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Effectiveness of *Quercus brantii* hydroalcoholic extract on dyspepsia: A randomized, double blind clinical trial

Hossein Nili-Ahmadabadi[1], Mohammad Hassan Emami[2], Navid Omidifar[3,4]

[1]Department of Internal Medicine, School of Medicine, Yasuj University of Medical Sciences, Yasuj, [2]Gastrointestinal and Hepatobiliary Diseases Research Center, Poursina Hakim Research Institute for Health Care Development, Isfahan, [3]Molecular Clinical Microbiology Subdivision, Clinical Pathology Division, Department of Pathology, School of Medicine, Shiraz University of Medical Sciences, [4]Clinical Education Research Center, Shiraz University of Medical Sciences, Shiraz, Iran

Address for correspondence:
Dr. Navid Omidifar, Molecular Clinical Microbiology Subdivision, Clinical Pathology Division, Department of Pathology, School of Medicine, and Clinical Education Research Centre, Shiraz University of Medical Sciences, Shiraz, Iran.
E-mail: omidifar@gmail.com

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Abstract:

CONTEXT AND AIMS: We aimed to evaluate the effectiveness of hydroalcoholic extract of *Quercus brantii*'s nut on clinical, endoscopic, and pathological findings of patients with dyspepsia.

PATIENTS AND METHODS: In this randomized, double-blind clinical trial, patients with symptomatic dyspepsia who had an endoscopic evaluation for dyspepsia were included and randomized into two groups. One Group (A) received drug extract with a dose of 100 mg twice a day for 10 days. Group B, as a control group, received placebo. Immediately and 2 months after intervention, the patients were followed up, and the characteristics of their dyspepsia (severity and frequency), endoscopic and pathologic findings were reevaluated and compared.

RESULTS: In this trial, 13 and ten patients participated in the study in Groups A and B, respectively. Two months after intervention, ten (76.9%) and six (60%) participants referred for follow-up and endoscopic evaluation. There were no significant changes in clinical presentations after intervention ($P > 0.05$). Two months after intervention, clinical presentations including severity and frequency of epigastric pain had significant decrease in Group A and endoscopic evaluation indicated significant improvement in Group A ($P < 0.05$). Pathologic findings were similar and not significantly different in two studied groups after intervention ($P > 0.05$).

CONCLUSIONS: The findings of this trial indicated that hydroalcoholic extract of *Q. brantii*'s nut could have delayed significant proper effect on clinical and endoscopic presentations of patients with dyspepsia. We recommend that this study should be considered as pilot one in this field. The results could be used as baseline data for more interventional studies. More surveys are needed to investigate the mechanism of extract action at molecular basis.

Keywords:

Clinical, dyspepsia, endoscopy, pathology, *Quercus brantii*

Introduction

Dyspepsia is one of the most common complaints of gastrointestinal disease and is considered a global concern.[1] It is defined as a syndrome and a chronic discomfort, which presents with epigastric pain, burning, fullness, early satiety, belching or nausea, and vomiting.[2]

Although the reported prevalence rate for dyspepsia has great variability, based on various definitions used in different studies, the overall reported range is 3%–40% in different populations.[3-5]

Proper management of dyspepsia is an important issue due to its long-lasting period, high costs as well as its effect on patients' quality of life. Presence of this problem could interfere with daily activities

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of the patients.[6] Although different pharmacological treatments have been recommended, there is no definite and standardized treatment. Recent guidelines are being proposed for each specific etiology including nutritional treatment, traditional herbal treatments, proton pomp inhibitors, and antibiotics.[7]

Recently, use of herbal medicine and traditional medicine recommendations for treatment of different diseases has increased. The general population is interested in using medicinal plants due to their low cost and availability.[8] According to the report of the World Health Organization, most of the world's population, especially developing countries, use medicinal herbs for their primary health-care necessities.[9]

Different herbal treatments have been reported for the treatment of dyspepsia and relieving its symptoms in different populations and geographical regions. There are also evidences in traditional Iranian medicine (TIM) for prevention, diagnosis, and treatment of dyspepsia.[10]

Quercus is one of the traditional herbal medicines which has been used to treat dyspepsia in South-West Iran. In general, oak belongs to the family *Fagaceae* and genus *Quercus* that in turn comprises many species.[11] Both the tree and its beans have long been used for 1000 years in Europe, Asia, North Africa, Middle East, and North America.[12] Rough analyses of *Quercus* nut have shown chemical components similar to cereals and carbohydrates. Tannins, phenols, Vitamins C, A, and B, linoleic and linolenic acids, proteins and minerals, and fatty acids are other components as well.[13]

There are some resources which describe the effectiveness of this medicinal plant for the treatment of dyspepsia, but it seems that applied studies and clinical trials as a complementary research to TIM reference should be conducted for obtaining more conclusive evidences. Thus, we aimed to evaluate the effectiveness of hydroalcoholic extract of *Quercus brantii*'s nut on clinical, endoscopic, and pathological findings of patients with dyspepsia.

