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A systematic review and meta-analysis of the effect of curcuminoids on adiponectin levels

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ABSTRACT

Introduction: Curcuminoids are known anti-inflammatory molecules with multiple mechanisms of action while adiponectin is an anti-inflammatory molecule secreted by the adipocytes. Curcuminoids may upregulate the expression of adiponectin and thus modulate their levels in serum. A meta-analysis was performed to identify randomized controlled trials evaluating the effect of curcuminoids on adiponectin concentrations.

Materials and Methods: The search included PubMed-Medline, Scopus, ISI Web of Science and Google Scholar databases (from inception to October 20, 2018) and the quality of studies was assessed according to Cochrane criteria. Quantitative data synthesis was conducted using a random-effects model and sensitivity analysis by the leave-one out method. Additional analysis was performed to assess the impact of potential confounders on adiponectin levels.

Results: The meta-analysis of five randomized clinical trials (n = 686) showed a significant elevation of plasma adiponectin concentrations following supplementation with curcuminoids (WMD: 6.47 ng/mL, 95% CI: 1.85, 11.10, p = 0.010; I^2 = 94.85%). The effect size was robust in the leave-one-out sensitivity analysis and the effect size was not driven by a single study in the meta-analysis.

Conclusion: This meta-analysis showed a significant increase in plasma levels of adiponectin following curcuminoids therapy, which may be one of the mechanisms of anti-inflammatory activity of curcumin.

Introduction

Curcuminoids are polyphe nolic compounds found in *Curcuma longa* L. (turmeric) widely known in Asian countries for their beneficial effects on human health [1]. These extracts from rhizomes of the plant have shown antioxidant [2,3], anti-inflammatory [4], immunomodulatory [5], antitumor [6], cardioprotective [7,8], hepatoprotective [9] and antidepressant properties [10]. The mechanism of the anti-inflammatory action of curcuminoids has been suggested to be mediated by downregulation of nuclear factor kB (NFκB) and the expression of inflammatory cytokines such as tumor necrosis factor-α, (TNF-α), Interleukin- (IL-) 6, IL-1, monocyte chemoattractant protein 1 (MCP-1) leptin and resistin [11].

Adiponectin is the most abundant peptide secreted by adipocytes, produced by both white and brown adipose tissues: its plasma concentration is significantly reduced in obesity, insulin resistance/type 2 diabetes and cardiovascular diseases [12,13]. In fact, adiponectin directly improves glucose metabolism and insulin sensitivity, and reduces atherogenesis [14]. At least a part of its antiatherogenic and antidiabetic properties could be related to its anti-inflammatory properties by inhibition of nuclear factor-kappa B (NF-kB) activation [12]. Moreover, adiponectin reduces the synthesis of proinflammatory cytokines including TNF-α and IL-6 [13].

Recent studies suggest that curcumin can activate the expression of adiponectin [15]. Given the relatively small sample size of previous clinical trial assessing the effect of curcumin on

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adiponectin plasma level, we carried out a meta-analysis of the available randomized controlled trials in order to clarify the impact of curcumin supplementation on the plasma level of this adipokine.

Materials and methods

Search strategy

This study was designed according to the guidelines of the preferred reporting items for systematic reviews and meta-analysis (PRISMA) statement [16]. PubMed-Medline, Scopus, ISI Web of Science and Google Scholar databases were searched using the following search terms in titles and abstracts:(curcumin OR curcuminoid OR curcuminoids OR *Curcuma* OR "*Curcuma longa*") AND (adiponectin). The wild-card term "*" was used to increase the sensitivity of the search strategy. The search was limited to articles published in English language. The literature was searched from inception to October 20, 2018.

Study selection

Original studies were included if they met the following inclusion criteria: (i) being a randomized controlled trial with either parallel or cross-over design, (ii) investigating the impact of curcuminoid products on plasma/serum concentrations of adiponectin, and, (iii) presentation of sufficient information on adiponectin concentrations at baseline and at the end of follow-up in each group or providing the net change values. Exclusion criteria were: (i) uncontrolled trials, (ii) observational studies with case-control, cross-sectional or cohort design, and (iii) lack of sufficient information on baseline or follow-up adiponectin concentrations.

Data extraction

Eligible studies were reviewed and the following data were abstracted: (1) first author's name; (2) year of publication; (3) Country were the study was performed; (4) study design; (5) number of participants in the curcuminoids and control groups; (6) dose of curcuminoids; (7) treatment duration; (8) age, gender and body mass index (BMI) of study participants; and (9) data regarding baseline and follow-up plasma concentrations of adiponectin.

