



## Comparing the Combined Effect of Garlic and Mint Extract with Metronidazole in Helicobacter Pylori Treatment

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### Abstract

Helicobacter pylori infection is one of the most common human infections which have been associated with many upper gastrointestinal complications. Different treatment regimens for Helicobacter pylori eradication have been used. One of these regimes is the quadruple therapy regimen which metronidazole is one of the medications. In recent years several reports on *H. pylori* resistance to this antibiotic has been presented. This study was performed to compare the effects of garlic and peppermint extract combination with metronidazole in the treatment of Helicobacter pylori infection. In this randomized double blind clinical trial, 142 patients who were eligible for inclusion in study after completing the questionnaire and consent form were randomly divided into two groups, receiving garlic and peppermint extract or metronidazole. Moreover, for both groups the drugs; amoxicillin, omeprazole and bismuth were also administrated. Two weeks after drug administration completion, urease breath test (UBT) was performed and based on the obtained data, the recovery rate in the two groups were compare using SPSS 16 software T-test and Ki square. The patients mean age was  $43.89 \pm 13.37$  years. Evaluating the age and sex factors, we found no significant difference between two groups. Results suggest that although the combination of amoxicillin, omeprazole, bismuth plus garlic and peppermint was not successful in the eradication of Helicobacter pylori such as the quadruple therapy, but less than half of cases lead to eradication of Helicobacter pylori infection.

**Keywords:** Garlic extract, Helicobacter pylori Peppermint extract, Urease breath test.

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## 1. Introduction

Peptic ulcer is a mucous lesion in stomach and duodenum, in which acid and pepsin play a major pathogenic role. Nowadays, scientific observations have shown that *Helicobacter pylori* has a pivotal role in developing these lesions. Many reported disorders of gastric acid secretion in the patients with peptic ulcer have been directly associated with infection with this bacterium. At present, *H. pylori* is the most prevalent chronic infectious disease in human that can cause gastritis, peptic ulcer, adenocarcinoma, and gastric B cell lymphoma. There is a variety of ways to detect this bacterium in human including rapid urease test, respiratory test, serology, and gastric tissue histology [1].

The antibiotics used for treating this infection consist of amoxicillin, tetracycline, metronidazole, and claritromycin. In addition, medicines such as bismuth, proton pump inhibitors (like omeprazole), and H<sub>2</sub>-blockers (like ranitidine) are used in treating this infection [2]. In a research a four-medicine regimen, consisting of amoxicillin, claritromycin, metronidazole, and omeprazole, was adopted for a week to examine the level of eliminating *H. pylori* in the patients with

peptic ulcer. The results showed that 91.7 % of the patients were not completely treated [3].

At present, the types resistant to antibiotal treatment have been observed in *H. Pylori*-positive patients, which is one of the reasons for treatment failure in the patients who follow treatment. On the other hand, a lot of studies have been conducted, so far, on the varieties of combined therapeutical regimens and their durations in patients with *H. Pylori*-positive peptic ulcer, and the anti-*H. pylori* effect of many versatile plants has been confirmed in traditional medicine. Garlic is one of these plants which have been used traditionally by people. Garlic is bulbous herb from Liliaceae family, scientifically called *Allium sativum* [4]. Many people and experts in herbal sciences believe that this plant is useful for gastrointestinal disorders including the disorders derived from food digestion. For many years this plant has been used as a medication in traditional and empirical medicine for treating meningitis and/or parasitic diseases like *Himenolepisnana* and *Lishmania* [5].

Garlic has important compounds such as alin, aleis, polysulphides, mercaptans, thioglycosides, sulphates, and adenosin. Its extract has numerous effects such as antibacterial, antiviral, antifungal, anticoagulant, and serum lipidocholesterol- and blood sugar-reducing [6, 7]. Kokar C examined inhibitory activity of alisin, ascorbic acid, and Karoten against *H. pylori* in 210 patients who whose biopsy was *H. pylori*-positive. The results showed that alisin can

potentially be effective in eradicating *H. pylori* [8].

Mint is one of the popular and useful vegetables. According to the traditional textbooks, it seems that this plant has been used, for the first time, by Iranians for treating some diseases. Mint extract has some volatile oils such as mentol, menten, carvon, limonene, 1, 8-cineol, linalool, and isamenthone. It also increased gastric muscle defence and decrease blood viscosity. In addition, it is considered strengthening and stimulating in depression, physical and mental tiredness, and also influences the nervous system by calming down the muscular and even vernacular spasm. Accordingly, it has been prescribed for dizziness, anxiety, migraine, and nervous diseases. Mint is antispasmodic, antifatulent, and, reduces LES pressure, and also contributes to food digestion. It is also used as an antiseptic agent and mouth smeller as well as for gastric disorders, diarrhea, and for stimulating bile secretion in jaundice and other liver diseases. In the United States, it is planted in large quantities for producing artificial volatile essences in chewing gum industry.

In an investigation to study the inhibitory effects of mint essential oil on the growth of pathogenic bacteria, Imani et al. found that mint essential oil is effective on *H. pylori*, *Salmonella*, and *Eschershia coli* [9].

