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A Complementary Therapy with *Trigonella foenum-graecum* L. and *Citrullus colocynthis* (L.) in Type 2 Diabetes Mellitus: A Double-Blind Randomized Controlled Clinical Trial

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Abstract

Background & Objectives: Diabetes is a known chronic disease affecting more than 400 million people and causing millions of deaths worldwide annually. The World Health Organization predicts that by 2030, diabetes will become the seventh leading cause of death. In the last decades, numerous chemotherapy approaches have been used. However, herbal remedies have accounted for more than 70 percent of the total administered antidiabetic treatments during the last decade. In this study, we aimed to develop a novel natural antidiabetic therapy with *Trigonella foenum-graecum* (*T. foenum-graecum*) L. and *Citrullus colocynthis* (*C. colocynthis*) (L.). Based on past studies, using *C. colocynthis* singly can cause diarrhea, abdominal pain, and heartburn, hence in order to reduce these complications, we applied this plant in combination with *T. foenum-graecum* based on the recommendations of Persian medicine references.

Materials & Methods: We admitted 34 diabetics aged 30-65 years old to design a double-blind parallel randomized controlled clinical trial. We prepared therapeutic capsules containing a combination of 40 mg of *C. colocynthis* and 350 mg of *T. foenum-graecum* L. We divided participants into an interventional (n=17) and placebo (n=17) groups and measured fasting blood sugar (FBS) levels, lipid profile, and liver function tests initially. After two weeks, all participants returned for a visit, and FBS and blood sugar (BS) were measured. At the end (12th week), all outcomes were measured and analyzed using an independent t-test and Chi-squared (χ^2).

Results: The FBS levels decreased significantly in the intervention group compared to that of the control group (171.8±54.9 versus 149.6±46.4, p=0.024), but the improvements in the lipid profile and liver function were not statistically significant.

Conclusion: This study unveiled that combination of *T. foenum-graecum* L. and *C. colocynthis* L. at safe levels significantly decreased the FBS levels among T2DM patients. Further studies are needed to provide more efficient antidiabetic effects with the low side effects.

Keywords: Diabetes, *Trigonella foenum-graecum*, *Citrullus colocynthis*, Herbal extracts, Treatment

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Introduction

Diabetes is a prevalent chronic disease affecting over 463 million individuals around the world as of 2019. Moreover, the World Health Organization estimated that diabetes cases would reach around 578 million by 2030 (1). Diabetes patients have quadrupled in 34 years, with their number increasing from 108 million in 1980 to 422 million in 2014, while the incidence of diabetes worldwide among adults over 18 years of age has increased from 4.7% in 1980 to 8.5% in 2014 (2). Unfortunately, diabetes caused 1.5 million deaths in 2012, and subsequent reports in 2014 revealed approximately 4.9 million diabetes-linked deaths (3). Previously**,** the WHO predicted that by 2030, diabetes would become the seventh leading cause of death (4). In the last decades, the number of diabetic cases has grown and resulted in a great burden on society (5). According to the International Diabetes Federation (IDF), 8.8% of the adult population have diabetes, with men having slightly higher rates (9.6%) than women (9.0%) (6). In total, different countries worldwide spend more than 370 billion dollars, and these costs would double in the next decade (1). The global percentage of end-stage renal disease (ESRD) patients with diabetes increased from 19.0% in 2000 to 29.7% in 2015 worldwide, while the percentage of incident ESRD patients due to diabetes increased from 22.1% to 31.3% (7). Therefore, we require novel promising therapies to prevent diabetes prevalence and mortality and decrease the health and economic burdens on societies (8).

A growing number of studies demonstrate the considerable efficacy of several herbal treatments against type II diabetes mellitus (T2DM) (9–11). The recent reports suggest that herbal remedies account for more than 70 percent of the total administered antidiabetic treatments in the last decade (12–18).

Among several available herbal treatments, fenugreek (*Trigonella foenum graecum*) is traditionally known as a valuable blood glucose regulator for patients with T2DM in many regions of Arab origin (15, 19, 20). Moreover, some studies have reported the anti-diabetic effects of *T. foenum-graecum* L. at different stages (21). Although early *in vivo* studies on *T. foenum-graecum* L. have revealed promising results in mitigating diabetic complications, there is no sufficient evidence to prove the anti-diabetic properties of *T. foenum-graecum* L. (22).

On the other hand, *Citrullus colocynthis* (*C. colocynthis*) is another therapeutic herb with ***many*** anti-inflammatory effects; however, studies on rodent models have inferred that high doses of this herbal medicine result in cardiac impairment and mortality (23,24). In addition, some studies have deciphered that diabetics treatment using high doses of this herbal medicine (300 to 800 mg per day) causes diarrhea, painful heartburn, abdominal pain, and bloody diarrhea and heartburn (25,26). Therefore, in order to reduce the complications, we used this plant in combination with *T. foenum-graecum* L. based on Persian medicine references (27, 28). In this study, we investigated the positive and negative effects of *C. colocynthis* combined with *T. foenum-graecum* L. on FBS levels and lipid profile in T2DM cases.