Quality assessment

The quality of involved studies in this meta-analysis was evaluated using the Cochrane criteria. Selection bias, performance bias, attrition bias, detection bias, reporting bias and other sources of bias were judged to be high, low or unclear in each of the included studies.

Quantitative data synthesis

Meta-analysis was conducted using Comprehensive Meta-Analysis (CMA) V2 software (Biostat, NJ) [17]. Effect size was calculated as: (measure at the end of follow-up in the treatment group – measure at baseline in the treatment group) – (measure at the end of follow-up in the control group – measure at baseline in the control group). Standard deviations (SDs) of the mean difference were calculated using the following formula: SD = square root (SD pre-treatment)2 + (SD post-treatment)2 122 – (2R × SD pre-treatment × SD post-treatment), assuming a correlation coefficient (R) = 0.5. A random-effects model (using DerSimonian–Laird method) and the generic inverse variance weighting method were used to compensate for the heterogeneity of studies in terms of study design, treatment duration, and the characteristics of populations being studied [18]. Inter-study heterogeneity was assessed using I_2 index and Q test. All values were collated as ng/mL. If the outcome measures were reported in mean and range, SD values were estimated using the method described by Hozo et al. [19]. Effect sizes were expressed as weighted mean difference (WMD) and 95% confidence interval (CI). In order to evaluate the influence of each study on the overall effect size, a sensitivity analysis was conducted using the leave-one-out method (i.e., removing one study each time and repeating the analysis) [20].

Results

Flow and characteristics of included studies

Overall, 124 articles were found following multi-database search. After screening the titles and abstracts and removing non-original (n = 41) and non-relevant (n = 73) studies, 10 articles were assessed in full text. Of these, five more papers were removed for not assessing plasma adiponectin levels, yielding five studies comprising seven curcuminoids treatment arms for the final analysis (Fig. 1) [21–25]. Data were pooled from five randomized placebo-controlled clinical trials comprising 686 subjects, including 379 and 336 participants in the curcuminoids and placebo arms, respectively. Two trials included more arms: one spitting children and adult patients. Included studies were published between 2012 [21] and 2017 [22]. The range of intervention periods was from 1 month [23] to 9 months [21]. All included trials were parallel design [21–25]. The characteristics of the selected studies are shown in Table 1.

Risk of bias assessment

Three studies were characterized by insufficient information regarding random sequence generation and allocation concealment [22–24]. Two trials showed lack of information with respect to blinding of participants, personnel and outcome assessors [22,24], and one study had high risk of bias for this criterion [23]. However, all evaluated trials exhibited low risk of bias for incomplete outcome data and selective outcome reporting [21–25]. Details of the risk of bias assessment are shown in Table 2.

Effect of curcuminoid supplementation on plasma adiponectin concentrations

Meta-analysis of data from five randomized clinical trials comprising 7 treatment arms showed a significant elevation of plasma adiponectin concentrations following supplementation with curcuminoids (WMD: 6.47 ng/mL, 95% CI: 1.85, 11.10, $p = 0.010$; $I^2 = 94.85\%$) (Fig. 2). The effect size was robust in the leave-one-out sensitivity analysis (Fig. 2) and the effect size was not driven by one single study.

Discussion

This meta-analysis showed that curcuminoids administration significantly increased plasma adiponectin concentrations in randomized controlled trials. This is in accord with the increased levels of serum adiponectin after curcuminoids therapy in patients with type 2 diabetes [24]. The potential mechanism that may explain the effect of curcumin is through increased expression of adiponectin in adipocytes [25] resulting in elevation of circulating adiponectin levels [26].

