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Antidiabetic activity and HPLC-PDA profile of herbal formulation in patients with type 2 diabetes: a randomized controlled trial

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The use of herbal medicines is widely common to control blood sugar. This study was performed in the way of a triple-blind clinical trial to study the effects of standardized herbal formulation (*Eryngium billardieri*, *Urtica dioica*, *Trigonella foenum-graecum*, *Abelmoschus esculentus*, *Cinnamomum zeylanicum* and *Rosa canina*) on fasting plasma glucose and Hemoglobin A1c. This placebo controlled trial was performed on 88 patients with type 2 diabetes. Patients were followed up at the beginning and after the end of the 3-months for assessment of fasting plasma glucose (FPG), Hb-A1c, and body mass index (BMI). The intervention group received 200 mg/day herbal formulation extract capsules and the control group received placebo. To standardize the herbal formulation, RP-HPLC-PDA was used. The amount of FPG and Hb-A1c were significantly reduced (p=0.001) in the intervention group compared to the control group; FPG difference=53.20 (95% CI: 34.51, 71.89; p=0.001); Hb-A1c difference=1.60 (95% CI: 1.15, 2.05; p=0.001). It is noteworthy that, no adverse events were observed during the study. According to HPLC analysis, the amount of benzoic acid, rutin, naringenin, gallic acid, caffeic acid, resveratrol, and apigenin (609.6, 265.4, 220.2, 188.4, 164, 109, 29.9 µg/capsule, respectively) was specified in the herbal formulation. The results of this trial indicated that standardized herbal formulation can be effective in reducing FPG and Hb-A1c among patients with type 2 diabetes. It may be used as a dietary or medical supplement to control blood glucose. However, further investigation is suggested.

Keywords: FPG, Hb-A1c, Herbal formulation, Standardization, Type 2 diabetes

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Diabetes mellitus is a chronic metabolic disorder in the endocrine system that could cause many serious consequences[1]. According to the statistics of the World Diabetes Federation in 2017, about 425 million people have diabetes and this figure is expected to reach about 642 million people by 2030 and more than 5 million people in the world die by suffering from diabetes annually. Among the different types of diabetes, the diabetes type 2 is most common and composes 90% of cases. This is due to the increase in obesity, inactivity, and stress in communities[2]. The disease, characterized by hyperglycemia, can lead to micro vascular (neuropathy, nephropathy, and retinopathy) and macro vascular problems (cardiovascular disease) and increase the risk of death in these patients. Although various medications have been proposed to control blood sugar, they have not been able to completely control it, and the side effects of diabetes such as hyperlipidemia and inflammation have not been eliminated and impose huge medical costs on the health system. In 2017, diabetes costs were estimated at $ 327 billion in the United States[3,4]. Moreover, the controller medications have side effects for example, metformin has gastrointestinal side effects and injection of insulin is painful and unpleasant to patients[5]. Therefore, the usage of drugs with low side effects and high efficacy is a necessity. According to the above, it's necessary to find a lower-risk and lower cost treatment to control this common disease.

Medicinal plants as a potential medicine source have long been used to treat patients by local people. Patients prefer them nowadays because they are deemed to be safer than chemical drugs and the other reasons for studying these plants are the universal popularity of herbal medicines, natural products and

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medicinal plants and also the encouragement of the World Health Organization (WHO)[4,6-8]. Among the plants used to treat diabetes by local people in different parts of Iran are *Eryngium billardieri*, *Urtica dioica*, *Trigonella foenum-graecum*, *Abelmoschus esculentus*, *Cinnamomum zeylanicum* and *Rosa canina* separately or a mixture of boiled plant part to control diabetes and the effectiveness of these plants has been specified in previous studies[9-11]. Especially in the west of Iran (Hawraman), a formulation containing a mixture of these plants is used to control diabetes (Hawraman-6).

Therefore, in this study, we conducted a clinical trial with ethical committee consent (IR.UMSHA.REC.1397.299) to evaluate the effectiveness of herbal formulations consisting of *E. billardieri*, *U. dioica*, *T. foenum-graecum*, *A. esculentus*, *C. zeylanicum*, and *R. canina* in control of type 2 diabetes patients. RP-HPLC-PDA was also used to determine the phytochemical profile of the herbal formulation.

