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Efficacy of the Hydroalcoholic Extract of *Tribulus terrestris* on the Serum Glucose and Lipid Profile of Women With Diabetes Mellitus: A Double-Blind Randomized Placebo-Controlled Clinical Trial

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Abstract

Aim. Considering traditional use of *Tribulus terrestris* in diabetes and proven antihyperglycemic and antihyperlipidemic effects of *T terrestris* in animal studies, we aimed to evaluate the efficacy of the hydroalcoholic extract of *T terrestris* on the serum glucose and lipid profile of women with non–insulin-dependent diabetes mellitus. *Methods.* Ninety-eight women with diabetes mellitus type 2 were randomly allocated to receive the *T terrestris* (1000 mg/d) or placebo for 3 months. The patients were evaluated in terms of the fasting blood glucose, 2-hour postprandial glucose, glycosylated hemoglobin, and lipid profile. *Results. Tribulus terrestris* showed a significant blood glucose–lowering effect in diabetic women compared to placebo ($P < .05$). Also, the total cholesterol and low-density lipoprotein of *T terrestris* group was significantly reduced compared with placebo, while no significant effect was observed in the triglyceride and high-density lipoprotein levels. *Conclusions.* The study showed preliminary promising hypoglycemic effect of *T terrestris* in women with diabetes mellitus type 2.

Keywords

diabetes mellitus, *Tribulus terrestris*, herbal medicine, traditional medicine

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Diabetes mellitus, as one of the most common chronic diseases, is considered as an outstanding problem in health care system, especially women's health. The incidence of diabetes mellitus is increasing, so diabetes will be one of the major leading causes of morbidity and mortality in not so distant future.[1] It is expected that the greatest increase in the burden of chronic noncommunicable diseases and related risk factors will occur in the Middle East in the near future. Since the prevalence of diabetes is higher in women and also it causes metabolic changes that may lead to early menopause and climacteric symptoms worsening in women affecting their health and quality of life, it seems that more attention to this issue is essential.[2-4] These patients should consider the risk factors of cardiovascular diseases such as hypertension and dyslipidemia and manage them along with blood glucose control to achieve the treatment goals and control diabetes complications.[5]

Since the treatment of diabetes and its related complications like some other chronic diseases has remained unresolved and the trend of using complementary and alternative remedies, especially among women with chronic diseases, is increasing, awareness of physicians and health care providers about the efficacy of these remedies is essential.[6,7] Herbal remedies are

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one of the common complementary and alternative remedies that diabetic patients use for control of their blood sugar or the diabetes complications.[8-10] *Tribulus terrestris* is one of these herbs used in Iranian folkloric medicine as a diuretic, analgesic, astringent, appetizer, and sexual tonic.[11-14] In traditional Persian medicine manuscripts such as *The Canon of Medicine* by Ibn-e-Sina or Avicenna (AD 980-1037)[15] and the *Storehouse of Medicaments of Aghili* (written in AD 1772),[16] *T terrestris* is considered for the properties such as antinephrolithiatic, antiseptic, diuretic, analgesic, and tonic to improve sexual ability. Also, it is used in Turkish, Indian, and Chinese traditional medicine for the treatment of a variety of diseases, including skin and liver diseases, diabetes, cardiovascular disorders, hypertension, hyperlipidemia, renal stones, fungal infections, and impaired sexual function, single or in combination with other herbs.[14,17-19] Moreover, previous studies have shown antihyperglycemic and antihyperlipidemic effects of *T terrestris* in animal models.[20-22] Although, to the best of our knowledge, there were no clinical trial studies that focused on the efficacy of *T terrestris* in diabetes and hyperlipidemia, some clinical studies have proved the androgenic effects of hydroalcoholic extract of this herb without any side effect.[23-25] Because of the folkloric use of *T terrestris* in diabetes, previous proven antihyperglycemic and antihyprlipidemic effects of hydroalcoholic extract of *T terrestris* in animal studies, and its safety shown in previous clinical studies, we aimed to evaluate the efficacy and safety of the hydroalcoholic extract of *T terrestris* on the serum glucose and lipid profile of women with diabetes mellitus in a double-blind randomized placebo-controlled clinical trial.

