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Efficacy and safety of alpha-pinene capsule in the management of functional dyspepsia and eradication of helicobacter pylori: a randomized clinical trial

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ABSTRACT

Aim: Our objective was to assess the efficacy and safety of adding alpha-pinene (a herbal terpenoid) to quadruple therapy compared to a placebo in improving symptoms and Helicobacter pylori (H. pylori) eradication rates in Functional dyspepsia (FD) patients.
Background: FD is a prevalent upper gastrointestinal condition, and no definitive pharmacological treatment is available for its management.
Methods: We conducted a randomized, double-blinded, placebo-controlled trial on FD patients diagnosed with H. pylori infection. We collected baseline demographic data and assessed FD symptoms in the participants. Patients were randomly allocated to receive either standard quadruple therapy with α-pinene capsules (0.25 mg/day) or quadruple therapy with a placebo for two weeks. We employed a validated questionnaire, the Short Form Leeds Dyspepsia Questionnaire (SF-LDQ), to evaluate FD symptoms. The eradication rate of H. pylori was compared between the two groups one month after completing the treatment regimens. Any reported adverse drug reactions (ADRs) were documented throughout the trial.
Results: Over four months, a total of 66 patients completed the trial. Notably, there were no significant differences in baseline SF-LDQ scores between the two groups (p=0.83); however, a significant divergence emerged at the trial's conclusion (p=0.03). The H. pylori eradication rates did not show notable differences between the two treatment arms (p=0.43). Importantly, there were no dropouts from the trial due to ADRs. Among reported ADRs, participants experienced abdominal pain, headache, diarrhea, and a metallic taste, with no significant variance in incidence rates observed between the two groups (p=0.62).
Conclusion: These findings suggest that α-pinene could be an effective and safe agent for reducing FD symptoms.

Keywords: Alphapinen, Helicobacter pylori, Functional dyspepsia, Clinical trial.

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Introduction

Functional dyspepsia (FD) is diagnosed when no organic cause for dyspeptic symptoms is identified (1). The community prevalence of FD typically ranges from 20% to 40%, and its exact etiology remains unclear (2). Management options for FD encompass acid-reducing medications like proton pump inhibitors (PPIs), neuromodulators, prokinetics, psychotropic

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agents, complementary and dietary approaches, as well as Helicobacter pylori (H. pylori) eradication (1). Managing FD is often challenging due to factors such as the heterogeneity of upper gastrointestinal symptoms and the limited efficacy of existing pharmacological treatments (3).

Alpha-pinene (α-pinene) is a hydrocarbon terpenoid commonly found in numerous herbal medicines. Its highly regarded safety profile makes it widely accepted as safe for various applications in the chemical industry (4). Previous research has demonstrated that α-pinene can effectively inhibit gastric mucosal lesions induced by ethanol, likely attributed to its ability to enhance mucus secretion and reduce gastric acid production (5). In a randomized, blinded clinical study, Eftekharafzali et al. evaluated the effects of Pistachia atlantica resin's rich source of α-pinene on FD symptoms. Volunteers received either the herbal resin or a placebo for four weeks. The intensity and frequency of FD symptoms were assessed using questionnaires before and after the trial. The mean symptom score during the second and fourth weeks of the study, as well as four weeks after follow-up, exhibited a significant reduction in the herbal resin group compared to the placebo group ($p<0.05$) (6). In a clinical trial, Afrasiabian et al. assessed the effects of oral Pistacia Atlantica gum on H. pylori eradication. Patients were divided into four groups, each completing a 14-day trial: Group one received triple therapy for H. pylori eradication, Group two received triple therapy like Group one but with the addition of a capsule containing 1 g of Pistacia Atlantica gum (twice daily), Group three received capsules containing 1 g of Pistacia Atlantica gum (twice daily), and the final group took an identical placebo (resembling the capsule containing Pistacia Atlantica gum) twice daily. The H. pylori eradication rates were as follows: 70.9%, 75%, 43.4%, and 8.3% in the four groups, respectively. Statistical analysis revealed that Pistacia Atlantica significantly contributed to H. pylori eradication (7).

