

The effects of berberine on inflammatory markers in Chinese patients with metabolic syndrome and related disorders: a meta-analysis of randomized controlled trials

Yuqiong Lu¹ · Xiwen Zhang¹ · Jiafang He¹ · Zhanjing Dai¹ · Penghua Shi¹ · Yun Lu¹ · Feng Chang¹

Received: 24 October 2021 / Accepted: 22 November 2021 / Published online: 29 March 2022 © The Author(s) 2022

Abstract

Background A meta-analysis of randomized controlled trials (RCTs) was conducted to systematically evaluate the effects of berberine on the inflammatory markers of metabolic syndrome (MetS) and related disorders.

Method Databases that were searched from inception to October 2020 included PubMed, Web of Science, the Cochrane Library, CNKI, VIP, WanFang Data, and ClinicalTrials.gov. Two reviewers independently selected articles and extracted data. The pooled evaluations were entered and analyzed in Review Manager 5.3.

Results Of the 7387 publications screened, 52 studies were included, and the related trials involved 4616 patients. Pooled estimates showed that the use of berberine could significantly reduce the concentration level of C-reactive protein (CRP) [standardized mean difference (SMD) = -1.54, 95% confidence intervals (CI) -1.86, -1.22, p < 0.05], tumor necrosis factor- α (TNF- α) [SMD = -1.02, 95% CI -1.27, -0.77, p < 0.05], and interleukin 6 (IL-6) [SMD = -1.17, 95% CI -1.53, -0.81, p < 0.05] among patients with MetS and related disorders. However, it did not affect the level of interleukin 1 β (IL-1 β) [SMD = -0.81, 95% CI -1.80, 0.17, p = 0.11].

Conclusion Overall, the use of berberine in patients with MetS and related disorders appeared to significantly decrease several inflammatory markers. Further multi-center and rigorous investigations with larger patient populations are encouraged to confirm the effect of berberine on MetS and related disorders.

Keywords Berberine · Metabolic syndrome · Inflammatory markers · Meta-analysis

Introduction

Metabolic syndrome (MetS) is a cluster of interconnected physiological and metabolic abnormalities characterized by obesity, insulin resistance, hypertension, and hyperlipidemia (Lee and Herceg 2017). The prevalence of MetS in adults worldwide is reportedly about 20–25% (Ranasinghe et al. 2017). MetS patients have increased risks of cardiovascular disease, diabetes, and some other chronic diseases (Grundy et al. 2006; Arnlöv et al. 2010; Noda et al. 2009). Previous reports have suggested that the development of MetS is associated with increased levels of inflammatory markers, including C-reactive protein (CRP), tumor necrosis factor- α (TNF- α), interleukin 6 (IL-6), interleukin 1 (IL-1), etc. (Festa et al. 2000; Wisse 2004; Akbari et al. 2018; Tabrizi et al. 2018, 2019). Pharmacological strategies to reduce inflammation have become more widespread and more useful in treating MetS and related disorders (Esser et al. 2015).

Berberine is an isoquinoline quaternary alkaloid that can be found in plant extracts produced from Berberis vulgaris and some traditional Chinese medicinal herbs, and it has been found to perform well in managing blood sugar, blood lipids, blood pressure, and without causing serious adverse events (Lan et al. 2015; Liang et al. 2019; Ju et al. 2018). Given that berberine costs less than many other drugs, it could have great potential for use in the management and control of MetS and related disorders. As for the effects of berberine on the concentration level of inflammatory markers, the results of randomized controlled trials (RCTs) have been inconsistent. A systematic review conducted by Beba et al. suggested that berberine could reduce the concentration

Feng Chang cpucf@163.com

¹ Center for Health Care Policy Research, School of International Pharmaceutical Business, China Pharmaceutical University, 639 Longmian Avenue, Jiangning District, Nanjing 211198, Jiangsu, China

level of CRP, but only five studies were included in the analysis, and the experimental and control groups of included studies were based on different populations (Beba et al. 2019; Chen et al. 2016; Hu et al. 2012). A more thorough evaluation of the effects of berberine on inflammatory markers in patients with MetS and related disorders needs to be further analyzed with multiple outcomes and evidence from more RCTs. To our knowledge, there are no RCTs relative to this study field in other nations, but many in China. Besides, these RCTs have not been included in systematic reviews or meta-analyses for qualitative or quantitative research.

The present study summarizes a meta-analysis that systematically reviewed and quantified the effects of berberine use on inflammatory markers in Chinese patients with MetS and related disorders to provide special evidence for supporting pharmacists' and physicians' clinical actions and decisions in China's MetS and related disorders management.

Materials and methods

Search strategy and study selection

The meta-analysis was conducted based on the recommendations of the Cochrane Collaboration (Higgins et al. 2020), and has been reported according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines (Page et al. 2021). The databases of PubMed, Web of Science, the Cochrane Library, China National Knowledge Infrastructure (CNKI), VIP Chinese periodical service platform, WanFang Data, and ClinicalTrials.gov (http://www.clinicaltrial.gov) were searched from the date of their inception to October 2020. Medical Subject Headings and text search words included patients ["metabolic syndrome" or "acute coronary syndromes" or "coronary artery disease" or "CVD" or "diabetic" or "T1DM" or "T2DM" or "overweight" or "obese" or "chronic kidney disease" or "end-stage renal disease" or "dialysis" or "heart failure" or "myocardial infarction" or "atherosclerotic" or "hypercholesterolemic" or "hypertension" or "high blood pressure" or "dyslipidemia" or "hyperlipidemia" or "polycystic ovary syndrome" or "stable angina" or "unstable angina" or "diabetic nephropathy" or "obesity" or "stable atherosclerotic plaques" or "atherosclerotic"] (Akbari et al. 2018, 2019; Tabrizi et al. 2018, 2019; Hamedifard et al. 2019), intervention ["berberine"], and outcomes ["CRP" or "IL-6" or "TNF- α " or "IL-1" or "inflammatory"]. References cited by the included studies were traced to uncover relevant additional studies.

Inclusion and exclusion criteria

All clinical trials that met the following criteria which were defined according to the PICO strategy recommended by Cochrane were included: (1) the study population consisted of Chinese patients diagnosed with MetS and related disorders. The MetS-related disorders included acute coronary syndrome, coronary artery disease, cerebrovascular disease, diabetes, obesity, chronic kidney disease, heart failure, myocardial infarction, atherosclerosis, hypercholesterolemia, hypertension, dyslipidemia, hyperlipidemia, polycystic ovary syndrome, angina pectoris, diabetic nephropathy, and stable atherosclerotic plaques; (2) the experimental group was treated with berberine or berberine combined with other treatments, and placebo or non-berberine treatments were used as the control group; (3) RCTs comparing outcomes in CRP, TNF- α , IL-6, and IL-1.

Studies with the following criteria were excluded from this meta-analysis: (1) duplicate and non-full-text publications; (2) reviews, non-human studies, and retrospective and observational studies; and (3) published in languages other than Chinese or English.

Data extraction and risk-of-bias assessment

Studies were independently selected by two authors (XWZ and JFH), and they achieved good agreement (κ = 0.879). Conflicts between the two authors were resolved by the opinion of a third author (YQL). Eligibility screening was performed in two steps: (1) title and abstract screening for relevance to the study objective, and (2) full-text screening for eligibility for meta-analysis. For each eligible study, the following information was extracted (1) basic information (e.g., first author, year of publication, sample size); (2) baseline characteristics of intervention and study population; and (3) relevant outcomes, including CRP, TNF- α , IL-6, and IL-1. Two authors (XWZ and JFH) independently extracted data from each selected RCTs using a standard abstraction excel sheet (κ =0.962).

The methodological quality of each RCT was evaluated by two independent investigators (XWZ and JFH) using the Cochrane Risk of Bias assessment tool (κ =0.973). The assessment domains of the Cochrane Risk of Bias assessment tool include selection bias, performance bias, detection bias, attrition bias, reporting bias, and other biases (Higgins et al. 2020).

Statistical analysis

The meta-analysis was undertaken in Review Manager version 5.3 (Cochrane Collaboration, Oxford, UK). Standardized mean differences (SMDs) and 95% confidence intervals (CIs) were used to assess continuous outcomes. p values ≤ 0.05 were considered to be statistically significant. Heterogeneity among the included studies was assessed using the I^2 estimate and the p value of the Chi-square test. I^2 values < 50% and p value > 0.10 were determined to indicate no significant heterogeneity, and the fixed-effect (FE) model was used for meta-analysis. When significant heterogeneity was determined, its source was further evaluated by sensitivity analyses or subgroup analyses. Sensitivity analyses were conducted to assess the effect of each trial on the validity of the pooled overall SMDs using the leave-one-out method. Subgroup analyses were conducted according to the following variables: dosage of berberine (< 0.9 g daily vs. ≥ 0.9 g daily), type of condition (metabolic syndrome vs. type 2 diabetes vs. diabetic nephropathy vs. cardiovascular disease vs. polycystic ovary syndrome vs. other), duration of study (<3 months vs. \geq 3 months vs. unclear), and sample size (< 30 vs. 30-60 vs. > 60). In the absence of clinical and methodological heterogeneity, the random-effects (RE) model was used to analyze the outcomes. The results of the meta-analysis were shown in forest plots. Publication bias was detected by funnel plot symmetry tests and Egger's regression tests. Egger's regression test was undertaken in Stata /MP version 16.0 (Stata Corp., College Station, TX, USA).

Results

Search results

A total of 7387 articles were retrieved from the initial search. After screening titles and abstracts, 152 studies were potentially eligible, and these were retrieved for full-text review. After reading the full text, 100 were excluded, because they failed to meet the inclusion criteria. Ultimately, 52 studies that fully satisfied the pre-established inclusion criteria of this meta-analysis were included. The search procedure and reasons for exclusion can be found in the flowchart presented in Fig. 1.

