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Original Research

Effects of the *Pistacia atlantica* subsp. *kurdica* Oleoresin on the Symptoms and Quality of Life in Functional Dyspepsia: A Randomized Controlled Trial

Saeed Kianbakht[1], Ahmad Khonche[2], Fataneh Hashem-Dabaghian[3], Hasan Fallah Huseini[1], Farzaneh Nabati[1], Reza Mohtashami[4]*

[1]Medicinal Plants Research Center, Institute of Medicinal Plants, ACECR, Karaj, Iran
[2]Department of Internal Medicine, Baqiyatallah University of Medical Sciences, Tehran, Iran
[3]Department of Traditional Medicine, Institute for Studies in Medical History, Persian and Complementary Medicine, School of Persian Medicine, Iran University of Medical Sciences, Tehran, Iran
[4]Medicine, Quran and Hadith Research Center, Baqiyatallah University of Medical Sciences, Tehran, Iran

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Abstract

The *Pistacia atlantica* subsp. *kurdica* oleoresin (OPA) is utilized for the treatment of dyspepsia and other gastrointestinal diseases in the Persian Medicine. Therefore, the therapeutic efficacy and safety of standardized OPA in functional dyspepsia (FD) were evaluated. To standardize OPA, the constituents of the OPA essential oil were determined by gas chromatography-mass spectrometry. Fifty patients were allocated to each of the OPA and placebo groups. The OPA and placebo groups consumed two 200 mg OPA or placebo capsules, respectively, every 12 hours along with one 40 mg famotidine tablet per day for 8 weeks. Dyspepsia severity was the primary outcome measured by the Hong Kong dyspepsia index. The secondary outcomes included quality of life measured by the sf-36 questionnaire, complete blood count, and the blood levels of alanine aminotransferase, aspartate aminotransferase, blood urea nitrogen, creatinine, triglyceride, total cholesterol, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol. The outcomes were measured at the baseline and endpoint. OPA contained 10% w/w essential oil, and the constituents of the OPA essential oil were α-pinene (96%), β- pinene (2%) and terpinolene (2%). Thirty five patients in each group completed the trial. OPA decreased the Hong Kong score significantly ($p = 0.013$), but the placebo had no significant effect on the Hong Kong score ($p = 0.651$), at the endpoint compared to baseline. The sf-36 questionnaire score of the OPA group increased significantly ($p = 0.027$), but it increased insignificantly in the placebo group ($p = 0.078$), at the endpoint compared to baseline. There was no significant effect on the blood tests, and also no side effect. Thus, OPA may mitigate the symptoms, and increase the quality of life of the FD patients without side effects. The OPA essential oil and the monoterpenes α-pinene, β- pinene and terpinolene may be responsible for the effects of OPA in FD.

Keywords: Wild pistachio; Gastrointestinal disease; Gastrointestinal system; Traditional medicine; Integrative medicine; Complementary and alternative medicine

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*Corresponding Author: Reza Mohtashami
Medicine, Quran and Hadith Research Center, Baqiyatallah University of Medical Sciences, Tehran, Iran
Email: reza_mohtashami@yahoo.com

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Introduction

Functional dyspepsia (FD) is diagnosed by existence of at least one of the symptoms epigastric pain or burning, early satiety, and postprandial fullness without any identifiable pathology [1]. FD is a common disease affecting around 10-30% of the society [1]. FD impairs quality of life and has substantial socioeconomic costs [1]. FD has 3 subtypes including epigastric pain syndrome (EPS), postprandial distress syndrome (PDS), and overlap of EPS and PDS [2]. The Hong Kong index of dyspepsia is a questionnaire used for the assessment of the severity of the FD symptoms [3]. Acid suppressive, prokinetic, fundus relaxing, and antidepressant drugs, and rifaximin have been used with inconsistent efficacy for the treatment of FD. Acid suppressants are the first line of treatment. Despite the prevalence of FD, effective treatments for FD have been limited. Development of therapeutics for FD has been difficult due to the complex and unclear mechanisms of the disease. Considering that multiple mechanisms are behind FD, a drug with a single mechanism is ineffective in all patients [4-7]. Therefore, more research is needed for development of efficacious therapies for FD [4-7]. Herbal medicines are one of the therapeutic options for FD [8-11]. Herbal medicines have various bioactive compounds which may act on the various mechanisms of FD [8-11]. The *Pistacia atlantica* subsp. *kurdica* Rech. f. oleoresin (OPA) is utilized in the Persian Medicine for the therapy of gastrointestinal disorders like dyspepsia, upper abdominal pain and discomfort, peptic ulcer [12,13], gastroesophageal reflux disease, and for strengthening the stomach [14]. As yet, the effects of OPA in the treatment of FD have not been examined. Therefore, the safety and effects of standardized OPA on the FD patients' symptoms and quality of life were studied.

