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The effect of curcumin and piperine co-supplementation on glycemic indices in prediabetes: A triple-blind randomized controlled trial

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Abstract

Objective: Patients with prediabetes are at a higher risk of cardiometabolic diseases. There has been growing attention to the role of phytochemicals and nutraceuticals against prediabetes. Previous research supports the efficacy of curcumin in controlling blood glucose level in diabetes but its effect on prediabetes has not been adequately studied. This study aimed to evaluate the effect of curcumin and piperine on prediabetes.

Materials and Methods: This triple-blind, randomized controlled trial was performed on patients with prediabetes. The intervention group (n=34) received curcumin + piperine tablets (containing 500 mg curcumin plus 5 mg piperine), while the control group (n=34) used placebo for three months. Before and after three months, fasting blood glucose (FBG), hemoglobin A1c (HbA1c), HOMA-IR, C-reactive protein (CRP), insulin, and anthropometric indices were assessed. The measurements were analyzed using SPSS software.

Results: The mean age of participants was 48.4±10.82 years, and 55.8% were females. After the intervention, FBG and HbA1c did not differ significantly between the groups. After 3 months, CRP was significantly reduced in the curcumin + piperine group (p=0.01), while the insulin level increased significantly (p=0.03). After adjustment for CRP and weight at baseline, the difference in changes in insulin, HOMA-IR, and CRP levels between the two groups disappeared. Moreover, there were no changes in anthropometric indices in either group during the study period.

Conclusion: Our study revealed that the combination of curcumin and piperine had no significant impact on glycemic indices in patients with prediabetes. Evaluation of the precise effect of this combination on prediabetes requires more clinical trials with varying dosages and durations.

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Introduction

Diabetes is a growing health burden across the globe, with its incidence rate rapidly increasing (Lovic et al. 2020). Prediabetes is a range of glycemia between normal glucose regulation and diabetes (Herman 2023). The American Diabetes Association (ADA) characterizes prediabetes by hemoglobin A1C level of 5.7–6.4%, impaired glucose tolerance, or impaired fasting glucose (Association 2020). It is estimated that by 2045, approximately 540 million people will have prediabetes, and 70% could develop type 2 diabetes mellitus (T2DM) (Carris et al. 2019; Duan et al. 2021). Studies conducted recently have shown that individuals in a prediabetic state are at a higher risk of cardiometabolic diseases (Association 2020). Lifestyle modification, education, and specific medications can delay or prevent T2DM occurrence in subjects with prediabetes (Jin and Ma 2021; Magge et al. 2020).

In addition, there has been growing attention to the pharmaceutical potential of natural products and phytochemicals such as ginseng, garlic, ginger, and curcumin against prediabetes and T2DM (Mahdavi et al. 2021; Naseri et al. 2022). Several studies have reported the efficacy of curcumin in the prevention and treatment of T2DM (Den Hartogh et al. 2019; Heidari et al. 2023). Curcumin (1,7-bis-(4-hydroxy-3-methoxyphenyl)-hepta-1,6-diene-3,5-dione) is a bioactive polyphenol extracted from *Curcuma longa* L. (Kotha and Luthria 2019). Curcumin has been reported to exert inhibitory activities against inflammation and oxidative stress (Kahkhaie et al. 2019; Mohammadi et al. 2019; Panahi et al. 2016; Panahi et al. 2012; Saberi-Karimian et al. 2020; Sahebkar et al. 2013), and provide a myriad of salutary effects against a variety of diseases and pathological states such as cancer, diabetes, bacterial and viral infection, rheumatism, and fibrosis (Abd El-Hack et al. 2021; Bagheri et al. 2020; Fereydouni et al. 2019; Hamzehzadeh et al. 2018; Panahi et al. 2019; Sahebkar and Henrotin 2016; Shafabakhsh et al. 2019). However, the clinical application of curcumin has been limited due to low absorption and rapid metabolism which culminate in a low oral bioavailability (Lavian et al. 2023). To overcome the current limitations, different techniques have been employed to enhance the absorption or metabolism of curcumin. These include complexation with phospholipids, coadministration with absorption-boosting adjuvants like piperine, and nanoparticulate formulation, among others (Hegde et al. 2023). A systematic review showed that curcumin could improve fasting blood glucose (FBG), hemoglobin A1c (HbA1c), body mass index (BMI), C-reactive protein (CRP), and lipid profile significantly in T2DM individuals (Marton et al. 2021). Moreover, Chuengsamarn and colleagues reported that taking 1500 mg of curcumin daily for 9 months could meaningfully prevent developing T2DM in individuals with prediabetes (Chuengsamarn et al. 2012). The mechanism of action of curcumin against T2DM is not exactly determined, but it is thought that curcumin anti-inflammatory and anti-oxidative potential plays a significant role (Bozkurt et al. 2022; Mohammadi et al. 2021; Panahi et al. 2021; Sadeghi et al. 2023). Although there is some evidence suggesting the potential of curcumin on patients with T2DM and prediabetes, further research is needed to determine its precise efficacy in regulating glycemic indices and preventing T2DM development in individuals with prediabetes. This should be achieved through conducting more well-designed studies focused on the use of curcumin as a medication.

