ORIGINAL ARTICLE

The efficacy of curcumin-piperine supplementation in patients with nonproliferative diabetic retinopathy: An optical coherence tomography angiography-based randomized controlled trial

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Background: Diabetic retinopathy (DR) is one of the complications of diabetes. This study was conducted to investigate the effect of curcumin-piperine on laboratory factors and macular vascular in DR. **Materials and Methods:** The present study was a randomized, placebo-controlled, double-blind, parallel-arm clinical trial that was conducted on 60 patients with DR aged 30–65 years. Patients were randomized into two groups to receive (i) 1010 mg/day of curcumin-piperine (two tablets per day, each tablet containing 500 mg curcuminoids and 5 mg piperine) (n = 30) or (ii) the matched placebo (n = 30) for 12 weeks. The investigated factors included optical coherence tomography (OCT), optical coherence tomography angiography (OCTA), oxidative stress factors, C-reactive protein (CRP), fasting blood glucose (FBG), triglycerides (TGs), blood urea nitrogen (BUN), and creatinine. **Results:** The trial was completed by 27 patients in the intervention group and 29 patients in the placebo group. Curcumin-piperine significantly increased total antioxidant capacity (0.86 ± 0.66 vs. 0.45 ± 0.89; P = 0.022) and superoxide dismutases (0.77 ± 2.11 vs. −0.45 ± 3.08; P = 0.031), while it decreased and malondialdehyde (MDA) (−1.06 ± 5.80 vs. 1.89 ± 6.12; P = 0.043) and creatinine (−0.04 ± 0.16 vs. 0.03 ± 0.05; P = 0.042) compared with placebo. However, this supplement had no significant effect on CRP, FBG, TG, BUN, OCT, and OCTA. There were no adverse reactions. **Conclusion:** Curcumin-piperine is effective in improving oxidative stress and reducing creatinine in DR. Further trials are necessary to confirm these promising findings.

Key words: Curcumin, diabetes mellitus, diabetic retinopathy, oxidative stress, piperine

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INTRODUCTION

Diabetic retinopathy (DR) is an ocular complication that occurs as a result of uncontrolled diabetes, which can culminate in blindness. About 22.27% of patients with diabetes worldwide have DR.[1] Patients with diabetes generally suffer from persistent inflammation. The abnormal death of retinal cells in patients with retinopathy is triggered by the activation of caspases due to an increase in inflammatory cytokines in the

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retina.[2] In addition, continuous hyperglycemia can lead to an excessive increase in superoxide radicals in the mitochondria. Hence, hyperglycemia-induced oxidative stress aggravates the symptoms of the disease.[3] Moreover, DR is generally associated with dyslipidemia.[4]

Treatment strategies for DR include pharmacotherapy to control blood glucose and lipids, reduce inflammation, laser therapy, and eye surgery. Vascular endothelial growth factor (VEGF) causes excessive angiogenesis in the retina and aggravates ocular symptoms.[5] Therefore, the administration of anti-VEGF agents is pivotal in the treatment of most patients.[6] The existing solutions have side effects, sometimes not very effective and add to the treatment burden as they are expensive.[6]

Herbal medicines have been a subject of interest for thousands of years due to their potential to improve diabetes and alleviate its complications, including DR.[7] Curcumin is a bioactive ingredient of turmeric, which has been reported to exert beneficial effects against various pathological states[8-17] including diabetes.[18,19] This phytochemical moderates inflammation through different mechanisms including the reduction of inflammatory cytokines.[20-23] Moreover, several studies have recognized curcumin as an antioxidant compound[24] (Ahmadi, 2022 #55). Curcumin significantly reduces fasting blood glucose (FBG) and hemoglobin A_1c (HbA_1c) in hyperglycemia.[25] Curcumin can also enhance insulin sensitivity via several mechanisms.[26] In addition, curcumin is effective in reducing triglycerides (TGs) and low-density lipoprotein cholesterol levels.[27,28]

In animal studies, curcumin has been reported to reduce DR via improving retinal and photoreceptor function, and mitigating excessive apoptosis in the retina. Moreover, curcumin has been shown to decrease angiogenesis in the retina through reducing the expression of VEGF.[29] Curcumin is considered a safe supplement, as even doses exceeding 8 g/day have not led to any significant side effect.[30] Despite the many benefits of curcumin, this phytochemical has a low oral bioavailability due to its limited water solubility and high clearance rate.[31] This limitation can be addressed to a reasonable extent through coadministration of curcumin with piperine (derived from black pepper), which is a well-known absorption enhancer.[32]

Optical coherence tomography angiography (OCTA) is a new method of imaging the healthy and diseased eyes, which is more effective compared to older imaging modalities. OCTA is non-invasive and can provide accurate images of retinal and choroidal vessels without the need to receive contrast material. The images obtained from OCTA have a wide field of view and high quality, offering excellent resolution.[33] To date, there have been no studies evaluating the impact of curcumin-piperine cosupplementation on macular vascular density confirmed by OCTA indices in patients with DR. Hence, the purpose of the present randomized, double-blind, controlled trial is to evaluate the effects of curcumin-piperine on various laboratory parameters (including oxidative stress, inflammation, blood glucose and lipids, and renal factors) as well as macular vascular density measured by OCTA in individuals diagnosed with non-proliferative DR.

MATERIALS AND METHODS

Trial design

The present study was conducted as a randomized, placebo-controlled, double-blind, parallel-arm clinical trial at Faiz Hospital affiliated with Isfahan University of Medical Sciences, Isfahan, Iran, from February 2022 to February 2023. This study was part of a larger study whose details have already been reported under a protocol article.[34] The study protocol was reviewed and approved by the Research Ethics Committee of Isfahan University of Medical Sciences (registration code: IR.MUI.RESEARCH.REC.1400.253), and registered in the Iranian Registry of Clinical Trials (registration code: IRCT20201129049534N5). This trial was conducted in accordance with the Declaration of Helsinki principles.[35]

Before entering the study, written informed consent was obtained from all of the participants. For illiterate patients, written informed consent was obtained from their legal guardian(s). In addition, verbal informed consent was obtained from the illiterate participants themselves. We confirm that the participants (in the case of illiterate patients, their legal guardian[s]) were aware of the purpose, risks, and benefits of the study. We do not publish any personally identifiable information about patients, so the identity information of the patients will remain completely confidential.

