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The Effect of Urtica Dioica Extract on Blood Lipids Profile in Patients with Type 2 Diabetes: A Randomized Double-blinded Clinical Trial

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ABSTRACT

Background: Diabetes is an endocrine disorder that is strongly associated with cardiovascular disease. The use of alternative therapy has recently increased and medicinal plants are one of the alternative therapies for diabetic patients. This study aimed to evaluate the protective effect of Urtica dioica (Nettle) on lipid profile in patients with type 2 diabetes (T2D). **Method**: This parallel randomized double-blinded clinical trial was conducted on 60 men and women with T2D for an 8-week period. The participants were randomly assigned to received 100mg/kg/day extract of Urtica Dioica (UG) and the placebo group (PG). Blood triglyceride (TG), total cholesterol (TC), low density lipoprotein cholesterol (LDLc) and high density lipoprotein cholesterol (HDLc) were measured at baseline and end of the study. The data were analyzed using SPSS 16.0 and $P < 0.05$ was considered significant. **Results**: The mean difference of total cholesterol showed no significant difference in the UG compared to the PG which were -10.56±40.5 and -19.5± 35.9 ($P = 0.14$), respectively. The study also showed no significant difference between TG and LDLc in the UG compared to the PG (-39.8±171.5 vs. -23.37±72.3 ($P = 0.68$) and -3.16±33.4 vs. -11.2±35.6 ($P = 0.15$), respectively). The mean difference of HDLc in the UG and PG were -2.68±8.11 and 2.62±10.6 ($P = 0.05$), respectively, indicating a significant increase in the UG compared to the PG. **Conclusion**: The results demonstrated that consumption of 100mg/kg/day extract of UD for 8 weeks by increasing HDL concentration can decrease the risk of cardiovascular disease in patients with T2D.

Keywords: *Diabetes mellitus; Urtica Dioica*; *Lipids profile*

Introduction

Diabetes is a complex metabolic disorder due to insulin insufficiency or insulin resistance (Modak *et al.*, 2007). This disease causes substantial mortality, morbidity, and some long-term complications, and is one of the risk factors of cardiovascular disease (CVD) (Said *et al.*, 2008) and is associated with increased serum triglyceride (TG) and decreased high density lipoprotein

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cholesterol (HDLc) and sometimes increased low density lipoprotein cholesterol (LDLc) concentration (Ahangarpour *et al.*, 2012). Diabetes is the leading cause of peripheral neuropathy (Abolghasem *et al.*, 2009) and patients with diabetes experience some microvascular and macrovascular complications. Microvascular complications such as retinopathy, nephropathy and macrovascular complications, such as CVD due to atherosclerosis, peripheral vascular disease, stroke, and CVD (Akbar *et al.*, 2012). Atherosclerosis is the common long-term complications of diabetes that lead to CVD (Namazi *et al.*, 2012). Diabetes is also associated with free radicals, increased oxidative stress, and decreased defense antioxidant that are pathogenically important in diabetes complications (Namazi *et al.*, 2012, Said *et al.*, 2008). Today epidemic diabetes has created in the world (Majid Mobaseri, 2012) and the number of this disease will rise from 4% in 1995 to 5.4% in 2025 (Modak *et al.*, 2007). Chronic hyperglycemia damage multiple organs, including eyes, nerves, kidney, blood vessels, and heart (Ceylan-Isik *et al.*, 2008). Risk of death from CVD in type 2 diabetes (T2D) is 2-4 times more than non-diabetic patients; therefore, it's very important to prevent factors that increase risk of heart disease in patients with diabetes (Namazi *et al.*, 2012).

The effective constituents have been derived from over 800 herbal compounds in the prevention and treatment of diabetes. The use of alternative therapy has recently increased and attracted the intention of many researchers worldwide. This raises a concern that such therapy may be harmful to the people in spite of their apparent innocuousness (Baldé *et al.*, 2006).

Urtica Dioica (UD) or Nettle is one medicinal plants used to control blood glucose in traditional medicine (Namazi *et al.*, 2012). Hypoglycemic effect of UD was detected in a large pharmacological screen of European species. All parts of UD contain different micronutrients, such as histamine, formic acid, acetic acid, acetylcholine, leukotrienes, buteric acid, hydroxy tryptamine, and other micronutrients (Ahangarpour *et al.*, 2012). Many studies have reported the effect of UD on some risk factor of CVD in diabetes, such as blood glucose indices, lipids profile, oxidative stress, and hypertension (Namazi *et al.*, 2012).

Given the recommendation of the World Health Organization (WHO) that traditional medicinal plants as a method of treating diabetes (Abdollahi *et al.*, 2012) and further investigation about it and high interest of people in medicinal plants compared to medicinal drugs (Namazi *et al.*, 2012), the present study aimed to investigate the effect of UD extract on blood lipids profile in patients with T2D.

