The Effect of Urtica Dioica Extract on Glycemic Control and Insulin Resistance Indices in Patients with Type2 Diabetes: A Randomized, Double-Blind Clinical Trial

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Abstract

Objective: Diabetes is a common endocrine disorder caused by deficiency of insulin secretion or insulin resistant. nowadays, in addition to trying to find a safe way to control diabetes, find the low side effect way is important. This study was designed to find the effect of Urtica dioica extract on glycemic control and insulin resistance in patients with type 2 diabetes.

Materials and Methods: A parallel randomized clinical trial was conducted with participating 60 patients with type 2 diabetes who met inclusion criteria were recruited. Patients were randomly assigned to receive 100mg/kg/day extract of Urtica dioica group (UG) and the other group which received placebo (PG) over an 8 weeks period. Fasting blood sugar (FBS) concentration and insulin resistance indices (insulin concentration, insulin resistance (IR), insulin sensitivity (S%) and β-cell function (β%)) were measured at baseline and end of the study. Data were analyzed using SPSS 16.0 and $P<0.05$ was considered significant.

Results: The mean difference of FBS in UG and PG were 20.16±52.6 mg/dl and -0.7±45.29 mg/dl (P-value=0.14) and the mean concentration of insulin in UG and PG were 2.5mU/L and 0.2mU/L (P-value=0.003), respectively, that showed a significant increase in insulin concentration in UG compared to PG and the mean IR in UG and PG were 0.3 and 0.1 (P-value=0.01) that showed a significant decrease in IR in UG compared to PG. The mean difference of β% in UG and PG were -24.16±35.07% and 1.22±18.14% (P-value=0.003), and the mean difference of S% in UG and PG were -54.72±69.3% and 1.1±74.01% (P-value=0.009), respectively that showed increase in insulin concentration, β% and S% and decrease in IR in UG compared to PG.

Conclusions: In the present study we demonstrated that consumption of 100mg/kg/day extract of U.dioica for 8 weeks did not have significant effect on FBS and it has significant effect on insulin resistance indices.

Keywords: Diabetes mellitus, Insulin resistance, U.dioica Extract.

Introduction

Diabetes mellitus (DM) is a chronic disorder in the metabolism of carbohydrate, protein and fat, due to deficiency of insulin secretion or varying degree of insulin resistance (1) and occurs when the body cannot utilize glucose normally

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(2). Patients with diabetes, experiences some microvascular (retinopathy, neuropathy, nephropathy) and macrovascular complications (peripheral vascular disease, stroke, cardiovascular disease) (3). In diabetic patients with uncontrolled blood sugar, resulting in hyperglycemia, non-enzymatic binding of glucose to proteins inside and outside the cells will be created (4).

The increasing rate of diabetes has changed this disease from a medical entity to a social challenge. The number of adults with diabetes in the world will rise from 285 million in 2010 to 439 million in 2030 (1). There were over 4.3 million cases of diabetes in Iran in 2013 and prevalence of diabetes in adults (20-79 years) was 8.4% (5) and 14.2% in Yazd that is the highest prevalence of diabetes in Iran (6).

Due to relatively chemical drugs side effects and many people using of herbal medicine compare to medical drugs, beneficial medicinal plants discovering is important (7). It is frequent that patients, in addition to pharmaceutical treatment, utilize alternative resources to control their disease (8). More than 1200 herbal medicine identify that can benefit effect in diabetes (4). Biological actions of these medicinal plants are related to the chemical composition of the plant products (9).

One of the herbal medicine that is used to control blood glucose in traditional medicine is Urtica dioica (U.dioica) (7). All parts of U. dioica has been reported to have some chemical materials such as histamine, formic acid, acetylcholine, acetic acid, butyric acid, lucoterians, 5-hydroxy tiryptamin and other stimulants (2).

Due to the high prevalence of diabetes in Iran, especially in Yazd (6) and interest of people for medicinal plants compare to chemical drugs (7) this study was designed to evaluate U.dioica extract consumption effects on glycemic control and insulin resistance indices in patients with type 2 diabetes.

