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Effects of curcumin on body weight, glycemic control and serum lipids in women with polycystic ovary syndrome: A randomized, double-blind, placebo-controlled trial

Mehri Jamilian [a], Fatemeh Foroozanfard [b], Elham Kavossian [b], Esmat Aghadavod [c], Rana Shafabakhsh [c], Asma Hoseini [c], Zatollah Asemi [c, *]

[a] Traditional and Complementary Medicine Research Center, Arak University of Medical Sciences, Arak, Iran
[b] Gametogenesis Research Center, Kashan University of Medical Sciences, Kashan, Iran
[c] Research Center for Biochemistry and Nutrition in Metabolic Diseases, Kashan University of Medical Sciences, Kashan, Iran

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SUMMARY

Objective: The aim of this study was to evaluate the effect of curcumin on body weight, glycemic control and serum lipids in women suffering from polycystic ovary syndrome (PCOS).
Methods: The current randomized, double-blinded, placebo-controlled clinical trial was performed on 60 subjects with PCOS, aged 18–40 years old. Subjects were randomly allocated to take 500 mg/day curcumin (n = 30) or placebo (n = 30) for 12 weeks. Glycemic control and serum lipids were measured at baseline and after the 12-week intervention. Using RT-PCR method, gene expression related to insulin and lipid metabolism was evaluated.
Results: Curcumin significantly decreased weight (−0.8 ± 0.9 vs. −0.2 ± 0.8 kg, P = 0.03) and BMI (−0.3 ± 0.4 vs. −0.1 ± 0.3 kg/m^2, P = 0.03). Curcumin, compared with the placebo, significantly reduced fasting glucose (β −2.63 mg/dL; 95% CI, −4.21, −1.05; P = 0.002), serum insulin (β −1.16 μIU/mL; 95% CI, −2.12, −0.19; P = 0.02), insulin resistance (β −0.26; 95% CI, −0.48, −0.03; P = 0.02), and significantly increased insulin sensitivity (β 0.006; 95% CI, 0.001, 0.01; P = 0.02). In addition, taking curcumin was associated with a significant reduction in total cholesterol (β −15.86 mg/dL; 95% CI, −24.48, −7.24; P = 0.001), LDL-cholesterol (β −16.09 mg/dL; 95% CI, −25.11, −7.06; P = 0.001) and total-/HDL-cholesterol ratio (β −0.62; 95% CI, −0.93, −0.30; P < 0.001), and a significant increase in HDL-cholesterol levels (β 2.14 mg/dL; 95% CI, 0.36, 3.92; P = 0.01) compared with the placebo. Additionally, curcumin administration up-regulated gene expression of peroxisome proliferator-activated receptor gamma (PPAR-γ) (P = 0.03) and low-density lipoprotein receptor (LDLR) (P < 0.001) compared with the placebo.
Conclusions: Overall, curcumin administration for 12 weeks to women with PCOS had beneficial effects on body weight, glycemic control, serum lipids except triglycerides and VLDL-cholesterol levels, and gene expression of PPAR-γ and LDLR. Registered under Clinical Trials.gov Identifier no. http://www.irct.ir: IRCT20170513033941N50.

1. Introduction

Polycystic ovary syndrome (PCOS) is one of the most prevalent disorders worldwide with its global prevalence ranges from 4% to 21% [1]. This endocrine disorder affects various aspects of women's health and demonstrates with multiple clinical features and related comorbidities, including reproductive abnormalities, prominent insulin resistance as well as increased risk of coronary heart disease, type 2 diabetes mellitus (T2DM) and dyslipidemia [2–5]. Patients suffering from PCOS represent with decreased insulin sensitivity as well as β-cell dysfunction. Besides, dyslipidemia is one of the most common complications of PCOS involving increased triglycerides and LDL-cholesterol as well as decreased HDL-cholesterol levels [6]. Additionally, gene expression of low-density lipoprotein receptor (LDLR) has been

* Corresponding author. Fax: +98 31 55463377.
E-mail address: asemi_r@yahoo.com (Z. Asemi).

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decreased in PCOS patients. Furthermore, evidence has shown an important role of gene expression of peroxisome proliferator-activated receptor gamma (PPAR-γ) in insulin signaling and androgen production in PCOS [7]. Currently, life style interventions including diet alterations are the first recommended approach for these patients. In addition, complementary and alternative medicine has become more popular in PCOS management, recently [8].