In the current clinical trial, we assessed the effect of curcumin-piperine supplement in controlling prediabetic status.

Materials and Methods

Study design

This study is a triple-blind, placebo-controlled, randomized controlled trial which was performed on 56 individuals with prediabetes. We conducted the study in Ghaem Hospital, Mashhad University of Medical Sciences, Mashhad, Iran, from June 2023 until March 2024. The eligible individuals were referred from the endocrinology clinic and Persian Cohort (Tohidinezhad et al. 2020) to Ghaem Hospital to undergo testing and participate in the research. After obtaining informed consent, individuals aged 18-70 years with impaired fasting glucose (FBG levels between 100 and 124 mg/dl) were enrolled in the study. We excluded patients who had confirmed T2DM, or severe systemic diseases such as chronic kidney disease (CKD) or hepatic failure or consuming anti-diabetic drugs, thiazides, glucocorticoids, antipsychotics, or anticoagulants (Kim et al. 2012). As the underlying diseases and medications may interfere with drug metabolism, causing hyperglycemia, hypoglycemia, and increasing risk of bleeding (Kim et al. 2012), we provided patients with detailed instructions about this medication and lifestyle modifications. It was recommended that they should adopt a healthier diet, lose weight, and exercise more frequently. At the baseline, anthropometric information such as weight, height, waist circumference (WC), blood pressure, and other information such as family history of T2DM, smoking, current and past illnesses, and drug history were taken from all participants. Then, we collected 5 ml blood samples of the brachial vein of each participant to measure FBG as the primary outcome, and HbA1c, insulin, and CRP levels as the secondary outcomes. Also, Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) was calculated as the secondary outcome using the following formula:

fasting insulin (microU/L) x fasting glucose (nmol/L)/22.5 (Salgado et al. 2010).

The blood samples were gathered in the morning, following a minimum of 8 hr of fasting. At the end of the study, we took the same measurements that were taken at the beginning. The participants were divided into two groups randomly. One group received curcumin + piperine treatment as the intervention, while the other group received placebo treatment as the control. The randomization was performed by a sealed envelope website, using block sizes of 4 and 6. In order to perform allocation concealment, each random number was written on a single paper and wrapped. By entering any eligible patient to the trial, we put and unwrapped a paper, and then, allocated a patient in the noted group (according to the codes). The patients, outcome assessors, and analyzers were unaware of which group was the intervention or placebo. All participants in both groups were instructed to take a daily tablet for three months. The intervention group tablets contained 500 mg curcumin plus 5 mg piperine (to increase bioavailability). In the placebo group, the tablets contained microcrystalline cellulose. The placebo and curcumin tablets were completely identical, with the same labels and packaging. Both curcumin and placebo tablets were manufactured by Sami-Sabinsa Group Limited. The study protocol was approved by the Ethics Committee of the Faculty of Medicine, Mashhad University of Medical Science, Mashhad, Iran (IR.MUMS.MEDICAL.REC.1401.593).
The study was registered in the Iranian Registry of Clinical Trials (IRCT) with the code IRCT20181022041407N2. The full study protocol was previously published in Herba Polonica (Emadzadeh et al. 2024).

Sample size calculation

Using the data from the study by Karandish et al. (Karandish et al. 2021) in which, fasting plasma glucose (FPG) was 103.48±8.87 and 110.8±10.46 in the intervention and placebo groups, respectively, we calculated the minimum

sample size based on the difference of two independent means by G*power software. Considering α= 0.05 and β=0.2, the sample size of 28 individuals was calculated in each group. Considering 20% drop-outs, 34 individuals were enrolled in each study group.