Sample size

The most important finding of this study is the effects of curcumin on the accumulation of small blood vessels in the eye area (based on OCTA findings). Due to the novelty of this evaluation method, according to the researcher's knowledge, no interventional study has been conducted on it using antioxidant supplements. Therefore, the sample volume formula was calculated based on fasting blood sugar as follows:

The number of samples considering the first type error $\alpha = 0.05$ and the second type error $\beta = 0.20$ with the power of the test 80% and the standardized effect size equal to $\Delta = 25$ (25 mg/dL blood sugar) for sugar changes fasting

blood was calculated using a previous study[36] from the following formula:

$$n = 2([Z1-\alpha/2 + Z1-\beta]^2 \times S^2]/\Delta 2 = 2([1.96 + 0.84]^2 \times [27]^2)/(25)^2$$

The required sample size was determined to be 25 people in each group, and taking into account the loss of people, we considered the actual sample size to be 30 people in each group and 60 patients in total.

Participants

Patients aged 30–65 years with DR were included in the present study. The endocrinologist diagnosed diabetes after observing FBG above 126 mg/dL in two measurements or HbA_1c ≥6.5%, and DR was diagnosed with an eye examination by an ophthalmologist.

The exclusion criteria were allergy to turmeric and pepper, following a special diet or taking any food supplements in the last 3 months, taking anticoagulants such as heparin, warfarin, aspirin, etc., receiving insulin, anti-VEGF therapy, laser therapy, eye surgery and intraocular injection, glaucoma, macular edema, and ocular uveitis. If the patient stopped continuing the study for any reason, he/she had the right to withdraw from the study immediately and without hindrance. Other factors for patients to drop out included taking <90% of the curcumin-piperine supplement, reporting side effects after taking the supplement, and any change in other medications.

Randomization and interventions

After accepting the informed consent, the patients were immediately randomized by the very popular and well-known website, (https://www.sealedenvelope.com/simple-randomiser/v1/lists) using permuted block randomization method using 4 blocks based on age and gender in a ratio of 1:1 they were placed in one of the two groups receiving curcumin-piperine or placebo.

The participants stratified based on age and gender. The patients were 30–65 years old. In age division, two groups of 30–49 and 50–65 years were considered for randomization. This division was determined by considering the age of menstruation and other metabolic changes related to aging.

Using an array of random numbers, an independent statistician provided the assignment sequences, which were then retained in sealed, and opaque envelopes until the eligibility criteria were assessed. Neither researchers nor patients were aware of the treatment assignment until the data analysis was completed.

Half of the patients (n = 30) were included in the curcumin-piperine intervention group. These patients received two curcumin-piperine tablets daily for 12 weeks (each tablet containing 500 mg of curcumin and 5 mg of piperine; a total of 1000 mg of curcumin and 10 mg of piperine per day). The other half of the patients (n = 30) were also placed in the same placebo group. These patients received two placebo tablets daily (each tablet containing 505 mg of maltodextrin, a total of 1010 mg/day) for 12 weeks. Tablets were received in both groups at 9:00 and 18:00. Curcumin-piperine and placebo tablets were manufactured by Sami Labs Limited (Bangalore, India).

In previous studies, the usual dose of curcumin-piperine for the improvement of metabolic diseases was between 500 and 1000 mg/day.[37,38] However, it has been reported to be safe even at a dose of 8,000 mg/day for 12 weeks.[39,40] Furthermore, a recent meta-analysis reported the dose of curcumin in diabetes in trials between 300 and 1500 mg per day and the intervention period between 8 and 24 weeks. In addition, most studies had a 12-week period and a dose of 1000–1500 mg per day.[41] Therefore, in this study, a dose of 1010 mg of curcumin-piperine (1000 mg of curcumin and 10 mg of piperine per day) and a period of 12 weeks were considered.

The amount of tablets consumed by the patients was evaluated and controlled by counting the number of tablets remaining in the bottles after every month. If the number of tablets consumed was <90% of the total tablets, the patient was excluded.

Every week, patients were reminded to take supplements by phone call and SMS. If the patient missed a dose of the supplement, the recommended course of action was to take the supplement immediately after the recall. If too much time had elapsed since the consumption time, it was deemed a missed turn. While these missed turns caused < 90% of the total pill intake, the patient was abandoned. Furthermore, in these calls, we asked about side effects.

Blinding

The intervention and placebo tablets were produced by the manufacturing company in the same way in terms of appearance and smell and were labeled A and B. So that all the people involved in the implementation of the research plan, including researchers, laboratory staff, outcome assessors, and data analysts, as well as patients, did not know about the label until after the final analysis of the data. Therefore, the study was conducted in a double-blind manner.

Measurements

Socio-demographic parameter assessment

Socio-demographic data including age, sex, family history of diabetes, family history of DR, education, smoking,

job, and marital status, were collected by a nutritionist through a structured interview from all persons at baseline. Furthermore, other medicines used by patients were evaluated.

Assessment of dietary intake and physical activity

To reduce confounding factors as much as possible, food intake and activity levels of patients were checked at the beginning and end of the study in 3 days including 2 working days and 1 day off. Food intake was first obtained by a 3-day food record, and then the Nutritionist 4 program was used to evaluate the number of calories and the number of macronutrients, and micronutrients. Physical activity was also obtained by a 3-day record. For an overall physical activity score based on MET minutes/week, the scores from all 3 activity categories including walking, moderate physical activity, and vigorous physical activity were added together.

Finally, statistical analysis of food intake and physical activity was done by SPSS software version 22 (SPSS Inc., Chicago IL, USA, Version 22).

Biochemical assessment

At the beginning and end of the study, 10 cc of blood samples was collected from each patient in fasting conditions at 8:00 AM. These blood samples were used to check oxidative stress (total antioxidant capacity [TAC], malondialdehyde [MDA], and superoxide dismutases [SOD]), C-reactive protein (CRP), FBG, TG, blood urea nitrogen (BUN), and plasma creatinine (Cr).

BUN and creatinine were analyzed using enzymatic methods (colorimetric technique) and available standard kits (AUDIT kit, Tehran, Iran). FBG, CRP, TAC, MDA, and SOD activity were evaluated using biochemical methods with commercial Kiazist kits, Hamadan, Iran. Serum TG level was measured by enzymatic and colorimetric methods with Parsazmoon kits (Parsazmoon, Karaj, Iran).

Optical coherence tomography angiography evaluation

OCTA is a new and noninvasive imaging method that depicts the density of small blood vessels in the retina.[42] At the beginning and end of this study, the density and thickness of small blood vessels in the retina were measured by the OCTA method and with Ophthalmic Optical Coherence Tomography System (OPTOVUE) (Germany serial number 32319R2).

