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Original Research Article

Rhus coriaria L. increases serum apolipoprotein-A1 and high-density lipoprotein cholesterol levels: a double-blind placebo-controlled randomized clinical trial

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ABSTRACT

Background: Lipid-lowering effect of *Rhus coriaria* L. (*Rhus*) has been investigated in multiple animal studies with promising results. Nonetheless, its clinical efficacy has not been adequately examined.
Objective: The aim of this study was to evaluate the lipid-lowering effects of *Rhus* among patients with hyperlipidemia.
Design, setting, participants and interventions: The study was designed as a two-arm, double-blind placebo-controlled randomized clinical trial, using a parallel design. Eighty patients with primary hyperlipidemia were randomly assigned to receive *Rhus* capsules or placebo for 6 weeks.
Main outcome measures: The serum lipid levels, apolipoprotein-A1 (Apo-A1) and apolipoprotein-B (Apo-B) were measured.
Results: Mean serum high-density lipoprotein cholesterol (HDL-C) and Apo-A1 levels were significantly increased in the *Rhus* group, compared with the placebo group, after 6 weeks of intervention ($P = 0.001$). The analysis of covariance test including age, gender, body mass index (BMI), and smoking as co-variables revealed that the increase in HDL-C and Apo-A1 levels remained significant, and increases in HDL-C were dependent on the increase in Apo-A1 levels. No significant difference was observed between *Rhus* and placebo groups in terms of mean reductions in total cholesterol, low-density lipoprotein cholesterol and triglyceride levels; however, more significant improvement was observed among obese patients (BMI $\geq$ 30 kg/m^2).
Conclusion: The study showed significant increases in HDL-C and Apo-A1 levels in response to *Rhus* supplementation in patients with hyperlipidemia.
Trial registration: ClinicalTrials.gov ID: NCT02295293.

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1. Introduction

Hyperlipidemia is a major risk factor for coronary heart disease (CHD) and atherosclerosis [1,2]. The prevalence of hyperlipidemia as well as its complications, such as CHD, is increasing on a global level [3]. Elevated serum level of low-density lipoprotein (LDL) and total cholesterol concentration increase the risk of CHD, while the concentration of high-density lipoprotein (HDL) was confirmed as a powerful predictor of CHD risk. The cholesterol content of HDL is not the only effective part in inverse association with CHD, but lower levels of apolipoprotein-A1 (Apo-A1) or of the HDL fractions defined by their Apo content were also associated with CHD risk as

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separate variables in the analysis. Therefore, low Apo-A1 levels appeared to be the most powerful HDL parameter for predicting CHD [4].

Treatment of hyperlipidemia brought out significant benefits in primary and secondary prevention of CHD [5]. Despite the advances in drug therapy for hyperlipidemia, some patients have a poor response to current treatments and/or cannot tolerate their adverse effects [6,7]. Consequently, much research effort has been invested in exploring new therapeutic options in this field. This includes research on complementary and alternative medicine (CAM) options including nutritional supplementations [8–12]. Among varying types of CAM, herbal-based supplements are the most popular options in many ailments, including treatment of hyperlipidemia [13–15].

Rhus coriaria L. (*Rhus*, *somagh* or sumac) is a well-known spice derived from the Anacardiaceae family, which can be found growing throughout Mediterranean countries, South Europe, North Africa and the Middle East [16]. The antioxidant, antimicrobial and anti-inflammatory properties of *Rhus* extract(s) are well documented [17]. Lipid-lowering effects of *Rhus* have been investigated in multiple animal studies with promising results [18–20]. Nonetheless, its clinical efficacy has not been examined adequately [21]. This study was aimed at evaluating the lipid-lowering effects of *Rhus* among patients with hyperlipidemia.

2. Patients and methods

2.1. Trial design

The study was designed as a two-arm, double-blind randomized placebo-controlled clinical trial, applying a parallel design with a 1:1 allocation ratio. There were no changes in methods after trial commencement.

2.2. Sample size

The sample size was determined by a statistician considering predicted efficacy level of 20 mg/dL [21], one-sided significance level of 0.05, and a power of 0.80. The required sample size was calculated to be 35 participants per group. Assuming a 15% risk for patient dropout during the study, 5 patients were added to each group in the investigation.