Patients and Methods

This study was designed as a randomized, double-blind clinical trial. During this study which was conducted from April 2015 to March 2016, in Isfahan, Iran, patients with dyspepsia who referred to Gastroenterology Clinic of Shahid Sadoughi Hospital were enrolled.

Protocol of the study was approved by regional Ethics Committee of Isfahan University of Medical Sciences with Ethical Code IR.MUI.REC.1391.3.074.

In this study, adult population with symptomatic dyspepsia who had an endoscopic evaluation for dyspepsia were included. Those who had a history of chronic disease or use of treatment were not included in the study.

Dyspepsia was defined as a frequency of 3–5 days a week and severity of symptoms that interrupt daily activities or force the patient give up work. From the included patients, those who had inflammation, erosions, and edema in the body and antrum (mid and distal parts of stomach) confirmed by endoscopy (Pentax) were selected finally.

Those who had normal endoscopy or other findings than that mentioned above were excluded from the study.

The aim and methods of the study were described for all the selected patients, and written informed consent was obtained from all the participants. Those who did not agree to participate or have not proper cooperation were excluded from the study.

Finally, 23 patients were selected and randomized into two groups. One Group (A) received drug extract with a dose of 100 mg twice a day for 10 days. Group B, as a control group, received placebo. The shape of both drug extract and placebo was the same and was manufactured by the Department of Pharmacology of Isfahan University of Medical Sciences, Isfahan, Iran.

Before intervention, demographic characteristics of the selected patients and also the characteristics of their dyspepsia including frequency and severity of epigastric pain were recorded in their medical file by the gastroenterologist.

Severity of the pain was categorized as mild (not interfering with daily activities or missing work), moderate (interfering with daily activity, no missing work), and severe (interfering with daily activities, no missing work). Frequency of the pain was classified as 1 day/week, 1–3 days/week, 3–5 days/week, and more than 5 days per/week.

The pathologic indexes which were evaluated from the endoscopic specimens were as follows; tissue lymphocytosis, cellular regeneration with gland invasion, and presence of *Helicobacter pylori*.

Patients in Groups A and B were advised not to use any additives or treatments after initial extract and placebo treatment. They were advised to refer before any attempt to undergo treatment elsewhere.

Immediately and 2 months after intervention, the patients were followed up and characteristics of their

dyspepsia as described above were also recorded. Two months after intervention, the second endoscopic evaluation was performed for the patients.

The endoscopic and clinical findings of the patients before, 10 days, and 2 months after intervention were recorded and compared in Groups A and B.

During intervention and follow-up period, the patients were in contact with their physician for reporting any complication related to the treatments. The possible complications were described for the patients before trial.

Hydroalcoholic extract preparation of *Quercus brantii*

Nuts of local oak, *Q. brantii*, were obtained from Yasuj, South-East Iran. All the solvents and materials needed for extract preparation were purchased from Merck Company.

Collected samples were ground into powders, immersed in solvents, and processed using an Soxhlet extractor. In brief, 20 g of the powder and 1000 ml of H_2O and 60% ethanol solution were mixed into the instrument to extract the dissolved components of the nut. Then, the extract was filtered by a Whatman paper and extracted once again with a new solvent. After 48 h, the vaporized remnant was dried in 30–35°C in a rotary evaporator with reduced pressure. The extract was encapsulated containing 100 mg of extract. It should be noted that starch was utilized as placebo in the same figure.

Statistical analysis

Collected data before and after intervention in the two studied groups were analyzed using SPSS version 9.1 software (SPSS Inc., Chicago, Illinois, USA). Continuous variables were expressed as mean (standard deviation) and categorical variables as number and percentage. Continuous and categorical variables before and after intervention in two studied groups were compared using Student's *t*-test and Chi-square test, respectively.