With the development of the optical coherence tomography (OCT) retinal imaging method, the OCTA method with a higher field of view and better image quality was created. In the OCTA method, the volumetric blood flow and vessel thickness can be seen. Furthermore, the movement of red blood cells in retinal vessels is depicted by changing the amplitude of its reflection signals.[42,43]

In this study, the data obtained from OCT and OCTA were the primary outcomes, while the laboratory data were the secondary outcomes.

Statistical methods

SPSS software version did data analysis 22 with a significance level of $P < 0.05$. The skewness index and the Q-Q diagram were used to assess the normalcy of the distribution of quantitative variables. By observing the skewness between −2 and +2, the data were considered normal. Furthermore, in the 1-sample KS test, if the P value was above 0.05, the data were considered normal.

The Chi-square test was used to compare the distribution of qualitative variables between the two groups. Quantitative variables were presented as means (standard deviation) and qualitative variables as numbers (percent). Intragroup analysis was conducted using paired t-tests, while between-group analysis was carried out using independent t-tests and analysis of covariance (ANCOVA). Baseline levels were adjusted in the ANCOVA analysis.

RESULTS

Participants characteristics

Out of 160 DR patients who were examined, 60 satisfied the inclusion and exclusion criteria of the study; therefore, these patients were included in the study. Half of the patients received curcumin-piperine tablets and the other half received placebo. Finally, 27 patients receiving curcumin-piperine and 29 patients receiving a placebo completed the study and entered the analysis. One patient on the placebo and two patients on the curcumin-piperine were excluded from the study because of their reluctance. In addition, a patient who received curcumin-piperine was excluded due to ocular surgery during the study [Figure 1]. None of the patients consumed <90% of the tablets, so no patients were excluded for this reason. Recruitment was done in February 2022 to February 2023.

Demographic characteristics of the two studied groups were not significantly different at the beginning of the study [Table 1]. The difference in the consumption of other medicines was not significant between the two groups [Table 1]. There were no significant changes in diet and physical activity in either group relative to baseline and between groups [Table 2]. All data were normal, so all were reported as mean ± SD.

The effects of curcumin-piperine on laboratory variables

Examining the changes within the group showed that TAC increased significantly in the intervention group (0.86 ± 0.66;

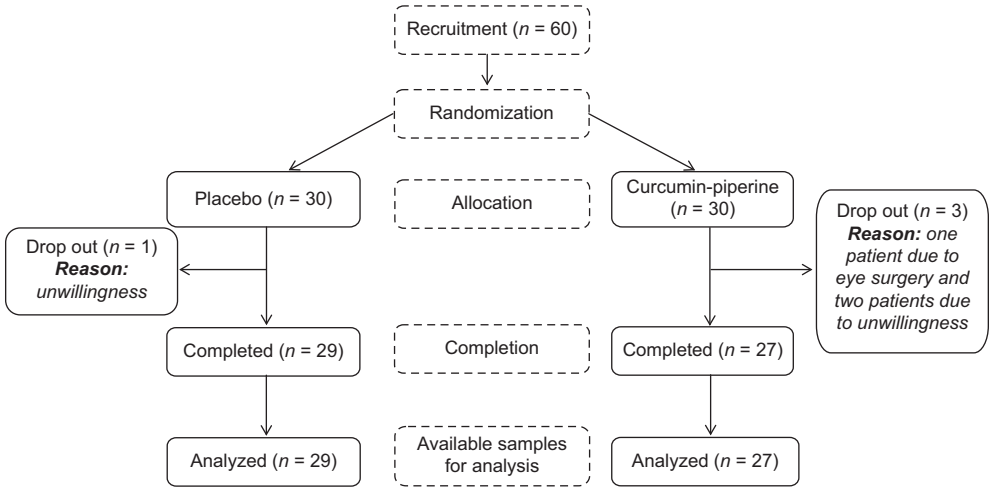

Figure 1: Flow chart of the trial

Table 1: Baseline characteristics of patients

Characteristics	Curcumin-piperin (*n*=27)	Placebo (*n*=29)	*P*
Age (years)*	55.85±8.22	55.86±7.99	0.996
BMI (kg/m^2)	27.87±5.02	27.93±3.76	0.96
Sex, *n* (%)			
Female	18 (66.7)	19 (65.5)	0.928
Male	9 (33.3)	10 (34.5)	
Family history of diabetes, *n* (%)			
Yes	27 (100)	29 (100)	0.99
No	0	0	
Family history of DR, *n* (%)			
Yes	12 (44.4)	16 (55.2)	0.422
No	15 (55.6)	13 (44.8)	
Education, *n* (%)			
Illiterate	5 (18.5)	4 (13.8)	0.733
Diploma or less	19 (70.4)	23 (79.3)	
College education	3 (11.1)	2 (6.9)	
Smoking, *n* (%)			
No	26 (96.3)	28 (96.6)	0.959
Yes	1 (3.7)	1 (3.4)	
Job, *n* (%)			
Housewife	17 (63)	19 (65.5)	0.748
Freelance	9 (33.3)	8 (27.6)	
Employee	1 (3.7)	2 (6.9)	
Marital status, *n* (%)			
Single	0	0	0.99
Married	27 (100)	29 (100)	
Medicines, *n* (%) (yes)			
Miglitol	12 (44.4)	9 (31)	0.3
Metformin	21 (77.8)	24 (82.8)	0.639
Gliclazide	17 (63)	16 (55.2)	0.554
Atorvastatin	18 (66.7)	19 (65.5)	0.928

*Value is presented as mean±SD. *P* values are for the comparison of the variable between curcumin-piperine and placebo groups. Quantitative variables (age and BMI) were evaluated by independent *t*-test, and qualitative variables (other factors) by Chi-square. BMI=Body mass index; SD=Standard deviation; DR=Diabetic retinopathy

$P < 0.001$) and the placebo group (0.45 ± 0.89; $P = 0.01$) compared with the baseline. This increase was significantly higher in the intervention group compared with the placebo (0.86 ± 0.66 vs. 0.45 ± 0.89; $P = 0.022$) [Table 3]. MDA changes compared with the baseline were not significant in any of the groups, but a significant decrease was observed in the intervention group in comparison to the placebo (−1.06 ± 5.80 vs. 1.89 ± 6.12; $P = 0.043$). SOD also did not significantly change in any of the groups in the intragroup comparison, but a significant increase was observed in the intervention group compared with the placebo (0.77 ± 2.11 vs.−0.45 ± 3.08; $P = 0.031$). Creatinine in the intervention group did not significantly change compared to the baseline (−0.04 ± 0.16; $P = 0.212$), but in the placebo group, a significant increase was observed compared with the baseline (0.03 ± 0.05; $P = 0.005$). Furthermore, in the intergroup comparison, a significant decrease in creatinine was observed in the intervention group compared with the placebo (−0.04 ± 0.16 vs. 0.03 ± 0.05; $P = 0.042$) [Table 3].