Materials and Methods

This study was a double-blind parallel randomized controlled clinical trial. Participants were selected among individuals with diabetes who were referred to the diabetic clinic. The eligible adult participants (30 to 65 years old) from both genders were recruited into the study via a face-to-face interview and signed the informed consent. The inclusion criteria included having a hemoglobin A1c greater than 6.4%, weight between 55 and 100 kg and a body mass index (BMI) between 24 and 35, and lack of experience of alcohol or drug addiction, medical disorders, such as high blood pressure, renal, rheumatologic or liver diseases, not being pregnant and not using herbal drugs.

All patients were fully aware of their rights to continue or withdraw from participation during the trial, and all patients signed the informed consent form. Moreover, any patient with extremely high FBS (FBS > 270 mg/dl), the presence of any study-related side effects, or receiving any kind of corticosteroid drugs during the study was excluded as well.

Sample Size

Upon several clinical trials on *T. foenum-graecum* L. and *C. colocynthis*, there are a wide range of sample sizes from 8 to more than 120 in the literature (29, 30). Initially, we chose 74 (a sample size of 60 plus a probable 14 drop-outs) as the sample size of our study. However, because of the numerous side effects that were reported in the first follow-up of the study, we decided to reduce the sample size to a minimum of about half of the originally chosen number.

Making drug and placebo capsules

Five samples of *T. foenum-graecum* L. and *C. colocynthis* plants were collected from several reputable grocery stores in Shiraz. The original samples were identified and assigned specific numbers, *T. foenum-graecum* L. (PM1384) and *C. colocynthis* (PM1383) by the traditional pharmacy department of the Shiraz pharmacy school. For preparing the required capsules, after removing the impurities, the *T. foenum-graecum* L. seeds and internal parts or pulp of *C. colocynthis* were powdered and then encapsulated, each capsule containing 350 mg of powdered *T. foenum-graecum* L. and 40 mg of *C. colocynthis*. The daily dosage of *C. colocynthis* is from 120 to 300 mg, and for *T. foenum-graecum* L., it is up to 6 g (PDR), 1-6 g 2 to 3 times a day (31). In Iran, two kinds of *T. foenum-graecum* L. tablets (220 mg and 335 mg) are available. Because it was the first time that a combination of these two plants was tested on humans, we chose the smallest amount of each plant with a proper safety margin. The same amount (390±5 mg) of corn flour was filled in similar capsules as a placebo, and at the end, all the placebo capsules were flavored with about 200 mg of *T. foenum-graecum* L. powder. All drugs were made in the medicinal plant manufacturing center of the Shiraz University of Medical Sciences Faculty of Pharmacy.

Randomization and Blinding Method

The participants were consequently recruited into study groups based on a blocked randomization list. This list was created using the Excel 2018 software with a 1:1 allocation and random block sizes of 4.

All capsules had the same size and shape and were placed in similar boxes, each containing 28 capsules. Each box was assigned a dedicated letter from A to D. The study pharmacist was the only person who knew the contents of the boxes. On the other hand, none of the physicians and participants involved in the study were aware of the prescribed drugs.

Intervention

All patients referred to the medical centers of Fasa University of Medical Sciences had their demographic and basic information taken**.** Then, we took a blood sample from all patients to measure the baseline level of all outcomes. Afterwards, they were asked to consume two capsules daily (after breakfast and dinner) for two weeks. Then, all participants were revisited to check their condition and monitor probable side effects. Another blood sample was taken from every participant to evaluate two outcomes, FBS and blood sugar (BS), for the second time. Then, the same drug boxes were given to them for an additional 10 weeks. At the end of the study (totally 12 weeks), the participants were revisited, and all initial laboratory tests were repeated. Meanwhile, every probable adverse event was recorded during and at the end of the study.

Measurement of outcomes

All measurements were implemented at the Noncommunicable Disease Research Center central laboratory (Fasa, Iran). All evaluations obtained the protocols of cohort studies by Farjam et al. (32) and the PERSIAN cohort study by Eghtesad et al. (33). To evaluate all the following outcomes, we collected a 10 mL venous blood sample from each participant at the

beginning and the end of the study (12th week), and a blood specimen for evaluating the glucose level during the study (at the 2nd week). Then, we stored the plasma and serum samples at -20°C and performed the measurements within 10-12 days after sample collection. All measurements were carried out by utilizing PARS AZMUN kits (34).

Lipid profile

To determine the lipid profile, we carried out measurements on cholesterol, high-density lipoprotein (HDL), low-density lipoprotein, and triglyceride (TG). All these factors were checked one time at the beginning of the study and the other time at the final checkpoint (12th week). We utilized enzymatic colorimetric methods (Boehringer Mannheim, Mannheim, Germany) to measure the level of serum TG, TC, and HDL. First, we sedimented apolipoprotein B-100-containing particles by using dextran sulfate to measure the HDL level. Then, we used the Friedewald formula to evaluate the LDL level (TG < 3.5 mmol/L).