Materials and Methods

Preparing of herbal formulation

First, the *E. billardieri* (aerial parts, a voucher specimen 406), *U. dioica* (aerial parts, 127), *T. foenum-graecum* (seed, 181), *A. esculentus* (fruit, 254), *C. zeylanicum* (bark, 334), and *R. canina* (fruit, 408) were gathered from the herbal store and were approved by Mahsa Sedaghat a botanist of the herbarium of the school of pharmacy, Hamadan university of medical sciences (Iran). Then these plants were cut into small pieces and dried in the shade. Based on the use of local people and traditional medicine (boiled), 10 g of each plant part was soaked in 1 liter of water at 70°C and then filtered by Whatman filter paper 12 h later. The final extract was concentrated by rotary evaporator apparatus (Heidolph, Germany) under vacuum conditions at 40°C[12]. According to the extract yield of plants, the extraction process was done for 4.2 kg of plants (700 g of each plant). Finally, the capsules were filled with 200 mg of dried herbals extract and microcrystalline cellulose for treatment and control groups, respectively.

Participants

One hundred Iranian males and females with type 2 diabetes mellitus who were selected from the endocrinology clinic of Shahid Beheshti Hospital related with Hamadan University of Medical Sciences (Hamadan/ Iran), contributed in the study. The inclusion criteria comprised: age of the participants in the study is between 30 and 65 years; clinical diagnosis of T2DM for at least 6 months in participants, Hb-A1c >7%, not dependent on insulin; participants with stable habitual diet and drug treatment (Metformin and Gliclazide) for a period of at least 3 months before the start of the study so that the side effects of this diet and medication changes are not confused with the effects of the drug. All the characteristics of the patients were examined before entering the study and the studied patients had a glomerular filtration rate above 60 and did not have any underlying cardiovascular diseases. The exclusion criteria comprised: patients with liver (liver failure), kidney (GFR <60), gastrointestinal disorder and cardiovascular disease.

Study design

For this trial, first, the ethics committee of Hamadan University of Medical Sciences approved this trial in accordance with the ethical principles of the Declaration of Helsinki (ethical code = IR.UMSHA.REC.1397.299), then its details were recorded and confirmed with code of IRCT20120215009014N229 in Iranian Registry of the clinical trial. Patients signed the consent form after being fully informed of the study. The data of these patients, which included FPG, Hb-A1c, BMI, history of disease and their drugs used, were recorded. This study was a randomized and triple-blind clinical trial (interventional study). The qualified patients were randomly allocated to intervention and control groups by block randomization. For this target, we prepared four pieces of paper, writing on two pieces “I” for “intervention” and on two “P” for “placebo”. The paper sheets were combined, placed in a box, and randomly drawn one at a time for each patient without replacement until all four sheets were drawn. The four paper pieces were then placed back into the box and this operation was repeated until the sample size was reached. The distributions remained hidden throughout the study. For this target, the random allocation was directed by a pharmacist (M. A. S. R.), who was the manager of the trial group, so that neither the study participants nor the result evaluator, who assessed the effect of the interventions, were informed of the administered drugs. As well as, the statistical consultant was uninformed of the trial groups until the data were analyzed and the labels were cracked. The intervention group received 200 mg/day herbal formulation extract capsules and

the other was given the similar amount of microcrystalline cellulose after the main meal with their daily drugs such as Metformin and Sulfonylurea for three months of trial. Both treatment and control groups received identical-looking drug packages marked with the code. All the patients, physicians, researchers, and the analyzer of the results were unaware of the type of drug used by patients until the completion of the project. Patients were evaluated weekly for side effects. Also after the end of the 3-month period, they were also asked to measure their FPG and Hb-A1c in the confirmed laboratory and these results were recorded, statistically analyzed and compared the effectiveness in the two groups of treatment and control. This trial was carried out between September 2019 and March 2020.

