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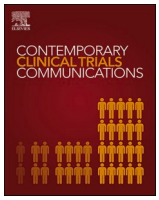

Efficacy of Ma'aljobon Aftimouni (*Cuscuta Reflexa* and whey) on HbA1c and blood glucose levels in patients with Type 2 Diabetes: A randomized triple-blind clinical trial

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ABSTRACT

Introduction and objective: Type 2 Diabetes is a common and chronic metabolic disease. Complementary and alternative medicine can provide a suitable option for demands for new treatments. Therefore, the present study aimed to investigate the effect of Persian medicine on the glycemic status of patients with Type 2 Diabetes.
Method: This randomized, controlled, and triple-blind trial study was conducted from November 2021 to August 2022 on 102 diabetic patients referred to the diabetes clinic in Iran. In this regard, patients with inclusion criteria were randomly divided into three groups *Ma'aljobon with Aftimoun* (n = 34), *Ma'aljobon without Aftimoon* (n = 34), and the control group (n = 34). The control group received a placebo of medicinal salt, light calcium carbonate, lactose, and carboxymethyl cellulose. In contrast, the treatment groups received 25 g of drug powder (in 250 cc of lukewarm water) on an empty stomach for 8 consecutive weeks. Patients' fasting blood sugar (FBS) levels and HbA1c were measured at the beginning and end of the intervention. Data were analyzed using SPSS 23, employing paired t-tests, ANOVA, and chi-square tests for comparison between groups.
Results: Data analysis was conducted on 90 patients with Type 2 Diabetes. The findings revealed a significant reduction in fasting blood sugar levels post-intervention in the Ma'aljobon Aftimouni group (134.27 ± 21.79 vs. 152.3 ± 31.37, mean difference 18.03 ± 5.63, 95 % CI: 6.53 to 29.53, p = 0.003). Additionally, a significant difference in HbA1c values was observed post-intervention in both the Ma'aljobon Aftimouni group (7.88 ± 0.77 vs. 8.09 ± 0.73, mean difference 0.21 ± 0.09, 95 % CI: 0.03 to 0.39, p = 0.031) and the Ma'aljobon without Aftimoun group (7.97 ± 0.84 vs. 8.25 ± 0.78, mean difference 0.28 ± 0.08, 95 % CI: 0.11 to 0.45, p = 0.002).
Conclusion: The findings showed that daily consumption of Ma'aljobon supplements on an empty stomach before breakfast may have a beneficial effect on the glycemic indices of patients. However, further studies seem to be necessary in this regard.

Summary box

What is already known about the topic?

- Type 2 Diabetes is a chronic condition with significant global prevalence, and there is a growing interest in complementary and alternative medicine to manage glycemic control.

What does this study add?

- This study provides evidence that Ma'aljobon Aftimouni, a traditional Iranian medicine formulation, can significantly reduce fasting blood sugar (FBS) and HbA1c levels in patients with Type 2 Diabetes.

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- The research highlights the potential of Ma'aljobon Aftimouni as an effective complementary treatment for managing glycemic indices in Type 2 Diabetes patients.

1. Introduction

Type 2 Diabetes is one of the most common chronic metabolic diseases and a leading cause of death in the world [1]. It has been reported that its prevalence has increased from 336 million people in 2011 to 488 million people in 2019, which is still on the rise [2]. The inability of the body to restore blood sugar to a normal level before a meal is its main pathology [3]. This chronic hyperglycemia is associated with the development of cardiovascular diseases and dysfunction of various organs such as kidneys and eyes [1].

Today, despite many oral medications used to lower blood sugar levels along with insulin, there is still no definitive treatment for it [4]. On the other hand, the demand for developing new treatments is increasing due to the numerous side effects associated with existing medications [5]. These side effects, along with the high costs of blood glucose-controlling drugs, have led to growing interest in research on complementary and alternative medicine for the treatment of diabetes [6]. The lower incidence of side effects and the affordability of these treatments have resulted in a growing preference and trust in traditional medicine therapies in some countries [7]. Persian medicine as a part of supplementary medicine and an alternative with a history of several thousand years has provided a simple and practical suggestion to treat diseases and keep people healthy by prescribing natural and herbal medications and nutrition [8,9]. *Ma'aljobon* as a traditional product is an example of a Persian medicine application in preventing and treating different diseases [10], which has a prominent role in Persian medicine due to its special properties [11]. According to the Persian medicine resources, by adding vinegar or oxymel to hot milk, most of the milk proteins are settled as curds [9] and the remaining liquid on the surface is called *Ma'aljobon* [8]. The name of this composition consists of two Arabic words: "*Ma*'" (meaning water) and "*aljobon*" (meaning cheese) [12]. In resources, it is known as a kind of whey protein [10]. Persian medicine physicians believe that it cleanses the body by penetrating the target organs and removing disease-causing waste from the digestive tract [8].

