

Economic evaluation of herbal versus antibiotic treatment in treating patients with *Helicobacter pylori* infection in the South of Iran: an analysis alongside a clinical trial

Received: 6 May 2025

Accepted: 6 March 2026

Published online: 17 May 2026

Cite this article as: Faramarzi H., Khajoei Z., Lotfi F. *et al.* Economic evaluation of herbal versus antibiotic treatment in treating patients with *Helicobacter pylori* infection in the South of Iran: an analysis alongside a clinical trial. *J Health Popul Nutr* (2026). <https://doi.org/10.1186/s41043-026-01296-9>

Hossein Faramarzi, Zahra Khajoei, Farhad Lotfi, Mehdi Rezaee, Khosro Keshavarz, Mohammad Mahdi Mojahedian, Seyedeh Azra Shamsdin & Kamran Bagheri Lankrani

We are providing an unedited version of this manuscript to give early access to its findings. Before final publication, the manuscript will undergo further editing. Please note there may be errors present which affect the content, and all legal disclaimers apply.

If this paper is publishing under a Transparent Peer Review model then Peer Review reports will publish with the final article.

Economic Evaluation of Herbal versus Antibiotic Treatment in Treating Patients with *Helicobacter pylori* Infection in the South of Iran: An Analysis alongside a Clinical Trial

Hossein Faramarzi¹, Zahra Khajoei², Farhad Lotfi³, Mehdi Rezaee^{2,3,4*}, Khosro Keshavarz^{3*}, Mohammad Mahdi Mojahedian⁵, Seyedeh Azra Shamsdin⁶, Kamran Bagheri Lankrani⁷

¹Department of Community Medicine, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran. E-mail: hossainfaramarzi@yahoo.com

²Student Research Committee, School of Health Management and Information Sciences, Shiraz University of Medical Sciences, Shiraz, Iran. E-mail: zahraKhajoei2579@gmail.com

³Health Human Resources Research Center, School of Health Management and Information Sciences, Shiraz University of Medical Sciences, Shiraz, IR, Iran. E-mail: lotfifarhad@gmail.com

⁴ Department of Management, Economics and Health Policy, School of Health, Bushehr University of Medical Sciences, Bushehr, Iran. E-mail: m.rezaee8666@yahoo.com

⁵ Department of Pharmacoeconomics and Pharmaceutical Administration, School of Pharmacy, Iran University of Medical Sciences, Tehran, Iran. E-mail: mahdimojahedian@gmail.com

⁶ Gastroenterohepatology Research Center, Shiraz University of Medical Sciences, Shiraz, Iran. E-mail: rozshams@yahoo.com

⁷ Health Policy Research Center, Shiraz University of Medical Sciences, Shiraz, Iran. E-mail: lankaran@sums.ac.ir

*Corresponding Author:

Khosro Keshavarz: Health Human Resources Research Center, Department of Health Economics, School of Health Management and Information Sciences, Shiraz University of Medical Sciences, Shiraz, Iran Tel.: +989173301430, Tel/Fax: 09173301430, E-mail: khkeshavarz2007@gmail.com, <https://orcid.org/0000-0002-5778-5502>

Mehdi Rezaee: Health Human Resources Research Center, Department of Health Economics, School of Health Management and Information Sciences, Shiraz University of Medical Sciences, Shiraz, Iran Tel.: +989176293292, Tel/Fax: 07733341976, E-mail: m.rezaee8666@yahoo.com, <https://orcid.org/0000-0002-2241-4402>

*** Mehdi Rezaee and Khosro Keshavarz, had equal participation as the corresponding authors and we would like to consider both as the corresponding authors.**

Abstract

Objectives: *Helicobacter pylori* (**H. pylori**) infection is highly prevalent worldwide and affects more than half of the world's population. Various treatment regimens to eliminate H. pylori have been evaluated; however, selecting the most cost-effective regimen remains a challenge for clinicians. Therefore, the present study aimed at analyzing the cost-effectiveness of using different methods to treat H. pylori in southern Iran. **Methods:** A cost-effectiveness analysis was conducted alongside a clinical trial that compared antibiotics versus herbal treatment in 132 patients with H. pylori referred to Shahid Motahari Clinic in Shiraz in 2020. A decision-tree model was developed to synthesize clinical and cost data. The patients were randomly divided into two groups, 64 of whom received an antibiotic regimen and 68 patients received a herbal treatment. The success rate of clinical trials in each treatment method was determined as the clinical outcome. This study was conducted from a societal perspective; therefore, direct and indirect costs were included. A data collection form was also used to collect the cost and effectiveness data. In addition, a one-way sensitivity analysis was performed to measure the robustness of the results. The data were analyzed using Tree Age Pro 2011 and Excel 2016 software.

Results: The results showed that antibiotic treatment was cheaper and more effective than herbal treatment and was the dominant strategy. The mean costs in the antibiotics and herbal treatment groups were \$446.14 and \$477.81, respectively, and the effectiveness was 62.5% and 38.2%. In addition, the one-way sensitivity analysis confirmed the robustness of the study results.

Conclusion: The results showed that the use of antibiotics was a cost-effective and dominant strategy compared to herbal treatment and could be suggested as a better alternative to a wide range of patients with H. pylori infection. This conclusion is tempered by the short-term perspective, single-center design, and modest sample size of the study, highlighting the need for confirmatory long-term, multicenter research.

Keywords: Cost-Effectiveness, Economic Evaluation, *Helicobacter pylori*, Antibiotic, herbal treatment

Introduction

Helicobacter pylori (H. pylori) is the most common bacterial infection worldwide, the prevalence of which among adults in developed countries is 30-70% [1]. However, the infection rate reaches 90% in the first 5 years of life in developing countries [2]. There are various methods for diagnosing H. pylori infection, which can be arranged in the following order based on the accuracy of the studied methods: qPCR > UBT > SAT > RUT > CagA IgG > Culture [3]. As the most common infectious agent, H. pylori is involved in a variety of common gastrointestinal disorders including gastritis, duodenal ulcer, peptic ulcer, adenocarcinoma, and gastric lymphoma[4], and in about 89% of non-cardiac gastric cancers in the world [5]. In addition, it can lead to many diseases of non-digestive origin, such as cardiovascular disease, autoimmunity, Parkinson's, obesity, and allergic disorders [6, 7]. Therefore, preventing or eradicating bacterial infections can help prevent these diseases.

Currently, the major challenge in eradicating H. pylori includes poor patient tolerance to medications, antibiotic resistance, side effects, and the high cost of antibiotic regimens [8]. The rate of antibiotic resistance in different countries shows somewhat similar results, such that in European and American countries, the rate of resistance to metronidazole, levofloxacin, and clarithromycin is more than 30% each and this rate was similar [9, 10]; it also shows that the rate of antibiotic resistance in the second 5 years is higher than in the first 5 years [11]. A similar pattern of resistance is observed in Asian countries[12], where various studies report metronidazole resistance exceeding 70% [13-15]. Studies conducted in Iran show that the highest antibiotic resistance was related to metronidazole (very high resistance between 64.1% and 82.4% in different studies), clarithromycin (variable resistance between 22.5% and 70.7%), and rifampicin/rifampin (significant resistance between 27.78% and 50%). The lowest was related to tetracycline (lowest resistance in most studies between 4.4% and 16%), amoxicillin (relatively low resistance between 18.37% and 30.9%), ciprofloxacin and levofloxacin (moderate resistance between 22.51% and 36.1%) [15-18].

Various treatment regimens containing several antimicrobial compounds have already been examined to eliminate H. pylori infection [19]. The failure of single drug methods has led to the development of drug regimens with a combination of three or four drugs, the most common of which is triple therapy. This treatment regimen includes a proton pump inhibitor and two antibiotics, i.e., amoxicillin and clarithromycin [19, 20]. Early studies suggested that eradication with triple therapy was cost-effective, and resistance to some strains was seen in more than 50% of the patients [8, 21, 22]. However, triple therapy has shown a gradual decrease in efficacy (eradication rate of