Statistical analysis

Data were analyzed using SPSS version 23. Categorical variables were assessed using Chi-square or Fisher's exact tests. To compare the laboratory findings and anthropometric indices between the two study groups, we used the independent sample t or Mann-Whitney tests (based on the normality of data distribution). The results of laboratory findings after 3 months from the beginning of the study were tested using analysis of covariance (ANCOVA) adjusting for CRP and weight at baseline. Intention-to-treat analysis was used to assess the intended outcomes. Statistical significance was considered at $p<0.05$.

Results

A total of 68 eligible participants including 38 (55.8%) females were enrolled in this study between June 2023 and March 2024. Recruited individuals were randomly divided into two groups. At the end of the study, 56 (82.3%) participants finished the tests and completed the final visit (Figure 1). The participants were between 30-70 years old, and the mean age was 48.4±10.82 years. Other demographic data are reported in Table 1.

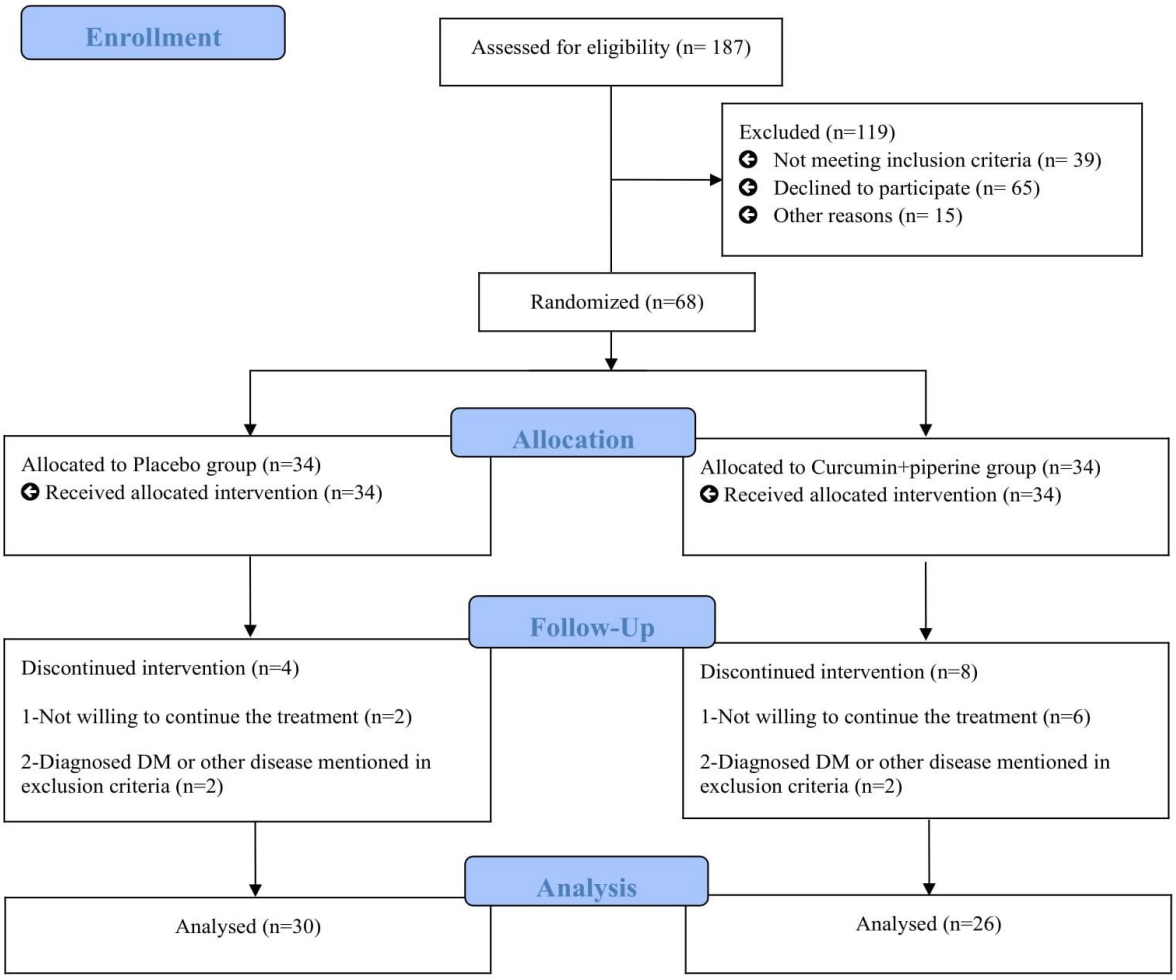

Figure 1. Flowchart of the study and assignment of participants to the curcumin plus piperine and placebo groups.

