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Research Article

The Hypoglycemic Effect of *Dorema aucheri* (Bilhar) Extract in Diabetic Type 2 Patients: A First Clinical Trial

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ABSTRACT
Dorema aucheri (Bilhar) is one of the medicinal plants traditionally used for treatment of diabetes in Iranian medicine. The effect of this plant has already been investigated on animal models; however, this is the first study conducted on human subjects. The aim of this study is to investigate the hypoglycemic and hypolipidemic effects of *D. aucheri* aqueous extract in type 2 diabetes patients. The study was a double-blind, one hundred Iranian male and female patients with type 2 diabetes were enrolled. The patients were randomly allocated into two groups. One group (n = 50) received *D. aucheri* leaves extract while the other group (n = 50) received placebo.Fasting blood samples were collected at the beginning of the study and after two months for determination of blood glucose level, HbA1c, lipid profiles, ALT and AST. Our analysis showed that serum fasting blood glucose level, HbA1c and lipid profiles were significantly improved in patients in the *D. aucheri* group compare with placebo group. However, there were no differences between groups in plasma level of hepatic enzymes AST and ALT. This study suggests that *D. aucheri* extract has a potential hypoglycemic and hypoglycemic and hypolipidemic action in patients with type 2 diabetes. However, further studies are needed to elucidate mechanisms of actions.

Key words: *D. aucheri,* HbA1c, lipid profiles, Diabetes mellitus, Glucose, Liver enzymes

INTRODUCTION

Diabetes Mellitus (DM) is a worldwide epidemic with an predicted globally prevalence of 246 million individuals in 2007 and forecasts to increase to 300 million by 2025[1] ; accordingly , diabetes presents a big problem to healthcare systems around the world . Diabetes is an extensive metabolic disease of numerous etiologies characterised by chronic hyperglycemia with disorder of carbohydrate , fat and also protein metabolism resulting from defects in insulin secretion , insulin action or both of them[2] . The manage of hyperglycemia is very crucial in the treatment of all forms of diabetes by reason that in the long term, acute and chronic problems may occur when the blood glucose level is not kept in the normal range[3, 4]. The medicines generally used in clinic to manage or handle diabetes are insulin, sulfonylureas, biguanide, glycosidase inhibitors, aldosereductase inhibitor, thiazolidinediones, carbamoylmethyl benzoic acid[5], but these agents have significant side effects, and some are insufficient in chronic diabetes patients[6].

Today, there has been increasing attention in the use of medicinal plants. Frequently, it is obligatory to provide scientific proof in order to justify the use of a plant or its active substances[7]. Various studies confirm the potential therapeutic efficacy of some medicinal plants in the treatment of diabetic patients[8]. Since natural products might provide much better treatments with lesser negative effects than the existing artificial medications, a major focus for appropriate anti-hyperglycemic agents have been on plants used in traditional medicine[9]. The probable efficacy of medicinal herbs for managing diabetes and their abundance in many countries aid their utilization.

Plants and also their extracts might also have a potential therapeutic role in treatment for diabetes. Conventional medical care systems , including herbal medicine , are renowned in developing countries[10] , and the care of diabetic patients have been influenced by an increasing interest in complementary and additional medicine .Iranian herbs such as *Juglans regia, Citrullus colocynthus, Ipomoea betatas, Silybum marianum* and *Trigonella foenum graecum*.have been reported to have a hypoglycemic effect in type 2 diabetes through stimulating or regenerating effects on β-cells or through extrapancreatic effects[11].

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Table 1: The demographic characteristics of patients in placebo and *D. aucheri* treated groups (mean ± SD)

Groups	Placebo	*D. aucheri*	p-value
Age (year)	53±7.22	52±7.89	P> 0.05
Sex (male/female)	27 M / 23 F	26 M / 24 F	P> 0.05
Duration of disease (year)	6±7.32	7±6.34	P> 0.05
Weight (kg)	72.1±10.32	71 ±11.62	P> 0.05

A P-value of <0.05 was considered as statistically significant

Table 2:.Para clinical characteristics of the two groups at the beginning of the study (mean ± SD)

	Placebo	*D. aucheri*	p-value
FBS (mg/dl)	182.44±49.34	200.42 ±55.22	P> 0.05
HbA1c (%)	9.13± 0.45	9.1± 0.85	P> 0.05
Total cholesterol (mg/dl)	236.33± 38.23	230.65± 31.78	P> 0.05
HDL-C(mg/dl)	42.34± 0.78	41.75± 0.45	P> 0.05
LDL-C (mg/dl)	157.67± 18.65	155.32± 20.32	P> 0.05
Triglycerides (mg/dl)	225.12± 37.54	230.41±28.46	P> 0.05
ALT (U/L)	22.44± 1.20	21.54± 1.24	P> 0.05
AST (U/L)	25.23±1.11	24.62± 1.24	P> 0.05

A P-value of <0.05 was considered as statistically significant

Dorema aucheri (Bilhar) is a member of the family Apiaceae . This plant grows in the beginning of spring season in cold mountainous regions of lorestan , Isfahan , Fars , Kohgiluyeh and boyer-ahmad provinces of Iran[12]. In Iranian traditional medicine , Dorema aucheri has been used as stimulant , nervonic , antispasmodic, antihyperlipidemic, antidiabetic, bronchodilator , expectorant, kidney stone resistant , emmenagogue and also analgesic for visceral pain[13, 14] In the present study , we evaluated the effect of *D* . *aucheri* aqueous extract on type II diabetic patients for the first time .

