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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

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ABSTRACT

Introduction Curcuminoids have been shown to reduce glycemia and related complications in diabetes. In the present study, we evaluated the impact of curcuminoids plus piperine administration on glycemic, hepatic and inflammatory biomarkers in type 2 diabetes (T2D) patients.

Methods T2D patients aged 18–65 years were enrolled in a randomized double-blind placebo-controlled trial and randomly allocated to standard-of-care treatment and dietary advises plus either curcuminoids (daily dose of 500 mg/day co-administered with piperine 5 mg/day) or placebo for a period of 3 months. Glycemic, hepatic and inflammatory parameters were measured at baseline and final conditions.

Results A total of 100 subjects (50 in each group) completed the 3-month period of trial. A significant reduction was found in serum levels of glucose (− 9 ± 16 mg/dL vs. − 3 ± 11 mg/dL in curcuminoids and placebo groups, respectively; p = 0.048), C-peptide (− 0.6 ± 0.8 ng/mL vs. 0.02 ± 0.6 ng/mL; p < 0.001) and HbA1c (− 0.9 ± 1.1 % vs. − 0.2 ± 0.5 %; p < 0.001) after curcuminoids supplementation versus placebo group. Additionally, participants in the intervention group showed lower serum alanine aminotransferase (− 2 ± 6 vs. − 1 ± 5; p = 0.032) and aspartate aminotransferase (− 3 ± 5 vs. − 0.3 ± 4; p = 0.002) levels compared with the placebo group. Finally, no significant differences in high-sensitivity C-reactive protein (hs-CRP) concentrations were observed between curcuminoids and placebo groups (p > 0.05).

Conclusion The results of the present trial revealed a beneficial effect of curcuminoids plus piperine supplementation on glycemic and hepatic parameters but not on hs-CRP levels in T2D patients.

* Institute where the work was conducted: Baqiyatallah Univeristy of Medical Sciences, Tehran, Iran.

Introduction

Curcuminoids are natural products, generally recognized as safe compounds that have been reported to possess numerous pharmacological effects and exert a plethora of beneficial effects against several human diseases [1–9] including type 2 diabetes (T2D) [10, 11]. Curcuminoids were shown to improve insulin resistance, decrease glucose and insulin levels and lead to increase in adiponectin and reductions in leptin, resistin, visfatin, interleukin (IL)-6, IL-1β and tumor necrosis factor-α levels in T2D patients [12]. These findings, suggest that curcuminoids may affect not only glucose homeostasis but also diabetic complications and the vascular risk of T2D patients [13]. Although curcuminoids show considerable health benefits, poor bioavailability and rapid biotransformation have hampered their widespread therapeutic application [14]. Coadministration of curcuminoids with an extract from black pepper (piperine) was shown to significantly enhance the bioavailability in both animals and human studies [15]. We have previously found that curcuminoid supplementation improves the lipid profile and increases total antioxidant capacity in T2D patients [16, 17], thereby supporting other available evidence on the role of curcuminoids in modifying cardiometabolic risk [18–24]. Previous experimental studies have also reported a protective effect of curcumin against hepatotoxicity [25–27]. In the present study, we evaluated the impact of curcuminoids plus piperine administration on glycemic, hepatic and inflammatory biomarkers in T2D patients.

Materials and Methods

Subjects

Patients with T2D aged 18–65 years were recruited from those referring to the Diabetes Clinic of the Baqiyatallah Hospital (Tehran, Iran). The inclusion criteria included the presence of T2D based on fasting plasma glucose ≥ 126 mg/dL, glycated hemoglobinA1c (HbA1c) ≥ 6.5 %, or the use of standard anti-diabetic treatments. Exclusion criteria were pregnancy or breastfeeding, impossibility to give informed consent, participation in a concomitant trial, presence of malignancies, chronic liver disease (alanine aminotransferase levels three times upper limit of normal value range), renal failure (serum creatinine ≥ 2.0 mg/dLor being on dialysis), chronic inflammatory diseases such as rheumatoid arthritis and acute infections, thyroid disorders (e.g. hypo-or hyperthyroidism), obsessive compulsive disorder, other types of diabetes, receiving hormone or other herbal therapies, and hypersensitivity to curcuminoids.