Materials and Methods

Participants and study design: A randomized doubled-blind clinical trial was conducted with participating 60 patients with type 2 diabetes in the Yazd Diabetic Research Center of Shahid Sadoughi University of Medical Sciences for 8 weeks. The inclusion criteria were: Over the age of 30 years old for both genders, usage of routine diabetes drugs and exclusion criteria were: Patients with renal disease, cardiovascular and liver disease, infection, thyroid disease, allergies, usage of non-steroid anti inflammatory drugs (NSAIDS), usage of estrogen and progesterone, pregnancy and lactation.

Patients randomly divided in two groups, U.dioica group (UG) and placebo group (PG). UG received 100mg/kg/day extract of U.dioica and the other received placebo into 3 portions after each 3 main meals for 8 weeks. Patients were asked to maintain his/her usual diet, drugs and exercise habits through the study. Compliance with U.dioica extract consumption was monitored every 2 weeks through phone interviews in the first of the study and then after the end of intervention period.

Measurements: A dietitian met with each participant at first of the study to explain the purpose of the study. The 24h dietary recall was recorded at beginning and at the end of study. The blood sample was obtained an overnight (12h) at the first and the end of the study. FBS concentration was measured with autoanalyser engine and enzymatic method and insulin concentration was measured with Chemireader Berthold engine and Chemiluminescenc method. Insulin resistance indices (IR, β-cell function and insulin sensitivity) were calculated with oxford HOMA calculator software (www.dtu.ox.ac.uk).

For anthropometric measurements, height was measured with a tape measure in standing position without wearing shoes while shoulders were relaxed and measurement of weight was done using a digital scale (Seca: Germany) with light clothing. Body mass

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index (BMI) was calculated as weight in kilograms divided by height in meters squared

***Statistical analyses*:** Data were analyzed with SPSS 16 and for checking the normal distribution of variables, we preformed Kolmogrov–Smirnov test. Continuous normally distributed data were expressed as means ± SD. Within each group changes in values were analyzed by paired t-test and between groups changes in values were analyzed by student t-test.

***Ethical consideration*:** This study was approved by the Ethical Committee of Shahid Sadoughi University of Medical Sciences, Yazd, Iran; informed written consents were obtained from all participants. Also, the study was registered at the Iranian website for registry of clinical trials with code IRCT2013062013727N1 (www.irct.ir).

Results

Forty nine (28 women, 21 men) of 60 participants completed the study and 11 were excluded. Two patients in UG and four patients in PG have withdrawn because of illness, two patients in UG and one patient in PG because of forgetting consumption of extract and placebo and in UG two patients because of journey were excluded (Figure 1). The mean of age in UG and PG were 54.21±7.9 year and 55.16±9.7 year (*P*-value=0.8), respectively that showed no

