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Meta-analysis

The effect of berberine supplementation on obesity parameters, inflammation and liver function enzymes: A systematic review and meta-analysis of randomized controlled trials

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SUMMARY

Introduction: So far, no study has summarized the findings on the effects of berberine intake on anthropometric parameters, C-reactive protein (CRP) and liver enzymes. This systematic review and meta-analysis were done based upon randomized controlled trials (RCTs) to analyze the effects of berberine on anthropometric parameters, CRP and liver enzymes.

Method: Following databases were searched for eligible studies published from inception to 30 July 2019: MEDLINE, EMBASE, Web of Science, Cochrane Library, PubMed and Google scholar. Necessary data were extracted. Data were pooled by the inverse variance method and expressed as mean difference with 95% Confidence Intervals (95% CI).

Result: 12 studies were included. Berberine treatment moderately but significantly decreased body weight (WMD = −2.07 kg, 95% CI -3.09, −1.05, P < 0.001), body mass index (BMI) (WMD = −0.47 kg/m^2, 95% CI -0.70, −0.23, P < 0.001), waist circumference (WC) (WMD = −1.08 cm, 95% CI -1.97, −0.19, P = 0.018) and C-reactive protein (CRP) concentrations (WMD = −0.42 mg/L, 95% CI -0.82, −0.03, P = 0.034). However, berberine intake did not affect liver enzymes, including alanine aminotransferase (ALT) (WMD = −1.66 I/U, 95% CI -3.98, 0.65, P = 0.160) and aspartate aminotransferase (AST) (WMD = −0.87 I/U, 95% CI -2.56, 0.82, P = 0.311).

Conclusion: This meta-analysis found a significant reduction of body weight, BMI, WC and CRP levels associated with berberine intake which may have played an indirect role in improved clinical symptoms in diseases with metabolic disorders. Berberine administration had no significant effect on ALT and AST levels.

1. Introduction

Increased body weight is associated with different diseases, particularly cardiovascular diseases (CVD), type 2 diabetes mellitus (T2DM), obstructive sleep apnea, some types of cancer, osteoarthritis and depression [1]. In addition, nonalcoholic fatty liver disease (NAFLD) and elevated liver enzymes are closely linked to several metabolic syndrome features [2,3]. Recent research proved that populations with elevated basal concentrations of C-reactive