Table 1. The demographic data of participants with prediabetes in intervention (Curcumin plus piperine) and control groups.

Variables	Total n (%)	Placebo group n (%)	Curcumin+piperine group n (%)	p value
Age (years; Mean (SD))	48.4±10.82	48.76 ±10.87	48.03 ± 10.93	0.78*
Gender				
Male	30 (44.1%)	12 (35%)	18 (52.9%)	0.14**
Female	38 (55.8%)	22 (64.7%)	16 (47.1%)	
Family History of T2DM	42 (62.7%)	19 (55.9%)	23 (69.7%)	0.24**
Smoking	6 (9%)	1 (2.9%)	5 (15.2%)	0.1***
HTN	13 (19.1%)	11 (32.4%)	2 (5.9%)	0.006**
Thyroid disease	9 (13.2%)	3 (8.8%)	6 (17.6%)	0.476***
CVD	1 (1.5%)	1 (2.9%)	0 (0%)	>0.99***
Dyslipidemia	13 (19.1%)	8 (23.5%)	5 (14.7%)	0.355**

*Independent sample t-test; **Chi-Square test; ***Fisher's exact test. SD: standard deviation; T2DM: type 2 diabetes mellitus; HTN: hypertension; CVD: cardiovascular disease.

All data are reported based on an intention-to-treat analysis. Moreover, all of the outcomes of interest were reassessed using per-protocol analysis, and no specific changes were found between them (data not shown).

As demonstrated in Table 2, the baseline FBG levels of the two groups were approximately the same. After treatment with curcumin plus piperine, we found no significant difference in the mean level of FBG between the groups. Additionally, the changes between the baseline and final levels of FBG in each group did not differ considerably. Similarly, HbA1c level and the changes in HbA1c after treatment showed no significant differences between the groups. In contrast, as seen in Table 2, both insulin and HOMA-IR increased in the intervention and decreased in the control group, but after adjustment for baseline weight and CRP levels, these significant results disappeared. These findings indicated that both weight and CRP at baseline (t0) act as covariates on insulin levels.

The CRP level of the intervention group was significantly higher than that in the control group at baseline. However, the mean CRP level of the groups was not significantly different after the treatment. Furthermore, supplementation with curcumin plus piperine significantly decreased CRP levels after treatment. The incidence of diabetes was assessed in both groups at the end of the study, and no difference in the frequency of individuals with FBG≥126 mg/dl (p=0.7) was found between the groups.

We also evaluated the effect of curcumin-piperine supplementation on other factors such as weight, WC, BMI, systolic and diastolic blood pressure (Table 3). The baseline weight in the intervention group was significantly higher compared with the control group, and this difference persisted after treatment ($p<0.05$). In addition, there was no significant difference in the magnitude of weight change rate between the groups. Other anthropometric indices did not differ between the groups at the assessed time points.

Table 2. The baseline and follow-up levels of glycemic indices in the two study groups.

Variables	**Placebo group (mean ± SD)**	**Curcumin+piperine group (mean ± SD)**	**p value**	**p value (Adjusted)** §
FBG (mg/dl)				
Baseline (t0)	109.44 ± 6.11	109.14 ± 7.17	0.63*	
After treatment (t1)	110.0 ± 16.17	108.65 ± 25.99	0.32*	0.78
t1 – t0	0.90 ± 12.53	-0.92 ± 24.43	0.53*	
p value§§	0.65	0.46		
HbA1c (mmol/mol)				
Baseline (t0)	5.87 ± 0.68	5.72 ± 0.61	0.32**	
After treatment (t1)	5.85 ± 0.62	5.96 ± 0.63	0.24*	0.56
t1 – t0	0.09 ± 0.82	0.30 ± 0.71	0.15*	
p value§§	0.87	0.03		
Insulin (micIU/ml)				
Baseline (t0)	11.96 ± 8.92	11.64 ± 8.04	0.90*	
After treatment (t1)	9.50 ± 4.79	14.19 ± 11.18	0.09*	0.31
t1 – t0	-2.74 ± 7.64	1.97 ± 5.38	0.03*	
p value§§	0.09	0.08		
HOMA-IR				
Baseline (t0)	3.25 ± 2.47	3.15 ± 2.22	0.95*	
After treatment (t1)	2.59 ± 1.34	3.88 ± 3.08	0.059*	0.31
t1 – t0	-0.72 ± 2.11	0.56 ± 1.51	0.02*	
p value§§	0.12	0.78		
CRP (mg/L)				
Baseline (t0)	2.59 ± 3.02	4.31 ± 5.77	0.01*	
After treatment (t1)	4.55 ± 3.14	3.50 ± 2.84	0.27*	0.34
t1 – t0	2.16 ± 4.39	-1.33 ± 6.95	0.01*	
p value§§	0.005	0.74		