Curcumin is a polyphenolic compound derived from the famous spice, turmeric. It is able to interact with a wide variety of molecular targets exerting many effects such as antioxidant, anti-inflammatory, hypoglycemic and lipid-lowering activities [9,10]. Interestingly, curcumin administration has been shown to be effective in improving various metabolic disorders such as obesity, diabetes, metabolic syndrome, and cardiovascular disease by improving body weight, insulin resistance, and lipid abnormalities [11,12]. However, some studies have also reported contradictory results [11,13,14]. A number of experimental and clinical studies have revealed that curcumin is able to increase insulin sensitivity by enhancing glucose homeostasis, β-cell function and insulin secretion [15–18]. Furthermore, curcumin has been demonstrated to be effective in controlling hyperlipidemic disorders by reducing triglycerides, LDL-cholesterol and total cholesterol as well as increasing HDL-cholesterol levels [19]. There are promising evidence shows the importance of curcumin administration in patients with PCOS. To our knowledge, no investigation is currently on-going to evaluate the effect of curcumin intake on metabolic profiles in women with PCOS. Therefore, in this study, we aimed to evaluate the effects of curcumin on body weight, glycemic control and serum lipids in women with PCOS.

2. Subjects and methods

In a randomized, double-blind, placebo-controlled clinical trial, sixty women were randomly enrolled to receive either 500 mg/day curcumin or placebo (starch) (n = 30 each group). Curcumin and placebo were manufactured by Dineh (Tehran, Iran) and Barij Essence (Kashan, Iran), respectively. Placebo and curcumin were totally the same in color, shape, size, and packaging. Randomization was made using computer-generated random numbers by a trained staff at the gynecology clinic. During the study, we asked patients to return medication containers to ensure that curcumin supplements were used. Also, we remind patients to take the supplements by cell phone. Study protocol was published in the Iranian website for registration of clinical trials (www.irct.ir;no: IRCT20170513033941N50). Eligible study participants were women with PCOS diagnosed based on the Rotterdam criteria [20], aged 18–40 years old whom referred to the outpatient Kosar Clinic in Arak, Iran, and was conducted between January and May 2019. The study protocol was approved by the Ethics Committee of Arak University of Medical Sciences (AUMS). Written informed consent was attained from all participants before the intervention. Exclusion criteria were as follows: individuals with neoplastic disorders cardiovascular diseases malabsorptive disorders current or previous (within the last 6 months), use of hormonal, antidiabetic and anti-obesity medications prior to study inclusion.

2.1. Anthropometric measures

Anthropometric measurements were assessed by an expert midwife at the clinic at baseline and the end of the intervention. Height and weight (Seca, Hamburg, Germany) were measured with light clothing without shoes. Body mass index (BMI) was calculated as weight (kilograms) divided by height (meters) squared.

2.2. Assessment of outcomes

The homeostatic model assessment for insulin resistance (HOMA-IR) and insulin levels were considered as the primary outcomes. Other metabolic profiles, peroxisome proliferator-activated receptor gamma (PPAR-γ), low-density lipoprotein receptor (LDLR) and glucose transporter 1 (GLUT-1) expression were recognized as the secondary outcomes.

2.3. Biochemical assessment

Fasting blood samples were collected from participants (15 mL) at baseline and the end of the intervention. To ascertain fasting plasma glucose (FPG) and serum lipids, enzymatic kits (Pars Azmun, Tehran, Iran) with inter- and intra-assay coefficient variances (CVs) lower than 5% were used. Serum insulin values were measured using an ELISA kit (Monobind, California, USA) with the intra- and inter-assay CVs lower than 6%. HOMA-IR and the quantitative insulin sensitivity check index (QUICKI) were calculated according to the suggested formulas [21].

2.4. RNA extraction and real-time PCR

Gene expression of PPAR-γ, GLUT-1 and LDLR were determined by quantitative RT-PCR, using the LightCycler technology (Roche Diagnostics, Rotkreuz, Switzerland) with SYBR green detection and Amplicon Kit (Table 1).

2.5. Sample size and statistical analyses

Type one (α) and type two errors (β) were defined as 0.05, and 0.20 (power = 80%), respectively. According to our previously published trial [22], we used 1.81 as the SD and 1.45 as the change in mean (d) of HOMA-IR as a primary outcome parameter. Based on the power analysis, we needed 25 subjects in each group; after allowing for 5 dropouts in each group, the final sample size was 30 persons in each group.

The Kolmogorov–Smirnov test was used to determine the normality of variables. Independent-sample *t*-test was applied to compare changes in anthropometric values, gene expression and dietary intakes between the two groups. To evaluate the effect of curcumin intake on metabolic status, we used multiple linear regression. Significance of the treatment effects was presented as

Table 1
Specific primers used for real-time quantitative PCR.