Standardization of herbal formulation

RP-HPLC-PDA was used to standardize the herbal formulation (200 mg capsule). Hence, a concentration of 20 mg/mL of formulation in HPLC mobile phase (methanol/water 20/80) was prepared and filtered by 0.45 μm filter to evaluate the amount of phenolic and flavonoids compounds such as gallic acid, quercetin, rutin, naringenin, caffeic acid, resveratrol, ferulic acid, apigenin, and catechin. Then 20 μL of the formulation and different concentrations of phenolic and flavonoid compounds standard (1 to 200 μg/mL) were injected into the HPLC with C18 column (25 × 0.46 cm, 5 μm). The mobile phase consisted of water and methanol, and the elution program was performed in a gradient manner (from 20% methanol to 100% methanol) with a flow rate of 1 ml/min for 65 min in wavelength 200 to 400 nm. The amount of each compound in the herbal capsule was determined by the calibration curve and external standardization method. All experiments were repeated three times[13].

Sample size

Pursuant to the results of the earlier study, the changes in mean ± SD for FBC and Hb-A1c, based on the confidence interval of 99%, $\alpha = 0.05$, and power of 98%, were considered to assess the sample size[14]. Thus, the sample size for each of the intervention and comparison groups will be 44 people. Since there was a possibility that patients to leave the study, we selected 50 patients for each group. After obtaining 150 patients, 50 of them met the inclusion criteria. A diagram showing the study design is shown in Figure 1.

Blood sampling, anthropometric, and biochemical parameters

To evaluate the body mass index factor at the beginning and end of the study according to the subsequent equation: (BMI= weight (kg) / height (m2)), height (m) and weight (kg) were measured. To evaluate the effect of the drug and placebo on serum levels of biochemical factors at the starting point phase and the end of the third month, 8 mL of intravenous blood obtained from each patient after 12-14 h of fasting. These samples were centrifuged at 2500 rpm for 10 min (Tashkhis Gostar Teb, Tehran, Iran). Separate serum samples were used to measure biochemical parameters such as FPG and HbA1c. Measurement of FPG and Hb-A1c was performed by using the standard enzymatic methods and was done by an alpha classic-AT plus auto-analyzer (Tajhizat Sanjesh, Isfahan, Iran) and standard A1C care (SD biosensor, Chungcheongbuk-do South Korea), respectively.

Statistical analysis

All statistical analyses were carried out using Stata software (version 14). Data results were represented as the mean and 95% confidence interval (CI) or number (%). The level of significance was considered as its p-value with $p<0.05$. The independent sample t-test was used for comparing between-group measureable variables. Chi-square was done to analyze qualitative variables. For missing data we performed multiple imputation methods.

Results

After initial screening according to the inclusion and exclusion criteria on 150 patients with T2DM, 50 patients weren't entered into the study due to lack of conditions (not meeting inclusion criteria or declining to participate). The remaining eligible patients were randomly allocated into intervention and control groups equally. Of these, 12 patients discontinued the intervention due to personal reasons, and finally, 88 patients were analyzed. In the two study groups, participants had good compliance with intervention during the follow-up period.

At the beginning of the study, to make ensure the selection of patients is random, we compared the various parameters and different characteristics of patients such as age, BMI, and gender in two treatment and control groups and the results are shown in Table 1. According to Table 1, the two treatments and control groups did not differ significantly.