Methods and Materials

Trial Design

This study is a double-blind randomized placebo-controlled clinical trial using a parallel group with a 1:1 allocation ratio. No change was applied in the methods of study after its beginning.

Participants

From November 2014 to July 2015, 265 diabetic women referred to 2 endocrinology clinics of Shiraz University of Medical Sciences, Iran (Mottahari clinics), were assessed for eligibility criteria to enroll in the trial. All patients were visited by an endocrinologist and an obstetrician for inclusion criteria. Women aged 40 to 60 years with definite laboratory diagnosis of type 2 diabetes mellitus who used oral glucose-lowering agents only and expressed willingness to cooperate and participate in the study by giving written informed consent form were included in the trial. Exclusion criteria for the participants were consumption of vasodilator agents, breast cancer or positive family history of the disease, uncontrolled hypertension, insulin therapy, patients with unstable cardiovascular, cerebral, renal, and hepatic diseases, and patients who have allergy to *T terrestris.*

Intervention

In the intervention group, the patients received capsule 500 mg containing *T terrestris* extract powder twice daily (after breakfast and dinner time) for 3 months. In the control group, the patients received placebo capsule containing cellulose in a similar way. It should be noted that in both groups, consumption of previous oral blood glucose–lowering agents continued without any changes. Both groups received routine advice on diet and physical activity of diabetic patients. During the intervention, the researcher contacted all the participants weekly to follow them up, ensure the regular and proper consumption of the study protocol drugs, and answer the patients' questions if needed. All patients visited 3 months after intervention again and outcomes measures were evaluated.

Drugs Preparation

The hydroalcoholic *T terrestris* was bought from Qingdao BNP Co, China (batch number: BNPTT140510). The extract contained 61.8% saponins according to ultraviolet assay and less than 2 ppm arsenic, mercury, and lead as heavy metals and negative results of microbiological cultures. The extract powder of *T terrestris* was filled into oral gelatin capsules (500 mg). Placebo capsule, as the drug for the control group, was prepared with cellulose powder instead of the extract by the same method and had similar appearance.

Outcomes

The fasting blood sugar (FBS) and 2-hour postprandial (2hpp) glucose as the primary outcome measures and glycosylated hemoglobin (HbA1c), triglyceride, total cholesterol, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) as the secondary outcome measures were determined for this trial at the baseline and 3 months after the intervention in both groups. Blood samples were drawn after 12 to 14 hours of overnight fasting and sent to certain hospital laboratory. No changes were applied to trial outcomes after the trial commenced.

Fasting plasma sugar (FBS), 2hpp, triglyceride, total cholesterol, LDL, and HDL were measured by using the enzymatic colorimetric (glucose oxidase technique) method and by Prestige machine with the scale of milligrams per deciliter. High-performance liquid chromatography was used as laboratory test method for assaying HbA1c.

Sample Size

Regarding the objectives and study type and according to previous study with assumptions of 5% error, 80% power and 50% effect size, we determined 45 patients in each group.[26]

Randomization

Patients who had inclusion criteria and filled the consent from were randomized into 2 parallel intervention and control groups by secretaries of the clinics. They were instructed to generate the random allocation sequence, enrolled participants, and assigned participants to the control and intervention groups by using permutated block randomization method. Patients and physicians were blind to the allocation of the groups due to the identical appearance of the intervention and placebo capsules. The person who delivered drugs and statisticians were also blind to the allocation of the patients.