* Mann-Whitney test; **Independent sample t-test §The effect of treatment type was tested using analysis of covariance (ANCOVA). Outcome variable was the after treatment findings (t1) and adjusting was done for both weight and CRP at baseline (t0). §§Within group comparison by Wilcoxon Signed rank test.SD: standard deviation; FBG: Fasting Blood Glucose; HbA1c: hemoglobin A1c; HOMA-IR: Homeostatic Model Assessment for Insulin Resistance; CRP: C-reactive protein

Table 2. Anthropometric indices and blood pressure assessments after the intervention in both intervention (curcumin plus piperine) and control groups.

Variables	Placebo group (mean ± SD)	Curcumin+piperine group (mean ± SD)	p value
Weight *(kg)*			
Baseline (t0)	72.15 ± 14.98	79.95 ± 15.08	0.02*
After treatment (t1)	71.62 ± 12.18	79.03 ± 13.79	0.03*
t1 – t0	-0.35 ± 2.97	0.16 ± 2.46	0.45*
p value§§	0.48	0.56	
WC *(cm)*			
Baseline (t0)	93.21 ± 12.80	98.30 ± 11.51	0.09**
After treatment (t1)	93.38 ± 12.17	97.00 ± 8.74	0.22**
t1 – t0	-0.86 ± 10.27	-0.65 ± 6.46	0.57*
p value§§	0.67	0.61	
BMI *(kg/m^2)*			
Baseline (t0)	26.69 ± 4.95	27.94 ± 3.70	0.10*
After treatment (t1)	26.29 ± 3.46	27.86 ± 3.12	0.08**
t1 – t0	-0.09 ± 1.1	0.07 ± 0.89	0.47*
p value§§	0.48	0.49	
SBP *(mmHg)*			
Baseline (t0)	122.03 ± 12.13	121.54 ± 12.48	0.87**
After treatment (t1)	123.48 ± 12.82	122.08 ± 8.09	0.85*
t1 – t0	1.50 ± 11.16	0.25 ± 9.77	0.90*
p value§§	0.51	0.89	
DBP *(mmHg)*			
Baseline (t0)	76.70 ± 11.59	78.54 ± 7.37	0.34*
After treatment (t1)	77.92 ± 7.65	76.95 ± 6.30	0.71*
t1 – t0	0.91 ± 11.22	-1.41 ± 5.67	0.37**
p value§§	0.71	0.22	

*Mann-Whitney test; **Independent sample t-test. §§Within group comparison by Wilcoxon Signed rank test or paired sample t-test.. SD: standard deviation; WC: waist circumference; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure. Note t0 and t1 represents the baseline and after treatment, respectively.

Discussion

In this randomized trial, we have demonstrated that 500 mg curcumin plus 5 mg piperine could not improve FBG, HbA1c, insulin, or HOMA-IR significantly. In addition, curcumin plus piperine did not have a significant effect on anthropometric indices such as weight, WC, BMI, systolic blood pressure (SBP), or diastolic blood pressure (DBP).

Many studies reported promising effects of curcumin on T2DM. A systematic review in 2019 showed that curcumin could significantly improve serum glucose, lipid profile, and antioxidant enzyme activities while reducing oxidative stress and lipid peroxidation in patients with T2DM (Den Hartogh et al. 2019). Moreover, another review in 2021 revealed that curcumin notably enhanced insulin resistance, serum glucose, HbA1c, lipid profile, and

