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Combination of *Nigella sativa* and Honey in Eradication of Gastric *Helicobacter pylori* Infection

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Abstract

Background: Gastric *Helicobacter pylori* is extremely common worldwide.
Objectives: The aim of this study was to assess the effectiveness of combination of *Nigella sativa* and honey (Dosin) in eradication of gastric *H. pylori* infection.
Patients and Methods: Nineteen patients who had positive result for *H. pylori* infection by urea breath test (UBT) without a past history of peptic ulcer, gastric cancer or gastrointestinal bleeding, were suggested to receive one teaspoon of the mixture of Dosin (6 g/day of *N. sativa* as ground seeds and 12 g/day of honey) three times a day after meals for two weeks. The second UBT was used to detect the presence of *H. pylori* four weeks after completion of the test. In addition, symptoms of dyspepsia were scored before and after the study and analyzed with Wilcoxon signed-rank test.
Results: Fourteen patients completed the study. Negative UBT was observed in 57.1% (8/14) of participants after intervention. The median and interquartile range (IQR) of total dyspepsia symptoms was significantly reduced from 5.5 (5 - 12) to 1 (0 - 4) (P = 0.005). All the patients tolerated Dosin except for one who was excluded due to mild diarrhea. No serious adverse events were reported.
Conclusions: Dosin was concluded to be an anti *H. pylori* and an anti-dyspeptic agent. Further studies are recommended to investigate the effect of Dosin plus antibiotics (concurrently or following another) on gastric *H. pylori* infection.

Keywords: Honey, Medicine, Traditional, Phytotherapy, *Nigella sativa*, *Helicobacter pylori*

1. Background

Gastric *Helicobacter pylorus* is extremely common worldwide. The prevalence of *H. pylori* is estimated as 50.7% in Iran (the range is between 19.2% in Tehran and 74.2% in Mazandaran provinces) (1).

Gastritis, peptic ulcer and gastric cancer have been ascribed to *H. pylori* (2). Eradication of *H. pylori* infection is important for prevention and treatment of gastroduodenal diseases, especially in developing countries with high prevalence of *H. pylori* (3, 4).

Owing to the alarming rate of anti-*H. pylori* drug resistance (14% - 45% for clarithromycin, 40% - 65% for metronidazole, and 2-37% for amoxicillin in Iran), eradication of *H. pylori* remains a global challenge (2, 5, 6).

Patient's compliance, medications side-effects, costs, accessibility and feasibility of regimens are some important factors in choosing medications (3, 7). Therefore, development and testing of new safe, feasible and affordable alternatives to these regimens is warranted.

Nigella sativa, from the Ranunculaceae family, is commonly known as black seed or black cumin. In Iranian traditional medicine (ITM), it is called "Shooniz" (8). It is traditionally used in India, Arabic countries, Europe and Iran as food additive as well as a natural remedy for many disorders like cough, jaundice and gastrointestinal disorders. It is known to have digestive, laxative and gastric tonic effects and also be effective on bloating (8-12). There is a common Islamic belief that the black seed is a panacea (universal healer) which is a remedy for all ailments (9, 12, 13).

The antibacterial activity of the phenolic fraction of *N. sativa* oil was first reported by Toppozada et al. (14). Then, the anti-*H. pylori* activity of *N. sativa* was presented by O'Mahony et al. (15) who found that the aqueous extract of *N. sativa* had 100% bactericidal activity against *H. pylori*. In 2009 and 2011, the anti-*H. pylori* effect of Iranian *N. sativa* was demonstrated in two in vitro studies (16, 17). In 2013, the urease enzyme inhibition potency of Iranian *N. sativa* extract was presented (18).

The anti-*H. pylori* effect of *N. sativa* was shown in a clinical trial in Saudi Arabia in 2010 and *N. sativa* seeds (2 g/day for 14 days) were concluded to possess clinically useful anti-*H. pylori* activity, comparable to 14 days of triple therapy (amoxicillin, clarithromycin, omeprazole) (19).

Honey that is called "Angabin" in Persian and "Asal-

al-Nahl" in ITM is known to be useful for gastrointestinal problems like abdominal pain, bloating, jaundice and also increasing the appetite (8).