Liver function

To determine the condition of liver function during the intervention, we measured serum glutamic oxaloacetic transaminase (SGOT), Serum glutamic pyruvic transaminase (SGPT), and alkaline phosphatase (ALP). All liver function tests were performed before and after the intervention (12th week). We evaluated all liver function factors, including ALP (1400.002, PARS AZMUN, Iran), SGPT, and SGOT (1400.019, PARS AZMUN, Iran) based on photometric methods.

Glucose level

We also measured FBS, BS, and Hemoglobin A1C (HBA1c) to determine the condition of glucose level before, during (two weeks after the first administration), and after the study. As mentioned before, we evaluated the levels of all glucose-related factors using PARS AZMUN kits. Plasma glucose was measured using Boehringer Mannheim reagents on a Hitachi 917 analyzer (Hitachi Ltd, Tokyo, Japan).

Statistical Analysis

The data were presented as mean ± standard deviation. The normality of the data was tested by the Shapiro-Wilk test. Comparison of variables between the control and intervention groups was done using an independent t-test and Chi-squared (X2) distribution based on the variables. Before and after analysis was done with a paired t-test. A $p<0.05$ was considered a significant level. All analyses were performed using IBM SPSS 24 (IBM SPSS, Chicago, Ill).

Results

Totally, of 418 patients considered to participate in the study, 34 cases passed the inclusion criteria and enrolled in the trial. We randomized participants into case and control groups (17 in each group). In the process of the trial, four patients withdrew their participation (two patients at the first follow-up from the control group and the other two cases at the second checkpoint from the intervention group). At the end of the study, the outcomes of the remaining 30 patients were analyzed (Figure 1).

The mean ± standard deviation (SD) of age (years), body mass index (BMI, kg/m^2), and the disease duration (months) of participants included 52.2±7.7, 26.6±2.5, and 67.0±44.3, respectively. There was no significant difference among the study groups at the beginning (Table 1). Furthermore, there was no significant difference between the intervention and the placebo groups in terms of gender distribution (70.6% females in the intervention group compared to 64.6% in the control group, P=0.99), disease duration (47.6±11.6 months for the intervention group compared to 42.1±10.2 months for the control group, P=0.817), and their anti-diabetic drugs (P=0.701). Therefore, all the assessed variables had a normal distribution.

Outcomes

Primary outcomes

After 12 weeks, FBS significantly decreased in the intervention group compared to the control group (171.8±54.9 versus 149.6±46.4, p=0.024). Analysis

of other measured outcomes inferred no remarkable difference between the study groups (Chart 1). The evaluations of the liver functional agents (SGOT and SGPT) and lipid profile (cholesterol and TG) outlined that our novel herbal treatment resulted in a statistically insignificant decrease in the intervention group (Table 2).