A variety of WPs in different isolated, concentrated, and hydrolyzed forms are available, which are different based on the processing methods [13]. In the concentrated form, the protein content is 35–80 %, along with amounts of lactose, fat, and minerals. While, in the isolated form, the carbohydrate content decreases and the protein content increases to 90 % [14]. The hydrolyzed form of WPs is formed by hydrolyzing its proteins by protolithic enzymes [15]. It should be noted that the conditions of milk production and the coagulation process (such as acidity and temperature) can change the final composition and percentage of solutes, minerals, and especially proteins [16]. Therefore, its composition is largely dependent on its type [17]. The results of previous studies have indicated the positive effects of WPs on the glycemic status of patients with Type 2 Diabetes [1,18–22]. It is believed that WPs can reduce blood sugar in patients with Type 2 Diabetes by stimulating the secretion of insulin and intestinal hormones, reducing the rate of gastric emptying, and suppressing appetite [15]. However, the results of investigations of different types of WPs showed vague evidence of their effectiveness and optimal doses [23].

According to persian medicine resources, the effectiveness of WPs protein can be increased by adding medicinal plants such as *Cuscuta Reflexa* [11]. *Cuscuta Reflexa* is known as dodder in English and as *Aftimoun* in Arabic [24]. *Cuscuta Reflexa* is a parasitic, leafless plant with yellowish-green stems [9]. This plant wraps around other plants and continues to grow by feeding on them [25]. In Persian medicine, this plant is also known as a medicine for old age and is used to treat psychiatric disorders and dysfunctions of the digestive and urinary systems [24]. It has been used in several clinical trial studies separately or in combination with other substances to treat health problems and different diseases, and its effectiveness and human doses have been reported [9] [24,26,27]. A study by Mehrbani et al. indicated the effect of the plant and WPs on atopic dermatitis in adults, showing a positive effect on the moisture and elasticity of the skin compared to the control group [9]. The findings of another study on the effect of *Cuscuta Reflexa* on depressed patients revealed its effectiveness [26]. This plant has traditionally been used by Indian and Bangladeshi tribes to control blood sugar levels [28]. Several preclinical studies have shown promising results regarding the effect of the methanolic extract of *Cuscuta reflexa* on blood sugar levels in rats [4,5,28,29]. In the study by Mostofa et al., the antidiabetic effects of the methanolic extract of *Cuscuta reflexa* were investigated in Wistar albino rats, demonstrating that this compound reduces HbA1C and improves insulin levels [5]. Previous studies on this plant in human samples and preclinical studies have reported no threatening side effects at normal doses. However, in cases of excessive consumption, diarrhea and intestinal colic are possible [9]. Additionally, there is evidence of enhanced therapeutic effects when combining Ma'aljobon with *Cuscuta reflexa* [11].

Upon reviewing the existing evidence, it was found that to date, no clinical trial has compared the effects of the combination of *Cuscuta reflexa* and Ma'aljobon in patients with Type 2 Diabetes. Therefore, this study aims to compare the effects of Ma'aljobon alone and in combination with Cuscuta reflexa on the glycemic status of patients with Type 2 Diabetes.

2. Method

2.1. Design

The present controlled randomized clinical trial study was conducted on 90 diabetic patients from November 2021 to August 2022 in three groups of patients referring to the diabetes clinic of Arak, Iran. The design of this study was based on the CONSORT statement. The samples were selected using a one-stage convenient sampling method. The variables under study were HbA1c and FBS. To blind the patients in this study, medication, and a placebo were provided to patients in similar containers so that none of the patients and researchers were aware of the allocation of the patients in the intervention or control group. The labels containing specific barcodes (A, B, C) were prepared. Then, a person other than the organizers of the project was asked to assign each group of barcodes to a group of three types of medications (*Ma'aljobon Aftimouni, Ma'aljobon without Aftimoun*, and placebo), and keep the sealed paper containing this information to decrypt if necessary, during the intervention. To analyze the data by SPSS 23, each sample was recorded with its specific code and the statistics expert was not aware of the allocation of groups. At the end of the study and upon completion of the analysis of the results, the codes assigned to the patients were matched by the information contained in the initial sheet sealed at the beginning of the study. Thus, the study was triple-blind. The randomization of the study samples was carried out using the block random permutation method through the Random Allocation software. For this purpose, patients were randomly assigned to three groups: Ma'aljobon Aftimouni, Ma'aljobon without Aftimouni, and placebo, based on a six-block randomization design. Randomization concealment was ensured using opaque envelopes, and the allocation remained hidden until the drug packages were administered. An independent statistician, external to the research team, conducted the randomization and concealment process. When the researchers approached the patients to distribute the drug packages, the envelopes were opened, and the patients were assigned to the study groups using coded labels (A, B, C).

