Clinical Nutrition 38 (2019) 549–556

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

Randomized Control Trials

Efficacy of cinnamon in patients with type II diabetes mellitus: A randomized controlled clinical trial

Roghayeh Zare [a, b], Azadeh Nadjarzadeh [c], Mohammad Mehdi Zarshenas [d, e], Mesbah Shams [f, **], Mojtaba Heydari [g, *]

[a] Department of Persian Medicine, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran
[b] Department of Persian Medicine, Faculty of Persian Medicine, Shahid Sadoughi University of Medical Sciences, Yazd, Iran
[c] Nutrition and Food Security Research Center, Shahid Sadoughi University of Medical Sciences, Yazd, Iran
[d] Department of Phyopharmaceuticals (Traditional Pharmacy), School of Pharmacy, Shiraz University of Medical Sciences, Shiraz, Iran
[e] Medicinal Plants Processing Research Center, Shiraz University of Medical Sciences, Shiraz, Iran
[f] Endocrine and Metabolism Research Center, Shiraz University of Medical Sciences, Shiraz, Iran
[g] Research Center for Traditional Medicine and History of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran

ARTICLE INFO

Article history:
Received 8 December 2017
Accepted 3 March 2018

Keywords:
Cinnamon
Type II diabetes mellitus
Body Mass Index
Anthropometric parameters
Glycemic indices

SUMMARY

Background & aims: Multiple studies have evaluated the hypoglycemic effect of cinnamon in patients with diabetes mellitus (DM) type II, with conflicting results. Differences in Baseline Body Mass Index (BMI) of patients may be able to explain the observed differences in the results. This study was designed to evaluate the effect of cinnamon supplementation on anthropometric, glycemic and lipid outcomes of patients with DM type II based on their baseline BMI.

Methods: The study was designed as a triple-blind placebo-controlled randomized clinical trial, using a parallel design. One hundred and forty patients referred to Diabetes Clinic of Yazd University of Medical Sciences with diagnosis of DM type II were randomly assigned in four groups: cinnamon (BMI $\geq$ 27, BMI < 27) and Placebo (BMI $\geq$ 27, BMI < 27). Patients received cinnamon bark powder or placebo in 500 mg capsules twice daily for 3 months. Anthropometric, glycemic and lipid outcomes were measured before and after the intervention.

Result: Cinnamon supplementation led to improvement of all anthropometric (BMI, body fat, and visceral fat), glycemic (FPG, 2hpp, Hb_{A1C}, Fasting Insulin, and Insulin Resistance), and lipids (Cholesterol Total, LDL-c and HDL-c) outcomes (except for triglycerides level). All observed changes (except for Cholesterol Total and LDL-c) were significantly more prominent in patients with higher baseline BMI (BMI $\geq$ 27).

Conclusion: Based on the study findings, cinnamon may improve anthropometric parameters, glycemic indices and lipid profile of patients with type II diabetes. These benefits are significantly more prominent in patients with higher baseline BMI (BMI $\geq$ 27).

The trial protocol was registered in Iranian Registry of Clinical Trials database (registration ID: IRCT2017031133015N1).

1. Introduction

Diabetes is a metabolic disease characterized by hyperglycemia resulting from pathologic change in insulin secretion and/or insulin action [1]. Diabetes is a disease with a significant global burden. The most important concern with the diabetes is the constant increase in mortality and morbidity related to the diabetes and its complications [2]. In 2000, there were over 171 million diagnosed cases of diabetes and it is estimated that just in 30 years the prevalence of diabetes will exceed 366 million patients with duplication in mortality rate [3]. Despite the shown clinical benefits of tight glycemic control in type II diabetes and the availability of various antidiabetic medications, the outcome of available interventions is not satisfactory [4].

* Corresponding author. Central building of Shiraz University of Medical Sciences, Zand St., Shiraz, PO Box: 71348-14336, Iran.
** Corresponding author. Central building of Shiraz University of Medical Sciences, Zand St., Shiraz, PO Box: 71348-14336, Iran.
E-mail address: mheydari@sums.ac.ir (M. Heydari).

https://doi.org/10.1016/j.clnu.2018.03.003
0261-5614/

Various types of traditional, complementary or alternative therapies have been increasingly used for different chronic diseases [5,6], including diabetes in both developing and developed countries [7]. Herbal medicines form the major part of these therapies [8]. Nevertheless, there is not enough evidence-based study about their efficacy and safety [9]. Among medicinal plants used for diabetes, cinnamon (*Cinnamomum verum* J. Presl from Lauraceae family) is one of the most popularly investigated one. It was mentioned in different traditional medicine books. For instance, Haly Abbas (930–994 AD) in the *Royal Book* [10], Avicenna (980–1037 AD) [11] in the Canon of Medicine, and *Aghili Shirazi* in his book, *The Storehouse of Medicaments* (18th century) [12], discussed its different medicinal uses.

Various studies have demonstrated different beneficial health effects of cinnamon including anti-inflammatory properties, antimicrobial activity, cognitive function enhancing effect and risk reduction in colon cancer [13]. Numerous animal and human studies have evaluated anti-diabetic effects of cinnamon with conflicting results [14–21]. Studies have demonstrated a decreasing effect of cinnamon on insulin resistance [22,23].

Some recent meta-analyses failed to reach a conclusive result on the potential benefit of cinnamon in patients with diabetes [15,24,25], due to the heterogeneity of the results of the included studies [15]. Different responses to hypoglycemic agents by obese and lean diabetic patients have been well documented previously [26,27]. Drugs targeting on the decrease of insulin resistance seems to be more effective in patients with obesity who are at greater risk of insulin resistance [28], but in most of the studies this point was not mentioned. Cinnamon is also considered more suitable for patients with obesity and diabetes based on traditional medicine theories [29]. According to the mentioned information, this study was designed to evaluate the efficacy of cinnamon bark crude powder in patients with diabetes mellitus type II with different Body Mass Indices in a triple blind randomized clinical trial.

2. Materials and methods

2.1. Preparation of the supplement and placebo

Fresh cinnamon bark was purchased from a local market in Shiraz, southern Iran. The plant sample was authenticated by a botanist at Shiraz School of Pharmacy with a specified voucher sample (PM-996).