Methods

Plant material

Dr. Ardeshir Qaderi (academic of Medicinal Plants Research Center, Institute of Medicinal Plants, ACECR, Karaj, Iran) identified the tree *Pistacia atlantica* subsp. *kurdica* Rech. f. (wild pistachio) (local names: baneh kordestani, kolkhoung, saghez), and after checking the tree name with http://www.theplantlist.org, collected 2 kilograms of the semifluid oleoresin by creating cuts in the tree trunk in the Kermanshah Province of Iran (Hawraman region, GPS coordinates: 35º08′07.1″N; 46º28′20.1″E) in August, 2018. Samples of the oleoresin, fruits and leaves of the tree were put in the herbarium of the Medicinal Plants Research Center, Institute of Medicinal Plants, ACECR, Karaj, Iran (herbarium number 982).

Preparation of the oral OPA and placebo capsules

Since OPA was viscous, it was mixed with toast powder in order to encapsulate it. Each OPA and placebo capsule contained 200 mg of OPA or toast powder, respectively. The OPA and placebo capsules were similar in every aspect, and produced in the Medicinal Plants Research Center, Institute of Medicinal Plants, ACECR, Karaj, Iran.

Standardization of OPA

As OPA did not dissolve in any solvent, analysis was performed on its essential oil. Using the Clevenger apparatus, 50 g of air-dried and ground OPA was subjected to water distillation for four hours. The essential oil was extracted, dried with sodium sulfate, and kept in a vial at 4 °C until it was analyzed by GC-MS (gas chromatography-mass spectrometry).

GC-MS

Agilent 6890 series instrument and Agilent 5973 mass detector were used for the GC–MS analysis. Helium was used as a carrier gas at a flow rate of 1 mL/min to drive an HPX-5 capillary column (30 m, 0.25 mm i.d., film thickness 0.25 µm) at 50 °C for 5 min, then the temperature was increased 3 °C/min to 240 °C and 15 °C/min to 300 °C. The acquisition mass range was 40–500 m/z, the split ratio was 1:35, the ionization energy was 70 eV, and the scan time was 1 s. After diluting the essential oil with hexane solvent (1:100), 1 µL was injected. The compounds were identified using Kovats indexes, retention times, and mass spectra comparisons with real compounds or those from a computer library.

Clinical trial

Design and setting

This trial was randomized, triple-blind, placebo-controlled, parallel-group, and conducted in the Baqiyatallah Hospital (Tehran, Iran) from 23/9/2018 to 20/3/2020.

Ethics and trial registry

Ethics committee of the Avicenna Research Institute (Tehran, Iran) approved this trial with the reference number IR.ACECR.Avicenna.REC.1396.22 at 16/1/2018. All patients signed an informed consent form before recruitment. The protocol was as per the revised Declaration of Helsinki 2013. This trial was registered in the Iranian Registry of Clinical Trials with the number IRCT20090804002288N14 at 16/7/2018.

Sample size

Fifty patients in each group was the sample size calculated by G*Power software to estimate the effect size 0.6 for Hong Kong dyspepsia index, considering type

I error 0.05, 80% power, and 30% attrition. The calculation of effect size was performed via conduction of a pilot trial.

Patients' eligibility criteria

The trial included patients aged 20 to 80 years with functional dyspepsia according to the Rome III criteria. Pregnant and lactating women, and women planning pregnancy were excluded.

Randomization

Random allocation was performed using the random allocation software (version 2), considering the blocking method with random block sizes, 50 patients, and 2 groups. A random list was prepared by the trial's methodologist who did not have a role in the treatment of the patients.

Allocation concealment

For allocation concealment, sealed envelopes were used with the number of patients on, and the type of intervention in them.