<80%) in recent years [8]. It also has side effects such as a metallic taste in the mouth, increased sensitivity to light, constipation, and diarrhea [23]. The use of a four-drug regimen containing proton pump inhibitor, bismuth, and two antibiotics (Metronidazole and Tetracycline) was associated with 80% eradication; it was recommended as a first-line treatment in areas with high resistance (over 15%) to Metronidazole and Clarithromycin in patients who did not respond to the three-drug regimen containing Metronidazole or Clarithromycin [24]. The four-drug regimen is not only very expensive but, in many cases, leads to treatment discontinuation before the end of the treatment course due to the complications such as seizures and polyneuropathy in patients who use metronidazole for a long time [25]. Despite various treatment methods, the recurrence of the disease has been reported in a number of cases after treatment completion. Therefore, the use of herbal medicines may be beneficial due to their numerous medicinal effects [26]. Today, the antimicrobial effects of many plant species (e.g., garlic) on *H. pylori* infection have been investigated and proposed as a way of increasing the efficacy of *H. pylori* treatment [27]. The antimicrobial properties of garlic are primarily attributed to its sulfur compound, allicin, which exerts direct antibacterial activity against a broad spectrum of bacteria, including *H. pylori*; this action is complemented by its ability to inhibit key host inflammatory pathways, such as by deactivating NF- κ B to reduce pro-inflammatory cytokines and by scavenging free radicals to mitigate the oxidative stress and carcinogenic byproducts of infection. Mint, containing essential oils like menthol and menthone, demonstrates direct inhibitory effects against pathogens and provides significant gastrointestinal symptom relief through its antispasmodic and antifatulent properties, which aid the host despite a less-defined biochemical mechanism compared to garlic. The main antimicrobial agent in Green tea, Epigallocatechin-3-gallate, functions crucially by inhibiting the bacterial enzyme urease, which is essential for *H. pylori* to survive the acidic environment of the stomach, thereby compromising its viability directly at the site of infection [28-30]. This specific combination was selected for our trial based on the complementary mechanisms and evidence of each component: Garlic's allicin exhibits direct bactericidal effects and has been shown in meta-analyses to increase eradication rates as an adjunct [31]. Mint's essential oils offer documented antibacterial and antispasmodic properties to alleviate symptoms [29]. Green tea's catechins, especially EGCG, potently inhibit *H. pylori* urease activity [32]. The results of a study showed that adding garlic extract to the standard anti-*H. pylori* infection regimen increased its eradication rate from 52.6% to 75.8% [31]; long-term consumption of garlic reduced the risk of gastric and colon cancers [33]. Thus, considering the high prevalence of gastrointestinal diseases in the

world, especially gastric adenocarcinoma and its relationship with *H. pylori*, choosing the best treatment method that causes the highest eradication rate at the lowest cost is one of the challenges facing physicians [32]. To the best of our knowledge, this study is the first investigation comparing herbal treatment with standard four-drug treatment for *H. pylori* eradication. Given the high antibiotic resistance in Iran and the promising bioactivity of herbal components, we hypothesized that the herbal treatment regimen would be a cost-effective alternative to the standard antibiotic regimen for the first-line treatment of *H. pylori* infection in our setting. Therefore, the present study aimed to analyze the cost-effectiveness of these different *H. pylori* treatment methods.

Materials and Methods

Model Structure

A decision tree model was used to estimate the cost and effectiveness results. A decision tree model visually maps out a series of decisions, potential outcomes, and their associated costs and probabilities to compare alternative courses of action, often used to assess the cost-effectiveness of treatments or interventions. These models feature decision nodes (squares) for choices, chance nodes (circles) for uncertain events, and terminal nodes where costs and health outcomes are quantified to calculate the expected value of each option [34]. Figure 1 shows a schematic diagram of the decision tree model for antibiotic versus herbal treatment strategies. The success and failure of the drugs and their side effects were plotted for each strategy to select the best one. In addition, the costs and effectiveness of each strategy were entered into the model separately. The model pathways were defined by treatment success or failure. Mild side effects that did not alter the treatment course were not represented as separate branches but were accounted for within the measured direct medical costs.

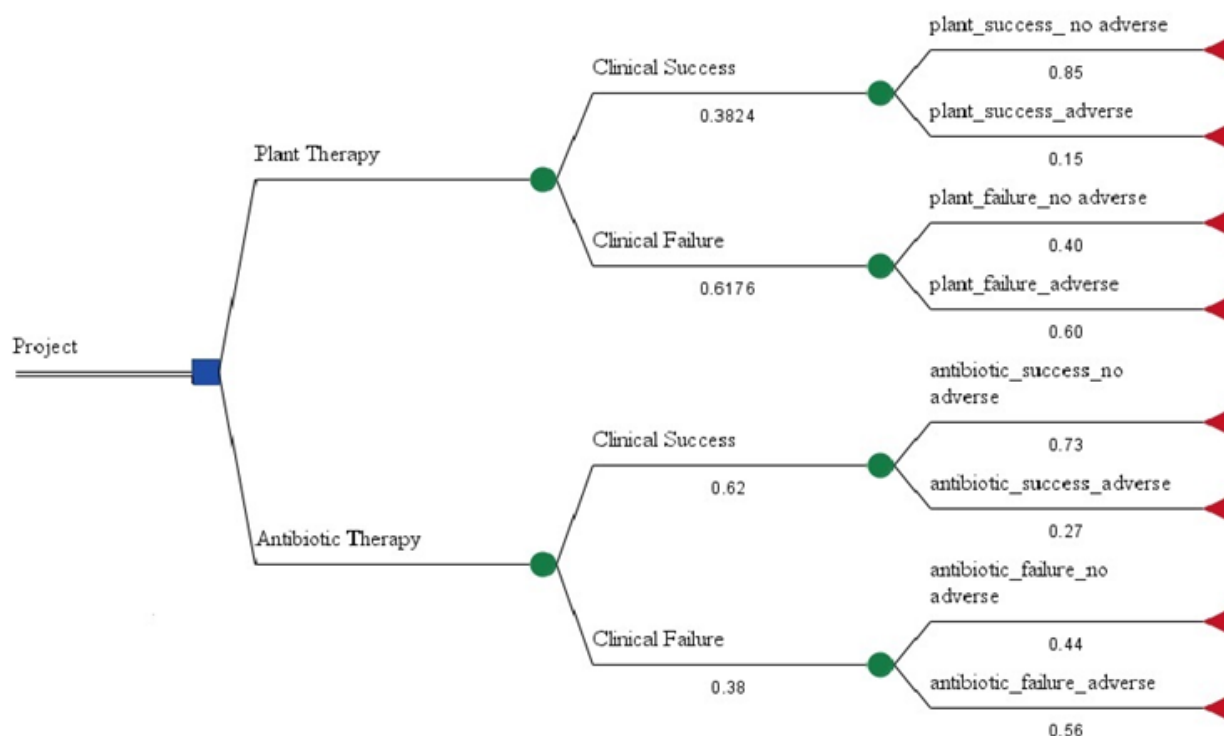


Figure 1: Schematic diagram of the decision tree structure to compare two herbal and antibiotic treatments in patients with *H. pylori* infection

Study population

We performed a cost-effectiveness analysis based on a prospective clinical trial of 132 *H. pylori* patients that compared antibiotic and herbal treatments at Shahid Motahari Clinic in Shiraz (referral clinic) in 2020. The patients were randomly divided into two groups that received antibiotic ($n = 64$) and herbal treatment ($n = 68$) regimens. The antibiotic group was given a drug regimen including pantoprazole 40 mg twice a day, bismuth subcitrate 120 mg and tetracycline 500 mg 4 times a day, and metronidazole 500 mg three times daily for 14 days [23]. The herbal treatment group was given Supermint Barij soft capsules 20 mg[35], [36], Alium S garlic tablets 400 mg[31],[37], and Green Teadin (green tea) tablets 500 mg three times a day for 14 days [38]. [30]. These doses were selected based on their established safety profiles and their use in prior clinical research [30, 36-38].

Randomization and Blinding

In this study, randomization was performed using a computer-generated random number sequence (generated with SPSS v.26 software) that assigned the participants to the two study groups in a 1:1 ratio. To ensure allocation concealment, we maintained the randomization list by an independent research assistant who was not

involved in patient recruitment or outcome assessment. The enrolled participants received their group allocation via sealed opaque envelopes to avoid selection bias. Blinding of participants after group assignment was not possible due to the study design. However, we took the following steps to minimize bias: Outcome assessors (e.g., laboratory technicians performing the urea breath test) were blinded to group allocation. Data collectors for economic outcomes used standardized questionnaires that avoided direct references to treatment type. Statistical and economic analysts were blinded until the final comparison stage.

Inclusion and Exclusion Criteria

The inclusion criteria were as follows: the patients with dyspepsia who had a positive antigen stool test result; lack of consumption of antibiotics for at least 4 weeks before the start of the study; no history of allergies to mint, green tea, and garlic pills; and no use of other adjunctive therapy or medicinal plants for at least two weeks before the start of the study. The exclusion criteria were liver disease, gallstones or biliary obstruction, any gastrointestinal risk symptoms that required endoscopic examination (e.g., weight loss, anemia, severe gastrointestinal symptoms, recurrent vomiting, dysphagia, and gastrointestinal bleeding), lack of consumption of the drugs for at least one day, and lack of taking daily doses. Also, the variables with missing values over 20% were excluded.

Diagnosis and Outcome Assessment

A positive Stool Antigen Test (SAT) was required for study enrollment to confirm active *H. pylori* infection. Eradication was assessed using the same SAT method. The post-treatment SAT was performed once, at least 4 weeks after completion of the 14-day treatment course; this ensured us that the patients had not taken proton pump inhibitors or antibiotics during this interval, in line with standard testing guidelines.

Adherence Measurement

Medication adherence was assessed using the pill count method. Patients were provided with exactly 14 pills at baseline and asked to return the medication bottle after 14 days. The remaining pills were counted by the research team, and adherence was calculated as: $(\text{Number of pills taken} / \text{Number of pills prescribed}) \times 100$. It is important to note that pill count does not capture the timing of dose intake or possible self-report bias.