Gene	Primer	Product size (bp)	Annealing temperature (C)
GAPDH	F: AAGCTCATTTCCTGGTATGACAACG R: TCTTCCTCTTGTGCTCTTGCTGG	126	61.3
PPAR-γ	F: ATGACAGACCTCAGACAGATTG R: AATGTTGGCAGTGGCTCAG	210	54
GLUT-1	F: TATCTGAGCATCGTGGCCAT R: AAGACGTAGGGACCACACAG	238	62.1
LDLR	F: ACTTACGGACAGACAGACAG R: GGCCACACATCCCATGATTC	223	57

GAPDH, glyceraldehyde-3-Phosphate dehydrogenase; GLUT-1, glucose transporter 1; LDLR, low-density lipoprotein receptor; PPAR-γ, peroxisome proliferator-activated receptor gamma.

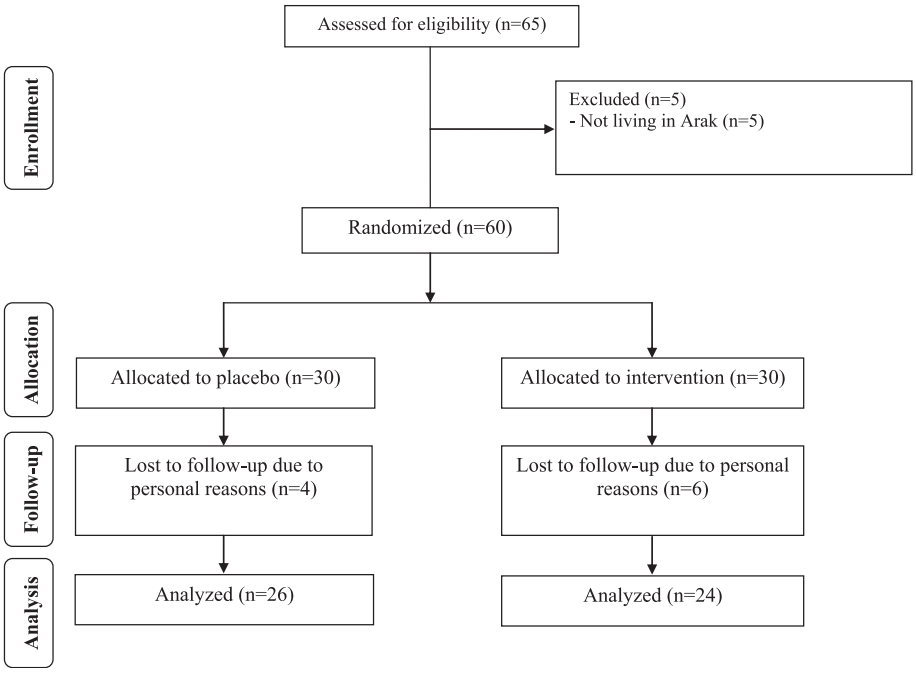

Fig. 1. Summary of patient flow diagram.

the mean differences with 95% confidence interval. P-values <0.05 were considered statistically significant.

3. Results

As demonstrated in the study flow diagram (Fig. 1), during the enrollment phase of the study, there were 65 women with PCOS; however, 5 participants did not meet the inclusion criteria and thus were excluded. During the follow-up, 6 participants in the curcumin group and 4 in the placebo group dropped out of the study due to personal reasons. Finally, 50 participants [placebo (n = 26) and curcumin (n = 24)] completed the trial.

Mean age, height, and baseline and end-of-trial weight and BMI were not statistically different between the two groups (Table 2). Curcumin significantly decreased weight (−0.8 ± 0.9 vs. −0.2 ± 0.8 kg, P = 0.03) and BMI (−0.3 ± 0.4 vs. −0.1 ± 0.3 kg/m^2, P = 0.03).

There was no statistically significant difference in terms of dietary macro- and micronutrients intakes between curcumin and placebo groups (Data not shown).

Curcumin, compared with the placebo, significantly reduced FPG (β −2.63 mg/dL; 95% CI, −4.21, −1.05; P = 0.002), serum insulin (β −1.16 μIU/mL; 95% CI, −2.12, −0.19; P = 0.02), HOMA-IR (β −0.26; 95% CI, −0.48, −0.03; P = 0.02), and significantly increased QUICKI (β 0.006; 95% CI, 0.001, 0.01; P = 0.02) (Table 3). In addition, taking curcumin was associated with a significant reduction in total cholesterol (β −15.86 mg/dL; 95% CI, −24.48, −7.24; P = 0.001), LDL-cholesterol (β −16.09 mg/dL; 95% CI, −25.11, −7.06; P = 0.001) and total-/HDL-cholesterol ratio (β −0.62; 95% CI, −0.93, −0.30; P < 0.001), and a significant increase in HDL-cholesterol levels (β 2.14 mg/dL; 95% CI, 0.36, 3.92; P = 0.01) compared with the placebo.