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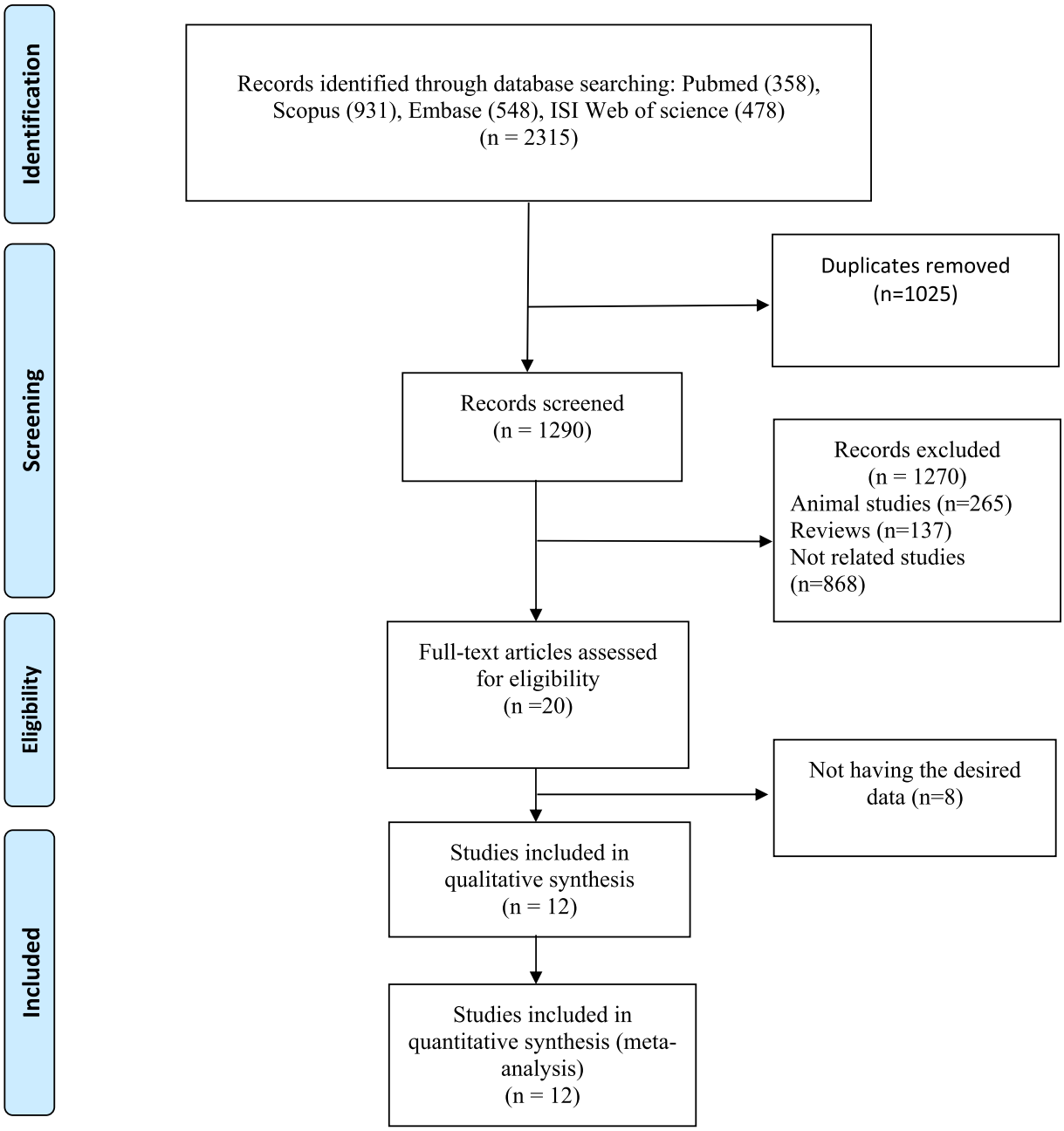

Fig. 1. Flowchart of the study selection for inclusion in the systematic reviews and meta-analyses.

protein (CRP) are at an increased risk of CVD, diabetes and hypertension [4,5]. There is a rising trend to use traditional medicinal plants, particularly in some parts of the world, because they are often cheaper and more available or because patients are reluctant to take drugs and they believe that plants are "more natural" [6,7]. There are some phytochemicals (or nutraceuticals), including capsaicin, resveratrol, curcumin, green tea epigallocatechin gallate (EGCG) and berberine, that have effects on thermogenic activation based upon different modes of action [8]. *Berberis vulgaris* (*B. vulgaris*) is used as pharmaceutical more than 2500 years [9].

Different parts of this plant have specific therapeutic effects. Berberine, an isoquinoline alkaloid, is the major active part of *B. vulgaris* [10]. A meta-analysis by Wei et al. [11] indicated that in patients with NAFLD, berberine intake was associated with an improvement in glycemic control, serum lipoproteins and liver function. Several randomized clinical trials (RCTs) have indicated a beneficial effect of berberine on anthropometric parameters and biomarkers of inflammation as well as on liver function in different conditions [12,13]. However, some other studies could not confirm such effects [14,15].

There is evidence suggesting that the activation of AMP-activated protein kinase (AMPK) signaling pathway, which is a key regulator of energy metabolism and controls inflammatory processes, can be affected by berberine [16,17]. Berberine can also

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downregulate the expression of pro-inflammatory genes and those involved in adipocyte differentiation like PPAR-γ [18]. Despite these studies, no earlier meta-analysis has summarized findings on the effects of berberine on anthropometric parameters, CRP and liver enzymes. Therefore, this meta-analysis was performed to summarize all the existing RCTs evidence and to evaluate the effects of berberine on anthropometric parameters, CRP and liver enzymes.

