Analysis of the Efficacy of Cinnamon for Patients with Diabetes Mellitus Type II Based on Traditional Persian Medicine Syndrome Differentiation: A Randomized Controlled Trial

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Abstract

Background: Conflicting results have been obtained from the studies on the hypoglycemic effect of cinnamon in patients with diabetes mellitus type II (T2DM).

Objectives: This research aimed at assessing the effect of applying the syndrome differentiation model based on traditional Persian medicine (TPM) to identify the patients who benefit more from cinnamon supplementation.

Methods: This study was a randomized, triple-blind, placebo-controlled trial based on a parallel design. One hundred and forty eligible patients referring to the Diabetes Clinic of Yazd University of Medical Sciences, who were diagnosed with T2DM, were randomly divided into the cinnamon and placebo groups. Then, 500-mg capsules of cinnamon bark powder or placebo were administered to them twice a day for three months. All the participants completed a standard questionnaire for syndrome diagnosis in traditional Persian medicine (TPM). Fasting plasma glucose (FPG), glycated hemoglobin (HbA1C), fasting insulin (FI), and insulin resistance (IR), calorie intake, and physical activity were measured before and after the interventions. The glycemic outcomes were analyzed according to the TPM syndrome.

Results: There was no statistically significant difference between the patients' demographic and clinical features in the two groups. Glycemic indices were improved in patients receiving cinnamon supplementation compared to placebo group (-13.1 ± 1.7, -1.7 ± 1.9, P < 0.001 for change in FPG and -0.27 ± 0.039 vs. 0.001 ± 0.019, P < 0.001 for change in HbA1C respectively). All the outcomes were more improved in the patients with wet syndrome compared to dry ones, which was compatible with Persian syndrome differentiation (P < 0.05).

Conclusions: Diabetic patients with wet syndrome based on TPM benefit more form cinnamon supplementation.

Keywords: Cinnamon, Diabetes Mellitus, Syndrome Differentiation, Traditional Medicine Phytotherapy

1. Background

Diabetes mellitus is a group of metabolic diseases with an increasing incidence throughout the world. It is known as one of the leading causes of mortalities and underlying conditions for cardiovascular diseases (1). Despite the growing success of conventional medicine, many diseases, especially chronic disorders, have been left untreated or inadequately treated and are sometimes associated with complications in the involved patients (2). This led some patients to take advantage of a variety of complementary and alternative therapies in order to be treated (3).

Recently, special attention has been paid to "personalized medicine" within the framework of conventional medicine. This branch of medicine aims to achieve an appropriate treatment for each person individually (4). Researchers in this field believe that treatment methods should focus on the hosts of diseases instead of the diseases themselves. Personalized medicine tries to establish a health/therapeutic model to enter the psychological, environmental, mental, and biological aspects of treatments for patients and help them maintain their health (5).

TPM is a traditional medical system highly used by patients with diabetes in Iran. TPM, like other traditional medical approaches, applies a specific type of diagnostic model for patients' individualization, known as syndrome differentiation in the literature (6). The syndromes in TPM are defined based on a concept which is called Mizaj.

Mizaj is a phenomenon created by the interactions of various elements in the body. Mizaj affects the phenotypic characteristics and physiological functions of the body (7, 8). Each person has a special Mizaj, which is evaluated based on the two spectra of warm/cold and wet/dry qualities (7). According to the theory of Mizaj, any treatments should be selected based on the Mizaj of the patient and the disease, using a drug with reverse Mizaj (hot drugs for cold diseases, dry drugs for wet diseases, and vice versa) (9). Therefore, different treatments may be considered for the same disease (such as diabetes) based on the patient's Mizaj (10).

Cinnamon (*Cinnamomum verum*) is a popular medicinal plant mostly investigated in the field of diabetes. Cinnamon induces auto-phosphorylation and dephosphorylation of the insulin receptors and synthesis of the glucose transporter GLUT4 receptors. Cinnamon also alters hepatic glucose metabolism through modulation in phosphoenolpyruvate carboxykinase and pyruvate kinase. Inhibition of intestinal glucosidases is another suggested mechanism responsible for the anti-glycaemic effect of cinnamon. Cinnamon's anti-diabetic effects have been evaluated through numerous human and animal studies, leading to conflicting results (11-15). According to the TPM syndrome differentiation model, cinnamon has a hot and dry Mizaj and is more effective on diabetic patients with cold and wet Mizaj.