Measurement of Costs and Effectiveness

Economic evaluation can be conducted from the perspective of the patient (first person), service providers (second person), payers (purchaser or third party), employers (fourth person), government, and society. Economic evaluation can include a narrow or broad dimension. The narrow dimension can only include costs and

consequences from the patient's perspective, but in the broad dimension, the evaluation is conducted from a societal perspective, which, in addition to the costs and benefits of the patient, also includes other providers and members of society in the calculations. In this study, the costs were collected from a societal perspective. Therefore, they included direct medical costs (DMCs), direct non-medical costs (DNMCs), and indirect costs (ICs).

The DMCs encompassed medication, diagnostic tests, physician consultations, and hospitalizations. These also incorporated the costs related to management of the side effects and any subsequent treatments required due to initial treatment failure. The DMC data were collected from the patients' medical records as well as the opinions of clinical experts in this field.

The DNMCs included transportation costs (intra-city and intercity) as well as food and accommodation costs for the patient and companions to receive medical services.

The ICs also included the mean days of absence from work of the patients and companions and reduced productivity lost due to illness, disability, and death. DNMC and IC data were gathered via patient self-reports through face-to-face interviews or telephone calls. While subject to recall bias, this approach was selected because precise records of absenteeism or productivity loss are typically unavailable. To reduce the possibility of recall bias, we used structured questionnaires with objective questions developed by Zare et al. [39]; all cost information was collected quarterly and then multiplied by 4 to obtain annual costs, and data were collected immediately after the end of treatment to minimize recall error [40]. The human capital approach was used to calculate the IC. In addition, all costs were calculated based on the tariffs of 2020 and converted into international dollars (purchasing power parity (PPP)) at the exchange rate of 1 dollar = 22057 Rials [41].

The effectiveness outcome was the success rate, determined by a positive/negative result from an SAT. In accordance with standard post-treatment assessment guidelines, the SAT was performed once, at least 4 weeks after the completion of the 14-day treatment course, ensuring us that the patients had not taken any antibiotics or proton pump inhibitors during this interval to avoid false-negative results [42]. A data collection form was also used to collect the cost and effectiveness data. The results were presented in terms of the incremental cost-effectiveness ratio (ICER). To calculate the ICER, the cost of the new treatment is subtracted from the cost of the previous treatment, and the result is then divided by the difference in effectiveness between the new and the previous treatment. Furthermore, the one-way sensitivity analysis was performed to measure the effects of parameter uncertainty in the model.

Cost-effectiveness analysis

The model was designed in TreeAge Pro 2011 software, and the extracted data were entered into it. The costs, effectiveness, and cost-effectiveness of the two drugs were then calculated and their ICERs were estimated using the following equation. TreeAge Pro 2011 was selected for this purpose as it is specialized, standard software for decision-tree modeling and cost-effectiveness analysis. Microsoft Excel 2016 was used for data management and preparatory calculations. Given the short-term (less than one year) horizon of the analysis, no discounting was applied to costs or outcomes.

$$\text{ICER} = \frac{\text{cost plant} - \text{cost Antibiotics}}{\text{Effectiveness plant} - \text{Effectiveness Antibiotics}}$$

Sensitivity Analysis

The one-way sensitivity analysis was performed to investigate the effects of parameter uncertainty on the results. To this end, some key parameters such as 1- the direct and indirect costs prices, 2- and Effectiveness were changed by 20% for each drug strategy; the results were presented as a Tornado Diagram. In addition, we conducted a probabilistic sensitivity analysis (PSA) using Monte Carlo simulation with 5,000 iterations. Cost parameters were assumed to follow a Gamma distribution (since costs cannot be negative), and effectiveness probabilities were modeled using Beta distributions (bounded between 0 and 1). The distribution parameters were derived from the observed means and standard deviations for each treatment arm. The results are presented as a cost-effectiveness acceptability curve (CEAC) and a scatterplot of the incremental cost-effectiveness plane.

As regards, due to the lack of a cost-effectiveness threshold in Iran and as proposed by the World Health Organization (WHO), the threshold of one to three times the Gross Domestic Product (GDP) per capita was considered for developing countries [43]. The GDP in Iran was \$ 12,547 in 2019 (1* GDP) [44], using which the threshold of willingness to pay (WTP) was \$ 12,547 (1* GDP) in the country [43, 45]. It is worth noting that a preprint of this manuscript has previously been published [46].

Results

A total of 132 patients with *H. pylori* were included in the study. All participants demonstrated perfect adherence, with a mean adherence rate of 100% as measured by the pill count. Table 1 provides descriptive results including the data on gender, age, employment status, and education. The demographic profile indicated that most participants were female (58%), under 50 years of age (76%), employed (25%), and had a high school diploma or lower level of education (79%). Demographic

characteristics were similar between the groups, with no statistically significant differences (Table 1). All 132 patients completed the 14-day treatment course. Adverse effects were reported in 15 patients (23.4%) in the antibiotic group, including nausea (n=8), metallic taste (n=5), and abdominal discomfort (n=2). All were mild and did not lead to discontinuation. No treatment-related adverse events were reported in the herbal group.

Table 1: Demographic variables among patients between the two groups of herbal and antibiotic treatment

Variable	Herbal treatment (n=68)	Antibiotic (n=64)	Total (n=132)	p-value
Sex, n (%)				0.638
Female	41 (60.3%)	36 (56.3%)	77 (58.3%)	
Male	27 (39.7%)	28 (43.8%)	55 (41.7%)	
Age, years				0.105
≤50	50 (73.5%)	50 (78.1%)	100 (75.8%)	
>50	18 (26.5%)	14 (21.9%)	32 (24.2%)	
Employment, n (%)				0.355
Employed/Self-employed	15 (22.1%)	18 (28.1%)	33 (25.0%)	
Unemployed/Other*	53 (77.9%)	46 (71.9%)	99 (75.0%)	
Education, n (%)				0.217
High school or less	57 (83.8%)	48 (75.0%)	105 (79.5%)	
Some college or higher	11 (16.2%)	16 (25.0%)	27 (20.5%)	

* Retired and daily worker

As shown in Table 2, DMCs accounted for the highest costs in both groups (\$ 204.18 PPP in antibiotic and \$ 210.47 PPP in herbal treatments). On the other hand, the lowest costs were associated with indirect costs with an average value of \$ 111.81 PPP in the antibiotic and \$ 119.83 PPP in the herbal treatment methods. Overall, the mean total cost of antibiotic treatment (\$ 446.14 PPP) was lower than herbal treatment (\$ 477.81 PPP).

Table 2: Estimated mean Direct medical and non-medical costs, Indirect costs, and Total costs per patient by Dollar in the herbal treatment and antibiotic groups

Type of Service	Herbal treatment	Antibiotic	p-value
	Mean± SD	Mean± SD	
Direct medical cost			
visit	49.96±9.34	45.33±9.33	0.0106
Drugs	64.86±23.57	72.03±26.73	0.1341
Tests	95.18±17.8	86.35±17.79	0.0106
Other services	0.47±1.9	0.47±1.31	1.0000
Total	210.47±52.61	204.18±55.16	0.5404
Direct non-medical cost			
Transport	100.39±92.95	85.67±70	0.3634
Foods	30.4±40.88	29.37±39.46	0.8938
Accommodation	16.72±26.25	15.11±33.19	0.7735
Total	147.51±160.08	130.15±142.65	0.5543
Indirect cost			
Time spent by the patient's accompany and patient	119.83±67.39	111.81±58.62	0.5130
Total cost			
Direct Medical Costs	210.47±52.61	204.18±55.16	0.5404
Direct Non-medical Costs	147.51±160.08	130.15±142.65	0.5543
Indirect Costs	119.83±67.39	111.81±58.62	0.5130
Total Costs	477.81±280.08	446.14±256.43	0.5414

According to Table 3 and Figure 2, the results of the cost-effectiveness analysis showed that the calculated effectiveness (success rate) of antibiotic and herbal treatment strategies were 62.5% and 38.24%, respectively, and the costs were \$ 446.14 and \$ 457.81 PPP, respectively. Thus, antibiotic treatment was less costly and more effective; therefore, this is a more cost-effective option and a dominant strategy.

