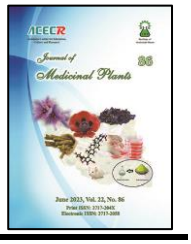
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Research Article

Antihyperglycemic efficacy and safety of AKROPOL, a Persian medicine poly-herbal extract mixture, in the treatment of type 2 diabetic patients: a randomized, double-blind and placebo-controlled clinical trial

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ABSTRACT

Background: In Iran, a variety of medicinal plants are used, either alone or in combination, for the treatment of diabetes mellitus (DM). However, scientific and clinical studies are needed to confirm the safety and efficacy of these medicinal plants. **Objective:** To evaluate the safety and efficacy of AKROPOL, a poly-herbal extract mixture used in Persian medicine, in the treatment of type 2 diabetic patients. **Methods:** Eighty six male and female patients, aged 40-60 years, registered at the Diabetes Clinic Registry of the Baqiyatallah Hospital, in Tehran, Iran, randomly allocated to two groups of 43 each. The patients in AKROPOL group received one capsule (containing 500 mg of poly-herbal extract mixture: chicory, turmeric, nettle, fenugreek and whortleberry) and the patients in placebo group received one capsule (containing 500 mg toast powder) twice a day in addition to their routine anti-diabetic medications for 3 months. The primary outcome measures were HbA1C and FBG (fasting blood glucose) levels, while lipid levels, liver enzymes and renal function tests were secondary outcome measures. **Results:** Compared with the placebo group and baseline, the AKROPOL group showed significant reductions in FBG, HbA1C, total cholesterol, and LDL-C levels. No significant hepatic, renal, gastrointestinal, or other side effects were observed during the study. **Conclusion:** The findings suggest that AKROPOL in addition to anti-diabetic and cholesterol-lowering effects, had no adverse effects in type 2 diabetic patients.

Abbreviations: FBG, Fasting Blood Glucose; HbA1C, Glycated Hemoglobin; TGL, Triglyceride; CT, Cholesterol; HDL-C, High Density Lipoprotein Cholesterol; LDL-C, Low Density Lipoprotein Cholesterol; BUN, Blood Urea Nitrogen; Cr, Creatinine; SGOT, Serum Glutamic-Oxaloacetic Transaminase; SGPT, Serum Glutamic-Pyruvic Transaminase; ALP, Alkaline Phosphatase; SD, Standard Deviation

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1. Introduction

Diabetes Mellitus (DM) and its associated complications pose a significant medical challenge worldwide [1]. Type 2 diabetes mellitus (T2DM) is a chronic metabolic disease with multifactorial origins and accounts for over 90 % of DM cases. In T2DM, there are many disorders, including decreased insulin secretion, decreased glucagon secretion, increased glucose production in the liver, insulin resistance, lipid metabolism disorders, altered intestinal microbiome and impaired glucose uptake in peripheral tissues, which lead to increased blood glucose in diabetic patients [2-3].

Although classical anti-diabetic medications are considered the first-line treatment options for T2DM, practically they cannot target all of the above markers of diabetes [4-5].

Currently, oral hypoglycemic drugs such as sulfonylureas, biguanides, thiazolidinediones, and alpha-glucosidase inhibitors are among the most commonly prescribed drugs for the treatment of diabetes. However, these drugs can produce side effects like digestive disorders, malabsorption of vitamin B12, overeating, weight gain, and impotence, and have limited efficacy [6-10]. Consequently, the global demand for anti-diabetic herbal remedies has surged in recent years [11-13].

The AKROPOL combination comprising *Cichorium intybus* L. (chicory), *Curcuma longa* L. (turmeric), *Urtica dioica* L. (nettle), *Trigonella foenum-graecum* L. (fenugreek) and *Vaccinium arctostaphylos* L. (whortleberry) has been used in the Persian medicine to treat DM. The longstanding traditional use of these herbs, alone or in combination, for controlling DM may testify to their safety and efficacy [14-17]. Furthermore, these herbs have demonstrated anti-diabetic effects in the animal models of DM [18-22]. Clinical studies have also reported the anti-hyperglycemic efficacy and safety of each individual plant in the AKROPOL combination [23-27].