2. Objectives

Accordingly, this study was designed to evaluate the effect of applying the syndrome differentiation model based on TPM to identify the patients who benefit more from cinnamon supplementation.

3. Methods

3.1. Study Setting

This study was a randomized, triple-blinded, placebo-controlled clinical trial. All the T2DM patients were invited to the Diabetes Research Center, Yazd University of Medical Sciences, Iran, from April to October 2017. After the research method was explained to the participants, all of them signed an informed consent form. Afterwards,

they were selected based on the eligibility criteria. The patients' demographic and clinical features were recorded. Moreover, their physical activities and dietary intakes were registered according to the International Physical Activity Questionnaire and Food Frequency questionnaire, respectively. Their baseline blood samples were taken in the laboratory.

The study was approved with the reference number: IR.SUMS.REC.1395.176 by the Local Medical Ethics Committee of Shiraz University of Medical Sciences. Registration of the trial protocol with the registration ID: IRCT2017031133015N1 was carried out in the Iranian Registry Database of Clinical Trials.

3.2. Inclusion and Exclusion Criteria

This study was performed on both male and female patients, aged 30 - 80 years, and diagnosed with T2DM by an endocrinologist based on the American Diabetes Association (ADA) criteria and a fasting blood glucose (FBG) level of 126 - 250 mg/dL. Those who consumed only oral hypoglycemic agents for their diabetes, and did not have any uncontrolled co-morbid diseases, were included in this study. The patients who were reporting a change of treatment during the study, having any allergic reactions to cinnamon, consuming less than 80% of the prescribed capsules and women with pregnancy or lactation were excluded from the study. No limitation on the duration of diabetes was applied for patient inclusion.

3.3. TPM Syndrome (Mizaj) Evaluation

All participants completed the 10-item Mizaj Questionnaires of Mojahedi et al. (10) based on a 3-point Likert scale (Table 1). The questions were asked by the researcher, and the results were recorded in the pre-designed forms. The researcher tried to equalize the perceptions of the items. The first (1-8) and the second (9, 10) domains of the questions were related to the warmness and wetness dimensions of Mizaj, respectively. In the mentioned domains, the total scores of ≤ 14, 15 - 18, and ≥ 19 indicated cold, moderate, and warm Mizaj conditions, and those of ≤ 3, 4, and ≥ 5 were considered as wet, moderate, and dry Mizaj states, respectively (10).

3.4. Drugs

Cinnamon bark was purchased from a store in Shiraz, and then was confirmed by a herbalist (Mrs. Khademian), and a voucher sample (PM-996) was deposited in the herbarium of Shiraz pharmacy school. After being rinsed, dried, and powdered, it was filled into 500 mg capsules. The placebo capsules with a similar amount of heated

Table 1. Mizaj Questionnaire[a, b]

	Question	1	2	3
1	When others touch your skin, what do they say about its warmness or coldness?	Cold	Not cold, not warm	Very warm
2	How big is the palm of your hand?	Small	Not small, not big	Big
3	How fast are you influenced by warmness and coldness?	I feel cold, fast.	I feel the same in both cases.	I feel warm, fast.
4	How do you pronounce several consequent sentences?	Articulate	Not articulate, not continuous	Continuous
5	How is your rage and anger?	I get angry late	I get angry no late no fast	I get angry fast
6	How fast are you influenced by warm nature foods like honey, spices, pepper or cold nature foods like buttermilk, yogurt and cucumber?	I feel cold, fast by cold nature foods	I feel the same in both cases.	I feel warm, fast by warm nature foods.
7	How is your voice power compared to others?	Weak	Not weak, not strong	Strong
8	How is your physical movements compared to others?	Very slow	Not slow, not fast	Fast
9	Are you fat or thin compared to others?	Very fat	Not fat, not thin	Very thin
10	How is the condition of your skin's softness and coarseness?	Very soft	Not soft, not coarse	very coarse

[a] The score of the hot-cold scale could be 8 to 24. Hot $\geq$ 19, cold $\leq$ 14.