Cinnamon barks were thoroughly washed, dried and ground in a mechanical grinder. The obtained powder was sieved (mesh of 50) and subsequently filled in 500 mg capsules. In parallel, placebo capsules were prepared containing the same amount of starch which was heated until turned to brown color. Both cinnamon and placebo capsules were packaged in similar bottles and labeled by specific numbers which were used in randomization list.

2.2. Chemical composition analysis of cinnamon bark

Gas chromatography-mass spectrometry (GC/MS) analysis was used for the analysis of the volatile content of cinnamon essential oil. Hydro-distillation procedure by Clevenger-type apparatus was used for the extraction of oil.

The GC/MS process was performed by a gas chromatograph (Agilent technologies-7890A) set with HP-5MS capillary column (phenyl methyl siloxane, 30 m × 0.25 mm i.d.), connected to a mass detector (Agilent technologies model-5975C). Carrier gas (Helium). Temperature was set at 250 and 280 °C for the injector and detector, respectively. Column temperature was adjusted linearly from 60 to 250 °C (ramp ~5°/min) and was set at 250 °C for 15 min. The interface temperature was adjusted at 280 °C. The flow rate was set at 1 ml/min. The split ratio was adjusted at 1:30. The mass range of 30–600 m/z was acquired for the spectrometer in EI mode (70 eV). Dichloromethane was used as the solvent for cinnamon essential oils (~1%) for injection. A series of homologous *n*-alkanes (C_8–C_{22}) were also injected. Determination of Kovats indices (KI) and comparison of the calculating KI and mass spectra data with reference values [30] were used for the identification of constituents of cinnamon essential oil.

2.3. Ethical issues

The trial procedure was in compliance with the guidelines of the Declaration of Helsinki; it was reviewed, approved, and monitored by the Local Medical Ethics Committee of Shiraz University of Medical Sciences (SUMS) [with reference number: IR.SUMS.REC.1395.176]. The trial protocol was registered in Iranian Registry of Clinical Trials database (registration ID: IRCT2017031133015N1).

2.4. Trial design

This study was designed as a randomized triple-blinded (the participants, investigator and the statistician) placebo-controlled clinical trial. Allocation ratio was 1:1 with no changes in the design and methods of the study after commencement of the trial.

2.5. Randomization and blinding

The bottles were divided into two groups labeled with A and B, and filled with supplement or placebo capsules by a person who was not involved in patients' visit, allocation, and follow up. The physician, the patient, and the person responsible for the allocation of the groups were not informed about the content of the bottles. The researcher could decode the contents of each bottle only based on the original form of the randomization results. Patients enrolled in the study received a bottle of capsules according to randomization table.

The results of the cinnamon and placebo groups under categories A and B were analyzed by a statistician.

2.6. Inclusion and exclusion criteria

Patients with type II diabetes based on American Diabetes Association (ADA) criteria, and aged between 30 and 80 years (male and female) were included in the study. Other eligibility criteria were lack of comorbid uncontrolled disease, Body Mass Index between 18.5 and 40, fasting plasma glucose between 126 and 250 mg/dl and only taking oral hypoglycemic agents for diabetes. They were excluded if they developed allergic reactions to cinnamon, changed their treatment during the study, and consumed less than 80% of the prescribed capsules.

2.7. Intervention

In this randomized clinical trial, type II diabetic patients were invited to a Yazd Diabetes Center Clinic affiliated by Yazd University of Medical Sciences from April to October 2017, using phone call and then the research topic, objectives, and method of the study were explained to them. After the final selection of patients based on eligibility criteria and signing the informed consent, demographic and clinical characteristics, anthropometric indices, physical activity (based on international physical activity questionnaire) and dietary intake (based on food frequency questionnaire) were registered for all participants. Then, the patients were referred to laboratory for taking their baseline blood sample.

Patients were asked to take their capsules twice a day (at morning on fasting and at night before bedtime) for 3 months. The supplement was delivered to the patient for only 1 month at the baseline visit. A follow-up phone call was made in 2 weeks of each visit to emphasize taking the drugs and checking for any potential side effect. The participants were visited 1 month later and asked to return the remaining capsules (The number of capsules taken was not registered). If more than 20% of them were left, the patient would be excluded from the study; otherwise, the rest of capsules for 2 months were delivered to the patients.

After 3 months, the patients were visited again and their biochemical and anthropometric outcomes as well as their compliance and observed adverse effects were re-evaluated.

2.8. Outcome measures

Biochemical and anthropometric outcomes were measured at the baseline and after 3 months of the intervention with the following methods. For biochemical measures, after 12 h of fasting, 5 ml blood was taken from all the patients to measure their fasting plasma glucose (FPG), glycated Hemoglobin (HbA1C), triglycerides (TG), total Cholesterol (Chol.), low density lipoprotein cholesterol (LDL-C), and high density lipoprotein cholesterol (HDL-C) concentrations. 2 h postprandial glucose (2hpp) was assayed 2 h after a standard breakfast. FPG and 2hpp were performed using the Pars Azmoon Co. assay kits (Tehran, Iran) by glucose-peroxidase method applying Echo Plus inc auto-analyzer device (Italy). Colorimetric method was used to measure HbA1C after primary separation via ion exchange chromatography (biosystems).

Insulin level was measured by ELISA kits (Diametra Corporation, Milan, Italy). Insulin resistance was determined by homeostasis model of insulin resistance index (HOMA-IR) which was calculated using the following equation [31,32];

[Fasting plasma glucose (mg/dL) × Serum insulin level (mU/mL)]/ 405

TG and Cholesterol were measured using Pars Azmoon Co assay kits (Tehran, Iran). The auto-analyzer device made in Echo Plus Inc company, Italy was applied using glycerol oxidase and cholesterol oxidase enzymatic methods. HDL-C and LDL-C was measured using same device after the precipitation of beta-lipoproteins by chloride magnesium and dextran sulfate by oxidase cholesterol method.

Weight (no shoes, minimum clothing) and body composition parameters (body fat percentage, skeletal muscle percentage, Body Mass Index (BMI) and visceral fat) were assessed using Body Composition Monitor (Model BF511, Japan).

2.9. Sample size calculation and statistical analyses

Sample size was estimated to be 120 patients divided into 4 subgroups (cinnamon BMI $\geq$ 27, cinnamon BMI < 27, placebo BMI $\geq$ 27 and placebo BMI < 27 groups) by considering one-sided significance level of 0.05 for a 0.80 power. Expected difference and variance in FPG as primary outcome was considered 13 and 306 based on a previous trial on cinnamon and diabetes [33]. Considering probability of 15 percent drop-out of the enrolled patients, 140 patients were enrolled in the study.