Study characteristics

The 52 included studies were published between 2008 and 2020 (Liu and Hu 2008; Xu et al. 2008; Zhang et al. 2008, 2010, 2014; Liu et al. 2010; Sheng and Xie 2010; Zhu 2010; Meng et al. 2011; Xiang et al. 2011; Zhou and Huang 2011, 2012; Deng et al. 2012; Dou et al. 2012; Liu and Wang 2012; Yu et al. 2012; Shu 2014; Dai et al. 2015; Chen et al. 2015; 2017; Zhan et al. 2015; Zhu et al. 2015; Li et al. 2016; Sun 2016, 2017; Wang 2016; Zhou et al. 2016; Dong et al. 2017; Li 2017a, b, c Yuan et al. 2017; Bai et al. 2018; He 2018; Fu and Zhang 2018; Fan et al. 2018; He et al. 2018; He 2018; Huang



Fig. 1 Flowchart of the search, inclusion, and exclusion study selection

et al. 2018; Li and Deng 2018; Lie et al. 2018a, b Lu et al. 2018; Ning 2018; Wang et al. 2018; Yang et al. 2018, 2020; Cao and Su 2019; Lai et al. 2019; Lan et al. 2019; Xie and Huang 2019; Yang and Yin 2019; Ye and You 2019). The collective patient population comprised 2304 individuals in the experimental group and 2312 individuals in the control group. There were 41 studies that reported the level of CRP, 26 that reported the level of TNF- α , 25 that reported the level of IL-6, and three studies that reported the level of IL-1 β . The main characteristics of these studies are presented in Table 1

Risk-of-bias assessment

Two studies exhibited a high risk of bias in the "random sequence generation" domain (Chen et al. 2017; Yang et al. 2018), since their methods taken to generate random sequences and arrange groups did not accord with the randomization standard. Twenty-four studies exhibited an unclear risk without information about concealment of the allocation sequence. All included studies exhibited an unclear risk in the "allocation concealment" domain because of the lack of detailed description of allocation. Only six studies illustrated the details of blinding (Zhang et al. 2008; Xiang et al. 2011; Deng et al. 2012; Li et al. 2016; Du and Zhang 2018; Li and Deng 2018). Forty-three studies exhibited a low risk of attrition bias without incomplete outcome data. The domain "reporting bias" exhibited an unclear risk of bias, because the measurement of the concentration of inflammatory markers was not mentioned. The domain "other bias" exhibited an unclear risk of bias due to insufficient information. In general, many domains were assessed as "unclear risk", which indicated that the included studies were likely to be at risk of bias. The risks of bias in each study are summarized in Fig. 2

Main outcomes

Forest plots that demonstrate the effects of berberine use on the evaluated inflammatory markers are shown in Fig. 3. The pooled findings using random-effects model showed that berberine use in patients with MetS and related disorders significantly decreased the concentration level of CRP (SMD = -1.54; 95% CI -1.86, -1.22; p < 0.05), TNF- α (SMD = -1.02; 95% CI -1.27, -0.77; p < 0.05), and IL-6 (SMD = -1.17; 95% CI -1.53, -0.81; p < 0.05). Moreover, pooled findings from the random-effects model showed that there was no significant impact of berberine on the level of IL-1 β (SMD = -0.81; 95% CI -1.80, 0.17; p = 0.11).

Heterogeneity

 $(I^2 = 87\%; p < 0.10)$, IL-6 $(I^2 = 93\%; p < 0.10)$, and IL-1 β $(I^2 = 91\%; p < 0.10)$, as shown in Fig. 3. Following sensitivity analyses, the heterogeneity did not change significantly and only reduced by 1–4%, with the elimination of individual studies. And there was not any statistically significant difference between before and after sensitivity pooled SMDs for CRP, TNF- α , IL-6, and IL-1 β concentration levels, as presented in Table 2.

Following subgroup analyses, heterogeneity was changed among some of the strata of subgroups. The heterogeneity changed significantly in the strata of polycystic ovary syndrome ($I^2 = 19\%$; p = 0.27) and ≥ 3 months ($I^2 = 10\%$; p = 0.35) for TNF- α . Furthermore, there were significant differences between before and after subgroup analyses in the stratum of metabolic syndrome for TNF- α (SMD = -1.42; 95% CI -3.38, 0.55; p > 0.05) and the stratum of cardiovascular disease for IL-6 (SMD = -0.42; 95% CI -1.24, 0.39; p > 0.05). These results of subgroup analyses suggested that type of condition and duration of study may be the source of heterogeneity in the meta-analysis. Table 3 shows the subgroup analysis of the influence of berberine on CRP, TNF- α , and IL-6.

Publication bias

Funnel plots and Egger's regression test were not evaluated for IL-1 β levels due to the relatively small number of studies with this endpoint. These tests showed no significant evidence of publication bias for meta-analyses assessing the effect of berberine on TNF- α (p=0.46; 95% CI – 1.38, 0.64) and IL-6 (p=0.43; 95% CI – 0.48, 1.09) concentration levels. However, as shown in Fig. 4, the asymmetry displayed in the funnel plot, and Egger's test (p < 0.05; 95% CI 1.27, 2.26) of CRP indicated some publication bias, which probably is attributed to unpublished studies with negative findings.

Discussion

Regulating inflammatory markers through various pathways to exert anti-inflammatory effects is one possible mechanism of action that berberine may have in the treatment of MetS and related disorders. An animal experiment conducted by Jeong HW found that berberine can restore damaged islet cells by activating the adenosine monophosphate-activated protein kinase (AMPK) signaling pathway (Jeong et al. 2009). In the adipose tissue of obese mice, berberine was shown to significantly down-regulate the expression of pro-inflammatory genes, including IL-1 β , IL-6, TNF- α , monocyte chemoattractant protein-1 (MCP-1), inducible nitric oxide synthase (iNOS), and cyclooxygenase 2 (COX-2), and continually inhibit peritoneal

Table 1 Characteristics of	f included studies							
Study	Population	Sample size	Age (years)		Intervention		Duration	Presented
		(C/E)	C	E	C	E		data
Liu and Hu (2008)	Type 2 diabetes	30/30	53.07 ± 8.51	52.00 ± 9.81	Metformin 1.5 g/d	Metformin + berberine 0.9–1.5 g/d	8 weeks	CRP
Xu et al. (2008)	Diabetic nephropathy	40/40	51 ± 3.5^{a}	51 ± 3.5^{a}	Pioglitazone 30 mg/d	Pioglitazone + berberine 0.9 g/d	12 weeks	CRP
Zhang et al. (2008)	Type 2 diabetes and dyslipidemia	58/52	N/A	51 ± 10	Placebo	Berberine 1.0 g/d	3 months	CRP, IL-6
Liu et al. (2010)	Type 2 diabetes	20/20 20/20	59.40 ± 15.40 64.45 ± 14.40	62.80 ± 12.20	Basic treatments ^b Basic treatments ^b + Rosigl- itazone 4 mg/d	Basic treatments ^b + berberine 0.9 g/d	3 months	CRP, TNF-α, IL-6
Sheng and Xie (2010)	Type 2 diabetes	30/30	51±8	52±11	Glipizide 10 mg/d + metformin 1.5 g/d	Glipizide + metformin + ber- berine 1.5 g/d	3 months	CRP, TNF-α, IL-1β, IL-6
Zhang et al. (2010)	Acute coronary syn- dromes	20/20	61.42 ± 8.60^{a}	61.42 ± 8.60^{a}	Basic treatments ^b	Basic treatments ^b + berberine 0.9 g/d	30 days	CRP
Zhu (2010)	Diabetic nephropathy	48/44	66.69 ± 8.32	65.71 ± 8.41	Irbesartan 0.15 g/d	Irbesartan + berberine 1.2 g/d	12 weeks	CRP, TNF- α
Meng et al. (2011)	Type 2 diabetes	30/30	53 ± 13.9	51 ± 13.3	Insulin	Insulin + berberine 0.9 g/d	12 weeks	TNF-α, IL-6
Xiang et al. (2011)	Type 2 diabetes	20/20 20/20	N/A N/A	N/A	Placebo Aspirin 0.1 g/d	Berberine 1.2 g/d	12 weeks	CRP, TNF-α, IL-6
Zhou and Huang (2011)	Hyperlipidemia	60/60	N/A	N/A	No treatment	Berberine 0.9 g/d	4 months	CRP
Deng et al. (2012)	Polycystic ovary syndrome and insulin resistance	28/31	26.75 ± 2.62	25.74 ± 2.66	Ethinylestradiol cyproterone 2 mg: 0.035 mg/d+placebo	Ethinylestradiol cyproter- one + berberine 0.9 g/d	3 men- strual cycles	CRP, TNF-α
Dou et al. (2012)	Obesity	60/58	47.68 ± 8.40	48.42 ± 8.60	Vitamin C 0.9 g/d	Berberine 0.9 g/d	4 weeks	CRP
Liu and Wang (2012)	Ischemic heart disease and heart failure	44/50	69.6±8.2	67.5 ± 10.3	Basic treatments ^b	Basic treatments ^b + berberine 0.9 g/d	8 weeks	TNF-α
Yu et al. (2012)	Type 2 diabetes	24/24	45.6 ± 5.4^{a}	45.6 ± 5.4^{a}	Glibenclamide 5 mg/d	Exenatide 5 μ g/d + berberine 0.9 g/d	12 weeks	CRP
Zhou and Huang (2012)	Obesity and type 2 diabetes	46/46	46.67 ± 8.52^{a}	46.67 ± 8.52^{a}	Metformin 1.5 g/d	Metformin + berberine 0.6 g/d	12 weeks	CRP
Shu (2014)	Type 2 diabetes	32/32	61.21 ± 13.52	62.80 ± 12.20	Insulin	Insulin + berberine 0.9 g/d	24 weeks	CRP
Zhang et al. (2014)	Cerebral infarction	30/30 30/30	54.1 ± 4.6 54.3 ± 4.9	55.6±5.2	Basic treatments ^b Basic treatments ^b + atorvas- tatin 40 mg/d	Basic treatments ^b + atorvasta- tin + berberine 0.4 g/d	4 weeks	CRP
Dai et al. (2015)	Hypertension and type 2 diabetes	33/39	53.06 ± 10.36	55.31 ± 11.79	Basic treatments ^b	Basic treatments ^b + berberine 0.3 g/d	2 years	CRP
Chen et al. (2015)	Coronary artery disease and hypercholesteremia	40/40	51.5 ± 10.4	52.1±9.8	Simvastatin 20 mg/d	Simvastatin 10 mg/d + ber- berine 0.5 g/d	1 month	CRP