[b] The score of the wet-dry scale could be 2 to 6. Dry $\geq$ 5, wet $\leq$ 3.

starch (turned into brown color) were prepared. The bottles of packaged cinnamon and placebo capsules were numbered and then were selected randomly. The cinnamon essential oil was extracted and analyzed by Gas Chromatography/Mass Spectrometry (GC/MS).

3.5. Intervention

The capsules were administered to the patients twice a day (after fasting overnight in the morning and before going to bed at night) for three months. During the first month, the supplements were delivered to the patients, and through a follow-up phone call every two weeks, they were asked whether they were taking the drugs regularly and if they were experiencing side effects. After the first month, only the patients who had used more than 80% of the capsules were treated using the same procedure for another two months; the rest of the patients were excluded from the study. Upon completing the three months of treatment, the patients' biochemical markers were reassessed.

3.6. Outcome Measures

Measurements of the biochemical outcomes were conducted at the admission and the end of the three-month intervention, in accordance with the following procedures: the patients' FBG levels were measured by taking 5 ml of their blood after 12 hours of fasting by glucose peroxidase method using an assay kit (Pars Azmoon Company, Tehran, Iran) and an auto-analyzer device (Echo Plus Inc Co, Italy). Glycated hemoglobin (HbA1C) was measured after its primary separation via the ion-exchange chromatographic

method (biosystems). Insulin level and resistance were determined using ELISA kits (Diametra Corporation, Milan, Italy) and Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) through the equation of [FBG (mg/dL) $\times$ serum insulin (mU/mL)]/405, respectively ([16], [17]).

3.7. Randomization and Blinding

This study was a randomized, triple-blinded, placebo-controlled clinical trial. Computer-generated block randomization lists using a 1:1 allocation ratio and block size of 4 were used. An independent person, who did not have any contacts with the patients, filled the bottles of the supplement and placebo capsules, labelled as the categories of A and B, the contents of which were not revealed for any of the patients or the responsible physician and the person allocating the groups. The patients could receive any randomized bottle decoded from the researcher according to the randomization table obtained from the original form of the randomization results.

Finally, a statistician analyzed the results obtained from the cinnamon (A) and placebo (B) groups.

3.8. Sample Size Calculation and Statistical Analyses

A sample size of 120 patients was estimated for a one-sided testing at a 0.05 significance level with a power of 0.80. Given the probability of 15% for the dropped-out patients, a total of 140 patients were enrolled in this study. The patients' demographics and clinical features were represented as mean $\pm$ SD or percentage where appropriate. Chi-square test and ANOVA were applied in the statistical

analyses using the Statistical Package for the Social Sciences, version 18.0 (SPSS Inc., Chicago, IL, USA). A P value of < 0.05 was considered significant.

4. Results

4.1. Drug Analysis

Gas chromatography/mass spectrometry (GC/MS) analysis revealed that cinnamaldehyde and 4-methoxycinnamaldehyde (3.26%), α-copaene (0.86%), δ-Cadinene (1.61%) and α-Muurolene (0.68%) are the major constituents of cinnamon bark essential oil, respectively.

4.2. Study Flow

140 patients out of 204 T2DM patients, who had agreed to take part in this study, were randomly assigned to the cinnamon and placebo groups during April to October 2017. According to the Mizaj distribution in each group, patients were categorized into six subgroups (wet, moderate, dry, cold, moderate, and hot). One patient in the cinnamon group was omitted due to migration (loss of follow-up). Another patient in the placebo group was also excluded due to self-reporting an allergic reaction which led to discontinuation of the medication. 138 patients were included in the data analysis (Figure 1).