Study design

This study was designed as a randomized double-blind placebo-controlled trial with a parallel-group design and performed between June 22, 2015 and April 20, 2016. Sample size was calculated with a power of 90 % considering a type I error (α) of 5 % based on the placebo-adjusted fasting glucose change or around 22 mg/dL in a previous randomized controlled trial [28]. Subjects who met the aforementioned inclusion criteria (n = 118) were randomly allocated to standard-of-care treatment and dietary advises plus either curcuminoids (Curcumin C3 Complex®, Sami Labs LTD, Bangalore, India; 500 mg/day) or placebo for a period of 3 months. The curcuminoids preparation (C3 Complex®) that was used in this study contained curcumin, demethoxycurcumin and bisdemethoxycurcumin in a patented ratio. Each curcuminoids capsule also contained 5 mg piperine (Bioperine®; Sami Labs LTD, Bangalore, India) which is a known enhancer of curcumin bioavailability and pharmacokinetics[15]. To maintain comparability of the study groups, the same amount of piperine was also added to placebo capsules.

The study was conducted according to the declaration of Helsinki and the protocol was approved by the Ethics Committee at the Baqiyatallah University of Medical Sciences, registered in the Iranian Registry of Clinical Trials (Code: IRCT201505301165N4), and written informed consent was obtained from all individuals.

Blood sampling and measurements

After an overnight fasting, blood samples were collected at baseline and at the end of the study. The samples were allowed to clot for about 30 min and then centrifuged at 750 G for 10 min to obtain serum. Serum samples were aliquoted and frozen at − 80 °C until measurements. Weight was measured with the subjects dressed in light clothing after an overnight fasting using a standard scale. Anthropometric indices were measured as previously described[29].

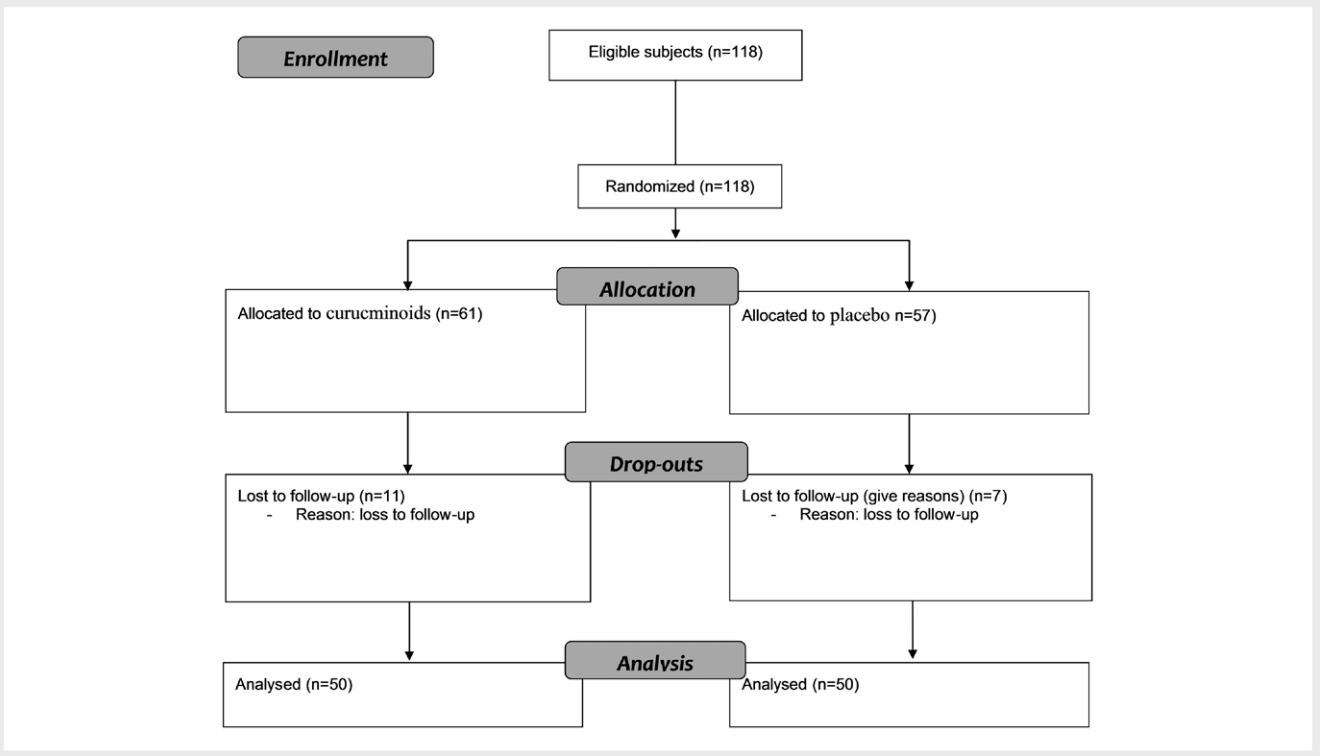
Fasting serum concentrations of insulin, glucose, HbA1c, C-peptide, aspartate aminotransferase (AST), alanine aminotransferase (ALT) and high-sensitivity C-reactive protein (hs-CRP), homeostatic model assessments (HOMA) of insulin resistance (HOMA-IR) and beta-cell function (HOMA-β) were measured at baseline and at the end of the study in each group. Biochemical parameters were measured using routine commercial kits. Hepatic steatosis index (HSI) was calculated as previously described[30].