Table 3: Comparison between cost and effectiveness in herbal treatment and antibiotic groups

Strategy name	Effectiveness	Incremental Effectiveness	Cost (PPP\$)	Incremental Cost (PPP\$)	ICER
---------------	---------------	---------------------------	--------------	--------------------------	------

Herbal treatment	0.382	-0.243	457.81	11.67	-48.024
Antibiotic	0.625		446.14		

*ICER= Incremental cost effectiveness ratio

Cost-Effectiveness Analysis

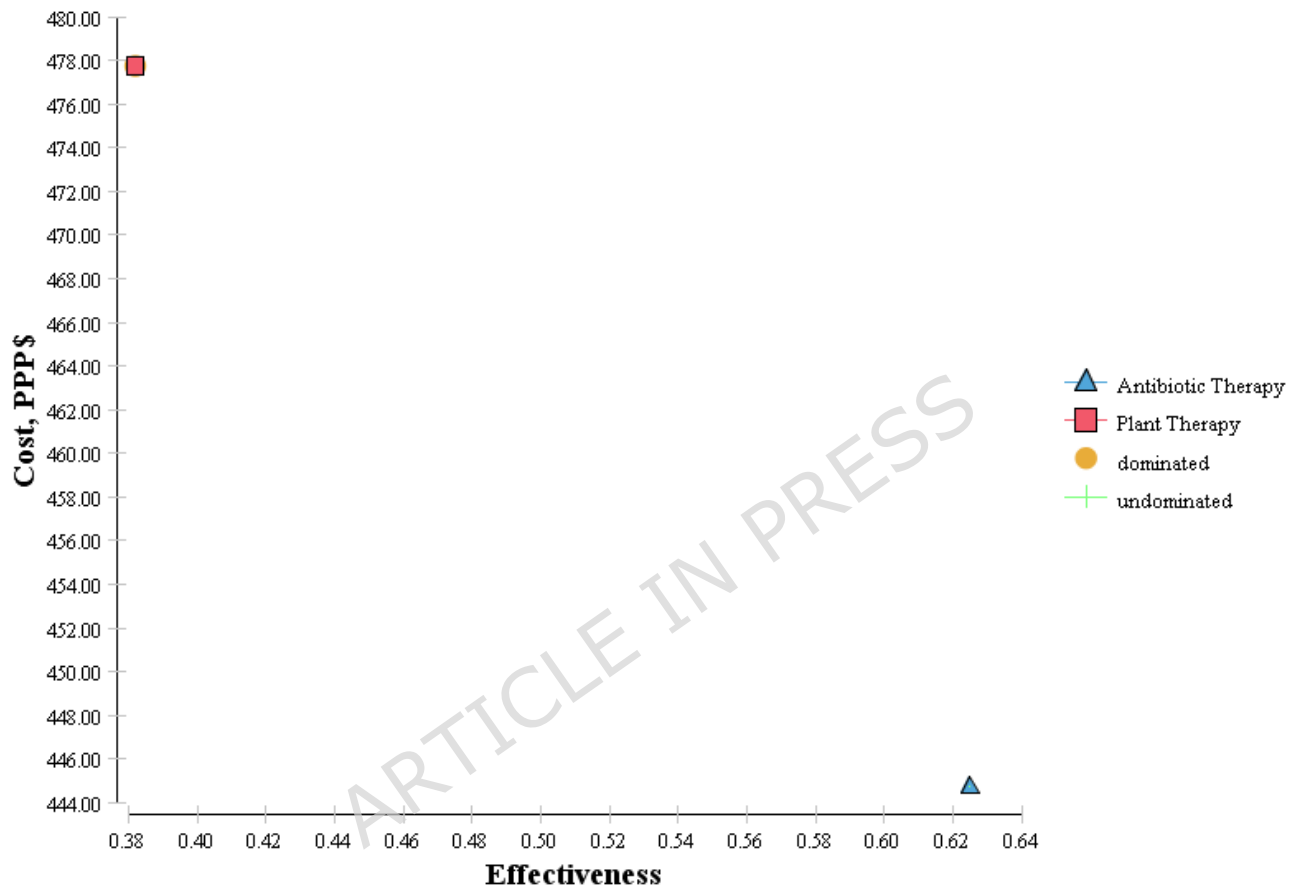


Figure 2: A cost-effectiveness analysis for the herbal and antibiotic treatments in patients with *H. pylori* infection

Uncertainty Analysis

One-way Sensitivity Analysis:

The effects of uncertainty were studied using the one-way sensitivity analysis, and the value of each variable was changed by 20%. Figure 3 presents the results of the one-way sensitivity analysis as a tornado diagram. As shown in the tornado diagram, with a 20% change in the effectiveness of herbal treatment medicines and antibiotics, the ICER remains negative; therefore, the antibiotic regimen is the dominant regimen. However, this change in costs may make the ICER positive, which requires comparison

with the threshold value to decide whether each treatment regimen is dominant. Given that the new ICER is below the threshold, the study results do not change, and the antibiotic regimen remains the dominant regimen. Therefore, it can be said that the changes in many parameters did not have significant effects on the study results. However, ICER had the highest sensitivity to herbal treatment cost and the lowest sensitivity to the effectiveness of herbal treatment in patients with *H. pylori*. In fact, the herbal treatment price was a determining parameter in ICER for the patients with *H. pylori*.

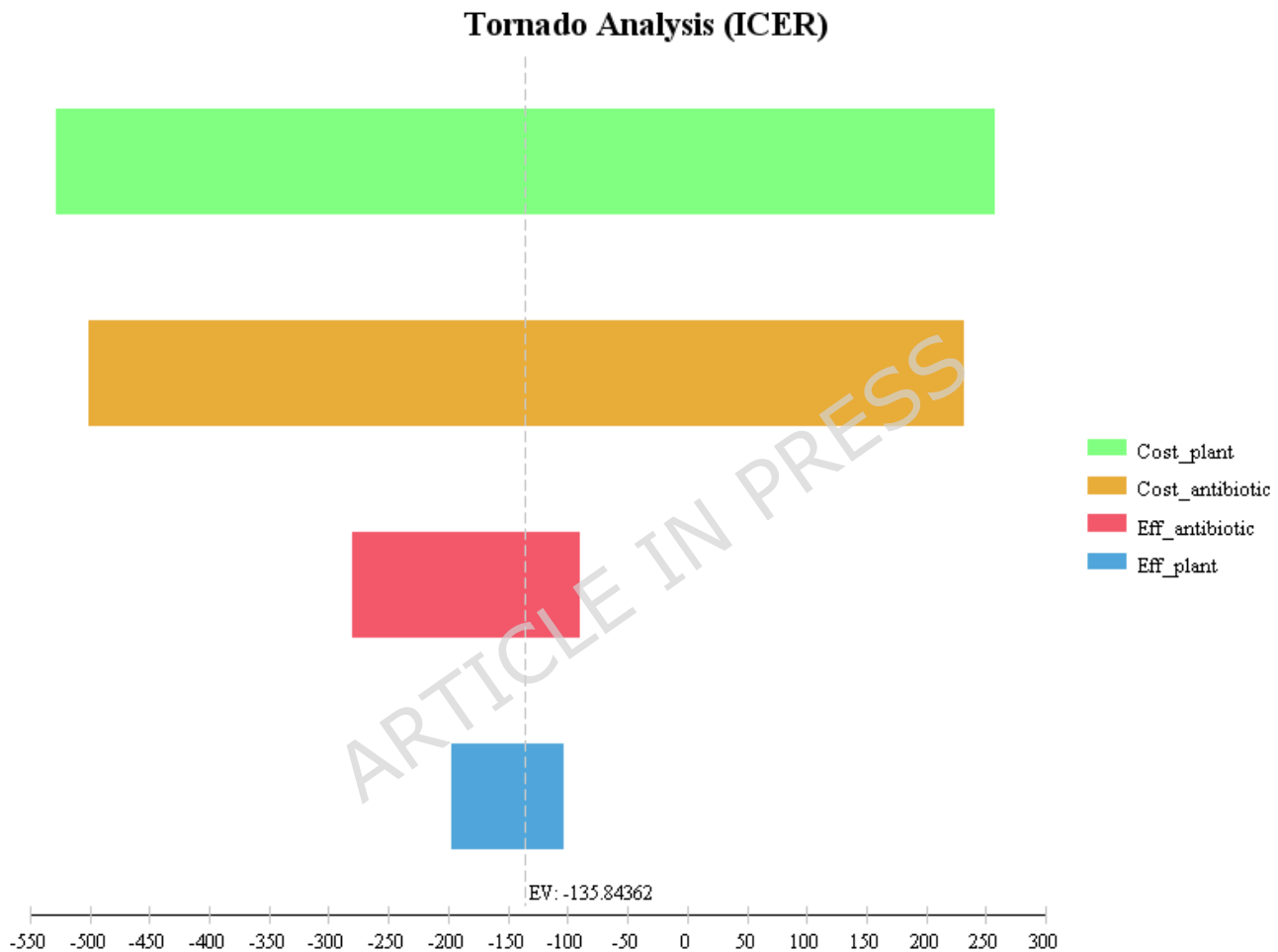


Figure 3: Tornado diagram for the cost-effectiveness of herbal and antibiotic treatments in patients with *H. pylori* infection

Probabilistic Sensitivity Analysis:

The PSA results confirmed the robustness of our base-case findings. At the willingness-to-pay threshold of \$12,547 ($1 \times$ GDP per capita), the antibiotic regimen had a 99.2% probability of being cost-effective, compared to 0.8% for the herbal regimen. The cost-effectiveness acceptability curve demonstrated that the probability of antibiotic therapy being cost-effective remained above 90% across a wide range of WTP thresholds, further supporting its economic favorability (Fig. 4). The scatterplot on the

incremental cost-effectiveness plane showed two distinct patterns: most simulated points for the comparison fell in the southeast quadrant (lower cost, higher effectiveness), confirming antibiotic therapy as the dominant strategy. Additionally, a proportion of points appeared in the northeast quadrant (higher cost, higher effectiveness) but remained below the threshold line, indicating that even when antibiotic therapy was marginally more costly, its superior effectiveness (mean: 67%) compared to herbal therapy (mean: 32%) rendered it cost-effective within conventional benchmarks.

