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The effect of saffron (*Crocus sativus* L.) hydro-alcoholic extract on liver and renal functions in type 2 diabetic patients: A double-blinded randomized and placebo control trial

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ABSTRACT

Background and aim: Uncontrolled diabetes causes liver and renal dysfunctions. Since, saffron may improve diabetes control and indicate renal and liver protection, this study purposed to illustrate for the first time the effects of saffron extract on some liver and renal functional parameters among diabetic patients.

Materials and methods: In this double-blind clinical trial, 54 type 2 diabetic patients were randomly recruited to consume either 15 mg saffron extract (n = 27) or placebo capsules (n = 27) twice a day for 8 weeks. Alkaline phosphatase, aspartate and alanine amino transferase, uric acid, blood urea nitrogen, and creatinine of the patients as well as their physical activity, dietary intakes, anthropometric measures and blood pressure were measured. Data were analyzed by SPSS.18 software.

Results: Uric acid and blood urea nitrogen were significantly decreased in the saffron group ($P < 0.05$), however, there were no significant differences between the two groups at the end of the study ($p = 0.29$ and 0.14, respectively). Moreover, changes in other profiles, including liver enzymes, were not statistically significant in the two groups. Also, no significant changes in blood pressure, dietary intakes, and physical activity were seen among the two groups.

Conclusion: Saffron hydro-alcoholic extract did not considerably improve renal and liver functions in T2DM patients in an 8-week randomized clinical trials. The results deserved further investigations with more accurate methods to confirm.

1. Introduction

Type 2 Diabetes Mellitus (T2DM) is a chronic costly public health problem which its prevalence is increasing worldwide [1,2]. In addition, recent evidences have shown a dramatic increase in the prevalence of diabetes in Iran, during the last decade [3]. Poorly controlled diabetes is associated with some complications including atherosclerosis, retinopathy, nephropathy, and neuropathy [4,5]. Because of hyperglycemia, liver diseases including fatty liver disease are also very prevalent among diabetic patients [5]. Clinically, Alanine Amino Transferase (ALT), Aspartate Amino Transferase (AST), and Alkaline Phosphatase (ALP) enzymes are commonly measured to determine the severity of liver damages [6–8]. In addition, due to the deleterious effects of hyperglycemia on renal function, a considerable number of diabetic patients also

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require dialysis [9].

According to the mentioned complications, blood glucose control in diabetes is very important. Life style and diet changes may improve diabetes control [10]. In addition, conventional drugs may also control blood glucose in short term. However, side effects of these medicines and inconclusive treatment have taken the attentions to new and complementary treatments, including herbal medicine [11,12]. Dried stigma of saffron (*Crocus sativus* L.) is an herbal medicine in Islamic-Persian traditional medicine. Saffron is a native plant in Iran which has been used as the most expensive traditional spice for many years [13–15]. Therapeutic values of saffron are contributed to its active constituents, including crocin, safranal, crocetin, and picrocrocin. Flavonoids and carotenoids are also found in the saffron extract [16,17]. Bandegi et al. have demonstrated that 30 mg/kg daily injection of saffron or crocin at similar doses for 21 days reduce oxidative stress in the animal liver, kidney, and brain [18]. In addition, a recent study have shown that saffron and its crocin dose-dependently alleviated levels of liver enzymes in male rats suffered from fatty liver disease [19]. Previous studies were also shown that saffron may protect kidney and liver from environmental toxins [20,21].

To the best of our knowledge, there is no separate human study about the effect of saffron hydro-alcoholic extract on liver and kidney function parameters in T2DM patients who are prone to the liver and renal dysfunctions. Beside the results from animal model studies, saffron may improve renal and liver protection because of its anti-inflammatory and antioxidant properties. In addition, saffron may independently alleviate diabetes, and by this way reduce diabetes complications. Given these reasons, current clinical trial aimed to study the effect of hydro-alcoholic extract of saffron (*Crocus sativus* L.) on the parameters of liver and renal functions in T2DM patients.

2. Materials and methods

2.1. Participants

This study was an 8-weeks randomized and double-blind clinical trial. The study was done on outpatients of Natanz Diabetes Society, Isfahan, Iran, between September 2014 and May 2015. The study sample size was calculated using standard formula for clinical trials by considering type I (a) and type II errors (b) as 0.05 and 0.20 (study power = 80%), respectively, and ALT as key variable. We predicted 30% reduction in ALT concentration due to the intervention [19].