The anti-*H. pylori* effect of honey has also been demonstrated in some in vitro studies (20-22). The effects of honey have been compared with clarithromycin in a rat model of gastric ulcer. All honey samples demonstrated anti-*H. pylori* activity (23).

In Iran, the combination of *N. sativa* with honey (Dosin) is used according to traditional (8) and Islamic medicine (24) for alleviating gastrointestinal symptoms like abdominal pain, bloating and diarrhea.

2. Objectives

The aim of the present pilot study was to investigate the effectiveness of Dosin in eradication of *H. pylori* infection in patients with non-ulcer dyspepsia.

3. Patients and Methods

3.1. Preparation of Dosin

Mixture of Dosin was made in the department of pharmacy, Tehran University of Medical Sciences. *N. sativa* and honey were bought from Hamadan province, Iran. The voucher specimen "PMP-735" was deposited to *N. sativa* in the herbarium of faculty of pharmacy, Tehran University of Medical Sciences, Tehran, Iran. *N. sativa* and honey were mixed together in proportion of 1 (6 g/day of *N. sativa* as ground seeds) to 2 (12 g/day of honey). The dosage of *N. sativa* and honey in the mixture were chosen based on ITM literature (8).

3.2. Patients and Protocol

The study was conducted in the gastroenterology clinic of "Rasool-e-Akram" hospital (a specialized and subspecialized, referral, governmental hospital with 850 beds in west of Tehran, Iran) in 2012. The medical ethics committee of the research institute for Islamic and complementary medicine approved the protocol (approval number and date: 1699/tm/p26, March 2012). The trial was registered in Iranian registry of clinical trials undet the number IRCT201209041957N3.

Patients with gastrointestinal complaints and positive urea breath test (UBT) were assessed and included according to the inclusion/exclusion criteria after signing a written informed consent. All the patients had positive results for *H. pylori* infection by UBT. UBT was performed by the Heliprobe® system made in Sweden, which was bought from Beta company. The test was performed according to the instructions of the manufacturers.

Eligible patients were interviewed and underwent a physical examination. A questionnaire regarding demographic data (age, gender, education and marital status) and dyspepsia symptoms was filled for each patient. Diagnosis of dyspepsia was based on ROME III criteria which include one or more of the following symptoms: a burning sensation or discomfort in the upper abdomen or lower chest, sometimes relieved by food or antacids, early satiation and bothersome postprandial fullness (25-27). Three questions were used to assess the dyspepsia symptoms: (1- pain or discomfort or burning in the upper abdomen or lower chest sometimes relieved by food or antacids, 2- early satiation, and 3- bothersome postprandial fullness). The answer to each question of dyspepsia was scored between 0-6 according to the severity of symptoms (zero for absence of symptom during the past three months and 6 for the severest symptom). The painting of the upper body abdomen and lower chest was added in the questionnaire to help patients localizing the area of discomfort. Total score of dyspepsia symptoms (0-18) presented the severity of dyspepsia.

Face and content validity of the questionnaire was evaluated by gastroenterologists and then was evaluated in a pilot study on 20 patients. Test-retest was performed on two separate occasions 4-7 days apart and the Pearson's coefficient was 0.84. Furthermore, the internal consistency of the questionnaire was measured using Cronbach's alpha coefficient, which was 0.69.

Patients were excluded if: 1) they had past history of peptic ulcer, gastric cancer or gastrointestinal bleeding; 2) they had taken nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, proton-pump inhibitors, bismuth or antibiotics in the last four weeks before endoscopy; 3) they were pregnant or lactating mothers; 4) they were intolerant or allergic to therapeutic regimens. Written consents were obtained.

All the included patients were suggested to receive one teaspoon of the mixture three times a day after meals for two weeks. The patients were followed up weekly during the two weeks of treatment with Dosin through telephone contact. No antibiotic or proton pump inhibitors were allowed during the study.

The second UBT was used to detect the presence of *H. pylori* four weeks after the end of the treatment (2, 3, 19).

The follow-up information regarding improvement of dyspepsia symptoms, appearance of side-effects and compliance of the patients was documented in the file of each patient.

The primary outcome measure was eradication of *H. pylori*, which was considered to be achieved on the basis of a negative UBT four weeks after the end of treatment. The secondary outcome measure included changes in the clin-

ical condition, assessed by an improvement in dyspepsia scores.