Demographic and clinical characteristics of the patients included in the analysis are shown as the mean ± standard deviation (SD) or number (percentage) where appropriate. The statistical analyses included Chi-square, paired and independent t-test. *p*-values less than 0.05 were considered as significant. The interaction between BMI categories and cinnamon/placebo groups were analyzed by General Linear Model. The Statistical Package for the Social Sciences, version 18.0 (SPSS Inc., Chicago, IL, USA), was used for statistical analyses.

3. Results

3.1. Drug analysis report

Cinnamaldehyde was found as the major constituent (92.06%) of cinnamon bark essential oil in GC/MS analysis. The analysis also revealed that 4-Methoxycinnamaldehyde (3.26%), δ-Cadinene (1.61%), α-Copaene (0.86%), and α-Muurolene (0.68%) were the minor constituents in the essential oil (Fig. 1).

3.2. Study flow

Two hundred and four patients diagnosed with diabetes mellitus type II based on ADA criteria were evaluated for eligibility criteria and willingness to participate in the study. A total of 140 eligible patients were randomized into cinnamon and placebo groups from April 2017 to October 2017. One patient in the cinnamon group lost the follow up (migration) and one patient in the placebo group was excluded from the study (due to self-reporting some allergic reaction). Finally, 138 patients completed the study and their data were analyzed. The flow of the assessment, enrollment, drop out and analysis of the patients are dedicated in Fig. 2.

3.3. Baseline characteristics

The baseline demographic and clinical characteristics of the patients in the two study groups are presented in Table 1. There was no statistically significant difference between the patients in the two groups.

3.4. Anthropometric outcomes

There was a significant decrease in patients' anthropometric indices, including their Body Mass Index (0.53 kg/m^2, 95% CI:

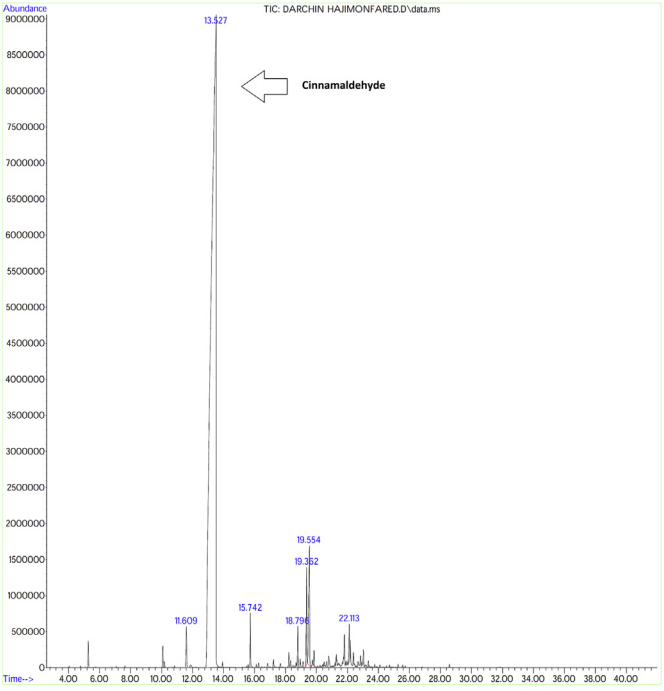

Fig. 1. GC/MS fingerprint of cinnamon bark essential oil.

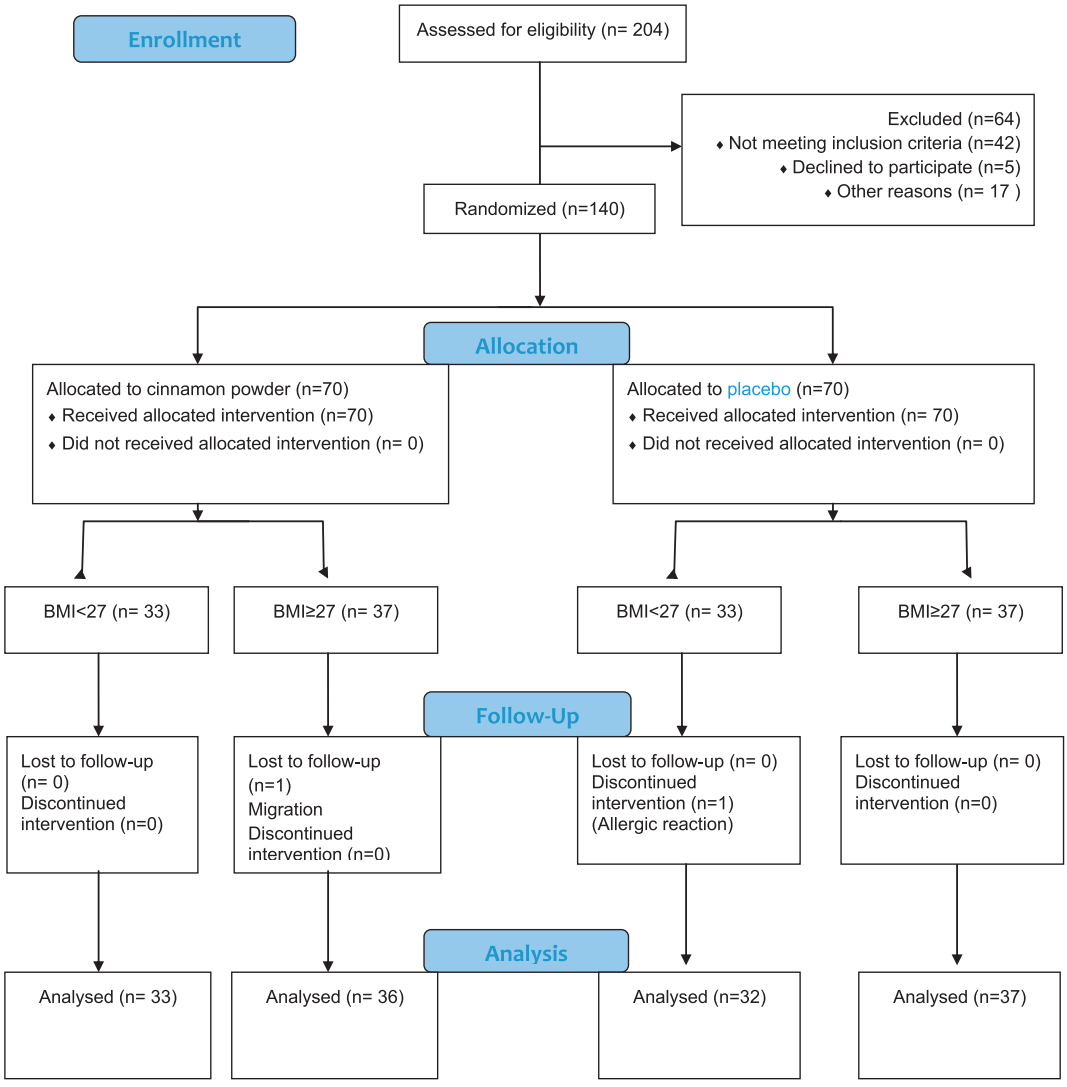

Fig. 2. The CONSORT flow diagram.