2.2. Participants

The participants in this clinical trial included all patients with a definite diagnosis of type 2 diabetes (by a specialist doctor) who were

under treatment with oral hypoglycemic medications. In this regard, the patients who had the inclusion criteria which were presented by the researcher based on the information obtained from a pre-prepared information form provided to patients at the beginning of the study. The inclusion criteria were the age range of 30–60 years old, willingness to participate in the study, signing the written consent form, controlled diabetes with medication (with an FBS between 150 and 250 mg/dL, HbA1c between 6.5 and 9.5 % for at least 2 past months), lack of smoking, alcohol, lack of other herbal drug consumption, absence of side effects of chronic diabetes based on the patients' descriptions, examinations, and para-clinic findings. The exclusion criteria were taking the medication less than 70 %, sensitivity to milk and its byproducts, pregnancy, and breastfeeding, being affected by a disease or side effects that prevent the person from continuing the study, and any change in the routine process of treatment (including type, doses of medications, and staring treatment with insulin).

The minimum sample size with a statistical power of 80 %, confidence level 95 %, and, effect size of 0.75 was determined to be 28 people in each group, using the following formula:

$$n \geq \frac{\left(Z_{\alpha/2} + Z_{\beta}\right)^2 \sigma^2}{\varepsilon^2}$$

Therefore, taking into account the probability of a 15 % sample fall in the follow-up process, the sample size was determined to be 34 in each group (a total number of 90 people for the study).

2.3. Intervention

According to Persian medicine texts, the best type of *Ma'aljobon* is produced by adding 13.7 cc of coriander and 0.3 cc of vinegar to 100 g of milk at a temperature of 75^{0}c [16]. In Persian medicine, this byproduct is usually used with *Aftimoun*. For this purpose, before adding vinegar, some *Aftimoun* in a clean cloth is placed in the milk 2 or 3 times for 10–15 s, and the *Aftimoun* extract is combined with the milk. This method is the main strategy for traditionally producing this byproduct. However, due to reasons such as the difficulties related to costs of production, collection, and storage of this liquid for this number of samples participating in the study and for 8 weeks and the possibility of sourness of milk, we were not able to produce this liquid traditionally, so we had to cooperate with a pharmaceutical company to dry the produced liquid by using industrial techniques such as spray dryer and lyophilization and use it in the form of powder [16]. The three by products were produced by the Niak Pharmaceutical Company, Golestan, Iran in the form of powder. It should be noted that according to the conditions of the population under study (high blood sugar), vinegar was used instead of coriander to precipitate milk proteins. The purity and potency of the products were checked. The products had appropriate purity and a lack of adulteration with pharmaceuticals or contamination with heavy metals or incorrect herbs.

The patients in the intervention group received 25 g [30] of *Ma'aljobon Aftimouni* powder in 250 cc of lukewarm water once a day on an empty stomach (around 6 or 7 o'clock) for eight consecutive weeks. The patients were asked to drink the liquid for at least 30–60 min before breakfast and to avoid sleeping during this period.

The patients in the group of *Ma'aljobon without Aftimoun* also received the medication as the other intervention group did. Since each can of medication contained 300 g of powder and it was enough for 2 weeks, the patients in all groups were visited every two weeks, and if they had taken more than 70 % of the medication, they received a new medication, otherwise, they were excluded from the study due to insufficient use of the medication. Also, in odd weeks of the study (weeks 1, 3, 5, 7), telephone follow-up was performed to ensure that the patients were taking the medication and to examine the possible side effects.

2.4. Placebo

The patients in the placebo group received placebo powder produced and packaged by the same pharmaceutical company based on consultation with the pharmacologist and the formulation of the original medication. The amount and time of consuming the medication were the same as the two intervention groups, with the same color as the original medication. The chemical composition of the placebo consisted of medicinal salt, light calcium carbonate, lactose, and carboxymethyl cellulose [31]. The groups under study were asked to take the medication as prescribed by the physicians and without any change in the amount or instruction during the study and avoid taking any other herbal medication (including infused, boiled, etc.) without consultation with the physicians.

2.5. Measurement

The parameters under measurement in this study were obtained from the venous blood tests of the patients. These tests required fasting with an interval of 10_12 h from the last meal of the night. The participants were referred to the same accredited laboratory, and the results of their tests were recorded as the basic values. After 8 weeks, the patients took another blood test in the same laboratory and the results were recorded. It should be noted that the tests were taken using the same laboratory kits and methodology. The test results before and after the intervention were compared and evaluated.

2.6. Fasting blood sugar

Fasting blood glucose is used to measure blood sugar level, which was reported in this study in mg/dL units a few hours' fasting by blood test and using Pars test kit using glucose oxidase method and Selectra XL device, Model XL.

2.7. Glycosylated hemoglobin

In conditions leading to an increase in blood glucose, some of the glucose is joined to the hemoglobin part of red blood cells and leads to the formation of a new compound glycosylated hemoglobin (HbA1c). Glycosylated hemoglobin is related to patients' blood glucose over the last months, which can be considered the best measure for patients' glycemic status. In this study, glycosylated hemoglobin was reported in the laboratory, as a percentage, and after 8–10 h of fasting by Column chromatography and using a Microlab 300 device and the kit manufactured by Pars Azmoun company in Iran.