Due to limited data on the effectiveness of α-pinene in alleviating FD symptoms and eradicating H. pylori in a clinical context, we initiated a double-blind, randomized clinical trial. The primary objective of this study was to evaluate the efficacy and safety of α-pinene as an adjuvant therapy for relieving FD symptoms. The secondary outcome involved assessing the impact of adding α-pinene to the standard quadruple therapy on H. pylori eradication in FD patients.

Methods

This randomized double-blind clinical trial was done in a gastroenterology referral center, affiliated to the Shahid Beheshti University of Medical Sciences, Tehran, Iran. The trial was accepted by the Ethics Committee of Pharmacy, nursing, and midwifery schools affiliated to the mentioned university by number IR.SBMU.PHARMACY.REC.1402.020. The study was also registered in the Iranian clinical trial registry with the number IRCT20121021011192N15.

Inclusion criteria encompassed individuals aged 18 years and older who had received a diagnosis of FD and were also confirmed to be infected with H. pylori. A fecal antigen test verified all participants' H. pylori infection status. The diagnosis of FD was established based on the presence of FD symptoms, adhering to the Rome IV criteria (8). Also, all the patients have been done with upper endoscopy to rule out any organic GI disorders such as peptic ulcers (PUD) and malignancy. The Short Form Leeds Dyspepsia Questionnaire (SF-LDQ) was employed in this study to assess FD symptoms. The SF-LDQ consists of eight items related to dyspeptic symptoms, each presenting two aspects: the frequency and severity of each symptom experienced over the past eight weeks. Scores for frequency and severity responses for each symptom were summed, ranging from 0 to 16 for each item. A total summed score was also calculated, spanning from 0 to 32. A higher numerical value on the SF-LDQ indicated a more severe and frequent dyspeptic condition (9). Following a comprehensive explanation of the study's objectives to the volunteers, informed written consent was obtained from each participant. Exclusion criteria comprised refusal to participate in the study, recent use of antibiotics effective against H. pylori/PPIs/histamine-2 blockers/bismuth salts within the past month, any prior allergic reactions to antibiotics or α-pinene, psychiatric disorders as well as pregnancy or breastfeeding. At the outset of the trial, demographic information, personal data, and SF-LDQ scores were collected. Subsequently, participants were randomly allocated into two groups, with treatment assignment determined through random sample allocation using a random numbers table. The patients, physician, and examiner were blinded to the

drug or placebo during the trial. Both groups were prescribed the same quadruple regimen for H. pylori eradication, consisting of omeprazole (40 mg/d), amoxicillin (2 g/d), bismuth (1.5 g/d), and metronidazole (1500 mg/d), to be taken for 14 days. Patients in the intervention group received a daily dose of 0.25 g α-pinene capsules (Zhiran Darou, Snnadaj, Iran), while those in the control group received identical placebo capsules, also daily for 14 days. The administration of quadruple therapy alongside α-pinene/placebo was concluded after 14 days. Patients were advised not to use any herbal medications during the trial due to the potential presence of α-pinene. A secondary assessment was conducted 28 days after discontinuation of the regimens. SF-LDQ scores, and H. pylori eradication status (by fecal antigen test) were re-evaluated during this follow-up. The identification of a positive result on the stool antigen test 28 days after the completion of the regimens indicated unsuccessful H. pylori eradication (10). Because of aggravating the symptoms, patients were asked to avoid the use of non-steroidal anti-inflammatory drugs (NSAIDs) during the treatment course. Throughout the trial, patients were assessed for potential adverse drug reactions (ADRs) using the Naranjo criteria (11), and any identified ADRs were duly recorded. Medication adherence among participants was monitored via telephone interviews during the trial.