Statistical Methods

Descriptive data analysis was done using descriptive statistical methods (frequencies, means, and standard deviations). Independent *t* test,

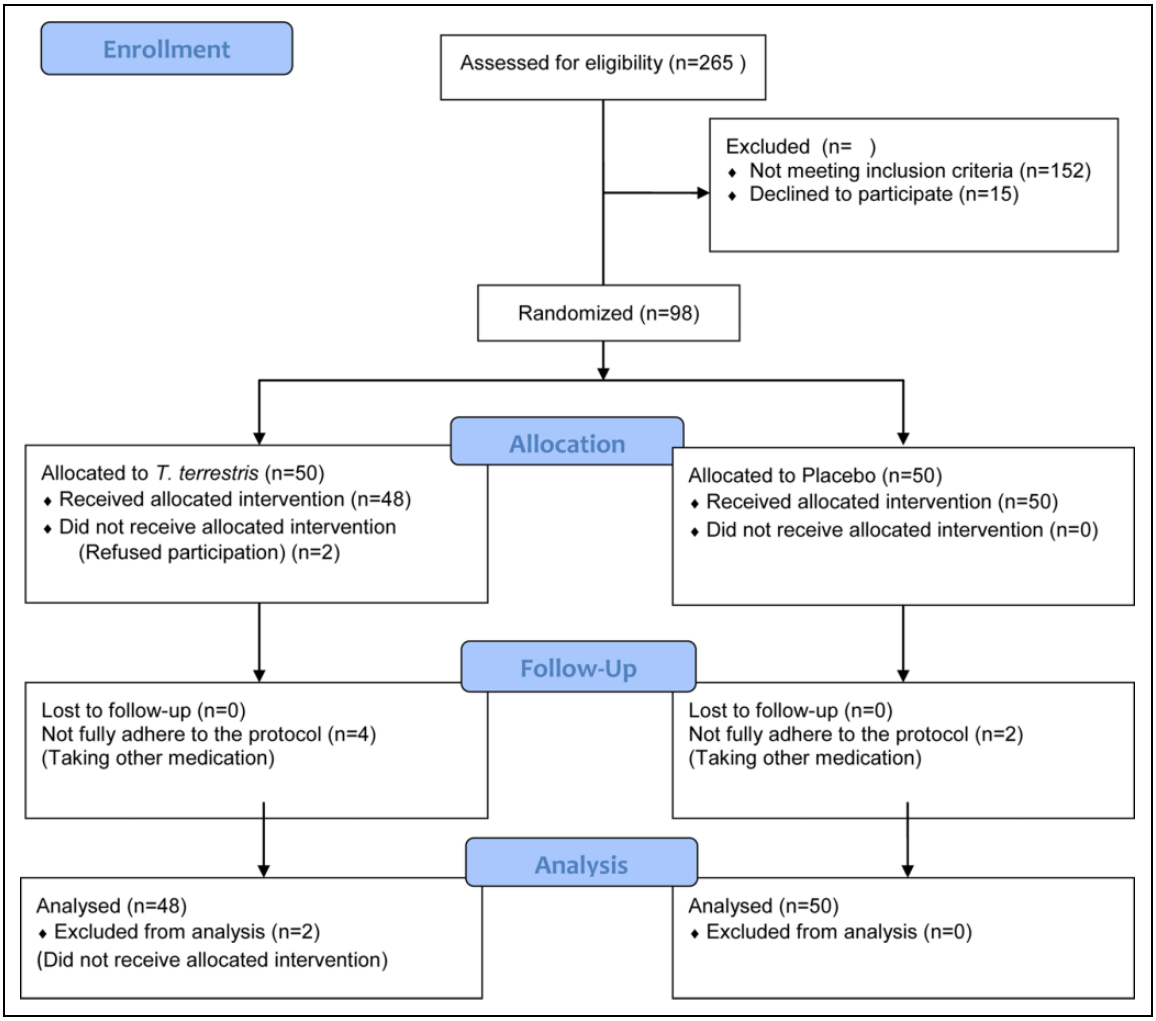

Figure 1. Flowchart of study inclusion, allocation, and follow-up.

chi-square test, and covariance analysis were used for statistical comparison of the baseline characteristics and outcomes between the 2 groups of the study. A *P* value less than .05 was considered significant. Intention-to-treat protocol was applied in data analysis as well. To analyze the data, we used SPSS (Statistical Package for the Social Sciences) software version 20.

