

Synergistic Effect of Cumin (*Cuminum cyminum* L.) Decoction Alongside with Three-drug and Four-drug Treatment Protocols on *Helicobacter pylori* Eradication

Abstract

Background: *Helicobacter pylori* is a major cause of peptic ulcer. On the other hand, cumin (*Cuminum cyminum* L.) is an effective medicinal plant for the treatment of gastrointestinal disease in traditional Persian medicine. This study aimed at investigating the synergistic effect of the decoction of cumin with the three- and four-drug protocols against *H. pylori* in patients with peptic ulcer. Patients with peptic ulcer infected with *H. pylori* were treated with cumin decoction, three- and four-drug protocols, and their co-administration to eradicate *H. pylori*. **Materials and Methods:** Patients were randomly divided into five groups, including group (1) omeprazole with cumin decoction, (2) cumin decoction with the three-protocol treatment, (3) cumin decoction with the four-drug protocol treatment, and (4 and 5) three- and four-drug protocols alone. The cumin fruit powder was given to patients in 3-g packages and decoction was prepared according to the traditional Iranian medicine guidelines. *H. pylori* eradication was measured by the ¹⁴C-urea breath test (¹⁴C-UBT) after 4 weeks of intervention. The Kolmogorov–Smirnov test, χ^2 test, logistic regression, and ANOVA (SPSS, 11.5) were used for data analyses. **Results:** In total, 75 patients (48 male and 27 female patients) participated in this study. The results showed that eradication of *H. pylori* was observed in all five study groups. Eradication of *H. pylori* in cumin decoction with the three-drug protocol group was more than the other groups (85.72%), although this difference was not statistically significant. In addition, this eradication was 61.5% in the cumin + omeprazole group, while the *H. pylori* eradication rates for the three-drug and four-drug protocols were 77.8% and 58.33%, respectively. **Conclusions:** The results showed that decoction of cumin could be used as a complementary treatment alongside conventional medicine therapy to increase the *H. pylori* eradication.

Keywords: *Cuminum cyminum* L., four-drug treatment protocol, *Helicobacter pylori* eradication, peptic ulcer, three-drug treatment protocol

Introduction

Helicobacter pylori, as a human pathogen, are a Gram-negative bacillus that exists in the gastrointestinal tract of humans. The prevalence of *H. pylori* is between 30 and 50% in industrialized countries and more than 80% in developing countries.^[1,2] According to statistical studies, *H. pylori* infection is greater than 74% in some provinces of Iran.^[3] This bacterium not only causes 70 to 90% of gastrointestinal ulcers, especially peptic ulcers, but also causes adenocarcinoma, chronic gastritis, and iron deficiency anemia.^[4-6] *H. pylori* cause gastric ulcers through various mechanisms, including the stimulation of the inflammatory response of gastric epithelial cells to the secretion of some *H. pylori* biomolecules and cytotoxins.^[7,8] According to approved guidelines, the three-

drug treatment protocol including one pump inhibitor (e.g., omeprazole) and two antibiotics (clarithromycin and amoxicillin), and the four-drug treatment protocol including a pump inhibitor (e.g., omeprazole) with bismuth subcitrate and two antibiotics (metronidazole and tetracycline) are the conventional treatments for *H. pylori* eradication.^[9-11] In the past, these treatments led to more than 90% eradication of *H. pylori*, but today the bacteria show resistance to the antibiotics in these protocols and sometimes lead to treatment failure.^[12-14] On the other hand, medicinal plants and their constitutions can treat several targets simultaneously, so they have always been one of the options for discovering new drugs for complex diseases, especially infectious diseases. Several medicinal herbs including *Acacia nilotica*, *Calotropis procera*, *Trachyspermum copticum*, *Glycyrrhiza glabra*,