Statistical analysis

Statistical analyses were performed using the SPSS Statistics for Windows Version 20.0 (IBM Corp., Armonk, NY, USA). Normal distribution of continuous variables was checked using Kolmogorov-Smirnov test. Data were expressed as mean ± SD or median (interquartile range) for normally and non-normally distributed data, respectively. Within-group comparisons were performed using paired samples t-test or Wilcoxon signed-ranks test for normally and non-normally distributed data, respectively. Between-group comparisons were performed using independent samples t-test or Mann-Whitney U test for normally and non-normally distributed data, respectively. Comparison of categorical variables between the groups was performed using Chi-square test. A two-sided p-value of < 0.05 was considered as statistically significant.

Results

A total of 100 subjects (50 in each group) completed the 3-month period of trial. Drop-out rate due to lost in follow-up did not significantly differ between the groups (15.2 % in each group) (▶ **Fig. 1**). During the course of trial, there was no report of any side effects suggesting the safety of the administered combination. Baseline parameters of the study groups are shown in ▶ **Table 1**.



▶ **Fig. 1** Flow diagram of the trial.

▶ **Table 1** Clinical and biochemical features of the study groups at baseline.

	Curcumi-noids	Placebo	p-Value
Gender (male/female)	25/25	26/24	1.00
Age (y)	43 ± 8	41 ± 7	0.190
Height (cm)	171 ± 7	169 ± 7	0.095
Weight(kg)	78 ± 7	78 ± 7	0.866
BMI(kg/m²)	26 ± 2	27 ± 2	0.047
Glucose (mg/dL)	163 ± 37	174 ± 33	0.074
Insulin (mIU/L)	20 ± 3	22 ± 3	0.029
HbA1c (%)	7.4 ± 0.7	7.5 ± 0.9	0.671
C-peptide (ng/mL)	4.5 ± 1.0	3.3 ± 0.7	< 0.001
ALT (U/L)	36 ± 6	32 ± 7	0.001
AST (U/L)	38 ± 5	29 ± 5	< 0.001
Hs-CRP (g/L)	13.3 ± 3.4	12.3 ± 3.3	0.150
Creatinine (mg/dL)	1.1 ± 0.3	1.1 ± 0.3	0.832
HOMA-IR	2.9 ± 0.5	3.2 ± 0.5	0.009
HOMA-β	82.3 ± 45.2	79.3 ± 35.5	0.963
HSI	37.3 ± 3.1	39.6 ± 3.3	0.001

Values are expressed as mean ± SD. BMI: body mass index; HOMA_IR: the homeostasis model assessment-estimated insulin resistance; HOMA-β: the homeostasis model assessment-β cell function; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphatase; hs-CRP: high-sensitivity C-reactive protein; HIS: hepatic steatotic index.

Effect of curcuminoids supplementation on glycemic parameters

Serum concentrations of insulin, HbA1cand HOMA-IR index were significantly reduced by the end of the trial in both study groups, whereas serum concentrations of glucose and C-peptide were significantly improved only in the curcuminoids group **(▶ Table 2)**. A significant reduction was found in serum levels of glucose, C-peptide and HbA1c after curcuminoids supplementation versus placebo group **(▶ Table 3)**.

Effect of curcuminoids supplementation on hepatic parameters

Within-group comparisons revealed that serum concentrations of ALT and AST were significantly improved in the curcuminoids but not in the placebo group (▶ **Table 2**). Reductions in serum ALT and AST levels, but not HSI, were lower in the intervention group compared with the placebo group **(▶ Table 3)**.