2. Methods

2.1. Search and studies selection strategies

Eligible RCTs were identified using Cochrane Library, Embase, Medline, Web of Science, PubMed and Google scholar databases for relevant articles published from inception until 30 July 2019, and by manually searching the reference list of the located articles. Studies that evaluated the of berberine intake on anthropometric parameters, CRP and liver enzymes were found by using the following MeSH and text words: intervention ["berberine" OR "huangliansu" OR "berberinum" OR "Xiaopojian"], and outcomes "body weight" OR "body mass index (BMI)" OR "waist circumference (WC)" OR "inflammation" OR "C-reactive protein (CRP)" OR "alanine aminotransferase (ALT)" OR "aspartate aminotransferase (AST)". Additional manual searches including reference lists of related and studies previously published reviews were reviewed to increase sensitivity of search strategy. Studies included in this meta-analysis had to fulfill the following criteria: 1) original trials, 2) human trials, 3) written in English and 4) the trials which reported mean changes or mean difference of anthropometric parameters, CRP and liver enzymes with standard deviation (SD) for the intervention and control groups. Other studies such as *in vitro* studies, animal experiments, case reports, trials without a control group, observational studies and studies that did not achieve the least quality score were excluded from this meta-analysis.

2.2. Data extraction and quality assessment

Two authors (OA and EA) independently extracted the data and assessed its quality using standard forms and the Cochrane Collaboration risk of bias tool [19,20], respectively. This tool is based on information on the following domains: randomization generation, allocation concealment, blinding of subjects and outcome assessment, incomplete outcome data, and selective outcome reporting, and other sources of bias. When there was disagreement among them, it was resolved by third author (ZA). From eligible studies the following data were taken: 1) first authors' name 2) publication year 3) age, sex, and body composition and/or metabolic parameters of study participants 4) study location 5) number of subjects in intervention and control groups 6) study design 7) duration of the intervention in each intervention group.

2.3. Data analysis

The effects of berberine intake on the changes of the following parameters were calculated: 1) anthropometric parameters, 2) CRP and 3) liver enzymes. Weighted mean difference (WMD) with 95% CI was used for pooling data to determine the effect sizes. The change score approach was used to calculate the effect size of berberine consumption on the analyzed parameters. The random-effect model was used to report the pooled effect sizes using 95% CI. To calculate the SD changes, the following formula was used: SD = square root [(SD pre-treatment)^2 (SD posttreatment)2 -

Table 1
Characteristics of included primary clinical trials.

Author	Year	Country	Study design	Participants	Sex	Mean age (intervention/ control)	Mean BMI (intervention/ control)	Trial duration (months)	Treatment group	Control group	Sample size (intervention/ control)	Outcomes
Wu et al. [53]	2005	China	Parallel	Allograft renal transplant operation	F/M	42.5/39.6	20.5/20.4	3	600 mg berberine	Nothing	52/52	ALT
Zhang et al. [25]	2008	China	Parallel	T2DM and dyslipidemia	F/M	51/51	25.2/25.9	3	1000 mg berberine	Placebo	58/52	BW, BMI, CRP
Gu et al. [14]	2010	China	Parallel	T2DM and dyslipidemia	F/M	51/50	25.1/26.2	3	1000 mg berberine	Placebo	30/30	BW, BMI
Wei et al. [26]	2012	China	Parallel	PCOS	F	25.7/26.7	25.6/24.9	3	1500 mg berberine + compound cyproterone acetate	Placebo + compound cyproterone acetate	31/28	BW, BMI, WC
Meng et al. [30]	2012	China	Parallel	Acute coronary syndrome	F/M	63.1/63.3	24.1/23.5	1	600 mg berberine	Nothing	61/69	CRP
Derosa et al. [54]	2013	Italy	Parallel	Low cardiovascular risk	F/M	53/54	25.6/25.5	3	1000 mg berberine	Placebo	68/69	BW, BMI, WC, ALT, AST
Pérez-Rubio et al. [55]	2013	Mexico	Parallel	Metabolic syndrome	F/M	36.9/38.1	36.1/34.2	3	1500 mg berberine	Placebo	12/12 F/M 7/7 F 5/5 M	BMI, WC
An et al. [56]	2013	China	Parallel	PCOS	F	28.2/28.4	24.6/24.2	3	1500 mg berberine	Placebo	44/43	BMI, WC
Yan et al. [12]	2015	China	Parallel	NAFLD	F/M	50.7/50.6	28.1/27.3	4	1500 mg berberine + lifestyle intervention	Lifestyle intervention	55/53	BW, BMI, ALT, AST
Dai et al. [13]	2015	China	Parallel	T2DM	F/M	55.3/53.1	24.5/24.1	24	300 mg berberine	Nothing	39/33	CRP
Zhu et al. [57]	2015	China	Parallel	Acute ischemic stroke	F/M	63.3/66.3	NR	3	1200 mg berberine + 20 mg atorvastatin	20 mg atorvastatin	16/28	CRP
Rashidi et al. [15]	2018	Iran	Parallel	T2DM	F/M	50.2/45.2	29.8/29.1	1	1000 mg berberine	Placebo	40/41	BMI, ALT, AST