Ethical Considerations

The study was performed in compliance with the Declaration of Helsinki (1989 revision) and approved by the Local Medical Ethics Committee of Shiraz University of Medical Sciences (CT- 9378-7208). In addition, the trial was registered with Iranian Registry of Clinical Trials (IRCT) (ID: IRCT2015062922971N1).

Table 1. The Baseline Characteristics Data of the Patients in the *Tribulus terrestris* and Placebo Groups.

Basic Characteristics	*Tribulus terrestris* (n = 48)	Placebo (n = 50)	*P*
Age, years, mean ± SD	52.70 ± 6.15	52.26 ± 6.04	.71
Body mass index, kg/m^2 mean ± SD	27.47 ± 6.00	27.45 ± 5.94	.98
Occupation, n (%)			.42
Unemployed	41 (91.1)	46 (95.8)	
Employed	4 (8.9)	2 (4.2)	
Education, n (%)			.76
Nonacademic	41 (89.1)	43 (86)	
Academic	5 (10.9)	7 (14)	

Results

From November 2014 to July 2015, from a total of 265 women evaluated for eligibility, 98 eligible diabetic patients were included in this study and 48 of them received *T terrestris* capsule; also, 50 of them received placebo capsule randomly. Figure 1 is a flow diagram of the enrolment, groups' allocation, interventions, follow-up, and analysis of results. All patients were evaluated at baseline and 3 months after the intervention. Six patients discontinued the protocol trial drugs but were included in the result analysis due to the intention-to-treat protocol. Baseline demographic data of both groups of the study (age, body mass index, education, and occupational status) are

Table 2. Diabetes-Related Data of the Patients in the *Tribulus terrestris* and Placebo Groups.

Diabetes-Related Data	*Tribulus terrestris* (n = 48)	Placebo (n = 50)	*P*
Duration of diabetes, years, mean ± SD	8.6 ± 5.79	7.71 ± 4.50	.37
Antihyperglycemic agent types			.68
≤2 type	24 (50)	27 (55.1)	
>2 type	24 (50)	22 (44.9)	
Regular exercise, n (%)			.42
Yes	28 (59.6)	25 (51)	
No	19 (40.4)	24 (49)	
Risk factors for cardiovascular diseases, n (%)			.005
Yes	37 (77.1)	25 (50)	
No	11 (22.9)	25 (50)	

Table 3. Midwifery-Related Data of the Patients in the *Tribulus terrestris* and Placebo Groups.

Midwifery-Related Data	*Tribulus terrestris* (n = 48)	Placebo (n = 50)	*P*
Age of menarche, years, mean ± SD	13.20 ± 1.54	12.77 ± 1.45	.17
Marital status, n (%)			.43
Married	36 (87.8)	39 (92.9)	
Not-married (single, divorced, or widowed)	5 (12.2)	3 (7.1)	
Mean number of children, n (%)	3.77 ± 1.91	3.88 ± 1.59	.75
Age at menopause, years, mean ± SD	5.61 ± 48.10	8.41 ± 47.29	.67

Table 4. Mean Values (±SD) for Serum Glucose and Lipids Profile in the *Tribulus terrestris* and Placebo Groups Before and After the Intervention.