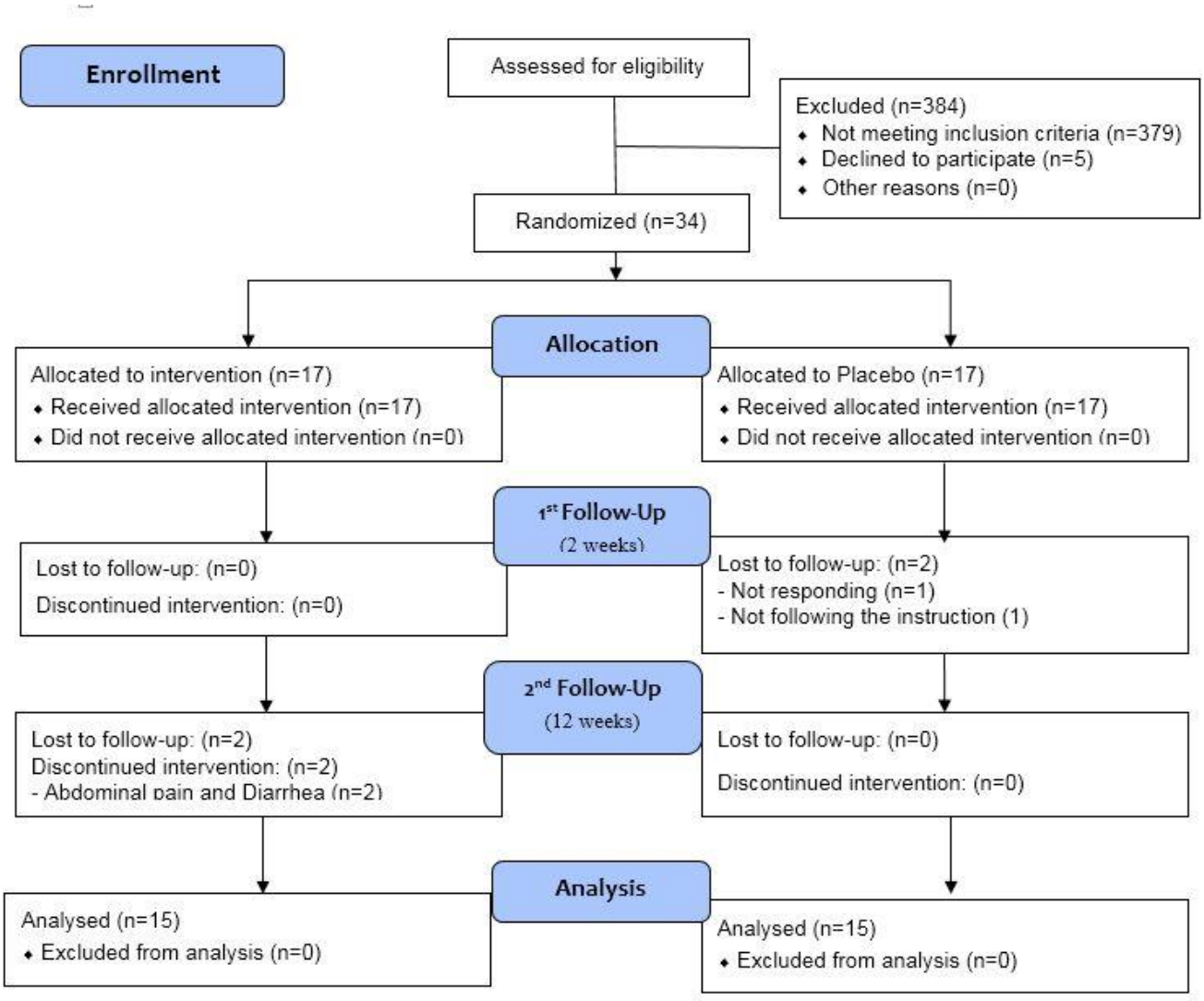


Figure 1. CONSORT Flow Diagram

Table 1. The comparison of demographic and basic outcome measures between two groups at the starting point of the study

	Control (n=17)		Intervention (n=17)		
Variable	**Mean**	**SD**	**Mean**	**SD**	**P-value**
Age (Year)	53.2	8.4	51.2	7.0	0.457
BMI (Kg/m^2)	26.0	2.3	27.1	2.7	0.226
FBS (mg/dl)	151.8	25.2	171.8	54.9	0.183
2hpp (mg/dl)	192.7	40.0	225.0	71.8	0.115
Hb A1C (%)	7.8	1.3	8.4	2.3	0.358
SGOT (mg/dl)	22.5	5.7	19.9	7.3	0.254
SGPT (mg/dl)	27.3	6.5	23.9	9.2	0.236
ALP (mg/dl)	211.7	51.4	222.1	49.9	0.563
Chol (mg/dl)	180.5	50.6	172.8	32.9	0.603
LDL (mg/dl)	87.0	27.1	83.4	33.7	0.738
HDL (mg/dl)	53.1	13.5	49.3	14.9	0.438
TG (mg/dl)	155.3	75.5	153.6	62.9	0.947

SD: Standard deviation, BMI: Body mass index, FBS: Fasting blood sugar, 2hpp: hour Post Prandial, Hb A1C: Hemoglobin A1C, SGOT: Serum glutamic-oxaloacetic transaminase, SGPT: Serum glutamic-pyruvic transaminase, ALP: Alkaline phosphatase, Chol: Cholesterol, LDL: Low density lipoprotein, HDL: High density lipoprotein, TG: Triglyceride

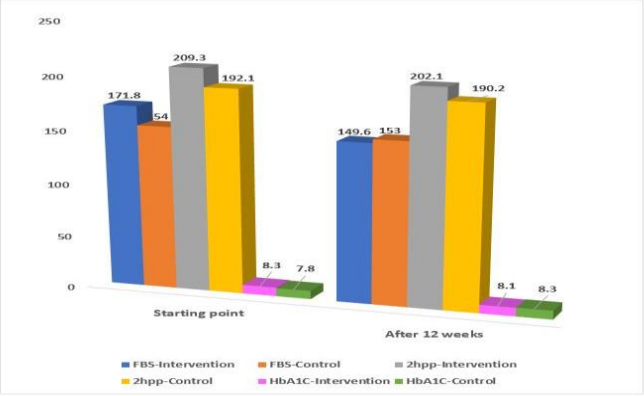


Figure 2. The comparison of the FBS, HbA1c and Bs at the starting point and end of the study (after 12 weeks)

Table 2. The comparison of the main study outcomes within and between two groups at the starting point and end of the study (after 12 weeks).