Despite experimental and clinical studies reporting the anti-diabetic efficacy and safety of each plant in this poly-herbal formulation, no clinical trial has yet reported the anti-diabetic efficacy and safety of the AKROPOL combination. Therefore, this study was conducted to evaluate the clinical anti-hyperglycemic efficacy and safety of the AKROPOL in patients with type 2 diabetes who were already under treatment with classical medications.

2. Materials and Methods

2.1. Plant Materials and Sources

Cichorium intybus L. (3026 IMPH) and *Urtica dioica* L. (744 IMPH) (aerial parts) were collected from Alamut region (Ghazvin province, Iran), and *Vaccinium arctostaphylos* L. (1439 IMPH) (fruits) was collected from Asalem to Khalkhal region (Guilan province, Iran. *Curcuma longa* L. (turmeric rhizomes) and *Trigonella foenum-graecum* L. (fenugreek seeds) were purchased from the local market. The collected plants were dried in the shade at room temperature and sent to the Institute of Medicinal Plants Herbarium for botanical identification and archiving.

2.2. Standardization of the AKROPOL extract

The AKROPOL poly-herbal extract mixture was standardized by measuring its flavonoid and phenolic contents. The flavonoid content of the extract was determined using a previously developed colorimetric assay in the laboratory of the Pharmacognosy Department at the Institute of Medicinal Plants [28]. The total phenol content was measured using the Folin and Ciocalteu's method [29].

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2.3. Preparation of the AKROPOL and placebo capsules

The dried plant materials were mixed, crushed and extracted with 70% hydro-alcoholic solvent. The extract was then dried to a powder using spray drying apparatus. Five hundred milligrams of the herbal extract powder was filled into each hard gelatin capsule with no added materials. Similarly, 500 mg toast powder filled capsules were prepared identically as placebo. The AKROPOL and placebo hard gelatin capsules were prepared in the Institute of Medicinal Plants and packed into coded packages with identical appearance.

2.4. Clinical trial

2.4.1. Sample size

A total of 86 eligible Iranian male and female outpatients completed the trial with 43 patients in each group. The sample size was calculated to measure 30 mg/dL difference of fasting blood glucose levels between the groups, with a type I error = 0.05 and power of 80 % [30].

2.4.2. Participants

Between May 1st and December1st 2021, 86 Iranian male and female type 2 diabetic patients aged 40 to 60 years who had medical records in the Diabetes Clinic of Baqiyatallah Hospital and regularly attended this clinic to follow up their diabetes treatment, completed the trial. The inclusion criteria were type 2 diabetic patients aged 40 to 60 years with fasting blood glucose levels between 130 to 180 mg/dL and blood glycosylated hemoglobin levels between 7.5 to 8.5 percent, under standard anti-hyperglycemic drug therapy with no change in drug doses in the past 2 months. The exclusion criteria were patients with type 1 diabetes and neurologic, renal, hepatic, cardiovascular and other chronic diseases.

2.4.3. Randomization, blinding and allocation concealment

Out of 118 patients screened, 32 patients did not meet the inclusion criteria and were excluded from the study. Eighty six patients (43 patients in each group) completed the trial (Fig. 1). The study was designed as a randomized double-blind placebo-controlled two-arm clinical trial using a parallel design with a 1:1 allocation ratio. Block randomization with computer-generated random numbers and sequentially numbered containers each representing a block consisting of two patients, were used for AKROPOL/placebo allocation. The AKROPOL and placebo capsules and containers had the same shape, color, and size, and thus, the physicians, researchers, statisticians, and patients were all blinded to the allocation of treatments.