Compliance was followed by a diary filled by the patients. Only patients who received more than 90% of the prescribed medication were included in the statistical analysis.

3.3. Statistical Analysis

The proportion of patients in whom eradication was successful (negative UBT after intervention) was reported. The severity of dyspepsia symptoms (total score of dyspepsia symptoms) before and after the treatment was presented as median and interquartile range (IQR), then compared using the Wilcoxon signed rank test (because the data did not have a normal distribution). $P < 0.05$ was considered as significant.

All the statistical analyses were performed using the statistical package of social sciences (SPSS) version 17.

4. Results

Fifty eight available patients with gastrointestinal complaints and positive UBT were assessed and 19 patients were included. Five of the 19 patients discontinued the study because of either traveling or loss of interest, and one of them was excluded due to mild diarrhea. Figure 1 presents the process of sampling, follow-up and attritions. Therefore, 14 patients, 6 (31.5%) males and 13 (68.5%) females, finally completed the study.

Mean $\pm$ SD of age was 36.7 $\pm$ 10.3 years. Thirteen patients (92%) were married. Mean $\pm$ SD of education was 12 $\pm$ 2.1 years. At the end of the study, the UBT results were negative for 8 (57.1%) participants (95% CI: 29.7-84.5).

The frequency of dyspepsia symptoms and their changes during the study are shown in Table 1. The score of dyspepsia symptoms significantly reduced after the intervention. Postprandial acid regurgitation and malodor of mouth were other complaints which were observed in 4 (21%) and 2 (10.5%) participants, respectively. Malodor of mouth also improved after the intervention. None of the participants experienced side-effects or worsening of the symptoms during the study.

Table 1. Symptoms of Dyspepsia Before and After the Intervention

	Number (%) of patients with this symptom	Median (IQR) before intervention	Median (IQR) after intervention
Epigastric burning sensation or discomfort	15 (78.9)	5 (4 - 6)	0.5 (0 - 2)
Early satiation	7 (36.8)	0 (0 - 5)	0 (0 - 0.25)
Bothersome postprandial fullness	6 (31.5)	0 (0 - 5)	0 (0 - 0)
Total score of dyspepsia		5.5 (5 - 12)	1 (0 - 4)
		P value= 0.005[a]	

[a] P value of Wilcoxon signed rank test.

5. Discussion

The high frequency of *H. pylori* and the rising prevalence of antibiotic resistance, especially in developing countries, emphasizes the need for discovery of new and safer medications for treatment of *H. pylori* infection (3).

Anti-*H. pylori* effects of *N. sativa* and honey (separately) have been approved in some in vitro and in vivo studies, as mentioned before (16, 19, 28).

The results of this study showed that Dosin eradicated *H. pylori* in about 57% of infected patients. It is lower than the eradication rate of triple therapy consisting of amoxicillin, clarithromycin and omeprazole (reported about 75-80% in developing countries) (2). However, it is almost similar to the reported results of the study in Iran to compare sequential with quadruple therapy. In the mentioned study, the eradication rate was seen in 50.9% of patients in sequential therapy (omeprazole, amoxicillin, each administered twice daily for the first five days, followed by omeprazole, clarithromycin and furazolidone, twice daily for the remaining nine days) and 49.1% in routine four-drug (omeprazole, clarithromycin, amoxicillin and bismuth twice daily for 14 days) therapeutic treatment ($P > 0.05$) (6).