Effect of curcuminoids supplementation on weight and BMI

At final conditions, significant reductions in weight and BMI were observed in the curcuminoids but not the placebo group **(▶ Table 2)**. Moreover, participants in the intervention group exhibited a significantly lower weight and BMI compared with those in the placebo group **(▶ Table 3)**.

Effect of curcuminoids supplementation on serum hs-CRP and creatinine

At the end of the trial, serum hs-CRP and creatinine concentrations were significantly decreased in both study groups **(▶ Table 2)**. How-

▶ **Table 2** Comparisons of biochemical indices before and after intervention in the study groups.

	Curcuminoids			Placebo		
	Before	After	p-Value	Before	After	p-Value
Weight (kg)	78 ± 7	76 ± 7	< 0.001	78 ± 7	79 ± 7	0.020
BMI (kg/m²)	27 ± 2	26 ± 2	< 0.001	27 ± 1	28 ± 1	0.023
Glucose (mg/dL)	163 ± 37	154 ± 34	< 0.001	174 ± 32	171 ± 26	0.074
Insulin (mIU/L)	20 ± 3	19 ± 2	0.017	21 ± 3	21 ± 2	0.039
HbA1c (%)	7.4 ± 0.7	6.5 ± 1.0	< 0.001	7.5 ± 0.9	7.3 ± 0.8	0.011
C-peptide (ng/mL)	4.5 ± 1.0	4.0 ± 0.7	< 0.001	3.3 ± 0.7	3.4 ± 0.7	0.844
ALT (U/L)	36 ± 6	34 ± 7	0.005	32 ± 6	31 ± 6	0.417
AST (U/L)	38 ± 5	34 ± 5	< 0.001	28 ± 5	28 ± 4	0.626
Hs-CRP (g/L)	13.3 ± 3.4	10.6 ± 3.3	< 0.001	12.3 ± 3.3	9.9 ± 2.4	< 0.001
Creatinine (mg/dL)	1.1 ± 0.3	1.0 ± 0.2	0.002	1.1 ± 0.3	1.0 ± 0.2	0.009
HOMA-IR	8.1 ± 2.1	7.4 ± 2.0	0.007	3.2 ± 0.5	3.1 ± 0.4	0.026
HOMA-β	82.3 ± 45.2	85.0 ± 45.8	0.251	79.3 ± 35.5	74.95 ± 24.04	0.379
HSI	37.3 ± 3.1	37.2 ± 3.3	0.491	39.6 ± 3.3	39.5 ± 2.7	0.881

Values are expressed as mean ± SD. BMI: body mass index; HOMA_IR: the homeostasis model assessment-estimated insulin resistance; HOMA_β: the homeostasis model assessment-β cell function; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphatase; hs-CRP: high-sensitivity C-reactive protein; HIS: hepatic steatotic index.

▶ **Table 3** Comparison of changes in biochemicalindicesbetween the study groups.

Difference	Curcuminoids	Placebo	p-Value
Weight (kg)	−1.4 ± 1	0.7 ± 2	< 0.001
BMI (kg/m²)	−0.5 ± 0.5	0.2 ± 0.7	< 0.001
Glucose (mg/dL)	−9 ± 16	−3 ± 11	0.048
Insulin (mIU/L)	−0.9 ± 3	−0.7 ± 2	0.660
HbA1c (%)	−0.9 ± 1.1	−0.2 ± 0.5	< 0.001
C-peptide (ng/mL)	−0.6 ± 0.8	0.02 ± 0.6	< 0.001
ALT (U/L)	−2 ± 6	−1 ± 5	0.032
AST (U/L)	−3 ± 5	−0.3 ± 4	0.002
Hs-CRP (g/L)	−2.7 ± 2.76	−2.4 ± 3.1	0.302
Creatinine (mg/dL)	−0.2 ± 0.3	−0.1 ± 0.3	0.450
HOMA-IR	−0.2 ± 0.4	−0.1 ± 0.3	0.511
HOMA-β	2.7 ± 16.2	−4.4 ± 16.1	0.102
HSI	−0.2 ± 1.9	0.001 ± 2.3	0.650

Values are expressed as mean ± SD. BMI: body mass index; HOMA_IR: the homeostasis model assessment-estimated insulin resistance; HOMA_β: the homeostasis model assessment-β cell function; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphatase; hs-CRP: high-sensitivity C-reactive protein; HIS: hepatic steatotic index.

ever, no significant differences were observed between curcuminoids and placebo groups with respect to these parameters (▶ **Table 3**).