Curcumin intake increased gene expression of PPAR-γ (P = 0.03) and LDLR (P < 0.001) compared with the placebo group (Figs. 2 and 3).

Curcumin consumption did not affect gene expression of GLUT-1 (P = 0.12) compared with the placebo (Fig. 2).

Table 2
General characteristics of study participants.[a]

	Placebo group (n = 26)	Curcumin group (n = 24)	P[b]
Age (y)	27.2 ± 3.4	28.6 ± 4.7	0.22
Height (cm)	164.2 ± 3.9	162.5 ± 4.4	0.15
Weight at study baseline (kg)	71.0 ± 9.5	72.1 ± 9.8	0.68
Weight at end-of-trial (kg)	70.8 ± 9.5	71.3 ± 9.8	0.83
Weight change (kg)	−0.2 ± 0.8	−0.8 ± 0.9	0.03
BMI at study baseline (kg/m^2)	26.4 ± 3.8	27.4 ± 3.9	0.37
BMI at end-of-trial (kg/m^2)	26.3 ± 3.8	27.1 ± 3.8	0.48
BMI change (kg/m^2)	−0.1 ± 0.3	−0.3 ± 0.4	0.03

[a] Data are means± SDs.
[b] Obtained from independent *t*-test.

4. Discussion

In this study, we evaluated for the first time the effects of the 12-week intervention of curcumin intake on body weight, and metabolic and genetic profiles related to insulin and lipid in women with PCOS. We found that curcumin administration for 12 weeks to women with PCOS had beneficial effects on body weight, glycemic control, serum lipids except triglycerides and VLDL-cholesterol levels, and gene expression of PPAR-γ and LDLR.

4.1. Effects on body weight and BMI

The prevalence of being overweight or obese is more among PCOS women in comparison to healthy women [23]. Our results indicated that curcumin consumption for 12 weeks significantly reduced body weight and BMI in PCOS patients. Our findings were in line with a clinical trial in which the role of curcumin on weight loss was investigated [24]. However, in another clinical study, curcumin intake did not improve body weight [25]. Obesity increases the risk of metabolic complications and decreases quality of life in PCOS patients. In addition, obese women with PCOS have been observed to represent more severe morbidities such as higher degrees of insulin resistance, hyperandrogenism and hyperinsulinemia [26,27]. Curcumin may ameliorate body weight by possible effects, including decreasing fat mass, endoplasmic

Table 3
Metabolic profiles at baseline and after the 12-week intervention in women with polycystic ovary syndrome that received either curcumin or placebo.[a]

Variables	Placebo group (n = 26)		Curcumin group (n = 24)		Difference in outcome measures between curcumin and placebo groups[a]	
	Baseline	Week 12	Baseline	Week 12	β (95% CI)	P[b]
FPG (mg/dL)	92.9 ± 4.2	92.5 ± 4.5	94.9 ± 6.1	91.2 ± 4.6	−2.63 (−4.21, −1.05)	0.002
Insulin (μIU/mL)	10.5 ± 2.5	10.6 ± 2.4	11.3 ± 3.6	10.1 ± 3.2	−1.16 (−2.12, −0.19)	0.02
HOMA-IR	2.4 ± 0.6	2.4 ± 0.5	2.7 ± 0.9	2.4 ± 0.8	−0.26 (−0.48, −0.03)	0.02
QUICKI	0.336 ± 0.011	0.335 ± 0.012	0.333 ± 0.018	0.338 ± 0.017	0.006 (0.001, 0.01)	0.02
Triglycerides (mg/dL)	155.6 ± 33.5	153.8 ± 33.3	163.6 ± 44.8	154.0 ± 29.4	−5.58 (−12.93, 1.77)	0.13
VLDL-cholesterol (mg/dL)	31.1 ± 6.7	30.8 ± 6.6	32.7 ± 8.9	30.8 ± 5.8	−1.11 (-2.58, 0.35)	0.13
Total cholesterol (mg/dL)	179.5 ± 29.9	179.7 ± 28.1	192.0 ± 36.6	175.5 ± 39.7	−15.86 (−24.48, −7.24)	0.001
LDL-cholesterol (mg/dL)	104.9 ± 32.1	106.4 ± 29.4	119.6 ± 35.8	103.6 ± 38.5	−16.09 (−25.11, −7.06)	0.001
HDL-cholesterol (mg/dL)	43.5 ± 7.7	42.5 ± 8.0	39.6 ± 9.8	41.0 ± 9.6	2.14 (0.36, 3.92)	0.01
Total-/HDL-cholesterol ratio	4.2 ± 1.0	4.4 ± 1.0	5.1 ± 1.3	4.4 ± 1.3	−0.62 (−0.93, −0.30)	<0.001