(2R × SD pre-treatment × SD post-treatment)], correlation coefficient (R-value) was considered 0.8 [21]. When an SEM or SE was reported instead of SD, the SD was calculated based on the following formula: SD= SEM × $\sqrt{n}$ (n = sample size in each group). Heterogeneity of included studies was assessed using Cochrane's Q test (with significant P-value <0.1) and I-square test (I^2 greater than 50 percent showing significant heterogeneity). The funnel plot was used to determine the publication bias. STATA 11.0 (Stata Corp., College Station, TX) was applied for data analysis.

3. Results

3.1. Study selection

After initial search in databases, 2315 articles were found. 1025 articles were duplicates and removed. 1290 articles were screened based on their title and abstract. 1270 publications were excluded because they were animal studies, reviews or were unrelated with the topic which was analyzed. 20 articles were eligible to be analyzed based on the full-text. 8 studies were omitted because the desired data were lacking. Finally, 12 studies were included in this systematic review and meta-analysis. The summary of selected studies is shown in Fig. 1.

3.2. Characteristics of included studies

The main characteristics of the eligible studies are presented in Table 1. Our analysis included data from 1040 volunteers, 518 in the berberine arm and 522 in the control arm. Eligible studies were published between 2005 and 2018. The studies were performed in China, Italy, Mexico and Iran. All studies were designed as parallel studies. The trials used different doses of berberine (ranging from 300 mg/day to 1500 mg/day) and trials duration was between 1 month and 24 months. Subjects enrolled in the eligible trials had allograft renal transplant surgery, T2DM, polycystic ovary syndrome (PCOS), acute coronary syndrome, low cardiovascular risk, metabolic syndrome, NAFLD and acute ischemic stroke. Subjects enrolled in 4 studies had normal body weight and others were overweight or obese. The quality assessment of studies is shown in Table 2.

3.3. Effect of berberine treatment on anthropometric parameters, CRP and liver enzymes

The effect of berberine intake on body weight, BMI, WC, CRP, ALT and AST was assessed in 5, 8, 5, 4, 4, and 3 studies, respectively. Berberine treatment significantly decreased anthropometric including body weight (WMD = −2.07 kg, 95% CI -3.09, −1.05, P < 0.001; Fig. 2A), BMI (WMD = −0.47 kg/m^2, 95% CI -0.70, −0.23, P < 0.001; Fig. 2B) and WC (WMD = −1.08 cm, 95% CI -1.97, −0.19, P = 0.018; Fig. 2C) as well as CRP concentrations (WMD = −0.42 mg/L, 95% CI -0.82, −0.03, P = 0.034; Fig. 2D). However, berberine intake did not affect liver enzymes, including ALT (WMD = −1.66 I/U, 95% CI -3.98, 0.65, P = 0.160; Fig. 2E) and AST (WMD = −0.87 I/U, 95% CI -2.56, 0.82, P = 0.311; Fig. 2F). It has to be stressed that there was significant heterogeneity for CRP (I^2 = 76.4 and P = 0.005); so we used random-model for pooling effect sizes. On the other hand, we used the fixed-model for all the other factors (Fig. 2 A-F).