Gender-specific effects of curcuminoids

A subgroup analysis according to gender was performed to compare the changes in the evaluated parameters between the study groups. Both genders receiving curcuminoids showed significant reductions in weight, BMI and serum concentrations of C-peptide compared with placebo. In contrast, the participants in the curcuminoids group had a significant decrease in glucose levels compared with placebo only in males, whereas the concentrations of HbA1c and AST were significantly lower in the intervention group versus placebo only in females (▶ **Table 4**).

Discussion

In this randomized double blind placebo controlled study we found that curcuminoids plus piperine administration significantly improved the glycemic and hepatic parameters in type 2 diabetic patients.

In agreement with the results of the present trial, there is clinical evidence supporting that curcuminoids intervention improves glucose homeostasis parameters [28, 31]. Anti-diabetic effect of curcuminoids could be attributed to the reduction in hepatic glucose production via activation of AMP kinase and inhibition of both glucose-6-phosphatase and phosphoenolpyruvate carboxykinase activity [32, 33]. Moreover, it has been demonstrated that chronic systemic inflammation disturbs the insulin signaling pathway, thus promoting the development of insulin resistance and β-cell dysfunction[34, 35]. Since curcuminoids are well known to reduce inflammatory and oxidative responses, it is likely that the antioxidant and anti-inflammatory properties could also be involved in the enhancement of insulin metabolism [36–38]. Curcuminoid administration exhibited a slight increase in HOMA-β reflecting improvement in the β-cell function, though it was not statistically significant. In this regard, there is evidence suggesting that curcuminoids may effectively protect pancreatic islets against oxidative stress by scavenging free radicals, and ameliorate βcell function[39], explaining another possible protective role of these polyphenolic compounds.

Even though two meta-analyses reported a significant reduction in hs-CRP concentrations following curcuminoids treatment[40, 41],our results did not show a significant difference between curcuminoids and placebo groups, however, the magnitude of change following curcuminoids supplementation was consist-

▶ **Table 4** Comparison of the changes in biochemical indicesbetween curcuminoids and placebo groups in each gender.

	Males			Females		
Difference	**Curcuminoids**	**Placebo**	**p-Value**	**Curcuminoids**	**Placebo**	**p-Value**
Weight (kg)	−1 ± 1	0.4 ± 2	< 0.001	−1 ± 2	1 ± 2	< 0.001
BMI (kg/m²)	−0.5 ± 0.4	0.1 ± 0.7	< 0.001	−0.5 ± 0.6	0.3 ± 0.7	< 0.001
Glucose (mg/dL)	−11 ± 18	−1 ± 11	0.020	−6 ± 13	−5 ± 11	0.548
Insulin (mIU/L)	−1 ± 2	−0.8 ± 2	0.319	−0.4 ± 3	−0.6 ± 1.9	0.709
HbA1c (%)	−0.7 ± 1.0	−0.2 ± 0.4	0.093	−1.1 ± 1.1	−0.1 ± 0.6	< 0.001
C-peptide (ng/mL)	−0.6 ± 0.7	0.1 ± 0.7	0.001	−0.6 ± 1.0	−0.1 ± 0.6	0.024
ALT (U/L)	−2 ± 5	−0.9 ± 6	0.129	−2 ± 6	−0.6 ± 5	0.127
AST (U/L)	−3 ± 4	−1 ± 4	0.255	−4 ± 6	0.9 ± 3	0.003
Hs-CRP (g/L)	−2.4 ± 2.7	−2.3 ± 3.6	0.384	−2.9 ± 2.8	−2.4 ± 2.3	0.541
Creatinine (mg/dL)	−0.2 ± 0.3	−0.1 ± 0.3	0.835	−0.2 ± 0.3	−0.1 ± 0.3	0.456
HOMA-IR	−0.3 ± 0.3	−0.1 ± 0.4	0.170	−0.1 ± 0.4	−0.1 ± 0.3	0.653
HOMA-β	2.3 ± 18.1	−6.2 ± 14.5	0.084	3.0 ± 14.4	−2.3 ± 17.8	0.353
HSI	−0.5 ± 1.2	0.2 ± 2.4	0.194	0.1 ± 2.4	−0.2 ± 2.2	0.618