4.3. Baseline Characteristics

As shown in Table 2, there was no statistically significant difference between the patients' demographic and clinical features in the two groups. No significant difference in Mizaj distribution was present in two groups (Table 3).

4.4. Glycemic Outcomes

Patients in the cinnamon group showed significantly higher improvement of the mean glycemic indices (FBS, HbA1c), insulin levels, and resistance (HOMA index) compared with the placebo group (Table 4). All the outcomes were improved in patients with cold and wet syndrome more than the hot and dry ones (Tables 4 and 5, Figure 2). This difference was statistically significant in patients with wet compared to dry syndrome.

However, the patients' glycemic outcomes, except 2hpp, showed a significant improvement regardless of the coldness and warmness of Mizaj (Table 5).

No adverse effects were reported by any of the patients in the cinnamon group. An allergic reaction to the placebo was reported by one patient of dry Mizaj syndrome, leading to the discontinuation of the intervention. After one week, his allergic symptoms disappeared with no need for further intervention. The patients reported no other adverse effects.

Table 2. Baseline Demographic and Clinical Characteristics of Type II Diabetes Mellitus Patients in Cinnamon and Placebo Groups[a]

Characteristics	Placebo	Cinnamon	P Value[b]
Age, y	53.20 ± 8.5	52.17 ± 9.7	0.51
Gender (female/male)	26/43	37/32	0.06
Physical activity	1.10 ± 0.30	1.13 ± 0.33	0.59
Duration of diabetes, y	5.27 ± 3.8	5.66 ± 4.1	0.56
Calorie intake, Kcal/d	501.92 ± 118.25	2471.82 ± 316.85	0.46
Weight, kg	74.37 ± 11.6	75.72 ± 11.6	0.49
BMI, kg/m²	29.33 ± 17.11	29.92 ± 12.3	0.81
HbA1C, mg/dL	7.43 ± 0.82	7.36 ± 0.71	0.59
FBS, mg/dL	159.39 ± 35.3	162.57 ± 30.06	0.56
2hpp, mg/dL	208.21 ± 47.8	210.47 ± 44.4	0.77
Insulin, mg/dL	11.46 ± 4.50	10.64 ± 4.26	0.27
Insulin resistance (HOMA-IR)	4.51 ± 2.13	4.24 ± 1.79	0.42

Abbreviations: BMI, body mass index; FBS, fasting blood glucose; 2hpp, two hour postprandial blood glucose; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance.
[a]Values are expressed as mean ± SE.
[b]Chi-square test for categorical variable and *t*-test for quantitative variable.

Table 3. Mizaj Distribution of Type II Diabetes Mellitus Patients in Cinnamon and Placebo Groups

| Mizaj	Cinnamon	Placebo	P Value[a]
Cold	29	19	
Moderate (coldness/warmness)	19	31	0.079
Warm	21	19	
Wet	27	21	
Moderate (wetness/dryness)	23	30	0.427
Dry	19	18	

[a]No significant.

5. Discussion

In this study, supplementation with a one-gram daily dose of cinnamon for three months led to improved glycemic indices (FPG and HbA1C) and insulin resistance compared with placebo. All the outcomes were more enhanced in patients with wet syndrome compared with the dry ones. These findings were compatible with Persian syndrome differentiation.

