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URTICA DIOICA L. IN TREATMENT OF PATIENTS WITH TYPE 2 DIABETES MELLITUS: A RANDOMIZED DOUBLE-BLIND PLACEBO-CONTROLLED CLINICAL TRIAL

KIANBAKHT S[1], KHALIGHI-SIGAROODI F[2], HEIDARI A[3], HOSEINI R[4], PARHAM M[5], ADELI S H[3], NOVIN L[6], HASHEM DABAGHIAN F[7]

1. **Department of Pharmacology and Applied Medicine, Research Institute of Medicinal Plants, ACECR, Karaj, Iran.**
2. **Department of Pharmacognosy and Pharmacy, Research Institute of Medicinal Plants, ACECR, Karaj, Iran.**
3. **Ethics, Religion and Medicine Research Center, Qom University of Medical Sciences, Qom, Iran.**
4. **Royan Research Center, Tehran, Iran.**
5. **Department of Endocrinology, Qom University of Medical Sciences, Qom, Iran.**
6. **Kamkar Hospital, Qom, Iran.**
7. **Research Institute for Islamic and Complementary Medicine, Tehran University of Medical Sciences, Tehran, Iran.**

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Corresponding Author

Dr. Heidari A

Abstract

Objective: Study on the efficacy and safety of *Urtica dioica* L. in the treatment of patients with type 2 diabetes mellitus resistant to conventional oral anti-hyperglycemic drugs requiring insulin. **Methodology:** In this randomized double-blind placebo-controlled clinical trial, the effects of taking nettle leaf extract (one 500 mg capsule t.i.d. for 3 months) combined with the conventional oral anti-hyperglycemic drugs on the blood levels of fasting glucose, postprandial glucose, glycosylated hemoglobin (HbA1c), lipids, creatinine and liver enzymes including SGOT and SGPT were evaluated in 12 patients and compared with the placebo group (n=10).

Results: The extract lowered the blood levels of HbA1c significantly (P=0.03) without any significant effects on the blood levels of fasting glucose, postprandial glucose, lipids, SGOT, SGPT and creatinine (P>0.05) compared with placebo at the endpoint. Further, the blood levels of fasting glucose and HbA1c were decreased significantly in the nettle group compared with baseline at the endpoint (P=0.03 and P=0.01 respectively). However, the blood levels of the other parameters in the nettle group did not change significantly compared with baseline at the endpoint (P>0.05). No adverse effects were reported. **Conclusions:** The results suggest that nettle may safely improve glycemic control in type 2 diabetic patients.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a common disease. Conventional anti-hyperglycemic drugs have limited efficacies and important adverse effects, so that better anti-hyperglycemic agents are needed [1]. Multiple anti-hyperglycemic drugs with different mechanisms are often used for effective treatment of type 2 diabetic patients [2]. T2DM is a progressive disease, characterized by a progressive decline of β-cell function up to its exhaustion so that adequate glycemic control with a logical combination of oral therapies cannot be achieved which leads to the need of insulin as sole therapy. Up to 50% of type 2 diabetic patients initially treated with oral anti-hyperglycemics ultimately need insulin [3].

The plant kingdom is a wide field to search for natural effective oral anti-hyperglycemic agents that have slight or no side effects [4]. The infusion of 6 g of powdered *Urtica dioica* L. (nettle) dry leaves daily in two or three divided doses is consumed in the traditional medicine as an anti-hyperglycemic agent to treat diabetes mellitus [5]. A variety of pharmacological effects have been demonstrated for the nettle leaves including insulin secretagogue [6], PPARγ agonistic [7] and alpha-glucosidase inhibitory activities [8, 9]. However, in a study, the methanolic extract of nettle aerial parts was unable to increase insulin sensitivity in the culture of human muscle cells and/or increase insulin and C-peptide secretion from the culture of rat pancreatic β cells [10]. Reports on the effects of nettle in the animal models of diabetes have been inconsistent [11]. Nevertheless, an infusion of a mixture consisting of three herbs

including nettle and also a mixture of dry leaf extracts of four herbs including nettle had anti-hyperglycemic effects in patients with T2DM [12, 13]. However, there is no clinical trial reporting the effects of nettle leaves as a single component herbal medicine in the treatment of type 2 diabetic patients. Thus, the efficacy and safety of nettle leaf extract in the treatment of type 2 diabetic patients needing insulin therapy but declining it were evaluated and compared with placebo. Since the antioxidant potential of the Iranian nettle has not been studied so far, the radical scavenging activity of the extract was evaluated too. Further, the extract was standardized through determining total flavonoid, total phenolic, Gallic acid, rutin and quercetin contents.