Values are expressed as mean ± SD. BMI: body mass index; HOMA_IR: the homeostasis model assessment-estimated insulin resistance; HOMA_β: the homeostasis model assessment-β cell function; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ALP: alkaline phosphatase; hs-CRP: high-sensitivity C-reactive protein; HSI: hepatic steatotic index.

ent with previous clinical trials [41]. It is well-known that elevated CRP levels are an important risk factor for the development of atherosclerotic cardiovascular disease [42]. Curcumin is a polyphenolic agent with well-described anti-inflammatory activities [43–46]. In this context, it has been described that curcumin inhibits the production of pro-inflammatory cytokines such as interleukin-6, tumor necrosis factor-α and interleukin 1β by suppression of the NF-κB signaling pathway resulting in a reduced expression of CRP in the human liver cells [47]. Furthermore, this natural agent downregulates cyclooxygenase-2, ICAM-1, MCP-1, and nitric oxide production [48] resulting in the mitigation of hepatic inflammation and oxidative stress[49, 50]. The above-mentioned mechanisms could explain the improvement in serum levels of transaminases after curcuminoids supplementation by decreased inflammation of hepatic tissue which is in agreement with the observed in both experimental[51] and clinical [5] studies. In our study we observed a gender specific reduction in glucose levels in males and HbA1c and AST levels only in female patients. This is a novel observation which warrants further investigation as there is no reported evidence of gender specific effect of curcuminoids

Some limitations of this study should be considered. First, the insufficient information regarding to standard-of-care treatment which may be involved in the lack of efficacy of curcuminoids on some parameters measured particularly hs-CRP. Second, dietary intake and physical activity were not assessed; nevertheless, by randomization, it is expected that these characteristics were distributed similarly in the study groups minimizing the risk of bias. Finally, the duration of trial was short and it remains to assess the efficacy of curcuminoids in future long-term trials.

In conclusion, the results of the present trial revealed a beneficial effect of curcuminoids plus piperine supplementation on glycemic and hepatic parameters but not on hs-CRP levels in T2D patients. However, longer-term clinical trials are mandatory to corroborate the anti-diabetic and hepatoprotective properties of curcuminoids in T2D patients and also to ascertain if curcuminoids can be useful for the prevention of diabetic macro- and microvascular complications.

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Conflict of Interest

Muhammed Majeed is the Founder & Chairman of Sabinsa Corporation and Sami Labs Limited.

References

[1] Ganjali S, Blesso CN, Banach M et al. Effects of curcumin on HDL functionality. Pharmacological research 2017; 119: 208–218

[2] Lelli D, Sahebkar A, Johnston TP et al. Curcumin use in pulmonary diseases: State of the art and future perspectives. Pharmacological research 2017; 115: 133–148

[3] Mirzaei H, Naseri G, Rezaee R et al. Curcumin: A new candidate for melanoma therapy? International journal of cancer 2016; 139: 1683–1695

[4] Momtazi AA, Shahabipour F, Khatibi S et al. Curcumin as a MicroRNA regulator in cancer: A Review. Reviews of physiology, biochemistry and pharmacology 2016; 171: 1–38

[5] Panahi Y, KP Mohtashami R et al. Efficacy and Safety of Phytosomal Curcumin in Non-Alcoholic Fatty Liver Disease: A Randomized Controlled Trial. Drug Res (Stuttg) 2017; 67: 244–251

[6] Panahi Y, Rahimnia AR, Sharafi M et al. Curcuminoid treatment for knee osteoarthritis: a randomized double-blind placebo-controlled trial. Phytotherapy research: PTR 2014; 28: 1625–1631

[7] Rahmani S, Asgary S, Askari G et al. Treatment of non-alcoholic fatty liver disease with curcumin: A randomized placebo-controlled trial. Phytotherapy research: PTR 2016; 30: 1540–1548

[8] Saberi-Karimian M, Katsiki N, Caraglia M et al. Vascular endothelial growth factor: An important molecular target of curcumin. Critical reviews in food science and nutrition 2017; 1–14

[9] Sahebkar A, Henrotin Y. Analgesic Efficacy and safety of curcuminoids in clinical practice: A systematic review and meta-analysis of randomized controlled trials. Pain medicine 2016; 17: 1192–1202

[10] Chuengsamarn S, Rattanamongkolgul S, Luechapudiporn R et al. Curcumin extract for prevention of type 2 diabetes. Diabetes care 2012; 35: 2121–2127

