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Original Article

Effects of Ginseng Extract on Chemerin, Apelin and Glycemic Biomarkers in Type 2 Diabetic Patients

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Abstract

Background: This study aimed to investigate the effect of a six-week intervention of ginseng extract (300 mg) on new adipocytokines levels, including chemerin, apelin, and glycemic biomarkers in patients with type 2 diabetes.

Methods: The study was conducted on forty-eight patients with type 2 diabetes. The participants were randomly divided into two groups: ginseng extract (n=24) and placebo (n=24).

Results: At the end of the study in the ginseng group, fasting blood glucose ($P<0.01$), and fasting insulin ($P<0.05$) showed a significant reduction compared to the baseline. No significant difference was seen in levels of apelin and chemerin between the two groups.

Conclusion: This study showed that short-term administration of ginseng extract does not have a significant effect on serum levels of apelin and chemerin, but it can improve fasting glucose and fasting insulin in patients with type 2 diabetes.

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Introduction

Diabetes mellitus, especially type 2 diabetes mellitus (T2DM) is known as one of the most common metabolic diseases in developed and developing countries. It is estimated that more than 366 million

people worldwide in 2030 will be suffering from type2 diabetes (1). Studies have reported the prevalence of diabetes in Iran from 9.9 to 13.6% (2, 3). During the five years, trend of DM publications increased with a growth rate of 22.5% for world and 23.4% in Iran (4).

A significant relationship exists between adipose tissue, insulin resistance and diabetes type 2. Fat tissue plays a role in the inflammatory status and insulin resistance by releasing a wide variety of hormones and adipokines (5). Chemerin and apelin are two recently discovered adipokines (6, 7). Recent studies have reported high levels of chemerin in people with type 2 diabetes (8). Chemerin also associated with complications of diabetes, such as nephropathy and cardiovascular complications (9, 10). High serum concentrations of apelin have been reported in obese and hyperinsulinemic people (11). On the other hand, the potential role of apelin in the treatment of type 2 diabetes has been mentioned in recent studies (12).

Despite the investigation and identification to provide many types of hypoglycemic drugs, there are no definitive treatment protocols exist for the treatment of type 2 diabetes, yet. In addition, there are the numerous reports of side effects (13). The use of complementary and alternative medicine in recent years has been widely welcomed by the public. In this context, ginseng is known as one of the most popular and best-selling herbs in the world, which have been used in Asian countries during earlier years (14). Various properties of ginseng, including anti-inflammatory, anti-obesity, anti-cancer, antioxidant and vasodilation have been identified and reported in several studies (15-18). In addition, ginseng is considered as a medicinal plant to improve the clinical status in patients with type 2 diabetes. Many animal and human studies have shown that ginseng can have hypoglycemic effects in patients with type 2 diabetes by a variety of mechanisms, including an increase in the sensitivity of tissues to insulin (19, 20).

However, the review of clinical studies conducted shows that evidence of the effects of ginseng on blood sugar control in patients with type 2 diabetes is not convincing and further studies are needed to confirm the effects of ginseng in improving the type 2 diabetic patients' situation (21).

Therefore, the aim of this double-blind clinical trial was to evaluate the effect of ginseng extract on glycemic parameters and serum concentrations of new adipokines (Chemerin and apelin) in patients with type 2 diabetes.

Materials and Methods

The study population

This double-blind clinical trial study was conducted on 46 patients (men and women) with type II diabetes. Among patients referred to the clinic of Endocrinology of Ahvaz Golestan hospital, Ahvaz, Iran, subjects were enrolled in the study.

Individuals were screened with regard to the inclusion and exclusion criteria. Inclusion criteria included: males and females 20-60 years, no taking supplements and herbal remedies in the last three months, and BMI<35. Exclusion criteria were: insulin therapy; change of the dosage of medicines; pregnancy; breastfeeding; smoking; participation in a weight loss program; heart disease; and kidney, digestive or respiratory problems; and cancer.

Study Design

At first, the study population was selected among patients attending the Endocrinology Clinic, Ahvaz Golestan Hospital. After a brief explanation of the study initial screening was performed and then, preliminary assessment was conducted by phone. Then, a justification meeting with a complete description of the protocol and the aim the study was held for volunteers. The final screening was carried out in accordance with inclusion and exclusion criteria. After the filling and signing of a written consent form, eligible individuals were divided randomly into two groups.