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Curcuma longa, *Zingiber officinale*, *Petroselinum crispum*, and *Pimpinella anisum* were showed anti-*H. pylori* activities in different studies.^[15-19] Besides, in Iranian traditional medicine, the fruit of cumin (*Cuminum cyminum* L.), as an annual herbaceous medicinal plant from the Apiaceae family, is used to treat the gastrointestinal diseases such as dyspepsia, bloating, and intestinal spasms.^[20] Also, the fruit of cumin showed prominent anti-*H. pylori* effects in several studies.^[21,22] *In vitro* study showed anti-*H. pylori* effects of cumin at minimum inhibitory concentration of 691 µg/mL.^[21] Nostro *et al.* showed that ethanolic extract of the cumin fruit eradicated 90% of the *H. pylori* at 0.075 mg/mL.^[22] O'Mahony *et al.* showed that 50 mg/mL of the cumin decoction eradicated 100% *H. pylori* in culture medium.^[17] Cumin has also been proven to have wound regenerative effects.^[23] On the other hand, several clinical trial investigations reported the anti-*H. pylori* activity of some medicinal plants such as *Cinnamomum zelanicum* and *Nigella sativa*.^[24,25] In a similar study, the use of *Pistacia atlantica* alongside the three-drug treatment protocol was the subject of clinical studies in the treatment of peptic ulcers. Their results showed a significant reduction of *H. pylori* infection ($P < 0.01$) compared to the control group (three-drug treatment protocol alone) in a 14-day treatment.^[26] Based on the above-mentioned need for eradicating *H. pylori*, the present study was designed to investigate the synergistic effect of cumin decoction with three- and four-drug treatment protocols against *H. pylori* in patients with peptic ulcer.

Subjects and Methods

Patients and design

In this study, patients with peptic ulcer in whom the presence of *H. pylori* was confirmed by biopsy tests were participated. They were randomly divided into one of the five study groups. Inclusion criteria were not being pregnant and not having the following cases: kidney, liver and lung failure, any cancer, gastrointestinal surgery, glucose-6-phosphate dehydrogenase enzyme deficiency and not to use NSAIDs and any antibiotics until the implementation of measures related to the project and not have any allergies to studied medications.

Each group is investigated based on age, sex, smoking, duration of illness, number of visits, and weight.^[26,27] The project is recorded before starting in the Ethics Committee of Kermanshah University of Medical Sciences by the number of c/7/420/4148 and the system for recording clinical trials by (I RCT) IRCT2012071510291N1 number. The five studied groups included were (1) 20 mg omeprazole before breakfast and one cup of cumin decoction (100 mL) after breakfast and dinner; (2) 20 mg omeprazole before breakfast, one cup of cumin decoction (100 mL) after breakfast and dinner, 500 mg clarithromycin every 12 h, and amoxicillin 500 mg every 6 h; (3) omeprazole 20 mg before breakfast, one cup of cumin decoction (100 mL) after breakfast and dinner, bismuth subcitrate 120 mg every 6 h, amoxicillin 500 mg every 6 h, and metronidazole 500 mg every 12 h. The fourth and fifth groups included the three-drug protocol (omeprazole

20 mg, clarithromycin 1000 mg, and amoxicillin 2000 mg) and four-drug treatment protocol (omeprazole 20 mg, bismuth subcitrate 480 mg, amoxicillin 2000 mg, and metronidazole 1000 mg). All patients were treated for 14 days.

Preparation of studied medicines

Cumin has been provided from a trusted store of medicinal plants and the plant identity was confirmed by the herbarium of Pharmacognosy Department, School of Pharmacy, Kermanshah University of Medical Sciences, Iran. The cumin fruit powder was given to patients in 3-g packages. The subjects, based on the traditional Iranian medicine guidelines, boiled every cumin powder package in two glasses of water (500 mL) for 5 min.^[20] It should be noted that patients prepared the other prescribed medicines from drug stores and approved by the physician.