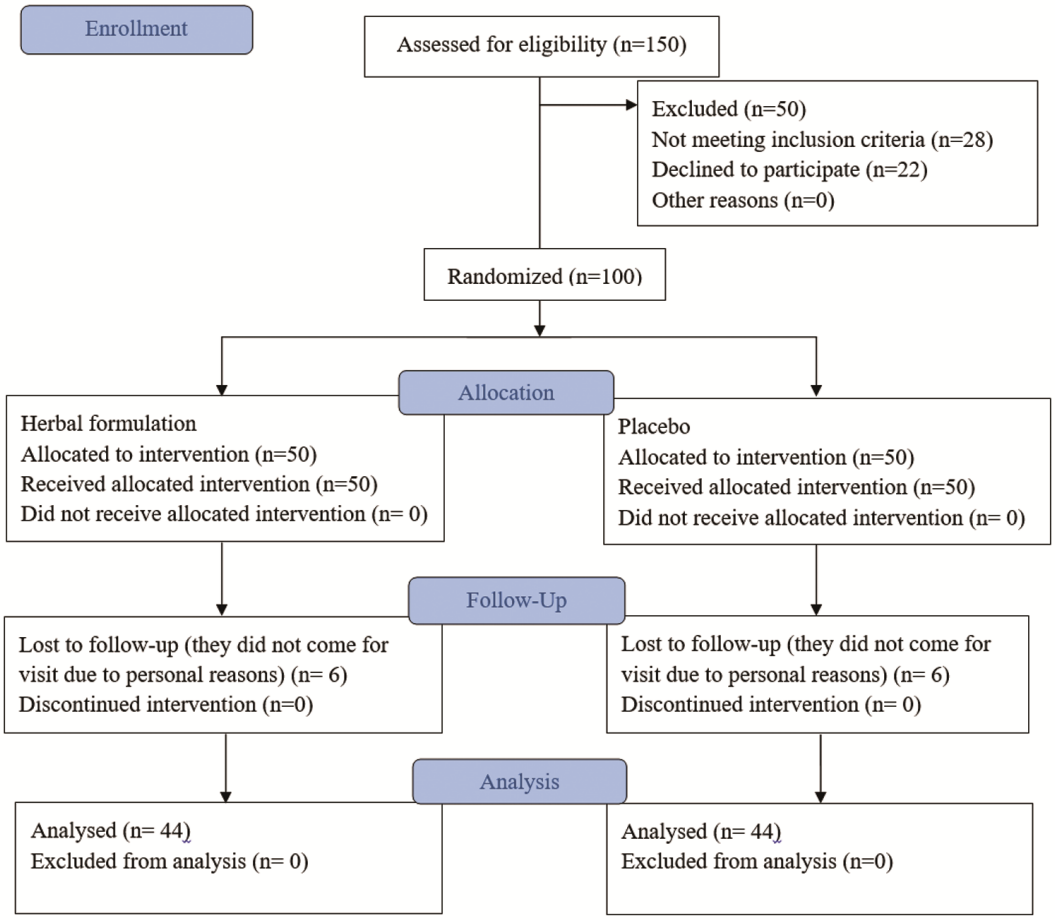

Fig. 1 — Flowchart of patients from enrollment to the end of the study

Table 1 — Baseline characteristics of patients in the intervention and control groups

	Control group		Intervention group		
Continuous variables	Mean	SD	Mean	SD	p-value
Age (yr)	57.61	11.55	59.02	9.73	0.537
Body mass index (kg/m^2)	28.84	4.16	29.54	4.33	0.444
Categorical variables	Number	Percent	Number	Percent	p-value
Sex					0.496
Male	16	36.36	13	29.55	
Female	28	63.64	31	70.45	

After collecting patients 'data including FPG, Hb-A1$_C$, and BMI at the beginning of the trial and after the treatment period, we compared the patients' information and observed the changes of these two parameters in patients of both groups, and the results have been brought in Table 2. Before the intervention, FPG, Hb-A1c, and BMI had no significant difference in the two groups ($p>0.05$). After the intervention, mean differences of FPG (53.20; 95% CI: 34.51, 71.89; $p=0.001$ and Hb-A1c levels (1.60; 95% CI: 1.15, 2.05; $p=0.001$) showed a significant reduction. BMI revealed no significant difference despite the decrease in the intervention group ($p=0.37$). It is noteworthy that, no adverse events were observed during the study. Considering that the drug under study contains herbal ingredients and no specific side effects were reported during previous studies[9-11], also through face-to-face or telephone interviews regarding gastrointestinal symptoms such as nausea, diarrhea, urinary symptoms (urine color change), skin symptoms (itching and hives, etc.) and other cardiac (blood pressure) and respiratory (cough) symptoms were examined and fortunately no complications were observed.

After collecting patients 'data including FPG, Hb-$A1_C$, and BMI at the beginning of the trial and after the treatment period, we compared the patients' information and observed the changes of these two parameters in patients of both groups, and the results have been brought in Table 2. Before the intervention, FPG, Hb-A1c, and BMI had no significant difference in the two groups ($p>0.05$). After the intervention, mean differences of FPG (53.20; 95% CI: 34.51, 71.89; $p=0.001$ and Hb-A1c levels (1.60; 95% CI: 1.15, 2.05; $p=0.001$) showed a significant reduction. BMI revealed no significant difference despite the decrease in the intervention group ($p=0.37$). It is noteworthy that, no adverse events were observed during the study.