0.24–0.73 kg/m^2, $p < 0.001$), Total Body Fat (1.92%, 95% CI: 1.46–2.49%, $p < 0.001$) and Visceral Fat (0.69%, 95% CI: 0.46–0.98%, $p < 0.001$) in cinnamon group. These changes were significantly more in the cinnamon group compared to those observed in the placebo group ($p < 0.001$) (Table 2)

3.5. Glycemic outcomes

A significant decrease was observed in glycemic indices (including FPG, 2hppG and HbA1c) of patients in the cinnamon group accompanied with a decrease in their insulin level and insulin resistance based on HOMA index. The observed changes were significantly higher in the cinnamon group compared to the placebo one (Table 3, see the "*total*" rows).

The analysis of interaction between BMI categories and cinnamon/placebo groups by General Linear Model showed statistically significant more prominent effect of cinnamon on glycemic outcomes in patients with higher BMI (Fig. 3).

Comparing the outcomes between patients in the cinnamon group with different BMI (BMI $\geq$ 27 and BMI < 27) showed that the decrease in all of glycemic outcomes were significantly more prominent in patients with higher BMI (Table 3, see the gray rows). Comparison of the glycemic outcomes of patients with BMI $\geq$ 27 between the cinnamon and placebo groups revealed that there was a significant difference in improvement of all glycemic outcomes (Table 3, see the first row for each outcome).

Adjustment for confounding variables such as weight, BMI, body fat, visceral fat, insulin and HOMA index by Univariate Model Analysis showed that the decrease in glycemic outcomes was through a decrease in the insulin resistance.

3.6. Lipid profile outcomes

A significant decrease in triglycerides, total cholesterol and LDL cholesterol and also a significant increase in HDL cholesterol were observed in patients in the cinnamon group. The observed changes were significantly higher in the cinnamon group compared to the placebo one, except for changes in triglyceride level (Table 4, see the "*total*" rows).

The analysis of interaction between BMI categories and cinnamon/placebo groups by General Linear Model showed statistically significant more prominent effect of cinnamon on triglyceride and

Table 1
Baseline demographic and clinical characteristics of patients with type II Diabetes Mellitus in cinnamon and placebo groups.

Characteristics	Cinnamon (Mean ± SD) (n = 69)	Placebo (Mean ± SD) (n = 69)	*p* value*
Gender (female/male)	37/32	26/43	0.06
Age (year)	52.1 ± 9.7	53.2 ± 8.5	0.51
Duration of diabetes (year)	5.6 ± 4.1	5.2 ± 3.8	0.56
Baseline physical activity	1.13 ± 0.3	1.10 ± 0.30	0.59
Final physical activity	1.16 ± 0.06	1.18 ± 0.07	0.78
Weight (kg)	75.7 ± 11.6	74.4 ± 11.6	0.49
BMI[a] (kg/m^2)	29.9 ± 12.3	29.3 ± 17.1	0.81
Baseline calorie intake (kcal/d)	2471.8 ± 316.8	2501.9 ± 118.2	0.46
Final calorie intake (kcal/d)	2486 ± 44.4	2495 ± 35.3	088
FPG[b] (mg/dl)	162.6 ± 30.0	159.4 ± 35.3	0.56
2hpp[c] (mg/dl)	210.5 ± 44.4	208.2 ± 47.8	0.77
HbA1C (mg/dl)	7.36 ± 0.7	7.43 ± 0.8	0.59
Insulin (mg/dl)	10.6 ± 4.2	11.4 ± 4.50	0.27
Insulin resistance (HOMA-IR)[f]	4.24 ± 1.8	4.51 ± 2.1	0.42
Triglyceride (mg/dl)	168.1 ± 57.07	165.1 ± 58.7	0.75
Total cholesterol (mg/dl)	167.8 ± 35.6	168.8 ± 35.1	0.18
LDL[d]-cholesterol (mg/dl)	103.8 ± 31.7	97.4 ± 27.9	0.21
HDL[e]-cholesterol (mg/dl)	42.4 ± 7.3	40.3 ± 7.4	0.99

*Chi-square test for categorical variable; t-test for quantitative variable.
[a] Body Mass Index.
[b] Fasting Plasma Glucose.
[c] 2 h post prandial blood glucose.
[d] Low-density lipoprotein.
[e] High-density lipoprotein.
[f] Homeostatic Model Assessment of Insulin Resistance.

HDL cholesterol levels in patients with higher BMI. BMI showed no significant interaction with cinnamon effect on total cholesterol and LDL.

Comparison of the outcomes between patients in cinnamon group with different BMI (BMI $\geq$ 27 and BMI < 27) showed that changes in triglyceride and HDL cholesterol level were significantly more prominent in patients with higher BMI (Table 4, see the gray rows). There was a significant difference in improvement of all lipid outcomes, when comparing the lipid outcomes of patients with BMI $\geq$ 27 between the cinnamon and placebo groups (Table 4, see the first row for each outcome).

3.7. Safety results

No patients reported any adverse event in the cinnamon group. Only one patient in the placebo group reported allergic reaction which led to withdrawal from the study intervention. The symptoms disappeared without any intervention after 1 week. No other serious or systemic adverse effects were reported by the patients.

Table 2
Changes in anthropometric outcomes of patients with type II Diabetes Mellitus in the cinnamon and placebo groups.