CRP, FBG, TG, and BUN did not have any significant changes in response to the curcumin-piperin supplementation ($P > 0.05$) [Table 3]. All data were adjusted based on the baseline levels.

The effects of curcumin-piperine on optical coherence tomography and optical coherence tomography angiography changes

The factors examined using OCT included volume and thickness, and the factors examined using OCTA included the following: (1) foveal avascular zone (FAZ), (2) thickness, (3) deep density, and (4) superior density. The second to fourth cases were examined in six modes: superior-hemi, inferior-hemi, whole image, fovea, parafovea, and perifovea. 54 eyes of 27 patients in the intervention group and 58 eyes of 29 patients in the placebo group were examined. In general, the intervention had no significant effects on OCT and OCTA ($P > 0.05$) [Table 4]. All data were adjusted for the baseline levels.

Table 2: Dietary intake and physical activity of participants

Variable	Intervention group				Placebo group				P^b
	Baseline	Week 12	Mean change	P^a	Baseline	Week 12	Mean change	P^a	
Energy (kcal/day)	2517.31±235.25	251,901±233.07	10.69±203.94	0.966	2518.14±317.54	2540.47±276.33	22.32±150.85	0.432	0.630
Carbohydrate (g/day)	432.96±63.08	432.47±67.66	−0.48±54.04	0.963	421.56±74.37	429.80±67.41	8.24±48.28	0.366	0.675
Protein (g/day)	82.31±20.52	80.50±19.88	−1.80±22.53	0.680	77.66±21.18	80.99±20.79	3.33±19.86	0.374	0.591
Lipid (g/day)	60.27±15.58	58.33±16.30	−1.94±7.25	0.176	65.48±19.20	65.96±18.39	0.48±4.56	0.571	0.091
Vitamin A (RAE)	1500.24±598.65	1532.32±573.13	32.08±229.70	0.475	1322.60±532.86	1303.85±548.03	−18.75±232.46	0.667	0.279
Betacaroten (µg)	13,323.11±6282.59	13,256.51±6393.32	−66.59±3019.53	0.910	11,932.07±5632.71	11,981.50±5449.74	49.42±1997.17	0.930	0.931
Alphacaroten (µg)	3394.94±425.32	3517.12±2137.41	122.17±1143.60	0.584	2939.75±1952.33	2795.19±1940.61	−144.56±1050.99	0.465	0.238
Lutein (µg)	11,669.72±6584.83	12,047.11±1249.05	377.39±1573.63	0.224	11,219.75±6073.20	11,017.99±5933.91	−201.75±987.44	0.281	0.090
Betacryptoxanthin (µg)	1017.80±422.71	1005.35±404.74	−12.45±212.73	0.763	919.72±376.02	877.93±401.03	−41.78±366.31	0.509	0.466
Lycopene (µg)	3817.42±2403.69	3303.46±2441.89	−513.95±1936.15	0.180	3492.51±2451.35	3744.40±2456.34	251.88±1547.24	0.388	0.128
Vitamin C (mg)	341.77±127.04	344.83±124.45	3.06±70.15	0.822	302.72±118.32	309.26±119.38	6.54±67.08	0.603	0.874
Vitamin E (mg)	11.83±2.43	11.83±2.35	−0.003±1.27	0.987	11.47±2.75	11.46±2.80	−0.009±1.56	0.973	0.871
Zinc (mg)	11.87±2.45	12.04±2.91	0.17±1.91	0.646	11.73±3.00	11.50±2.58	−0.23±2.70	0.648	0.433
Selenium (µg)	104.56±27.81	106.61±29.66	2.04±25.44	0.680	106.64±29.92	103.42±28.09	−3.22±32.03	0.592	0.537
Physical activity (MET)	2478.40±454.28	2478.11±456.32	−0.29±5.05	0.763	2726.86±766.69	2701.06±778.62	−25.79±149.42	0.361	0.400

[a]*P*-values for comparison of variables within groups by paired *t*-test; [b]*P*-values for comparison of mean change of variables between two groups by ANCOVA test adjusted for baseline values. Mean±SD change for the 12 weeks. SD=Standard deviation; ANCOVA=Analysis of covariance; MET=Metabolic equivalent of task; RAE= Retinol activity equivalent

Safety

In the present study, we observed that curcumin-piperine supplementation was safe as no serious side effects were reported by any of the patients.

DISCUSSION

The current clinical trial showed that consumption of curcumin-piperine tablets at the dose of 1010 mg per day (1000 mg of curcumin and 10 mg of piperine per day) in patients with DR for 12 weeks improves oxidative stress status and decreases serum creatinine levels. To our knowledge, this is the first study to investigate the effect of curcumin-piperine on macular vessel density and thickness on OCTA in patients with DR. However, no significant change was observed in other assessed parameters between the studied groups. Considering the high prevalence of diabetes and its obnoxious consequences, especially DR,[1] the present findings may be useful in a clinical setting to improve oxidative stress.

Oxidative stress is caused by excessive production of free radicals, which damages β-cells of the islets of Langerhans in the pancreas and disrupt insulin production, thereby causing hyperglycemia. In addition, high blood glucose evokes oxidative pathways by increasing the production of advanced glycation end products and subsequent inflammation.[44] Inflammation caused by oxidative stress has many destructive effects on the insulin signaling pathway. Therefore, oxidative stress can causes insulin resistance via increasing inflammatory factors.[45] A recent systematic review reported the beneficial effect of curcumin in improving inflammation and oxidative stress in type 2 diabetes mellitus and fatty liver disease.[46]

Since high blood glucose damages the walls of the vessels, especially small vessels, by increasing oxidant and inflammatory factors, diabetic patients are very susceptible to renal microvasculature damage. Hence, it is useful to control renal factors including creatinine.[47] In the present study, curcumin-piperine supplementation reduced creatinine in patients with DR. In accordance with our findings, a recent meta-analysis including 14 trials showed that oral curcumin supplementation improves creatinine.[48] Curcumin is able to reduce inflammation and oxidative stress by increasing the regulation of the transcription factor nuclear factor erythroid 2-related factor 2, which increases the levels of many antioxidants, including glutathione-s-transferase. Therefore, following the reduction of inflammatory and oxidative factors, curcumin can relieve renal complications.[49]