Results

In this trial, from initially selected patients (13 in each group), 13 and 10 patients participated in the study in Groups A and B, respectively. Two months after intervention, 10 (76.9%) and 6 (60%) participants were referred for follow-up and endoscopic evaluation [Figure 1].

Demographic characteristics of the two studied groups are shown in Table 1. Patients in Groups A and B were similar regarding their age, sex distribution, and degree of education ($P > 0.05$).

Clinical, endoscopic, and pathologic findings of patients in Groups A and B 10 days and 2 months after intervention are shown in Table 2.

Clinical presentations including severity and frequency of epigastric pain had significant decrease in Group A,

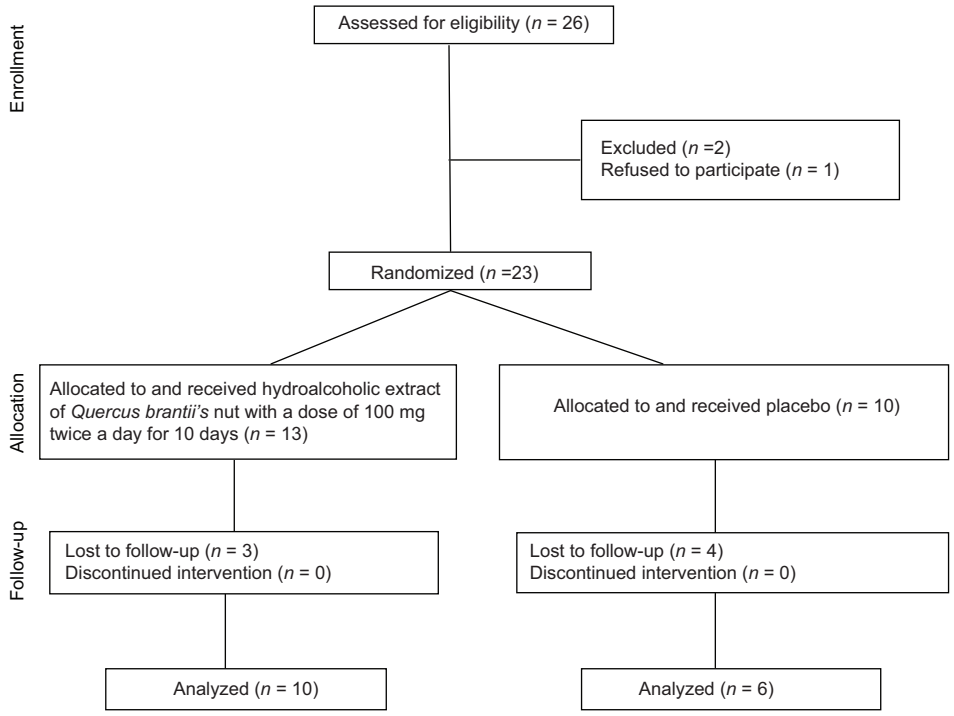

Figure 1: Consort diagram of the study

2 months after intervention ($P < 0.05$). Endoscopic evaluation indicated significant improvement in Group A, 2 months after intervention ($P < 0.05$).

Pathologic findings were similar and not significantly different in two studied groups, 2 months after intervention ($P > 0.05$).

There was no report regarding the possible complications of the plant extract or placebo.

Only a weird case of very small ulcer at the second endoscopy was biopsied and reported as signet-ring adenocarcinoma that was confirmed on re-biopsy. The patient had no history of familial or acquired risk factor but sometimes used to have foods containing native oak nuts.

Discussion

In this trial, we have investigated the effect of *Q. brantii* on clinical and paraclinical findings of patients with dyspepsia. It had no appropriate short-term effect regarding clinical presentation of the disease. However, as a long-term effect, it had significant effect on both severity and frequency of symptoms as well as endoscopic improvement in the disease-related features.