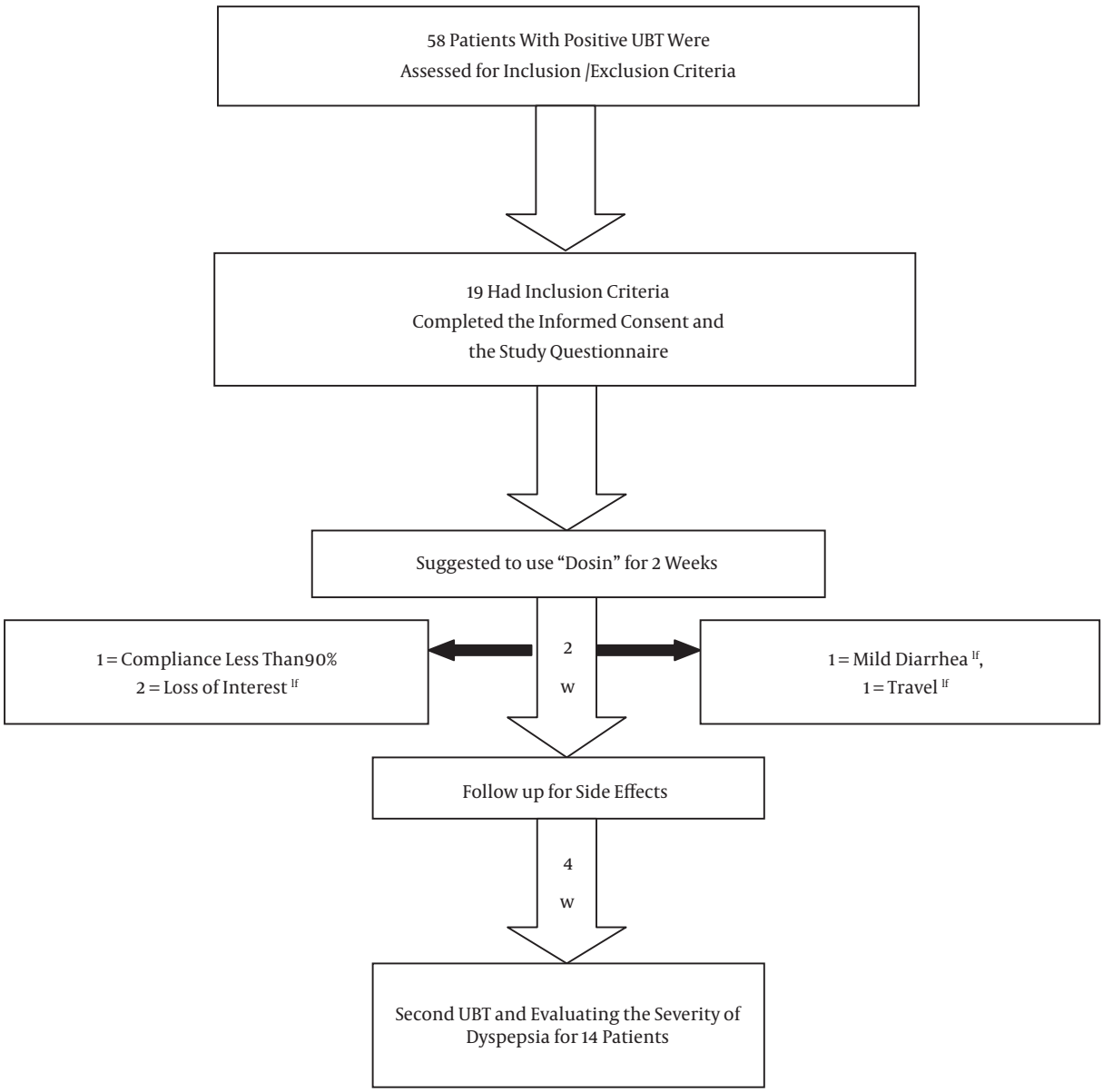
In the study of Eyad M. Salem et al. in Saudi Arabia in 2010, *H. pylori* eradication was 82.6, 47.6%, 66.7%, and 47.8% with triple therapy (clarithromycin, amoxicillin and omeprazole), using 1, 2, and 3 g/day of *N. sativa*, respectively. Eradication rates with 2 g *N. sativa* and triple therapy were not statistically different from each other, whereas *H. pylori* eradication with other doses was significantly less than that with triple therapy ($P < 0.05$) (19).

The difference of the results of our study with the study in Saudi Arabia (19) may be due to expected differences in resistance rate of *H. pylori* reported in different countries (5, 29).

The seeds of *N. sativa* have been widely used in the treatment of various disorders and it has been known as a miracle herb among Muslims. It has been said that black seed is the remedy for all diseases except death in a prophetic hadith. It is also recommended for use on a regular basis in Tibbe-Nabwi (prophetic medicine) (24).

A wide spectrum of its pharmacological actions has

Figure 1. Flow Diagram of the Study



W, weeks; if, loss to follow up.

been evaluated, which may include antidiabetic, anticancer, immunomodulator, analgesic, antimicrobial, anti-inflammatory, spasmolytic, bronchodilator, hepatoprotective, renal protective, gastro-protective, antioxidant properties, etc. (12).