Data are mean ±SDs.
FPG, fasting plasma glucose; HOMA-IR, homeostasis model of assessment-insulin resistance; HDL-cholesterol, high density lipoprotein-cholesterol; LDL-cholesterol, low density lipoprotein-cholesterol; QUICKI, quantitative insulin sensitivity check index; VLDL-cholesterol, very low density lipoprotein-cholesterol.
[a] "Outcome measures" refers to the change in values of measures of interest between baseline and week 12. β [difference in the mean outcomes measures between treatment groups (curcumin group = 1 and placebo group = 0)].
[b] Obtained from multiple regression model (adjusted for baseline values of each biochemical variables).

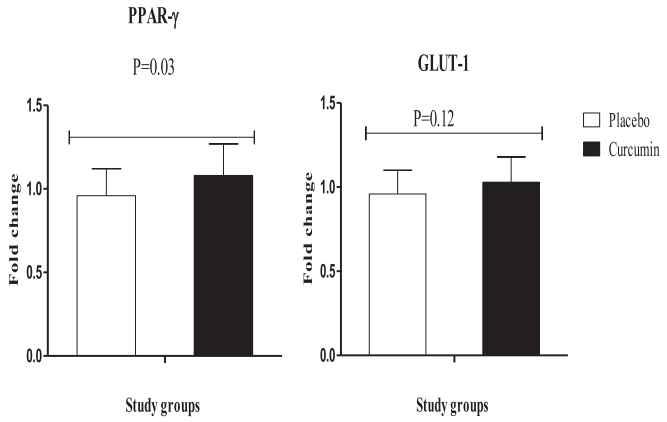

Fig. 2. Effect of the 12-week intake with curcumin or placebo on expression ratio of PPAR-γ and GLUT-1 gene in PBMCs of PCOS women.

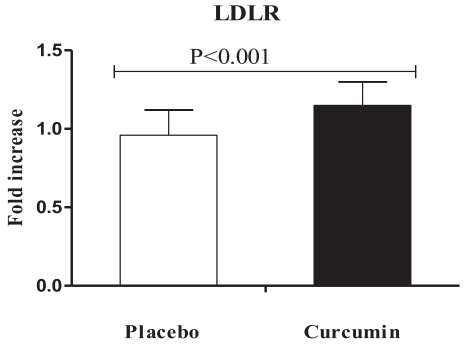

Fig. 3. Effect of the 12-week intake with curcumin or placebo on expression ratio of LDLR gene in PBMCs of PCOS women. GLUT-1, glucose transporter 1; LDLR, low-density lipoprotein receptor; PPAR-γ, peroxisome proliferator-activated receptor gamma; PCOS, polycystic ovary syndrome; PBMCs, peripheral blood mononuclear cells.

reticulum stress in adipocytes, insulin resistance, and increasing energy expenditure [28].

4.2. Effects on glycemic control

In current study, we observed that curcumin intake for 12 weeks in PCOS subjects improved glycemic control. According to two previous meta-analyses, curcumin could decrease fasting glucose, HbA1c and HOMA-IR [29,30]. However, two another meta-analyses reported that curcumin consumption significantly decreased fasting glucose and HbA1c, but did not affect HOMA-IR [31,32]. In addition to mentioned effects, some randomized clinical trials reported that curcumin intake in patients with T2DM and non-alcoholic fatty liver disease significantly increased QUICKI [22,33]. Evidence revealed that long-term worsening of insulin resistance in PCOS patients is a potent risk factor for developing of T2DM [34]. In addition, insulin resistance may be associated with decreased levels of adiponectin and accumulation of ectopic fat in different tissues of PCOS women. Curcumin improves these conditions via inducing glucokinase activity in the liver, increasing peripheral glucose uptake, and reducing insulin resistance. Furthermore, in our study curcumin intake increased gene expression of PPAR-γ, but did not affect gene expression of GLUT1. *In vitro* and *in vivo* studies demonstrated that curcumin exerts anti-diabetic effects by increasing the gene expression of PPAR-γ [35–37]. PPAR-γ has pleiotropic effects in improvement of glucose homeostasis, insulin sensitivity and controlling gene expression which play key roles in lipid and glucose metabolisms [38]. Curcumin may exert glucose-lipid-lowering effects by increasing gene expression of PPAR-γ which leads to improvement of insulin secretion and lipid homeostasis [39].