OCTA is an eye imaging method that carefully examines the tiny vessels of the retina. This technology has a higher

Table 3: The effect of 12 weeks of curcumin-piperine supplementation on laboratory factors of diabetic retinopathy patients

Variable	Intervention group (*n*=27)				Placebo group (*n*=29)				*P*[b]
	Baseline	After 12 weeks	Change	*P*[a]	Baseline	After 12 weeks	Change	*P*[a]	
TAC (nmol Trolox equivalent/mL)	4.75±0.63	5.62±0.60	0.86±0.66	<0.001	4.72±0.53	5.18±0.78	0.45±0.89	0.010	0.022
MDA (nmol/mL)	24.43±7.33	23.37±1.78	−1.06±5.80	0.350	24.65±8.00	26.54±10.22	1.89±6.12	0.107	0.043
SOD (U SOD activity/mL)	15.07±1.16	15.84±2.11	0.77±2.11	0.069	14.81±2.16	14.36±2.65	−0.45±3.08	0.437	0.031
CRP (mg/L)	3.47±2.72	3.82±2.60	0.34±1.91	0.354	3.94±1.77	4.05±2.54	0.10±2.38	0.817	0.866
FBG (mg/dL)	168.74±64.70	163.44±45.73	−5.29±49.18	0.581	173.27±57.44	174.10±56.83	0.82±46.53	0.924	0.446
TG (mg/dL)	140.37±72.78	147.14±81.31	6.77±45.79	0.449	156.79±73.25	175.93±148.61	19.13±124.55	0.415	0.645
BUN (mg/dL)	10.40±2.45	10.93±2.33	0.52±2.71	0.324	11.33±4.26	11.24±2.29	−0.09±3.45	0.886	0.986
Cr (mg/dL)	0.87±0.19	0.83±0.12	−0.04±0.16	0.212	0.83±0.13	0.87±0.14	0.03±0.05	0.005	0.042

[a]*P*-values for comparison of variables within groups by paired *t*-test; [b]*P*-values for comparison of mean change of variables between two groups by ANCOVA test adjusted for baseline valuse. Mean±SD change for the 12 weeks. TAC=Total antioxidant capacity; MDA=Malondialdehyde; SOD=Superoxide dismutases; CRP=C-reactive protein; FBG=Fasting blood glucose; TG=Triglyceride; BUN=Blood urea nitrogen; Cr=Creatinine; SD=Standard deviation; ANCOVA=Analysis of covariance

Table 4: The effect of 12 weeks of curcumin-piperine supplementation on optical coherence tomography and optical coherence tomography angiography of diabetic retinopathy patients

Variable	Intervention group (*n*=54 eyes of 27 patients)				Placebo group (*n*=58 eyes of 29 patients)				*P*[b]
	Baseline	After 12 weeks	Change	*P*[a]	Baseline	After 12 weeks	Change	*P*[a]	
OCT									
Volume	8.52±0.44	8.56±0.49	0.038±0.22	0.215	8.71±0.69	8.74±0.65	0.03±0.19	0.199	0.830
Thickness	264.27±23.20	266.25±26.54	1.98±11.92	0.227	271.48±54.76	271.50±50.57	0.01±21.79	0.995	0.747
OCTA									
FAZ	0.32±0.15	0.29±0.12	−0.02±0.11	0.093	0.32±0.17	0.32±0.10	−0.002±0.13	0.888	0.120
Thickness									
Superior-Hemi	281.29±14.81	281.81±16.79	0.51±9.46	0.689	289.07±16.66	290.23±17.85	1.16±7.02	0.225	0.578
Inferior-Hemi	278.07±15.67	278.83±17.72	0.75±8.7	0.524	287.38±22.73	290.77±25.62	3.38±8.09	0.003	0.180
Whole image	279.53±14.32	279.14±17.70	−0.38±12.98	0.827	288.48±21.96	288.03±23.15	−0.44±10.32	0.742	0.770
Fovea	251.00±24.39	254.64±29.27	3.64±19.11	0.167	256.70±44.55	258.10±42.26	1.39±18.62	0.570	0.662
Parafovea	314.46±18.06	315.50±20.97	1.03±10.07	0.453	324.22±30.08	321.17±29.99	−3.05±16.79	0.172	0.264
Perifovea	278.29±15.09	280.88±22.66	2.59±15.66	0.229	287.77±21.98	289.84±22.23	2.07±8.84	0.083	0.896
Deep density									
Superior-Hemi	46.13±7.67	45.2±8.05	−0.92±7.08	0.345	47.45±7.68	45.66±7.2	−1.79±8.17	0.103	0.880
Inferior-Hemi	45.26±7.69	44.93±7.27	−0.33±6.55	0.714	46.83±8.21	45.59±6.73	−1.24±8.84	0.294	0.980
Whole image	44.59±7.64	43.93±8.53	−0.65±8.74	0.583	47.00±8.11	45.46±8.95	−1.53±9.61	0.229	0.756
Fovea	31.91±10.06	32.67±9.63	0.75±7.89	0.485	31.53±10.85	31.90±10.85	0.36±7.35	0.706	0.710
Parafovea	50.08±7.89	50.66±7.10	0.57±5.93	0.478	51.11±8.21	50.87±6.05	−0.24±7.51	0.806	0.781
Perifovea	45.73±8.37	45.18±9.37	−0.54±9.61	0.678	48.40±8.95	47.72±7.37	−0.68±8.61	0.550	0.336
Superior density									
Superior-Hemi	46.27±4.9	45.37±5.55	−0.89±4.54	0.152	47.21±4.64	46.13±5.83	−1.08±5.57	0.146	0.866
Inferior-Hemi	46±4.82	45.48±5.42	−0.51±4.15	0.365	46.89±4.84	45.93±5.89	−0.96±6.1	0.235	0.925
Whole image	45.76±4.54	45.66±4.57	−0.10±4.36	0.867	47.09±5.31	54.06±58.88	6.97±58.48	0.367	0.385
Fovea	16.35±7.45	16.63±6.76	0.28±4.90	0.675	16.62±9.11	16.35±8.30	−0.27±6.33	0.743	0.625
Parafovea	46.16±6.76	45.37±7.29	−0.78±5.65	0.312	46.20±9.08	46.15±6.84	−0.05±9.21	0.966	0.520
Perifovea	46.02±5.65	46.73±4.65	0.71±5.01	0.301	48.14±5.43	47.31±5.03	−0.82±5.48	0.262	0.685