	Groups		
	Tribulus terrestris	Placebo	*P*
Fasting blood sugar (mg/dL)			
Before	169.25 ± 51.16	146.82 ± 46.33	.02
After	143.87 ± 47.13	151.10 ± 48.95	<.001
2-hour postprandial glucose (mg/dL)			
Before	233.81 ± 69.69	195.20 ± 84.25	.69
After	195.16 ± 56.45	201.85 ± 62.59	.00
Glycosylated hemoglobin (HbA1c) (%)			
Before	8.16 ± 1.86	7.33 ± 1.88	.03
After	7.67 ± 1.65	7.50 ± 1.96	.04
Triglycerides (mg/dL)			
Before	145.32 ± 71.40	142.10 ± 60.35	.74
After	129.85 ± 54.06	137.31 ± 52.59	.18
Total cholesterol (mg/dL)			
Before	178.96 ± 39.08	175.16 ± 35.00	.61
After	159.79 ± 36.48	169.76 ± 32.89	<.001
Low-density lipoproteins (mg/dL)			
Before	102.93 ± 34.89	93.53 ± 31.63	.21
After	86.19 ± 29.01	91.44 ± 28.35	.01
High-density lipoproteins (mg/dL)			
Before	49.66 ± 11.45	48.09 ± 11.82	.34
After	46.25 ± 9.77	47.84 ± 10.95	.12

shown in Table 1. The information about their diabetes is shown in Table 2 and midwifery-related data (age of menarche and menopause, number of children, and marital status) as the mean ± standard deviation for continuous variables are shown in Table 3.

No significant differences were observed in baseline demographic and midwifery related and diabetes related data (duration of diabetes, the number of antihyperglycemic agent types, cardiovascular risk factors such as smoking, stress, hypertension) between the 2 groups of the study ($P > .05$); however, there was a significant difference in the field of cardiovascular risk factors ($P < .05$), showing that patients in the *T terrestris* group had more risk factors for cardiovascular diseases compared with those in the placebo group.

Among all baseline outcome measures in the 2 groups of the study, there was a significant difference between the states of FBS ($P = .02$) and HbA1c ($P = .03$) (Table 4).

We used covariance analysis to eliminate the confounding effect of the baseline outcome measures. Covariance analysis showed a statistically significant reduction in FBS, 2hpp, HbA1c, total cholesterol, and LDL after the intervention in the *T terrestris* group compared with the placebo group ($P < .05$).

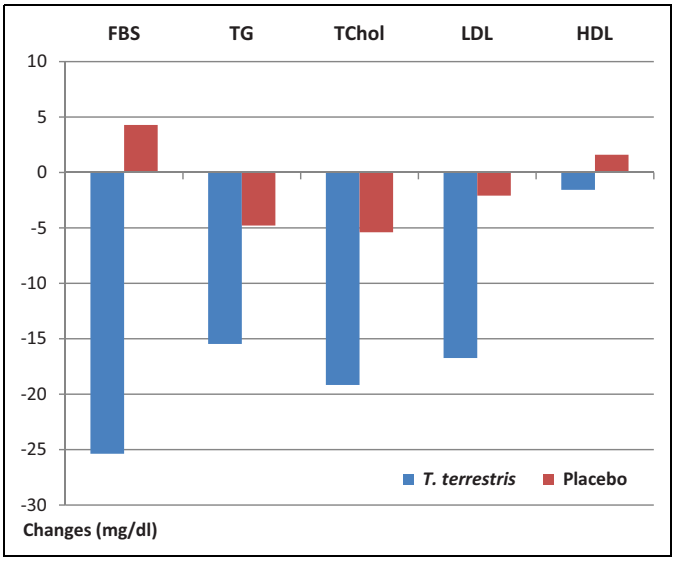

Figure 2. Mean changes in fasting serum glucose (fasting blood sugar [FBS]), triglyceride (TG), total cholesterol (TChol), low-density lipoprotein (LDL), and high-density lipoprotein (HDL) in the 2 study groups.

There was no significant difference between the 2 study groups in the levels of triglyceride and HDL ($P = .18$ and $P = .12$, respectively). Details of the changes of outcome measures are shown in Table 4 and Figure 2. No adverse event was reported along the study period in the 2 groups of the study.