Measurement of *H. pylori* eradication rate

The amount of *H. pylori* eradication was measured by ¹⁴C-urea breath test (¹⁴C-UBT) for each patient after 4 weeks of interventions. Subjects take orally a capsule containing 37 kBq (1 µCi) ¹⁴C-urea with 20 mL of drinking water. After 10 min, patients were asked to exhale in the indicator card for 5–10 s, the card was connected to UBT device and the results were recorded. This test was performed before treatment and 4 weeks after completion of the treatment, and eradication rates were calculated in percentage.^[28,29]

Statistical analysis

The SPSS 11.5 software (IBM Corp., Armonk, NY, USA) was used for data analysis. Kolmogorov–Smirnov test, χ^2 test, logistic regression, and ANOVA were utilized for comparative data.

Results

In this study, 75 patients, including 48 male and 27 female patients, with peptic ulcer and with *H. pylori* infection diagnosed by urease test after endoscopy at the baseline participated. All subjects were divided into five groups. The mean age and body weight of subjects were 43.97 ± 15.72 years and 69.73 ± 12.18 kg, respectively. Furthermore, the average number of visits was 1.7 times and the average length of disease was 262 days. The number of smokers was 21 subjects who all were male patients. Quantitative variables has been separately listed for study groups in [Table 1]. Kolmogorov–Smirnov test was used to confirm the normal distribution of the variables.

According to χ^2 test for qualitative variables and variance analysis for quantitative variables related to background variables (age, sex, smoking, duration of illness, number of visits, and weight), there was no significant difference between the study groups ($P > 0.05$). Chi-square test was used to compare the consequence between groups, i.e., elimination of *H. pylori*. The results of this test showed that there was no significant difference between the groups in terms of elimination of *H. pylori* ($P > 0.05$). The results showed that the co-administration of omeprazole and cumin decoction eradicated 61.5% of *H. pylori*. However, the eradication rates

for the three-drug and four-drug protocols were 77.8% and 58.33%, respectively [Table 2]. On the other hand, the cumin plus three-drug protocol (85.3%) and three-drug protocol without cumin (77.8%) had the highest rate of eradication of *H. pylori*.

Discussion

Today, drug resistance to antibiotics by microorganisms has become a global problem. Drug resistance of some bacteria such as *H. pylori* is also growing rapidly. Accordingly, finding new treatment strategies to eradicate *H. pylori* has been always an important issue for researchers. One of these new approaches is the use of herbs as a complementary treatment for their synergistic effects with other antibiotics. This makes

not only the eradication of *H. pylori* consumption alongside other antibiotics but also reduces drug resistance and side effects of these drugs.^[30,31] In this study, the efficacy of cumin on *H. pylori* eradication has been investigated (as it was seen *in vitro* studies) for patients with peptic ulcers infected by these bacteria. On the basis of our results, high efficacy of adding cumin to four- and three-drug treatment protocols can be explained by the synergistic effect of cumin on the eradication of *H. pylori*. Besides, the anti-*H. pylori* activities of aqueous cumin fruit extract may be attributed to the presence of alkaloids, flavonoids, sesquiterpene glycosides, saponins, and essential oil that these phytochemicals showed antimicrobial activity in several studies.^[32-35] However, the healing role of cumin wounds should not be overlooked. Al

Table1: General characteristics of the groups in the study of the synergistic effect of cumin decoction (*C. cyminum* L.) alongside three-drug and four-drug treatment protocols on *H. pylori* eradication