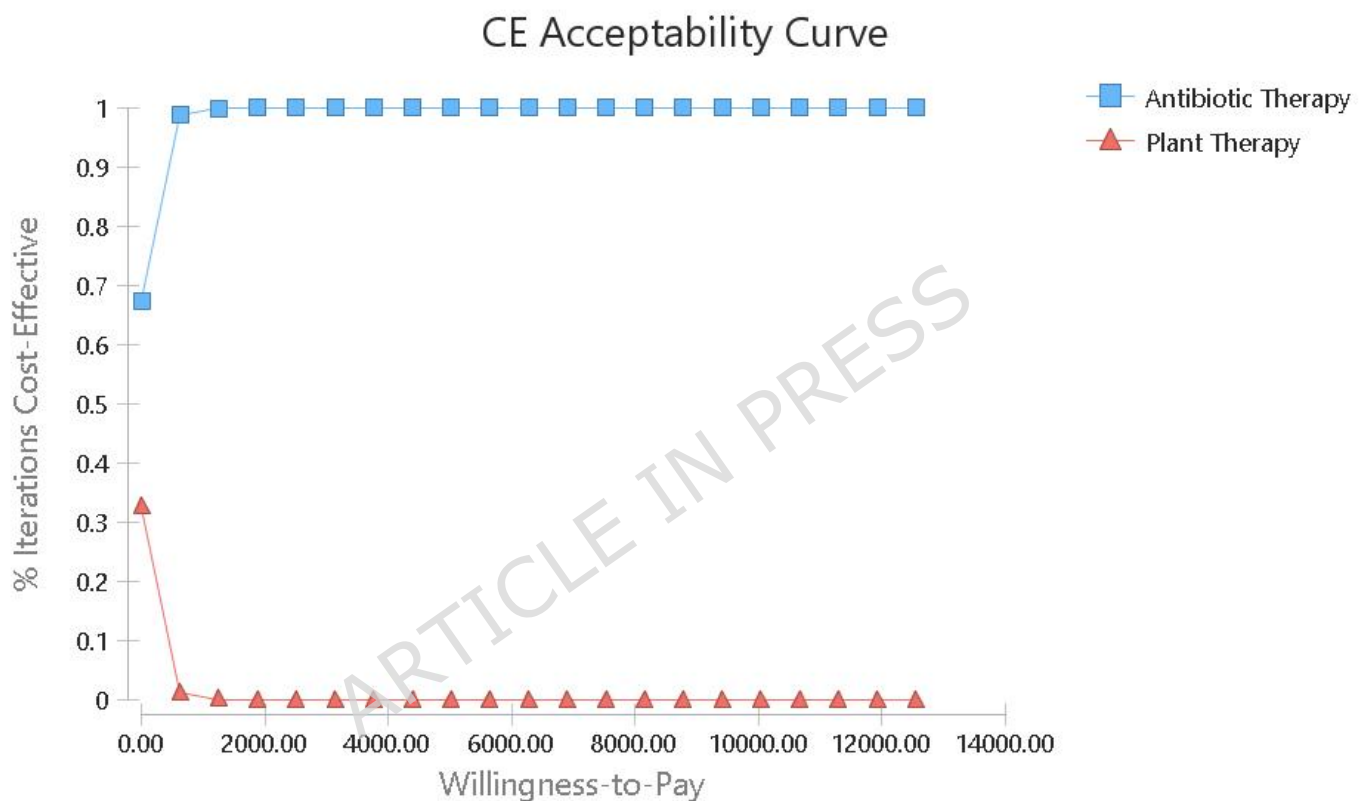


Figure 4: Cost-effectiveness acceptability curve (CEAC) for antibiotic vs. herbal therapy

Incremental Cost-Effectiveness, Antibiotic Therapy v. Plant Therapy

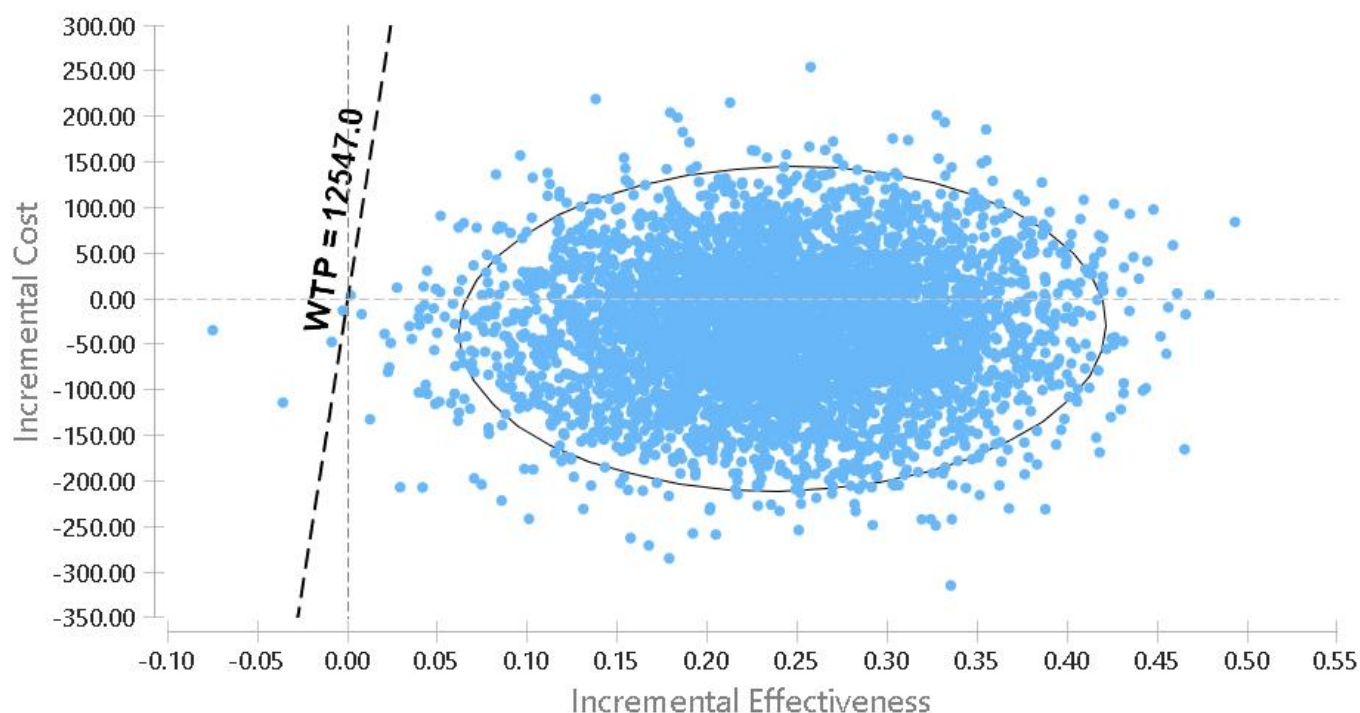


Figure 5: Scatterplot on the incremental cost-effectiveness plane for antibiotic vs. herbal therapy

Discussion

This research represents the first economic analysis from Iran assessing the cost-effectiveness between antibiotic and herbal treatments for *H. pylori*. The main conclusion is that the quadruple antibiotic treatment was more cost-effective than the herbal treatment analyzed.

This finding aligns with previous research. For example, in Korea, modified bismuth quadruple therapy (PAM-B therapy) was more cost-effective than tailored therapy and even more than Korean guidelines [24]. The high cost-effectiveness of various antibiotic regimens is well documented. In Iran and other countries, various studies positioned antibiotics as the first-line treatment, highlighting the success rates of 74% to 89.7% for *H. pylori* eradication with combinations of different antibiotics [47-50]. Still, with other treatment strategies, the 4-drug regimen's cost-effectiveness may not be as favorable. For example, in the U.S., vonoprazan triple therapy was considered the most cost-effective therapy when compared to other regimens which included bismuth quadruple therapy and other bismuth quadruples [51]. Also, in that case, a 14-day IA (Ilaprazole-amoxicillin) dual therapy was cost-effective compared to the quadruple IAFB therapy as it had similar efficacy while costing less; therefore, the dual therapy was more cost-effective when compared to the quadruple therapy for that analysis [52].

In response to rising antibiotic resistance, current guidelines recommend bismuth quadruple therapy or concomitant therapy as first-line options, underscoring their critical role in effective eradication strategies[53]. The choice of first-line regimen should take into account the accessibility and the cost of bismuth and the results of susceptibility testing in the region [54].