2.4.4. Interventions and outcomes

Patients were advised to take one capsule of AKROPOL or placebo two times daily after meal in addition to their previously used medications without changing the doses ordered by the internists. The 1000 mg dosage was selected according to the dose used by herbalists. Additionally, patients were advised not to start taking any herbal anti-diabetic except AKROPOL or new anti-diabetic medications, nor to change their diet regimen or exercise. Before and after 3 months of intervention, patients were evaluated for fasting blood glucose (FBG) and glycated hemoglobin (HbA1C) as primary outcome measures and total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C) and triglyceride (TGL) blood levels as secondary outcome measures. To evaluate the safety of AKROPOLL, indices such as serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), alkaline

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phosphatase (ALP), blood urea nitrogen (BUN) and creatinine (Cr) blood levels were measured as secondary outcome measures. Patients were asked to check for FBG drop or increase at home once a week for first month and then every two weeks until the end of the study.

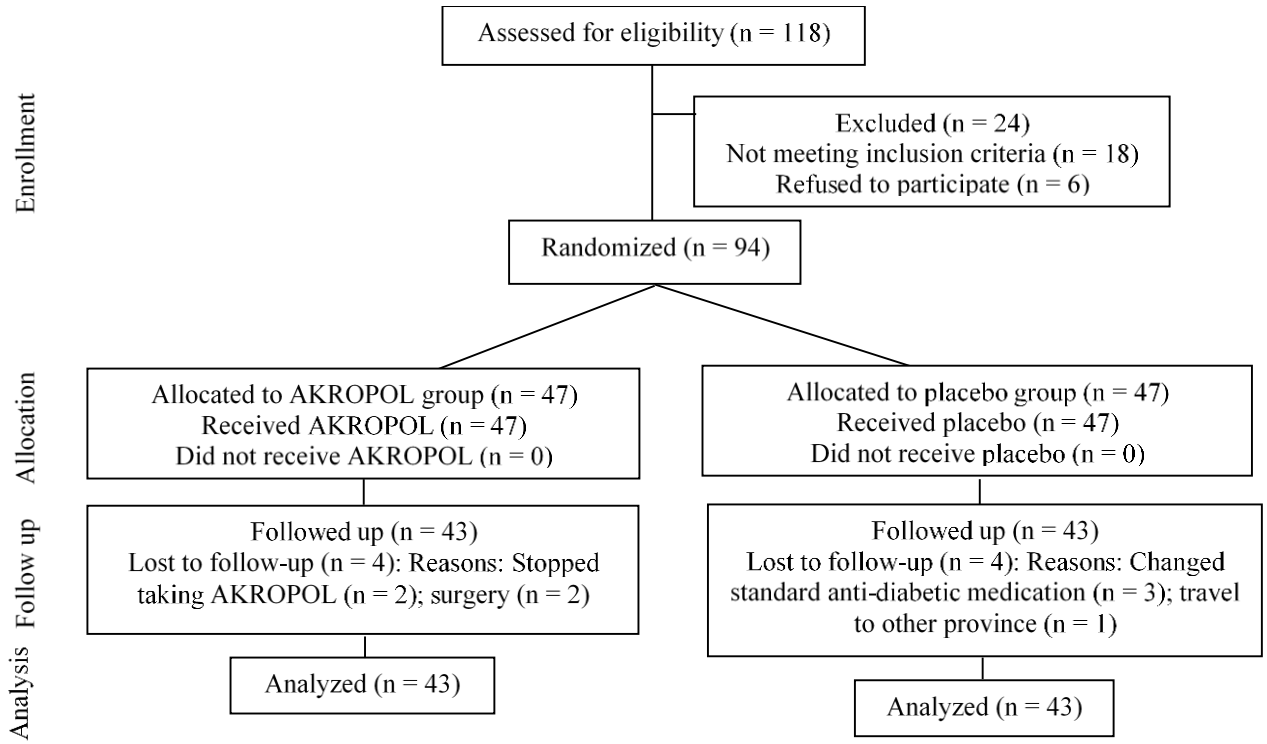


Fig. 1. The 3 months flow up CONSORT diagram of the trial

2.4.5. Assessment of adverse effects

Patients were instructed to promptly report any abnormal condition to their physician during the study.