Anthropometric measurements

Weight and height were measured to the nearest 0.1

kg and 0.5 cm, respectively (Seca, Germany). Waist circumference was measured in a standing position using the mean of two measures obtained at the superior edge of the iliac crest. Body mass index (BMI) was calculated with the formula: weight (kg) / height^2 (m2).

Study protocol

Participants were divided randomly into two groups: ginseng (n=24) and placebo (n=24). The intervention group received 300 mg of standardized ginseng extract (G115) daily (100 mg capsule three times a day) for six weeks. The control group received three capsules identical in color and size (containing starch) as the placebo. According to the manufacturer, each capsule contained 3/4 kcal of energy and 4% ginsenoside. After extraction, to ensure sameness of administering doses and the convenience of taking medicine by a patient, capsules (100 mg) with the same-size ginsenosides was standardized and formulated by high- performance liquid chromatography (HPLC). At the end of the study, in order to determine the medication compliance, participants were asked to hand over the empty boxes. In addition to monitoring the use and possible side effects of drugs, weekly phone call was made by the participants.

Biochemical assessment

In a fasting state, blood samples (5 ml) were collected at the beginning and the end of the study. Samples were centrifuged with a Low around and their serum was separated. Sera were kept at –70°C until analysis. Fasting blood glucose (FBG) was measured by auto-analyzer (Hitachi, USA). Serum insulin levels (Q-1-DIAPLUS, USA), apelin and chemerin (Hangzhou Eastbiopharm Co. CHINA) were quantified with ELISA kits. HOMA-IR = [FPS (mg/DL)* fasting insulin (FINS (µU/ml)]/405. Quantitative insulin sensitivity check index (QUICKI) was calculated on the basis of suggested formulas: 1/[log (Insulin µU/ml) + log (Glucose mg/DL)].

This study was taken from the approved research project (No. NRC-9302) and was conducted with the permission of the Ethics Committee of Ahvaz Jundishapur University of Medical Sciences (Act No. AJUMS.REC.1393.133).

Statistical analysis

Statistical analyses were conducted using SPSS version 19.0 (SPSS Inc., Chicago, IL, USA). The data were checked for normality using Kolmogorov-Smirnov test. Independent sample-t test (for normally distributed variables) and Mann-Whitney U test (for non-normally distributed variables) were used to compare baseline values between two groups. Moreover, in order to assay differences between before and after intervention within groups, paired sample-t test (for normally distributed variables) and Wilcoxon test (for non-normally distributed variables) were used. Data are reported were the Mean±Standard error. The P<0.05 was considered as significant.

Results

Baseline characteristics

Of the 48 participants in this study, 45 (23 patients in the intervention group and 22 patients in the placebo group) completed the study. During the study, a patient in the intervention group (Medication change) and two patients in the placebo group (Decline to participate and Medication change) were excluded. No side effect from taking supplements was seen in any of the two groups. The study diagram is shown in Fig. 1. Baseline characteristics are shown in Table I. No significant difference was observed in the baseline characteristics between the two groups (P>0.5).

TABLE I: Basic characteristics of study subjects.

Variables	*Intervention group (n=23)*	*Placebo group (n=22)*	*P-value*[†]
Age (yrs)	47.9±4.7	47.3±6.4	0.71
Male/female	5/18	6/16	0.72
Weight (kg)	74.75±10.49	72.25±14.98	0.54
BMI (kg/m^2)	29.29±3.61	27.19±4.71	0.12

Data are presented as Mean±SD. BMI, body mass index

[†]Compare baseline characteristics between two groups (Independent-sample t-test for normally distributed variables and Mann-Whitney U test for non-normally distributed variables).