Characteristics	Cinnamon (Mean ± SE) (n = 69)	Placebo (Mean ± SE) (n = 69)	*p* value**
Body Mass Index (kg/m^2)	−0.63 ± 0.06	0.11 ± 0.02	<0.001
Weight (kg)	−1.90 ± 0.26	0.19 ± 0.15	<0.001
Body fat (%)	−1.92 ± 0.26	−0.15 ± 0.22	<0.001
Body muscle (%)	1.85 ± 0.23	−0.41 ± 0.21	<0.001
Visceral fat (%)	−0.69 ± 0.13	−0.10 ± 0.08	<0.001

Mean values demonstrate changes in the mentioned outcomes (end-baseline values).
**t-test.

4. Discussion

In this study, supplementation of diabetic patients with cinnamon (daily dose of 1 g) led to improvement of all anthropometric (BMI, body fat, and visceral fat), glycemic (FPG, 2hpp, Hb_{A1C}, Fasting Insulin, and Insulin Resistance), and lipids (Cholesterol Total, LDL-c and HDL-c) outcomes (except for triglycerides level) in the cinnamon group compared to the placebo group. All observed changes were significantly more prominent in patients with higher BMI (BMI $\geq$ 27).

The observed improvement in the glycemic and lipids outcomes of diabetic patients in this study was compatible with the results of previous studies (in decreasing of FPG [15,34,35], 2hpp [36,37], of HbA1c [34,38], and reduction of insulin resistance [23,39]).

Regarding anthropometric outcomes, similar to our observation, Ziegenfuss et al. showed that cinnamon supplementation can decrease the body fat and increase the lean body mass in patients with metabolic syndrome [35]. In contrast, some other studies failed to show such improvements in glycemic, lipids and anthropometric outcomes of diabetic patients [15,16,21,25].

This inconsistency may be due to the different doses and duration of intervention as well as the patients' baseline BMI. As illustrated in our results, higher baseline BMI may lead to better improvement in outcomes of patients who take cinnamon supplementation. To the best of our knowledge, the role of baseline BMI as a predictor of response of diabetic patients to cinnamon supplementation was not previously reported.

4.1. Possible mechanism

Different mechanisms have been suggested for the observed hypoglycemic effects of cinnamon [40]. It is reported that cinnamon extract activates the insulin receptor kinase and inhibits the insulin receptor dephosphorylation which improves the insulin sensitivity [41]. Cinnamon also showed to be able to inhibit glycogen synthase kinase-3 which leads to increased glucose uptake [41].

Previous studies also showed that cinnamon could increase UCP3gene expression which plays a critical role in fatty acid metabolism. UCP3gene expression contributes to lipid and carbohydrate oxidation, and as a result with BMI and percentage of lean body mass in human [42]. The expression of UCP3 in brown adipose tissue and skeletal muscle regulates the energy consumption by fatty acid oxidation [43]. Therefore, it can contribute to the mechanism of the effect of cinnamon on energy metabolism. Cinnamon increases the amount of GLUT4 receptors as well as Insulin Receptor and its substrates [44–46], which is associated with increase in the glucose uptake.

Cinnamon extracts can also activate the glycogen synthase through stimulating glucose uptake, and inhibiting glycogen synthase kinase 3β [41,47,48]. These effects can be considered as the potential mechanism of the observed increases in lean mass in the cinnamon group.

The most important limitation of this study was the generalizability of the results. Exclusion of diabetic patients taking insulin and patients with a diagnosed micro- and macro-vascular diabetes complication seems to cause a study population with less advanced disease compared to general population of patients with type II diabetes.

Recording the patient's physical activity level and calorie intake by standard questionnaires, applying the sufficient sample size and duration of the intervention, in addition to the chemical analysis of cinnamon as the intervention can be considered as the strengths of the trial.

Table 3
Changes in Glycemic outcomes of patients with type II Diabetes Mellitus in the cinnamon and placebo groups based on their BMI.

Characteristics		Cinnamon (Mean ± SE) (n: 36/33)[b]	Placebo (Mean ± SE) (n: 37/32)[a]	*p* value*
Fasting Plasma Glucose (mg/dl)	BMI ≥ 27	−19.37 ± 2.3	−0.22 ± 1.53	<0.001
	BMI < 27	−5.8 ± 1.62	−3.3 ± 1.02	0.18
	Total	−13.1 ± 1.7	−1.7 ± 0.9	<0.001
	p	<0.001	0.110	
2 h post prandial blood glucose (mg/dl)	BMI ≥ 27	−21.35 ± 3.8	1.97 ± 6.5	0.003
	BMI < 27	−11.9 ± 2.7	−9.5 ± 5.4	0.03
	Total	−16.9 ± 2.5	−3.5 ± 4.3	0.008
	p	0.049	0.182	
Glycosylated hemoglobin (HbA1c) (%)	BMI ≥ 27	−0.42 ± 0.06	0.044 ± 0.01	<0.001
	BMI < 27	−0.93 ± 0.02	−0.048 ± 0.03	0.24
	Total	−0.27 ± 0.04	0.001 ± 0.02	<0.001
	p	<0.001	0.014	
Insulin (mIU/L)	BMI ≥ 27	−2.38 ± 0.30	0.003 ± 0.02	<0.001
	BMI < 27	−1.07 ± 0.24	0.008 ± 0.03	<0.001
	Total	−1.77 ± 0.41	0.005 ± 0.02	<0.001
	p	<0.001	0.918	
HOMA-IR[b]	BMI ≥ 27	−1.41 ± 0.16	−0.004 ± 0.05	<0.001
	BMI < 27	−0.55 ± 0.10	−0.06 ± 0.03	<0.001
	Total	−1.01 ± 0.11	−0.03 ± 0.03	<0.001
	p	<0.001	0.366	

Mean values demonstrate changes in the mentioned outcomes (end-baseline values).
*t-test.
[a] n: BMI ≥ 27, BMI < 27, total.
[b] Homeostatic Model Assessment of Insulin Resistance.