Outcomes	Intervention (n=15)		Control (n=15)		p-value
	Before	After	Before	After	
FBS[1] (mg/dl)	171.8±54.9	149.6±46.4	154±25.1	153±41.5	0.834
P-Value	0.024		0.916		
2hpp[2] (mg/dl)	209.3±60.5	202.1±64.4	192.1±37.1	190.2±69.1	0.539
P-Value	0.784		0.904		
HbA1C[33] (%)	8.3±2.4	8.1±1.4	7.8±1.3	8.3±2.1	0.714
P-Value	0.671		0.114		
SGOT[4] (mg/dl)	20.6±7.6	21.3±7.8	22.8±6	24±9.7	0.402
P-Value	0.266		0.689		
SGPT[5] (mg/dl)	23.8±9.4	25.5±10.6	27.5±6.8	28.7±13.6	0.469
P-Value	0.352		0.726		
Chol.[6] (mg/dl)	172.4±29.5	175.1±32.6	184.7±52.5	179.2±44.2	0.778
P-Value	0.725		0.603		
TG[7] (mg/dl)	154.6±62.9	144±45	162.9±78	147±53.1	0.671
P-Value	0.468		0.373		

FBS: Fasting blood sugar, 2hpp: hour Post Prandial, Hb A1C: Hemoglobin A1C, SGOT: Serum glutamic-oxaloacetic transaminase, SGPT: Serum glutamic-pyruvic transaminase, Chol: Cholesterol, TG: Triglyceride

The comparison between the last amounts of the outcomes of the study groups
The comparison within each group

Discussion

This study aimed to determine the efficiency and side effects of a novel combination of *T. foenum-graecum* L. and *C. colocynthis* in diabetic patients. According to Persian medicine sources, Hanzal (*C. colocynthis*) would ameliorate different complications induced by diabetes (35, 36). More relevantly, *T. foenum-graecum* L. seeds improving effects in the diabetics have been documented (37, 38). We hypothesized that the combination of *T. foenum-graecum* L. with *C. colocynthis* would substantially restrict the diabetes complications. Our study had two main results. First, the results revealed that FBS reduces in the intervention group after 12 weeks of treatments, but the analysis showed no improvement in other outcomes. Second, this study

1. Fasting blood sugar
2. 2-hour Post Prandial
3. Hemoglobin A1C
4. Serum glutamic-oxaloacetic transaminase
5. Serum glutamic-pyruvic transaminase
6. Cholesterol
7. Triglyceride

showed that diabetics treated with our novel complementary therapy face more serious side effects than the placebo group. We observed a slightly higher rate of abdominal pain and diarrhea in the intervention group. Therefore, adding *C. colocynthis* to *T. foenum-graecum* L. with this ratio presents many side effects that may be difficult for patients to tolerate.

In 2016, Heydari et al. demonstrated that topical administration of 2 mL *C. colocynthis* two times a day for three months diminished diabetes-related pain with no remarkable adverse effects (39). In a recent study by Rostami et al., the same regimen for a shorter period (four weeks) in breast cancer patients presented no significant complication (40). In 2010, Rahbar and Nabipour indicated that oral usage of daily 300 mg *C. colocynthis* for six weeks would ameliorate hyperlipidemia in non-diabetic patients with no mentioned serious adverse effects (41). In an earlier study by Huseini et al., oral administration of daily 100 mg *C. colocynthis* in 25 diabetics unraveled promising effects on glycemic properties after two months with the least adverse effects (12% mild diarrhea). Hence, in comparison to the previous studies, our patients significantly experienced a remarkably higher rate of abdominal pain and diarrhea (more than 50%) (42). However, in Persian medical sources, side effects such as diarrhea and cramps have been mentioned for *C. colocynthis* (35, 36), highlighting that in diabetic patients, this dose of *C. colocynthis* would cause more severe side effects. Accordingly, it is possible that more care is needed in choosing this plant for diabetics. Based on Qin-Yuan's study, *C. colocynthis* is used as a remedy for gastro-intestinal disorders like indigestion, gastroenteritis, and intestinal parasites. The plant is also used to treat diabetes, liver problems, lazy bowel syndrome, and obstruction, paralytic ileus or gastroparesis (43–46).

From the first observations in 1990, studies have revealed that consumption of 100 mg *T. foenum-graecum* L. daily for 10 days exert promising benefits in the amelioration of blood sugar and lipid profiles in patients with diabetes type I (37). The efficiency of *T. foenum-graecum* L. seeds to control diabetes complications has attracted a lot of attention in the last two decades (29, 47). In one of the first clinical trials on the antidiabetic effects of *T. foenum-graecum* L., Gupta et al. observed that 1 gr of this herbal therapy a day provides acceptable improvement in FBS and lipid profiles in patients with T2DM (38). In a small study, Najdi et al. demonstrated that oral usage of *T. foenum-graecum* L. seeds (2 gr/day) would control blood sugar in diabetic patients and improve the effects of glibenclamide, with lower adverse effects (48). In a recent study on cardiometabolic risk factors, Rao et al. deciphered that daily administration of 5.45 gr of a combination of *T. foenum-graecum* L. with *Nigella sativa* led to reliable outcomes in HbA1c, lipid profiles, and other factors with no significant adverse effects after 12 weeks (44, 45, 49). Based on recent studies, due to *T. foenum-graecum* L. components such as bioactive compounds like alkaloids, amino acids, and flavonoids, it acts as a proper antioxidant as well as an anti-inflammatory agent. Additionally, the clinical applications of *T. foenum-graecum* L. are also attributed to its diverse chemical composition, which makes this plant a strong candidate to alleviate the dependence on various synthetic drugs for curing diseases (50).