4. Discussion

In this meta-analysis of RCTs, we evaluated the effects of berberine on anthropometric parameters, CRP and liver enzymes. This meta-analysis demonstrated that berberine intake was associated with improved anthropometric parameters such as body weight, BMI and WC as well as CRP values, but did not change the plasma levels of liver enzymes.

4.1. Effects on obesity

Obesity is an important component of metabolic syndrome (MetS) and considered as an important risk factor for different diseases [22]. Increased inflammatory markers and metabolic profiles increase the risk of CVD and diabetes [4,5,23,24]. This meta-analysis demonstrated that berberine reduced body weight, BMI and WC. Some trials have reported that berberine consumption had beneficial effects on anthropometric mesurments. For example, Yan et al. [12] reported that 1500 mg of berberine consumption during four months decreased body weight, BMI and WC in NAFLD patients. Zhang et al. [25] also showed that three months of berberine consumption at a dosage of 500 mg twice per day decreased body weight and BMI in T2DM patients with dyslipidemia. Another study proved that in women with PCOS berberine intake during 3 months decreased WC and WHR but without weight and BMI changes [26]. However, a meta-analysis of animal models of cancer indicated that berberine intake did not affect body weight [27]. Obesity can cause insulin resistance and impaired glucose metabolism which are all components of MetS [28]. Obesity-induced inflammation can exacerbate insulin resistance [29] and it has been shown that berberine has anti-inflammatory effects [30]. Most recently it has been shown that berberine can promote the recruitment and activation of brown adipocyte differentiation and thermogenesis epigenetically through

Table 2
Quality assessment of included studies.

Study (year)	Random Sequence Generation	Allocation concealment	Selective outcome reporting	Other sources of bias	Blinding of participants personnel	Blinding of outcome assessors	Incomplete outcome data
Wu et al. [53]	U	H	H	H	H	H	H
Zhang et al. [25]	L	U	L	U	L	U	L
Gu et al. [14]	U	H	H	H	L	U	L
Wei et al. [26]	L	U	L	U	H	L	L
Meng et al. [30]	U	U	L	H	L	L	L
Derosa et al. [54]	L	U	L	L	L	U	L
Pérez-Rubio et al. [55]	L	U	H	H	L	U	L
An et al. [56]	L	U	L	H	L	U	L
Yan et al. [12]	L	L	L	L	H	H	L
Dai et al. [13]	U	U	L	H	H	H	H
Zhu et al. [57]	U	U	L	H	H	H	L
Rashidi et al. [15]	L	U	L	U	L	U	L

L is low risk of bias; H is high risk of bias; U is unclear risk of bias.

