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ORIGINAL ARTICLE

Lipid-Lowering Effect of *Citrullus colocynthis* in Diabetic Patients

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ABSTRACT

Background: *Citrullus colocynthis* (*C. colocynthis*) is a traditional medicinal plant used as an antidiabetic herb in the northeast of Iran. However, its effects on diabetes-related disorders, such as diabetic dyslipidemia have not been extensively studied. This study aimed to evaluate the effect of *C. colocynthis* on the lipid profile of type 2 diabetes patients with dyslipidemia.

Methods: Seventy-six diabetic patients with dyslipidemia who attended the diabetes clinic in Sabzevar, Iran were randomly assigned to either an intervention group (n=38) to receive *C. colocynthis* capsules (125 mg) or a placebo group (n=38) receiving starch and Tragacanth powder (125 mg) once daily for 8 weeks. The primary outcome was the change in low-density lipoprotein cholesterol (LDL-C) level at 8th week. Secondary outcomes included modifications in total cholesterol, triglycerides, and high-density lipoprotein cholesterol (HDL-C) levels.

Results: After 8 weeks, the intervention group showed a significant reduction in LDL-C level compared to baseline (p=0.001) and to the placebo group (p=0.006). No significant differences were observed between the *C. colocynthis* and placebo groups for total cholesterol (p=0.1), HDL-C (p=0.6), and triglycerides (p=0.06). No adverse events were recorded during the study.

Conclusion: In type 2 diabetic patients with dyslipidemia, *C. colocynthis* supplementation could significantly decline the LDL-C level over 8 weeks when compared to placebo. Further studies with larger sample sizes and longer follow-up periods are needed to confirm these findings and evaluate the long-term efficacy and safety of *C. colocynthis*.

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Introduction

Diabetes prevalence is projected to rise globally, with estimates suggesting that by 2030, 7.7% of the world's population will be affected (1). In Iran, the number of diabetic patients is expected to increase from 3.78 million in 2009 to 9.24 million in 2030 (2, 3). Despite advancements in diabetes management, cardiovascular complications remain a leading cause of morbidity and mortality among diabetic patients (4, 5). One major contributor to these

complications is dyslipidemia, a key risk factor for cardiovascular diseases, which is often resulting from insulin resistance (4-8). On the other hand, dyslipidemia can exacerbate other risk factors, such as hypertension (4). Diabetic dyslipidemia is characterized by elevated triglycerides, low HDL cholesterol, and high LDL cholesterol levels (4).

Pharmaceutical treatments with statin therapy play a crucial role in the management of diabetic dyslipidemia (4, 9). However, alongside pharmaceutical approaches, herbal medicines are widely used by diabetic patients either on prescription or as self-medication (9-11). Many of these herbal remedies lack adequate clinical validation, and unregulated self-medication carries risks, including drug interactions and inconsistent dosing (9, 12, 13). In Iran, the use of herbal medicines, such as *C. colocynthis* is prevalent among diabetic patients (9, 12, 13). *Citrullus colocynthis Schrad.*, an annual plant native to central, southern, and eastern regions of Iran, has been used commonly in Iran as a traditional medicine for its purported anti-inflammatory and antioxidant properties (12, 14). *C. colocynthis* in fatty liver disease has a lipid-lowering effect too (15). Also, previous studies have indicated potential antidiabetic effects of *C. colocynthis*, suggesting that its benefits may improve lipid profiles in diabetic patients (16). Given the high prevalence of herbal supplement use among diabetic patients and the potential benefits of *C. colocynthis* (15, 17), this study aimed to explore its effects on the lipid profile of diabetic patients with dyslipidemia.

Material and Methods

A double-blind clinical trial was conducted from last April to February at the Diabetes Clinic of Sabzevar University of Medical Sciences, Sabzevar, Iran. The study was adhered to Declaration of Helsinki and received approval from the Research and Ethics Committee of Sabzevar University of Medical Sciences (IR.MEDSAB.REC.1394.83). All participants provided written informed consent prior to enrollment. Eligible participants were adult patients with type 2 diabetes mellitus who were diagnosed for at least one year period, were on maximally tolerated lipid-lowering therapy of statins and maintained a low-fat diet. They required having a fasting low-density lipoprotein cholesterol (LDL-C) level of 100 mg/dL or higher at least four months before the first screening visit. The exclusion criteria were age above 65 years, triglyceride level of 500 mg/dL or higher, body mass index (BMI) below 18.5 or above 35 Kg/m^2, severe renal impairment, severe gastrointestinal diseases, recent coronary heart disease events, clinically significant diseases, pregnancy or breastfeeding, use of lipid-lowering therapies other than statins, or changes in lipid-lowering therapy or diet during the study.