Group	Frequency	Statistical characteristics	Age	Weight (kg)	Duration (days)	Number of visits	Sex		Smoking	
							Male	Female	Yes	No
Cumin + Omeprazole	13	Mean	43.62	72.62	92.15	2.00	8 (61.5%)	5 (38.5%)	3 (23.1%)	10 (76.9%)
		Std. deviation	12:25	11:22	124.23	1.91				
		Minimum	22:00	53.00	14:00	0.00				
		Maximum	59.00	100	365.00	6.00				
Three-drug protocol + Cumin	14	Mean	38.07	70.86	88.07	1.86	8 (57.1%)	6 (42.9%)	5 (35.7%)	9 (64.3)
		Std. deviation	15:16	17.90	187.37	1.70				
		Minimum	19:00	40.00	3.00	0.00				
		Maximum	62.00	100.00	730	7.00				
Four-drug protocol + Cumin	18	Mean	49.44	67.94	424.06	2.67	10 (55.6%)	8 (44.4%)	5 (27.8%)	13 (72.2%)
		Std. deviation	19:11	10:15	444.9	1.82				
		Minimum	24.00	55.00	0.00	0.00				
		Maximum	85.00	84.00	1400	6.00				
Three-drug protocol	18	Mean	43.28	67.28	408.06	1.28	12 (66.7%)	6 (33.3%)	4 (22.2%)	14 (77.8%)
		Std. deviation	16:47	9.83	467.23	1.02				
		Minimum	20:00	50.00	0.00	0.00				
		Maximum	69.00	83.00	1400.00	3.00				
Four-drug protocol	12	Mean	44.08	71.67	192.83	.7500	10 (83.3%)	2 (16.7%)	4 (33.3%)	8 (66.7%)
		Std. deviation	12:27	11.98	271.04	0.87				
		Minimum	25.00	48.00	3.00	0.00				
		Maximum	65.00	90.00	730.00	3.00				
Total	75	Mean	43.97	69.73	262.97	1.76	48 (64%)	27 (36%)	21 (28%)	54 (72%)
		Std. deviation	15.73	12:18	371.97	1.63				
		Minimum	19:00	40.00	0.00	0.00				
		Maximum	85.00	100.00	1400.00	7.00				

Table2: Comparison of the results of different *H. pylori* eradication groups based on χ^2 test

Group	Test		Pearson χ^2 value	P-value	Degree of freedom
	Eradication	No eradication			
Cumin + omeprazole	8	5	5.93	0.205	4
	61.5%	38.5%			
Three-drug protocol + cumin	12	2	85.72%	14.28%	
	85.72%	14.28%			
Four-drug protocol + cumin	13	5	72.2%	27.8%	
	72.2%	27.8%			
Three-drug protocol	14	4	77.8%	22.8%	
	77.8%	22.8%			
Four-drug protocol	7	5	58.33%	41.67%	
	58.33%	41.67%			

Kofahi and Atta reported that the ethanolic extract of cumin fruit has gastroprotective effects against the ethanol-induced peptic ulcer in rats at 400 mg/kg.^[23] On the other hand, the similar results were reported for *H. pylori* eradication with medicinal plants. Imani *et al.* showed that adding cinnamon extract (40 mg) to three-drug protocol (clarithromycin 500 mg, amoxicillin 1000 mg, and pantoprazole 20 mg) after 14 days increased *H. pylori* elimination to 73.47% in patients. However, eradication was 53.06% in patients taking the three-drug protocol without cinnamon extract.^[25] Also Alizadeh-naini *et al.* reported that administration of 1 g of *N. sativa* for twice a day plus four-drug protocol therapy including metronidazole, amoxicillin, bismuth subcitrate, and omeprazole for 14 days significantly ($P = 0.1$) eradicates *H. pylori* (87.5%) compared to the control group (four-drug protocol without *N. sativa*, 54.54%).^[24] One of the noticeable results of this study was the low efficacy of four-drug protocol treatment which it had response only in 58.3% of patients. This low response can be due to the small size of samples or the drug resistance of *H. pylori* to antibiotics (amoxicillin and metronidazole) as reported in other studies.^[14,36] Finally, the effectiveness of cumin decoction studied in the first group can be considered for further investigation.

Conclusion

The results of this study showed that the decoction of cumin could be used as a complementary treatment along with common protocols to increase their effectiveness. In addition, the results showed that there is no significant difference between the intervention groups to eradicate *H. pylori*, so it may be possible to use cumin fruit instead of antibiotics with high side effects, although its confirmation requires large-scale clinical trial studies. The small size of samples and the lack of patients' return after receiving one of the treatment protocols were limitations of this study. Therefore, cultural policies and necessary training are required for patients to assist in clinical research activities.

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Conflict of interest

There is no conflict of interest.

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