Although several trials have revealed positive effects of these herbs on diabetics with low adverse effects, our study outlined the same efficiency with limited adverse effects of this combination. Accordingly, we hypothesize that two conditions may play the main role in these results. First, the development of diarrhea in several intervened cases may decrease the absorption of oral antidiabetic drugs. On the other hand, the insufficient dose of each herb would lower the efficiency of interventions.

Limitations

Despite attempting to achieve valuable results, our study had several limitations. We administered a

lower dose of *C. colocynthis* compared to similar trials, but we still encountered some adverse effects in almost half of the patients. This limited the study duration to 12 weeks, preventing us from evaluating the long-term effects of the treatment. Although this duration was sufficient to achieve reliable results for the measured outcomes, a longer study period would be necessary to assess long-term effects. Due to the potential side effects, we also limited the sample size. Therefore, further studies with a larger sample size are warranted to confirm our findings and assess long-term effects.

For more effective results, it may be better to reconsider the dose of both plants, or as mentioned in Persian medicine, the side effects of *C. colocynthis* can be reduced by adding a certain dose of tragacanth.

Conclusion

Our findings indicated that the combination of *T. foenum-graecum* L. and *C. colocynthis* L. decreases FBS in 12 weeks, with no adverse effects on liver function. HbA1c and lipid profile did not change during the treatment period. However, this combination was associated with a mild increase in abdominal pain and diarrhea. Therefore, further studies with a larger sample size are warranted to explore the potential for improved efficacy and tolerability through dosage and formulation adjustments.

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Conflict of interest

None.

Funding

None.

Code of Ethics

The ethics committee of Fasa University of medical sciences has approved the protocol of this study (Code: IR.FUMS.REC.1396.219), and the registration number of this study in the Iranian registry of clinical trials (irct.ir) is; IRCT20140715018490N3

Consent for publication

Pending journal policy.

Authors' Contributions

Study concept and design: Mahsa Rostami Chijan, Massih Sedigh Rahimabadi, Foroogh Namjoyan.

Acquisition of data: Seyed Mohammadreza Torabi.

Drafting of the Manuscript: Seyed Mohammadreza Torabi, Foroogh Namjoyan, Mahsa Rostami Chijan, Hossein Pourmontaseri, Elham Zarenezhad.

Critical revision of the manuscript for important intellectual content: Mahsa Rostami Chijan, Hossein Pourmontaseri.

Study supervision: Babak Pezeshki.

Data Availability Statement

The datasets generated and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

References

1.Zimmet PZ, Magliano DJ, Herman WH, Shaw JE. Diabetes: a 21st century challenge. Lancet Diabetes Endocrinol. 2014 Jan;2(1):56–64.
2.Alam S, Hasan MdK, Neaz S, Hussain N, Hossain MdF, Rahman T. Diabetes Mellitus: Insights from Epidemiology, Biochemistry, Risk Factors, Diagnosis, Complications and Comprehensive Management. Diabetology. 2021 Apr 16;2(2):36–50.
3.Ogurtsova K, da Rocha Fernandes JD, Huang Y, Linnenkamp U, Guariguata L, Cho NH, et al. IDF Diabetes Atlas: Global