Descriptive data were presented as mean ± standard deviation (SD). All statistical analyses were conducted using Statistical Package for the Social Sciences (SPSS) version 11.5, and unpaired two-tailed t-tests, paired t-tests, and chi-square tests were employed for data analysis. P-values greater than 0.05 were designated as non-significant. The sample size was determined based on the primary outcome of symptom relief in FD. Sample size calculations for both the α-pinene and placebo groups were adapted from the study by Eftekharafzali et al. (6). To achieve SF-LDQ scores of 15 in the α-pinene group and 17 in the placebo group after one month while considering a standard deviation of 2.5, an alpha of 0.05, and a beta of 90%, a minimum of 33 patients were required in each group.

Results

In Figure 1 the flow schematic of the trial has been represented. A total of 81 patients with a diagnosis of FD

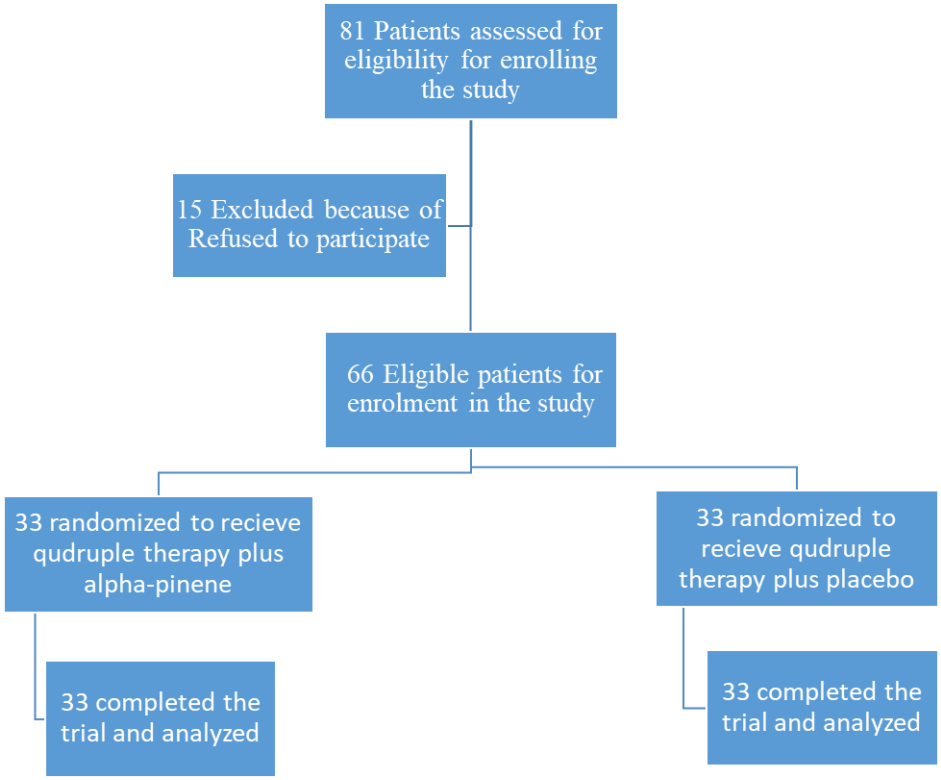

Figure 1. Study Flowchart

Table 1. Demographic of participants in two arms

		α-pinene (n = 33)	Placebo (n = 33)	p-value
Mean age (year) (± SD)		38.18±13.28	35.62±11.2	0.14
Sex	Female	19	18	0.81
	Male	14	15	
Body Mass Index (kg/m2) (± SD)		24. 53±3.18	23.01±3.58	0.43
Smoker	No	28	31	0.76
	Yes	5	2	

who met the inclusion criteria were initially assessed at the referral clinic for potential inclusion in the trial. Ultimately, 66 patients with FD agreed to participate and were enrolled in the study between July and October 2023, with 33 patients allocated to the α-pinene group and 33 to the placebo group. Importantly, all participants successfully completed the trial were no dropouts. The demographic data of the participants are presented in Table 1. Notably, there were no significant differences between the two groups for mean age, sex distribution, body mass index (BMI), and smoking habits.