2.8. Data analysis

To analyze the data, SPSS 23 was used. The data were reported using descriptive statistical indices such as frequency, frequency percentage, mean, and standard deviation in the form of tables and diagrams. The normal distribution of the data was checked using the Shapiro-Wilk test. To compare treatment groups, paired t-tests, ANOVA, and analysis of covariance and to evaluate of relationship between qualitative variables chi-square and Fisher's exact tests were used. The significance level was considered to be $P < 0.05$.

2.9. Ethics approval and consent to participate

The present study was registered under code no. IR.ARAKMU.REC.1398.255 from the Research Ethics Committee of Arak University of Medical Sciences, Iran. Also, this study has been approved under code no (IRCT20190524043687N1||https://irct.behdasht.gov.ir/trial/44810). in the International Clinical Trials Center of Iran. The researchers of the present study felt committed to the principle of the latest version of the Declaration of Helsinki. Before the intervention, the participants

were informed of the purposes of the study. They were also ensured that the information would be confidential and they were free to withdraw from the project at any stage of the study. All costs (including tests and drugs) were paid by the researchers and no additional costs would be imposed on the participants. Written informed consent forms were also obtained.

3. Results

At first, 102 patients were included in the study, 12 of whom did not meet the inclusion criteria and so were excluded from the study; 2 patients took the medication less than the minimum prescribed dosage, one patient changed the type and dosage of the medication, and 9 patients were not willing to continue due to special and unpleasant taste of the powder. It is interesting to note that about 80 % of the patients who withdrew from the study were excluded from the study in the final weeks of the study and the remaining 20 % in the first week of the study. Finally, the data obtained from 90 patients were analyzed (Fig. 1). The mean age of participants in the intervention group of *Ma'aljobon Aftimouni*, *Ma'aljobon without Aftimoun*, and the placebo group was 46.76 ± 7.34, 48.6 ± 6.90, and 47.16 ± 8.14, respectively.

According to Table 1, there was no significant difference between the three groups in terms of sex, marital status, education, occupation, length of disease, history of taking medications, and physical activities ($P > 0.05$). BMI had no homogeneity among the three groups ($p < 0.05$). A majority of three groups in 18.5–24.5. But in the placebo group, 33.3 % of patients had a BMI <18.5.

Table 2 shows the frequency of side effects. The presence of complications among the groups was not significant (Table 2). Table 3 shows mean ± SD. The mean of post-intervention FBS in *Ma'aljobon Aftimouni* was significantly decreased (134.27 ± 21.79 vs. 152.3 ± 31.37, mean difference 18.03 ± 5.63, 95 % CI: 6.53 to 29.53, $p = 0.003$). The mean of post-intervention HbA1c in both groups, *Ma'aljobon Aftimouni* (7.88 ± 0.77 vs. 8.09 ± 0.73, mean difference 0.21 ± 0.09, 95 % CI: 0.03 to 0.39, $p = 0.031$) and *Ma'aljobon without Aftimoun* was significantly decreased (7.97 ± 0.84 vs. 8.25 ± 0.78, mean difference 0.28 ± 0.08, 95 % CI: 0.11 to 0.45, $p = 0.002$) (Fig. 2)

Results of ANCOVA show statistically significant differences in post-intervention FBS between the three groups when adjusted for pre-intervention FBS and BMI ($P < 0.05$). According to the LSD post-hoc test, the mean of post-intervention FBS in the placebo was significantly different with *Ma'aljobon Aftimouni* ($P < 0.05$) but not *with Ma'aljobon without Aftimoun* ($p > 0.05$). The mean of the post-intervention FBS in the two intervention groups did not show a significant difference ($p > 0.05$) (Table 4).

Also, the Results of ANCOVA show statistically significant differences in post-intervention HbA1c between the three groups when adjusted for pre-intervention HbA1c and BMI ($P < 0.05$).

According to the LSD post-hoc test, the mean of post-intervention HbA1c in the placebo was significantly different with both *Ma'aljobon Aftimouni* and *Ma'aljobon without Aftimoun* ($p < 0.05$). The mean of the post-intervention HbA1c in the two intervention groups did not show a significant difference ($p > 0.05$) (Table 5) (Fig. 3).

4. Discussion

In this study, we examined the effect of *Ma'aljobon* powder alone and in combination with the herb *Cuscuta Reflexa*, compared to a placebo, on blood sugar levels in patients with Type 2 Diabetes. The findings of this study showed that the use of this combination after 8 weeks led to an improvement in glycemic indices in the intervention groups compared to the control group.