The anti-*H. pylori* action of *N. sativa* is probably due to its urease inhibitory effect. *H. pylori* uses ammonia, the urease enzyme product, to protect itself from the stomach acidic condition (18).

N. sativa seeds contain a number of essential oils, including thymoquinone, dihydrothymoquinone, and terpenes. It is revealed that most of the therapeutic properties of *N. sativa* are due to the presence of thymoquinone which is a major bioactive component of essential oil (12). Thymoquinone has gastroprotective mechanisms and anti-ulcer activity via an inhibiting proton pump, acid secretion and neutrophil infiltration, while enhancing mucin secretion and nitric oxide production (30).

The role of *H. pylori* infection in functional dyspepsia is still controversial. Some studies indicated that eradication of *H. pylori* infection was associated with a significant therapeutic effect on dyspepsia (31). Many guidelines now recommend *H. pylori* eradication in uninvestigated simple dyspepsia following noninvasive diagnosis; others also recommend treatment in functional dyspepsia (2).

Dosin successfully reduced the dyspepsia symptoms in our study. Even if it is not so effective for eradicating *H. pylori*, it will be able to subside gastrointestinal symptoms in non-ulcer dyspepsia.

In the study in Saudi Arabia (19), dyspepsia symptoms improved in all the three groups of *N. sativa* (1, 2 and 3 g/day) to the same extent as in triple therapy. As mentioned before, thymoquinone in *N. sativa* has an inhibitory effect on proton pump and as a result has inhibitory activity on gastric acid secretion (30).

Honey has long been known as a home remedy to alleviate dyspepsia. In addition, based on ITM literature, honey is said to be warm and dry in nature and effective for gastric symptoms (bloating, pain, loss of appetite and early satiation), which are now called as dyspepsia (8).

The elements responsible for the antibacterial activity of honey are not fully known, but have been attributed to various polyphenolic compounds found in honey (propolis, flavonoids, flavones, tannins) and to glucose oxidase and osmosis (13). Molan et al. (31) attributed the antibacterial activity of honey to its content of glucose oxidase, which liberates hydrogen peroxide when it is diluted.

Somerfield ascribed the antibacterial effect of honey to the osmotic effect of its sugar content. Honey contains 38% fructose, 31% glucose and 17% water, while its PH is 3.9 (32).

It may be concluded that the improvement of dyspepsia symptoms in our study was due to the *N. sativa* gastroprotective and anti-secretory activities and also due to the anti-dyspeptic effects of honey.

The weak point of this study was being a pilot study. It was performed on a small sample size without any concurrent control groups and the results were compared to historical controls. Hence, we suggest conducting a randomized controlled parallel clinical trial to compare the eradication rate of Dosin with some different antibiotic regimens. In addition, Dosin can be examined as the first regimen before taking the standard anti-*H. pylori* regimen and then the eradication rate can be investigated. There is a probability that the combination of Dosin with antibiotics could decrease the possibility of emergence of resistant colonies of *H. pylori* and improve the efficacy of antibiotic regimens.

Further studies are also recommended to investigate the effect of Dosin plus antibiotics or proton pump inhibitors (concurrently, following another or sequential therapy) on gastric *H. pylori* infection.

Although even Dosin did not achieve complete eradication rate, it could be used as an alternative regimen in patients unwilling to use triple or quadruple therapy regimens.

5.1. Conclusion

Dosin, in a dose of 6 g/day of *N. sativa* seeds, possessed anti-*H. pylori* activity. It was also concluded to be an effective anti-dyspeptic agent. Further studies with larger sample size are recommended to investigate the effects of Dosin plus antibiotics or proton pump inhibitors (concurrently or following another) on gastric *H. pylori* infection.

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Footnote

Authors' Contribution: The main idea was presented by Fataneh Hashem-Dabaghian. Ali Ghobadi prepared the medication. Fataneh Hashem-Dabaghian and Shahram Agah carried out the study. Maryam Taghavi-Shirazi helped in data collecting. Fataneh Hashem-Dabaghian1 performed the statistical analysis of the data, drafted the manuscript and submitted the article. All the authors read and approved the final manuscript.

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