estimates for the prevalence of diabetes for 2015 and 2040. Diabetes Res Clin Pract. 2017 Jun;128:40–50.
4.Mathers CD, Loncar D. Projections of Global Mortality and Burden of Disease from 2002 to 2030. PLoS Med. 2006 Nov 28;3(11):e442.
5.Esteghamati A, Gouya MM, Abbasi M, Delavari A, Alikhani S, Alaedini F, et al. Prevalence of Diabetes and Impaired Fasting Glucose in the Adult Population of Iran. Diabetes Care. 2008 Jan 1;31(1):96–8.
6.Pradeepa R, Mohan V. Epidemiology of type 2 diabetes in India. IJO. 2021;69(11):2932.
7.Cheng HT, Xu X, Lim PS, Hung KY. Worldwide Epidemiology of Diabetes-Related End-Stage Renal Disease, 2000–2015. Diabetes Care. 2021 Jan 1;44(1):89–97.
8.Nathan DM, Davidson MB, DeFronzo RA, Heine RJ, Henry RR, Pratley R, et al. Impaired Fasting Glucose and Impaired Glucose Tolerance. Diabetes Care. 2007 Mar 1;30(3):753–9.
9.Pang B, Zhao LH, Zhou Q, Zhao TY, Wang H, Gu CJ, et al. Application of Berberine on Treating Type 2 Diabetes Mellitus. Int J Endocrinol. 2015;2015:1–12.
10.Liu Q, Liu S, Gao L, Sun S, Huan Y, Li C, et al. Anti-diabetic effects and mechanisms of action of a Chinese herbal medicine preparation JQ-R in vitro and in diabetic KK Ay mice. Acta Pharm Sin B. 2017 Jul;7(4):461–9.
11.Yang L xia, Liu T hua, Huang Z tao, Li J e, Wu L li. Research progress on the mechanism of single-Chinese medicinal herbs in treating diabetes mellitus. Chin J Integr Med. 2011 Mar 27;17(3):235–40.
12.Porqueddu T. Herbal medicines for diabetes control among Indian and Pakistani migrants with diabetes. Anthropol Med. 2017 Jan 2;24(1):17–31.
13.Adib-Hajbaghery M, Rafiee S. Medicinal plants use by elderly people in Kashan, Iran. Nurs Midwifery Stud. 2018;7(2):67.
14.Al-Rowais NA. Herbal medicine in the treatment of diabetes mellitus. Europe PMC.
15.Ali-Shtayeh MS, Jamous RM, Jamous RM. Complementary and alternative medicine use amongst Palestinian diabetic patients. Complement Ther Clin Pract. 2012 Feb;18(1):16–21.
16.Zayneb A, Hayat A, Bouchra A, Youssef H, Hanane L. Herbal medicines use among diabetic patients in Oriental Morocco.JPP. 2015 Feb 28;7(2):9.
17.Argáez-López N, Wacher NH, Kumate-Rodríguez J, Cruz M, Talavera J, Rivera-Arce E, et al. The Use of Complementary and Alternative Medicine Therapies in Type 2 Diabetic Patients in Mexico. Diabetes Care. 2003 Aug 1;26(8):2470–1.
18.Balamurugan .E, Ganesh.k. Prevalence and pattern of self medication use in coastal regions of south India. BJMP. 2011;4.
19.Otoom SA, Al-Safi SA, Kerem ZK, Alkofahi A. The use of medicinal herbs by diabetic Jordanian patients. J Herb Pharmacother. 2006;6(2):31–41.
20.Kamel FO, Magadmi RM, Hagras MM, Magadmi B, AlAhmad RA. Knowledge, attitude, and beliefs toward traditional herbal medicine use among diabetics in Jeddah Saudi Arabia. Complement Ther Clin Pract. 2017 Nov;29:207–12.
21.Xue WL, Li XS, Zhang J, Liu YH, Wang ZL, Zhang RJ. Effect of Trigonella foenum-graecum (fenugreek) extract on blood glucose, blood lipid and hemorheological properties in streptozotocin-induced diabetic rats. Europe PMC. 2007;
22.Pundarikakshudu K, Shah PA, Patel MG. A comprehensive review of Indian medicinal plants effective in diabetes management: Current status and future prospects. In: Antidiabetic Medicinal Plants. Elsevier; 2024. p. 3–73.
23.Al-Yahya MA, AL-Farhan AH, Adam SEI. Preliminary toxicity study on the individual and combined effects of Citrullus colocynthis and Nerium oleander in rats. Fitoterapia. 2000 Aug;71(4):385–91.
24.Bakhiet AO, Adam SE. An estimation of Citrullus colocynthis toxicity for chicks. Vet Hum Toxicol. 1995 Aug;37(4):356–8.
25.Goldfain D, Lavergne A, Galian A, Chauveinc L, Prudhomme F. Peculiar acute toxic colitis after ingestion of colocynth: a clinicopathological study of three cases. Gut. 1989 Oct 1;30(10):1412–8.
26.Faraj S Al. Haemorrhagic colitis induced by *Citrullus colocynthis*. Ann Trop Med Parasitol. 1995 Dec 15;89(6):695–6.
27.Ziyyat A, Legssyer A, Mekhfi H, Dassouli A, Serhrouchni M, Benjelloun W. Phytotherapy of hypertension and diabetes in oriental Morocco. J Ethnopharmacol. 1997 Sep;58(1):45–54.
28.Abdel-Hassan IA, Abdel-Barry JA, Tariq Mohammeda S. The hypoglycaemic and antihyperglycaemic effect of Citrullus colocynthis fruit aqueous extract in normal and alloxan diabetic rabbits. J Ethnopharmacol. 2000 Jul;71(1–2):325–30.
29.Geberemeskel GA, Debebe YG, Nguse NA. Antidiabetic Effect of Fenugreek Seed Powder Solution (*Trigonella foenum-graecum L* .) on Hyperlipidemia in Diabetic Patients. J Diabetes Res. 2019 Sep 5;2019:1–8.
30.Najdi RA, Hagras MM, Kamel FO, Magadmi RM. A randomized controlled clinical trial evaluating the effect of Trigonella foenum-graecum (fenugreek) versus glibenclamide in patients with diabetes. Afr Health Sci. 2019 Apr 18;19(1):1594.
31.Duke JA. Handbook of medicinal herbs}. CRC press; 2002.
32.Farjam M, Bahrami H, Bahramali E, Jamshidi J, Askari A, Zakeri H, et al. A cohort study protocol to analyze the predisposing factors to common chronic non-communicable