*Significant difference between groups (P<0.05)

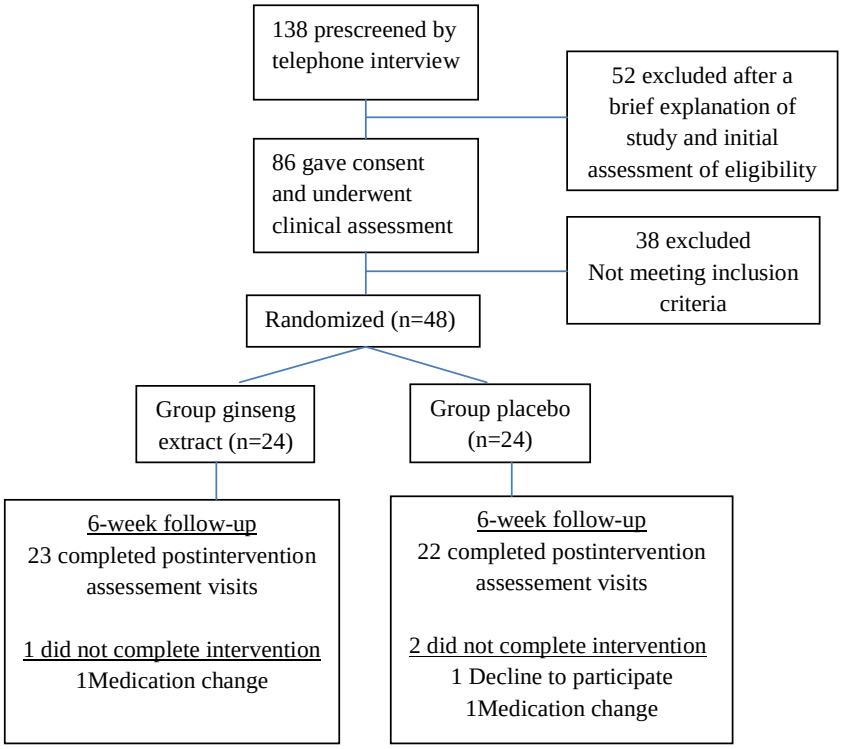

Fig. 1: Flow chart of the study.

TABLE II: Glycemic biomarkers in type 2 diabetic patients at baseline and after 6 weeks in both groups.

Variables	*Intervention group (n=23)*	*Placebo group (n=22)*	*P-value*
FBS (mg/dl)			
Baseline	169.06±73.99	168.63±67.56	0.98
After 6 weeks	131.62±65.69	164.10±69.78	0.16
P-value	0.01	0.69	
FINS (µIU/ml)			
Baseline	14.08±16.31	6.72±8.39	0.09
After 6 weeks	4.60±2.11	5.85±10.12	0.11
P-value	<0.05	0.78	
HOMA-IR			
Baseline	4.49±9.69	1.10±1.63	0.14
After 6 weeks	0.75±0.40	0.84±1.27	0.78
P-value	0.14	0.75	
HOMA-B			
Baseline	57.59±66.33	30.11±17.99	0.12
After 6 weeks	43.56±28.70	34.71±50.53	0.53
P-value	0.47	0.69	
HOMA-S			
Baseline	142.85±100.95	155.11±69.98	0.67
After 6 weeks	176.99±70.58	195.21±72.76	0.46
P-value	0.33	0.25	
QUICKI			
Baseline	0.35±0.08	0.35±0.04	0.86
After 6 weeks	0.34±0.43	0.21±0.61	0.48
P-value	0.96	0.32	

All values are Means±SD.
FBS, Fasting blood sugar; FINS, Fasting insulin; HOMA-IR, Homeostasis model assessment insulin resistance index; QUICKI, Quantitative insulin sensitivity check index.
†Baseline ginseng extract group vs. baseline placebo group (Independent-sample t-test for normally distributed variables and Mann-Whitney U for non-normally distributed variables).
‡Differences between before and after intervention within groups (Paired sample-t test for normally distributed variables and wilcoxon test for non-normally distributed variables)

Serum levels before and after intervention

The results of biochemical evaluation are shown in Table II and Table III. No significant difference was observed in levels of glycemic biomarkers, including fasting blood glucose and fasting insulin and indicators of HOMA-IR and QUICKI between the two groups at the beginning and end of the study. An intragroup analysis showed that a six-week ginseng

TABLE III: Apelin and Chemerin in type 2 diabetic patients at baseline and after 6 weeks in both groups.