Study	Population	Sample size	Age (years)		Intervention		Duration	Presented
		(C/E)	С	Ε	C	E		data
Zhan et al. (2015)	Type 2 diabetes with hyperlipidemia	40/40	51.6 ± 3.8^{a}	51.6 ± 3.8^{a}	Basic treatments ^b + met- formin 1.5 g/d	Basic treatments ^b + met- formin + berberine 0.6 g/d	3 months	CRP
Zhu et al. (2015)	Acute ischemic stroke	28/16	66.25 ± 8.83	63.31 ± 8.10	Atorvastatin 20 mg/d+aspirin 0.1 g/d	Atorvastatin 20 mg/d + aspi- rin + berberine 0.4 g/d	3 months	CRP
		11/16	66.45 ± 8.86		Atorvastatin 40 mg/d+aspirin 0.1 g/d			
Li et al. (2016)	Insulin resistance with schizophrenia	, 33/31	40.18±12.21	40.14 ± 9.40	Risperidone 3.85±0.94 mg/d+pla- cebo	Risperidone 3.77±0.85 mg/d+berber- ine 0.9 g/d	12 weeks	TNF-α, IL-1β, IL-6
Sun (2016)	Obesity and type 2 diabetes	48/48	52.37±4.48	52.32 ± 4.45	Sitagliptin 0.1 g/d	Sitagliptin + berberine 0.9 g/d	12 weeks	CRP, IL-6
Wang (2016)	Type 2 diabetes	25/25	N/A	N/A	Basic treatments ^b	Basic treatments ^b + berberine 0.3 g/d	3 months	CRP, IL-6
Zhou et al. (2016)	Obesity and type 2 diabetes	30/30	55.6 ± 12.7	56.4 ± 10.9	Basic treatments ^b	Basic treatments ^b + berberine 0.6 g/d	3 months	CRP, TNF-α, IL-6
Chen et al. (2017)	Metabolic syndrome with renal damage	10/10	40.20 ± 5.89	38.70 ± 10.3	Losartan 0.1 g/d	Losartan + berberine 0.9 g/d	8 weeks	TNF-α
Dong et al. (2017)	Type 2 diabetes	49/49	51.34 ± 4.43	52.23 ± 4.41	Metformin 1.5 g/d	Metformin + berberine 0.9 g/d	12 weeks	CRP, TNF-α, IL-6
Li (2017a)	Metabolic syndrome with schizophrenia	42/40	42.14±11.61	41.86 ± 10.22	Olanzapine + metformin 0.75 g/d	Olanzapine + berberine 0.9 g/d	12 weeks	TNF-α, IL-1β, IL-6
Li (2017b)	Obesity and type 2 diabetes	30/30	51.24 ± 3.91	50.54 ± 3.78	Sitagliptin 0.1 g/d	Sitagliptin + berberine 0.9 g/d	3 months	CRP, IL-6
Li (2017c)	Acute cerebral ischemic stroke	09/09	61.94 ± 3.77	62.84 ± 4.67	Basic treatments ^b	Basic treatments ^b + berberine 0.9 g/d	14 days	CRP, IL-6
Sun (2017)	Type 2 diabetes	91/91	58.34±11.21	58.95 ± 10.57	Metformin 1.5 g/d	Metformin + berberine 0.09 g/d	8 weeks	CRP, TNF-α, IL-6
Yuan et al. (2017)	Type 2 diabetes	41/41	65.78±8.96	66.13 ± 9.06	Glimepiride 1 mg/d	Glimepiride + Gegen Qinlian Decoction + berberine 0.6 g/d	2 weeks	CRP, TNF-α
Bai et al. (2018)	Hyperlipidemia	75/75	63.38 ± 7.24	63.29 ± 7.85	Ezetimibe 10 mg/d	Ezetimibe + berberine 0.4 g/d	1 month	CRP
Du and Zhang (2018)	Coronary heart disease	12/18	66 ± 10	60±6	Basic treatments ^b	Basic treatments ^b + berberine 0.9 g/d	3 months	CRP, TNF-α, IL-6
Fan et al. (2018)	Type 2 diabetes	40/40	52.71 ± 7.89	53.27 ± 8.15	Metformin 1.5 g/d	Metformin + berberine 1.5 g/d	3 months	CRP, TNF-α, IL-6
He et al. (2018)	Diarrhea with hyperlipi- demia	62/62	55.16 ± 6.79	56.78 ± 6.74	Basic treatments ^b + levo- floxacin 0.5 g/d	Basic treatments ^b + berberine 0.36 g/d	8 weeks	CRP, TNF-α, IL-6
He (2018)	Diabetic nephropathy	52/52	56.4±7.3	56.2±7.5	Basic treatments ^b valsartan 80 mg/d	Basic treatments ^b + valsar- tan + berberine 1.2 g/d	12 weeks	CRP, TNF-α

 $\underline{\textcircled{O}} Springer$

Table 1 (continued)

Study	Domilation	Comple cize	A ra (vaare)		Interrention		Duration	Dracantad
Juuy	1 opulation		Age (years)				DUIAHU	r resulted
		(11)	С	Ε	С	E		uala
Huang et al. (2018)	Type 2 diabetes	65/65 6	7.16 ± 8.54	66.09 ± 8.67	Insulin	Insulin + berberine 1.8 g/d	1 month	TNF-α
Li and Deng (2018)	Nonalcoholic fatty liver disease	53/53 7	4.68±4.32	74.07 ± 5.16	Polyene phosphatidyl cho- line 1.368 g/d	Polyene phosphatidyl cho- line + berberine 0.36 g/d	12 weeks	TNF-α
Lie et al. (2018a)	Polycystic ovary syn- drome	38/38 N	V/A	N/A	Ethinylestradiol cyproterone 2 mg: 0.035 mg/d + placebo	Ethinylestradiol cyproter- one + berberine 0.9 g/d	21 days	CRP
Lie et al. (2018b)	Type 2 diabetes	57/57 5	7±12	53±15	Basic treatments ^b	Basic treatments ^b + berberine 1.2 g/d	6 months	CRP
Lu et al. (2018)	Acute ischemic cerebral infarction	9 09/09	0.7 ± 5.2	59.9±6.1	Basic treatments ^b + rosuvas- tatin 10 mg/d	Basic treatments ^b + rosuvasta- tin + berberine 0.9 g/d	N/A	CRP
Ning (2018)	Acute cerebral infarction	39/39 6	1.00 ± 1.26	60.00 ± 1.47	Basic treatments ^b + atorvas- tatin 40 mg/d	Basic treatments ^b + atorvasta- tin + berberine 0.9 g/d	15 days	CRP, IL-6
Wang et al. (2018)	Metabolic syndrome with renal damage	10/10 3.	5.62 ± 1.43	37.30 ± 1.96	Basic treatments ^b	Basic treatments ^b + berberine 0.9 g/d	8 weeks	IL-6
Yang et al. (2018)	Symptomatic atheroscle- rotic intracranial artery stenosis	60/60 6	1.98±4.09	61.98±4.09	Simvastatin 40 mg/d+aspi- rin 0.1 g/d	Simvastatin + aspirin + ber- berine 1.2 g/d	6 months	CRP
Cao and Su (2019)	Metabolic syndrome and insulin resistance	40/40 6	5.6 ± 1.8	65.5 ± 1.8	Basic treatments ^b	Basic treatments ^b + berberine 1.2 g/d	1 month	CRP, TNF-α, IL-6
Lai et al. (2019)	Polycystic ovary syndrome and insulin resistance	48/48 2	8.48±6.34	29.53±5.21	Metformin 1 g/d	Peikun pills 18 g/d + berber- ine 0.9 g/d	3 months	CRP, TNF-α, IL-6
Lan et al. (2019)	Hypertensive atheroscle- rosis	40/40 6	3.3±6.2	64.2±5.5	Basic treatments ^b	Basic treatments ^b + berberine 0.9 g/d	8 weeks	TNF-α, IL-6
		40/40		65.1 ± 5.0		Basic treatments + berberine 1.8 g/d		
Xie and Huang (2019)	Diabetic nephropathy	53/53 6	1.3 ±1.2	62.1±1.6	Basic treatments ^b + trip- terygium wilfordii polyg- lycosides 60 mg/d	Basic treatments ^b + tripteryg- ium wilfordii polyglyco- sides + berberine 1.5 g/d	90 days	TNF-α, IL-6
Yang and Yin (2019)	Coronary heart disease	30/40 6	1.37 ± 8.79	60.63 ± 8.53	Basic treatments ^b + rosuvas- tatin 10 mg/d	Basic treatments ^b + berberine 0.9 g/d	4 weeks	CRP, TNF-α
Ye and You (2019)	Acute ischemic cerebral infarction	33/33 5	6.65 ± 7.12	57.36 ± 6.79	Rosuvastatin 10 mg/d	Rosuvastatin + berberine 0.9 g/d	12 days	CRP, IL-6
Yang et al. (2020)	Type 2 diabetes	96/96 4	9.7 ± 7.4	49.9±7.8	Metformin 2 g/d	Metformin + berberine 1.5 g/d	3 months	TNF-α, IL-6
<i>N/A</i> The date was not rep	orted, CRP C-reactive prote	in, $TNF-\alpha$ tumo	r necrosis factor-	alpha, <i>IL-6</i> interle	ukin-6, <i>IL-1β</i> interleukin-1 bets	V, C control group, E experiment	tal group, X	g/d X g daily

1069

^aOnly demographic characteristics of the total sample population were reported

^bDifferent patients used different drugs for basic treatments

macrophages and RAW264.7 cell pro-inflammatory genes (IL-16, IL-6, iNOS, MCP-1, COX-2, and alkaline metalloproteinase-9) expression induced by lipopolysaccharide (LPS) (Jeong et al. 2009). Additionally, berberine can reduce the phosphorylation of MAPK by intervening in the activation of TNF- α and other inflammatory markers on MAPK (Li et al. 2014). Wan Q reported that berberine inhibits the activation of the extracellular-signal-regulated kinase (ERK) signaling pathway, and down-regulates the expression of TNF- α and IL-6, through in-vitro experiments on human umbilical vein endothelial cells (HUVECs) (Wan et al. 2014). Inflammatory markers like IL-6 and IL-1 β regulate and induce the expression of CRP. Furthermore, an increase in CRP levels can facilitate those inflammatory markers when inflammation occurs (Yang et al. 2012).

As an extract from traditional Chinese herbs, berberine has a long history of clinical application and many efficacy trials on humans in China. The meta-analysis included 52 RCTs involving 4616 Chinese patients with MetS and related disorders, which complemented the evidence of the effects of berberine use on inflammatory markers in humans and in China. The results suggested that berberine could reduce the concentration level of CRP significantly, which was consistent with the results of a previous study (Beba et al. 2019). Furthermore, this meta-analysis analyzed three other important inflammatory markers of metabolic syndrome (MetS) and related disorders. The results suggested that berberine could reduce the concentration level of TNF- α , and IL-6 significantly, but could not reduce the concentration level of IL-1β. Sensitivity analyses and subgroup analyses indicated that the results of the meta-analysis were relatively stable. The type of condition had the greatest impact on the heterogeneity and pooled estimates of the meta-analysis. However, due to the small number of included studies and the estimated heterogeneity, there were additional doubts about the pooled estimate result of IL-1 β , which need to be resolved in further trials.

There are a few limitations to this meta-analysis. First, the result of the risk-of-bias assessment presented a large proportion of uncertain risks for insufficient information in trial methods. To a certain extent, the potential differences in the methods of random sequence generation, allocation concealment, and concentration measurement among the included studies have caused the high heterogeneity of the meta-analysis results. Second, the study population of all the included studies was Chinese patients, and the sample size of individual clinical trial was small. The results of this meta-analysis are accordingly hard to extrapolate to other ethnic populations or geographical regions. Therefore, more studies with larger sample size, ideally multi-centers, and rigorous design are needed to confirm the effect of berberine on the inflammatory markers of MetS and related disorders.