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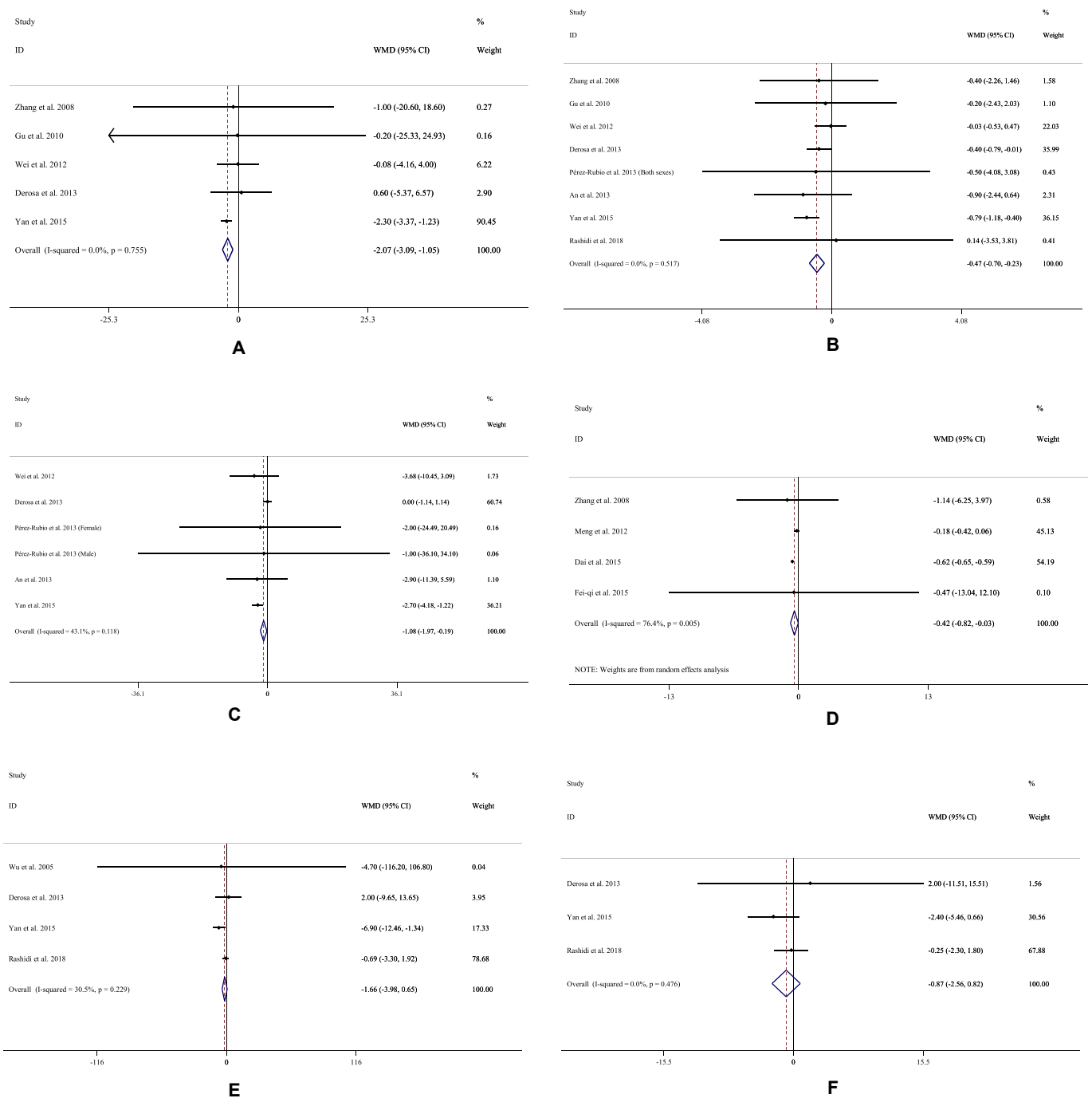

Fig. 2. A-F. Meta-analysis metabolic profiles and anthropometric measurements weighted mean difference estimates for A) Body weight, B) BMI, C) Waist circumference, D) C-reactive proteine, E) ALT, F) AST in the berberine and placebo groups (CI = 95%).

AMPK–PRDM16 axis, contributing to elevated systemic energy expenditure and therefore it might have antiadipose effects [31].

It has been shown without any doubt that overweight, obesity and higher WC are associated with increased mortality [32,33]. Obesity is not only an important risk factor for cardiovascular diseases and T2DM but also risk factor for different types of cancer [34]. Therefore, weight management has many favorable effects. Weight reduction decreases the risk of developing diabetes [35,36]. In obese subject and patients with essential hypertension, weight reduction is associated with a decrease in blood pressure [37,38]. It has been demonstrated that modest weight loss improves pulse wave velocity which is a marker of arterial stiffness [39]. Berberine most probably achieves anti-obesity effects by modulating the expression of transcription factors and genes involved in the adipogenesis such as cAMP-response element-binding (CREB) protein [40], GATA-2 and GATA-3 [41], and PPAR-γ [42] which are associated with the inhibition of adipocyte differentiation. Berberine also enhances the expression of uncoupling protein 1 (UCP1) and other thermogenic genes in white and brown adipose tissue and primary adipocytes by a pathway involving AMPK and PPAR-γ coactivator-1 alpha [43]. Moreover, evidence from animal studies indicated that berberine modifies

gut microbiota, which decrease insulin resistance, and inflammation and finally improve body weight [44].