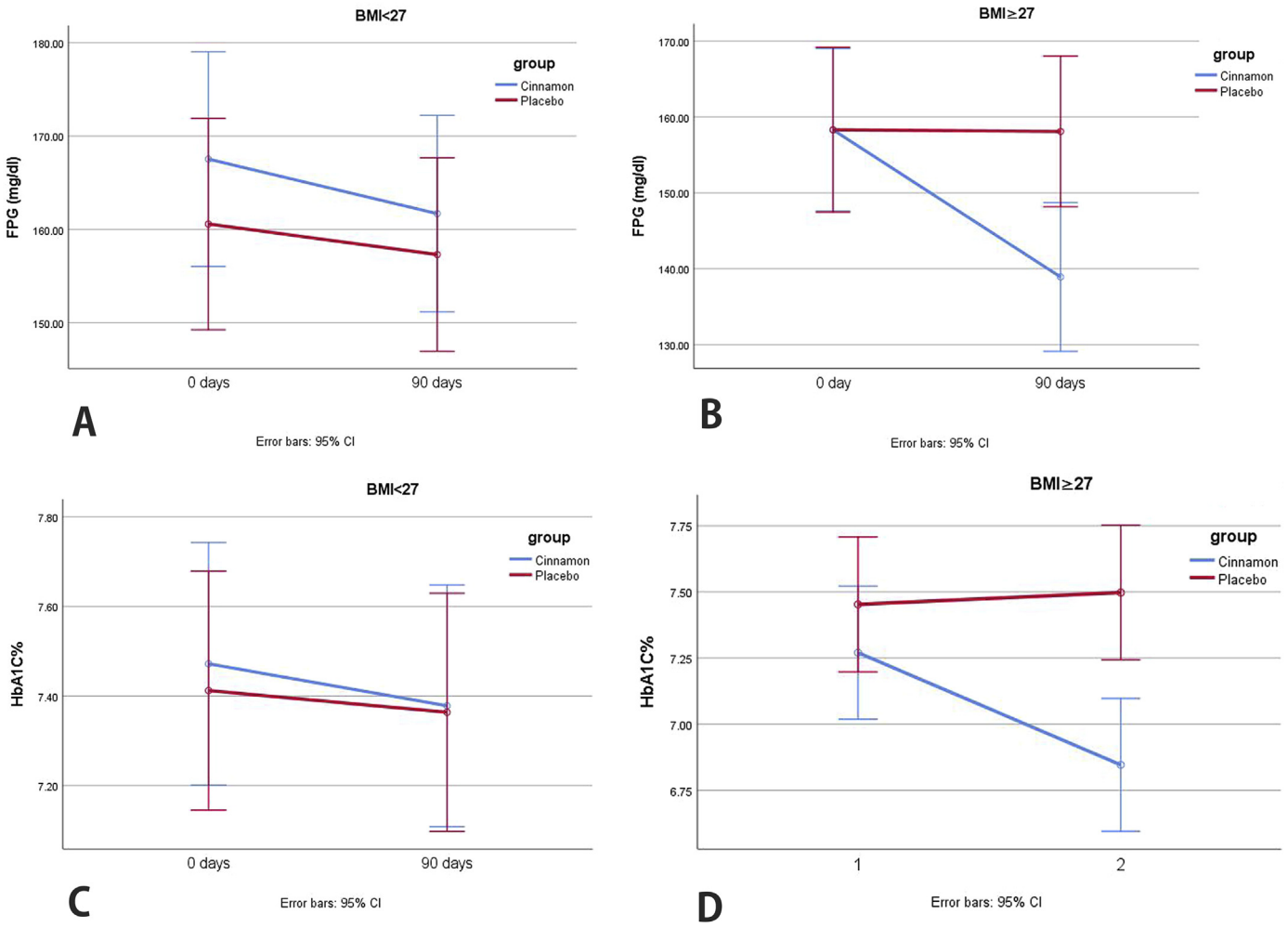

Fig. 3. Interaction between BMI categories and cinnamon/placebo groups effect on Fasting Plasma Glucose (FPG) (A-B) and Glycosylated Hemoglobin (HbA1C) (C-D).

Table 4
Changes in the lipid profile outcomes of patients with type II Diabetes Mellitus in the cinnamon and placebo groups based on their BMI.

Characteristics		Cinnamon (Mean ± SE) (n: 36/33)[c]	Placebo (Mean ± SE) (n: 37/32)[c]	*p* value
Triglyceride (mg/dl)	BMI ≥ 27	−19.05 ± 4.5	10.5 ± 4.4	<0.001[b]
	BMI < 27	8.5 ± 6.1	−4.15 ± 6.1	0.079[b]
	Total	−6.2 ± 4.0	3.5 ± 2.9	0.055[a]
	p	<0.001	0.013	
Total cholesterol (mg/dl)	BMI ≥ 27	−17.4 ± 3.9	−1.9 ± 3.9	0.005[a]
	BMI < 27	−14.3 ± 4.3	−3.8 ± 2.03	0.033[a]
	Total	−16.2 ± 2.9	−2.8 ± 2.3	<0.001[a]
	p	0.551	0.656	
Low density lipoprotein (mg/dl)	BMI ≥ 27	−9.2 ± 2.9	4.7 ± 3.9	0.005[a]
	BMI < 27	−1.7 ± 4.5	−0.2 ± 0.8	0.750[a]
	Total	−5.7 ± 2.6	2.3 ± 2.1	0.018[a]
	p	0.155	0.253	
High density lipoprotein (mg/dl)	BMI ≥ 27	2.83 ± 0.8	−2.05 ± 0.9	<0.001
	BMI < 27	−1.06 ± 0.9	0.03 ± 1.03	0.470[a]
	Total	1.02 ± 0.07	−1.05 ± 0.7	0.038[a]
	p	0.006	0.134	

Mean values demonstrate changes in the mentioned outcomes (end-baseline values).
[a] t-test.
[b] Mann–Whitney Test.
[c] n: BMI ≥ 27, BMI < 27.

5. Conclusion and implication

Based on the study findings, it can be concluded that cinnamon supplementation (500 mg capsules twice daily) can improve anthropometric parameters, glycemic indices, and lipid profile of patients with type II diabetes. These benefits are significantly more prominent in patients with higher BMI (BMI ≥ 27).

Statement of authorship

Roghayeh Zare

Roles: Conceptualization, Data curation, Methodology, Investigation, Writing – original draft.
Affiliations: Department of Persian Medicine, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran. Department of Persian Medicine, Faculty of Persian Medicine, Shahid Sadoughi University of Medical Sciences, Yazd, Iran.

Azadeh Nadjarzadeh

Roles: Conceptualization, Supervision, Visualization, Writing – review & editing.
Affiliations: Nutrition and Food Security Research Center, Shahid Sadoughi University of Medical Sciences, Yazd, Iran.