2.4.6. Ethical considerations

The study protocol abided by the ethical principles outlined in the Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects [31], and was approved by the Medical Ethics Committee of the Ebne–Sina Institute of the Iranian Academic Centre for Education, Culture and Research (Tehran, Iran) (approval code: IR.ACECR. Avicena.REC.1396.33; approval date: 2018-01-16). The trial was registered in the Iranian Registry of Clinical Trials (registration ID: IRCT20080901001157N14). All participants signed a written informed consent prior to enrolment.

2.4.7. Statistical methods

Statistical analysis was performed using the SPSS version 17.0 (SPSS Inc., IBM Corporation, Chicago, IL, USA) with Chi-squared test and Student's t- test. P-values less than 0.05 were considered statistically significant. The data were analyzed using intention- to-treat method.

3. Results

The poly-herbal dried extract was standardized by determination of total flavonoid and phenolic contents as main components. The total flavonoid content was found to be 161.48 ± 4.12 mg rutin equivalents per gram and total phenolic content of the extract was 85.54 ± 3.62 mg gallic acid per gram.

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A total of 86 male and female volunteers with type 2 diabetes, 62.7 % female and 37.3 % male, completed the study. Of these, 43 patients took AKROPOL and 43 took placebo. Eight patients, 4 from AKROPOL group and 4 from placebo group were lost to follow-up (Fig. 1). There was no significant difference between the demographic characteristics of the patients in the two groups (Table 1).

The laboratory glycemic and lipid data at the baseline and endpoint in the herbal and placebo groups are presented in the Table 2. The data analysis showed significant decrease of FBG, HbA1C, TC and LDL-C at the end of the study in the AKROPOL group compared with the baseline (P = 0.000, P = 0.005, P = 0.001 and P = 0.000, respectively).

Furthermore, statistically significant decrease was observed in the FBG, HbA1C, TC and LDL-C levels at the end of the study in the AKROPOL group compared with placebo (P = 0.000, P = 0.000, P = 0.001 and P = 0.007, respectively). As regards other lipids (TGL and HDL-C), the data indicated that no statistically significant differences were observed at the endpoint between groups and also compared with the baseline.

Evaluation of laboratory data in both groups showed that no significant changes existed in the levels of kidney and liver blood parameters, indicating the interventions' safety at the end of the study (Table 3). AKROPOL and placebo did not have any side effect on the kidneys and liver, and the patients did not report any side effect.

Table 1. Demographic characteristics of the patients in the two groups

	AKROPOL (mean ± SD)	**Placebo (mean ± SD)**	**P**
Age (years)	54.8 ± 6.2	53.8 ± 5.72	0.447[a]
Gender (male/female)	40 % (20)/60 % (30)	46 % (23)/(27) 54 %	0.163[b]
Duration of disease (years)	6.46 ± 2.83	7.38 ± 3.01	0.153[c]

[a] P-value based on independent *t*-test; [b] P-value based on Chi-squared test; [c] P-value based on Mann-Whitney U test. Values are presented as mean ± standard deviation.
P < 0.05 was considered statistically significant (paired t-test and Chi-squared test).

Table 2. Glycemic and lipid blood levels at baseline and endpoint in AKROPOL and placebo groups

Test Type	**Time**	**AKROPOL (mean ± SD)**	**Placebo (mean ± SD)**	**P Between AKROPOL and placebo groups at endpoint**
FBG (mg/dL)	Before	175.26 ± 20.88	172.53 ± 24.63	0.590
	After	146.85 ± 27.43	172.09 ± 38.83	0.000
	P	0.005	0.934	
HbA1C (%)	Before	8.34 ± 0.88	8.38 ± 0.62	0.771
	After	7.93 ± 0.79	8.61 ± 0.96	0.000
	P	0.000	0.070	
TGL (mg/dL)	Before	168.74 ± 69.32	159.30 ± 48.25	0.478
	After	159.23 ± 48.67	155.37 ± 47.95	0.682
	P	0.296	0.567	