In this study, fasting blood sugar levels in the intervention groups were significantly lower than those in the control group. Derosa et al., in

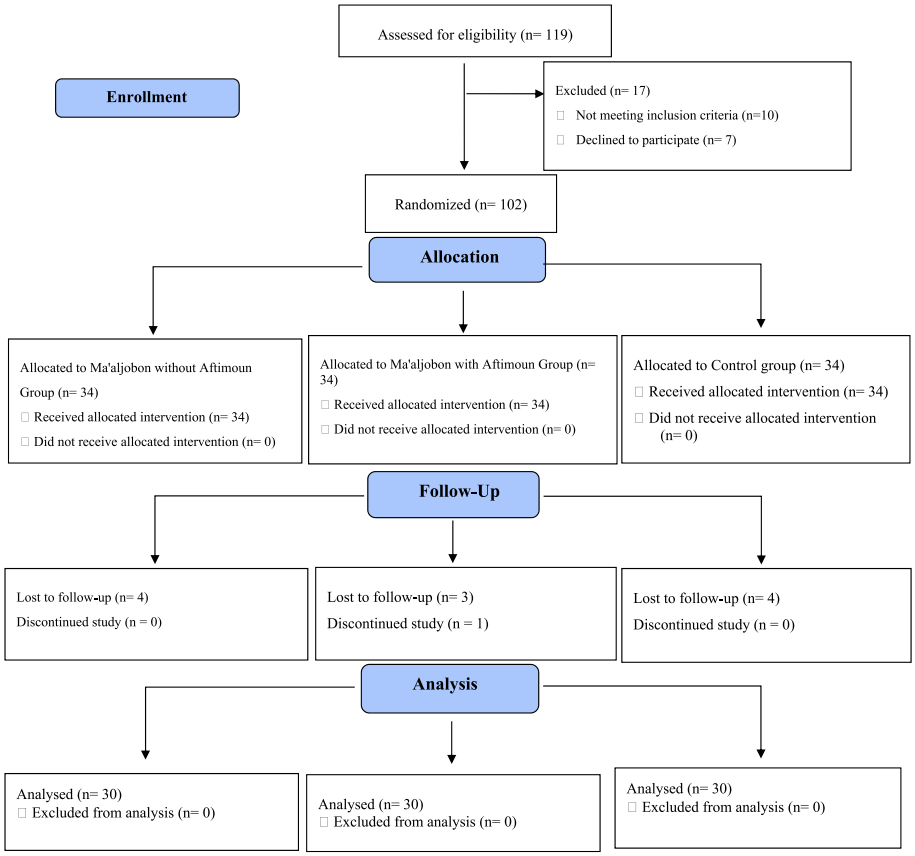

Fig. 1. CONSORT flowchart of the research.

Table 1
Characteristics of patients in three groups.

Variable		Group			
		Ma'aljobon Aftimouni n (%)	*Ma'aljobon without Aftimoun* n (%)	Placebo n (%)	P-value
Age (years) (Mean ± SD)		46.76 ± 7.34	48.6 ± 6.90	47.16 ± 8.14	0.610
Sex	Male	16 (53.3)	16 (53.3)	19 (63.3)	0.774
	Female	14 (46.7)	14 (46.7)	11 (36.7)	
Marital status	Single	4 (13.3)	2 (6.7)	5 (16.7)	0.611
	Married	26 (86.7)	28 (93.3)	25 (83.3)	
Education	Illiterate	3 (10.0)	2 (6.7)	6 (20.0)	0.392
	Elementary school	9 (30.0)	12 (40.0)	9 (30.0)	
	Middle school	8 (26.7)	3 (10.0)	8 (26.7)	
	Diploma	9 (30.0)	10 (33.3)	5 (16.7)	
	Bachelor and above	1 (3.3)	3 (10.0)	2 (6.7)	
Occupation	Housewife	15 (50.0)	12 (40.0)	10 (33.3)	0.561
	Employed	13 (43.3)	16 (53.3)	15 (50.0)	
	Unemployed	2 (6.7)	2 (6.7)	5 (16.7)	
BMI	<18.5	0 (0.0)	2 (6.7)	10 (33.3)	0.003
	18.5–24.9	21 (70.0)	18 (60.0)	15 (50.0)	
	25–34.9	9 (30.0)	10 (33.3)	5 (16.7)	
Length of disease (years)	1–5	10 (33.3)	5 (16.7)	10 (33.3)	0.543
	5–10	10 (33.3)	16 (53.3)	14 (46.7)	
	10–15	7 (23.3)	5 (16.7)	4 (13.3)	
	>15	3 (10.0)	4 (13.3)	2 (6.7)	
Physical activities (minutes)	0	15 (50)	18 (60)	17 (56.7)	0.671
	<30	10 (33.3)	5 (16.7)	8 (26.7)	
	30–60	5 (16.7)	7 (23.3)	5 (16.7)	
Underlying disease	None	12 (40)	16 (53.3)	13 (43.3)	0.946
	Blood pressure	6 (20)	6 (20)	5 (16.7)	
	Blood fat	3 (10)	4 (13.3)	4 (13.3)	
	Heart disease	2 (6.7)	1 (3.3)	2 (6.7)	
	More than one	7 (23.3)	3 (10)	6 (20)	
Drug	Metformin	19 (63.3)	15 (50)	10 (33.3)	0.082
	Glibenclamide	6 (20)	3 (10)	3 (10)	
	Other	3 [(10)	7 (23.3)	8 (26.7)	
	More than one	2 (6.7)	5 (16.7)	9 (30)	

Table 2
Frequency of side effects of patients in three groups.