Our results suggest much lower eradication rates with herbal therapies (38.2%) than with the antibiotic regimen, contrary to reports indicating the cheaper cost and fewer side effects of herbal therapies [55, 56]. Other studies, as ours, on herbal monotherapies have shown little success, such as the one by Si et al. in which a garlic-containing regimen was ineffective against *H. pylori* when compared to metronidazole [31]. Overall, the evidence is clear regarding herbal therapies; the side effects may be fewer and costs lower, but the eradication of *H. pylori* is much lower with herbal monotherapy, as is the case with probiotics [57, 58]. The mean weighted eradication rate of probiotics, for example, is a mere 14% [59] and no substantial evidence exists to support their use as effective stand-alone treatments to eradicate *H. pylori* [60]; however, a few strains may be effective [61, 62].

With respect to alternative treatment options, the main role is as an adjunct, not a standalone therapy to conventional antibiotic treatment [63]. Adding probiotics to treatment helps eliminate *H. pylori* and reduces the treatment side effects due to the benefits derived from gut microbiota restoration, immune system interactions, and direct antagonism to *H. pylori* [60, 64]. Therefore, the limited success of herbal monotherapies against *H. pylori*, as compared to the high success rates necessary to achieve effective management, can be understood. Overall, the evidence is clear: these adjunct therapies are helpful, but conventional antibiotic treatment is still necessary to achieve success rates that are essential to *H. pylori* management, which are between 70 percent and greater than 90 percent.

Still, the scientific literature is somewhat contradictory, as some works have found that herbal therapies have beneficial effects [65-67]. For instance, Nagata and colleagues reported successful eradication of a *H. pylori* strain with the herbal medicine goshuyuto [68], and Si et al found that adjunctive garlic extract increased the eradication rate of a standard treatment by 93.3% [31]. Other works regarding garlic extract and green tea and conventional therapy reported some level of beneficial impact as well [28, 32, 69, 70].

Many promising preclinical reports involve the use of herbal components as adjuncts to standard antibiotics or testing isolated compounds in vitro [71]. In contrast, our trial evaluated a specific herbal combination as a stand-alone monotherapy, which may not achieve sufficient antibacterial potency in the clinical setting. More specifically, the

standardized extract formulation used, while ensuring quality control, may not have delivered the optimal concentration or bioavailability of active compounds (e.g., allicin, EGCG) at the gastric site of infection. The chosen dose (e.g., 400 mg garlic tablet, 500 mg green tea tablet three times daily) was based on general safety and common use, but may be sub-therapeutic for eradicating an established *H. pylori* biofilm in vivo. Furthermore, a 14-day course—though aligned with our antibiotic arm for comparison—might be insufficient for an herbal monotherapy to achieve eradication, especially if bacterial replication cycles are slower under herbal pressure. The factors related to formulation, dosage, and treatment duration likely explain the discrepancy between the favorable preclinical reports and our negative findings. Moreover, the suboptimal efficacy underscores that antibiotic resistance profiling, as a key component of personalized medicine, could enhance clinical relevance and cost-effectiveness by tailoring treatment [72, 73]. Future trials could explore higher doses, enhanced delivery systems (e.g., enteric-coated capsules), or longer durations to determine whether these adjustments can bridge the efficacy gap. Beyond formulation challenges, the efficacy of any antibacterial regimen, including the quadruple antibiotic therapy used in this study, is highly dependent on local antibiotic resistance patterns. In Southern Iran, where this study was conducted, high reported rates of resistance to metronidazole and clarithromycin [15-18] likely contributed to the moderate eradication rate (62.5%) observed with our bismuth-based quadruple therapy, which still includes metronidazole. This context underscores that even a guideline-recommended regimen may have reduced effectiveness in high-resistance settings. Conversely, the low efficacy of the herbal regimen may also be indirectly influenced by the local bacterial ecology; strains which survive in a high-resistance environment might possess broader adaptive mechanisms [74]. Therefore, the cost-effectiveness results presented here are specific to our regional context and may differ in areas with markedly different resistance profiles. This highlights the importance of developing and continuously updating regional resistance registries to inform empirical therapy choices and economic evaluations.

The robustness of the primary conclusion was also verified through a one-way sensitivity analysis. This indicates that even when varying this parameter, the treatment cost remains favorable (negative), confirming the reliability of the antibiotic regimen as the more cost-effective option across a range of assumptions. Furthermore, the PSA, which incorporated the full uncertainty around cost and effectiveness parameters, strongly supported the primary conclusion. Even when accounting for joint parameter uncertainty through Monte Carlo simulation, the antibiotic regimen

maintained a high probability of being cost-effective at the conventional WTP threshold.

The comprehensiveness of this analysis is one of its strengths and this was apparent through the inclusion of DMCs, DNMCs, and ICs. As the first study of this nature in the Iranian context, it serves as a rich source of evidence for guiding clinical and policy actions surrounding the management of *H. pylori* infection.

Limitation:

This study has several limitations. First, the study was conducted at a single center in Fars province with a modest sample size ($n=132$), which may limit statistical power and the generalizability of the findings to other regions of Iran or different healthcare settings. However, the single-center design was chosen to ensure strict control over confounding variables, diagnostic procedures, and treatment protocols, thereby reducing inter-center variability. Second, due to the inherent differences between the herbal and antibiotic interventions, complete blinding of participants and healthcare providers was not feasible. Although outcome assessors and data analysts were blinded to minimize bias, this partial blinding should be considered when interpreting the results. Third, medication adherence was measured by pill count, which indicated perfect adherence but does not capture the exact timing of dose intake and may be subject to self-report bias. Fourth, our analysis focused on short-term cost-effectiveness using eradication rates as the outcome and did not incorporate quality-adjusted life years (QALYs) or capture long-term outcomes such as recurrence, complications, or sustained quality-of-life changes. Consequently, the findings reflect short-term efficiency and cannot be directly compared to cost-utility analyses or used to assess the long-term economic and health value. Fifth, the study did not include baseline antibiotic resistance profiling of the *H. pylori* strains, which could have provided deeper insights into the efficacy results and allowed for a personalized medicine approach. Finally, this study evaluated herbal and antibiotic treatments only as monotherapies; the cost-effectiveness of their conjunctive use remains unexplored. Future research should address these limitations through larger, multicenter trials with longer follow-up periods (e.g., 12 months) to capture recurrence and long-term outcomes. Incorporating baseline antibiotic resistance profiling and QALY measurement (e.g., using the EQ-5D) would enable more personalized and comprehensive cost-utility analyses. Investigating the cost-effectiveness of combining herbal therapies with antibiotic therapies is also recommended. Given the suboptimal efficacy of herbal monotherapy, future research should explore its potential not as a replacement, but as an adjunct to conventional antibiotic regimens. Investigating whether such combination therapy can improve eradication success, reduce antibiotic-

associated side effects, or lower the risk of resistance could provide a more clinically relevant and valuable application for these herbal components.

Conclusion

This economic evaluation demonstrates that, in the setting of Southern Iran, the bismuth-based quadruple antibiotic regimen is a cost-effective and dominant strategy compared to the tested herbal monotherapy for the first-line treatment of *H. pylori* infection. While the herbal regimen showed lower efficacy and higher cost in this trial, its suboptimal performance likely reflects limitations related to dosage, bioavailability, and treatment duration as a stand-alone therapy, rather than a definitive rejection of all herbal approaches. Importantly, the moderate eradication rate achieved even by the standard antibiotic regimen underscores the significant local challenge of antibiotic resistance. Therefore, the primary clinical implication is that the quadruple antibiotic therapy remains a more economically viable first-line option in our region. Future research should prioritize investigating optimized herbal formulations as adjuncts to antibiotic regimens, along with region-specific antibiotic resistance profiling, to develop more effective and sustainable eradication strategies in the era of rising antimicrobial resistance.

Acknowledgements

This study was extracted from a master's thesis approved by the Ethics Committee (IR.SUMS.NUMIMG.REC. 1399.128) and sponsored by Shiraz University of Medical Sciences. The authors appreciate all the patients and their companions who patiently contributed to this study despite the suffering caused by the disease. The authors would like to thank Shiraz University of Medical Sciences, Shiraz, Iran, and Center for Development of Clinical Research of Nemazee Hospital and Dr. Nasrin Shokrpour for editorial assistance.

List of abbreviations

H. pylori: Helicobacter pylori, ICER: Incremental Cost-Effectiveness Ratio, DMC: Direct Medical Costs, DNMC: Direct Non-Medical Costs, IC: Indirect Costs, WHO: World Health Organization, PPP: Purchasing Power Parity, GDP: Gross Domestic Product, PSA: Probabilistic Sensitivity Analysis, WTP: Willingness to Pay

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Shiraz University of Medical Sciences, Shiraz, Iran. Written informed consent was further obtained from all the patients (Approval NO: IR.SUMS.REC. 1399.128)

Consent for publication:

All participants completed a consent form, stating that they were well-informed about the content of questionnaires and that they agreed upon the publication of anonymized data.

Availability of data and material:

The data used in this study is not publicly available because the participants were promised that the raw data would remain confidential. However, they are available from the corresponding author on reasonable request.

Competing interests:

The authors declare that there is no conflict of interest.