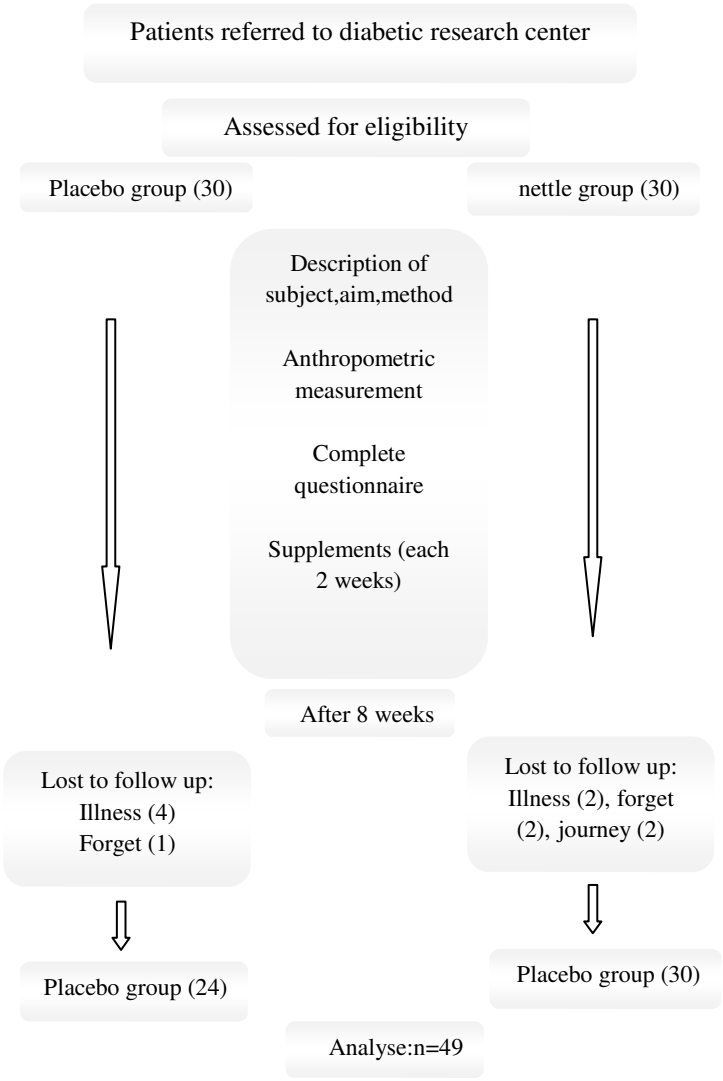


Figure 1. Study diagram

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significant differences between two groups. Baseline characteristics of the participants are shown in Table 1 that showed no significant differences between groups.

The means of FBS are shown in Table 2. It was not found significant differences between groups at the beginning and end of the study, but with 20mg/dl decrease in UG. Table 3 showed the mean concentration of insulin and IR in UG and PG. The mean concentration of insulin in UG and PG were -2.5 mU/L and -0.2 mU/L (*P*-value=0. 003), respectively, that showed a significant increase in insulin concentration in UG compared to PG and the mean IR in UG and PG were 0.3 and 0.1 (*P*-value=0.01) that showed a significant decrease in IR in UG compared to PG.

The mean β% in UG and PG were -24.16±35.07% and 1.22±18.14% (*P*-value=0.003), FBS concentration was measured with autoanalyzer engine and enzymatic method and insulin concentration was measured with a Chemireader Berthold engine and Chemiluminescenc method that showed a significant increase in β% in UG compared to PG and the mean S% in UG and PG were -54.72±69.3% and 1.1±74.01% (*P*-value=0.009), respectively (Table 4).

Discussion

Our study showed that consumption of 100mg/kg/day extract of U.dioica for 8 weeks in patients with type 2 diabetes increase insulin concentration, β-cell function and insulin sensitivity and decrease insulin resistance and no differences in FBS.

Consumption of medicinal plants is one of the alternative therapies in diabetes (10). Some medicinal herbs modulate the expression, synthesis and degradation of insulin. Induction of insulin release is the mechanism of action for some other antidiabetic plants. However increase in islet number and size as well as producing the antioxidative effects could be accounted as anti-diabetic mechanism of some other medicinal plants(9).

U.dioica is one of herbal medicine that use for control of blood glucose for diabetic patients (7). Possible mechanisms to affect blood glucose with U.dioica briefly are increasing insulin secretion of β-cells, reduce glucose uptake, reduce albuminglycosilation and fructoseaminand reduce intestine Alpha-glycosidase (11).

Mobaseri et al conducted a study that was designed to determine the possible mechanisms of the hypoglycemic effects of U.dioica on the glucose utilization by the human muscle cells in an in vitro study. The mean glucose level in the muscle cell cultures with U.dioica alone and with U.dioica plus insulin did not change significantly. The results of this study showed that the alcoholic extract of U.dioica was unable to enhance the glucose utilization directly or by increasing the insulin sensitivity in the muscle cells (1).

Table 1. Baseline characteristics of patients in two groups

Variables	PG (n=24)	UG (n=25)	*P*-value*
Age (year)	55.16±9.7	54.21±7.9	0.7
Height (cm)	158±7.62	159.64±9.69	0.51
Weight (kg)	70.25±8.59	75.94±12.07	0.06
BMI (kg/m2)	28.18±3.13	29.79±3.66	0.1
Gender	**N (%)**	**N (%)**	
Female	14(58.3%)	14(56%)	0.8
Male	10(41.7%)	11(44%)	

*:Student T-test

Table2. Comparison mean of FBS (mg/dl) between two groups at the baseline and the end of study

Variables	Before	After	Change	*P*-value*
UG	191.56±67.66	171.4±65.74	20.16±52.6	0.06
PG	159.33±57.82	160.04±53.52	-0.7±45.29	0.94
P*-value*	0.08	0.51	0.14	

*: Student T-test, **: paired T-test

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Table3. Comparison of insulin concentration (mU/L) and IR between two groups at the baseline and the end