Fig. 2 Quality assessment of included studies

B Experimental Control SD Total Mean Difference St. Total Mean Difference Lum Hetal 2006 -0.22 -0.10 -0.00 0.8% -1.512 (17.96, -1.22.7) 2006 - Auge Status -0.62 -0.62 0.62 0.62 0.64 -0.22.4% -0.21 (0.96, 1.11) 2006 - Num F etal 2006 -0.62 -0.62 2.03 -0.02.4% -0.02 (0.96, 1.11) 2006 - Duu S etal 2010 -6.83 1.06 4.43 2.02 -0.02 (0.11) -0.02 -0.02 (0.01) -0.02 (0.01) - Duu S etal 2010 -6.84 -6.86 0.47 30 2.3% -0.72 (1.93, -0.08) 2011 - Topu V etal 2010 -1.57 1.74 20 -0.02 (2.33) -0.02 (0.70, 0.54) 2011 - - Amang W etal 2012 -1.77 1.74 20 -0.02 (2.33) -0.02 (0.70, 0.51) - - Dend etal 2012 -1.77 1.42 2.04 -0.22 (0.05, 0.22 (0.	-	_									
Submy of subgroup Mean SD Instance Desc Distance Distance Distance Distance Zhang Yet al. 2008 -0.82 4.87 52 0.32 6.26 68 2.4% -0.2016.05.017 2008 - Jun Yet al. 2008 -0.82 4.87 2.0 2.6 68 2.4% -0.2114.09.01.79 0.217 2008 - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - -	a	Expe	eriment	al	с	ontrol			Std. Mean Difference		Std. Mean Difference
Lu Hetal 2008 - 0.2 4.16 0.11 30 - 2.5 0.1 30 0.8% - 15.12 (17.9%, 12.27) 2008	Study or Subgroup	Mean	SD	Total	Mean	SD	lotal	weight	IV, Random, 95% CI	Year	IV, Random, 95% Cl
Zhang Yir Bi Zu008 -0.82 4.87 bi Zu 20 columbra Columbra <thcolumbra< th=""> Columbra</thcolumbra<>	Liu H et al. 2008	-4.16	0.11	30	-2.55	0.1	30	0.8%	-15.12[-17.96, -12.27]	2008	
Dub et al. 2006 -4.6 2.97 4.0 -3.83 3.03 4.0 2.48 -10.24 0.16 0.12 2008 Luu et al. 2010(a) -3.84 4.97 20 -4.64 4.44 2.2 2.38 0.073 1.051 0.73 2010 -73 Zhung H et al. 2010 -6.83 4.497 20 -6.64 4.34 2.2 2.38 0.073 1.051 0.73 0.010 -73 Zhung H et al. 2010 -1.637 10.46 4.4 -3.61 10.73 48 2.4% -1.18 0.071 2.010 -73 Zhung V et al. 2011 -1.73 10.66 0.653 2.19 600 2.3% -1.271 1.183, 0.071 2010 -74 1.06 1.07 1.07 1.06 2.3% -721, 1.18, 0.071 2010 -74 1.06 1.07 1.07 1.07 1.07 1.07 1.07 1.07 1.07 1.07 1.07 1.07 1.07 1.07 1.07 1.07 1.07 1.07 1.07 1.07 1.07 1.07 1.07 <th< td=""><td>Zhang Y et al. 2008</td><td>-0.82</td><td>4.87</td><td>52</td><td>0.32</td><td>6.26</td><td>58</td><td>2.4%</td><td>-0.20 [-0.58, 0.17]</td><td>2008</td><td>]</td></th<>	Zhang Y et al. 2008	-0.82	4.87	52	0.32	6.26	58	2.4%	-0.20 [-0.58, 0.17]	2008]
$ \begin{array}{ c c c c c c c c c c c c c$	Xu F et al. 2008	-4.6	2.97	40	-3.63	3.03	40	2.4%	-0.32 [-0.76, 0.12]	2008	1
$ \begin{array}{ c c c c c c c c c c c c c c c c c c c$	Liu J et al. 2010(b)	-3.94	4.97	20	-4.54	5.43	20	2.3%	0.11 [-0.51, 0.73]	2010	J
$ \frac{2}{2} \operatorname{hang} \operatorname{peta}_{a} 2 \operatorname{vol}_{a} $	Liu J et al. 2010(a)	-3.94	4.97	20	-0.46	4.34	20	2.3%	-0.73 [-1.37, -0.09]	2010	_
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	Zhang Hiet al. 2010 Zhui Loodo	-5.89	2.18	20	-1.92	2.07	20	2.2%	-1.60 [-2.32, -0.88]	2010	
$\frac{1}{2} \operatorname{Pins}_{2} \operatorname{Pins}_$	Zhu J Zoto Obana Ziatali 2010	-10.37	10.40	44	-3.01	10.73	48	2.4%	-1.19 [-1.04, -0.75]	2010	
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	Sheng Z et al. 2010	-2.25	1.08	30	-0.66	0.47	30	2.3%	-1.27 [-1.83, -0.71]	2010	
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	Zhou Y et al. 2011 Vieng W et al. 2011(e)	-1.7	1.00	20	-0.53	2.18	20	2.4%	-0.00 [-0.97, -0.23]	2011	1
Analy We tak 2011(0) -1.32 1.33 2.33 -1.03 PU/1, 0.34 2011 Uir Fital 2012 -1.73 1.94 21 -1.32 23.53 -1.03 PU/1, 0.84 2011 Deng Het al. 2012 -1.73 1.94 31 -1.26 2.05 22 2.4% -0.31 PU/2, 0.28 2012 - Doul Jet al. 2012 -1.33 2.45 0.03 1.04 PU/2, 0.84 2012 - - Zhou Oet al. 2012 -1.33 2.86 0.06 2.4% -0.31 PU/2, 0.08 2011 - Zhang Yet al. 2014(a) -3.38 2.86 30 -2 31.2 30 2.4% -0.40 PU/2, 0.51 - - Zhang Yet al. 2016(a) -2.16 5.47 16 -1.78 1.28 -0.07 PU 6.06, 0.54 2015 - - - - - - -0.28 0.27 0.27 0.27 0.27 0.27 - -0.07 PU 6.06, 0.54 2015 - - - - - - <td>Xiang Wetal. 2011(a)</td> <td>-1.57</td> <td>1.74</td> <td>20</td> <td>-0.17</td> <td>2.07</td> <td>20</td> <td>2.3%</td> <td>-0.72 [-1.30, -0.08]</td> <td>2011</td> <td>1</td>	Xiang Wetal. 2011(a)	-1.57	1.74	20	-0.17	2.07	20	2.3%	-0.72 [-1.30, -0.08]	2011	1
Dur et al. 2012 -14.0 2.80 2.43 -1.81/2.14, -0.84 2012 Deng H et al. 2012 -1.31 2.43 -0.33 [-0.67, 0.08] 2012 - Dou J et al. 2012 -1.43 2.45 68 -0.33 [-0.67, 0.08] 2012 - Shu J 2014 -2.02 1.1 32 -0.09 1.54 32 2.3% -0.42 [-0.76, 0.08] 2014 - Zhang Y et al. 2014(b) -3.38 2.86 30 -0.1 3.2 30 2.3% -0.04 [-0.87, 0.06] 2014 - DaP et al. 2015(a) -3.8 2.86 30 -0.1 3.2 30 2.3% -0.07 [-1.61, 0.52] 2014 - DaP et al. 2015(a) -2.16 5.47 16 -1.69 7.1 28 2.3% -0.07 [-0.68, 0.54] 2015 - - Zhu G et al. 2015(a) -2.16 5.47 16 -7.89 2.33 2.04% -0.07 [-0.68, 0.54] 2015 - - - - - - - 2.01 2.04 2.02 2.011 - - <t< td=""><td>Xiang wet al. 2011(b)</td><td>-1.57</td><td>1.74</td><td>20</td><td>-1.42</td><td>1.94</td><td>20</td><td>2.3%</td><td>-0.08 [-0.70, 0.54]</td><td>2011</td><td>-</td></t<>	Xiang wet al. 2011(b)	-1.57	1.74	20	-1.42	1.94	20	2.3%	-0.08 [-0.70, 0.54]	2011	-
Derig ret at. 2012 -1.73 1.34 31 -1.26 2.03 2.04 -0.23 10.07 2.012 Zhou Q et al. 2012 -2.36 0.81 46 0.82 0.81 46 0.82 0.81 46 0.82 0.81 46 0.82 0.81 4.87 2.37 1.38 2.012 - Zhou Q et al. 2012 -2.35 0.81 46 0.82 0.81 4.87 2.37 1.38 0.82 0.01 3.2 30 2.3% -0.46 4.99 0.81 2.014 - Zhang Y et al. 2014(a) -3.35 0.07 39 0.27 0.05 33 1.4% -9.95 1.616 4.02 2.015 - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - -	Tur et al. 2012	-4.0	2.80	24	-0.2	2.95	24	2.3%	-1.49 [-2.14, -0.84]	2012	
DOUD et al. 2012 -1.43 2.43 -0.31 (D.00, 0.00) 2012 Shu J 2014 -202 1.1 32 0.09 1.54 32 2.3% -1.42 (1.96, 0.87) (2014 Zhang Y et al. 2014(b) -3.38 2.86 30 -0.1 32 30 2.4% -0.06 (0.97, 0.06) (2014 DalP et al. 2015 -0.35 0.07 0.31 (20, 0.73) (2014 - - DalP et al. 2015 -1.9 0.41 40 -1.73 0.43 40 2.4% -0.04 (0.94, 0.04) (2015 Zhan H et al. 2015 -1.26 5.47 16 -7.81 7.10 2.8 -0.07 (0.68, 0.54) (2015 Zhu F et al. 2015(b) -2.16 5.47 16 -7.81 7.27 30 1.4% -9.09 (1.08, 7.33) (2016 - Sun 4 2016 -2.84 0.33 0.33 2.34 -2.34 -2.34 2.34 2.34 2.34 -2.34 -2.34 -2.34 -2.34 -2.34 -2.34 -2.34 -2.34 -2.34 -2.34 -2.34 -2.34 -2.34 -2.34 -2.34 -2.34 -2.34 <t< td=""><td>Deng Hietal, 2012</td><td>-1.73</td><td>1.94</td><td>51</td><td>-1.20</td><td>2.05</td><td>28</td><td>2.4%</td><td>-0.23 [-0.75, 0.28]</td><td>2012</td><td>1</td></t<>	Deng Hietal, 2012	-1.73	1.94	51	-1.20	2.05	28	2.4%	-0.23 [-0.75, 0.28]	2012	1
Dub Ob et al. 2012 -2.33 0.81 +40 -0.82 0.061 +00 2.4% -1.07 2.31, -1.38 2.012 Zhang Y et al. 2014(a) -3.38 2.86 30 -2 3.12 30 2.3% -1.04 [1.6], 0.52 2014 Dal P et al. 2015	Zhou O ot ol. 2012	-1.43	2.40	36	-0.09	2.30	40	2.4%	-0.31 [-0.07, 0.00]	2012	-
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	2012 Chu 1 2014	-2.35	0.61	40	-0.82	1.64	40	2.4%	-1.07 [-2.37, -1.38]	2012	
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	Thong Vistol 2014	-2.02	1.1	32	-0.09	1.54	32	2.3%	-1.42 [-1.90, -0.87]	2014	<u>_</u>
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	Zhang Y et al. 2014(0) Zhang Y et al. 2014(0)	-3.38	2.00	30	-2	3.12	30	2.4%	-0.40 [-0.97, 0.00]	2014	_
$b_{\text{rest}} = b_{\text{rest}} (215) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-33) - (-$	Znany retal. 2014(a) Doi Riot of 2015	-3.30	2.00	30	-0.1	0.05	30	2.370	-1.07 [-1.01, -0.52]	2014	
Chen Net al. 2015 1-13 0-11 30 1-13 0-14 1-13 0-14 2.4% -0.57 [+1.0], -0.12 2015 Zhu F et al. 2015 (a) 2-16 5.47 16 -1.69 7.1 2.2% -0.07 [-0.68, 054] 2015 Zhu F et al. 2016 (b) 2-16 5.47 16 -7.81 17.03 11 22% -0.07 [-0.68, 054] 2015 Jou Que tal. 2016 -2.04 0.23 30 0.27 0.27 30 1.4% -9.09 [-10.85, -7.33] 2016	Chop Notel 2015	-0.35	0.07	39	1.72	0.05	33	1.470	-9.95[-11.00, -0.21]	2015	
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	Zhon Histol, 2015	-1.9	1.27	40	-1.73	1.26	40	2.4%	-0.40 [-0.84, 0.04]	2015	1
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	Zhan Hietal, 2015 Zhu Eistial, 2015(a)	-2.20	5.47	40	1.60	7.1	40	2.470	-0.57 [-1.01, -0.12]	2015	1
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	Zhu Fetal. 2015(a) Zhu E et al. 2016(b)	-2.10	5.47	10	-1.09	17.02	20	2.370	-0.07 [-0.06, 0.04]	2015	Ļ
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	Zhu Felal. 2015(b) Zhau O at al. 2015	-2.10	0.00	10	-7.81	17.03	20	2.2%	0.47 [-0.31, 1.25]	2015	
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	21100 Q 81 al. 2010 Sup LI 2016	2.04	1 1 0	30	0.27	1.22	30	2.400	-9.09[-10.00, -7.00]	2010	1
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	Wong V 2016	-3.00	0.02	40	-3.23	0.07	40	2.470	-0.52 [-0.92, -0.11]	2010	
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	Wang 1 2016	-0.39	0.03	25	0.69	0.07	25	0.4%	-23.40 [-28.21, -18.59]	2010	-
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	Cup C 2017	4.30	0.33	41	-0.07	0.33	41	2.3%	-2.07 [-2.01, -1.03]	2017	
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	5011 5 2017	4.00	1.00	31	-2.37	1.24	31	2.4%	-2.10 [-2.00, -1.01]	2017	
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	Depart Cot of 2017	-4.02	1.21	30	0.27	1.24	30	2.270	-3.40 [-4.27, -2.04]	2017	
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	DUNG K et al. 2017	-3.02	1.24	49	-3.32	1.15	49	2.470	-0.41 [-0.62, -0.01]	2017	
$ \begin{array}{ c c c c c c c c c c c c c c c c c c c$	LIT 2017	10.00	1.02	20	6.24	1 40	20	2.470	-1.10[-1.49,-0.72]	2017	-
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $		-10.39	1.22	39	-0.34	1.49	39	2.370	-2.94 [-3.59, -2.50]	2010	-
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	Lu Fielai. 2010	-3.78	11.04	60	-2.00	0.00	60	2.4%	-0.90 [-1.34, -0.30]	2010	
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	He F et al. 2010	-00.1	0.06	62	-39.33	0.00	62	2.4%	-1.50 [-1.97, -1.10]	2010	-
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	LiV at al 2010	-10.1	9.00	32	0.27	0.06	32	2.4%	-1.50 [-2.00, -1.12]	2010	4
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	Vana Zatal 2010	-0.03	0.92	00	-0.22	0.90	00	2.470	-0.04 [*1.10, *0.18]	2010	-
$\frac{1}{2} \text{ Liz et al. 2018} - 2.42 + 3.94 + 57 + 2.08 + 6.8 + 57 + 2.4\% + 0.060 + 1.11, -0.211 + 2018 + 0.060 + 1.11, -0.211 + 2018 + 0.060 + 1.11, -0.211 + 2018 + 0.060 + 1.11, -0.211 + 2018 + 0.060 + 1.11, -0.211 + 2018 + 0.060 + 1.11, -0.211 + 2018 + 0.060 + 1.11, -0.211 + 2018 + 0.060 + 1.11, -0.211 + 2018 + 0.060 + 1.11, -0.211 + 2018 + 0.060 + 1.11, -0.211 + 2018 + 0.060 + 1.11, -0.211 + 2018 + 0.060 + 1.11, -0.211 + 2018 + 0.060 + 1.11, -0.211 + 2018 + 0.060 + 1.11, -0.211 + 2018 + 0.060 + 1.11, -0.211 + 2018 + 0.060 + 1.11, -0.211 + 2018 + 0.060 + 1.11, -0.211 + 2018 + 0.060 + 1.11, -0.211 + 2018 + 0.060 + 1.11, -0.211 + 2018 + 0.060 + 1.11, -0.211 + 2018 + 0.060 + 1.11, -0.211 + 2018 + 0.060 + 1.11, -0.211 + 2018 + 0.060 + 1.11, -0.211 + 2018 + 0.060 + 1.11, -0.211 + 2018 + 0.060 + 1.11, -0.211 + 2018 + 0.060 + 1.11, -0.211 + 2018 + 0.060 + 1.11, -0.211 + 2018 + 0.060 + 1.11, -0.211 + 2018 + 0.060 + 1.11, -0.211 + 2018 + 0.060 + 0.011 + 1.11, -0.21 + 2.031 + 0.011 + 1.11, -0.21 + 2.031 + 0.011 + 1.11, -0.21 + 2.031 + 0.011 + 1.11, -0.21 + 2.031 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.011 + 0.01$	Fan Cetal 2010	-0.10	1.2	40	-3.6	1.00	40	2.470	-1.04 [-1.80, -1.13]	2010	4
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	li7 otol 2019	-3.0	2.04	40	2.90	6.9	40	2.4 %	-0.00[-1.11,-0.21]	2010	~
$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$	Du V at al 2010	-2.42	0.41	19	-0.76	0.0	12	2.470	-0.00 [*1.15, *0.42]	2010	1
Can C et al. 2019 -17.1 1.18 40 -14.1 1.25 40 -2.44 50.33 1.60 2019 Ye x et al. 2019 -17.1 1.18 40 -14.1 1.25 40 2.3% -2.44 2.03.3 1.60 2019 - Ye x et al. 2019 -17.1 1.18 40 -2.33 2.3% -1.48 [-2.03, -1.68] 2019 - Yang R et al. 2019 -4.7 0.48 40 -2.33 0.5 30 2.1% -4.80 [-5.74, -3.85] 2019 - Lai S et al. 2019 -4.61 1.2 48 -3.36 1.19 48 2.4% -1.04 [-1.46, -0.61] 2019 - Total (95% Cl) 1794 1788 100.0% -1.54 [-1.86, -1.22] - - -20 -10 0 10 20 Test for overall effect: Z = 9.45 (P < 0.00001)	Bai7 at al 2010	-0.77	0.41	76	-1.64	0.27	75	2.2.70	-1 31 61 66 -0.061	2010	-
Vex Vet al. 2019 -15.08 3.44 33 9.44 4.05 33 2.3% -1.48 [-3.03, -0.93] 2019 Yang R et al. 2019 -4.7 0.48 40 -2.33 0.5 30 2.1% -4.80 [-5.74, -3.85] 2019 Lai S et al. 2019 -4.61 1.2 48 -3.36 1.19 48 2.4% -1.04 [-1.46, -0.61] 2019 Total (95% Cl) 1794 1788 100.0% -1.54 [-1.86, -1.22] -100 10 20 Heterogeneity: Tau ² = 1.06; Chi ² = 755.81, df = 44 (P < 0.00001); P = 94%	Can Catal 2010	-2.12	1 1 9	10	-1.04	1.34	40	2.4 %	-1.31 [-1.00, -0.95]	2010	-
Vang R et al. 2019 -4.7 0.48 40.3 5.3 2.3% -4.80 [5.36] 2019 Lai S et al. 2019 -4.61 1.2 48 -2.33 0.5 30 2.1% -4.80 [5.44-385] 2019 Total (95% Cl) 1794 1788 100.0% -1.04 [-1.46, -0.61] 2019 - Heterogeneily: Tau ² = 1.06; Chi ² = 755.81, df = 44 (P < 0.00001); I ² = 94% -1.54 [-1.86, -1.22] -20 -10 0 10 20 Test for overall effect: Z = 9.45 (P < 0.00001)	Vo X ot al 2019	-15.09	3.4.4	20	-14.1	4.05	30	2.370	-2.44 [-3.03, -1.00]	2019	-
Lai S et al. 2019 -4.7 0.48 40 -2.33 0.3 30 2.1% -4.8.0 [2.7,4,-3.80] 2019 Lai S et al. 2019 -4.61 1.2 48 -3.36 1.19 48 2.4% -1.04 [-1.46, -0.61] 2019 Total (95% Cl) 1794 1788 100.0% -1.04 [-1.46, -0.61] 2019 -20 -10 0 10 20 Heterogeneity: Tau ² = 1.06; Chi ² = 755.81, df = 44 (P < 0.00001); P = 94%	Vong Plot of 2019	-15.00	0.44	33	-9.44	4.05	30	2.370	-1.40 [-2.03, -0.93]	2019	-
Laro Betal: 2013 4.01 1.2 40 43.01 1.13 40 2.4.01 41.04 (1.40, 40.01) 2013 Total (95% Cl) 1794 1788 100.0% -1.54 [-1.86, -1.22] -20 -10 0 10 20 Heterogeneity: Tau ² = 1.06; Chi ² = 755.81, df = 44 (P < 0.00001); P = 94%	laightetal. 2019	-4.61	1.2	40	-2.33	1 10	40	2.1%	-4.00 [-3.74, -3.03]	2019	-
Total (95% Cl) 1794 1788 100.0% -1.54 [-1.86, -1.22] Heterogeneity: Tau ² = 1.06; Chi ² = 755.81, df = 44 (P < 0.00001); l ² = 94% -1.54 [-1.86, -1.22] -20 -10 0 10 20 Experimental Control Experimental Control Std. Mean Difference Std. Mean Difference V. Random, 95% Cl V. Random, 95% Cl Study of Subgroup Mean SD Total Mean SD Total Veight V. Random, 95% Cl Vear V. Random, 95% Cl	Lai 5 et al. 2019	-4.01	1.2	40	-3.30	1.19	40	2.470	-1.04 [-1.40, -0.01]	2019	
b -20 -10 10 b Experimental Control Std. Mean Difference Study or Subgroup Mean SD Total Weight W, Random, 95% CI State 20 -20 -10 0 10 Control Std. Mean Difference Std. Mean Difference Study or Subgroup Mean SD Total Weight W, Random, 95% CI	Total (95% CI)			1794			1782	100 0%	1541.186 .1221		1
b Experimental Control Std. Mean Difference Std. Mean Difference Study or Subgroup Mean SD Total Mean SD Total <t< td=""><td>Hotorogonoity Tou2 - 4</td><td>06 Chiz</td><td>- 766 04</td><td>df = A</td><td>1 /P ~ 0</td><td>000041</td><td>12-04</td><td>06</td><td>- 1.54 [- 1.60, - 1.22]</td><td></td><td></td></t<>	Hotorogonoity Tou2 - 4	06 Chiz	- 766 04	df = A	1 /P ~ 0	000041	12-04	06	- 1.54 [- 1.60, - 1.22]		
b Experimental Control Std. Mean Difference Std. Mean Difference Study of Subgroup Mean SD Total Weight W. 0.86 (148) 0.441 0.010	Tect for overall effect: 7	- 0 46 /P	~ 0.000	01) 101	4 (F ~ U.	00001)	1 - 34				-20 -10 0 10 20
b Experimental Control Std. Mean Difference Std. Mean Difference Std. Mean Difference Study of Subgroup Mean SD Total Mean SD Total Weight V, Random, 95% CI Year V, Random, 95% CI Shore 7 of cl 20 20 6 20 20 20 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 <t< td=""><td>restion overall effect. Z</td><td> 3.40 (P</td><td>~ 0.000</td><td>01)</td><td></td><td></td><td></td><td></td><td></td><td></td><td>Experimental Control</td></t<>	restion overall effect. Z	3.40 (P	~ 0.000	01)							Experimental Control
b Experimental Control Std. Mean Difference Std. Mean Difference Std. Mean Difference Study or Subgroup Mean SD Total Mean SD Total Weight N. Random, 95% CI Year N. Random, 95% CI Storp 7 of al 2010 2 20 6 2 20 25% 0.665 (1418, 0.414) 2010 Total											
Study or Subgroup Mean SD Total Mean SD Total Weight NV, Random, 95% CI Year NV, Random, 95% CI	b	E.m.	orimort	al		Control			Std Maan Difference		Std Mean Difference
<u>Study of study out</u> mean <u>SU 10(a) Mean SU </u>	Study or Subgroup	Exp	erment	di	Macro	Jontrol	Total	Moint	Stu. Mean Difference	Vear	Std. Mean Difference
	Shang 7 at al. 2010	mean	<u>, 30</u>	20	mean	30	20	2 50	0.66 [1 10 .0 44]	2010	

Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year	IV, Random, 95% Cl
Sheng Z et al. 2010	-8	3	30	-6	3	30	3.5%	-0.66 [-1.18, -0.14]	2010	
Zhu J 2010	-30.92	18.21	44	-6.57	20.29	48	3.6%	-1.25 [-1.70, -0.80]	2010	
Liu J et al. 2010(a)	-3.02	6.74	20	0.65	7.25	20	3.2%	-0.51 [-1.14, 0.12]	2010	
Liu J et al. 2010(b)	-3.02	6.74	20	7.04	15.11	20	3.2%	-0.84 [-1.49, -0.19]	2010	
Meng X et al. 2011	-0.32	0.08	30	-0.27	0.06	30	3.5%	-0.70 [-1.22, -0.18]	2011	
Xiang W et al. 2011(a)	-0.53	0.17	20	-0.08	0.2	20	2.8%	-2.38 [-3.20, -1.55]	2011	
Xiang W et al. 2011(b)	-0.53	0.17	20	-0.52	0.19	20	3.2%	-0.05 [-0.67, 0.57]	2011	
Deng H et al. 2012	-1	0.94	31	-0.57	1.16	28	3.5%	-0.40 [-0.92, 0.11]	2012	
Liu Y et al. 2012	-10.42	9.07	50	-5.13	6.57	44	3.7%	-0.66 [-1.07, -0.24]	2012	
Li J et al. 2016	-1.94	2.57	31	-1.59	2.59	33	3.5%	-0.13 [-0.62, 0.36]	2016	-
Zhou Q et al. 2016	-0.44	0.23	30	-0.24	0.18	30	3.4%	-0.96 [-1.49, -0.42]	2016	
Dong K et al. 2017	-49.06	10.07	49	-42.31	12.09	49	3.7%	-0.60 [-1.01, -0.20]	2017	
Li J 2017	-5.37	4.91	40	-2.42	5.47	42	3.6%	-0.56 [-1.00, -0.12]	2017	
Sun S 2017	-20.59	3.28	91	-14.4	3.1	91	3.8%	-1.93 [-2.28, -1.58]	2017	
Chen X et al. 2017	-15.93	71.84	10	-3.98	39.96	10	2.7%	-0.20 [-1.08, 0.68]	2017	
Yuan F et al. 2017	-15.81	3.66	41	-11.48	3.73	41	3.6%	-1.16 [-1.63, -0.69]	2017	
Huang J et al. 2018	-4.13	4.58	65	-1.35	7.37	65	3.8%	-0.45 [-0.80, -0.10]	2018	
Li J et al. 2018	-14.42	3.98	53	-5.36	3.45	53	3.5%	-2.41 [-2.92, -1.91]	2018	
Du Y et al. 2018	-16.12	7.32	18	-4.02	6.85	12	2.7%	-1.65 [-2.51, -0.79]	2018	<u> </u>
Fan C et al. 2018	-48.56	16.56	40	-37.36	15.92	40	3.6%	-0.68 [-1.13, -0.23]	2018	
He T 2018	-30.9	18.36	52	-9.1	20.07	52	3.7%	-1.13 [-1.54, -0.71]	2018	-
He P et al. 2018	-149.68	22.86	62	-101	21.51	62	3.6%	-2.18 [-2.63, -1.73]	2018	
Yang R et al. 2019	-11.62	3.29	40	-6.54	2.91	30	3.4%	-1.60 [-2.15, -1.06]	2019	
Lan P et al. 2019(a)	-2.17	3.44	40	0.57	4.15	40	3.6%	-0.71 [-1.16, -0.26]	2019	
Cao C et al. 2019	-169.9	6.8	40	-144.7	7.5	40	3.1%	-3.49 [-4.19, -2.78]	2019	
Xie X et al. 2019	-30.81	11.85	53	-25.37	13.09	53	3.7%	-0.43 [-0.82, -0.05]	2019	
Lan P et al. 2019(b)	-2.23	3.25	40	0.57	4.15	40	3.6%	-0.74 [-1.20, -0.29]	2019	
Lai S et al. 2019	-13.04	6.8	48	-7.41	7.49	48	3.7%	-0.78 [-1.20, -0.37]	2019	-
Yang X et al. 2020	-57.1	10.58	96	-47.3	13	96	3.8%	-0.82 [-1.12, -0.53]	2020	-
Total (95% CI)			1204			1187	100.0%	-1.02 [-1.27, -0.77]		•
Heterogeneity: Tau ² = 0.	40; Chi ² =	220.00.	df = 28	(P < 0.0	00001);	2 = 879	6		-	
Test for overall effect: Z =	= 8.04 (P <	0.0000	11)							-4 -Z U Z 4
										Experimental Control