Curcumin treatment acts by reducing macrophage infiltration in white adipose tissue, decreasing hepatic NF-kB activity and inhibiting the production of inflammatory markers such as TNF-α, IL-6, IL-1β, and IL-8 [26,27] resulting in protective car-

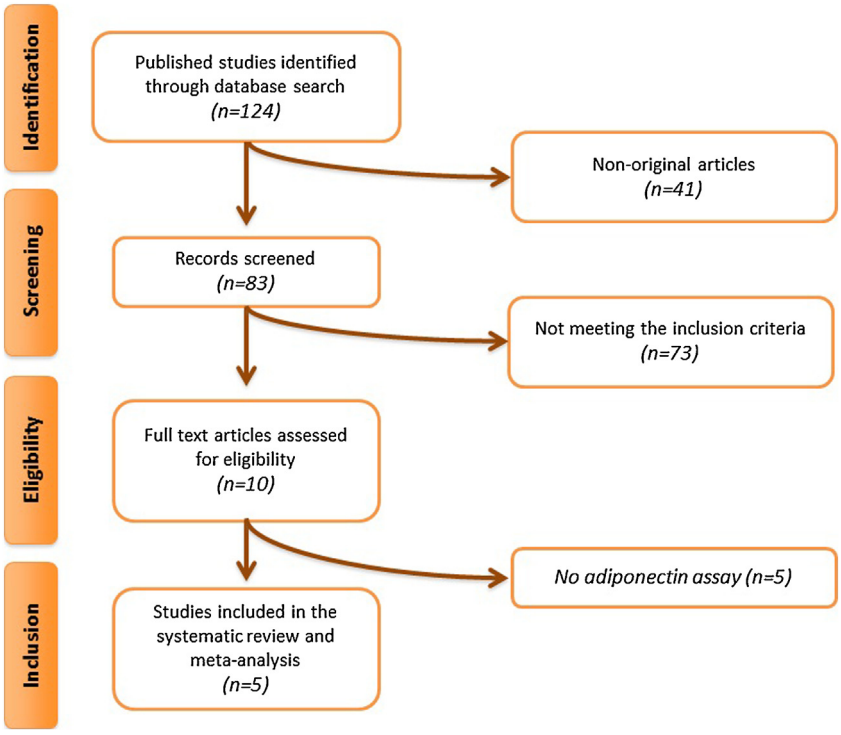

Fig. 1. Flow chart of the number of studies identified and included into the meta-analysis.

Table 1
Main characteristics of the included studies.

Author (year)	Study design	Target population	Treatment duration	N	Study groups	Age, years	Females (n, %)	BMI (kg/m^2)	Adiponectin (ng/ml)
Chuengsamarn et al. [21]	Randomized double-blind, placebo-controlled	Prediabetes	9 months	119	Curcumin 1.5 g/day	56.9 ± 11.9	77 (64.9%)	26.6 ± 5.2	18.1 ± 13.0
				116	Placebo	57.9 ± 12.7	74 (64.4%)	26.6 ± 5.4	18.6 ± 13.4
Chuengsamarn et al. [24]	Randomized double-blind, placebo-controlled	Type 2 diabetes	6 months	107	Curcumin 1.5 g/day	59.1 ± 10.3	57 (53.3%)	27.0 ± 5.3	9.2 (1.3–34.6)[a]
				106	Placebo	50.5 ± 10.2	59 (55.7%)	26.8 ± 4.3	9.9 (1.7–49.5)[a]
Ismail et al. [23]	Randomized open-label, placebo-controlled	Obese children and adults	1 months	29	Children	14.7 ± 4.5	ND	33.9 ± 6.2	16.7 ± 5.5
				15	Curcumin 500 mg/day	ND	ND	ND	16.2 ± 3.8
				14	Placebo	ND	ND	ND	17.2 ± 7.0
				29	Adults	37.5 ± 9.9	ND	ND	17.3 ± 3.9
				15	Curcumin 500 mg/day	ND	ND	ND	15.7 ± 3.3
				14	Placebo	ND	ND	ND	16.9 ± 4.0
Panahi et al. [25]	Randomized double-blind, placebo-controlled	Metabolic syndrome	2 months	50	Curcumin 1 g/day	44.8 ± 8.6	23 (46%)	25.4 ± 2.4	12.6 ± 2.1
				50	Placebo	43.4 ± 9.7	27 (34%)	22.8 ± 5.3	12.7 ± 2.1
Salahshooh et al. [22]	Randomized double-blind, placebo-controlled	Metabolic syndrome	6 weeks		Curcumin	40.0 ± 10.	ND	30.6 ± 5.0	33.9 ± 18.0
				37	Phospholipid 1 g/day	4	ND	30.6 ± 3.5	28.3 ± 17.2
				36	Curcumin	37.5 ± 9.3	ND	31.2 ± 4.6	52.2 ± 24.9
				36	Placebo	38.5 ± 10.2			

Values are expressed as mean ± SD.
BMI = Body Mass Index; IQR = Interquartile range; NAFLD = non-alcoholic fatty liver disease; ND = No data.
[a] Mean (IQR).