It is necessary to determine the chemical profile of herbal medicines, especially in clinical studies. Therefore standardization of herbal formulation capsule was performed according to benzoic acid (609.6 µg), rutin (265.4 µg), naringenin (220.2 µg), gallic acid (188.4 µg), caffeic acid (164 µg), resveratrol (109 µg), and apigenin (29.9 µg) (Table 3, Fig. 2 & Fig. 3). The yield of extract for *E. billardieri*, *U. dioica*, *T. foenum-graecum*, *A. sesculentus*, *C. zeylanicum*, and *R. canina* was 13.2, 14.1, 12.3, 17.2, 13.1 and 15.2 %, respectively. According to herbal formulation the concentration of *E. billardieri*, *U. dioica*, *T. foenum-graecum*, *A. sesculentus*, *C. zeylanicum*, and *R. canina* extract in each capsule were 30.94, 33.34, 28.56, 40.48, 30.96 and 35.72 mg, respectively.

Discussion

In this study, for the first time, the effect of the herbal formulation containing *E. billardieri*, *U. dioica*, *T. foenum-graecum*, *A. esculentus*, *C. zeylanicum*, and *R.canina* are evaluated in type 2 diabetic patients aged 30 to 65 years without any history of kidney, liver, cardiovascular and gastrointestinal disorders. Clinical results of the study displayed that the herbal formulation significantly reduced the mean changes in FPG and Hb-A1c levels at the end of the third month compared to baseline versus the placebo group but BMI did not change significantly despite the reduction.

One of the inclusion criteria was medication therapy by Metformin 1000 mg and sitagliptin 50 mg as baseline characteristics for the selection of the patients. So, the reason for the increase of glycemic factors in the placebo group was that the patients were selected from people who could not be controlled with available drugs.

In many studies, the effectiveness of the plants used in herbal formulations has been already studied in human, animal and laboratory studies, separately and it has been reported the antioxidant properties,

Table 2 — Effect of intervention versus control group on glucose indices and BMI

Groups	Control group, mean (95% CI)	Intervention group, mean (95% CI)	Difference group, mean (95% CI)
Fasting plasma glucose (mg/dL)			
Baseline	176.34 (158.99, 193.68)	172.88 (156.36, 189.39)	3.46 (-20.18, 27.10)
After 3nd month	180.86 (163.87, 197.85)	127.66 (119.32, 135.99)	53.20 (34.51, 71.89)
HbA1c (%)			
Baseline	8.32 (7.89, 8.75)	8.44 (8.10, 8.78)	-0.12 (-0.66, 0.41)
After 3nd month	8.71 (8.32, 9.11)	7.11 (6.88, 7.35)	1.60 (1.15, 2.05)
Body mass index (kg/m^2)			
Baseline	28.85 (27.69, 30.01)	29.31 (28.04, 30.57)	-0.45 (-2.15, 1.24)
After 3nd month	28.88 (27.73, 30.03)	28.14 (26.97, 29.32)	0.73 (-0.88, 2.35)

Table 3 — Phenolic compounds of herbal formulation

Compounds	RT (min)	Absorbance maximum wavelength (nm)	LOD (ng/mL)	LOQ (ng/mL)	RSD (%)	Amount of compounds (µg/capsule)
Gallic acid	6.1	270	500	1000	1.8	188.4
Apigenin	52.4	336	200	500	1.4	29.9
Rutin	32.2	360	20	50	1.3	265.4
Benzoic acid	28.2	250	5	25	1.2	609.6
Caffeic acid	21.7	295	50	100	2.3	164
Naringenin	30.2	295	50	200	1.6	220.2
Resveratrol	33.7	302	50	100	1.4	109.0

