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Original Article

The Effect of Common Hawthorn (*Crataegus monogyna* Jacq.) Syrup on Gastroesophageal Reflux Disease Symptoms

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Abstract

Common Hawthorn has been known as a traditional remedy to relieve gastroesophageal reflux disease symptoms and to improve stomach function. This study aims to investigate the effectiveness and safety of common hawthorn fruit in patients who suffer from gastroesophageal reflux disease.Eighty male and female patients with clinically diagnosed gastroesophageal reflux disease were included in the study. The patients were randomly assigned into experimental (treatment) and control groups. Experimental group members took common hawthorn syrup and those in the control group received placebo syrup for 4 weeks (5 ml after each meal). Gastroesophageal reflux disease symptoms were assessed based on an available validated questionnaire, before and after the treatment in both groups. The side effects were monitored according to old and new medical resources. In order to assess the probable effect on hepatic or renal function, the levels of alanine transaminase, aspartate transaminase, blood urea nitrogen, and creatinine were measured before and after the treatment.After four weeks of taking the hawthorn and placebo syrups, a significant improvement was observed in two main symptoms of gastroesophageal reflux disease in the experimental group compared with the control one. Heartburn and regurgitation were alleviated by 93.5% and 94.2% respectively. The impact of the common hawthorn syrup on atypical symptoms of gastroesophageal reflux disease such as dyspnea, chest pain, cough and dysphagia was also evaluated and differences were not statically significant. Any adverse effects of the medicine on the functions of liver and kidney were not observed. Our findings suggest common hawthorn fruit as a natural source to control the main symptoms of gastroesophageal reflux disease.

Keywords: Hawthorn; Gastroesophageal reflux disease; Regurgitation; Heartburn, Traditional medicine.

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1. Introduction

Gastroesophageal reflux disease (GERD) is a common disease which accounts for 17.5% of all digestive system diseases. It is more prevalent in western communities than in Asian countries. Its prevalence is 27% in Finland, 23% in Spain, 7.5% in India, 5% in Switzerland, 3% in Malaysia and 0.8% in China. Disparity of the prevalence is due to differences in dietary habits and lifestyle differences in various areas [1, 2]. According to previous studies, the prevalence of the disease in Iran, in 2013 was 23.5% [1, 3].

Gastroesophageal reflux disease ranges from a disease with no symptoms to a complicated one that may require invasive treatments. It may affect patients' quality of life [3, 4]. The complications of the disease are esophageal ulcer (5%), peptic esophageal strictures (4-20%) and Barrett's esophagus (8-20%) that can lead to esophageal adenocarcinoma. The risk of cancer in patients with Barrett's esophagus is 40-100 times higher than in normal population [3, 5]. The annual incidence of cancer in patients with GERD is about 0.5%. The rates for dental erosion, irritable bowel syndrome, and psychological disorders are 22.6%, 36%, and 41%, respectively.

Heartburn and regurgitation are two main symptoms of GERD, although some patients are refered with atypical symptoms like chest pain, cough, hoarseness, wheezing, signs of sinusitis, signs of otitis, jaw pain, and sleep disorders [6, 7].

GERD has not been mentioned certainly in the ancient and traditional medicine references, but some symptoms such as heartburn and sour belching, which are the main symptoms of GERD, have been defined. According to ancient medical books, the main cause of such symptoms is lower esophageal sphincter relaxation which contributes to accumulation of excessive juice in the stomach. When the stomach juice exceeds, the stomach tissue relaxes and fails to perform its functions of digestion and excretion properly [8].

According to recent literature and latest articles, people with reflux disease should receive long-term, and occasionally lifetime treatment. The medications administered along with these modifications include antacids, histamine-2 receptor antagonists, and proton-pump inhibitors [8].

Long-term use of PPIs is associated with adverse effects; they especially increase the risk of pneumonia and *Clostridium difficile* infection. In some studies, long-term, daily use of the PPIs is linked to higher risk of osteopenia and bone fractures (hip, wrist and vertebra) [9]. Long-term use of these medications cause bacterial infections and impaired intestinal absorption of vitamins [10].

Considering the side effects of such medications and the chronicity of GERD, the use of herbal medicines in the treatment of reflux disease can reduce symptoms and improve quality of life. According to ancient medical books, in addition to lifestyle modification, to treat the disease, the patients' excess gastric juice was disposed by administering appropriate medications, and then the stomach was strengthened with the administration of medications like emblic (*Phyllanthus emblica* L.), ginger, apple and quince
[11].