Table 2
Quality of bias assessment of the included studies according to the Cochrane guidelines.

Author (year)	Sequence generation	Allocation concealment	Blinding of participants, personnel and outcome assessors	Incomplete outcome data	Selective outcome reporting	Other sources of bias
Chuengsamarn et al. [21]	L	L	L	L	L	L
Chuengsamarn et al. [24]	L	L	L	L	L	L
Ismail et al. [23]	U	U	H	L	L	U
Panahi et al. [25]	U	U	U	L	L	U
Salahshooh et al. [22]	U	U	U	L	L	U

L = Low risk of bias; H= High risk of bias; U = Unclear risk of bias.

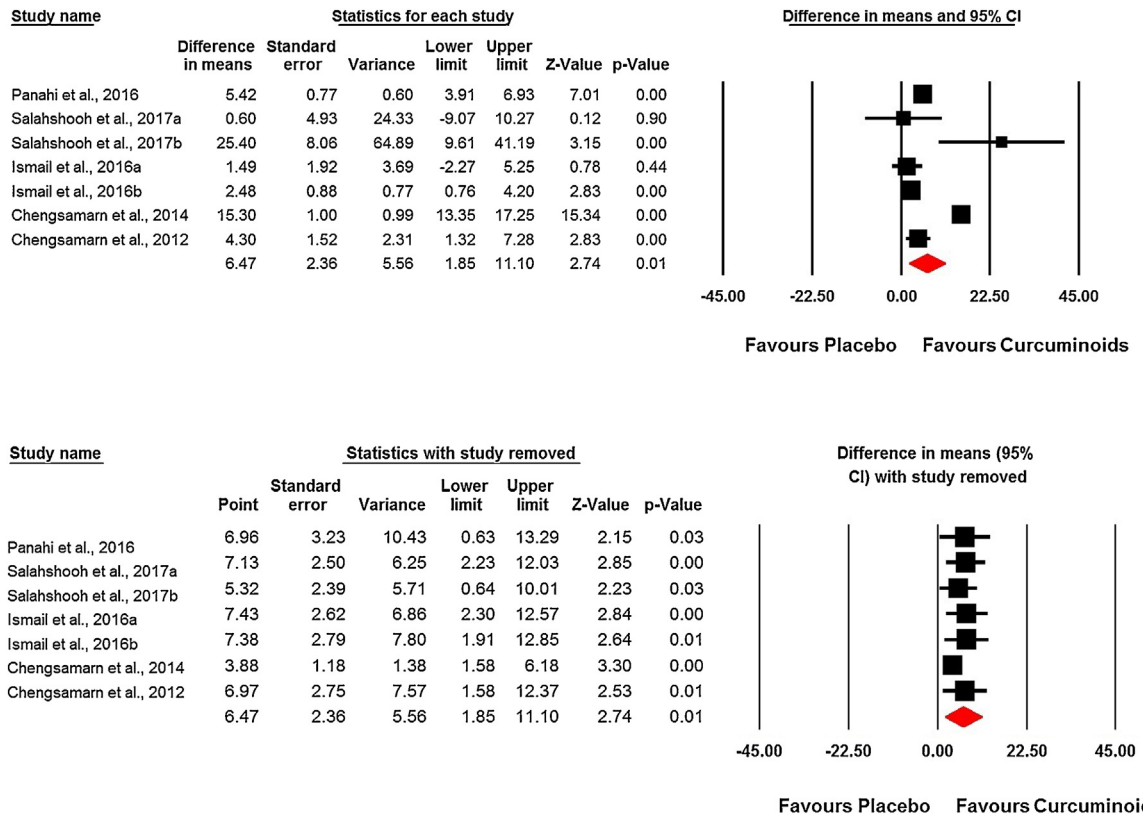

Fig. 2. Forest plot displaying weighted mean difference and 95% confidence intervals for the impact of curcuminoids supplementation on plasma adiponectin concentrations. Lower Plot shows the results of leave-one-out sensitivity analysis.

diometabolic effects of this polyphenol [28]. Moreover, it has been suggested that curcumin therapy reduces inflammation due to visceral adiposity along with adiponectin elevation [26], and may inhibit adipogenesis [29]. Adiponectin plays a pertinent role in the pathogenesis of obesity-related diseases including metabolic syndrome, diabetes, dyslipidemia, hypertension, and cardiovascular disease [16,17,30,31]. The favourable impact of curcuminoids supplementation on cardiometabolic disorders may be attributed, at least in part, due to the increased serum adiponectin concentrations leading to its protective effects including anti-inflammatory, antioxidant, antithrombotic, and antiatherosclerotic activities [32].