Materials and Methods

Participants and study design: A randomized double-blinded clinical trial was done on patients with T2D in the diabetes clinic of Afshar hospital in Yazd, Iran, for 8 weeks. The inclusion criteria were age over 30 years and consuming common drugs for diabetes (metformin, glibenclamid*)*. The exclusion criteria included patients with renal disorder, cardiovascular disease, liver and thyroid disease, infection and allergies, consuming non-steroid anti-inflammatory drugs (NSAIDS), consuming progesterone and estrogen, pregnancy and lactation, and taking part in another study.

One of the authors met with each participant and explained the purpose of the study, each participant who consented to enter the study signed an informed consent form. After adjusting the participants based on inclusion and exclusion criteria, they were randomly divided in two groups of Urtica Dioica group (UG) and placebo group (PG).

The patients were asked to maintain their usual dietary intake, exercise habit, and drug usage during the study. They received 100 mg/kg/day extract of UD and placebo in 3 portions after each 3 main meals. They were also instructed to dissolve each portion into a glass of water with a dropper and consume it at the baseline and end of the study to calculate the habitual dietary energy and nutrient intake. International physical activity (IPA) questionnaires were completed by the

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researcher with a face to face interview at baseline and end of the study. The researcher asked the patients to inform the dietitian of any changes in the amount and kind of drugs, dietary changes, and exercise.

To ensure the consumption of the extracts by the patients, they were given the extract for 2 weeks and after 2 weeks, in exchange for receiving empty bottles, the bottles containing the extract were given to them for the next 2 weeks. In order to prevent falls and reminders, people were contacted every week and asked about the consumption process.

Placebo was chlorophyll color. UD extract and placebo were provided from Giah-Essence phytopharm Co., Iran-Gorgan. The extract and placebo were not different in terms of color and alcohol percentage.

Measurements: Anthropometric measurements were recorded at baseline and end of the study. Weight was measured with digital scale (SECA: Germany) with light clothing and height was measured with a tape measure in the standing position without shoes and in standard condition. The blood sample was measured a 12-h overnight fast at baseline and end of the study. Total cholesterol (TC) and TG concentration was measured using Bionik kit and autoanalyser engine and enzymatic method. HDLc concentration was measured using Man kit and autoanalyser engine and enzymatic method and LDLc concentration was calculated by Friedewald Formula [LDLc=TC-(TG/5+HDLc)] (Freidewald, 1972).

Data analyses: The data were analyzed by SPSS 16 and kolmogrove-smirnov test was used to check the normal distribution of variables. Normally distributed data were reported as means ± SD. Mean difference between the two groups was performed by Student *t-test* and the data at the end of the study were compared to their own baseline values by paired *t-test* and for multiple comparisons ANOVA test was used. The data were analyzed with a two-factor repeated-measures analysis of variance (ANOVA) with time and treatment as the 2 factors. The P-values less than 0.05 were considered significant.

Ethical considerations: Purpose and method of the study were explained to the participants and each participant who was satisfied to enter the study signed the informed consent form. This study was approved by the ethical committee of Shahid Sadoughi University of Medical Science, Yazd, Iran. The study was registered at Iranian website for registry of clinical trials with code IRCT2013062013727N1(www.irct.ir).

Results

Of 60 participants, 6 patients due to illness, 3 patients due to forgetting the consumption of the extract, and two patients due to journey were excluded. Forty nine of the participants completed the study and the data were analyzed. Baseline characteristics of the patients are shown in **Table 1**, indicating no significant difference in the two groups.

The mean of blood lipids profile is shown in **Table 2**. The mean differences of TC concentration in the UG and PG were -10.56± 40.5 and -19.54±35.9 mg/dl (P = 0.41), respectively, indicating no significant difference between the two groups. Moreover, the mean concentrations of TG in the UG and PG were -39.08±171.5 and 23.37±72.3 mg/dl (P = 0.68), respectively, and the mean concentrations of LDLc in the UG and PG were 3.16±33.4 and 11.2±35.6 mg/dl (P = 0.15), respectively, indicating no significant difference between the groups. The mean concentrations of HDL in the UG and PG were 2.68±8.11 and -2.65± 10.6 mg/dl (P = 0.05), respectively, that showed a significant increase in the UG compared to the PG.