Table 2 presents the baseline parameters of SF-LDQ for the α-pinene and placebo groups separately. Notably, no significant differences were observed between the two groups regarding baseline indigestion, heartburn, regurgitation, nausea, and total scores, whether in terms of frequency or severity. Table 3 displays the total SF-LDQ and sub-item scores at the end of the trial. Both groups exhibited a reduction in scores for indigestion, heartburn, regurgitation, nausea, and the total score by the end of the trial. However, there was a statistically significant difference in each SF-LDQ item and the total score between the two groups. This suggests that symptom relief was notably more pronounced in the α-pinene group compared to the placebo group.

After the trial, the H. pylori eradication rates in the α-pinene arm were compared to those in the placebo arm. It was found that 76% of patients in the α-pinene group tested negative for H. pylori one month after discontinuing the combination regimens. In the placebo group, H. pylori was eradicated in 72% of the participants during the same period. Statistical analysis indicated no significant difference between the two groups regarding H. pylori eradication (p=0.43).

No significant difference was noted in the total number of patients experiencing ADRs between the α-pinene and placebo arms (42.4% vs. 45.4%, p=0.62). Importantly, there were no dropouts from the study due to the occurrence of ADRs. Among the reported ADRs, abdominal pain was the most commonly reported (14 cases in α-pinene and 15 in placebo arms), with headache (13 in α-pinene and 12 in placebo), diarrhea (7 in α-pinene and 6 in placebo), and metallic taste (6 in α-pinene and 5 in placebo) being other frequently mentioned ADRs among the participants.

Table 2. SF-LDQ scores (total and separate item) at the baseline in two arms

	Frequency			Severity		
	α-Pinene arm	Placebo arm	P	α-Pinene arm	Placebo arm	p
Indigestion	3.8± 0.1	3.6± 0.2	0.64	3.2± 0.2	3.3± 0.2	0.78
Heartburn	3.1± 0.2	3.0 ± 0.1	0.23	3.4± 0.1	3.6± 0.2	0.69
Regurgitation	3.2± 0.3	3.2± 0.2	0.89	3.4± 0.2	3.5± 0.2	0.88
Nausea	2.3± 0.1	2.5± 0.2	0.61	2.9± 0.2	2.7± 0.2	0.72
Total Score	12.5± 0.3	12.2± 0.3	0.87	12.9± 0.2	13.3± 0.2	0.57
Total Score frequency plus severity	25.4± 0.2	24.3± 0.2	0.83			

Table 3. SF-LDQ scores (total and separate item) at the end of the study in two arms

	Frequency			Severity		
	α-Pinene arm	Placebo arm	P	α-Pinene arm	Placebo arm	p
Indigestion	1.9± 0.1	3.2± 0.2	0.03	2.1± 0.2	3.0± 0.2	0.02
Heartburn	2.3± 0.2	2.8 ± 0.4	0.04	2.3± 0.1	2.8± 0.2	0.04
Regurgitation	2.2± 0.3	2.9± 0.4	0.03	1.9± 0.2	2.9± 0.2	0.01
Nausea	2.1± 0.1	2.0± 0.3	0.04	1.8± 0.3	1.9± 0.2	0.04
Total Score	8.5± 0.3	10.2± 0.3	0.01	7.8± 0.2	9.3± 0.2	0.03
Total Score frequency plus severity	15.0± 0.3	18.3± 0.2	0.03			

Discussion

FD is a prevalent disorder in the world with unsatisfactory treatment. Still, in this modern era of technology, the pharmacologic agents available for treating FD are not up to the mark (12). In a review article, Gwee et al. assessed the efficacy and safety of various herbal medicines (excluding those containing α-pinene) in the treatment of FD. Their conclusion emphasized herbal medicine as a promising alternative for the future management of FD (13). Conversely, given the absence of definitive treatments for FD, H. pylori eradication remains a primary management option due to its curative potential (3). International guidelines recommend triple/quadruple therapy for H. pylori eradication; however, the use of multiple medications can decrease patient adherence to treatment regimens and may elevate the risk of side effects (14). Numerous approaches have been explored to enhance H. pylori eradication rates, including modifying combinations or durations of regimens, incorporating adjuvant medications like herbal agents, and developing new therapeutic agents (15).