Limitations of this meta-analysis include that there were relatively few studies to include in the analysis and therefore a limited number of participants leading to a small sample. In addition, three of the five studies included were of short treatment duration (≤2 months) that may have been too short to fully show the efficacy of curcuminoid products on plasma adiponectin levels. Finally, the differences in the bioavailability of tested products might explain different findings and thus made it impossible to perform a meta-regression analysis on the association of adiponectin levels with the administered dosages of curcuminoids.

In conclusion, the results of this meta-analysis showed a significant increase in plasma levels of adiponectin after curcuminoids therapy. However, further studies are warranted of larger power and longer duration for confirmation of this curcuminoid effect.

Conflict of interest

Muhammed Majeed is the Founder & Chairman of Sabinsa Corporation and Sami Labs Limited. No other author has direct or indirect conflict of interest in the publication of this paper.

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Ethical statement

This paper is a meta-analysis of randomized clinical trials approved by the Ethical boards of the studies' authors.

References

[1] Kochhar PK. Dietary spices in health and diseases (II). Indian J Physiol Pharmacol 2008;52:327–54.
[2] Panahi Y, Alishiri GH, Parvin S, Sahebkar A. Mitigation of systemic oxidative stress by curcuminoids in osteoarthritis: results of a randomized controlled trial. J Diet Suppl 2016;13:209–20, http://dx.doi.org/10.3109/19390211.2015.1008611.
[3] Panahi Y, Khalili N, Sahebi E, Namazi S, Karimian MS, Majeed M, et al. Antioxidant effects of curcuminoids in patients with type 2 diabetes mellitus: a randomized controlled trial. Inflammopharmacology 2017;25:25–31.
[4] Sahebkar A, Cicero AFG, Simental-Mendía LE, Aggarwal BB, Gupta SC. Curcumin downregulates human tumor necrosis factor-α levels: a systematic review and meta-analysis ofrandomized controlled trials. Pharmacol Res 2016;107:234–42.
[5] Abdollahi E, Momtazi AA, Johnston TP, Sahebkar A. Therapeutic effects of curcumin in inflammatory and immune-mediated diseases: a nature-made jack-of-all-trades? J Cell Physiol 2018;233:830–48.
[6] Momtazi AA, Shahabipour F, Khatibi S, Johnston TP, Pirro M, Sahebkar A. Curcumin as a MicroRNA regulator in cancer: a review. Rev Physiol Biochem Pharmacol 2016;171:1–38.
[7] Ganjali S, Blesso CN, Banach M, Pirro M, Majeed M, Sahebkar A. Effects of curcumin on HDL functionality. Pharmacol Res 2017;119:208–18.
[8] Panahi Y, Khalili N, Sahebi E, Namazi S, Reiner Z, Majeed M, et al. Curcuminoids modify lipid profile in type 2 diabetes mellitus: a randomized controlled trial. Complement Ther Med 2017;33:1–5.
[9] Panahi Y, Kianpour P, Mohtashami R, Jafari RR, Simental-Mendía LE, Sahebkar A. Efficacy and safety of phytosomal curcumin in non-alcoholic fatty liver disease: a randomized controlled trial. Drug Res 2017;67:244–51.