MATERIALS AND METHODS

Plant material and extraction procedure

The plants were collected from the heights of Alvand, Zagros Mountains Iran in May 2014. The plant was botanically identified and authenticated by local Plant Biotechnologist, Department of Natural Resources, Yazd, Iran. Then, the aerial part (flowers, leaves and stems) of *DA* were provided, dried, hydrodistillation-extracted and manufactured by a drug manufacturing industry, under sterile conditions in capsules containing 200 or 500 mg doses of extraction of *DA*.

Study design

One hundred patients with type II diabetes, whom were referred to Yazd Diabetes Research Center, Shahid Sadoughi University of Medical Sciences, Yazd, Iran, were included in this study. Eligibility for the study was a diagnosis of diabetes for a minimum of 24 months. The patients were entered based on HbA1c levels (ranges 7.5-12.5%; mean of 9.6 $\pm$ 1.3%), fasting blood glucose (FBS)>126 mg/dL, OGTT≥200 mg/dL, Triglycerides (TG)>150 mg/dL, total cholesterol (TC)>200 mg/dL. All participants continued their routine oral anti-diabetic agents and remained in a constant drug regimen while followed a stable weight-controlling diet starting for at least 3 months before enrolling in the study. All participating individuals were asked to stay with the same medications and refrain from nuts and supplements. Those patients who were treated with steroid or non-steroidal anti-inflammatory drugs, pregnant or lactating, smoking, with specific disease (kidney, liver) and insulin injections, were not included in the experiment.

The patients were divided randomly into three groups; I) receiving placebo (n=50), II) receiving capsules containing 200 mg doses of *DA* hydroalcoholic extraction (n=50).

The patients were advised to take a capsule daily before the lunch, for 45 days, while the diet and their lifestyle was not changed. Once a week during the study, the patient was contacted to be aware of potential problems.

The study protocol was approved by the Institutional Review Board and also by the ethics committee at Shahid Sadouqhi University of Medical Sciences, and written consent was obtained from each participant before participation in the study. The date of trial registration in the Institutional Review Board and the medical ethics committee was 2013/2/18, with registration NO. 16893.

Biochemical analysis

Fasting blood glucose, A1C, and lipid profile were measured at baseline and days 45 of the study period. Blood glucose, triglycerides, total and HDL cholesterol, AST, ALT, creatinine and BUN were estimated by spectrophotometric assays on automated clinical chemistry analyzer (Hitachi 902) using commercial kits (Pars Azmoon Co., Tehran, Iran), while LDL cholesterol was calculated from primary measurements using the empirical formula of the Friedewald equation (14). Glycosylated Hb (A1C) levels were measured by a D-10 hemoglobin testing system (Bio-Rad Laboratories, Inc.)

Statistical analysis

Obtained data were expressed by SPSS software version 16 by the equation mean $\pm$ standard deviation (SD). The student paired t-test was performed to evaluate the difference between the baseline and washout values of study outcomes. The results showed that there were differences between dependent samples pre- and post-treatment within the corresponding, diagnostic treatment groups. For the comparison of groups, variance analysis

Table 3: The serologic parameters in Placebo and *D. aucheri* treated groups (mean ± SD)

	Placebo			*D. aucheri*		
	Beginning	After 45 day	p-value	Beginning	After 45 day	p-value
FBS (mg/dl)	182.44±49.34	177.04±38.37	P> 0.05	200.42 ±55.22	176.40 ±51.74	P<0.05
HbA1c (%)	9.13± 0.45	9.09± 0.97	P> 0.05	9.1± 0.85	7.78± 0.51	P<0.05
Total cholesterol (mg/dl)	236.33± 38.23	230.32± 34.67	P> 0.05	230.65± 31.78	198.12± 28.62	P<0.05
HDL-C(mg/dl)	42.34± 0.78	41.07± 0.65	P> 0.05	41.75± 0.45	48.04± 1.02	P<0.05
LDL-C (mg/dl)	157.67± 18.65	160.07± 19.64	P> 0.05	155.32± 20.32	115.34± 18.99	P<0.05
Triglycerides (mg/dl)	225.12± 37.54	218.23 ± 32.78	P> 0.05	230.41±28.46	191.32± 26.87	P<0.05
ALT (U/L)	11.44± 1.20	12.28± 2.01	P> 0.05	11.54± 1.24		P> 0.05
AST (U/L)	12.23±1.11	11.89± 1.81	P> 0.05	12.62± 1.24		P> 0.05

A P-value of <0.05 was considered as statistically significant

(one-way ANOVA) and the Pearson correlation test were used. Values of $P< 0.05$ were considered to be statistically significant.