Implementation

Different individuals generated the random allocation sequence, recruited patients, and assigned patients to interventions.

Blinding

The patients, care providers, and data analyzer were unaware of the treatment assignment. The OPA and placebo capsules were identically packaged and coded.

Interventions

Fifty patients were assigned to each of the OPA and placebo groups. The patients took 2 OPA or placebo capsules every 12 hours for 8 weeks. All the patients used one 40 mg famotidine tablet per day orally along with the OPA or placebo capsules. Patient compliance with the therapy was determined by questioning the patients and counting unused drugs. The patients were told to report any adverse effect and abnormal condition.

Outcomes

The primary outcome variable was the dyspepsia severity measured by the Hong Kong dyspepsia index [3]. Quality of life, complete blood count, and the blood levels of alanine aminotransferase, aspartate aminotransferase, blood urea nitrogen, creatinine, triglyceride, total cholesterol, low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL–C) were the secondary outcome variables. The outcome variables were evaluated before and after 2 months of intervention. Quality of life was determined by the SF-36 (Short-Form 36 Item Health Survey) questionnaire [15]. The blood parameters were measured by an auto-analyzer (Hitachi 917, Japan) for evaluation of the safety of OPA. The patients were told to report any side effect and abnormal condition.

Practitioners

The practitioners were gastroenterologist and internist with knowledge about herbal medicine, trained in the Baqiyatallah University of Medical Sciences (Tehran, Iran), and practicing medicine for about 22 years.

Statistical methods

Data were analyzed using SPSS software (version: 27) and intention-to-treat method. The qualitative variables were described by percentage of frequency, and compared between groups by Chi-squared or Fisher's exact test. The quantitative variables were presented as mean and standard deviation. The Hong Kong score was compared within groups by Wilcoxon signed-rank test. The SF-36 questionnaire score and biochemical variables were compared within groups by paired t test. P values < 0.05 were significant.

Results

Standardization of OPA

The essential oil formed 10% w/w of the OPA and consisted of α-pinene (96%), β- pinene (2%) and terpinolene (2%).

Clinical trial

The patients consumed more than 87% of the administered drugs. Thirty five patients in each group completed the trial. Figure 1 shows the CONSORT flow diagram of the trial. Mean ± standard deviation of age was 37.14 ± 10.3 years in the OPA group, and 40.31 ± 11.7 years for the placebo group ($p = 0.235$). Forty five percent of patients in each group were male. The distribution of gender was identical in both groups ($p = 0.345$). Mean ± standard deviation of body mass index was 24.49 ± 3.29 kg/m^2 in the OPA group, and 24.47 ± 3.82 kg/m^2 in the placebo group ($p = 0.096$). Table 1 presents the frequency of symptoms of dyspepsia in each group throughout the trial and comparisons between groups. Table 1 shows no significant difference between groups for the frequency of symptoms during the trial. Compared to baseline, the Hong Kong score was significantly decreased in the OPA group after 8 weeks ($p = 0.013$), but it was not significantly changed in the placebo group ($p = 0.651$) (Table 2). While compared to baseline, the SF-36 questionnaire score of the OPA group was significantly increased after 8 weeks ($p = 0.027$), it increased insignificantly in the placebo group ($p = 0.078$) (Table 3). All the blood variables

were in the normal range at the baseline. No significant change was observed in the blood variables, indicating the safety of OPA. Also, no side effect was identified.

Discussion

The purpose of this trial was study of the effects of OPA on the symptoms and quality of life of FD patients. The results show that the essential oil of OPA was composed of the monoterpenes α-pinene, β-pinene and terpinolene. Alpha-pinene was the major compound and the other two monoterpenes were the minor compounds of the essential oil. Also, the OPA reduced the Hong Kong index of dyspepsia, indicating reduction of the severity of symptoms. Further, the OPA increased the SF-36 questionnaire score, indicating improvement of the patients' quality of life. Notably, no side effect was noted in the patients, which is in line with the safety of OPA reported previously [12,13]. As regards the related research, the resin of *Pistacia lentiscus* var. *chia* (PLC) reduced the Hong Kong index of dyspepsia in a clinical trial on FD patients [16]. The result of the present trial is comparable to that of the just-mentioned trial. While PLC had significant effects on pain and heartburn [16], OPA had no significant effect on any specific symptom. Additionally, a systematic review and meta-analysis of 49 randomized clinical trials involving 6987 patients on the efficacy of herbal treatments for FD concluded as follows: Herbal remedies are more efficacious than placebo in improving the symptoms and quality of life of FD patients, and the rates of side effects of herbal remedies and placebo are not significantly different. There are no significant difference between the outcomes of treatment of FD with herbal remedies and standard drugs. Also, herbal remedies may be effective, safe, and as effective as standard drugs in the treatment of FD [17]. The results of the present trial align with those of the aforementioned systematic review and meta-analysis. FD has a complex and unclear pathophysiology [2,6]. The mechanisms underlying FD include delayed gastric empty-