Nowadays, different parts of common hawthorn (CH) -as a member of Rosaceae- are available in the market as capsules, syrup, tablets, and drops. The therapeutic effects of CH are documented and it is indicated for congestive heart failure, hypertension, atherosclerosis, hyperlipidemia, etc [12]. CH improves the stomach function and it brings about contraction of the stomach tissue. CH improves liver function, relieves nausea and vomiting, alleviates thirst, stops diarrhea, and cleanses the stomach [13]. Effective chemical compounds of hawthorn fruit are flavonoids, procyanidins, anthocyanidins, and phenolic acids [14, 15]. CH gastroprotective properties have been found to be equal to those of ranitidine in a study in rats [12]. CH has even been recently shown to be effective in the treatment of dyspnea and nephrolithiasis [14].

In the light of above-mentioned points, we aimed to evaluate the possible effects of the syrup of common hawthorn fruit in controlling gastroesophageal reflux disease symptoms. Its potential side effects were also taken into account and recorded using a valid questionnaire and blood test.

2. Materials and Methods

2.1. Syrup Preparation

The fruits of CH were purchased from a local market in Tehran, Iran and were confirmed by a botanist (M. Kamalinejad). In order to prepare CH extract, 100 grams of the fruits were sunk into 1000 mL of boiling water for 15 minutes. After cooling, the supernatant was separated using a paper filter. A syrup containing 66.7 % of sugar and 10 % of dried extract of CH extract was prepared. The syrup was poured into a 250 mL opaque bottle.

The placebo syrup was prepared with the same percentage of sugar and a small amount of a standard natural color.

2.2. Patients

This randomized, double blinded placebo-controlled clinical trial was conducted on a population of 80 patients with gastroesophageal reflux disease. Patients matching the inclusion criteria were entered into the study after giving written informed consent. The project was approved by the ethics committee of Iran University of Medical Sciences on March 3, 2013 and registered in Iranian Registry of

Clinical Trials under code: IRCT2013081314345N1.

Patients between 20-60 years, with symptoms of GERD (e.g. heartburn and regurgitation) at least twice a week, those never suffering from complications of GERD, such as peptic ulcer, gastrointestinal hemorrhage, etc or those suffering from GERD and having not taken any medication for at least 2 months were included into the study. Patients with high blood urea nitrogen (BUN), creatinine, aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels, patients having taken a nonsteroidal anti-inflammatory drug every day and patients who were using cardiac glycosides, antiarrhythmic drugs, antiplatelet drugs or cisapride were excluded from the study. The diagnosis was established based on the clinical symptoms of GERD and patients were identified [12]. The patients were divided randomly into two groups (treatment and control group); patients in the treatment group received CH syrup and those in the control group took the placebo.

A validated questionnaire, which had already been applied for other research projects, was initially filled out by a physician and the severity of the patients' symptoms was recorded.

The patients' blood levels of the ALT, AST, BUN and creatinine were measured at baseline. Two weeks later they were evaluated for any change in the severity of the symptoms and appearance of possible complications. At the end of the fourth week, the patients were evaluated clinically and changes were recorded.

Since one of the main methods in treatment of this disease is lifestyle changes, and all patients do not follow these principles equally, any recommendations were not given for lifestyle modification to remove the effects of confounding factors.

2.3. Data Analysis

GraphPad Prism 5.0 was used to perform statistical analysis. Results of the 4-week treatment were compared in both groups. Analysis of the qualitative variables between the two groups was performed using Fisher's exact test. The quantitative variables between the two groups were analyzed with the t-test. P-value less than 0.05 was considered as statically significant.

3. Results and Discussion

Eighty patients with GERD participated in the study (Table 1). All the patients completed the treatment period; only one of the patients complained of an exacerbation of bloating symptom, and one other experienced mild nausea after taking the medication that disappeared after the fifth day of the treatment. Both of the complications were mild and did not lead to withdrawal of the patients from the study.

A significant difference was observed between the main symptoms of GERD within the experimental group before and after the

Table 1. Demographic data of the control and treatment groups.