RT: Retention time

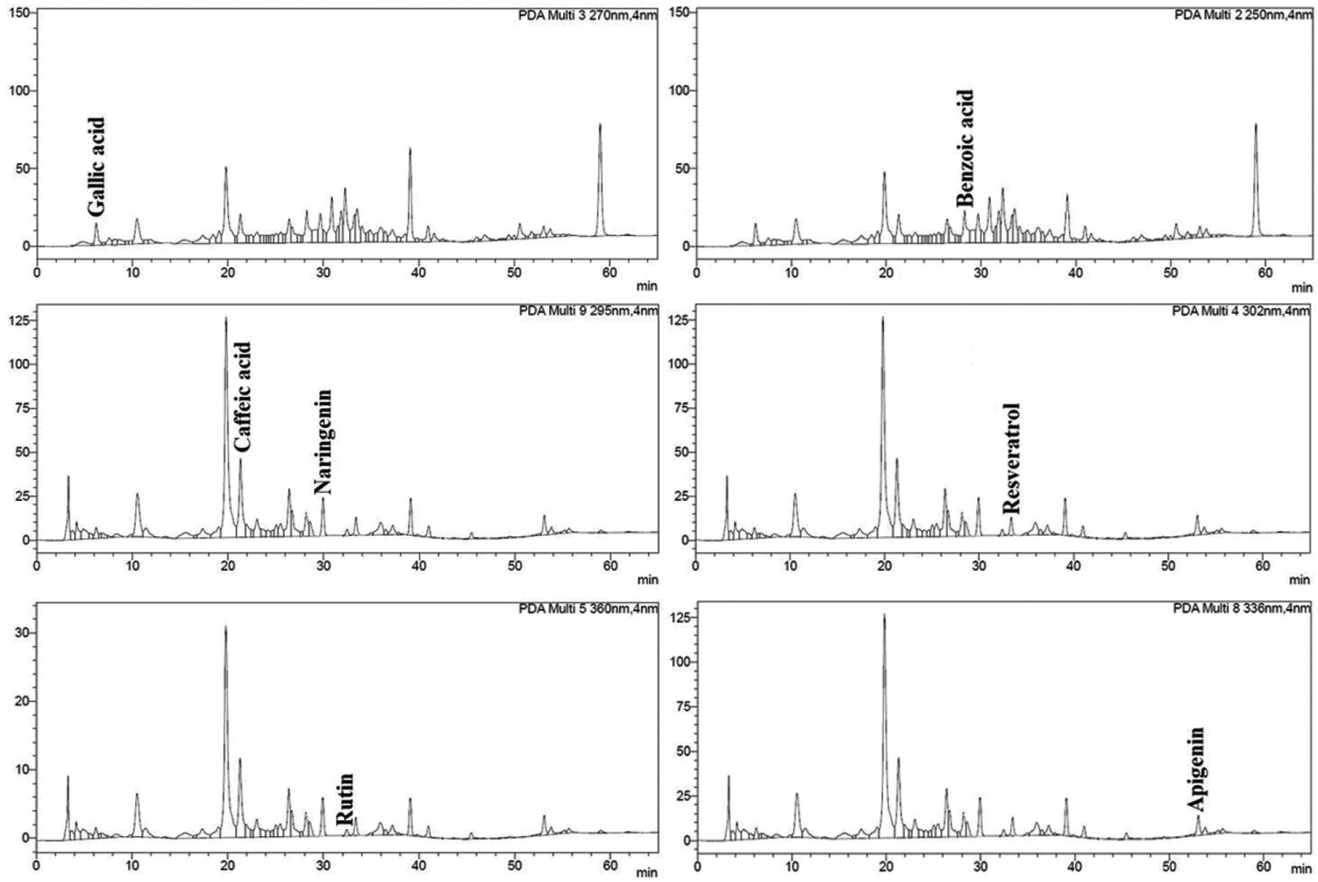

Fig. 2 — HPLC-UV chromatogram of herbal formulation

increased insulin secretion and also increasing sensitivity of cells to insulin in each of them that caused the decreasing of blood glucose, and had significant effects in controlling diabetes[15,16]. For example, the effect of *E. billardieri* was tested on diabetic mice by Pena-Montes *et al.*[16] and the results showed significant effects of hyperglycemia and hypolipidemia and the other study represented that this plant contains a group of active compounds including phenols, flavonoids, tannins and polyphenols[16,17]. *U. dioica* as a combination of our herbal formulation has been used in the past as a blood sugar-lowering agent to treat diabetes mellitus. According to an animal and clinical study, *U. dioica* leaves extract can reduce FPG and Hb-A1c in Streptozocin-diabetic rats and patients with type 2 diabetes significantly, by increasing insulin secretion, PPAR-γ agonistic, and alpha-glucosidase inhibitory effects[16,18].