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Table 2. Glycemic and lipid blood levels at baseline and endpoint in AKROPOL and placebo groups (Continued)

Test Type	Time	AKROPOL (mean ± SD)	Placebo (mean ± SD)	P Between AKROPOL and placebo groups at endpoint
	P	0.296	0.567	
TC (mg/dL)	Before	188.88 ± 27.54	180.81 ± 27.25	0.164
	After	163.18 ± 34.86	185.41 ± 25.03	0.001
	P	0.000	0.133	
HDL-C (mg/dL)	Before	47.09 ± 6.61	44.97 ± 6.65	0.125
	After	46.13 ± 6.61	46.62 ± 8.05	0.823
	P	0.300	0.137	
LDL-C (mg/dL)	Before	136.25 ± 23.64	129.02 ± 24.24	0.156
	After	114.30 ± 30.57	130.83 ± 21.75	0.007
	P	0.000	0.493	

FBG: fasting blood glucose; HbA1C: glycated hemoglobin; TGL: triglyceride; TC: total cholesterol; HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; SD: standard deviation.
**P*-value by paired and unpaired t-tests.

Table 3. Blood levels of renal and hepatic parameters

Test Type	Time	AKROPOL (mean ± SD)	Placebo (mean ± SD)	*P* Between AKROPOL and placebo groups at endpoint
BUN (mg/dL)	Before	23.54 ± 5.24	24.64 ± 4.67	0.340
	After	22.02 ± 4.78	23.44 ± 5.68	0.259
	P	0.071	0.229	
Cr (mg/dL)	Before	1.00 ± 0.15	0.95 ± 0.11	0.089
	After	0.93 ± 0.23	0.96 ± 0.11	0.493
	P	0.076	0.219	
SGPT (U/L)	Before	32.16 ± 12.11	30.97 ± 15.28	0.511
	After	30.16 ± 7.14	32.25 ± 13.64	0.560
	P	0.143	0.235	
SGOT (U/L)	Before	32.00 ± 8.56	29.16 ± 9.68	0.175
	After	29.48 ± 9.41	31.25 ± 9.72	0.329
	P	0.074	0.176	
ALP (U/L)	Before	152.79 ± 18.54	150.32 ± 18.97	0.546
	After	146.88 ± 18.27	149.46 ± 17.75	0.500
	P	0.147	0.709	

BUN: blood urea nitrogen; Cr: creatinine; SGOT: serum glutamic-oxaloacetic transaminase; SGPT: serum glutamic-pyruvic transaminase; ALP: alkaline phosphatase; SD: standard deviation.
*P -value by paired and unpaired t-tests.

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4. Discussion

The present study suggests that treatment of type 2 diabetic patients who are on conventional oral anti-hyperglycemic medications, with the anti-diabetic AKROPOL formula consisting of chicory, turmeric, nettle, fenugreek and whortleberry extracts is superior to placebo in reducing FBG, HbA1C, TC and LDL-C levels. The AKROPOL formula was well tolerated and safe. However, our study had limitations, such as lack of monitoring of the patients' physical activity and diet, although all patients were requested not to change their physical activity and diet during the study period. Furthermore, short treatment duration and lack of comparison of the results obtained in the present study with any of the plants alone in similar conditions were other shortcomings of this study. The results of this study are not applicable to patients with severe diabetes or insulin users because they were excluded from the study.

Several mechanisms may be suggested for the anti-hyperglycemic effect of the AKROPOL, given that each plant in this combination is used in Persian medicine for the treatment of diabetes and undoubtedly, any anti-diabetic effect observed from this combination is related to the combined effects of the extracts that make up this mixture.