		Female	Male
	Control group	21	18
	Treatment group	16	25
	Total	37	43
Age	Control group	15	24
	Treatment group	19	22
	Total	34	46
BMI	Control group	29	10
	Treatment group	26	15
	Total	55	25

treatment. The P-value in the control group was 0.4793, while it was less than 0.0001 in the experimental group. In the evaluation of the regurgitation symptom the P-value was 0.2295 in the control group, and it was less than 0.0001 in the experimental group (Table 2). 3 patients (3.7%) complained of chest pain, 2.5% of dysphagia, 5% of coughing and one patient (1.2%) of dyspnea, and any significant differences were found in both groups before and after the treatment.

In this project, the effects of a syrup prepared from common hawthorn fruit and those of the placebo on the main symptoms of gastroesophageal reflux disease in the control and experimental groups were evaluated and compared. The results revealed statically significant difference between the two groups, indicating the possible effectiveness of the common hawthorn fruit in controlling the symptoms of GERD.

Table 2. Changes in the incidence of heartburn and regurgitation symptoms in the control and experimental groups before and after the treatment.

Symptom	Group	Before	After	P-value	RR (GI 95%)
Heartburn	Control	16/39*	12/39	0.4793	1.242 (0.8004-1.928)
	Treatment	31/41	2/41	<0.0001	4.603 (2.630-8.057)
Regurgitation	Control	16/39	10/39	0.2295	1.391 (0.9043-2.14)
	Treatment	35/41	2/41	<0.0001	7.095 (3.354-15.01)

* The results are shown as the ratio of the number of patients with a symptom to the total number of the group. The P-value < 0.05 indicates that there exists a significant change in the incidence of a symptom in the cores of ponding group.

The ALT, AST, BUN and creatinine levels were not significantly different between the experimental and control group before and after the treatment (Figure 1 and Figure 2).

Common hawthorn various parts have been reported to be effective against cardiovascular complications, such as heart failure, hypertension with myocardial injuries, angina

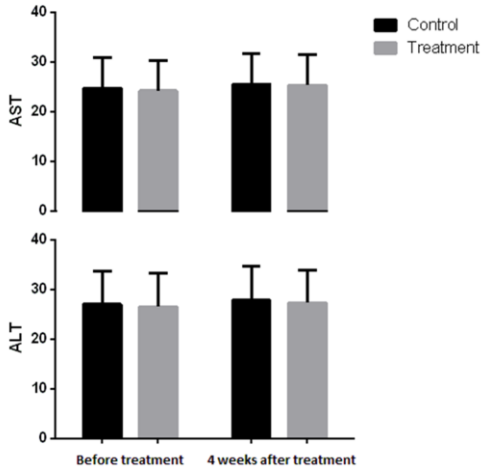

Figure 1. Changes in serum levels of liver enzymes (U/L) before and after the 4 week treatment in the control and experimental groups. The t-test analysis shows no significant changes in any of these values between the control and experimental groups. All values are expressed as means ± SD.

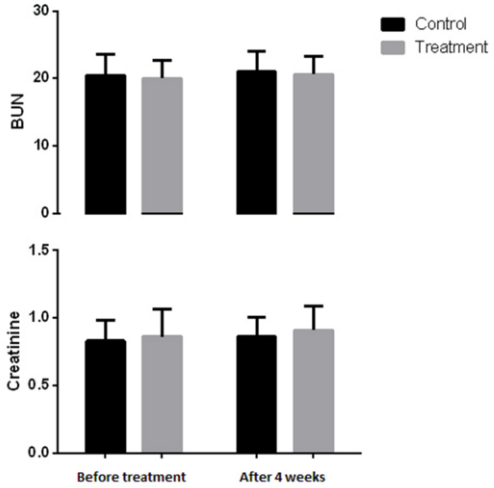

Figure 2. Changes in the concentration of renal indices (mg/dL) before and after the 4 week treatment in the control and experimental groups. The t-test analysis did not show any significant change in the values between the control and experimental groups. Values are expressed as means ± SD.

pectoris, arrhythmia, and atherosclerosis. In addition, they have been used for improving blood circulation, treatment of gastrointestinal diseases, stimulation of digestion, and promoting the stomach functions. Moreover, common hawthorn has had application in the treatment of indigestion, epigastric distension, abdominal pain, and diarrhea. In the European traditional medicine, common hawthorn is known as an anti-spasmodic, cardiotonic, astringent, and diuretic agent [10, 12, 16].

In view of the traditional medicinal uses of CH, modern scientists have extensively investigated the chemical constituents, to which the pharmacological effects could be attributed. The secondary metabolites, extracted from the different parts of the plant, range from simple fatty acids to terpenoid and polyphenolic compounds [12, 17].