Discussion

In this trial, we evaluated the efficacy of the hydroalcoholic extract of *T terrestris* on the serum glucose and lipid profile of women with diabetes mellitus in a double-blind randomized clinical trial that showed *T terrestris* has a significant effect on lowering blood glucose (FBS, 2hpp, HbA1c) in diabetic women compared with placebo. This study also showed that the total cholesterol and LDL of the *T terrestris* group was significantly reduced after the intervention compared with the placebo group, while no such effect was observed in triglyceride and HDL.

The study findings are compatible with the results of some previous studies but different from others. The results of our study as to the blood sugar indices showed that *T terrestris* significantly reduced the blood sugar. Although there are no human study on antihyperglycemic effect of *T terrestris* on diabetic patients, there are several animal studies on this effect. Mali and Yupeng[27] showed *T terrestris* had hypoglycemic effect on the normal mice after intragastric administration, decreasing the blood sugar level significantly, increasing the serum insulin and improving their glucose tolerance in alloxan diabetic mice. Also it was shown that the *T terresteis* can significantly inhibit the gluconeogenesis, influence glycometabolism in normal mice and cause a significant decrease in the blood glucose level of diabetic mice.[12,21] Saponins are one of the main components of the *T terresteis* and previous studies have shown that saponins can significantly reduce the serum glucose and inhibit hepatic gluconeogenesis.[14,20,26] In addition, it is alleged that oral administration of the *T terrestris* saponins in rats can delay the absorption of glucose by inhibiting α-glucosidase in the small intestine and lowering the postprandial glucose.[22]

The results of our study as to serum lipid profile showed that *T terrestris* significantly reduces total cholesterol and LDL in diabetic women while changes of HDL and triglycerides were not significant. Hussain and colleagues[12] in an animal study concluded that treatment of diabetic mice by *T terrestris* extract resulted in a significant reduction in triglycerides, total cholesterol, and LDL cholesterol compared with the untreated diabetic mice.[12] Also, Tuncer et al[28] indicated that dietary intake of *T terrestris* can significantly lower the serum lipid profiles in rabbits on a high-cholesterol diet. But the point in some studies is that the HDL level reduced along with other lipid profile. Chang et al[29] reported a dose-dependent effect of *T terrestris* on the lipid profile. In this study, we used a dose of 1 g per day; however, in traditional Persian Medicine[30-33] manuscripts, the maximum dose of the *T terrestris* extract reported was 1.8 g per day.[34] Moreover, according to several human studies doses of less than 2 g daily of the *T terrestris* extract have no side effects.[23,24,35,36] As the main active ingredient of *T terrestris* is saponin, which has androgenic activity, its effect was thought to be different in men and women, So in this study only women were included.

There were some limitations in our study. Despite the use of randomization method to have good distribution of allocated patients in the 2 groups of the study, we found a statistically significant difference in patients' base risk factors for cardiovascular diseases that is a very important factor in diabetes and dyslipidemia diseases. Moreover, limiting the participants to women could only lead to some limitations in the generalizability of the study results to all diabetic patients.

Conclusion

As a conclusion, the current study showed hydroalcoholic extract of *T terrestris* has a significant effect on lowering blood glucose (FBS, 2hpp, HbA1c) in diabetic women compared with placebo. In addition, the total cholesterol and LDL levels of the *T terrestris* group were significantly reduced after the intervention compared with the placebo group, while no such effect was observed in triglyceride and HDL levels.

Authors' Note

This article is extracted from a thesis by Nasrin Babadaei Samani, submitted to the School of Nursing and Midwifery (Shiraz University of Medical Sciences, Shiraz, Iran) for fulfillment of a MS degree in Midwifery.

Author Contributions

The work presented in this article was carried out through collaboration between all authors. NBS, AJ, and MH made the initial hypothesis. All authors participated in defining the research theme and providing the proposal. NBS visited the patients, enrolled them, and followed them. MH and SHM interpreted the data and wrote the first draft of the article. All authors edited the article. AJ and MS supervised the work. All authors contributed to, edited, and approved the article.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical Approval

The study was approved by the Local Medical Ethics Committee of Shiraz University of Medical Sciences (CT- 9378-7208).

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