The anti-diabetic effects of the other plants used in an herbal formulation, such as *T. foenum-graecum*, *A. esculentus*, *C. zeylanicum* have also been proven in animal studies[19-21], so that the hypoglycemic properties of *T. foenum-graecum* were studied and reported by Zarvandi[22]. Also the antioxidant properties of *A. esculentus* and its hypoglycemic properties have been identified in animal and laboratory studies and the decreasing effect of *C. zeylanicum* on Hb-A1c in diabetic patients has been also reported by Paul Crawford[23]. Also, Zare *et al.* has confirmed the affectedness of this plant on 140 type 2 diabetes patients and led to an improvement of glycemic indices such as FPG, 2HPP, HbA1C, Fasting Insulin, and Insulin Resistance[24]. Another study on *R. canina* indicated that taking 750 mg of fruit extract two times a day for 3 months in type 2 diabetic patients reduced FBG significantly.

Hence, many previous studies have shown that each of these plants separately due to its antioxidant properties, increase insulin secretion and also increase the sensitivity of cells to insulin, has considerable effects in the control of diabetes that is corresponding to the results of the present study as well as the use of these plants by local people and traditional medicine[15,21].

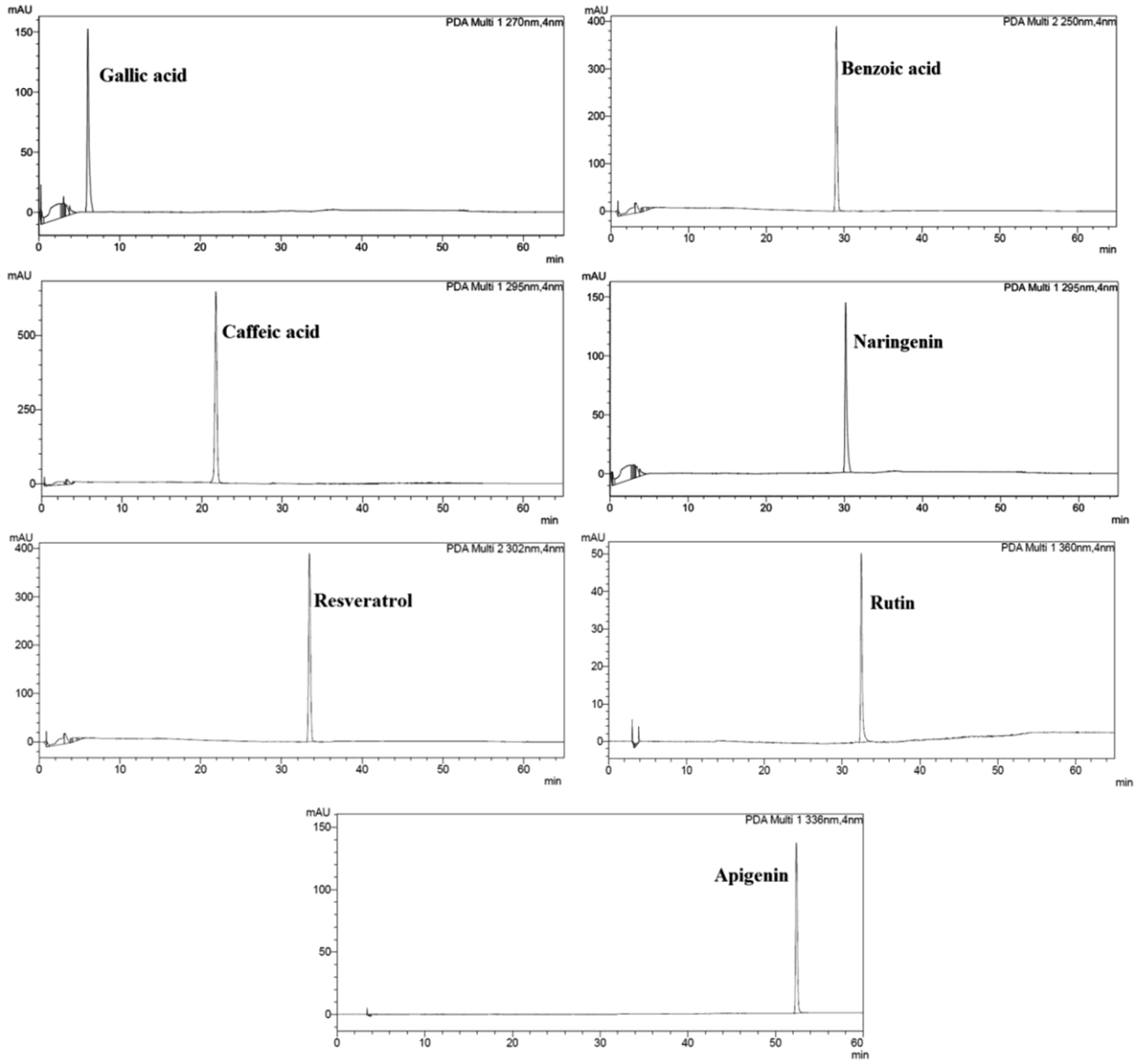

Fig. 3 — HPLC-UV chromatogram of standards

Formulations containing medicinal plants have various effective compounds that the anti-hyperglycemic effects have been researched in some studies. So, herbal formulations are standardized based on one or more constituents. In this study, according to the plants used in herbal formulation and also their constituents that have been reported in previous studies, the standardization was carried out on them based on simple phenolic and flavonoid compounds by RP-HPLC-PDA. The standardization of benzoic acid, rutin, naringenin, gallic acid, caffeic acid, resveratrol, and apigenin compounds in each capsule was 609.6, 265.4, 220.2, 188.4, 164, 109,29.9 µg, respectively.

Several studies have reported the role of some of these compounds present in the herbal formulation in controlling diabetes. Flavonoid compounds have protective effects against diseases such as diabetic nephropathy by moderating different pathways related to oxidative stress, inflammation, and apoptosis in animal models[25]. For example, naringenin increases insulin sensitivity and improves glucose intolerance, or reduces visceral obesity in patients[26-28]. Also, HPLC results showed rutin in the herbal formulation and its reducing effect on blood sugar was studied by Sun *et al.*[29] on diabetic rats. The herbal formulation, in addition to having flavonoids, contains large amounts of simple phenolic acids such