[a]*P*-values for comparison of variables within groups by paired *t*-test; [b]*P*-values for comparison of mean change of variables between two groups by ANCOVA test adjusted for baseline valuse. Mean±SD change for the 12 weeks. OCT=Optical coherence tomography; OCTA=Optical coherence tomography angiography; FAZ=Foveal avascular zone; SD=Stanadard deviation; ANCOVA=Analysis of covariance

accuracy and resolution compared to older methods.[42] In the present study, some factors including FAZ, deep density (in 4 cases of the whole image, fovea, parafovea, and perifovea), and superior density (in 2 cases of fovea and perifovea), showed improvement or prevention of worsening symptoms in the intervention group compared with placebo. However, between-group differences did not reach a statistical significance. Therefore, it might be plausible to achieve a clinical benefit in longer intervention periods but this needs to be verified by future studies. In In a trial by Allegri *et al*., the effect of twice-daily oral phospholipidic curcumin for 12 months was evaluated in recurrent anterior uveitis, which resulted in an improvement of eye discomfort symptoms.[50]

Through improving oxidative stress and inflammation, curcumin can lessen the ocular complications of diabetes. The anti-VEGF effects that reduce excessive angiogenesis in the retina have been previously reported for curcumin.[51]

The observed changes in some laboratory factors such as FBG and TGs were not statistically significant. However, it seems that these findings had clinically significant changes. For example, FBG decreased by 6.11 mg/dl in the intervention group compared to the control group. In the case of TGs, an increase of 6.77 mg/dl was observed in the intervention group and 19.13 mg/dl in the placebo group. Therefore, there was a difference of 12.36 mg/dl compared to the control group.

A previous trial showed that the consumption of curcumin-piperine (500 mg curcumin with 5 mg piperine per day) for 120 days in patients with type 2 diabetes reduced glycemia, glycated hemoglobin, homeostatic model assessment index and TG.[52] Another trial reported that supplementation with 1000 mg curcumin plus 10 mg piperine daily for 12 weeks in patients with type 2 diabetes reduced serum leptin, tumor necrosis factor-α and leptin: adiponectin ratio.[53] Moreover, Panahi *et al*. found that the consumption of 1000 mg curcumin plus 10 mg piperine per day for 3 months in patients with type 2 diabetes caused a significant decrease in serum levels of glucose, C-peptide, HbA1c, alanine aminotransferase and aspartate aminotransferase compared to the placebo group.[54] Another trial reported the ameliorative effects of curcumin (1500 mg/day for 10 weeks) on FBG in patients with type 2 diabetes.[55]

Thus far, only one trial has explored the effect of curcumin on DR. In this study, two tablets/day of a phospholipid-based delivery system of curcumin (each tablet containing 500 mg Meriva® corresponding to 100 mg curcumin) was used for 4 weeks. The results of this study showed improvement in visual acuity, microangiopathy, response of retinal arterial vessels, and improvement of retinal edema. However, the referred study did not employ OCTA evaluation.[56]

It is important to note that in the present study, we used a combination of curcumin and piperine. Piperine, which is found naturally in *Piper nigrum* (black pepper), has the ability to interact with the enzyme responsible for the glucuronylation of curcumin in the gut. Therefore, inhibition of curcumin glucuronylation increases the bioavailability of this phytochemical.[57]

In the present study, no side effects were observed in any of the patients. The safety of this herbal extract has also been reported in past studies.[58]

There were several strength points in the present study. Our study was well-randomized and blinded. Another strength was that we used curcumin together with piperine, which increases the effectiveness of curcumin. The dose of curcumin used to cure diabetes is usually 300–1500 mg/day.[41] Therefore, the dose of 1010 mg/day curcumin piperine (1000 mg of curcumin and 10 mg of piperine per day) used in this study is quite reasonable.

This study had limitations, such as the relatively small sample size and lack of long-term monitoring. Furthermore, because of ethical problems, we could not exclude other treatments received by patients and examine the effect of curcumin-piperine only. In addition, no dose-response relationship could be tested due to the inclusion of only one dose group in the trial.

CONCLUSION

The findings of the present trial showed that curcumin-piperine supplementation is effective in improving oxidative stress parameters including TAC, MDA, and SOD, and reducing creatinine. However, other investigated factors including FBG, TG, BUN, and CRP, as well as OCT and OCTA indices were not affected significantly. Larger and long-term randomized controlled trials are needed in this field.

Ethics approval and consent to participate

All aspects of the present study were approved by the Ethical Committee of Isfahan University of Medical Sciences, Isfahan, Iran, under ethical code IR.MUI.RESEARCH.REC.1400.253. Furthermore, the present study was conducted under the scientific code 3400358 and the IRCT code IRCT20201129049534N5. The study was done in accordance with the Helsinki Declarations of ethics. Written informed consent was obtained from the patients before entering the study. For illiterate patients, written informed consent was obtained from their legal guardian(s). In addition, verbal informed consent was obtained from the illiterate participants themselves. We confirm that the participants (in the case of illiterate patients, their legal guardian[s]) were aware of the purpose, risks, and benefits of the study. We do not publish any personally identifiable information about patients, so the identity information of the patients will remain completely confidential.

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code IR.MUI.RESEARCH.REC.1400.253. Furthermore, the present study was conducted under the scientific code 3400358 and the IRCT code IRCT20201129049534N5.