Table 1: Demographic characteristics of studied population in Group A (*Quercus brantii* extract) and Group B (placebo)

Variables	Group A (*n*=13)	Group B (*n*=10)	*P*
Age (years)*	45.5 (7.5)	44.6 (8.7)	0.83
Sex (female/male)** (%)	9/4 (69.2/30.8)	5/5 (50/50)	0.30
Grade of education** (%)			
<9th grade	5 (38.5)	7 (70)	0.14
≥9th grade	8 (61.5)	3 (30)	

*Mean (SD), **n (%). SD=Standard deviation

The effectiveness of herbal medicine in the treatment of different human aliments has been reported in many worldwide and regional studies.[14,15] Evidences indicated that different regions of Iran have a good ethnobotanical potential for medicinal plants, and use of these plants for different diseases is common in local people of each region.[16,17]

It has been suggested that using native medicinal plants lonely or along with pharmacological agents could improve the disease treatment process as well as increase the quality of life of native population.[14,15]

Dolatkhahi *et al*. have investigated the most important and useful medicinal plants used in the treatment of ailments in Fars Province. They documented 85 medicinal plants used for the treatment of various diseases. According to their findings, the plants are mainly used in the treatment of disease of intestinal digestive system. *Q. brantii* is included in the list of medicinal plants documented for intestinal digestive system disease.[16] In another study, Dolatkhahi *et al.* have investigated herbal remedies used for functional dyspepsia through the TIM references. They reported 105 plants from 37 families for the treatment of different dyspepsia symptoms. *Q. brantii* is not included in their reported traditional medicinal plants.[17] Thus, it seems that current reports are not accurately enough for providing final treatment plan in this regard. We planned this trial for determination of the effectiveness of the plant for dyspepsia.

Antimicrobial, anti-inflammatory, and anti-proliferative effects of *Q. brantii* have been reported in previous studies.[18-20] Sadeghian *et al*. showed that *Q. brantii* has antimicrobial effect for gastrointestinal bacterial pathogens which is greater than standard antibiotics. Their study was performed *in vitro*.[18]

Table 2: Clinical, endoscopic, and pathologic findings of patients in Group A (*Quercus brantii* extract) and Group B (placebo) 10 and 60 days after intervention

	Group A (*n*=10), *n* (%)	Group B (*n*=6), *n* (%)	*P*
Clinical presentations			
Reduction in pain severity at			
10th day	10 (76.9)	5 (50)	0.39
60th day	8 (61.5)	0	0.014
Reduction in pain frequency at			
10th day	10 (76.9)	6 (60)	0.137
60th day	8 (61.5)	2 (20)	0.016
Endoscopic findings			
Endoscopic improvement at second endoscopy	7 (70)	1 (16.7)	0.026
Pathologic findings			
Lymphocytic infiltration at second endoscopy	2 (20)	1 (16.7)	0.74
Regenerative changes at second endoscopy	1 (10)	2 (33.3)	0.68
Gland invasion at second endoscopy	1 (10)	0	0.44
Helicobacter pylori at second endoscopy	5 (50)	3 (50)	-

In another study, Azizi *et al*. have investigated the outcome of hydroalcoholic extract of *Q. brantii* seed flour in the treatment of experimentally gastric ulcer in Wistar rats. They indicated that the extract has an active component, tannin, which could have appropriate therapeutic effect on ulcer healing.[19]

In literature review, we did not find any similar study. In a study conducted by Dolatkhahi *et al*., they found only seven human studies which have evaluated the effectiveness of seven single plants other than *Q. brantii* on dyspepsia.[17]

In our trial, the two studied groups were similar at baseline regarding their demographic characteristics. Short-term evaluation showed no significant changes in clinical presentation of dyspepsia. However, after a 2-month period, we found significant improvement both in clinical and endoscopic findings.

The findings could explain that the extract has delayed therapeutic effect, or the duration and administrated dose of the extract are not enough for inducing short-term effect. Further, it seems that a delayed but sustained clinical and endoscopic improvement is reached after 10 days of treatment.

We have not detected any significant changes in pathological findings of the studied population 2 months after intervention. It is suggested that symptom relief maybe due to biochemical changes and not histological effects. Tannin in extract may form an overlying barrier to shield against acid and reinstitute mucosa. We did not examine the effectiveness of the extract on biochemical factors, which is considered one of the limitations of this trial and should be evaluated in future researches.

The most important limitation of this study was small sample size of the patients.

The strength of this trial was its novelty. However, our findings could be considered as a pilot study for future studies which include more patients as well as investigate different dosages of extract with longer duration of intervention.

Conclusions

The findings of this trial indicated that hydroalcoholic extract of *Q. brantii*'s nut could have delayed significant effect on clinical and endoscopic presentations of patients with dyspepsia. We recommend that this study should be considered as pilot one in this field. The results could be used as baseline data for more interventional studies. More surveys are needed to investigate the mechanism of extract action at molecular basis.

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Conflicts of interest

There are no conflicts of interest.

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