Mohammad Mehdi Zarshenas

Roles: Conceptualization, Data curation, Investigation, Supervision, Writing – review & editing.
Affiliations: Medicinal Plants Processing Research Center, Shiraz University of Medical Sciences, Shiraz, Iran.

*Mesbah Shams***

Roles: Conceptualization, Methodology, Supervision, Writing – review & editing.
Affiliations: Endocrine and Metabolism Research Center, Shiraz University of Medical Sciences, Shiraz, Iran.

*Mojtaba Heydari**

Roles: Conceptualization, Data curation, Investigation, Methodology, Software, Project administration, Supervision, Formal analysis, Writing – original draft, Writing – review & editing.
Affiliations: Research Center for Traditional Medicine and History of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran.

Conflicts of interest

The authors have declared that there is no conflict of interest.

Acknowledgments

This article was extracted from the thesis written by Dr. Roghayeh Zare as partial fulfillment of the requirements for obtaining her Ph.D degree in the field of Traditional Persian Medicine at Shiraz University of Medical Sciences, Shiraz, Iran.

Hereby the authors wish to thank Dr. Majid Emtiazi, Dr. Masoud Rahmanian and the Diabetes Research Center of Shahid Sadoughi University of Medical Sciences, yazd, Iran for their collaboration in the study.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.clnu.2018.03.003.

References

[1] Association AD. Diagnosis and classification of diabetes mellitus. Diabetes Care 2014:S81–90.
[2] Currie CJ, Poole CD, Evans M, Peters JR, Morgan CL. Mortality and other important diabetes-related outcomes with insulin vs other antihyperglycemic therapies in type 2 diabetes. J Clin Endocrinol Metab 2013;98(2):668–77.
[3] Whiting DR, Guariguata L, Weil C, Shaw J. IDF diabetes atlas: global estimates of the prevalence of diabetes for 2011 and 2030. Diabetes Res Clin Pract 2011 Dec 1;94(3):311–21.
[4] Cusick M, Meleth AD, Agrón E, Fisher MR, Reed GF, Knatterud GL, et al. Associations of mortality and diabetes complications in patients with type 1 and type 2 diabetes. Diabetes Care 2005;28(3):617–25.