4.3. Effects on serum lipids

We found that curcumin intake for 12 weeks in patients with PCOS had positive effects on serum lipids except triglycerides and VLDL-cholesterol levels. Lipid-lowering effects of curcumin have been well investigated. In a meta-analysis conducted by Simental-Mendía et al. [34], curcumin administration could significantly decrease triglycerides and increase HDL-cholesterol, but did not affect total cholesterol and LDL-cholesterol concentrations [40]. In another meta-analysis, curcumin intake has indicated to reduce total cholesterol, LDL-cholesterol and triglycerides, but did not change HDL-cholesterol levels. In contrast, another meta-analysis declared that curcumin administration had no significant effect on triglycerides, total cholesterol, LDL-cholesterol and HDL-cholesterol levels [32]. In addition, a significant reduction in total cholesterol and triglycerides following the intake of curcumin among patients with metabolic syndrome and related disorders was seen, while HDL-cholesterol and LDL-cholesterol levels did not change [30]. Dyslipidemia characterized by elevated triglycerides, total cholesterol and LDL-cholesterol, and decreased levels of HDL-

cholesterol, which is common in patients with PCOS especially obese ones [41,42]. Curcumin ameliorates dyslipidemia and activates lipid metabolism through elevating lipoprotein lipase activity to decrease triglycerides levels [43]. In addition, curcumin attenuates free fatty acid of plasma, affects gastrointestinal absorption and transportation of cholesterol, as well as limits the risk of lipid peroxidation which induces inflammatory response [19]. Furthermore, the current study indicated that gene expression of LDLR significantly increased after curcumin intervention. Multiple experimental and animal studies have reported that curcumin is able to induce gene expression of LDLR leading to ameliorate hypercholesterolemia [44–47]. Increased expression of LDLR leads to increased catabolism of LDL-cholesterol and improvement of cholesterol homeostasis. Thus, curcumin intake may reduce complications related to dyslipidemia in PCOS patients via improving lipid profiles and increasing expression of LDLR.

4.4. Limitation

Curcumin and placebo were provided two various companies. This should be considered in the interpretation of our findings.

5. Conclusions

Overall, curcumin administration for 12 weeks to women with PCOS had beneficial effects on body weight, glycemic control, serum lipids except triglycerides and VLDL-cholesterol levels, and gene expression of PPAR-γ and LDLR.

Authors' contributions

ZA contributed in conception, design, statistical analysis and drafting of the manuscript. MJ, FF, EK, EA, RS and AH contributed in data collection and manuscript drafting. All authors approved the final version for submission. ZA supervised the study.

Declaration of Competing Interest

None.