Considering people's willingness towards consuming medicinal plants and numerous reported medicinal resistances to the common antibiotics such as metronidazole, Rojas Feria et al. conducted a study in a hospital on the

resistance of *H. pylori* to antimicrobial treatment and found that resistance to metronidazole was 42% in a group of patients. In a study by Vincent R et al. On fighting *H. pylori* in the patients with peptic ulcer, the treatment failure was 60% (24/40) and also 80 (49.9% of) species were resistant to metronidazole [10]. Therefore, considering the resistance developed toward metronidazole, which has been observed in many studies of *H. Pylori* treatment, few side effects of garlic and mint, their useful properties for gastrointestinal diseases, the anti- *H. pylori* effects of mint (which removes the potential side effects of consuming garlic), as well as existence of the two plants in people's diet, in this study we examined anti- *H. pylori* effects of their simultaneous consumption through introducing and replacing them simultaneously in common therapeutical regimens for fighting *H. pylori*.

## 2. Materials and Methods

In a randomized clinical trial study, endoscopy and urease test were done on the patients referring to Gastrointestinal Disease Center for gastrointestinal problems, such as pain in the stomach, with endoscopy indication according to gastrointestinologist of the project team and those with positive test were enrolled .

The criteria to enter into the study consisted of positive urease test and the gastric mucosal sample, being consent to cooperate, not having coagulant disorder, not consuming anticoagulant drugs and NSAIDS, not having

allergy to the plants under study, not having stomach or duodenom cancer, not being pregnant, and not breast feeding.

The criteria to exclude from the study consisted of failure to endure therapeutical regimen, failure to continue the treatment, as well as development of coagulant problems.

This study was conducted on 150 patients referring to Endoscopy Ward of Hajar hospital, Shahrekord. In this study, endoscopy and rapid urease test were done on the patients referring to Gastrointestinal Disease Center for gastrointestinal problems, such as epigastric pain, with endoscopy indication according to gastrointestinologist of the project team and those with positive test were enrolled. The research objectives were explained for the patients who were willing to participate in the study. Then, the consent form was filled out by the patients. Having made arrangements with the hospital pharmacy, we introduced the patients enrolled into the study to the pharmacy by reference letters. The pharmacy provided the referred patients randomized with drugs of A or B groups and registered the code of the drugs delivered to the patients in the reference letter. At the end of the study, the pharmacy gave us the patients' names and the delivered drugs for analysis. This study was double-blinded and the physician and the patients were not informed of the kind of the drug prescribed for treatment. Garlic and mint tablets called respectively Garlet and Menta (with similar dates and production numbers) made by a single drug company were used. The visits were done by the physician every week and also the treatment endurance and

acceptance were examined by the intern of the project team and the specialist. Treatment groups were as follows:

Group A: amoxicillin, omeprazole, subsitrate bismuth, and the capsule containing garlic and mint.

Group B: amoxicillin, metronidazole, omeprazole, subsitrate bismuth.

These therapeutical regimens were prescribed for two weeks with the following doses:

Group A: Capsule containing garlic and mint accompanied with 20mg omeprazole capsule twice daily, two subsitrate bismuth tablets twice daily and two 500mg amoxicillin capsules twice daily. Group B: 500mg metronidazole tablet in a capsule similar to that of the other group twice a day, two 500mg amoxicillin capsules twice a day, 20mg omeprazole capsule twice daily, as well as two subsitrate bismuth tablets twice daily. Both regimens were given to the patients in different groups for two weeks, and then they were asked to refer on a prespecified day to be visited and give the required tests. In this visit, the patients were examined and interviewed carefully and also respiratory urease test was done on them two meet later. The complete response to *H. pylori* treatment was decided to be negative respiratory urease test two weeks after treatment completion. After a 14-day treatment according to the above protocol, routine antacid treatments were followed in both groups based on the patients' condition. In order to observe ethical considerations in case of failure to eradicate *H. pylori*, alternative treatment was adopted in the final

examination. Eight patients were omitted from the study for pregnancy, affliction with cancer, migration, occupational problems, and failure to cooperate. Data were analyzed based on the project's statistics expert's opinion by SPSS 15 software using descriptive statistics (mean, etc.) and referential statistics (like independent *t* test).