Availability of data and material

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Teo ZL, Tham YC, Yu M, Chee ML, Rim TH, Cheung N, *et al.* Global prevalence of diabetic retinopathy and projection of burden through 2045: Systematic review and meta-analysis. Ophthalmology 2021;128:1580-91.
2. Krady JK, Basu A, Allen CM, Xu Y, LaNoue KF, Gardner TW, *et al.* Minocycline reduces proinflammatory cytokine expression, microglial activation, and caspase-3 activation in a rodent model of diabetic retinopathy. Diabetes 2005;54:1559-65.
3. Brownlee M. The pathobiology of diabetic complications: A unifying mechanism. Diabetes 2005;54:1615-25.
4. Chang YC, Wu WC. Dyslipidemia and diabetic retinopathy. Rev Diabet Stud 2013;10:121-32.
5. Behl T, Kotwani A. Exploring the various aspects of the pathological role of vascular endothelial growth factor (VEGF) in diabetic retinopathy. Pharmacol Res 2015;99:137-48.
6. Mansour SE, Browning DJ, Wong K, Flynn HW Jr., Bhavsar AR. The evolving treatment of diabetic retinopathy. Clin Ophthalmol 2020;14:653-78.
7. Zhang HW, Zhang H, Grant SJ, Wan X, Li G. Single herbal medicine for diabetic retinopathy. Cochrane Database Syst Rev 2018;12:CD007939.
8. Bagheri H, Ghasemi F, Barreto GE, Rafiee R, Sathyapalan T, Sahebkar A. Effects of curcumin on mitochondria in neurodegenerative diseases. Biofactors 2020;46:5-20.
9. Cicero AF, Sahebkar A, Fogacci F, Bove M, Giovannini M, Borghi C. Effects of phytosomal curcumin on anthropometric parameters, insulin resistance, cortisolemia and non-alcoholic fatty liver disease indices: A double-blind, placebo-controlled clinical trial. Eur J Nutr 2020;59:477-83.
10. Keihanian F, Saeidinia A, Bagheri RK, Johnston TP, Sahebkar A. Curcumin, hemostasis, thrombosis, and coagulation. J Cell Physiol 2018;233:4497-511.
11. Marjaneh RM, Rahmani F, Hassanian SM, Rezaei N, Hashemzehi M, Bahrami A, *et al.* Phytosomal curcumin inhibits tumor growth in colitis-associated colorectal cancer. J Cell Physiol 2018;233:6785-98.
12. Mohajeri M, Sahebkar A. Protective effects of curcumin against doxorubicin-induced toxicity and resistance: A review. Crit Rev Oncol Hematol 2018;122:30-51.
13. Mokhtari-Zaer A, Marefati N, Atkin SL, Butler AE, Sahebkar A. The protective role of curcumin in myocardial ischemia-reperfusion injury. J Cell Physiol 2018;234:214-22.
14. Panahi Y, Fazlolahzadeh O, Atkin SL, Majeed M, Butler AE, Johnston TP, *et al.* Evidence of curcumin and curcumin analogue effects in skin diseases: A narrative review. J Cell Physiol 2019;234:1165-78.
15. Rezaee R, Momtazi AA, Monemi A, Sahebkar A. Curcumin: A potentially powerful tool to reverse cisplatin-induced toxicity. Pharmacol Res 2017;117:218-27.
16. Ahmadi A, Jamialahmadi T, Sahebkar A. Polyphenols and atherosclerosis: A critical review of clinical effects on LDL oxidation. Pharmacol Res 2022;184:106414.
17. Gorabi AM, Kiaie N, Hajighasemi S, Jamialahmadi T, Majeed M, Sahebkar A. The effect of curcumin on the differentiation of mesenchymal stem cells into mesodermal lineage. Molecules 2019;24:4029.
18. Lu W, Khatibi Shahidi F, Khorsandi K, Hosseinzadeh R, Gul A, Balick V. An update on molecular mechanisms of curcumin effect on diabetes. J Food Biochem 2022;46:e14358.
19. Rivera-Mancía S, Trujillo J, Chaverri JP. Utility of curcumin for the treatment of diabetes mellitus: Evidence from preclinical and clinical studies. J Nutr Intermed Metab 2018;14:29-41.
20. Ghosh S, Banerjee S, Sil PC. The beneficial role of curcumin on inflammation, diabetes and neurodegenerative disease: A recent update. Food Chem Toxicol 2015;83:111-24.
21. Kahkhaie KR, Mirhosseini A, Aliabadi A, Mohammadi A, Mousavi MJ, Haftcheshmeh SM, *et al.* Curcumin: A modulator of inflammatory signaling pathways in the immune system. Inflammopharmacology 2019;27:885-900.
22. Shafabakhsh R, Pourhanifeh MH, Mirzaei HR, Sahebkar A, Asemi Z, Mirzaei H. Targeting regulatory T cells by curcumin: A potential for cancer immunotherapy. Pharmacol Res 2019;147:104353.
23. Mohammadi A, Blesso CN, Barreto GE, Banach M, Majeed M, Sahebkar A. Macrophage plasticity, polarization and function in response to curcumin, a diet-derived polyphenol, as an immunomodulatory agent. J Nutr Biochem 2019;66:1-16.
24. Jakubczyk K, Drużga A, Katarzyna J, Skonieczna-Żydecka K. Antioxidant potential of curcumin-a meta-analysis of randomized clinical trials. Antioxidants (Basel) 2020;9:1092.
25. de Melo IS, Dos Santos AF, Bueno NB. Curcumin or combined curcuminoids are effective in lowering the fasting blood glucose concentrations of individuals with dysglycemia: Systematic review and meta-analysis of randomized controlled trials. Pharmacol Res 2018;128:137-44.
26. Yang J, Miao X, Yang FJ, Cao JF, Liu X, Fu JL, *et al.* Therapeutic potential of curcumin in diabetic retinopathy (review). Int J Mol Med 2021;47:75.
27. Rahimi HR, Mohammadpour AH, Dastani M, Jaafari MR, Abnous K, Ghayour Mobarhan M, *et al.* The effect of nano-curcumin on HbA1c, fasting blood glucose, and lipid profile in diabetic subjects: A randomized clinical trial. Avicenna J Phytomed 2016;6:567-77.
28. Qin S, Huang L, Gong J, Shen S, Huang J, Ren H, *et al.* Efficacy and safety of turmeric and curcumin in lowering blood lipid levels in patients with cardiovascular risk factors: A meta-analysis of randomized controlled trials. Nutr J 2017;16:68.
29. Yang F, Yu J, Ke F, Lan M, Li D, Tan K, *et al.* Curcumin alleviates diabetic retinopathy in experimental diabetic rats. Ophthalmic Res 2018;60:43-54.
30. Mirzaei H, Shakeri A, Rashidi B, Jalili A, Banikazemi Z, Sahebkar A. Phytosomal curcumin: A review of pharmacokinetic, experimental and clinical studies. Biomed Pharmacother 2017;85:102-12.
31. Liu W, Zhai Y, Heng X, Che FY, Chen W, Sun D, *et al.* Oral bioavailability of curcumin: Problems and advancements. J Drug Target 2016;24:694-702.
32. Liu Z, Smart JD, Pannala AS. Recent developments in formulation design for improving oral bioavailability of curcumin: A review. J Drug Deliv Sci Technol 2020;60:102082.