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References

[1] Bozdag G, Mumusoglu S, Zengin D, Karabulut E, Yildiz BO. The prevalence and phenotypic features of polycystic ovary syndrome: a systematic review and meta-analysis. Hum Reprod (Oxf, Engl) 2016;31:2841–55.
[2] DeUgarte CM, Bartolucci AA, Azziz R. Prevalence of insulin resistance in the polycystic ovary syndrome using the homeostasis model assessment. Fertil Steril 2005;83:1454–60.
[3] Norman RJ, Masters L, Milner CR, Wang JX, Davies MJ. Relative risk of conversion from normoglycaemia to impaired glucose tolerance or non-insulin dependent diabetes mellitus in polycystic ovarian syndrome. Hum Reprod (Oxf, Engl) 2001;16:1995–8.
[4] Krentz AJ, von Muhlen D, Barrett-Connor E. Searching for polycystic ovary syndrome in postmenopausal women: evidence of a dose-effect association with prevalent cardiovascular disease. Menopause (New York, NY) 2007;14:284–92.
[5] Legro RS, Kunselman AR, Dunaif A. Prevalence and predictors of dyslipidemia in women with polycystic ovary syndrome. Am J Med 2001;111:607–13.
[6] Cussons AJ, Stuckey BG, Watts GF. Cardiovascular disease in the polycystic ovary syndrome: new insights and perspectives. Atherosclerosis 2006;185:227–39.
[7] Faubert J, Battista M-C, Baillargeon J-P. Physiology and endocrinology symposium: insulin action and lipotoxicity in the development of polycystic ovary syndrome: a review 1. J Anim Sci 2016;94:1803–11.
[8] Ong M, Peng J, Jin X, Qu X. Chinese herbal medicine for the optimal management of polycystic ovary syndrome. Am J Chin Med 2017;45:405–22.
[9] Kunnumakkara AB, Bordoloi D, Padmavathi G, Monisha J, Roy NK, Prasad S, et al. Curcumin, the golden nutraceutical: multitargeting for multiple chronic diseases. Br J Pharmacol 2017;174:1325–48.
[10] Shin SK, Ha TY, McGregor RA, Choi MS. Long-term curcumin administration protects against atherosclerosis via hepatic regulation of lipoprotein cholesterol metabolism. Mol Nutr Food Res 2011;55:1829–40.
[11] Mohammadi A, Sahebkar A, Iranshahi M, Amini M, Khojasteh R, Ghayour-Mobarhan M, et al. Effects of supplementation with curcuminoids on dyslipidemia in obese patients: a randomized crossover trial. Phytother Res – PTR 2013;27:374–9.
[12] Chuengsamarn S, Rattanamongkolgul S, Luechapudiporn R, Phisalaphong C, Jirawatnotai S. Curcumin extract for prevention of type 2 diabetes. Diabetes Care 2012;35:2121–7.
[13] Baum L, Cheung SK, Mok VC, Lam LC, Leung VP, Hui E, et al. Curcumin effects on blood lipid profile in a 6-month human study. Pharmacol Res 2007;56:509–14.
[14] Alwi I, Santoso T, Suyono S, Sutrisna B, Suyatna FD, Kresno SB, et al. The effect of curcumin on lipid level in patients with acute coronary syndrome. Acta Med Indones 2008;40:201–10.
[15] Murugan P, Pari L, Rao CA. Effect of tetrahydrocurcumin on insulin receptor status in type 2 diabetic rats: studies on insulin binding to erythrocytes. J Biosci 2008;33:63–72.
[16] Song Z, Wang H, Zhu L, Han M, Gao Y, Du Y, et al. Curcumin improves high glucose-induced INS-1 cell insulin resistance via activation of insulin signaling. Food Funct 2015;6:461–9.
[17] Arun N, Nalini N. Efficacy of turmeric on blood sugar and polyol pathway in diabetic albino rats. Plant Foods Hum Nutr (Dordrecht, Netherlands) 2002;57:41–52.
[18] Seo KI, Choi MS, Jung UJ, Kim HJ, Yeo J, Jeon SM, 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.
[19] Panahi Y, Ahmadi Y, Teymouri M, Johnston TP, Sahebkar A. Curcumin as a potential candidate for treating hyperlipidemia: a review of cellular and metabolic mechanisms. J Cell Physiol 2018;233:141–52.
[20] Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. Fertil Steril 2004;81:19–25.
[21] Pisprasert V, Ingram KH, Lopez-Davila MF, Munoz AJ, Garvey WT. Limitations in the use of indices using glucose and insulin levels to predict insulin sensitivity: impact of race and gender and superiority of the indices derived from oral glucose tolerance test in African Americans. Diabetes Care 2013;36:845–53.
[22] Na LX, Li Y, Pan HZ, Zhou XL, Sun DJ, Meng M, 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;57:1569–77.
[23] Lim SS, Davies MJ, Norman RJ, Moran LJ. Overweight, obesity and central obesity in women with polycystic ovary syndrome: a systematic review and meta-analysis. Hum Reprod Update 2012;18:618–37.
[24] Di Pierro F, Bressan A, Ranaldi D, Rapacioli G, Giacomelli L, Bertuccioli A. Potential role of bioavailable curcumin in weight loss and omental adipose tissue decrease: preliminary data of a randomized, controlled trial in overweight people with metabolic syndrome. Preliminary study. Eur Rev Med Pharmacol Sci 2015;19:4195–202.
[25] Yang YS, Su YF, Yang HW, Lee YH, Chou JI, Ueng KC. Lipid-lowering effects of curcumin in patients with metabolic syndrome: a randomized, double-blind, placebo-controlled trial. Phytother Res – PTR 2014;28:1770–7.
[26] Moghetti P. Insulin resistance and polycystic ovary syndrome. Curr Pharm Des 2016;22:5526–34.
[27] Morales AJ, Laughlin GA, Butzow T, Maheshwari H, Baumann G, Yen SS. Insulin, somatotropic, and luteinizing hormone axes in lean and obese women with polycystic ovary syndrome: common and distinct features. J Clin Endocrinol Metabol 1996;81:2854–64.
[28] Jin T, Song Z, Weng J, Fantus IG. Curcumin and other dietary polyphenols: potential mechanisms of metabolic actions and therapy for diabetes and obesity. Am J Physiol Endocrinol Metabol 2018;314:E201–5.
[29] Huang J, Qin S, Huang L, Tang Y, Ren H, Hu H. Efficacy and safety of Rhizoma curcumea longae with respect to improving the glucose metabolism of patients at risk for cardiovascular disease: a meta-analysis of randomised controlled trials. 2019.
[30] Tabrizi R, Vakili S, Lankarani KB, Akbari M, Mirhosseini N, Ghayour-Mobarhan M, et al. The effects of curcumin on glycemic control and lipid profiles among patients with metabolic syndrome and related disorders: a systematic review and metaanalysis of randomized controlled trials. Curr Pharmaceut Des 2018;24:3184–99.
[31] Poolsup N, Suksomboon N. Effects of curcumin on glycemic control and lipid profile in prediabetes and type 2 diabetes mellitus: a systematic review and meta-analysis 2019;14:e0215840.
[32] Sahebkar A. A systematic review and meta-analysis of randomized controlled trials investigating the effects of curcumin on blood lipid levels. Clin Nutr (Edinb Scotl) 2014;33:406–14.
[33] Jazayeri-Tehrani SA, Rezayat SM, Mansouri S, Qorbani M, Alavian SM, Daneshi-Maskooni M, et al. Nano-curcumin improves glucose indices, lipids,