MATERIALS AND METHODS

Nettle

Nettle was collected from the lands of the Mazandaran province of Iran in August and its identity was authenticated by a botanist (Y. Ajani). A voucher specimen of the plant (number 591) was deposited in the Central Herbarium of the Research Institute of Medicinal Plants. The leaves were separated from the plant, washed and dried in shade at room temperature. The dry leaves were ground into powder.

Preparation of the nettle extract for patients use

The dry leaf powder (20 kg) was extracted with ethanol/water (70/30) as the solvent in a percolator for 72 h, the solvent was completely removed from the extract in a rotary evaporator, toast powder as an excipient was added to and mixed with the concentrated extract and the mixture was ground to a powder. The quantity of the extract powder produced was 4.6 kg. The excipient constituted 12% of the extract powder.

Preparation of the extract and placebo capsules:

The extract powder as the phytomedicine and toast powder as the placebo were separately filled into oral gelatin capsules with identical appearance by a hand-operated capsule-filling machine (Scientific Instruments and Technology Corporation, USA). The nettle capsules contained 500 mg of the extract powder.

Phytochemical studies of the extract

Following preparation of the extract for spectrophotometric analyses [14], 2, 2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging assay using DPPH from Fluka (USA) [15] and determination of total flavonoid [16] and phenolic[17] contents were performed. Further, gallic acid, rutin and quercetin were quantified in the extract by HPLC [18].

Patients

Inclusion criteria: Type 2 diabetic outpatients aged 40 to 60 years with fasting glucose and HbA1c levels above 200 mg/dl and 8% resistant to conventional oral anti-hyperglycemic drugs (glibenclamide, metformine, gliclazide, acarbose, pioglitazone and repaglinide) needing insulin therapy but refusing it.

Exclusion criteria: Patients with cardiac, renal, hepatic and infectious diseases; pregnant and breast-feeding women; women planning pregnancy.

Protocol

Twenty two Iranian male and female patients who were eligible according to the inclusion and exclusion criteria participated in this study. The demographic data of the subjects are given in the table 1. A group of twelve patients took the nettle extract capsules at the dose of one 500 mg capsule every 8 hours by the oral route for 3 months and another concurrently parallel group of ten patients took the placebo capsules orally every 8 hours for 3 months. The dosage of the nettle extract was based on the anti-hyperglycemic dose of nettle leaves in the traditional medicine (6 g per day), the yield of the extraction process used in this study (20.24%) and the fact that the excipient (toast powder) constituted 12% of the extract powder. Block randomization was used for treatment allocation. The study was double-blind. All patients also used a combination of conventional oral anti-hyperglycemic drugs including glibenclamide, metformine, gliclazide, acarbose, pioglitazone or repaglinide. The treatment, diet and physical activity of the patients remained unchanged throughout the study. At the beginning and also the end of the study, the blood levels of fasting (after fasting for 12 hours) and 2 hour postprandial glucose, HbA1c, creatinine, SGOT and SGPT and fasting lipids (triglycerides, total cholesterol, VLDL, LDL and HDL) of all patients were determined with standard enzymatic kits

produced by the Pars Azmoon company (Tehran, Iran) and an auto analyzer (Hitachi 902, Japan). The levels of parameters including HbA1c were measured using enzymatic method (colorimetry) [19]. The t test was used for data analyses and P values below 0.05 were considered as significant. All participants were requested to report any adverse effects. Written informed consent was obtained from the patients. The medical ethics committee of the Qom University of Medical Sciences approved the protocol (approval number: 39257). Further, the trial was registered in the Iranian Registry of Clinical Trials with the number IRCT138809022288N2.

RESULTS AND DISCUSSION

Phytochemical studies of the extract

The IC_{50} of the extract was 357.75 ± 0.05 µg/ml (mean ± SD), while the IC_{50} of ascorbic acid was 5.626 ± 0.001 µg/ml (mean ± SD). The total flavonoid content as milligrams of rutin equivalents per gram of the extract was 293.02 ± 27.37 (mean ± SD). The total phenolic content of the extract as milligrams of Gallic acid per gram of the extract was 207.29 ± 21.03 (mean ± SD). Further, the amounts of Gallic acid, rutin and quercetin in the extract were 2.99%, 3.56% and 0% respectively.