2.3. Participants

One hundred and fifty-three patients attending the endocrinology clinic of the Shiraz University of Medical Sciences, from December 2014 to May 2015, with a diagnosis of hyperlipidemia (serum triglyceride >150 mg/dL and/or total cholesterol $\geq$240 mg/dL), were evaluated for inclusion in the study; patients were between the ages of 20 and 65. Patients with serum LDL cholesterol (LDL-C) at the level which would necessitate drug treatment, according to the patient risk stratification (NCEP-ATP III) [22], in addition to patients with serum triglyceride level greater than 500 mg/dL, were excluded from the study. Subjects with diabetes mellitus, hypo- or hyperthyroidism and any systemic illness (e.g., liver cirrhosis, acute or chronic renal failure, heart failure) were also excluded from this investigation. Those taking lipid-lowering agents, thiazides, glucocorticoids and hormone contraceptives were excluded as well. Pregnancy, lactation, alcoholism and a history of allergic reaction to *Rhus* were other exclusion criteria. Finally, 80 patients were equally allocated to the intervention and placebo groups after signing the informed consent forms.

2.4. Drug preparation

Rhus coriaria L. fruits were purchased from local market in Shiraz city. Plant material was identified by a botanist at the Department of Phytopharmaceuticals, School of Pharmacy, Shiraz University of Medical Sciences. A voucher specimen was deposited in the Shiraz School of Pharmacy collection (Registered Number: PM 533). Plant material was air dried under shade for 28 d (Temperature 20–37 °C) before being powdered in a hammer mill and sieved through 250 μm mesh. Quality control tests including microbial contamination and weight control test for capsules were performed, based on *United States Pharmacopeia* guidelines [23]. For chemical analysis, the total flavonoid content of powder was determined using the Dowd method [24]. In brief, quercetin (as a positive control) and the ethanolic extract of *Rhus* powder were separately dissolved in 5 mL aliquots of 2% aluminium trichloride to make a final range of concentrations from 0 to 80 mg/L. A standard curve was made by measuring the absorbance of the quercetin solutions at 415 nm (PG instrument T90 spectrophotometer). The total flavonoid content of the ethanolic extract of *Rhus* powder was determined. The mean of three readings ((252.374 ± 32.405) mg/g) showed the phenolic content of dry plant powder (25.2% of dry plant powder). The powder was encapsulated in such a manner that each was filled with 500 mg of *Rhus* powder (or, alternatively, placebo). Placebo capsules were filled with 500 mg of starch.

2.5. Randomization, blinding, and allocation concealment

Eighty eligible patients were randomly allocated to two parallel groups (i.e., the drug and placebo groups) by the clinic secretary, who had been instructed on how to apply a statistically randomized list. The randomized list was generated using the block randomization method, as previously described [25]. The physicians and researchers were blinded to the allocation of patients as the patients were allocated to treatment group by the clinic secretary. The statistician also received the data with the label of A and B groups without the disclosure of treatment groups. Based on the same shape and size of both the drug and the placebo capsules and containers, the patients were blinded to the drug allocation as well.

2.6. Interventions

Patients in both groups were instructed to take 500 mg of *Rhus* or placebo capsules twice daily after their meals, for 6 weeks. This dose of *Rhus* (1000 mg daily) was determined according to the minimum dose recommendation in the traditional Persian medicine (TPM) literature and previous studies [26]. All patients were also recommended to make no change in their previous state of physical activity and diet for the course of study. They were also advised to report any side effect to the on-call physician via telephone conversation.

2.7. Outcomes

Patients were evaluated prior to, and following 6 weeks of the intervention in terms of serum triglyceride, total cholesterol, LDL-C and HDL cholesterol (HDL-C). Anthropometric measures, systolic and diastolic blood pressures, serum biochemistry profile (including fasting blood sugar, liver and kidney function tests) and complete blood cell count were evaluated both before the enrolment of patients and after the intervention. Three-day dietary records were used to calculate food and beverage intake at baseline and during the intervention for each visit. Each three-day record consisted of two weekdays and one weekend. Energy calculation

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