Side effect	Group			
	Ma'aljobon Aftimouni n (%)	*Ma'aljobon without Aftimouni* n (%)	Placebo n (%)	P-value
No side effect	13 (43.3)	14 (46.7)	13 (43.3)	0.873
Diarrhea	4 (13.3)	2 (6.7)	3 (10)	
Nausea	9 (30)	7 (23.3)	6 (20)	
Blowing	1 (3.3)	1 (3.3)	0 (0.0)	
Diarrhea + Nausea	1 (3.3)	4 (13.3)	3 (10)	
Nausea + Blowing	0 (0.0)	1 (3.3)	1 (3.3)	
Diarrhea + Blowing	2 (6.7)	1 (3.3)	4 (13.3)	

Table 3
Fasting blood sugar levels and HbA1c levels pre and post-intervention in three groups.

Variable		Group		
		Ma'aljobon Aftimouni	*Ma'aljobon without Aftimoun*	Placebo
FBS	pre-intervention	152.3 ± 31.37	142.7 ± 28.43	169.8 ± 40.98
	Post-intervention	134.27 ± 21.79	136.7 ± 25.49	162.9 ± 43.66
Mean difference		18.03 ± 5.63	6.00 ± 5.90	6.90 ± 6.78
95 % Confidence Interval of the mean difference		(6.53, 29.53)	(-6.07, 18.07)	(-6.96, 20.76)
P-value[a]		0.003	0.322	0.325
HbA1c	pre-intervention	8.09 ± 0.73	8.25 ± 0.78	8.11 ± 0.82
	Post-intervention	7.88 ± 0.77	7.97 ± 0.84	8.18 ± 0.70
Mean difference		0.21 ± 0.09	0.28 ± 0.08	−0.07 ± 0.11
95 % Confidence Interval of the mean difference		(0.03, 0.39)	(0.11, 0.45)	(-0.30, 0.15)
P-value[a]		0.031	0.002	0.514

[a] Paired *t*-test.

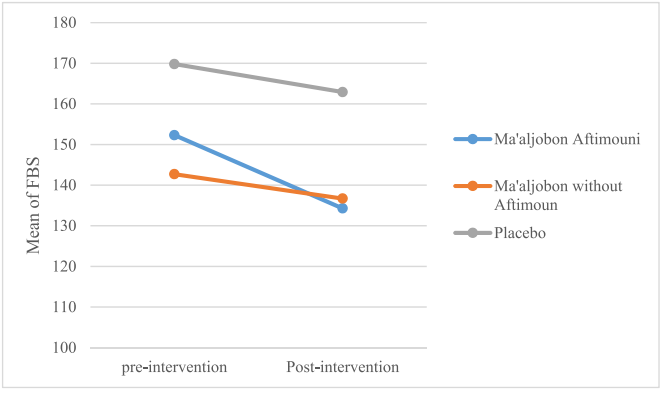

Fig. 2. Fasting blood sugar levels pre and post the intervention in three groups.

Table 4
Results of ANCOVA of post-intervention FBS with adjusting pre-intervention FBS and BMI.

Variable	Sum of Squares	df	Mean Square	F	P-value
Group	3898.81	2	1949.40	2.49	0.082
pre-intervention FBS	19959.23	1	19959.23	25.51	0.0001
BMI	1724.69	2	862.346	1.102	0.341

Table 5
Results of ANCOVA of post-intervention HbA1c with adjusting pre-intervention HbA1c of HbA1c and BMI.

Variable	Sum of Squares	df	Mean Square	F	P-value
Group	1.41	2	0.70	2.84	0.064
pre-intervention HbA1c	29.70	1	29.70	119.88	0.0001
BMI	0.12	2	0.06	0.23	0.793

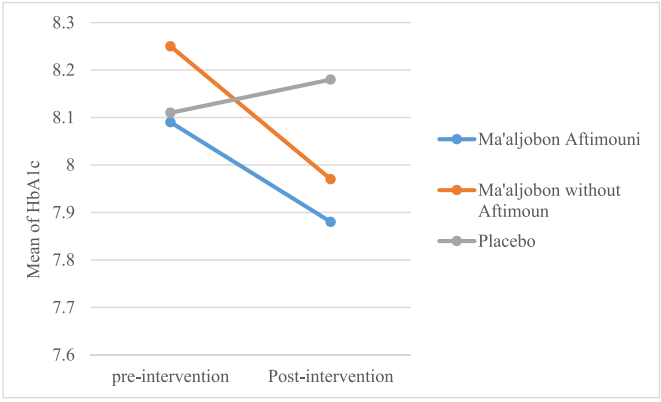

Fig. 3. HbA1c levels pre and post the intervention in three groups.