Variables		UG			PG			*P*-value**
		25	50	75	25	50	75	
Insulin	Before	0.9	2.5	6.9	1.4	4.3	6.5	0.35
	After	3.6	7	11.8	2.05	4.9	7.3	0.06
	Change	-7.9	-2.5	-0.6	-1.4	-0.2	2.8	0.003
	P-value*		<0.001			0.7		
IR	Before	0.6	1	1.8	0.5	0.7	1.1	0.5
	After	0.4	0.7	1.05	0.4	0.6	1	0.05
	Change	0.0	0.3	0.8	-0.4	0.1	0.2	0.01
	P-value*		0.003			0.7		

*: Wilcoxon, **: Mann-whitney

Table4. Comparison of mean of β% and S% between two groups at the baseline and the end of study

Variables		UG	PG	*P*-value**
β%	Before	19.96±11.82	34.85±28.7	0.02
	After	44.12±36.44	30.39±20.49	0.1
	Change	-24.16±35.07	1.22±18.14	0.003
	P-value*	0.002	0.7	
S%	Before	111.1±67.7	152.44±64.87	0.4
	After	165.82±72.47	151.27±67.15	0.03
	Change	-54.72±69.3	1.1±74.01	0.009
	P-value*	0.001	0.9	

*: Student T-test, **: paired T-test

Das et al was designed the study that the aim of this study was to explore the effects of the aqueous extract of U.dioica on glycemic and serum lipids status in type 2 diabetic model rats. Results showed U.dioica extract decrease FBS and cholesterol level and no effect on TG and LDL (12). Morshed et al in the same study conducted a study that purpose of this study was to explore the effect of U.dioica on FBS, insulin and the chronic inflammatory status of type 1 diabetic model rats that results showed decrease FBS and CRP and increase insulin concentration. They hypothesis that U.dioica water extract has hypoglycemic properties, which may have an association with improved insulinemic status linked to an anti-inflammatory effect of the plant product on pancreatic β-cells (13). An in vivo studies showed that U.dioica extract before streptozotosin-induced diabetic rats caused positively effect in prevent increasing glucose level (14). The exact mechanism of the changes due to U.dioica in animal diabetic models is not clear, but there are some possible mechanisms of these alterations. These changes may be influenced by components in the extract of U.dioica, which contains both organic and inorganic constituents (14).

In the study of Asghari et al showed no differences between insulin concentrations after consumption U.dioica extract (3). Tarighat et al. did a study on patients with type2 diabetes. They observed U.dioica extract caused decrease FBS and no changed in insulin concentration and insulin resistance (4).

In addition, in diabetes, increase blood glucose is responsible for the development of oxidative stress. The oxidation state and free radical species impair structure of the cell membrane. Lipid peroxidation and oxidative stress are hallmarks of cell death in diabetes. Any compound, natural or synthetic, with antioxidant properties that might contribute towards the alleviation of these damages may have a beneficial role in the treatment of DM (14). Durdi et al conducted the study that the aim of this study was to assess in vivo and in vitro effects of aqueous and alcoholic extracts of U.dioica leaves on the activities of Acetyl coenzyme A carboxylase (ACC), Nucleoside diphosphate kinase (NDPK) and insulin level and serum glucose concentration. Results

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showed significantly lower levels of glucose, elevated levels of insulin in the group of rats that were treated with ethanol extract of U.dioica leaves as compared with the control group. Also, results showed significantly elevated activity of ACC and NDPK in the group of rats treated with ethanol and aqueous extract of U. dioica leaves as compared with the control group (15). The antioxidant compounds of U.dioica may be anticipated to have biological significance in eliminating reactive free radicals (14) and it may consider as one of the possible mechanism of antidiabetic effect of U.dioica.

In this study duration of intervention was low and HbA1c levels were not measured that are limitation of our study. It is suggested that a large study with higher duration and measure HbA1c should be done in the future. More studies are suggested for determination of antidiabetic effect of U.dioica in patients with diabetes by longer time intervention and longer sample size.

Conclusion

Our study showed that consumption of 100mg/kg/day extract of U.dioica for 8 weeks in patients with type 2 diabetes increase insulin concentration, β-cell function and insulin sensitivity and decrease insulin resistance and no differences in FBS.

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