[11] Na LX, Li Y, Pan HZ et al. Curcuminoids exert glucose-lowering effect in type 2 diabetes by decreasing serum free fatty acids: A double-blind, placebo-controlled trial. Molecular nutrition & food research 2013; 57: 1569–1577

[12] Hajavi J, MA Johnston TP et al. Curcumin: A naturally occurring modulator of adipokines in diabetes. J Cell Biochem 2017

[13] Katsiki N, YJ Gotzamani-Psarrakou A et al. Adipokines and vascular risk in type 2 diabetes mellitus. Angiology 2011; 62: 601–604

[14] Wahlstrom B, Blennow G. A study on the fate of curcumin in the rat. Acta pharmacologica et toxicologica 1978; 43: 86–92

[15] Shoba G, JD Joseph T et al. Influence of piperine on the pharmacokinetics of curcumin in animals and human volunteers. Planta Med 1998; 64: 353–356

[16] Panahi Y, KN Sahebi E et al. Antioxidant effects of curcuminoids in patients with type 2 diabetes mellitus: a randomized controlled trial. Inflammopharmacology 2017; 25: 25–31

[17] Panahi Y, KN Sahebi E et al. Curcuminoids modify lipid profile in type 2 diabetes mellitus: A randomized controlled trial. Complement Ther Med 2017; 33: 1–5

[18] Cicero AFG, Colletti A, Bajraktari G et al. Lipid-lowering nutraceuticals in clinical practice: Position paper from an International Lipid Expert Panel. Nutrition reviews 2017; 75: 731–767

[19] Cicero AFG, Colletti A, Bajraktari G et al. Lipid lowering nutraceuticals in clinical practice: Position paper from an International Lipid Expert Panel. Archives of medical science:AMS 2017; 13: 965–1005

[20] Johnston TP, Korolenko TA, Pirro M et al. Preventing cardiovascular heart disease: Promising nutraceutical and non-nutraceutical treatments for cholesterol management. Pharmacological research 2017; 120: 219–225

[21] Sahebkar A, Serban MC, Gluba-Brzozka A et al. Lipid-modifying effects of nutraceuticals: An evidence-based approach. Nutrition 2016; 32: 1179–1192

[22] Ward N, Sahebkar A, Banach M et al. Recent perspectives on the role of nutraceuticals as cholesterol-lowering agents. Current opinion in lipidology 2017; 28: 495–501

[23] Cicero AF, Colletti A. Role of phytochemicals in the management of metabolic syndrome. Phytomedicine: International journal of phytotherapy and phytopharmacology 2016; 23: 1134–1144

[24] Sahebkar A. Curcuminoids for the management of hypertriglyceridaemia. Nature reviews Cardiology 2014; 11: 123

[25] Granados-Castro LF, R-RD Fernández-Rojas B et al. Curcumin prevents paracetamol-induced liver mitochondrial alterations. J Pharm Pharmacol 2016; 68: 245–256

[26] Naik SR, TV Patil SR. Protective effect of curcumin on experimentally induced inflammation, hepatotoxicity and cardiotoxicity in rats: Evidence of its antioxidant property. Exp Toxicol Pathol 2011; 63: 419–431

[27] Yousef MI, OS El-Guendi MI et al. Potential protective effects of quercetin and curcumin on paracetamol-induced histological changes, oxidative stress, impaired liver and kidney functions and haematotoxicity in rat. Food Chem Toxicol 2010; 48: 3246–3261

[28] Chuengsamarn S, RS Luechapudiporn R et al. Curcumin extract for prevention of type 2 diabetes. Diabetes care 2012; 35: 2121–2127

[29] Panahi Y, KN Hosseini MS et al. Lipid-modifying effects of adjunctive therapy with curcuminoids-piperine combination in patients with metabolic syndrome: Results of a randomized controlled trial. Complement Ther Med 2014; 22: 851–857

[30] Lee JH, KD Kim HJ et al. Hepatic steatosis index: A simple screening tool reflecting nonalcoholic fatty liver disease. Dig Liver Dis 2010; 42: 503–508

[31] Na LX, LY Pan HZ et al. Curcuminoids exert glucose-lowering effect in type 2 diabetes by decreasing serum free fatty acids: A double-blind, placebo-controlled trial. Mol Nutr Food Res 2013; 57: 1569–1577

[32] Fujiwara H, HM Zhou X et al. Curcumin inhibits glucose production in isolated mice hepatocytes. Diabetes Res Clin Pract 2008; 80: 185–191