a similar study, reported a significant reduction in fasting blood glucose in patients with Type 2 Diabetes following the isolated consumption of WPs [1]. Another study also showed that the daily consumption of 15 g of WPs protein over 7 days can reduce the duration of daily hyperglycemia in patients [19]. In the study by Derosa et al., patients in the whey protein isolate group showed significant improvements in lipid profiles and reductions in fasting plasma glucose levels [1]. Jakubowicz et al. demonstrated that the consumption of whey protein before a high glycemic index breakfast led to increased insulin secretion and reduced postprandial blood glucose levels in patients with type 2 diabetes [32]. Watson et al. reported similar findings regarding blood glucose levels in their study [33]. Frid et al., while examining the effect of WPs on insulin secretion and blood sugar levels in patients with Type 2 Diabetes, demonstrated that adding WPs to high glycemic index meals can increase insulin secretion and reduce blood sugar levels, although this difference was not significant at breakfast [20]. However, the results of the research by Gaffney et al. did not report a significant effect of this combination on the blood sugar of patients with Type 2 Diabetes during exercise [3], which contradicts our findings. Possible reasons for this discrepancy could be differences in the composition of the whey protein used and the potential impact of physical exercises on the results of the two studies. Today, the use of complementary medicine for diabetes and hypoglycemic indicators has gained strength. according to studies, the use of essential oils is also one of the other things that can be effective in reducing blood sugar [34].

The data analysis of the current study reported a significant effect of this combination on HbA1c levels in patients. Ma et al., in similar research, showed that although the daily consumption of 25 g of WPs for 4 weeks can reduce blood sugar in Type 2 Diabetes patients, this reduction in HbA1c compared to placebo is not significant; which contradicts our study. Researchers attribute this finding to the short duration of the intervention and the small sample size [22]. Flaim et al., in a study, examined the impact of a type of isolated whey protein, branded as *ProLYOtin*®, on glucose metabolism parameters and oxidative stress in overweight diabetic patients or those with fasting glucose disorders. Their study results did not show a significant effect of this combination on insulin levels, HbA1c, and blood sugar levels of patients at the end of 12 weeks [35]. The findings of Miller et al. also yield a similar result [36]. One potential reason for this discrepancy could be due to the type and amount of WPs compounds produced by different methods [14,16]. The frequency of WPs consumption per day and the duration of the study are other possible reasons for this difference [23]. Also, the timing of WPs consumption in relation to meals may influence the study results through changes in incretin hormone levels [37], as per Iranian traditional medicine, an empty stomach or fasting leads to easier absorption of medication [30]. In our study, patients received the medication on an empty stomach in the morning, which may have a different effect on the glycemic indices of patients compared to studies where this combination was consumed with meals. Nonetheless, our studies did not have some of the limitations of previous studies. In the study by Miller et al., due to the absence of a suitable placebo formulation, the study design was conducted without the use of placebo [36]. A strength of our study was the use of a suitable placebo in the control group. Triple-blind design was another strength of our study. Nevertheless, some studies also support our findings. Watson et al., in their clinical trial on Type 2 Diabetes patients, showed that taking 150 mL of preload containing 17 g of WPs protein and 5 g of guar 15 min before two meals (breakfast and dinner) for 12 weeks is effective in reducing blood sugar and HbA1c in patients [21]. Mortensen et al. also demonstrated that whey hydrolysate and whey isolate, due to their insulinotropic effects, may offer nutritional benefits in the treatment of patients with type 2 diabetes [38]. Pezeshki et al. in their study showed that the use of WPs supplement for 12 weeks is associated with a significant reduction in FBS and HgA1C [39], which aligns with our findings. Several potential mechanisms for the insulinotropic effects of whey protein have been proposed. It seems that the leucine content leads to the stimulation of insulin secretion. Additionally, an increase in the incretin hormone glucagon-like protein-1 (GLP-1) [22] may play a role in delaying gastric emptying [40]. It is also possible that compounds with higher protein content may reduce food intake by creating a feeling of satiety [41]. WPs are composed of biological proteins and amino acids like alpha-lactalbumin, beta-lactoglobulin, lactoferrin, and immunoglobulins [9]. An increase in insulin secretion in β cells of the pancreas following the consumption of the amino acids isoleucine, leucine, and lysine present in WPs has been reported [37].

The results of this study do not show a significant difference from *Cuscuta Reflexa* in the two groups with and without *Ma'aljobon*. This is the first time that *Cuscuta Reflexa* has been measured in a clinical trial for blood sugar in Type 2 Diabetes patients, and past studies have examined its impact on blood sugar in preclinical studies in diabetic mice. Therefore, there is no possibility to compare these findings in human samples with previous findings. However, this combination has been repeatedly studied in various studies in human samples. Firoozabadi et al. have reported effective effects of this herb on patients with major depression [26]. Findings by Parvizi et al., examining the impact of *Cuscuta Reflexa* along with risperidone on cognitive symptoms in patients with schizophrenia, also showed that daily use of 500 mg of processed capsule from this plant for 8 weeks led to a reduction in cognitive disorders and also negative and positive symptoms of patients [24]. The results of another study on major depressive disorder accompanied by anxiety show a positive effect of syrup made from the combination of lavender and *Cuscuta Reflexa* on major depressive disorder with anxiety compared to citalopram [27]. Mehrbani et al., while examining the effect of the combination of whey water and *Cuscuta Reflexa* on adult atopic dermatitis, showed that daily consumption of 30 mg of whey powder (15 mg before breakfast and 15 mg before dinner) and 4 capsules of 500 mg of dried aqueous extract of dodder seeds for 15 days can improve the elasticity and moisture level of the skin [9].