as benzoic acid, which has strong antioxidant properties and due to reducing blood sugar in laboratory tests, its anti-diabetic effects have been proven[30]. The other simple phenolic compound in an herbal formulation is gallic acid its modulating effects on hyperglycemia were shown by Abdel-Moneim *et al*.[31] in diabetic rats. Flavonoids in plant formulations such as naringenin, apigenin, and rutin have antioxidant properties and prevent the destruction of cells by oxidative agents, thus repairing damaged beta cells and increasing the level of insulin secretion from these cells[32]. Moreover, it is necessary for further studies to determine the mechanism of action of herbal formulation.

We had limitations due to ethical issues in this trial that we could not use this drug alone, other limitations were small sample size, low duration time for treatment, and do not measures stress oxidative, lipid profile, other glucose indices, and mechanism of action. However, further investigations to determine the mechanism of action and also characterization of the constituents of the herbal formulation by LC-MS/MS are suggested.

Conclusions

The results of this trial indicated that standardized herbal formulation can be effective in reducing FPG and Hb-A1c among patients with type 2 diabetes with no adverse effects. It may be used as a dietary or medical supplement to control blood glucose. However, further investigations by conducting randomized clinical trials with greater sample sizes and longer treatment periods are suggested.

Acknowledgments

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Conflict of Interest

The authors declare no conflict of interest.

Author Contributions

Conception and design by DD; performed the experiments by MASR, SB, DD; analyzed the data by DD, SB, MASR, JP; wrote the paper, MASR, DD, SB; All authors read and approved the final version of the manuscript.

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Ethical Approval

After obtaining the code of ethics from the ethics committee of the university and obtaining consent from the patients, the study was conducted.

Data Availability

Study data will be available upon request.

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