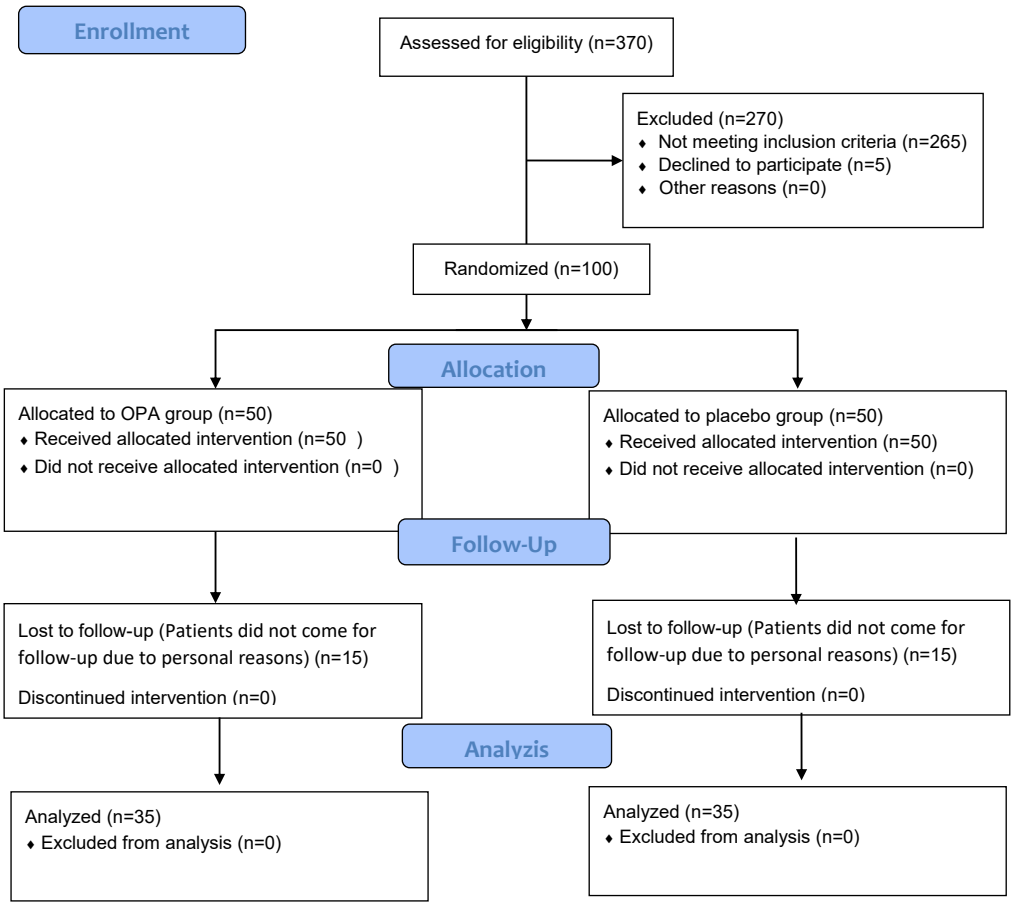

Figure 1. CONSORT flow diagram of the trial. OPA: *Pistacia atlantica* oleoresin

Table 1. Frequency of dyspepsia symptoms in each group at baseline, and 4th and 8th weeks of the trial