Participants were selected through convenience sampling method and were randomly allocated into two groups using a concealed random allocation method with blocking to ensure balanced group sizes and to minimize the selection bias. The intervention group received *C. colocynthis* capsules (125 mg) and the placebo group received capsules containing starch and Tragacanth powder (125 mg). Both capsules were identical in shape and color and were manufactured by the Institute of Toba in Tehran, Iran. The herbal plants used for the study were verified by botanists, while quality control measures ensured the consistency and purity of *C. colocynthis* capsules. The capsules were packaged and labeled by a second blinded researcher. Both the researchers and participants were blind to the treatment assignments and lipid measurements throughout the study.

Participants in both groups took their assigned capsules once daily before lunch for eight weeks. Blood samples were collected after 12 hours of fasting at baseline and at the end of the study (week 8) to measure levels of LDL-C, high-density lipoprotein cholesterol (HDL-C), total cholesterol, and triglycerides. Participants were instructed to maintain their existing statin and antidiabetic regimens without introducing any other new medications, herbal or non-herbal, during the study period. Participant's compliance was monitored through biweekly phone calls, during which, they reported any issues to confront with the adherence in their monthly visits to the diabetes clinic by the general practitioner. Adherence was assessed by using pill counts and self-reported data. Participants were asked to report any changes in their medications or diet too. Any participant who developed side effects related to the study drugs was referred to an internal medicine specialist for further evaluation. Safety and tolerability were assessed through treatment-emergent adverse events, laboratory findings, vital signs, physical examination results, and specific adverse events including gastrointestinal bleeding, diarrhea, abdominal pain, nausea, vomiting, or any new medical complications.

The primary outcome of the study was the change in LDL-C level from baseline to te 8^{th} week. Secondary outcomes included changes in HDL-C, total cholesterol, and triglyceride levels, evaluated by employing standard laboratory assays over the same period. The study protocol was registered in the Iranian Registry of Clinical Trials (IRCT: IRCT20140505017585N3). Data were analyzed using SPSS software (Version 20, SPSS Inc., Chicago,

USA). Independent and paired t-tests were employed to compare baseline and follow-up measurements. Analysis of covariance (ANCOVA) was used to adjust for potential confounding variables and heterogeneity between groups. Missing data were handled by complete case analysis, and lost data was excluded from the analysis. A *p* value of less than 0.05 was considered statistically significant.

Results

A total of 111 diabetic patients were screened and 76 were randomized to receive *C. colocynthis* capsule (n=38) or placebo (n=38). Seventy randomized patients completed the study (92.0%, Figure 1). The participants were predominantly men [40 (57%)] and had a mean age of 53 (SD=7.7) years. Most participants (94.5%) reported a history of diabetes for more than 5 years. Mean baseline LDL-C level was 120±28 mg/dL. All participants received a background statin therapy. Demographics and baseline characteristics were generally balanced between the two groups of study (Table 1). At week 8th, *C. colocynthis* was shown to significantly lower the LDL-C level when compared to the baseline in