The improvements of the diabetic patients' glycemic outcomes were compatible with those observed in the previous studies in terms of reducing FBS (12, 18, 19), 2hpp (20, 21), HbA1c (11, 22), and IR (23, 24) and increasing insulin secretion (22). In contrast, some other studies did not report
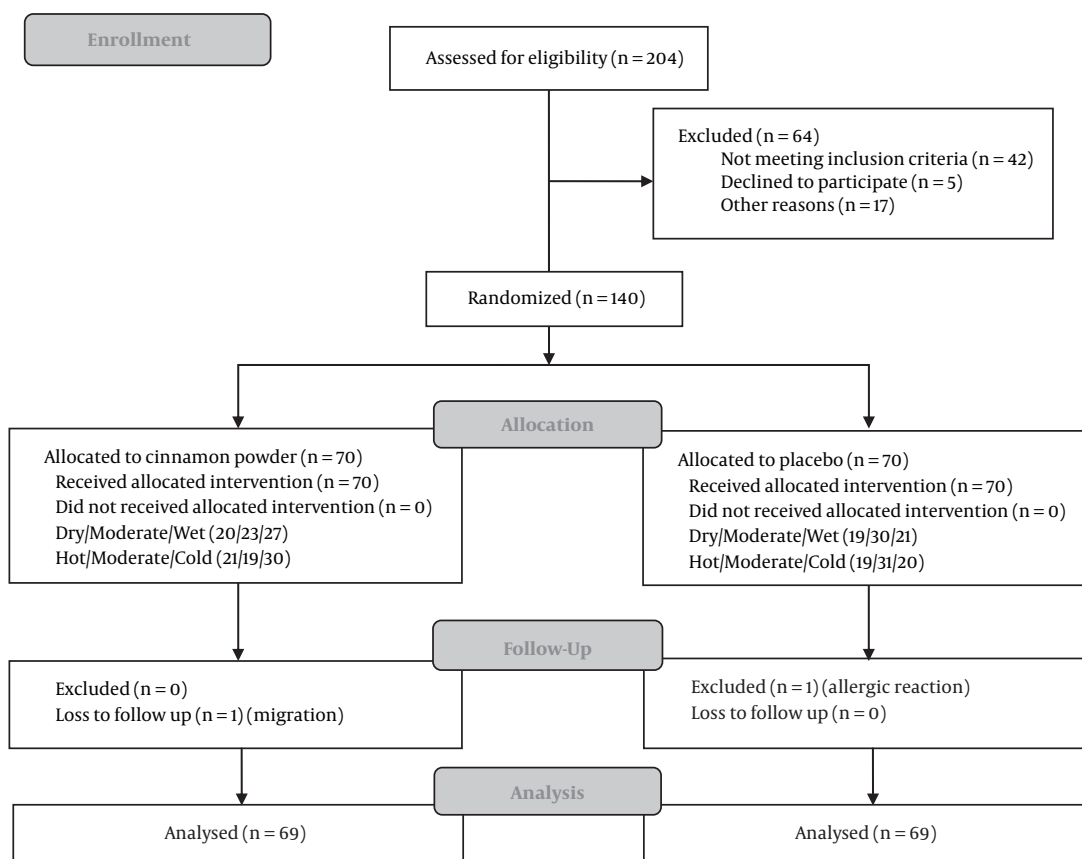
Figure 1. Flowchart of study
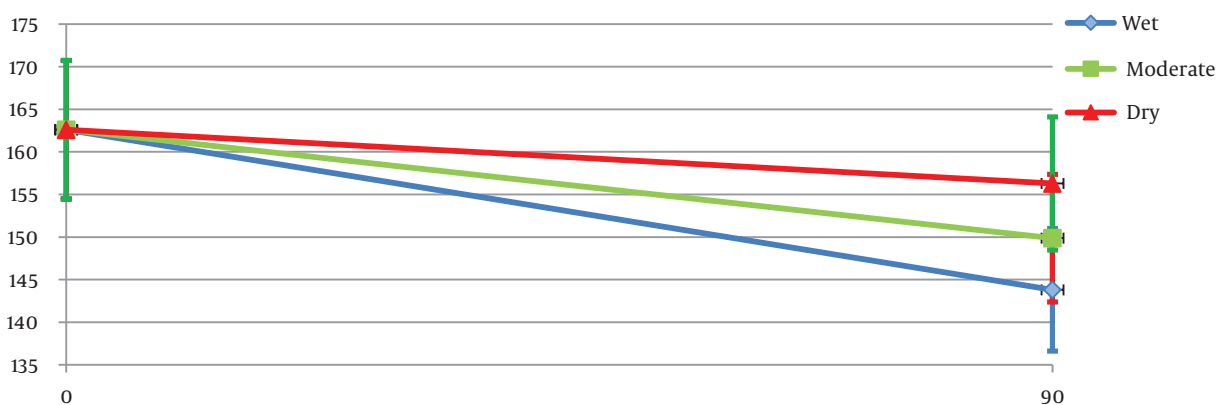
Figure 2. Changes of Fasting Blood Glucose differentiated by Traditional Persian Medicine syndromes in patients receiving cinnamon