While there have been reports on the gastro-protective effects of α-pinene (5), there is limited clinical data available regarding the impact of α-pinene or herbal medicines on managing FD symptoms or H. pylori eradication (7). In the current trial, we sought to assess the efficacy and safety of α-pinene in controlling symptoms and eradicating H. pylori in a population of FD patients who were also infected with the bacterium. We employed the Rome IV criteria to define FD for precise diagnosis in this trial. Functional gastrointestinal diseases, including conditions such as irritable bowel syndrome (IBS) and FD, are now characterized as disorders of gut-brain interaction. These are common ailments featuring chronic or recurrent gastrointestinal symptoms (17).

Moreover, the study participants in both arms exhibited similar mean age, sex distribution, BMI, and smoking habits. In a prior clinical study, Pistacia atlantica powder (which contains α-pinene) was administered to 101 patients diagnosed with FD, with 53 in the active arm and 48 in the placebo arm, for four weeks (6). Notably, the severity and frequency of common FD symptoms significantly decreased in the active arm compared to the placebo arm. In alignment with the trial by Eftekharafzali et al., we also assessed the total FD score using the SF-LDQ in our study. At our trial's conclusion, the SF-LDQ total score and each FD symptom item exhibited significant reductions in the α-pinene group compared to the placebo group. This underscores the positive impact of α-pinene on FD symptoms.

Unlike our study, Eftekharafzali et al. did not assess the H. pylori eradication rate in their trial. Although Afrasiabian et al. reported a 75% eradication rate in patients receiving a combination of triple therapy plus Pistacia gum, as compared to 70.9% in patients receiving triple therapy alone, they did not discuss the statistical significance of this result in their study (6). Our findings indicate no statistically significant difference in H. pylori eradication among FD patients undergoing treatment with quadruple therapy plus α-pinene or placebo. It is worth noting that Afrasiabian et al. used a daily dose of 1 g of total herbal extract containing α-pinene, whereas we administered 0.25 mg/day of pure α-pinene, which may be a lower dose. This difference in dosing could potentially explain the lack of disparity between the two groups in terms of H. pylori eradication rates in our trial. Previous studies have explored herbal formulations containing α-pinene, whereas our focus was on examining the direct effect of α-pinene on FD symptoms and H. pylori eradication rates. It is possible that the quantity of α-pinene varied across different herbal sources, so we opted for a standardized preparation of α-pinene in our study to ensure reliable results.

In our trial, both α-pinene and the placebo were well-tolerated, and there were no dropouts due to severe ADRs. Previous studies have frequently reported the occurrence of abdominal pain, headache, diarrhea, and metallic taste during quadruple therapy for H. pylori eradication (14). Given that participants in our study were concurrently taking α-pinene or the placebo alongside the quadruple therapy medications, these symptoms are unlikely to be attributed to α-pinene or the placebo.

We conducted assessments of FD symptoms at only two time points, namely the baseline and at the end of the trial. It is strongly recommended to consider more frequent evaluations of patients and also extend the follow-up period for participants in future studies. While we observed a better response in the α-pinene group compared to the placebo group, it is worth noting that we used a dose of 0.25 mg of α-pinene for a two-week

duration. It is possible that using higher doses or prolonging the duration of α-pinene therapy may lead to an increased rate of H. pylori eradication. It is worth exploring these possibilities in future research. Importantly, at the 0.25 mg/day dose, α-pinene was well-tolerated, suggesting the potential for investigating higher doses and longer durations in subsequent studies.

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Conflict of interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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