Fig. 3 Forest plots of the effect of berberine on a CRP, b TNF-a, c IL-6, and d IL-1β. CRP C-reactive protein, TNF-a tumor necrosis factoralpha, *IL-6* interleukin-6, *IL-1\beta* interleukin-1 beta

С	Expe	rimental		С	ontrol			Std. Mean Difference		Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	Year	IV, Random, 95% Cl
Zhang Y et al. 2008	-1.46	3.03	52	-1.06	4.79	58	3.9%	-0.10 [-0.47, 0.28]	2008	+
Liu J et al. 2010(a)	-5.03	6.33	20	-1.42	5.51	20	3.6%	-0.60 [-1.23, 0.04]	2010	
Sheng Z et al. 2010	-11	11	30	-4	3	30	3.7%	-0.86 [-1.39, -0.33]	2010	-
Liu J et al. 2010(b)	-5.03	6.33	20	-5.87	5.36	20	3.6%	0.14 [-0.48, 0.76]	2010	+
Xiang W et al. 2011(b)	-66.67	21.25	20	-63.06	24.07	20	3.6%	-0.16 [-0.78, 0.46]	2011	+
Xiang W et al. 2011(a)	-66.67	21.25	20	1.81	21.34	20	3.2%	-3.15 [-4.11, -2.20]	2011	
Meng X et al. 2011	-0.37	0.14	30	-0.12	0.14	30	3.6%	-1.76 [-2.36, -1.16]	2011	
Zhou Q et al. 2016	-79.77	19.47	30	-61.44	18.16	30	3.7%	-0.96 [-1.50, -0.42]	2016	+
Li J et al. 2016	-3.64	1.27	31	-2.19	3	33	3.8%	-0.61 [-1.12, -0.11]	2016	+
Wang Y 2016	4.03	0.19	25	14.29	1.34	25	1.6%	-10.55 [-12.78, -8.33]	2016	
Sun H 2016	-4.52	1.55	48	-3.2	1.54	48	3.8%	-0.85 [-1.27, -0.43]	2016	*
Dong K et al. 2017	-4.61	1.48	49	-1.22	1.52	49	3.8%	-2.24 [-2.75, -1.73]	2017	+
Li Y 2017	-8	2.2	60	-6.16	2.06	60	3.9%	-0.86 [-1.23, -0.48]	2017	-
Sun S 2017	-10.63	1.42	91	-6.87	1.43	91	3.9%	-2.63 [-3.03, -2.23]	2017	+
Li P 2017	-4.61	1.55	30	-3.13	1.61	30	3.7%	-0.92 [-1.46, -0.39]	2017	+
Li J 2017	-4.25	5.37	40	-3.19	6.38	42	3.8%	-0.18 [-0.61, 0.26]	2017	-
Ning M 2018	-8.54	1.07	39	-5.95	1.32	39	3.7%	-2.13 [-2.70, -1.57]	2018	+
Wang L et al. 2018	-8.92	1.83	10	-0.58	1.63	10	2.0%	-4.61 [-6.43, -2.79]	2018	
He P et al. 2018	-275.57	35.25	62	-237	37.52	62	3.9%	-1.05 [-1.43, -0.68]	2018	+
Fan C et al. 2018	-3.84	1.68	40	-1.26	1.68	40	3.8%	-1.52 [-2.02, -1.02]	2018	+
Du Y et al. 2018	0.28	0.49	18	-2.32	0.78	12	2.6%	4.08 [2.75, 5.40]	2018	
Lai S et al. 2019	-15.34	4.02	48	-12.35	4.11	48	3.9%	-0.73 [-1.14, -0.32]	2019	+
Lan P et al. 2019(b)	-4.27	5.11	40	0.14	5	40	3.8%	-0.86 [-1.32, -0.40]	2019	-
Xie X et al. 2019	-8.78	2.2	53	-7.65	2.38	53	3.9%	-0.49 [-0.88, -0.10]	2019	+
Lan P et al. 2019(a)	-3.11	5.81	40	0.14	5	40	3.8%	-0.59 [-1.04, -0.15]	2019	+
Cao C et al. 2019	-0.26	0.05	40	-0.19	0.05	40	3.8%	-1.39 [-1.88, -0.90]	2019	+
Ye X et al. 2019	-43.58	6.32	33	-37.93	6.25	33	3.8%	-0.89 [-1.40, -0.38]	2019	-
Yang X et al. 2020	-4.1	1.37	96	-1.2	1.51	96	3.9%	-2.00 [-2.35, -1.66]	2020	+
Total (95% CI)		,	1115			1119	100.0%	-1.17 [-1.53 -0.81]		•
Heterogeneity: Tau ² = (184: Chi² =	381 15 0	4f = 27	(P < 0.0	0001\-	I ² = 939	%			
Test for overall effect: 7	′=635/P≤	001010,0) }	(i · 0.0	00017,	,				-10 -5 0 5 10
	0.00 (i	0.00001	<i>′</i>							Experimental Control
d	-						~			041 11
Church and Carbon and	Experin	nental		Contr			Std.	Mean Difference		Std. Mean Difference
Study or Subgroup	mean	SU IOTA	ai Me	ean S	D IOta	ai we	eight N	V, Random, 95% CI Y	ear	IV, Random, 95% Cl
Sheng Z et al. 2010	-0.3 0	.42 3	0 -0	.29 0	.3 3	30 33	3.5%	-0.03 [-0.53, 0.48] 20	J10	
Li J et al. 2016	-5.76 1	.67 3	1 -2	.29 1.9	15 3	33 32	2.4%	-1.88 [-2.48, -1.29] 20	D16	
Li J 2017	-3.09 3	.07 4	0	-1 4.1	64	2 34	.2%	-0.56 [-1.01, -0.12] 20	017	
										I

Total (95% CI) 101 105 100.0% Heterogeneity: Tau² = 0.69; Chi² = 22.36, df = 2 (P < 0.0001); l² = 91% Test for overall effect: Z = 1.61 (P = 0.11)



2

Fig. 3 (continued)

Outcomes	Pre-sensitivit	y analyses		Upper and	Post-sensitivity ana	lyses	
	No. of stud- ies included	Pooled SMD (RE)	95% CI	lower of effect size	Pooled SMD (RE)	95% CI	Excluded studies
CRP	45	-1.54	- 1.86, - 1.22	Upper	- 1.39	- 1.69, - 1.09	Dai et al. (2015)
				Lower	-1.58	- 1.90, - 1.26	Zhu et al. (2015)
TNF-α	29	-1.02	-1.27, -0.77	Upper	-0.94	-1.17, -0.72	Cao and Su (2019)
				Lower	-1.05	-1.30, -0.80	Xiang et al. (2011), Li et al. (2016)
IL-6	28	-1.17	-1.53, -0.81	Upper	-1.02	-1.35, -0.69	Wang (2016)
				Lower	-1.29	-1.63, -0.95	Du and Zhang (2018)
IL-1β	3	-0.81	-1.80, 0.17	Upper	-0.31	-0.84, 0.22	Li et al. (2016)
				Lower	- 1.21	-2.50, 0.08	Sheng and Xie (2010)

 Table 2
 Sensitivity analyses of berberine's influence on inflammation

CRP C-reactive protein, TNF-a tumor necrosis factor-alpha, IL-6 interleukin-6, IL-1 interleukin -1 beta, SMD standardized mean differences, RE, random effect

The effects of berberine on inflammatory markers in Chinese patients with metabolic syndrome...