Among all registered patients in the society, 54 T2DM patients were selected according to the inclusion criteria: suffering from type 2 diabetes mellitus (fasting blood sugar≥ 126 mg/dL), 40 to 65 years old, controlled diabetes (fasting blood glucose< 170 mg/dl), Body Mass Index (BMI) 18.5–30 kg/m^2. Subjects were excluded if: being less than 40 and more than 65 years old, consuming other drugs except blood glucose controlling drugs or higher than determined doses (up to 1.5 gr metformin, or 10 mg glibenclamide), tobacco or opium use, insulin injection, uncontrolled blood glucose (≥170 mg/dl), pregnancy or lactating or patients were preparing for pregnancy, other diseases than diabetes, BMI less than 18.5 or more than 40 kg/m^2.

Study protocol and the consent form were approved by the Tehran University of Medical Sciences Ethics committee (ir.tums.rec.1394.9211468004–143703; research.tums.ac.ir). The trial has registered at Iranian Registry of Clinical Trials (IRCT2015082623776N1; www.irct.ir).

2.2. Study design

Before intervention, participants were explained about study aims and details, then were asked to sign an informed consent form.

Participants were stratified based on sex (male/female) and age (<50 or ≥50 years), then randomly divided into two similar groups (n = 27) to receive either placebo or saffron capsules twice a day for 8 weeks. This deviation was blinded from all of the project performers, participants, and analyzers until end of data analysis and conducted by the physician of the society. Randomization was performed using computer-generated random numbers.

In this study we used Safrotin as a commercially available saffron capsule containing concentrated hydro-alcoholic stigma extract of saffron. Each capsules contained 15 mg of placebo or saffron hydro-alcoholic extract which was standardized by crocin. Each capsule contains starch, lactose, magnesium stearate, and gelatin. Safrotin capsules were donated by Green Plants of Life Co. (IMPIRAN; Tehran, Iran). Placebo capsules were similar to the saffron capsules in appearance, color, and size. Placebo capsules also contained starch, lactose, magnesium stearate, and gelatin as well as saffron essence. Placebo and saffron capsules were labeled as 1 and 2, respectively, by IMPIRAN Co.

Participants were asked not to change their diet, physical activity, and drugs during the intervention. They were also asked to refer every 2 weeks (2nd, 4th, 6th, and 8th weeks) to receive their capsules. To assessing their compliance, participants brought their capsule's boxes in every periodical visits to determining total consumed capsules.

At the beginning of study, 4th week, and the end of study three 24-h dietary recalls were taken from participants, by a skilled nutritionist. Dietary intakes of macronutrients and total energy were determined using the Nutritionist IV (N- IV) software, modified for Iranian food items. To assess physical activity, participants completed the International Physical Activity Questionnaire (IPAQ) at the beginning, during each periodical visits, and the end of study. Physical activity measured by the IPAQ were then converted to Metabolic Equivalents (METs) [22,23].

2.3. Assessment of exposure

At the study beginning, participants were referred to the central laboratory of Natanz, Isfahan, Iran. After 12 h fasting, patients' blood samples were recruited, then, their serum was separated and kept at −70 °C. ALT, AST, ALP, Creatinine (Cr), Blood Urea Nitrogen (BUN), and uric acid concentrations were measured using calorimetric method by commercial kit (Pars Azmoon Co., Tehran, Iran). After 8 weeks intervention, these examinations were repeated.

2.4. Assessment of other variables

Participants' weight, height, Waist circumference (WC), and blood pressure were measured at the study beginning. Weight measured using a digital scale (Sega 707, Hamburg, Germany) with the nearest of 100 g without shoes and with light clothes, height by the use of a stadiometer (Seca, Hamburg, Germany) without shoes to the nearest of 0.1 cm, and WC at the narrowest level using a non-stretchable tape to the nearest of 0.1 cm. Body Mass Index (BMI) was calculated by deviation of weight (kg) to squared height (cm^2). Systolic and diastolic blood pressure were measured twice, from the right arm of participants who were sitting for at least 10 min. Blood pressure was measured using a standard barometer which was calibrated by the Institute of Standard and Industrial Research of Iran.

During the periodical visits, participants were assessed by the