Funding:

This study was financially supported by a grant from Shiraz University of Medical Sciences, Shiraz, Iran (Grant No. -98-01-62-19887).

Authors' contributions:

Conception and design: H.F., Z.Kh., F.L., Kh.K.; Material preparation and data collection: H.F., SA. SH., K.BL., Z.Kh., F.L., M.R., M.M.M, Kh.K.; Data analysis: Z.Kh.; Interpretation of data: H.F., SA. SH., K.BL., Kh., F.L., M.R., M.M.M, Kh. K; The first draft of the manuscript was written by SA. SH., K.BL., Supervision: Kh.K. and All authors read and approved the final manuscript.

References:

1. Chen Y-C, Malfertheiner P, Yu H-T, et al. Global Prevalence of *Helicobacter pylori* Infection and Incidence of Gastric Cancer Between 1980 and 2022. *Gastroenterology*. 2024;166:605-19.
2. Hooi JKY, Lai WY, Ng WK, et al. Global Prevalence of *Helicobacter pylori* Infection: Systematic Review and Meta-Analysis. *Gastroenterology*. 2017;153:420-9.
3. Hussein RA, Al-Ouqaili MTS, Majeed YH. Detection of *Helicobacter Pylori* infection by invasive and non-invasive techniques in patients with gastrointestinal diseases from Iraq: A validation study. *PLoS One*. 2021;16:e0256393.
4. Arenas A, Serrano C, Quiñones L, et al. High prevalence of clarithromycin resistance and effect on *Helicobacter pylori* eradication in a population from Santiago, Chile: cohort study and meta-analysis. *Sci Rep*. 2019;9:20070.
5. Yang L, Kartsonaki C, Yao P, et al. The relative and attributable risks of cardia and non-cardia gastric cancer associated with *Helicobacter pylori* infection in China: a case-cohort study. *Lancet Public Health*. 2021;6:e888-e96.
6. Kim SE. Changes in Metabolic Parameters by *Helicobacter pylori* Eradication According to Sex Differences. *Gut Liver*. 2023;17:1-2.
7. Pădureanu V, Dop D, Caragea DC, et al. Cardiovascular and Neurological Diseases and Association with *Helicobacter Pylori* Infection—An Overview. *Diagnostics*. 2024;14:1781.
8. Kim SY, Chung J-W. Best *Helicobacter pylori* Eradication Strategy in the Era of Antibiotic Resistance. *Antibiotics*. 2020;9:436.
9. Mégraud F, Graham DY, Howden CW, et al. Rates of Antimicrobial Resistance in *Helicobacter pylori* Isolates From Clinical Trial Patients Across the US and Europe. *Official journal of the American College of Gastroenterology | ACG*. 2023;118.
10. Ho JJC, Navarro M, Sawyer K, et al. *Helicobacter pylori* Antibiotic Resistance in the United States Between 2011 and 2021: A Systematic Review and Meta-Analysis. *Official journal of the American College of Gastroenterology | ACG*. 2022;117:1221-30.
11. Saracino IM, Fiorini G, Zullo A, et al. Trends in Primary Antibiotic Resistance in *H. pylori* Strains Isolated in Italy between 2009 and 2019. *Antibiotics*. 2020;9:26.
12. Hussein RA, Al-Ouqaili MTS, Majeed YH. Detection of clarithromycin resistance and 23S rRNA point mutations in clinical isolates of *Helicobacter pylori* isolates: Phenotypic and molecular methods. *Saudi J Biol Sci*. 2022;29:513-20.
13. Geng T, Yu Z-S, Zhou X-X, et al. Antibiotic resistance of *Helicobacter pylori* isolated from children in Chongqing, China. *European Journal of Pediatrics*. 2022;181:2715-22.
14. Shetty V, Lamichhane B, Tay CY, et al. High primary resistance to metronidazole and levofloxacin, and a moderate resistance to clarithromycin in *Helicobacter pylori* isolated from Karnataka patients. *Gut Pathogens*. 2019;11:21.
15. Farzi N, Yadegar A, Sadeghi A, et al. High Prevalence of Antibiotic Resistance in Iranian *Helicobacter pylori* Isolates: Importance of Functional and Mutational Analysis of Resistance Genes and Virulence Genotyping. *Journal of Clinical Medicine*. 2019;8:2004.
16. Alihosseini S, Ghotaslou R, Heravi FS, et al. Management of antibiotic-resistant *Helicobacter pylori* infection: current perspective in Iran. *Journal of Chemotherapy*. 2020;32:273-85.
17. Jafari-Sales A, Jafari B, Khaneshpour H, et al. *Helicobacter pylori*: a systematic review of drug resistance in Iran. *Reviews and Research in Medical Microbiology*. 2024;35:36-41.
18. Hamidi S, Badmasti F, Sadeghpour Heravi F, et al. Antibiotic resistance and clonal relatedness of *Helicobacter pylori* strains isolated from stomach biopsy specimens in northeast of Iran. *Helicobacter*. 2020;25:e12684.
19. De Francesco V, Zullo A, Manta R, et al. First-line therapies for *H. pylori* infection in Italy: a pooled-data analysis. *Acta Gastroenterol Belg*. 2022;85:295-9.
20. Vieira RR, Fontes LES, Pacheco RL, et al. Proton pump inhibitor- and clarithromycin-based triple therapies for *Helicobacter pylori* eradication. *Cochrane Database Syst Rev*. 2020;16.
21. Suzuki S, Esaki M, Kusano C, et al. Development of *Helicobacter pylori* treatment: How do we manage antimicrobial resistance? *World J Gastroenterol*. 2019;25:1907-12.
22. Savoldi A, Carrara E, Graham DY, et al. Prevalence of Antibiotic Resistance in *Helicobacter pylori*: A Systematic Review and Meta-analysis in World Health Organization Regions. *Gastroenterology*. 2018;155:1372-82.e17.

23. Liang JW, Xiong S, Jia YG, et al. Comparison of vonoprazan bismuth-containing triple therapy with quadruple therapy in *Helicobacter pylori*-infected treatment-naïve patients: a prospective multicenter randomized controlled trial. *J Gastroenterol Hepatol*. 2024;39:2293-8.
24. Cho JH, Jin SY, Park S. Comparison of tailored *Helicobacter pylori* eradication versus modified bismuth quadruple therapy in Korea: a randomized controlled trial. *Expert Rev Anti Infect Ther*. 2022;20:923-9.
25. Sørensen CG, Karlsson WK, Amin FM, et al. Metronidazole-induced encephalopathy: a systematic review. *J Neurol*. 2020;267:1-13.
26. Al-Ouqaili MTS, Saleh RO, Amin HIM, et al. Synthesize of pluronic-based nanovesicular formulation loaded with *Pistacia atlantica* extract for improved antimicrobial efficiency. *Arabian Journal of Chemistry*. 2023;16:104704.
27. Nam SY, Jeon SW, Kwon JG, et al. Association of Soy Foods With Gastric Cancer Considering *Helicobacter pylori*: A Multi-Center Case-Control Study. *J Gastric Cancer*. 2024;24:436-50.
28. Wu J, Zhang J, Jin L, et al. Analysis of garlic intake on atrophic gastritis risk in different infectious states of *Helicobacter pylori* in a case-control study. *scientific reports*. 2025;15:8481.
29. Soleimani M, Arzani A, Arzani V, et al. Phenolic compounds and antimicrobial properties of mint and thyme. *Journal of Herbal Medicine*. 2022;36:100604.
30. Edraki M, Mousazadeh Moghaddampour I, Banimahd Keivani M, et al. Characterization and antimicrobial properties of Matcha green tea. *Chemical Review and Letters*. 2022;5:76-82.
31. Si XB, Zhang XM, Wang S, et al. Allicin as add-on therapy for *Helicobacter pylori* infection: A systematic review and meta-analysis. *World J Gastroenterol*. 2019;25:6025-40.
32. Fakharian T, Omidvar L. The Effect of Green Tea (*Camellia sinensis*) on Eradication of *Helicobacter Pylori* Infection in Patients Afflicted in Birjand. *Journal of Birjand University of Medical Sciences*. 2018;25:172-80.
33. Wang Y, Huang P, Wu Y, et al. Association and mechanism of garlic consumption with gastrointestinal cancer risk: A systematic review and meta-analysis. *Oncology letters*. 2022;23:125.
34. Rautenberg T, Gerritsen A, Downes M. Health Economic Decision Tree Models of Diagnostics for Dummies: A Pictorial Primer. *Diagnostics (Basel)*. 2020;10.
35. Chumpitazi BP, Kearns GL, Shulman RJ. Review article: the physiological effects and safety of peppermint oil and its efficacy in irritable bowel syndrome and other functional disorders. *Aliment Pharmacol Ther*. 2018;47:738-52.
36. Drugs.com-Peppermint. Natural Products (Pro). [cited 12-13-2025]. Available from: <https://www.drugs.com/npp/peppermint.html>.
37. Drugs.com-Garlic. Natural Products (Pro). [cited 12-13-2025]. Available from: <https://www.drugs.com/npp/garlic.html>.
38. Hu J, Webster D, Cao J, et al. The safety of green tea and green tea extract consumption in adults - Results of a systematic review. *Regul Toxicol Pharmacol*. 2018;95:412-33.
39. Zare F, Fattahi MR, Sepehrimanesh M, et al. Economic Burden of Hepatitis C Virus Infection in Different Stages of Disease: A Report From Southern Iran. *Hepat Mon*. 2016;16:e32654.
40. Mojahedian MM, Toroski M, Keshavarz K, et al. Estimating the cost of illness of prostate cancer in Iran. *Clinical therapeutics*. 2019;41:50-8.
41. World Bank . PPP conversion factor, private consumption (LCU per international \$) US: The World Bank. ExRates/rates_fa.aspx. [Available from: <http://www.cbi.ir/>].
42. Malfertheiner P, Megraud F, Rokkas T, et al. Management of *Helicobacter pylori* infection: the Maastricht VI/Florence consensus report. *Gut*. 2022.
43. Kazibwe J, Gheorghe A, Wilson D, et al. The use of cost-effectiveness thresholds for evaluating health interventions in low-and middle-income countries from 2015 to 2020: a review. *Value in Health*. 2022;25:385-9.
44. Iran - 2022 GDP per capita. [cited 5-22-2024]. Available from: <https://data.worldbank.org/indicator/NY.GDP.PCAP.PP.CD?locations=IR>.
45. Iran - GDP per capita [Available from: <https://fa.tradingeconomics.com/iran/gdp-per-capita>]
46. Faramarzi H, Khajoei Z, Lotfi F, et al. Cost-effectiveness Analysis of Plant versus Antibiotic Regimens in Treating Patients with *Helicobacter pylori* (*H. pylori*) Infection in the