One of the side effects of CH that has been mentioned in ancient medical books is kidney dysfunction [18]. Performing the renal function tests before and after the treatment revealed that administration of CH fruit at the administrated dose, does not have any effect on the BUN and creatinine level of the patients. The ALT and AST were not affected by the prepared syrup, suggesting that it has no adverse effect on the liver function.

4. Conclusion

According to the statistical data and the results obtained and given that the GERD is a chronic disease, and patients have to take the

remedies for a long time, sometimes lifelong, and because of possible adverse effects of chemical medicines, [10] CH syrup may be a candidate to be added to the drug regimen or even as an alternative agent.

Further investigations are necessary to confirm the relieving effect of common hawthorn on gastroesophageal reflux disease symptoms and to find the possible contributing mechanisms.

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References

[1] Stoll B and Kliegman R, *Jaundice and hyperbilirubinemia in the newborn*, in *Nelson Textbook of Pediatrics*, Behemen R, Kliegman R, and Jenson H, Editors. 2008, Saunders: Philadelphia. p. 756–65.

[2] Azadbakht, M., et al., *The effect of purgative manna on the infant jaundice.* Iranian Journal of Pharmaceutical Sciences, 2005. 1(2): p. 95-100.

[3] Ambalavanan N and Carloa WA, *Kernicterus*, in *Nelson text book of Peadiatrics*, B.R. Kliegman RM, Stanton BF, Schor NF, St Geme III JW, Editor. 2015, Elseviers: New Delhi. p. 876.

[4] Bhutani, V.K., et al., *Clinical trial of tin mesoporphyrin to prevent neonatal hyperbilirubinemia.* J Perinatol, 2016. 36(7): p. 533-539.

[5] Davies, G.A., et al., *Obesity in Pregnancy: No. 239, February 2010.* International Journal of Gynecology & Obstetrics, 2010. 110(2): p. 167-173.

[6] Basiri-Moghadam, M., et al., *The effect of massage on neonatal jaundice in stable preterm newborn infants: a randomized controlled trial.* J Pak Med Assoc, 2015. 65(6): p. 602-6.

[7] Fok, T.F., *Neonatal Jaundice-Traditional Chinese Medicine Approach.* Journal of Perinatology, 2001. 21(8).

[8] Ebrahimimd, S., S. Ashkani-Esfahani, and A. Poormahmudibs, *Investigating the Efficacy of Zizyphus Jujuba on Neonatal Jaundice.* Iranian Journal of Pediatrics, 2011. 21(3): p. 320-324.

[9] Dennery, P.A., *Pharmacological interventions for the treatment of neonatal jaundice.* Semin Neonatol, 2002. 7(2): p. 111-9.

[10] Aghili Khorasani MH, *Makhzan-ul-Advieh (Encyclopedia of ancient medical drugs)*. 2001, Tehran: Choogan.

[11] Kermani, N.A., *Sharh-ol-Asbab val Alamat*. Vol. 2. 2008, Tehran: Almoa.

[12] Hosseini MM, *Tohfeye Hakim Momen*. 1979, Tehran: Mahmoudi.

[13] Ernst, E., *Herbal medicinal products during pregnancy: are they safe?* BJOG: An International Journal of Obstetrics & Gynaecology, 2002. 109(3): p. 227-235.

[14] Montvale J, Brendler T, and Jaenicke C, *PDR for herbal medicines*. 2000, Montvale: Medical Economics Company.

[15] Mousavinejad, G., et al., *Identification and quantification of phenolic compounds and their effects on antioxidant activity in pomegranate juices of eight Iranian cultivars.* Food Chemistry, 2009. 115(4): p. 1274-1278.

[16] Yildiz, H., H. Bozkurt, and F. Icier, *Ohmic and conventional heating of pomegranate juice: effects on rheology, color, and total phenolics.* Food Science

and Technology International, 2009. 15(5): p. 503-512.

[17] Mahboubi, A., et al., *Total phenolic content and antibacterial activity of five plants of Labiatae against four foodborne and some other bacteria.* Iranian Journal of Pharmaceutical Research, 2014. 13(2): p. 559-566.

[18] Tabatabaei, M.H., *Almizan Fi Tafsir Al-Quran.* Translated by: Muhammad Bagher Mussavi, Publisher: The Office of Qum Hawze Ilmieh Teachers' society, 1996. 16: p. 313-415.