Considering chicory as one of the ingredients of the AKROPOL, in line with the present study, its anti-diabetic effect with the daily dose of 10g of chicory for two months has been reported in human clinical studies [32]. In another clinical trial, intake of 30 g of dried chicory root by subjects at risk for type 2 diabetes had beneficial effects on bowel function and glycemic control [23]. The proposed anti-hyperglycemic mechanisms were improvement in bowel function, increased insulin levels and sensitivity, and improvement of glucose metabolism as well as increase of glucose uptake into muscle cells [23, 33-35]. Turmeric, another ingredient of the AKROPOL, showed anti-diabetic effect in clinical studies. In one study, 2 grams of turmeric powder per day was given to patients with type 2 diabetic as an adjunct for 4 weeks. The findings showed significant improvement in diabetes-related factors as well as improvement of oxidative stress, dyslipidemia and inflammation in type 2 diabetes [36]. In another study nano-curcumin intake for 12 weeks had beneficial effects on the metabolic profile in diabetic patients [37].

In an experimental study, it has been reported that the anti-hyperglycemic effects of turmeric and its principal constituent, curcumin, may be due to improvement of pancreatic β-cell function and insulin secretion, and reduction of insulin resistance, in addition to increased peripheral glucose and fatty acid uptake [19, 38-40].

Nettle is another ingredient of this formulation that is used in the Persian medicine for the treatment of diabetes. The efficacy of nettle extract 1500 mg daily for 3 months in the treatment of type 2 diabetic patients has been reported in previous studies [25, 41]. Although the anti-diabetic mechanism of nettle is not known, in an animal study it has been reported that its antidiabetic effect may be due to decreasing insulin resistance, improved pancreatic β-cell function and increasing insulin sensitivity and blood insulin level [42]. In another experimental study, the blood glucose lowering effect of the nettle extract was due to the enhancement of insulin secretion by the Langerhans Islets [43], Furthermore, the antioxidant properties of nettle has been reported

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to be an important factor in preventing streptozotocin-induced neurotoxicity and nephropathy in diabetic rats [44].

Fenugreek is a medicinal plant widely used in Persian medicine for the treatment of diabetes, and it is another ingredient in this combination. Consistent with our findings, a daily dose of 2 g of fenugreek seed extract for 12 weeks has shown beneficial effects in diabetic patients [26, 45]. The antidiabetic mechanism of fenugreek may be increasing blood insulin levels and reducing insulin resistance [46].

Whortleberry, another ingredient in this study formulation, has shown positive anti-diabetic and anti-hyperlipidemic effects with daily dose of 1500 mg of the fruit extract in clinical studies [27, 47, 48]. This effect is believed to be due to its potent inhibitory activity on the pancreatic α-amylase activity [49]. In addition, its anti-diabetic mechanism may be due to its phenolic acids and flavonoids, including quercetin and anthocyanins, which inhibit insulin resistance and pancreas beta-cell apoptosis [50-51]. Overall, flavonoids and other phenolic compounds identified in the AKROPOL may contribute to its anti-hyperglycemic and anti-dyslipidemic effects.

The strengths of this study lie in its documentation of the efficacy, safety and effective dose of this herbal extract mixture. In Persian medicine, the AKROPOL extract is used based on experience without evidence-based knowledge of the precise dose, efficacy and side effects, leading some physicians to distrust it and forbid its use by patients. This study can change the physicians' views and enhance their willingness to prescribe it. Furthermore, the antidiabetic efficacy and safety of AKROPOL extract indicate synergistic anti-diabetic effects of plants with different mechanisms and reduction of side effects due to the lower dose of mixed plants compared to single herbal therapy.

5. Conclusion

The results of the present study provide additional evidence of the efficacy, safety and dose of the AKROPOL mixture (chicory, turmeric, nettle, fenugreek and whortleberry) as a supplement in the treatment of patients with type 2 diabetes. The findings of this study show that short-term use of this formulation, in addition to anti-diabetic and cholesterol-lowering effects, has no adverse effects. It is suggested that in the future, a larger multi-center study be conducted on this polyherbal mixture with more patients and longer duration and to further evaluate its efficacy and safety in higher doses.