South of Iran. Research square. 2022 , Available from:

<https://www.researchsquare.com/article/rs-1377344/v1>.

47. Arj A, Mollaei M, Razavizadeh M, et al. The Comparison of Levofloxacin- and Clarithromycin-Based Bismuth Quadruple Therapy Regimens in *Helicobacter pylori* Eradication. *J Res Pharm Pract*. 2020;9:101-5.
48. Dekhnich NN, Tryapyshko AA, Trushin IV, et al. Results of an open-label, randomized, comparative clinical trial of nifuratel in the eradication of *Helicobacter pylori* infection in adult patients. *Clinical microbiology and antimicrobial chemotherapy*. 2020;22:119-27.
49. Hojo M, Asaoka D, Takeda T, et al. Randomized controlled study on the effects of triple therapy including vonoprazan or rabeprazole for the second-line treatment of *Helicobacter pylori* infection. *Therap Adv Gastroenterol*. 2020;13:1756284820966247.
50. Tariq H, Patel H, Kamal MU, et al. Reevaluation of the Efficacy of First Line Regimen for *Helicobacter pylori*. *Clin Exp Gastroenterol*. 2020;13:25-33.
51. Yunusa I, Love BL. Cost-Effectiveness of Vonoprazan-Based and Rifabutin-Based vs Other Regimens as First-Line Treatment of *Helicobacter pylori* Infection in the United States. *Official journal of the American College of Gastroenterology | ACG*. 2023;118:635-44.
52. Niu M, Zhou Y, Xie Y, et al. Comparison of the Dual Therapy of Ilaprazole-Amoxicillin and the Bismuth Quadruple Therapy of Ilaprazole-Amoxicillin-Furazolidone-Bismuth Glycyrrhizinate for Eradication of *Helicobacter pylori*. *Frontiers in Pharmacology*. 2022;13:771876.
53. Fallone CA, Moss SF, Malfertheiner P. Reconciliation of Recent *Helicobacter pylori* Treatment Guidelines in a Time of Increasing Resistance to Antibiotics. *Gastroenterology*. 2019;157:44-53.
54. Ouyang Y, Zhang W, He C, et al. Susceptibility-Guided Therapy vs. Bismuth-Containing Quadruple Therapy as the First-Line Treatment for *Helicobacter pylori* Infection: A Systematic Review and Meta-Analysis. *Frontiers in Medicine*. 2022;9:844915.
55. Yousef-Nezhad H, Hejazi N. Anti-Bacterial Properties of Herbs against *Helicobacter Pylori* Infection: A Review. *International Journal of Nutrition Sciences*. 2017;2:126-33.
56. Ahmed A, Shuaib M, Shirsat MK, et al. Herbal Medicines and Recent Development on Novel Herbal Drug Delivery System. *Indonesian Journal of Pharmaceutical and Clinical Research*. 2023;6:13-24.
57. Nikolić I, Chua EG, Tay ACY, et al. Savory, Oregano and Thyme Essential Oil Mixture (HerbELICO®) Counteracts *Helicobacter pylori*. *Molecules*. 2023;28:2138.
58. Garcia-Castillo V, Marcial G, Albarracín L, et al. The Exopolysaccharide of *Lactobacillus fermentum* UCO-979C Is Partially Involved in Its Immunomodulatory Effect and Its Ability to Improve the Resistance against *Helicobacter pylori* Infection. *Microorganisms*. 2020;8:479.
59. Losurdo G, Cubisino R, Barone M, et al. Probiotic monotherapy and *Helicobacter pylori* eradication: A systematic review with pooled-data analysis. *World J Gastroenterol*. 2018;24:139-49.
60. Penumetcha SS, Ahluwalia S, Irfan R, et al. The Efficacy of Probiotics in the Management of *Helicobacter Pylori*: A Systematic Review. *Cureus*. 2021;13:e20483.
61. Wang S, Zhang M, Yu L, et al. Evaluation of the Potential Protective Effects of *Lactobacillus* Strains against *Helicobacter pylori* Infection: A Randomized, Double-Blinded, Placebo-Controlled Trial. *Can J Infect Dis Med Microbiol*. 2022;2022:6432750.
62. Ermolenko EI, Molostova AS, Baryshnikova NV, et al. The clinical effectiveness of probiotics and autoprobiotics in treatment of *Helicobacter pylori* -associated dyspepsia. *iimm*. 2022;12:726-34.
63. Elghannam MT, Hassanien MH, Ameen YA, et al. *Helicobacter pylori* and oral-gut microbiome: clinical implications. *Infection*. 2024;52:289-300.
64. Baryshnikova NV, Ilina AS, Ermolenko EI, et al. Probiotics and autoprobiotics for treatment of *Helicobacter pylori* infection. *World J Clin Cases*. 2023;11:4740-51.
65. Tai W-C, Liang C-M, Kuo C-M, et al. A 14 day esomeprazole- and amoxicillin-containing high-dose dual therapy regimen achieves a high eradication rate as first-line anti-*Helicobacter pylori* treatment in Taiwan: a prospective randomized trial. *Journal of Antimicrobial Chemotherapy*. 2019;74:1718-24.
66. Barakat SH, Hanafy HM, Guimei M, et al. Different regimens for eradication of *Helicobacter pylori* infection in children: a randomized controlled trial. *European Journal of Pediatrics*. 2024;184:13.

67. Alvarez-Aldana A, Uribe PAF, Valencia TM, et al. Antimicrobial susceptibility of clinical *Helicobacter pylori* isolates and its eradication by standard triple therapy: a study in west central region of Colombia. *Microbiology Spectrum*. 2024;12:e00401-24.
68. Nagata Y, Nagasaka K, Koyama S, et al. Successful eradication of *helicobacter pylori* with a herbal medicine, goshuyuto (Wu Zhu Yu tang), plus rabeprazole after failure of triplet therapy with vonoprazan: a report of three cases. *Journal of digestive diseases*. 2018;19:439-42.
69. Almatroodi SA, Alsahli MA, Almatroudi A, et al. Garlic and its Active Compounds: A Potential Candidate in The Prevention of Cancer by Modulating Various Cell Signalling Pathways. *Anticancer Agents Med Chem*. 2019;19:1314-24.
70. Wang C, Yao M, Zhong H, et al. Natural foods resources and dietary ingredients for the amelioration of *Helicobacter pylori* infection. *Front Med (Lausanne)*. 2023;10:1324473.
71. Vale FF, Oleastro M. Overview of the phytomedicine approaches against *Helicobacter pylori*. *World J Gastroenterol*. 2014;20:5594-609.
72. Al-Ouqaili MTS, Hussein RA, Majeed YH, et al. Study of vacuolating cytotoxin A (vacA) genotypes of ulcerogenic and non-ulcerogenic strains of *Helicobacter pylori* and its association with gastric disease. *Saudi J Biol Sci*. 2023;30:103867.
73. Hussein RA, Al-Ouqaili MT, Majeed YH. Association between alcohol consumption, cigarette smoking, and *Helicobacter pylori* infection in Iraqi patients submitted to gastrointestinal endoscopy. *Journal of Emergency Medicine, Trauma & Acute Care*. 2022;2022:12.
74. Tshibangu-Kabamba E, Yamaoka Y. *Helicobacter pylori* infection and antibiotic resistance - from biology to clinical implications. *Nat Rev Gastroenterol Hepatol*. 2021;18:613-29.