similar results for diabetic patients' glycemic outcomes ([12], [15], [25], [26]). Therefore, this study tried to address this discrepancy by differentiating patients responsive to cinnamon supplementation based on the traditional Persian medicine syndrome differentiation method. The findings show that cinnamon supplementation in patients with a wet Mizaj may be more effective on improvement of the glycemic parameters. To the best of our knowledge, the ef-

Table 4. Changes in Glycemic Outcomes of Type II Diabetes Mellitus Patients Based on the Wetness and Dryness of Mizaj in the Cinnamon and Placebo Groups

Characteristics	Mizaj	Cinnamon (N = 27/23/19)[b]	Placebo (N = 21/30/18)[b]	Mean Difference	P Value[c]
Fasting blood glucose, mg/dL	Wet	-18.18 ± 2.69	0.76 ± 1.18	18.94 ± 3.4	< 0.001
	Moderate	-12.73 ± 3.19	-2.23 ± 1.5	10.50 ± 3.2	0.002
	Dry	-6.31 ± 2.26	-3.6 ± 0.56	2.70 ± 2.7	0.328
	P[d]	0.016	0.201		
	Total	-13.1 ± 1.7	-1.7 ± 1.9		< 0.001
Glycosylated hemoglobin (HbA1c), %	Wet	-0.366 ± 0.03	0.05 ± 0.017	0.42 ± 0.04	< 0.001
	Moderate	-0.33 ± 0.09	0.013 ± 0.015	0.43 ± 0.100	< 0.001
	Dry	-0.063 ± 0.053	-0.088 ± 0.056	-0.025 ± 0.06	0.688
	P	0.003	0.012		
	Total	-0.27 ± 0.04	0.001 ± 0.02		< 0.001
Insulin, mIU/L	Wet	-2.19 ± 0.21	-0.003 ± 0.04	2.18 ± 0.22	< 0.001
	Moderate	-2.06 ± 0.54	-0.006 ± 0.02	2.05 ± 1.54	0.001
	Dry	-0.85 ± 0.16	0.03 ± 0.05	0.892 ± 0.18	< 0.001
	P	0.026	0.709		
	Total	-1.77 ± 0.41	0.005 ± 0.02		< 0.001
HOMA-IR	Wet	-1.35 ± 0.14	-0.008 ± 0.05	1.34 ± 0.16	< 0.001
	Moderate	-1.04 ± 0.24	-0.020 ± 0.05	1.02 ± 0.22	< 0.001
	Dry	-0.50 ± 0.10	-0.070 ± 0.04	0.43 ± 0.11	0.001
	P	0.006	0.766		
	Total	-1.01 ± 0.11	-0.03 ± 0.03		< 0.001

[a]Values are expressed as mean ± SE.
[b]N (Cinnamon): wet = 27, moderate = 23, dry = 19/N (placebo): wet = 21, moderate = 30, dry = 18.
[c]Post Hoc tests (multiple comparisons).
[d]ANOVA (between groups).

fects of Mizaj, as a predictor of diabetic patients' responses to supplementation of cinnamon, have not been investigated previously.

Applying syndrome differentiation model based on TPM to identify the patients who will benefit more from cinnamon supplementation was reported in multiple previous studies. Kamali et al. (27) investigated the effects of pomegranate extract on patients with ulcerative colitis. They reported significantly better outcomes in patients with hot syndrome compared with cold syndrome. Another study by Niazi et al. (28) assessed the effects of topical rose oil on migraine and reported that the oil leads to more short-term pain relief in hot type patients compared with the cold ones. TPM-based syndrome differentiation also successfully differentiated patients responding to the lipid-lowering effects of Sumac in another study carried out by Hajmohammadi et al. (29).