Variables	*Intervention group (n=23)*	*Placebo group (n=22)*	*P-value*
Apelin (ng/ml)			
Baseline	604.37±256.39	556.87±397.64	0.17†
After 6 weeks	641.13±151.71	665.61±177.88	0.65†
P-value	0.55‡	0.43‡	
Chemerin (ng/ml)			
Baseline	514.62±478.45	556.87±397.64	0.77
After 6 weeks	522.29±402.97	533.84±426.62	0.91
P-value	0.82	0.15	

All values are Means±SD.
†Baseline ginseng extract group vs. baseline placebo group (Independent-sample t-test for normally distributed variables and Mann-Whitney U for non-normally distributed variables).
‡Differences between before and after intervention within groups (Paired sample-t test for normally distributed variables and wilcoxon test for non-normally distributed variables)

supplementation caused a significant reduction in fasting blood glucose levels (P 0.01) and fasting insulin (P 0.05) at the end of the study compared to baseline (Table II).

Chemerin and apelin levels at the beginning and the end of the study showed no significant difference between two groups (Table III).

Discussion

The present study showed that supplementation of ginseng extract with a dose of 300 mg daily for six weeks cannot cause significant changes in the level of apelin and chemerin, but it can cause significant reduction in fasting blood glucose and fasting insulin in patients with type 2 diabetes. This study is the first double-blind clinical trial that has evaluated the effects of ginseng extract on apelin and chemerin levels.

In the field of the effects of ginseng in improving the glycemic status the studies' results are contradictory.

Double-blind clinical trial conducted by Hyangju *et al*. showed that the Korean red ginseng supplementation (5 g) for 12 weeks can improve glucose control in people with impaired glucose tolerance (22). In another study, anti-diabetic effects of eight-week supplementation of ginseng extract (960 mg/d) were evaluated. The results of study showed that ginseng extract can reduce levels of FPG and postprandial glucose in the impaired fasting glucose participants (23). A double-blind clinical trial conducted by Mi-Ra *et al.* showed that administration of fermented red ginseng for four weeks can cause significant changes in fasting blood glucose and fasting insulin levels in patients with type 2 diabetes (24). Recently, a systematic review and meta-analysis showed that ginseng supplementation can cause a significant reduction in fasting blood glucose, postprandial insulin and insulin resistance although significant changes in glycated hemoglobin levels, postprandial glucose and fasting insulin were not reported (25). In our study, the effects of ginseng investigated in the short-term. However, the animal studies shown anti-diabetic effects of ginseng in a shorter period (2 weeks) of our study (26).

Several mechanisms have been suggested for anti-diabetic effects of ginseng. According to the study by Shang et al, through activation insulin signaling pathway and up-regulate the expression of GLUTs in adipose tissue, Ginsenoside-Rb1 (one of the active components of ginseng) can cause a significant decrease in HOMA-IR (27). The ginseng extract promotes pancreatic β cell function and migration. Also, increase islet β cell insulin release (28). In addition, the extracts of Panax notoginseng root improve hyperglycemia and insulin sensitivity by enhancing glucose uptake in skeletal muscle (29). Jiang et al. suggested that Compound K (a metabolite of ginsenosides) increases insulin sensitivity through PI3K/Akt signaling pathway (30).

In contrast, some studies did not support the hypoglycemic effects of ginseng. Cho *et al.*'s study was inconsistent with our study. They examined in a double-blind clinical trial the effect of 6 g/day Korean red ginseng for 12 weeks on glycemia in obese and overweight (non-diabetic). Their results showed that ginseng cannot cause significant changes in fasting blood glucose, fasting insulin, HOMA-IR and QUICKI (31). In another study it was found that ginseng root extract and Ginsenoside-Re cannot improve β-cell function or insulin sensitivity in overweight/obese subjects with impaired glucose tolerance (32). In addition, Realy *et al.*'s study has shown the lack of long-term effects of standardized ginseng extract (G115) in the regulation of blood glucose levels in healthy individuals (33). The results of a recent study showed that ginseng cannot have effect in improving glycemic status in Postmenopausal women (34).

The difference in the population studied, ginseng type, dose and duration of treatment were some of the factors related to the difference of the result of our study with these studies. This study has strengths and limitations. Use of standardized ginseng extracts with the amount of same ginsenosides per capsule was considered as the strength of this

study. A study limitation can be short duration of the study; so, the repetition of such a study with a larger sample size and longer duration can be recommended.

This double-blind clinical trial found that supplementation with ginseng extract (300 mg/d) significantly improved insulin resistance, but cannot affect the adipokines of apelin and Chemerin.

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