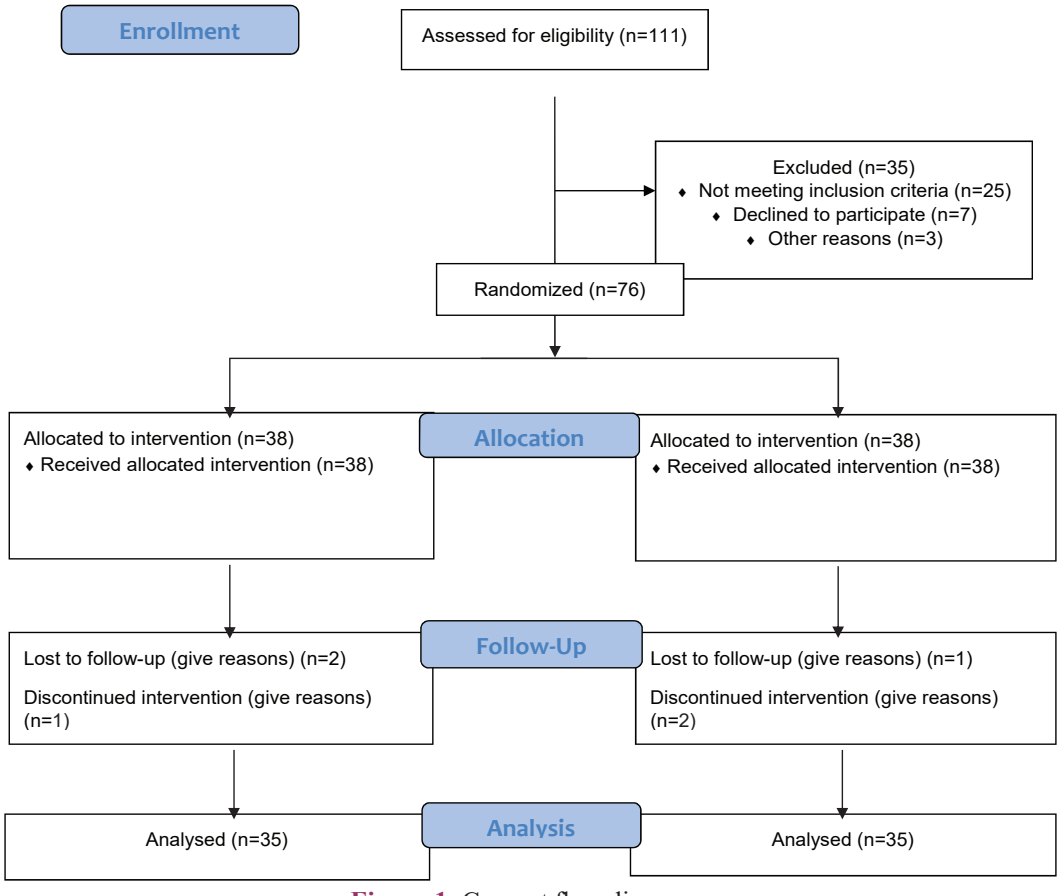

Figure 1: Consort flow diagram.

Table 1: Demographic characteristics of participants in two study groups.

Variable		Case group (%)	Placebo group (%)	Total (%)	*P value
Gender	Male	16 (23)	14 (20)	30 (43)	0.63
	Female	19 (27)	21 (30)	40 (57)	
Occupation	Employed	16 (23)	11 (16)	27 (39)	0.22
	Unemployed	19 (27)	24 (34)	43 (61)	
Duration of diabetes (year)	≤5	10 (14)	13 (18.5)	23 (32.5)	0.45
	>5	25 (36)	22 (31.5)	47 (67.5)	
BMI (Kg/m^2)	<25	4 (6)	6 (8.5)	10 (14.5)	0.5
	25-30	14 (20)	14 (20)	28 (40)	
	≥30	17 (24)	15 (21.5)	32 (45.5)	
Age (year) Mean ±SD		53±7.7	53±7.7	53±7.7	0.8

*p-value of < 0.05 was considered statistically significant

Table 2: Comparison of primary outcome (LDL-C Level) within and between the two groups.

Variable		Intervention group (n=35) (Mean±SD)	Placebo group (n=35) (Mean±SD)	*P value
LDL (mg/dL)	Baseline	121±25	118±31	0.6
	At 8 weeks	103±25	123±32	0.006
	*P value	0.001	0.2	

*A *p* value of <0.05 was considered statistically significant. LDL-C: Low-density lipoprotein cholesterol.

Table 3: Comparison of the secondary outcomes within and between the two groups.

Variable		Intervention group (n=35) (Mean±SD)	Placebo group (n=35) (Mean±SD)	*P value
Triglyceride (mg/dL)	Baseline	186.5±96	136.8±40.4	0. 6
	At 8 weeks	178±81	145±63	0.06
	*P value	0.03	0.47	
Cholesterol (mg/dL)	Baseline	199.3±53.6	186.4±37.5	0.24
	At 8 weeks	179.5±28	192±35	0.1
	*P value	0.04	0.36	
HDL (mg/dL)	Baseline	55±11.3	57.6±12.9	0.38
	At 8th weeks	53.5±11	54.9±10.8	0.6
	*P value	0.21	0.06	

*A *p* value of <0.05 was considered statistically significant. HDL-C: High-density lipoprotein cholesterol.

the intervention group (103±25 vs. 121±25 mg/dL, respectively; p=0.001). In addition, *C. colocynthis* could significantly lower the LDL-C level more than the placebo treatment (103±25 vs. 123±32 mg/dL, respectively; p=0.006) at week 8th (Table 2).

In the *C. colocynthis* group, the mean total cholesterol level decreased at week 8th in comparison to the baseline (199.3±53.6 vs. 179.5±28 mg/dL, respectively; p=0.04). However, no significant reductions with *C. colocynthis* vs. placebo were observed at week 8th for the total cholesterol (179.5±28 vs. 192±35, respectively; p=0.1) and HDL-C (53.5±11 vs. 54.9±10.8, respectively; p=0.6). Also, no clinically significant changes were noticed in triglyceride level between the two groups (p=0.06, Table 3). There were no adverse events recorded during the study period.