inflammatory biomarkers in patients with diabetes (Marton et al. 2021). By considering the beneficial effects of curcumin on T2DM, its possible role in preventing pre-diabetic condition from developing into T2DM needs to be evaluated. In 2012, a clinical study evaluated the effect of daily administration of 1500 mg curcumin for 9 months in individuals with prediabetes. After treatment, FBG, HbA1c, oral glucose tolerance test (OGTT) at 2 hr, HOMA-IR, weight, and WC were significantly reduced, and β-Cell function was meaningfully improved (Chuengsamarn et al. 2012). Another study used 180 mg of curcumin for 3 months in patients with impaired fasting glucose (IFG) or impaired glucose tolerance (IGT). It was observed that the treatment reduced insulin and HOMA-IR levels, while it had no effect on FBG, HbA1c, CRP, or anthropometric indices (Thota et al. 2019). Karandish et al. evaluated the effect of 500 mg of curcumin on overweight individuals with prediabetes for 90 days. It was revealed that curcumin improved FPG, HbA1c, insulin, and insulin resistance (IR) while it had no effect on weight or β -cell function (Karandish et al. 2021).

Due to the low bioavailability of curcumin, a widely utilized strategy has been the co-administration of curcumin and piperine, which has been shown to improve the pharmacokinetic properties of curcumin (Hegde et al. 2023; Shoba et al. 1998) and exert favorable clinical effects (Heidari et al. 2023). Neta and colleagues demonstrated that 500 mg curcumin plus 5 mg piperine could enhance hyperglycemia in T2DM patients after 3 months (Neta et al. 2021). In addition, a systematic review reported that 3 studies that used 1000 mg curcuminoids plus 10 mg piperine improved lipid profile and inflammation in T2DM patients after 3 months (Heidari et al. 2023). Another systematic review and meta-analysis in 2024 reported that curcumin and piperine supplementation in diabetes and prediabetes did not significantly reduce FPG, HOMA-IR, or BMI (Widjanarko et al. 2024). Moreover, a clinical trial in 2018 showed that 500 mg curcumin plus 5 mg piperine significantly decreased serum glucose, HbA1c, C-peptide, weight, and BMI after 3 months. However, this treatment did not have a notable effect on CRP, insulin, and HOMA-IR of the T2DM group compared to placebo (Panahi et al. 2018). The study conducted by Panahi et al. administered 1000 mg curcuminoids plus 10 mg piperine for 2 months in patients with metabolic syndrome. They demonstrated that this treatment alleviated oxidative and inflammatory status and caused a significant reduction in CRP level (Panahi et al. 2015).

There has been a lack of recent clinical evidence on the combined effect of piperine and curcumin in individuals with prediabetes. In this study, we administered 500 mg curcumin plus 5 mg piperine to improve its bioavailability and assessed its efficacy on the pre-diabetic condition. It is important to highlight that our findings are not entirely consistent with previous research, which may stem from a variety of factors. This inconsistency could arise from differences in medication dosages, the combinations of drugs used, the duration of the treatment regimen, and potentially varying patient demographics. Variations such as genetics, comorbid diseases, and interaction with other medications can significantly influence the effectiveness and outcomes of the treatments studied, underscoring the complexity of clinical research in this area.

The strength of our study was using a standard combination of medications, appropriate duration, and assessment of all related parameters. The limitation of our study was the small population of participants. Finally, a single dose of curcumin was tested in this trial, and it remains to be clarified if higher doses or longer treatment could have led to a greater effect.

Our study revealed that the combination of curcumin and piperine had no significant impact on glycemic indices in subjects with prediabetes. Investigation of precise effect of this combination on prediabetes requires more well-designed clinical trials with varying dosages and supplementation durations.

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Conflicts of interest

There was no conflict of interest.

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Ethical Considerations

The study protocol was approved by the Ethics Committee of the Faculty of Medicine, Mashhad University of Medical Science, Mashhad, Iran (IR.MUMS.MEDICAL.REC.1401.593).
The study was registered in the Iranian Registry of Clinical Trials (IRCT) with the code IRCT20181022041407N2.

Code of Ethics

IR.MUMS.MEDICAL.REC.1401.593

Authors' Contributions

Maryam Emadzadeh: Idea & Conceptualization, Research & Investigation, Analysis, Supervision, Writing, Revision & Editing, Funding Acquisition.
Hossein Ghazaee: Data curation, Original Draft Preparation, Writing
Amirhossein Sahebkar: Idea & Conceptualization, Research & Investigation, Project Administration, Supervision, Revision & Editing.
Zahra Mazloum Khorasani: Data curation, Revise & Editing, Supervision
All authors read and approved the final manuscript.

Artificial Intelligence (AI) Declaration:

We have used the Grammarly tool to fix grammatical issues.

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