### 3. Results and Discussion

In this study of 142 outpatients referring to Endoscopy Ward of Hajar Hospital, Shahrekord to compare the combined effect of

Regarding this, there was no significant difference between the two groups (Tables 2-4). There were 29 men (40.8%) and 42 women (59.2%) in the intervention group and 35 men (49.3%) and 36 women (50.7%) in the control. The two groups were not significantly different in this regard (Tables 1-4). Examining the pain intensity in two groups showed that the two groups did not differ from each other significantly in terms of pain intensity (Table 4-4). Out of 142 patients who completed the study, 29 (40.8%) and 58 (81.7%) of the patients had negative respiratory urea test in the intervention and

**Table 1.** The two groups' gender.

Groups	Female	Male	Total Sum
<b>Intervention</b>	42(%59.2)	29 (%40.8)	71 (%100)
<b>Control</b>	36(%50.7)	35(%49.3)	71 (%100)
<b>Total Sum</b>	78(%54.9)	64(%45.1)	142(%100)

garlic and mint extract with metronidazole in treating *H. pylori* infection within a seven-month period, the following results were obtained: The patients in both groups were 17-81 years old; patients' mean age was  $45.96 \pm 13.09$  and  $41.82 \pm 13.43$  years in the intervention and control groups, respectively.

control groups, respectively. Two (2.8%) of the patients in the intervention group had suspected respiratory urea test (Table 3-4). Finally, the level of uprooting *H. pylori* infection in the intervention group was lower compared to the control group, with a significant difference ( $P < 0.001$ ).

**Table 2.** The two groups' ages.

Groups	Maximum	Minimum	mean $\pm$ SD	CI=95%	P
<b>Intervention</b>	81	17	45.96 $\pm$ 13.09	-0.259 0.065	8.541
<b>Control</b>	81	17	41.82 $\pm$ 13.43		

**Table 3.** The result of respiratory urease test (UBT) at the end of the study.

Groups	Positive	Negative	Suspected	Total Sum
<b>Intervention</b>	40(%56.3)	29(%40.8)	2(%2.8)	71(%100)
<b>Control</b>	13(%18.3)	58(%81.7)	0	71(%100)

In this study which was conducted in the form of a double-blinded clinical trial study, the result of respiratory urease test showed that there was a significant difference between the intervention and control groups. The results obtained from respiratory urea test showed that the level of uprooting *H. pylori* infection in the intervention group in which metronidazole tablet was replaced with the combination of garlic and mint extract in the four-drug treatment was lower compared to the control

treatment caused a 13% increase in the level of infection removal compared to the four-drug treatment alone [11]. The studies conducted by Noorizadeh., et al. on the antibacterial effect of mint extract on *H. pylori* [12] and by Mahdi GB et al., on sensitivity of *H. pylori* to the mint extract agree with the present study [13]. Recent studies have shown that garlic has antibacterial property on a wide variety of positive- and negative-gram bacteria, especially *H. pylori* attributable to alicin, in

**Table 4.** Pain intensity at the end of the study.

Groups	No pain	Low and Tolerable	Mean	Severe	Total Sum
<b>Intervention</b>	31(%43.7)	22 (%31)	16(%22.5)	2(%2.8)	71 (100%)
<b>Control</b>	45(%63.4)	15(%21.1)	11(%15.5)	0(0)	71 (100%)

group. While the level of uprooting the *H. pylori* infection in the intervention group was lower than that in the control group, infection removal in 40.8% of the patients treated by garlic and mint extract confirmed that this combination can potentially uproot *H. pylori* infection, which agrees with the study by Kokar et al., in which the garlic extract alone caused the infection removal in 27% of the patients (8). In addition, the results of the present study agree with those obtained in a study conducted by Ghobeh et al., in which introducing garlic powder to the four-drug

such a way that separating or preventing alicin formation destroys the antimicrobial activity of alicin [14, 15]. According to a study conducted by Inder et al., a mechanism of garlic effect is exerted through preventing the nuclear factor activity; activating this factor is done through signaling by receptors called TLR4. TLR4 is the main receiver in feeling different microbial products and stimulating immunity responses [16]. These receptors have several compounds containing syste in their cytoplasm and extracellular parts. Studies have shown that the alicin, existing in garlic,

contains some compounds called thiosulphinates which can, accompanied with cysteine, participate in the reaction [16] and prevent the nuclear factor activation by signaling prevention [17]. This prevention is considered as one of the anti-inflammatory mechanisms of garlic. *H. pylori* assists in its own colonization through the synthesis of IL8, TNF $\alpha$ , and CRP (18, 19) On the other hand, the thiosulphinates compounds in garlic can react rapidly with groups in IL8, TNF $\alpha$ , and CRP, can inhibit these factors' activities, and finally causes this microbe's colonization to decrease [20]. The level of *H. pylori* resistance to metronidazole has been pronouncedly reported differently in numerous studies. In the population under our study, this resistance was 18.3%, which shows a significant difference from 42% obtained in the study by Rojas Feria et al [21]. Besides, the results of the present study did not agree with those obtained by the study of Vicente et al., in which the level of resistance to metronidazole was reported as 49.9% [10]. It seems that the difference in the level of resistance is due to the following reasons: Different bacteria species in the populations under study. Type of the antibiotic used accompanied with metronidazole in the process of treatment. Investigating the pain intensity in this study showed that there was no significant difference between the two groups in this regard.

#### 4. Conclusion

The combination of garlic and mint extracts, compared to metronidazole, was unsuccessful in removing *H. pylori* infection.

Metronidazole can still be used as an effective medication in treating *H. pylori* infection. The combination of garlic and mint extract accompanied with conventional treatments can improve therapeutic process of *H. pylori* to a plausible extent.

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