Symptom	Number of patients presenting with the symptom in the OPA group (%)	Number of patients presenting with the symptom in the placebo group (%)	*p* value [c]
Early satiation at baseline	13 (37.1)	19 (54.3)	0.23
Early satiation at 4th week	13 (37.1)	15 (42.9)	0.808
Early satiation at 8th week	8 (22.9)	10 (28.6)	0.785
Bloating at baseline	19 (54.3)	19 (54.3)	1
Bloating at 4th week	8 (22.9)	14 (40)	0.197
Bloating at 8th week	5 (14.3)	13 (37.1)	0.054
Fullness at baseline	10 (28.6)	9 (25.7)	1
Fullness at 4th week	6 (17.1)	6 (17.1)	1
Fullness at 8th week	4 (11.4)	5 (14.3)	1
Belching at baseline	12 (34.3)	18 (51.4)	0.227
Belching at 4th week	9 (25.7)	11 (31.4)	0.792
Belching at 8th week	6 (17.1)	9 (25.7)	0.561
Nausea at baseline	29 (82.9)	29 (82.9)	1
Nausea at 4th week	9 (25.7)	15 (42.9)	0.208
Nausea at 8th week	7 (20)	11 (31.4)	0.413
Vomiting at baseline	20 (57.1)	16 (45.7)	0.473
Vomiting at 4th week	1 (2.9)	3 (8.6)	0.614
Vomiting at 8th week	0	2 (5.7)	0.493
Burning at baseline	25 (71.4)	25 (71.4)	1
Burning at 4th week	14 (40)	21 (60)	0.151
Burning at 8th week	9 (25.7)	13 (37.1)	0.44
Pain at baseline	26 (74.3)	26 (74.3)	1
Pain at 4th week	4 (11.4)	6 (17.1)	0.734
Pain at 8th week	2 (5.7)	3 (8.6)	1

c Chi-squared test. OPA: *Pistacia atlantica* oleoresin

Table 2. The Hong Kong dyspepsia index in each group

Hong Kong dyspepsia index	OPA group (mean ± standard deviation)	Placebo group (mean ± standard deviation)
Baseline	18 ± 6.11	18 ± 5.86
8th week	15.03 ± 4.23	18 ± 6.12
p value [w]	0.013	0.651

w: Wilcoxon matched pairs signed rank test. OPA: *Pistacia atlantica* oleoresin

Table 3. The SF-36 questionnaire score in each group

SF-36 questionnaire score	OPA group (mean ± standard deviation)	Placebo group (mean ± standard deviation)
Baseline	21. 47 ± 7.17	23.12 ± 8.40
8th week	32.17 ± 9.11	26.15 ± 8.76
p value [t]	0.027	0.078

t: paired *t*-test. OPA: *Pistacia atlantica* oleoresin

ing, impaired gastric accommodation, gastroduodenal hypersensitivity, altered duodenal mucosa, central sensitization, low-grade duodenal inflammation, and oxidative stress [6, 18]. Given that FD is a complex and multifactorial disease with unclear pathophysiology, the mechanisms of effective drugs in FD are unknown [4-7,18,19]. Theoretically, the monoterpenes and essential oil of OPA, due to their pharmacological actions, may target some of the FD mechanisms. The monoterpenes of OPA have demonstrated a variety of anti-inflammatory and analgesic effects in experimental studies [21-24]. Alpha-pinene inhibited H_2O_2-stimulated oxidative stress in U373-MG cells [25]. Also, OPA showed antioxidant effect in the diabetic rats [25]. These anti-inflammatory, analgesic and antioxidant actions may play a part in the effects of OPA on the symptoms of FD. Additionally, essential oils have spasmolytic, carminative and local anesthetic properties [26]. Thus, the essential oil of OPA may reduce the severity of FD symptoms through spasmolytic, carminative and local anesthetic actions.

The results of this trial suggest that OPA may have therapeutic value and safety for FD, and at least a portion of the efficacy of OPA in FD may stem from the monoterpenes of the OPA essential oil. Short duration, small sample size, and lack of investigation of the OPA effects on the FD subtypes are limitations of this study.

Conclusions

Oral intake of two 200 mg OPA capsules every 12 hours safely reduces the severity of FD symptoms and improves the FD patients' quality of life. The monoterpenes (α-pinene, β-pinene, and terpinolene) of the OPA essential oil may be partly involved in the OPA effects in FD. Further research into the OPA effects on the FD subtypes is recommended.

Conflict of Interests

None.

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None.

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