[33] Seo KI, CM Jung UJ et al. Effect of curcumin supplementation on blood glucose, plasma insulin, and glucose homeostasis related enzyme activities in diabetic db/db mice. Mol Nutr Food Res 2008; 52: 995–1004

[34] Hotamisligil GS, PP Budavari A et al. IRS-1-mediated inhibition of insulin receptor tyrosine kinase activity in TNF-alpha- and obesity-induced insulin resistance. Science 1996; 271: 665–668

[35] Naugler WE.KM The wolf in sheep's clothing: The role of interleukin-6 in immunity, inflammation and cancer. Trends Mol Med 2008; 14: 109–119

[36] Panahi Y, Alishiri GH, Parvin S et al. Mitigation of systemic oxidative stress by curcuminoids in osteoarthritis: Results of a randomized controlled trial. Journal of dietary supplements 2016; 13: 209–220

[37] Panahi Y, Ghanei M, Hajhashemi A et al. Effects of Curcuminoids-Piperine Combination on Systemic Oxidative Stress, Clinical symptoms and quality of life in subjects with chronic pulmonary complications due to sulfur mustard: A randomized controlled trial. Journal of dietary supplements 2016; 13: 93–105

[38] Sahebkar A, Serban MC, Ursoniu S et al. Effect of curcuminoids on oxidative stress: A systematic review and meta-analysis of randomized controlled trials. Journal of Functional Foods 2015; 18: 898–909

[39] Meghana K, SG Ramesh B. Curcumin prevents streptozotocin-induced islet damage by scavenging free radicals: A prophylactic and protective role. Eur J Pharmacol 2007; 577: 183–191

[40] A.S Are curcuminoids effective C-reactive protein-lowering agents in clinical practice? Evidence from a meta-analysis. Phytother Res 2014; 28: 633–642

[41] Panahi Y, HM Khalili N et al. Antioxidant and anti-inflammatory effects of curcuminoid-piperine combination in subjects with metabolic syndrome: A randomized controlled trial and an updated meta-analysis. Clin Nutr 2015; 34: 1101–1108

[42] Lloyd-Jones DM, LK Tian L et al. Narrative review: Assessment of C-reactive protein in risk prediction for cardiovascular disease. Ann Intern Med 2006; 145: 35–42

[43] Ganjali S, Sahebkar A, Mahdipour E et al. Investigation of the effects of curcumin on serum cytokines in obese individuals: A randomized controlled trial. TheScientificWorldJournal 2014; 2014: 898361

[44] Mollazadeh H, Cicero AFG, Blesso CN et al. Immune modulation by curcumin: The role of interleukin-10. Critical reviews in food science and nutrition 2017; 1–13

[45] Panahi Y, Hosseini MS, Khalili N et al. Antioxidant and anti-inflammatory effects of curcuminoid-piperine combination in subjects with metabolic syndrome: A randomized controlled trial and an updated meta-analysis. Clinical nutrition 2015; 34: 1101–1108

[46] Sahebkar A, Cicero AFG, Simental-Mendia LE et al. Curcumin downregulates human tumor necrosis factor-alpha levels: A systematic review and meta-analysis ofrandomized controlled trials. Pharmacological research 2016; 107: 234–242

[47] Moshage HJ, RH van Pelt JF et al. The effect of interleukin-1, interleukin-6 and its interrelationship on the synthesis of serum amyloid A and C-reactive protein in primary cultures of adult human hepatocytes. Biochem Biophys Res Commun 1988; 155: 112–117

[48] Meng Z, YC Deng Q et al. Curcumin inhibits LPS-induced inflammation in rat vascular smooth muscle cells in vitro via ROS-relative TLR4-MAPK/NF-κB pathways. Acta Pharmacol Sin 2013; 34: 901–911

[49] Leclercq IA, FG Sempoux C et al. Curcumin inhibits NF-kappaB activation and reduces the severity of experimental steatohepatitis in mice. J Hepatol 2004; 41: 926–934

[50] Vizzutti F, PA Galastri S et al. Curcumin limits the fibrogenic evolution of experimental steatohepatitis. Lab Invest 2010; 90: 104–115

[51] Ramirez-Tortosa MC, R-T C, Mesa MD et al. Curcumin ameliorates rabbits's steatohepatitis via respiratory chain, oxidative stress, and TNF-alpha. Free Radic Biol Med 2009; 47: 924–931