Discussion

Herbal medicine has always been a successful window in treatment of diabetes (18-20) and its efficacy on lipid profile (21). In this study, we demonstrated that the addition of *C. colocynthis* capsules (125 mg) that could be maximally tolerated in lipid-lowering therapy was able to significantly reduce the LDL-C level in type 2 diabetic patients with dyslipidemia when compared to placebo. In Iran, *C. colocynthis* is widely used in treatment of diabetes, and previous clinical trials have suggested its efficacy in lowering the fasting blood sugar and HbA1c without any adverse effects (14, 16). In the current study, using the same dosage, we observed both antidiabetic and antilipidemic effects with no reported side effects. Other herbal drugs, such as fenugreek, have also been investigated for their potential in lowering blood glucose and total cholesterol level; however, their impact on triglycerides, LDL-C, and HDL-C was less clear (22, 23).

Similarly, herbs like *Gymnema sylvestre* and *Artemisia absinthium* exhibited antidiabetic properties, but did not clearly affect the lipid profile of diabetic patients (24). In contrast, the hypolipidemic effect of *C. colocynthis* has been studied in non-diabetic patients. Rahbar *et al.* indicated that daily administration of 300 mg of powdered *C. colocynthis* seeds could significantly decrease the triglyceride and cholesterol levels (25). But; Li *et al.* conducted a study on diabetic patients who used a high dose of *C. colocynthis* (500 mg, twice daily for 30 days) sourced from local markets. Unlike our findings, their study did not demonstrate any significant hypolipidemic effect, suggesting that the source and preparation of the herbal product, as well as dosage variations, may influence outcomes (24). In another study, Yaghoobi *et al.* administered 100 mg of *C. colocynthis* as three times daily and found significant reductions in blood glucose, cholesterol, and LDL-C levels with no side effects being reported over one-month period (13). Similar findings were reported by Fallah Huseini *et al.*, who used the same dosage; but did not observe any significant effect on lipid profile (26). Our study suggests that, *C. colocynthis* even at lower doses was

effective when combined with statin therapy.

It was shown that herbal medications such as *C. colocynthis* can have side effects toobased on their narrow therapeutic indices. The most common adverse effects associated with *C. colocynthis* can be gastrointestinal disorders including colic, diarrhea, and hematochezia (27, 28). Traditional medicine and modern phytotherapy have recommend doses ranging from 0.6 to 1.75 g/day and 0.1 to 0.4 g/day, respectively, to have adverse effects typically arising from inappropriate dosing or prolonged use of *C. colocynthis* (29-31). Notably, Javadzadeh *et al.* reported cases of *C. colocynthis* intoxication involving mucosal erosion and lower gastrointestinal bleeding in patients who consumed doses exceeding the recommended limits (32). To mitigate these risks, we utilized the minimum effective dose of *C. colocynthis* in our study, with no observed adverse effects.

Additionally, potential drug interactions with herbal medicines should be considered, especially given the polypharmacy common in diabetes management (33, 34). To avoid interactions, we restricted the use of other herbals or non-herbal medications during our study, allowing only statins and standard antidiabetic regimens to be administered.

Our study had some limitations too, including a relatively small sample size and a short duration of only 8 weeks. A portion of the data acquired from the participants was self-reported; consequently, recall bias and self-report bias can pose significant challenges to mitigate. Nevertheless, the implementation of trained investigators and standardized methodologies for investigation can effectively diminish the bias. Moreover, our trial did not assess very-low-density lipoprotein cholesterol (VLDL-C), which could provide a more comprehensive understanding of its effects on lipid metabolism.

Conclusion

In type 2 diabetic patients with dyslipidemia, the addition of *C. colocynthis* (125 mg) to existing lipid-lowering therapy with statin was demonstrated to significantly reduce the LDL-C level over an 8-week period. Further studies with larger sample sizes and longer follow-up periods are needed to confirm these findings and to evaluate the long-term efficacy and safety of *C. colocynthis.*

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Authors' Contribution

B.B, as the corresponding author, conceptualized the study, coordinated the research, and contributed to writing and revising the manuscript. F.G and R.P contributed to the research design, supervised the clinical trial, and reviewed the manuscript. A.K contributed to statistical analysis, data interpretation, and drafting the manuscript. A.D assisted in data collection and drafting the initial manuscript. All authors read and approved the final manuscript.

Conflict of Interest

The authors declare that they have no competing interests.

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