[5] Hashempur MH, Sadrneshin S, Mosavat SH, Ashraf A. Green tea (Camellia sinensis) for patients with knee osteoarthritis: a randomized open-label active-controlled clinical trial. Clin Nutr 2018;37(1):85–90.
[6] Mohtashami R, Huseini HF, Heydari M, Amini M, Sadeqhi Z, Ghaznavi H, et al. Efficacy and safety of honey based formulation of Nigella sativa seed oil in functional dyspepsia: a double blind randomized controlled clinical trial. J Ethnopharmacol 2015;175:147–52.
[7] Pandey A, Tripathi P, Pandey R, Srivatava R, Goswami S. Alternative therapies useful in the management of diabetes: a systematic review. J Pharm BioAllied Sci 2011;3(4):504.
[8] Jabbari M, Daneshfard B, Emtiazy M, Khiveh A, Hashempur MH. Biological effects and clinical applications of Dwarf Elder (Sambucus ebulus L): a Review. J Evid Based Complement Altern Med 2017;22(4):996–1001. 2156587217701322.
[9] Khiveh A, Hashempur MH, Shakiba M, Lotfi MH, Shakeri A, Kazemeini S, et al. Effects of rhubarb (Rheum ribes L.) syrup on dysenteric diarrhea in children: a randomized, double-blind, placebo-controlled trial. J Integr Med 2017;15(5):365–72.
[10] Heydari M, Dalfardi B, Golzari SE, Mosavat SH. Haly abbas and the early description of obstructive jaundice. Iran J Public Health 2014;43(8):1161–2.
[11] Akrami R, Hashempur MH, Tavakoli A, Nimrouzi M, Sayadi M, Roodaki M, et al. Effects of Fumaria parviflora L on uremic pruritus in hemodialysis patients: a randomized, double-blind, placebo-controlled trial. Jundishapur J Nat Pharm Prod 2018:e39744. in press.
[12] Hashempur MH, Khademi F, Rahmanifard M, Zarshenas MM. An evidence-based study on medicinal plants for hemorrhoids in medieval persia. J Evid Based Complement Altern Med 2017;22(4):969–81. 2156587216688597.
[13] Jayaprakasha G, Rao LJM. Chemistry, biogenesis, and biological activities of *Cinnamomum zeylanicum*. Crit Rev Food Sci Nutr 2011;51(6):547–62.
[14] Akilen R, Tsiami A, Devendra D, Robinson N. Glycated haemoglobin and blood pressure-lowering effect of cinnamon in multi-ethnic Type 2 diabetic patients in the UK: a randomized, placebo-controlled, double-blind clinical trial. Diabet Med 2010;27(10):1159–67.
[15] Allen RW, Schwartzman E, Baker WL, Coleman CI, Phung OJ. Cinnamon use in type 2 diabetes: an updated systematic review and meta-analysis. Ann Fam Med 2013;11(5):452–9.
[16] Blevins SM, Leyva MJ, Brown J, Wright J, Scofield RH, Aston CE. Effect of cinnamon on glucose and lipid levels in Non–insulin-dependent type 2 diabetes. Diabetes Care 2007;30(9):2236–7.
[17] Khan A, Safdar M, Khan MMA, Khattak KN, Anderson RA. Cinnamon improves glucose and lipids of people with type 2 diabetes. Diabetes Care 2003;26(12):3215–8.
[18] Khan R, Khan Z, Shah S. Cinnamon may reduce glucose, lipid and cholesterol level in type 2 diabetic individuals. Pakistan J Nutr 2010;9(5):430–3.
[19] Lu T, Sheng H, Wu J, Cheng Y, Zhu J, Chen Y. Cinnamon extract improves fasting blood glucose and glycosylated hemoglobin level in Chinese patients with type 2 diabetes. Nutr Res 2012;32(6):408–12.
[20] Mang B, Wolters M, Schmitt B, Kelb K, Lichtinghagen R, Stichtenoth D, et al. Effects of a cinnamon extract on plasma glucose, HbA1c, and serum lipids in diabetes mellitus type 2. Eur J Clin Invest 2006;36(5):340–4.
[21] Vanschoonbeek K, Thomassen BJ, Senden JM, Wodzig WK, van Loon LJ. Cinnamon supplementation does not improve glycemic control in postmenopausal type 2 diabetes patients. J Nutr 2006;136(4):977–80.
[22] Anderson RA. Chromium and polyphenols from cinnamon improve insulin sensitivity: plenary lecture. Proc Nutr Soc 2008;67(1):48–53.
[23] Qin B, Panickar KS, Anderson RA. Cinnamon: potential role in the prevention of insulin resistance, metabolic syndrome, and type 2 diabetes. J Diabetes Sci Technol 2010;4(3):685–93.
[24] Davis PA, Yokoyama W. Cinnamon intake lowers fasting blood glucose: meta-analysis. J Med Food 2011;14(9):884–9.
[25] Leach MJ, Kumar S. Cinnamon for diabetes mellitus. Cochrane Database Syst Rev 2012;(9).
[26] Brunetti P. The lean patient with type 2 diabetes: characteristics and therapy challenge. Int J Clin Pract Symp Suppl 2007;(153):3–9.
[27] George AM, Jacob AG, Fogelfeld L. Lean diabetes mellitus: an emerging entity in the era of obesity. World J Diabetes 2015;6(4):613.
[28] DeFronzo R. Insulin resistance, lipotoxicity, type 2 diabetes and atherosclerosis: the missing links. The Claude Bernard Lecture 2009. Diabetologia 2010;53(7):1270–87.
[29] Sina I. The Canon of Medicine. 2010. p. 71. Sharafkandi A, trans),[in Persian] Tehran.
[30] Adams RP. Identification of essential oil components by gas chromatography/mass spectroscopy. Illinois, USA: Allured Publishing Corporation; 1995.
[31] Legro RS, Castracane VD, Kauffman RP. Detecting insulin resistance in polycystic ovary syndrome: purposes and pitfalls. Obstet Gynecol Surv 2004;59(2):141–54.
[32] Menik L, Palangasinghe S. Comparison of insulin resistance by indirect methods-HOMA, QUICKI and McAuley-with fasting insulin in patients with type 2 diabetes in Galle, Sri Lanka: a pilot study. Online J Health Allied Sci 2006;5(1).
[33] Vafa M, Mohammadi F, Shidfar F, Sormaghi MS, Heidari I, Golestan B, et al. Effects of cinnamon consumption on glycemic status, lipid profile and body composition in type 2 diabetic patients. Int J Prev Med 2012;3(8):531–6.
[34] Akilen R, Tsiami A, Devendra D, Robinson N. Cinnamon in glycaemic control: systematic review and meta analysis. Clin Nutr 2012;31(5):609–15.
[35] Ziegenfuss TN, Hofheins JE, Mendel RW, Landis J, Anderson RA. Effects of a water-soluble cinnamon extract on body composition and features of the metabolic syndrome in pre-diabetic men and women. J Int Soc Sports Nutr 2006;3(2):45.
[36] Hlebowicz J, Hlebowicz A, Lindstedt S, Björgell O, Höglund P, Holst JJ, et al. Effects of 1 and 3 g cinnamon on gastric emptying, satiety, and postprandial blood glucose, insulin, glucose-dependent insulinotropic polypeptide, glucagon-like peptide 1, and ghrelin concentrations in healthy subjects. Am J Clin Nutr 2009;89(3):815–21.
[37] Magistrelli A, Chezem JC. Effect of ground cinnamon on postprandial blood glucose concentration in normal-weight and obese adults. J Acad Nutr Diet 2012;112(11):1806–9.
[38] Ranasinghe P, Jayawardana R, Galappaththy P, Constantine G, de Vas Gunawardana N, Katulanda P. Efficacy and safety of 'true'cinnamon (Cinnamomum zeylanicum) as a pharmaceutical agent in diabetes: a systematic review and meta-analysis. Diabet Med 2012;29(12):1480–92.
[39] Tangvarasittichai S. Oxidative stress, insulin resistance, dyslipidemia and type 2 diabetes mellitus. World J Diabetes 2015;6(3):456.
[40] Hajimonfarednejad M, Nimrouzi M, Heydari M, Zarshenas MM, Raee MJ, Jahromi BN. Insulin resistance improvement by cinnamon powder in polycystic ovary syndrome: a randomized double-blind placebo controlled clinical trial. Phytother Res 2017;32(2):276–83.
[41] Imparl-Radosevich J, Deas S, Polansky MM, Baedke DA, Ingebritsen TS, Anderson RA, et al. Regulation of PTP-1 and insulin receptor kinase by fractions from cinnamon: implications for cinnamon regulation of insulin signalling. Hormone Res Paediatr 1998;50(3):177–82.
[42] Oliveira BA, Pinhel MA, Nicoletti CF, Oliveira CC, Quinhoneiro DC, Noronha NY, et al. UCP1 and UCP3 expression is associated with lipid and carbohydrate oxidation and body composition. PLoS One 2016;11(3):e0150811.
[43] Golmohammadi E, Mahmazi S, Rahnema M. Cinnamon hydro alcoholic extract increased expression level of UCP3 gene in skeletal muscle of obese male Wistar Rats. bioRxiv 2017:105155.
[44] Shen Y, Honma N, Kobayashi K, Jia LN, Hosono T, Shindo K, et al. Cinnamon extract enhances glucose uptake in 3T3-L1 adipocytes and C2C12 myocytes by inducing LKB1-AMP-activated protein kinase signaling. PLoS One 2014;9(2):e87894.
[45] Cao H, Polansky MM, Anderson RA. Cinnamon extract and polyphenols affect the expression of tristetraprolin, insulin receptor, and glucose transporter 4 in mouse 3T3-L1 adipocytes. Arch Biochem Biophys 2007;459(2):214–22.
[46] Qin B, Nagasaki M, Ren M, Bajotto G, Oshida Y, Sato Y. Cinnamon extract (traditional herb) potentiates in vivo insulin-regulated glucose utilization via enhancing insulin signaling in rats. Diabetes Res Clin Pract 2003;62(3):139–48.
[47] Broadhurst CL, Polansky MM, Anderson RA. Insulin-like biological activity of culinary and medicinal plant aqueous extracts in vitro. J Agric Food Chem 2000;48(3):849–52.
[48] Anderson RA, Broadhurst CL, Polansky MM, Schmidt WF, Khan A, Flanagan VP, et al. Isolation and characterization of polyphenol type-A polymers from cinnamon with insulin-like biological activity. J Agric Food Chem 2004;52(1):65–70.