[10] Panahi Y, Badeli R, Karami GR, Sahebkar A. Investigation of the efficacy of adjunctive therapy with bioavailability-boosted curcuminoids in major depressive disorder. Phytother Res 2015;29:17–21.
[11] Aggarwal BB. Targeting inflammation-induced obesity and metabolic diseases by curcumin and other nutraceuticals. Ann Rev Nutr 2010;30:173–99.
[12] Ajuwon KM, Spurlock ME. Adiponectin inhibits LPS-induced NF-kappaB activation and IL-6 production and increases PPARgamma2 expression in adipocytes. Am J Physiol Regul Integr Comp Physiol 2005;288:R1220–5.
[13] Ouchi N, Kihara S, Arita Y, Okamoto Y, Maeda K, Kuriyama H, et al. Adiponectin, an adipocyte-derived plasma protein, inhibits endothelial NF-kappaB signaling through a cAMP-dependent pathway. Circulation 2000;102:1296–301.
[14] Ghadge AA, Khaire AA, Kuvalekar AA. Adiponectin: a potential therapeutic target for metabolic syndrome. Cytokine Growth Factor Rev 2018;39:151–8, http://dx.doi.org/10.1016/j.cytogfr.2018.01.004.
[15] Shehzad A, Ha T, Subhan F, Lee YS. New mechanisms and the antiinflammatory role of curcumin in obesity and obesity-related metabolic diseases. Eur J Nutr 2011;50:151–61.
[16] Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 2009;339:b2535.
[17] Borenstein M, Hedges L, Higgins J, Rothstein H. Comprehensive metaanalysis version 2. Englewood, NJ: Biostat; 2005.
[18] Sutton AJ, Abrams KR, Jones DR, Sheldon TA, Song F. Methods for meta-analysis in medical research. West Sussex: John Wiley & Sons; 2000, 2000.
[19] Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol 2005;5:13.
[20] Cicero AF, Pirro M, Watts GF, Mikhailidis DP, Banach M, Sahebkar A. Effects of allopurinol on endothelial function: a systematic review and meta-analysis of randomized placebo-controlled trials. Drugs 2018;78(1):99–109, http://dx.doi.org/10.1007/s40265-017-0839-5.
[21] Chuengsamarn S, Rattanamongkolgul S, Luechapudiporn R, Phisalaphong C, Jirawatnotai S. Curcumin extract for prevention of type 2 diabetes. Diabetes Care 2012;35:2121–7.
[22] Salahshooh MM, Parizadeh SM, Pasdar A, Saberi Karimian M, Safarian H, Javandoost A, et al. The effect of curcumin (*Curcuma longa* L.) on circulating levels of adiponectin in patients with metabolic syndrome. Comp Clin Pathol 2017;26:17–23.
[23] Ismail NA, Abd El Dayem SM, Salama E, Ragab S, El Baky AN, Ezzat WM. Impact of curcumin intake on gluco-insulin homeostasis, leptin and adiponectin in obese subjects. Res J Pharm Biol Chem Sci 2016;7:1891–7.
[24] Chuengsamarn S, Rattanamongkolgul S, Phonrat B, Tungtrongchitr R, Jirawatnotai S. Reduction of atherogenic risk in patients with type 2 diabetes by curcuminoid extract: A randomized controlled trial. J Nutr Biochem 2014;25:144–50.
[25] Ohara K, Uchida A, Nagasaka R, Ushio H, Ohshima T. The effects of hydroxycinnamic acid derivatives on adiponectin secretion. Phytomedicine 2009;16:130–7.
[26] Weisberg SP, Leibel R, Tortoriello DV. Dietary curcumin significantly improves obesity-associated inflammation and diabetes in mouse models of diabesity. Endocrinology 2008;149:3549–58.
[27] Jain SK, Rains J, Croad J, Larson B, Jones K. Curcumin supplementation lowers TNF-alpha, IL-6, IL-8, and MCP-1 secretion in high glucose-treated cultured monocytes and blood levels of TNF-alpha, IL-6, MCP-1, glucose, and glycosylated hemoglobin in diabetic rats. Antioxid Redox Signal 2009;11:241–9.
[28] Aggarwal BB, Sung B. Pharmacological basis for the role of curcumin in chronic diseases: an age-old spice with modern targets. Trends Pharmacol Sci 2009;30:85–94.
[29] Ejaz A, Wu D, Kwan P, Meydani M. Curcumin inhibits adipogenesis in 3T3-L1 adipocytes and angiogenesis and obesity in C57/BL mice. J Nutr 2009;139:919–25.
[30] Lara-Castro C, Fu Y, Chung BH, Garvey WT. Adiponectin and the metabolic syndrome: mechanisms mediating risk for metabolic and cardiovascular disease. Curr Opin Lipidol 2007;18:263–70.
[31] Li S, Shin HJ, Ding EL, van Dam RM. Adiponectin levels and risk of type 2 diabetes: a systematic review and meta-analysis. JAMA 2009;302:179–88.
[32] Esfahani M, Movahedian A, Baranchi M, Goodarzi MT. Adiponectin: an adipokine with protective features against metabolic syndrome. Iran J Basic Med Sci 2015;18:430–42.