No previous study was found on syndrome differentiation based on traditional Persian medicine in patients with

diabetes. However Chinese medicine based syndrome differentiation theories such as QI stagnation due to liver depression, liver and stomach heat stagnation, phlegm and heat stasis, excess heat in the stomach and intestine, intestinal damp and heat syndromes, and dual deficiency of Qi and Yin are previously used to describe differences in patients with diabetes (30).

The most important limitation of this study was the instrument used for Mizaj evaluation. Mojahedi questionnaire, which was used to differentiate patients with different Mizaj in our study, has been used and validated in multiple studies. However, it has not been previously approved in patients with diabetes.

5.1. Conclusions

The results of the current study, along with the previous studies applying the syndrome differentiation model of TPM, showed the potential of this theory to differentiate patients responding to herbal supplements. This person-

Table 5. Changes in Glycemic Outcomes of Type II Diabetes Mellitus Patients Based on the Coldness and Warmness of Mizaj in the Cinnamon and Placebo Groups[a]

Characteristics	Mizaj	Cinnamon (N = 29/19/21)[b]	Placebo (N = 19/31/19)[b]	Mean Difference	P Value[c]
Fasting blood glucose, mg/dL	Cold	-14.06 ± 3.37	2.00 ± 1.34	16.06 ± 4.3	0.001
	Moderate	-14 ± 2.4	-3.12 ± 0.37	10.87 ± 2.5	< 0.001
	Warm	-10.9 ± 2.18	-3.00 ± 2.1	7.95 ± 3.04	0.013
	P[d]	0.708	0.056		
	Total	-13.1 ± 1.7	-1.7 ± 1.9		< 0.001
Glycosylated hemoglobin (HbA1c), %	Cold	-0.32 ± 0.08	0.05 ± 0.025	0.38 ± 0.106	0.001
	Moderate	-0.31 ± 0.04	0.019 ± 0.018	0.29 ± 0.03	< 0.001
	Warm	-0.15 ± 0.03	-0.021 ± 0.05	0.13 ± 0.06	0.042
	P	0.154	0.012		
	Total	-0.27 ± 0.04	0.001 ± 0.02		< 0.001
Insulin, mIU/L	Cold	-2.24 ± 0.41	-0.03 ± 0.03	2.20 ± 0.51	< 0.001
	Moderate	-1.53 ± 0.32	-0.005 ± 0.03	1.52 ± 0.32	< 0.001
	Warm	-1.36 ± 0.27	0.06 ± 0.04	1.42 ± 0.28	< 0.001
	P	0.177	0.224		
	Total	-1.77 ± 0.41	0.005 ± 0.02		< 0.001
HOMA-IR	Cold	-1.23 ± 0.19	0.05 ± 0.044	1.29 ± 0.20	< 0.001
	Moderate	-1.91 ± 0.17	-0.06 ± 0.045	1.84 ± 0.14	< 0.001
	Warm	-0.80 ± 0.17	-0.052 ± 0.084	0.75 ± 0.19	< 0.001
	P	0.220	0.287		
	Total	-1.01 ± 0.11	-0.03 ± 0.03		< 0.001

[a]Values are expressed as mean ± SE.
[b]N (Cinnamon): cold = 29, moderate = 19, warm = 21/N (placebo): cold = 19, moderate = 31, warm = 19.
[c]Post Hoc tests (multiple comparisons).
[d]ANOVA (between groups).

alized approach can especially be beneficial in the explanation of the discrepancies in results of clinical studies on specific herbal drugs for a particular disease, for instance, cinnamon for diabetes mellitus.

Footnotes

Authors' Contribution: Roghayeh Zare did conceptualization, data curation, methodology, investigation, writing. Azadeh Najarzadeh did conceptualization, supervision, visualization, writing, review, and editing. Mohammad Mehdi Zarshenas did conceptualization, data curation, investigation, supervision, writing, review, and editing. Mesbah Shams did conceptualization, methodology, supervision, writing, review, and editing. Mojtaba Heydari did conceptualization, data curation, investigation, methodology, software, project administration, supervision, formal analysis, writing, original draft, writing, review, and editing.

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