4.2. Effects on liver function and CRP

In this meta-analysis, we found that berberine intake decreased CRP, while ALT and AST levels remained unchanged. Overall, pooling information from all qualified RCTs, provides more precise and powerful evidence than those from the individual studies. However, these studies are heterogeneous with respect to study duration, sampling method, age ranges, dosage of berberine used, the characteristics of participants, differences between intervention and control groups, cross-over design or parallel design, allocation concealment, and dietary intake of participants. In particular, the wide variation in the amount and formulation of berberine may be the most important contributor to the heterogeneity seen in our results. In a study by Meng et al. [30], 600 mg/day of berberine did not have any effect on AST or ALT. Although our meta-analysis indicated that berberine had no significant effect on liver enzymes, some animal studies suggested that berberine treatment might have some hepatoprotective effects by suppression of oxidative stress, inflammatory responses and hepatocyte necrosis [45,46]. A study by Dai et al. [13] indicated that the consumption of 300 mg/day of berberine with a two-week no-treatment interval every five months decreased CRP levels in patients with T2DM during 24 months. A previous meta-analysis by Wei et al. [11] suggested that berberine can improve liver function in NAFLD patients. Nevertheless, in two studies on T2DM patients with dyslipidemia [25] and patients with ACS [30], berberine did not improve CRP levels. Inflammation is associated with the pathogenesis of atherosclerosis [47]. There is evidence that elevated CRP is associated with a number of diseases including hypertension, CVD, T2DM and its complications, as well as some other diseases such as Alzheimer and Parkinson disease [48]. In general population, increased CRP levels can independently predict the risk of all-cause and cardiovascular mortality [49]. Several mechanisms have been proposed for the anti-inflammatory effects of berberine, including modulation of gut microbiota and intestinal permeability [50], decreased expression of nuclear factor-kappa B (NF-κB) [51], and activation of AMPK/mTOR signaling pathway [16] as well as some other possible mechanisms [52].

The present meta-analysis is among rare studies that summarize findings from earlier studies on anthropometric parameters, CRP and liver enzymes. Therefore it is important to consider some limitations of this meta-analysis when interpreting the results and producing conclusions. This meta-analysis had few limitations. One of the most important was that subjects in the included studies had different diseases, including diabetes, non-alcoholic fatty liver disease, PCOS and CVD which might have an influence on the results. Moreover, due to the heterogeneity between studies, evident from the variations in duration of berberine intake, the dosage and frequency of berberine used, results should be interpreted with caution. The number of studies and sample size of participant's study that finally entered to the current meta-analysis was low. This meta-analysis cannot support the beneficial effects of berberine supplementation on body weight, BMI, WC and CRP levels due to low number of studies and high heterogeneity in the included studies.

5. Conclusions

This meta-analysis found a significant reduction of body weight, BMI, WC and CRP levels associated with berberine intake. Berberine administration had no significant effect on ALT and AST levels. Therefore, berberine intake may have played an indirect role in improved clinical symptoms in diseases with metabolic disorders due to its effect on body weight, BMI, WC and CRP levels.

Practical applications

This meta-analysis demonstrated that berberine supplementation significantly reduced decrease body weight, BMI, waist circumference and C-reactive protein plasma levels, but did not affect ALT and AST levels. Therefore, berberine supplementation may have played an indirect role in improved clinical symptoms in diseases with metabolic disorders due to its effect on anthropometric indices and C-reactive protein plasma levels.

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Author contribution

OA and ZA contributed in conception, data collection and manuscript drafting. NG, MS, ZR, EA, JH and LM contributed in conception, data collection and manuscript drafting. All authors read and approved the final version of the paper.

Declaration of Competing Interest

All the authors declared that they have no conflicts of interest.

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