inflammation, and Nesfatin in overweight and obese patients with non-alcoholic fatty liver disease (NAFLD): a double-blind randomized placebo-controlled clinical trial. Nutr Metabol 2019;16:8.
[34] 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.
[35] Jimenez-Flores LM, Lopez-Briones S, Macias-Cervantes MH, Ramirez-Emiliano J, Perez-Vazquez V. A PPARgamma, NF-kappaB and AMPK-dependent mechanism may be involved in the beneficial effects of curcumin in the diabetic db/db mice liver. Molecules (Basel, Switz) 2014;19:8289–302.
[36] Chen R, Peng X, Du W, Wu Y, Huang B, Xue L, et al. Curcumin attenuates cardiomyocyte hypertrophy induced by high glucose and insulin via the PPARgamma/Akt/NO signaling pathway. Diabetes Res Clin Pract 2015;108:235–42.
[37] Ghorbani Z, Hekmatdoost A, Mirmiran P. Anti-hyperglycemic and insulin sensitizer effects of turmeric and its principle constituent curcumin. Int J Endocrinol Metabol 2014;12:e18081.
[38] Janani C, Ranjitha Kumari BD. PPAR gamma gene–a review. Diabetes Metab Syndrome 2015;9:46–50.
[39] Sahebkar A. Why it is necessary to translate curcumin into clinical practice for the prevention and treatment of metabolic syndrome? BioFactors (Oxford, Engl) 2013;39:197–208.
[40] Simental-Mendia LE, Pirro M. Lipid-modifying activity of curcuminoids: a systematic review and meta-analysis of randomized controlled trials 2019;59:1178–87.
[41] Musunuru K. Atherogenic dyslipidemia: cardiovascular risk and dietary intervention. Lipids 2010;45:907–14.
[42] Padala S, Thompson PD. Statins as a possible cause of inflammatory and necrotizing myopathies. Atherosclerosis 2012;222:15–21.
[43] Jimenez-Osorio AS, Monroy A, Alavez S. Curcumin and insulin resistance-Molecular targets and clinical evidences. BioFactors (Oxf, Engl) 2016;42:561–80.
[44] Fan C, Wo X, Qian Y, Yin J, Gao L. Effect of curcumin on the expression of LDL receptor in mouse macrophages. J Ethnopharmacol 2006;105:251–4.
[45] Kang Q, Chen A. Curcumin suppresses expression of low-density lipoprotein (LDL) receptor, leading to the inhibition of LDL-induced activation of hepatic stellate cells. Br J Pharmacol 2009;157:1354–67.
[46] Liu Y, Hong XQ. [Effect of three different curcumin pigmens on the prdiferation of vascular smooth muscle cells by ox-LDL and the expression of LDL-R]. Zhongguo Zhong yao za zhi = Zhongguo zhongyao zazhi = China journal of Chinese materia medica 2006;31:500–3.
[47] Dou X, Fan C, Wo L, Yan J, Qian Y, Wo X. Curcumin up-regulates LDL receptor expression via the sterol regulatory element pathway in HepG2 cells. Planta Med 2008;74:1374–9.