RESULTS

All 100 patients completed the study with no further dropouts. The patients' demographic characteristics are summarized in Table 1.

The baseline findings of patients in the two groups (*D. aucheri* and placebo) were compared for FBS, HbA1c, lipid profile and liver enzymes. The two groups were completely comparable regarding baseline and demographic characteristics (Table 2).

Theaverage fasting blood glucose level in the *D. aucheri* group was 200.42 ±55.22 mg /dL in the beginning of the study which significantly decreased ($p < 0.05$) to ±51.74 176.40mg /dL after 45 days of treatment with *D. aucheri*. The average fasting blood glucose level in the placebo group was not significantly changed after 45 days of the study.

The average HbA1c level in the *D. aucheri* group at the beginning of the study was 9.13± 0.45, which decreased significantly ($p < 0.05$) to 7.78± 0.51 after 45 days of *D. aucheri* treatment. The average HbA1c level in the placebo group was not significantly decreased after 45 days of the study. There was also a considerable improvement in the plasma level of TC, after *DA* receiving. The blood profile of lipids were significantly improved (P<0.05).

The results of the clinical findings in both groups in the beginning and after 45 days of the study are summarized in Table 3. Finally, No liver functional or other gastrointestinal side effects of the treatment were reported during the study.

DISCUSSION

Diabetes mellitus is a chronic metabolic disorder identified by hyperglycemia due to insulin insufficiency and/or insulin resistance contributing to excess blood glucose[16]. Approaches to the management of and also reduction of hyperglycemia are central to the control of diabetes . Although medicines , daily diet , and physical exercise are the cornerstone for the treatment of diabetes, there is certainly increasing interest in complementary and additional drug for diabetes, not only among the general public , but additionally among medical care providers , researchers , and educators[17].

Traditionally, various parts of herbs were used directly as a medication. Clinically effective substances are now being obtained from plants, even those that have not been categorized before as medicinal herbs. Recently, traditional medicine (Phytotherapy) is often used to treat several diseases, besides modern medicine. A lot of natural extracts have been reported to have antidiabetic activities and are utilized for the treatment of diabetes. Herbal extracts have been used perfectly or ultimately for the processing of numerous modern medicines[18-20].

D. aucheri (ivy gourd) grows widely in center and west area of Iran. The plant has been used since ancient times as an antidiabetic drug[13]. This study presents the first published results on the effects of *D. aucheri* on blood glucose level and other parameters in patients with diabetes.

The results suggest that *D. aucheri* improves glycemic in the type 2 diabetic patients without any adverse effects on the kidney and hepatic function. The outcomes confirmed that though there were no significant variations in the main parameters between the two groups of patients at the beginning of the study, *D. aucheri* extract therapy significantly reduced fasting blood glucose and HbA1c . Many researchers have mentioned that flavonoids are the essential ingredient in *D . aucheri*[21] . Song et al (2005) revealed that flavonoids , that have antioxidant and antidiabetic attributes , are able to protect the β-cells function via free radical scavengering in pancreatic tissue[22]. *D. aucheri* extract is prepared to decrease oxidative stress in beta cells and improve their function and this possibly is because of the flavonoides presence in this plant. Therefore the serum level of insulin raises which leads to blood sugar decrease[23].

It is well identified that hyperlipidemia happens in diabetic patients . Actually when insulin level reduced , the failure of lipoprotein lipase activation occurs which enhances lipolysis cycle[24], and leads to hypertriglyceridemia and improve in plasma free fatty acid concentration[25]. Significant decrease in serum lipid levels in diabetic patients which received the extract , possibly caused as a cause of insulin levels increment , these findings are in the agreement with the other studies that have characterized anti-hyperlipidemic, anti-hypercholesterolemic and hepatoprotective effects of *D. aucheri* extract in animal models [26-28]

The same study showed that in diabetic rats treated with walnut leaf extract, serum AST and ALT had a significant decrease when compared to diabetic rats. The decrease in the plasma levels of AST and ALT is due to the decrease in liver cells injury, glucose, cholesterol, triglyceride, hepatic lipid levels and subsequently prevention from the formation of fatty liver .Our findings also indicated that treatment with D. aucheri did not adversely affects AST and ALT levels as indication of its safety.

CONCLUSION

The data of our study suggest that *D. aucheri* leave extract has antihyperglycemic effects and also has optimal effects on improvement of lipid profiles levels of diabetic patients. Since this study was conducted on human samples for the first time, therefore the lowest dose of the drug was used. However, the limitation of the present study is that insulin levels were not measured. *D. aucheri* could be useful in treatment of diabetes mellitus as mentioned in traditional medicine. Considering the hypoglycemic effect of *D. aucheri* in present study and to obtain better results, we suggest the efficacy of higher doses investigated in future clinical trials. However, comprehensive pharmacological and chemical experiments are required to discover the active component(s) responsible for these effects.

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AUTHORS' CONTRIBUTIONS

All authors had equal role in design, work, statistical analysis and manuscript writing.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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