Cusseta Reflexa has played an effective role in controlling blood sugar in diabetic patients in the folk medicine of Bangladesh and has also led to improvements in glycemic indices in animal models. Its insulinotropic effects can be attributed to the phenolic compounds, flavonoids, alkaloids, and tannins present in this plant [4,5].There is also evidence of its antioxidant effects and reduction of oxidative stress associated with its use [42]. Sharma et al. reported the antioxidant and antimicrobial effects of the methanolic extract from the stem of *Cuscuta reflexa* in a study [43]. Mishra et al. also demonstrated that *Cuscuta reflexa Roxb* has the potential to protect liver cells in a murine model and may potentially be used in the treatment of liver disorders [44]. Preclinical studies examining the impact of this plant on mice have reported positive results on the blood sugar levels of diabetic mice [4,28]. For instance, Al-Sultany et al. demonstrated that a dose of 400 mg per kilogram for 60 days was an effective dose for controlling the blood sugar of type 1 diabetic mice [4]. Rahmatullah et al. also found the methanolic

extract of this plant effective in reducing hyperglycemia in mice [29]. Kaur et al., in their investigation of the effects of ethanolic extract of *Cuscuta reflexa* on diet-induced obesity in Wistar rats, demonstrated that treatment with the ethanolic extract of this plant for 6 weeks resulted in a significant reduction in body weight, as well as decreased serum levels of glucose and LDL [45].The study by Mostofa et al. on the impact of *Cuscuta Reflexa* on alloxan-induced diabetic mice showed that consuming this compound at 400 mg per kilogram for 45 days led to a significant reduction in blood glucose levels and HbA1C [5], which contrasts with our findings. This difference in our study results might be due to the dosage used in animal studies compared to ours. Also, inducing diabetes in mice using drugs may yield different results compared to human samples. One study showed that although the methanolic and aqueous extracts of this plant significantly reduced blood glucose in diabetic mice, these effects were not reported in healthy mice [28]. However, obtaining conclusive evidence requires more evidence-based studies.

It should be noted that given the HbA1c range considered for entry into the study and the necessity of using oral diabetic control drugs, generalizing the results of this study to patients with higher HbA1c values or Type 2 Diabetes patients using insulin is not possible. In this study, no serious side effects were reported; however, some patients complained about the unpleasant taste, and some were unwilling to tolerate it, leading to their withdrawal from the study. This finding emphasizes the need to pay attention to flavoring or suitable essence for this compound to ensure its continued use.

The use of fixed doses of WPs protein and the short follow-up period to examine the continuity or temporary effects of the products were some of the limitations of the present study. Since this study was the first clinical trial study that investigated the effect of Cuscuta Reflexa on treating Type 2 Diabetes, the minimum dose was selected according to the previous investigations and fortunately, no side effect was observed. Further studies with larger sample sizes and higher doses may show different results. It is also suggested to conduct more photochemical studies on the plant and extract its chemical compounds. Examining the number of hormones affecting the blood sugar of patients, such as insulin and intestinal hormones (such as PYY, ghrelin, or GIP) may reveal more and more accurate results of the effect of this Persian medicine compound. Since the consumption of this compound was associated in some participants with adverse symptoms such as nausea and bloating, it is suggested to produce this compound in the form of capsules and tablets instead of powder.

5. Conclusion

The findings of this study demonstrated the potential effect of the WPs protein, derived from Persian medicine, on FBS and HbA1c levels in patients with Type 2 Diabetes. However, given the limitations of this study, the long-term effects of Ma'aljobon and its impact on other glycemic indices, such as postprandial glucose and insulin sensitivity, remain unknown. Future research should explore these aspects, especially through studies investigating higher doses of Ma'aljobon over extended periods to assess its long-term efficacy and safety. Additionally, the role of WPs in influencing broader metabolic markers in diabetic patients warrants further investigation to solidify its potential therapeutic benefits.

CRediT authorship contribution statement

Fatemeh Mehrabi: Writing – review & editing, Methodology, Data curation. **Ali Safdari:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Project administration, Investigation, Conceptualization. **Azam Moslemi:** Software, Formal analysis, Data curation. **Mehdi Salehi:** Methodology, Investigation. **Ali Agharazi:** Methodology, Data curation. **Mohammad Reza Rezvanfar:** Validation, Methodology.

Clinical implications

- Incorporating Ma'aljobon Aftimouni into Type 2 Diabetes treatment regimens may offer an additional therapeutic option, potentially improving glycemic control and patient outcomes. Further studies are needed to confirm these findings and explore long-term benefits.

Consent for publication

Not applicable.

Data statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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The present study was approved by the Vice-Chancellor for Research, Arak University of Medical Sciences, Arak, Iran (Ethics code: IR.ARAKMU.REC.1398.255).

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Abbreviations

HbA1c	Glycated Hemoglobin
WPs	Whey proteins
FBS	Fasting blood sugar

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