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Table 1. Baseline characteristics of the patients in the two groups

Variables	Placebo (n=24)	Urtica Dioica (n=25)	P-value[a]
Height (cm)	158.0 ± 7.6	159.6 ± 9.6	0.51
Weight (kg)	70.2 ± 8.5	75.9 ± 12.0	0.06
Body mass index (kg/m^2)	28.1 ± 3.1	29.7 ± 3.6	0.10
Gender	N (%)	N (%)	
Women	10 (41)	11 (44)	0.20
Men	14 (69)	14 (56)	

[a]: Student *t-test*

Table 2. Comparision of blood lipids profile within and between the two groups

	Before	After	Change	P-value[a]
Total cholesterol(mg/dl)				
Urtica Dioica	198.16 ± 50.46	187.60 ± 36.20	-10.56 ± 40.51	0.20
Placebo	207.00 ± 39.32	187.45 ± 46.88	-19.54 ± 35.93	0.01
P-value[b]	0.49	0.99	0.41	
Triglyceride(mg/dl)				
Urtica Dioica	218.88 ± 183.25	179.80 ± 78.02	-39.08 ± 171.56	0.26
Placebo	208.91 ± 122.89	185.54 ± 95.53	23.37 ± 72.32	0.12
P-value	0.82	0.81	0.68	
Low density lipoprotein cholesterol(mg/dl)				
Urtica Dioica	107.85 ± 45.19	111.01 ± 35.43	3.16 ± 33.49	0.26
Placebo	122.32 ± 38.80	111.11 ± 41.27	11.20 ± 35.6	0.12
P-value	0.23	0.99	0.15	
High density lipoprotein cholesterol(mg/dl)				
Urtica Dioica	47.16 ± 9.40	49.84 ± 11.24	2.68 ± 8.11	0.11
Placebo	52.12 ± 10.24	49.50 ± 11.54	-2.62 ± 10.63	0.23
P-value	0.08	0.91	0.05	

[a]: Student *t-test*; [b]: Paired *t-test*

Discussion

Medicinal plants can be used as an alternative therapy in diabetes (Namazi *et al.*, 2011). UD has been widely consumed for controlling blood glucose (Namazi *et al.*, 2012) and treating diabetes worldwide (Gülçin *et al.*, 2004). Some studies have shown the effects of UD on some risk factors of CVD in patients with T2D, such as lipid profile and oxidative stress (Namazi *et al.*, 2012). The antioxidant activity of UD have been attributed to some mechanisms, such as prevention of chain initiation, binding of transition metal ion catalysts, decomposition of peroxides, prevention of continued hydrogen abstraction, reductive capacity, and radical scavenging (Gülçin *et al.*, 2004). Das et al. conducted a study to determine the effects of the aqueous extract of UD on glycemic status and lipid status in T2D model rats. They reported that UD extract decreased fasting blood sugar (FBS) and cholesterol level and had no effect on TG and LDLc (Das *et al.*, 2011).

Nazli et al. conducted a systematic review to explore the effect of aerial portion of UD on some cardiovascular risk factors on diabetes mellitus. They found that UD extract decreased FBS, HbA1c, and TG concentration and increased HDLc level (Namazi *et al.*, 2012). Some studies have shown the decreasing effect of UD on blood glucose (Das *et al.*, 2011, Morshed *et al.*, 2011).

Also some studies have investigated the antioxidant effect of UD. UD decreases lipid peroxidation and liver enzyme and increases antioxidant defense (Kanter *et al.*, 2005). Mehmet

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et al. conducted a study and showed the antioxidant effect of UD due to phenolic compound in UD. Phenolic compounds may attribute to the antioxidative action. It is reported that polyphenolic compounds may have inhibitory effects on carcinogenesis and mutagenesis in humans. In addition, it was suggested that phenolic compounds were associated with antioxidant activity and play an important role in stabilizing lipid peroxidation. In a study that was designed a study to explore the antioxidant, antimicrobial, antiulcer, and analgesic activities of UD. They reported antioxidant, antimicrobial, and antiulcer effects of UD and showed that UD extract exhibited free radical inhibitor as well as a primary antioxidant that reacts with free radicals, which may decrease free radical damage occurring in the human body. Iron can stimulate lipid peroxidation by Fenton reaction, and this study showed that UD extract chelating with iron and scavenging of H2O2 by UD extract may be attributed to their phenolic (Das *et al.*, 2011). Some studies have suggested other effects of antioxidant compounds in UD. Antioxidant compound, such as quercitin, caffeic acid, carotenoids, and other flavonoids destroyed free radicals, so lipid metabolisa was performed better (Namazi *et al.*, 2012).

Conclusion

The present study was done on 60 patients with T2D and showed that UD extract caused no change in TG, LDLc, and TC and increased HDLc concentration. Limited studies have been conducted on the effect of blood lipids profile on patients with T2D and in vivo and in vitro studies showed conflicting results. Duration of diabetes, dose and amount of the extract, and period of study may cause these differences in results of studies. More studies are required to be conducted to determine the positive effects of UD in lipid profile in patients with diabetes by longer time intervention and longer sample size.

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Authors' contribution

Mozaffari-khosravi H designed and supervised the research and finalized the manuscript draft. Khajeh Merizi R and Parisa A participated in data collection and analysis, searched for the literature, revised, and corrected the manuscript. Final manuscript was approved by all authors for publication.

Conflict of interest

There is not any conflict of interest.

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