with the findings of Ali *et al*. (2018) [2], suggesting variable phytochemical content depending on the extraction method or plant maturity. The high standard deviations observed for the top performers imply potential inconsistencies in phytoconstituent levels, reinforcing the need for standardized extraction and quality control in herbal pharmacology (Zhang *et al*., 2022) [55].

Conclusion

This study highlights the promising potential of herbal alternatives, particularly *Solanum nigrum*, *Terminalia chebula*, and *Phyllanthus niruri*, which demonstrate superior urease inhibition compared to the standard inhibitor, thiourea. These plants likely exert their effects through diverse phytochemicals, such as flavonoids, tannins, and alkaloids. Their multitargeted mechanisms, low toxicity, and cost-effectiveness make them suitable candidates for complementary or alternative therapies. However, the significant variability in the IC_{50} values underscores the need for standardization and further pharmacological validation. Integrating such botanicals into modern treatment regimens could enhance the therapeutic outcomes for PUD while helping mitigate the global challenge of antimicrobial resistance. Further studies on bioactive compounds, toxicity, and clinical efficacy are essential.

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