Patients:

All subjects finished the study and no adverse effects were reported. The groups were matched in regard to demographic data (age, gender, duration of diabetes and body mass index) (table 1) and the baseline blood parameter levels (table 2).

The extract lowered the HbA1c level significantly (P = 0.03) without any significant effects on the other blood parameter levels (P > 0.05) compared with placebo at the endpoint. Further, the fasting glucose and HbA1c levels were decreased significantly in the nettle group compared with baseline at the endpoint (P = 0.03 and P = 0.01 respectively). However, the other blood parameter levels in the nettle group did not change significantly compared with baseline at the endpoint (P > 0.05). The percentages of endpoint reductions of the fasting glucose and HbA1c levels in the nettle group compared with baseline were 11.6% and 7% respectively. Moreover, the blood parameter levels of the placebo group did not change

significantly compared with baseline at the endpoint (P > 0.05) (table 2).

Discussion

The extract had a moderate antioxidant activity compared with ascorbic acid. Since oxidative stress is contributory to diabetes complications [20], the nettle antioxidant effect could be useful in prevention of diabetes complications. The fasting glucose and HbA1c levels decreased significantly in the nettle group at the endpoint compared with baseline. The extract lowered the HbA1c level significantly compared with placebo at the endpoint. However, the low level of HbA1c may be indicative of increased rate of hemoglobin turnover rather than reduced exposure of hemoglobin to glucose. The study power to detect a significant difference between the fasting glucose and 2 hour postprandial glucose levels of the two groups are 30% and 63% respectively. Thus, the main shortcoming of this study is the small number of patients. The lack of significant effects of the extract on the levels of fasting glucose, 2 hour postprandial glucose and lipids compared with placebo at the endpoint may be attributed to the small number of patients. Whereas, the lack of significant effects of the extract on the levels of SGOT, SGPT and creatinine may indicate that nettle does not have hepatic and renal toxicities. Further, no adverse effects were reported by the patients. Thus, the results suggest that nettle could be effective and safe in improvement of glycemic control in type 2 diabetic patients.

The bioactives mediating the glycemic effects of nettle are not yet characterized. The only bioactives quantified in the extract were total flavonoids, total phenolics, gallic acid, rutin and quercetin. The extract did not contain quercetin. Further, the bioactives and mechanisms involved in the anti-diabetic effects of the extract were not examined in the present trial. Thus, considering the results of this study, further trials with larger number of patients assessing the efficacy and safety of nettle in the treatment of T2DM as well as more studies addressing the mechanisms and bioactives involved in the anti-diabetic effects of nettle seem necessary.

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Author Disclosure Statement

No competing financial interests exist.

Table 1

The demographic data of the trial participants. The data are given as mean ± SD.

Parameter	Nettle group	Placebo group
Age (years)	52.2 ± 7.1	58.4 ± 6.7
Gender	17% male, 73% female	10% male, 90% female
Duration of type 2 diabetes mellitus (years)	12.2 ± 4.7	13.3 ± 6
Body mass index (kg/m^2)	29 ± 4.4	28.8 ± 7.3

Table 2

The blood fasting glucose, 2 hour postprandial glucose and glycosylated hemoglobin (HbA1c) levels before and after intervention and their changes during the study. * = P<0.05 = significant (t test). N (nettle); P (placebo); SD (standard deviation).

Parameter	Mean (SD) before	P value	Mean (SD) after	P value	Decrease (before – after) (SD)	P value	Percent change Mean (SD)	P value
Fasting glucose	248.08(34.9) N 262.6 (33.4) P	0.33	219.1 (30.3) N 231.4 (37.5) P	0.42	32.3(43.2) N 31.2(57.8) P	0.96	11.6 (15.4) N 10.1 (20.8) P	0.86
2 hour postprandial glucose	331.3 (82.7) N 371.2 (21.8) P	0.16	339.1 (86.4) N 371.6 (99.4) P	0.44	-7.8(106.6) N -2.8(112.1) P	0.92	-7.0 (34.8) N -1.8 (31. 9) P	0.76
HbA1c	9.7 (1.3) N 10.5 (0.9) P	0.14	9.02 (1.1) N 10.4 (1.5) P	0.03*	0.71(0.75) N 0.13 (1.9) P	0.38	7 (6.8) N 0.2 (20.1) P	0.82

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