1073

Table 3 Subgroup analyses of	
the influence of berberine on	
CRP, TNF-α, and IL-6	

Variables	N	$I^{2}(\%)$	SMD (95% CI)	p value
CRP				
Total	45	94	-1.54[-1.86, -1.22]	< 0.00001
Dosage of berberine				
<0.9 g/d	14	96	-2.45[-3.23, -1.67]	< 0.00001
>0.9 g/d	31	92	-1.24 [-1.56, -0.93]	< 0.00001
Type of condition				
Metabolic syndrome	1		-2.44 [-3.03, -1.86]	< 0.00001
Type 2 diabetes	21	96	-2.38[-3.02, -1.75]	< 0.00001
Diabetic nephropathy	3	92	-1.03 [-1.75, -0.30]	< 0.00001
Cardiovascular disease	13	92	-1.20[-1.72, -0.67]	< 0.00001
Polycystic ovary syndrome	3	65	-0.65[-1.11, -0.20]	0.005
Other	4	89	-0.94 [-1.51, -0.37]	< 0.001
Duration of study			••••••	
< 3 months	25	93	-1.50[-1.88, -1.12]	< 0.00001
> 3 months	19	95	-1.72[-2.32, -1.12]	< 0.00001
Unclear	1	_	-0.96[-1.34, -0.58]	< 0.00001
Sample size	1		0.00[1.01, 0.00]	0.00001
< 30	10	93	-1.02[-1.86] - 0.18]	0.02
30-60	32	95	-1.71[-2.09] -1.34]	< 0.0001
> 60	3	83	-1.68[-2.21, -1.16]	< 0.00001
TNF-a	5	05	1.00 [2.21, 1.10]	< 0.00001
Total	20	87	-1.02 [-1.27 -0.77]	< 0.00001
Dosage of berberine	29	87	-1.02[-1.27, -0.77]	< 0.00001
	5	84	_174[_225 _122]	< 0.00001
> 0.9 g/d	24	80	-0.85[-1.08, -0.63]	< 0.00001
≥ 0.9 g/u	24	80	-0.05 [-1.06, -0.05]	< 0.00001
Metabolic syndrome	3	96	_1 42 [_3 38 0 55]	0.16
Type 2 diabetes	13	82	-0.89[-1.19, -0.58]	< 0.00001
Disbatic nonbronathy	2	82 78	-0.39[-1.19, -0.58]	0.00001
Cardiovascular disease	5	70 66	-0.95[-1.44, -0.41]	< 0.0004
Polycystic overy syndrome	2	10	-1.00[-1.39, -0.00]	0.00001
Other	2	04	-0.02 [-0.99, -0.20]	0.0008
Duration of study	5	94	-1.38 [-2.97, -0.18]	0.001
Substantial of study	10	01	1 16 [1 52 0 80]	< 0.00001
< 3 months	19	91	-1.10[-1.32, -0.60]	< 0.00001
≥5 months	10	10	-0.72 [-0.80, -0.57]	< 0.00001
	6	91		0.008
< 50	0	81	-0.92[-1.39, -0.24]	0.008
50-00 > 60	19	80 05	-0.96[-1.20, -0.70]	< 0.00001
>00 II (4	95	-1.34 [-2.12, -0.33]	0.0009
	20	02	1 17 5 1 52 0 011	-0.00001
Total	28	93	-1.17 [-1.55, -0.81]	< 0.00001
Dosage of berberine	4	07		.0.0001
< 0.9 g/d	4	97	-3.16[-4.73, -1.59]	< 0.0001
≥0.9 g/d	24	91	-0.95 [-1.29, -0.61]	< 0.00001
Type of condition	2			0.02
Nietabolic syndrome	3	93	-1.72[-3.19, -0.25]	0.02
Type 2 diabetes	15	94	-1.57 [-2.14 , -1.00]	< 0.00001
Diabetic nephropathy	1		-0.49 [-0.88, -0.10]	0.01
Cardiovascular disease	6	93	-0.42 [-1.24, 0.39]	0.31
Polycystic ovary syndrome	1		-0.73[-1.14, -0.32]	0.0005
Other	2	85	-0.87 [-1.29, -0.44]	0.0002

Table 3 (continued)

Variables	N	$I^{2}(\%)$	SMD (95% CI)	<i>p</i> value
Duration of study				
< 3 months	16	91	-1.36 [-1.78, -0.95]	< 0.00001
\geq 3 months	12	95	-0.91 [-1.57, -0.26]	0.006
Sample size				
< 30	7	97	-1.92 [-3.77, -0.06]	0.04
30-60	18	83	-0.98 [-1.24, -0.71]	< 0.00001
>60	3	94	-1.89 [-2.76, -1.02]	< 0.0001

N number of SMD included, *CRP* C-reactive protein, *TNF-\alpha* tumor necrosis factor alpha, *IL-6* interleukin-6, *SMD* standardized mean differences, *X* g/d X g daily, -- not applicable



Fig. 4 Funnel charts based on a CRP, b TNF-α, and c IL-6. CRP C-reactive protein, TNF-α tumor necrosis factor alpha, IL-6 interleukin-6

Conclusion

Despite the limitations of meta-analysis, the robust methodology followed in selecting RCTs for inclusion and in completing the evaluation does facilitate the conclusion that berberine use in patients with MetS and related disorders appears to have significantly decreased inflammatory markers, including CRP, TNF- α , and IL-6. This study provides new and useful evidence for supporting clinical medication decisions for MetS and related disorders and encourages undertaking further RCTs.

Funding This work was supported by the National Natural Science Foundation of China (Grant number 71673298).

Data availability All data generated or analyzed during this study are included in this published article.

Declarations

Conflict of interest The authors declare no conflict of interest.

Ethics approval Neither ethics approval nor participant consent was required as this study was based solely on the summary results of previously published articles. Individual patient data were not obtained or accessed.

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/.

References

- Akbari M, Ostadmohammadi V, Tabrizi R et al (2018) The effects of melatonin supplementation on inflammatory markers among patients with metabolic syndrome or related disorders: a systematic review and meta-analysis of randomized controlled trials. Inflammopharmacology 26:899–907
- Akbari M, Tamtaji OR, Lankarani KB et al (2019) The effects of resveratrol supplementation on endothelial function and blood pressures among patients with metabolic syndrome and related disorders: a systematic review and meta-analysis of randomized controlled trials. High Blood Press Cardiovasc 26:305–319
- Arnlöv J, Ingelsson E, Sundström J et al (2010) Impact of body mass index and the metabolic syndrome on the risk of cardiovascular disease and death in middle-aged men. Circulation 121:230–236
- Bai Z, Zhang D, Pu X (2018) Clinical study of ezetimibe combined with berberine capsules in the treatment of hyperlipidemia. Neural Inj Funct Reconstr 13:469–471 (in Chinese)
- Beba M, Djafarian K, Shab-Bidar S (2019) Effect of berberine on C-reactive protein: a systematic review and meta-analysis of randomized controlled trials. Complement Ther Med 46:81–86
- Cao C, Su M (2019) Effects of berberine on glucose-lipid metabolism, inflammatory cytokines and insulin resistance in patients with metabolic syndrome. Exp Ther Med 17:3009–3014
- Chen N, Chen X, Yang H et al (2015) Simvastatin combined berberine in patients with coronary artery disease and hypercholesteremia. Cent South Pharm 13:203–205 (in Chinese)
- Chen L, Lu W, Li Y (2016) Berberine ameliorates type 2 diabetes via modulation of Bifidobacterium species, tumor necrosis factor-α, and lipopolysaccharide. Int J Clin Exp Med 9(6):9365–9372
- Chen X, Fu T, Huang C et al (2017) Effect of berberine on expression of CHOP mRNA, GRP78mRNA and inflammatory cytokines in patients with metabolic syndrome and renal damage. J Nephrol Dial Transplant 26:333–338 (in Chinese)
- Dai P, Wang J, Lin L et al (2015) Renoprotective effects of berberine as adjuvant therapy for hypertensive patients with type 2 diabetes mellitus: evaluation via biochemical markers and color Doppler ultrasonography. Exp Ther Med 10:869–876