Author contributions

H.F.H conceived and designed research. K.M. and M.S. collected data. S.K. analyzed data. B.F. and S.M.M. wrote the manuscript, revised and approved the final draft. M.A. collected and identified herbs. N.K., M.S.H. and R.M. supervised and conducted the clinical trial.

All authors have read and approved the final manuscript. All data were generated in-house and no paper mill was used.

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Conflicts of interest

We wish to confirm that there are no known conflicts of interests associated with this publication.

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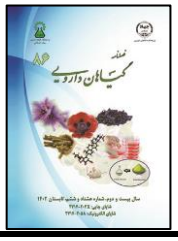
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مقاله تحقیقاتی

اثر کاهش‌دهنده گلوکز خون و ایمنی آکروپل، یک مخلوط عصاره‌های گیاهی طب ایرانی در درمان بیماران دیابتی نوع ۲: کارآزمایی بالینی تصادفی دوسوکور و کنترل شده با دارونما

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اطلاعات مقاله

گل‌واژگان:
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طب ایرانی
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داروی گیاهی

چکیده

مقدمه: گیاهان دارویی زیادی به تنهایی یا به صورت ترکیبی در درمان بسیاری از بیماری‌ها از جمله دیابت در ایران بکار می‌روند. مطالعات علمی و بالینی روی این گیاهان دارویی برای تایید اثربخشی و ایمنی آنها ضروری است. **هدف:** بررسی اثربخشی و ایمنی ترکیبی از عصاره‌های گیاهان دارویی به نام آکروپل مورد استفاده در طب ایرانی در درمان بیماران دیابتی نوع ۲. **روش بررسی:** تعداد ۸۶ بیمار آقا و خانم ۴۰ تا ۶۰ ساله پذیرش شده در کلینیک دیابت بیمارستان بقیه‌الله در شهر تهران، ایران در دو گروه هر کدام ۴۳ نفر کارآزمایی را به پایان رساندند. گروه آکروپل روزانه ۲ کپسول (حاوی ۵۰۰ میلی‌گرم مخلوط عصاره گیاهان شامل: کاسنی، زردچوبه، گزنه، شنبلیله و قره قاط) و گروه دارونما روزانه ۲ کپسول (حاوی ۵۰۰ میلی‌گرم پودر نان سوخاری) علاوه بر داروهای معمول ضد دیابت به مدت ۳ ماه دریافت نمودند. نمونه‌های خونی ۱۲ ساعت ناشتا در شروع و پایان مطالعه جهت تعیین سطوح گلوکز ناشتا و هموگلوبین گلیکوزیله به عنوان معیارهای اصلی و چربی‌های خون، آنزیم‌های کبدی و آزمایش‌های عملکرد کلیه به عنوان معیارهای ثانویه جمع‌آوری گردید. **نتایج:** سطوح خونی گلوکز ناشتا، هموگلوبین گلیکوزیله، کلسترول تام و LDL-C در گروه آکروپل در مقایسه با دارونما و شروع مطالعه به طور معنی‌داری کاهش یافتند. هیچ‌گونه عوارض جانبی کبدی، کلیوی، گوارشی و سایر عوارض در طی مطالعه مشاهده نگردید. **نتیجه‌گیری:** یافته‌ها حاکی از آن است که AKROPOL در کاهش سطح گلوکز، کلسترول تام و LDL-C خون در بیماران دیابتی نوع ۲ بدون ایجاد عوارض جانبی مؤثر است.

مخففها: FBG، قند خون ناشتا؛ HbA1C، هموگلوبین گلیکوزیله؛ TGL، تری گلیسیرید؛ TC، کلسترول تام؛ HDL-C، لیپوپروتئین-کلسترول با چگالی بالا؛ LDL-C، لیپوپروتئین-کلسترول با چگالی کم؛ BUN، نیتروژن اوره خون؛ Cr، کراتینین؛ SGOT، گلوتامیک-اگزالواستیک ترانس آمیناز سرم؛ SGPT، گلوتامیک-پیرورویک ترانس آمیناز سرم؛ ALP، آلکالین فسفاتاز؛ SD، انحراف معیار

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