diseases in rural areas: Fasa Cohort Study. BMC Public Health. 2016 Dec 18;16(1):1090.
33.Sareh Eghtesad, Zahra Mohammadi. The PERSIAN Cohort: Providing the Evidence Needed for Healthcare Reform.
34.AZMUN. https://labshop.fardadco.com/.
35.Shirazi MHAK. Makhzan al-adviyah. Tehran University of Medical Sciences; 1992.
36.Razi M, *Al-Havi (the large comprehensive).* Beirut: Dare Ehia Attorath Al Arabi, 2001.
37.Sharma RD, Raghuram TC, Rao NS. Effect of fenugreek seeds on blood glucose and serum lipids in type I diabetes. Europe PMC.
38.Gupta A, Gupta R, Lal B. Effect of Trigonella foenum-graecum (fenugreek) seeds on glycaemic control and insulin resistance in type 2 diabetes mellitus: a double blind placebo controlled study.JAPI. 2001 Nov;49:1057–61.
39.Heydari M, Homayouni K, Hashempur MH, Shams M. Topical <*scp*>*C*</*scp*> *itrullus colocynthis* (bitter apple) extract oil in painful diabetic neuropathy: A double-blind randomized placebo-controlled clinical trial. J Diabetes. 2016 Mar 29;8(2):246–52.
40.Rostami N, Mosavat SH, Heydarirad G, Arbab Tafti R, Heydari M. Efficacy of topical <scp> *Citrullus colocynthis* </scp> (bitter apple) extract oil in chemotherapy-induced peripheral neuropathy: A pilot double-blind randomized placebo-controlled clinical trial. Phytotherapy Research. 2019 Oct;33(10):2685–91.
41.Rahbar AR, Nabipour I. The Hypolipidemic Effect of Citrullus colocynthis on Patients with Hyperlipidemia. PJBS. 2010 Dec 1;13(24):1202–7.
42.Fallah Huseini H, Heshmat R, Larijani B, Fakhrzadeh H, Jafariazar Z, Darvishzadeh F, et al. The clinical investigation of Citrullus colocynthis (L.) Schrad. fruit in treatment of type II diabetic patients a randomized, double-blind, placebo-controlled study. jmpir [Internet]. 2006 Mar 1;5(17):31–5. Available from: http://jmp.ir/article-1-599-en.html
43.Li QY, Munawar M, Saeed M, Shen JQ, Khan MS, Noreen S, et al. Citrullus colocynthis (L.) Schrad (Bitter Apple Fruit): Promising Traditional Uses, Pharmacological Effects, Aspects, and Potential Applications. Front Pharmacol. 2022 Jan 25; vol12.
44.Rahimi R, Amin G, Ardekani MRS. A Review on *Citrullus colocynthis* Schrad.: From Traditional Iranian Medicine to Modern Phytotherapy. JICM. 2012 Jun;18(6):551–4.
45.Hussain AI, Rathore HA, Sattar MZA, Chatha SAS, Sarker SD, Gilani AH. Citrullus colocynthis (L.) Schrad (bitter apple fruit): A review of its phytochemistry, pharmacology, traditional uses and nutritional potential. J Ethnopharmacol. 2014 Aug;155(1):54–66.
46.Shi C, Karim S, Wang C, Zhao M, Murtaza G. A review on antidiabetic activity of Citrullus colocynthis Schrad. Acta Pol Pharm. 2014;71(3):363–7.
47.Abdel-Barry JA. Hypoglycaemic effect of aqueous extract of the leaves of Trigonella foenum-graecum in healthy volunteers. EMHJ. 2000; 6 (1), 83-88
48.Najdi RA, Hagras MM, Kamel FO, Magadmi RM. A randomized controlled clinical trial evaluating the effect of Trigonella foenum-graecum (fenugreek) versus glibenclamide in patients with diabetes. Afr Health Sci. 2019 Apr 18;19(1):1594.
49.Rao AS, Hegde S, Pacioretty LM, DeBenedetto J, Babish JG. *Nigella sativa* and *Trigonella foenum-graecum* Supplemented Chapatis Safely Improve HbA1c, Body Weight, Waist Circumference, Blood Lipids, and Fatty Liver in Overweight and Diabetic Subjects: A Twelve-Week Safety and Efficacy Study. J Med Food. 2020 Sep 1;23(9):905–19.
50.Syed QA, Rashid Z, Ahmad MH, Shukat R, Ishaq A, Muhammad N, et al. Nutritional and therapeutic properties of fenugreek (*Trigonella foenum-graecum*): a review. Int J Food Prop. 2020 Jan 1;23(1):1777–91.