33. Kalra G, Zarranz-Ventura J, Chahal R, Bernal-Morales C, Lupidi M, Chhablani J. Optical coherence tomography (OCT) angiolytics: A review of OCT angiography quantitative biomarkers. Surv Ophthalmol 2022;67:1118-34.
34. Amini S, Sahebkar A, Dehghani A, Iraj B, Rezaeian-Ramsheh A, Askari G, *et al.* The effect of curcumin-piperine on cardiometabolic, inflammatory and oxidative stress factors and macular vascular density in optical coherence tomography angiography (OCTA) in patients with non-proliferative diabetic retinopathy: Study protocol for a randomized, double-blind controlled trial. Avicenna J Phytomed 2023;13:153-64.
35. World Medical Association. World Medical Association declaration of helsinki: Ethical principles for medical research involving human subjects. JAMA 2013;310:2191-4.
36. Seyyedebrahimi S, Khodabandehloo H, Esfahani EN, Meshkani R. Reply to letter to the editor "the effects of resveratrol on markers of oxidative stress in patients with type 2 diabetes: A randomized, double-blind, placebo-controlled clinical trial". Acta Diabetol 2018;55:755-6.
37. Saadati S, Hatami B, Yari Z, Shahrbaf MA, Eghtesad S, Mansour A, *et al.* The effects of curcumin supplementation on liver enzymes, lipid profile, glucose homeostasis, and hepatic steatosis and fibrosis in patients with non-alcoholic fatty liver disease. Eur J Clin Nutr 2019;73:441-9.
38. Pivari F, Mingione A, Brasacchio C, Soldati L. Curcumin and type 2 diabetes mellitus: Prevention and treatment. Nutrients 2019;11:1837.
39. Chainani-Wu N. Safety and anti-inflammatory activity of curcumin: A component of tumeric (*Curcuma longa*). J Altern Complement Med 2003;9:161-8.
40. Hsu CH, Cheng AL. Clinical studies with curcumin. In: The Molecular Targets and Therapeutic Uses of Curcumin in Health and Disease. Switzerland: AG; 2007. p. 471-80.
41. Zhang T, He Q, Liu Y, Chen Z, Hu H. Efficacy and safety of curcumin supplement on improvement of insulin resistance in people with type 2 diabetes mellitus: A systematic review and meta-analysis of randomized controlled trials. Evid Based Complement Alternat Med 2021;2021:4471944.
42. Kashani AH, Chen CL, Gahm JK, Zheng F, Richter GM, Rosenfeld PJ, *et al.* Optical coherence tomography angiography: A comprehensive review of current methods and clinical applications. Prog Retin Eye Res 2017;60:66-100.
43. Schwartz DM, Fingler J, Kim DY, Zawadzki RJ, Morse LS, Park SS, *et al.* Phase-variance optical coherence tomography: A technique for noninvasive angiography. Ophthalmology 2014;121:180-7.
44. Newsholme P, Keane KN, Carlessi R, Cruzat V. Oxidative stress pathways in pancreatic β-cells and insulin-sensitive cells and tissues: Importance to cell metabolism, function, and dysfunction. Am J Physiol Cell Physiol 2019;317:C420-33.
45. Singh A, Kukreti R, Saso L, Kukreti S. Mechanistic Insight into oxidative stress-triggered signaling pathways and type 2 diabetes. Molecules 2022;27:950.
46. Mokgalaboni K, Ntamo Y, Ziqubu K, Nyambuya TM, Nkambule BB, Mazibuko-Mbeje SE, *et al.* Curcumin supplementation improves biomarkers of oxidative stress and inflammation in conditions of obesity, type 2 diabetes and NAFLD: Updating the status of clinical evidence. Food Funct 2021;12:12235-49.
47. Thomas MC, Brownlee M, Susztak K, Sharma K, Jandeleit-Dahm KA, Zoungas S, *et al.* Diabetic kidney disease. Nat Rev Dis Primers 2015;1:15018.
48. Sadeghian M, Rahmani S, Jafarieh A, Jamialahmadi T, Sahebkar A. The effect of curcumin supplementation on renal function: A systematic and meta-analysis of randomized controlled trials. J Funct Foods 2023;100:105396.
49. Ali BH, Al-Salam S, Al Suleimani Y, Al Kalbani J, Al Bahlani S, Ashique M, *et al.* Curcumin ameliorates kidney function and oxidative stress in experimental chronic kidney disease. Basic Clin Pharmacol Toxicol 2018;122:65-73.
50. Allegri P, Mastromarino A, Neri P. Management of chronic anterior uveitis relapses: Efficacy of oral phospholipidic curcumin treatment. Long-term follow-up. Clin Ophthalmol 2010;4:1201-6.
51. Aldebasi YH, Aly SM, Rahmani AH. Therapeutic implications of curcumin in the prevention of diabetic retinopathy via modulation of anti-oxidant activity and genetic pathways. Int J Physiol Pathophysiol Pharmacol 2013;5:194-202.
52. Neta JF, Veras VS, Sousa DF, Cunha MD, Queiroz MV, Neto JC, *et al.* Effectiveness of the piperine-supplemented *Curcuma longa* L. in metabolic control of patients with type 2 diabetes: A randomised double-blind placebo-controlled clinical trial. Int J Food Sci Nutr 2021;72:968-77.
53. Panahi Y, Khalili N, Sahebi E, Namazi S, Atkin SL, Majeed M, *et al.* Curcuminoids plus piperine modulate adipokines in type 2 diabetes mellitus. Curr Clin Pharmacol 2017;12:253-8.
54. Panahi Y, Khalili N, Sahebi E, Namazi S, Simental-Mendía LE, Majeed M, *et al.* Effects of curcuminoids plus piperine on glycemic, hepatic and inflammatory biomarkers in patients with type 2 diabetes mellitus: A randomized double-blind placebo-controlled trial. Drug Res (Stuttg) 2018;68:403-9.
55. Hodaei H, Adibian M, Nikpayam O, Hedayati M, Sohrab G. The effect of curcumin supplementation on anthropometric indices, insulin resistance and oxidative stress in patients with type 2 diabetes: A randomized, double-blind clinical trial. Diabetol Metab Syndr 2019;11:41.
56. Steigerwalt R, Nebbioso M, Appendino G, Belcaro G, Ciammaichella G, Cornelli U, *et al.* Meriva®, a lecithinized curcumin delivery system, in diabetic microangiopathy and retinopathy. Panminerva Med 2012;54:11-6.
57. Patil VM, Das S, Balasubramanian K. Quantum chemical and docking insights into bioavailability enhancement of curcumin by piperine in pepper. J Phys Chem A 2016;120:3643-53.
58. Heidari H, Bagherniya M, Majeed M, Sathyapalan T, Jamialahmadi T, Sahebkar A. Curcumin-piperine co-supplementation and human health: A comprehensive review of preclinical and clinical studies. Phytother Res 2023;37:1462-87.