- Deng H, Wei W, Guan Y (2012) The clinical study of berberine in patients with polycystic ovarian syndrome and insulin resistance. Tianjin Med J 40:1009–1011 (in Chinese)
- Dong K, Shang J, Tao L (2017) Effect of berberine combined with metformin on serum inflammatory factors and islet function in type 2 diabetes mellitus. J Clin Pathol Res 37:1418–1422 (in Chinese)
- Dou J, Xing Y, Zhang R (2012) Effect of berberine on serum C-reactive protein in obese patients. Pract Pharm Clin Rem 15:147–148 (in Chinese)
- Du Y, Zhang J (2018) Effect of berberine hydrochloride on plasma LDLR level in patients with coronary heart disease and its correlation analysis. Pract Pharm Clin Rem 21:1244–1248 (in Chinese)
- Esser N, Paquot N, Scheen AJ (2015) Anti-inflammatory agents to treat or prevent type 2 diabetes, metabolic syndrome and cardiovascular disease. Expert Opin Investig Drugs 24:283–307
- Fan C, Li Y, Song H et al (2018) Effectiveness evaluation analysis on berberine tablets combination with metformin treating type 2 diabetes. Mod Hosp 18:731–733 (in Chinese)
- Festa A, D'Agostino R Jr, Howard G et al (2000) Chronic subclinical inflammation as part of the insulin resistance syndrome: the Insulin Resistance Atherosclerosis Study (IRAS). Circulation 102:42–47
- Grundy SM, Cleeman JI, Daniels SR et al (2006) Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute scientific statement. Curr Opin Cardiol 21:1–6
- Hamedifard Z, Milajerdi A, Reiner Ž et al (2019) The effects of spirulina on glycemic control and serum lipoproteins in patients with metabolic syndrome and related disorders: a systematic review and meta-analysis of randomized controlled trials. Phytother Res 33:2609–2621
- He T (2018) Clinical efficacy and safety of berberine combined with valsartan in the treatment of diabetic nephropathy. Pract Clin J Integr Tradit Chin West Med 18:8–10 (in Chinese)
- He P, Wang C, Liu S (2018) Effects of berberine therapy on serum triglyceride, total cholesterol and inflammatory cytokines in patients with diarrhea complicated by hyperlipidemia. Hebei Med J 40:2276–2283 (in Chinese)
- Higgins JPT, Thomas J, Chandler J et al (2020) Cochrane handbook for systematic reviews of interventions version 6.1. Cochrane. https:// www.training.cochrane.org/handbook. Accessed on 27 May 2020
- Hu Y, Ehli EA, Kittelsrud J et al (2012) Lipid-lowering effect of berberine in human subjects and rats. Phytomedicine 19:861–867
- Huang J, Hu W, Lin X (2018) The improving effect of berberine hydrochloride on insulin resistance in type 2 diabetes and its mechanism. Chin J Gerontol 38:4130–4132 (**in Chinese**)
- Jeong HW, Hsu KC, Lee JW et al (2009) Berberine suppresses proinflammatory responses through AMPK activation in macrophages. Am J Physiol Endocrinol Metab 296:E955-964
- Ju J, Li J, Lin Q et al (2018) Efficacy and safety of berberine for dyslipidaemias: a systematic review and meta-analysis of randomized clinical trials. Phytomedicine 50:25–34
- Lai S, Zhong Y, Liang J (2019) Effects of berberine combined with Peikun pill on lipid and glucose metabolism, inflammatory factors and hormone levels in patients with insulin resistance of polycystic ovary syndrome. World Chin Med 14:2683–2687 (in Chinese)
- Lan J, Zhao Y, Dong F et al (2015) Meta-analysis of the effect and safety of berberine in the treatment of type 2 diabetes mellitus, hyperlipemia and hypertension. J Ethnopharmacol 161:69–81
- Lan P, Zhong Y, Yang Y et al (2019) Effect of berberine on TNF-alpha and IL-6 in patients with hypertensive atherosclerosis. Mod Diagn Treat 30:1976–1978 (in Chinese)
- Lee HS, Herceg Z (2017) Chapter 30—nutritional epigenome and metabolic syndrome. In: Tollefsbol TO (ed) Handbook of epigenetics: the new molecular and medical genetics (2rd). Academic Press, US, pp 465–475

- Li J (2017a) A control study of efficacy and safety treated by berberine and metformin on metabolic syndrome in patients with schizophrenia. Tianjin Medical University (**in Chinese**)
- Li P (2017b) Effects of berberine combined with sitagliptin on blood glucose and inflammation indexes in obese patients with type 2 diabetes. Henan Med Res 26:903–904 (in Chinese)
- Li Y (2017c) The Effects of berberine on anti-inflammatory and antiatherosclerotic plaques in patients with acute cerebral ischemic stroke. Chengde Medical University (**in Chinese**)
- Li J, Deng Z (2018) Effect of compound berberine tablets combined with polyene phosphatidylcholine on elderly patients with nonalcoholic fatty liver. Chin J Gerontol 38:5224–5227 (in Chinese)
- Li Z, Geng YN, Jiang JD et al (2014) Antioxidant and anti-inflammatory activities of berberine in the treatment of diabetes mellitus. Evid Based Complement Alternat Med 2014:1–12
- Li J, Zhao Y, Liu Y et al (2016) The impact of berberine on insulin resistance and cytokines in patients with schizophrenia. Tianjin Med J 44:1143–1146 (in Chinese)
- Li Y, Lin Y, Wang X et al (2018a) Effects of berberine on blood glucose, blood lipids and insulin resistance in patients with polycystic ovary syndrome. Chron Pathematol J 19:125–126 (in Chinese)
- Li Z, Liu B, Zhuang X et al (2018b) Effects of berberine on the serum cystatin C levels and urine albumin/creatine ratio in patients with type 2 diabetes mellitus. Natl Med J China 98:3756–3761 (in Chinese)
- Liang Y, Xu X, Yin M et al (2019) Effects of berberine on blood glucose in patients with type 2 diabetes mellitus: a systematic literature review and a meta-analysis. Endocr J 66:51–63
- Liu H, Hu Q (2008) Effect of berberine on islet β-cell function in type 2 diabetes mellitus (Damp-Heat Type). Chin J Inf TCM 15:18–20 (**in Chinese**)
- Liu Y, Wang S (2012) Observation of the curative effect of berberine in treatment of ischemic heart disease and heart failure. Chin J Integr Med Cardio-Cerebrovasc Dis 10:519–520 (in Chinese)
- Liu J, Wang D, Lin Z et al (2010) Effects of berberine on serum TNF- α and IL-6 levels of type 2 diabetic patients. Zhejiang Med 32:207–209 (**in Chinese**)
- Lu H, Cui H, Yang X et al (2018) Effects of risuvastatin combined with berberine hydrochloride on the indicators of acute ischemic cerebral infarction patients. J Clin Exp Med 17:1729–1732 (in Chinese)
- Meng X, Zeng Y, Kong H et al (2011) Research on the effect of berberine on the function of endothelial vessels, IL-6 and TNF-a in newly diagnosed patients with type 2 diabetes mellitus. Chin J Prev Contr Chron Dis 19:504–505 (in Chinese)
- Ning M (2018) Clinical effects of berberine combined with atorvastatin in treatment of patients with acute cerebral infarction. Med J Chin People's Health 30:16–20 (in Chinese)
- Noda H, Iso H, Saito I et al (2009) The impact of the metabolic syndrome and its components on the incidence of ischemic heart disease and stroke: the Japan public health center-based study. Hypertens Res 32:289–298
- Page MJ, McKenzie JE, Bossuyt PM et al (2021) The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. Syst Rev 10:89
- Ranasinghe P, Mathangasinghe Y, Jayawardena R et al (2017) Prevalence and trends of metabolic syndrome among adults in the Asia-Pacific region: a systematic review. BMC Public Health 17:101
- Sheng Z, Xie D (2010) The level of inflammatory cytokines in patients with type 2 diabetes and the effect of adjuvant berberine treatment on it. New Med 41:177–180 (**in Chinese**)
- Shu J (2014) Effects of berberine on serum adiponectin and high-sensitivity C-reactive protein levels in type 2 diabetic patients. China Pharm 23:33–34 (**in Chinese**)

- Sun H (2016) Clinical observation of berberine hydrochloride combined with sitagliptin in treatment of diabesity type 2 diabetes mellitus. Drugs Clin 31:1020–1023 (**in Chinese**)
- Sun S (2017) Effect of berberine on the serum levels of IL-10, IL-6 and CRP in patients with type 2 diabetes mellitus. Journal of Changchun University of Chinese Medicine 33:431–433 ((In Chinese))
- Tabrizi R, Tamtaji OR, Lankarani KB et al (2018) The effects of resveratrol supplementation on biomarkers of inflammation and oxidative stress among patients with metabolic syndrome and related disorders: a systematic review and meta-analysis of randomized controlled trials. Food Funct 9:6116–6128
- Tabrizi R, Tamtaji OR, Mirhosseini N et al (2019) The effects of statin use on inflammatory markers among patients with metabolic syndrome and related disorders: a systematic review and meta-analysis of randomized controlled trials. Pharmacol Res 141:85–103
- Wan Q, Cui X, Jia Y et al (2014) Berberine reduce TNF- α and IL-6 secreted in HUVEC induced by visfatin through ERK1/2 signal pathway. Chin J Exp Tradit Med Formulae 20:125–129 (in Chinese)
- Wang Y (2016) Berberine blood lipids in patients with type 2 diabetes mellitus and the effect of insulin resistance and mechanism research. Diabetes New World 19:27–28 (**in Chinese**)
- Wang L, Huang C, Chen X et al (2018) Effects of berberine on intestinal bifidobacterium and inflammatory factors in metabolic syndrome patients with renal damage. Nephrol Dialy Transplant 27:440–444 (in Chinese)
- Wisse BE (2004) The inflammatory syndrome: the role of adipose tissue cytokines in metabolic disorders linked to obesity. J Am Soc Nephrol 15:2792–2800
- Xiang W, Huang X, Huang G (2011) A study of two anti-inflammatory drugs in the treatment of newly diagnosed type 2 diabetes patients. J Pract Diabetol 7:51–52 (in Chinese)
- Xie X, Huang G (2019) Clinical effect of *Tripterygium wilfordii* polyglycosides combined with berberine on early diabetic patients with early diabetic nephropathy. Med Innov China 16:38–41 (**in Chinese**)
- Xu F, Yu F, Li Q et al (2008) Observation of berberine plus pioglitazone in the treatment of early diabetic nephropathy and the level of adiponectin. Chongqing Med 37:2102–2103 (**in Chinese**)
- Yang R, Yin J (2019) Effects of berberine combined with rosuvastatin calcium on blood lipids, serum inflammatory cytokines and endothelial function in patients with coronary heart disease. J Mod Med Health 35:431–433 (in Chinese)
- Yang J, Luo M, Liu C et al (2012) Effect of berberine on C-reactive protein in rats with diabetic nephropathy. Sichuan J Physiol Sci 34:51–53 (in Chinese)
- Yang Z, Deng X, Wang D (2018) Clinical study of the effect of berberine combined with simvastatin on Lp-PLA2 in patients with symptomatic atherosclerotic intracranial artery stenosis. China Med Pharm 8:83–85 (**in Chinese**)
- Yang X, Liu Z, Yang H (2020) Clinical study on berberine hydrochloride tablets combined with metformin in the treatment of primary type 2 diabetes. SH J TCM 54:59–62 (in Chinese)
- Ye X, You L (2019) Analysis of clinical efficacy of berberine hydrochloride combined with rosuvastatin calcium in the treatment of 33 patients with acute ischemic cerebral infarction. Heilongjiang Med Pharm 42:148–149 (in Chinese)
- Yu F, Xu F, Li Q et al (2012) Effects of exenatide combinated with berberine therapy on early phase insulin secretion in the patients with new onset type 2 diabetes mellitus. Chin J Clin Ration Drug Use 5:32–33 (**in Chinese**)
- Yuan F, Fang L, Dong G (2017) Effect of Gegenqinlian decoction combined with berberine in the treatment of biguanides resistant type 2 diabetes in elderly patients in glycosylated hemoglobin

and homocysteine. Chin J Biochem Pharm 37:55-58 (in Chinese)

- Zhan H, Chen H, Lin C et al (2015) Effects of berberine on T2DM and high lipid serum NO level in patients with hyperlipidemia and the activity of SOD. J North Pharm 12:119–121 (**in Chinese**)
- Zhang Y, Li X, Zou D et al (2008) Treatment of type 2 diabetes and dyslipidemia with the natural plant alkaloid berberine. J Clin Endocrinol Metab 93:2559–2565
- Zhang H, Xiao J, Zhang H et al (2010) Effect of berberine on high sensitivity C-reactive protein and homocysteine in patients with acute coronary syndromes. Chin J Esthetic Med 19:156–157 (**in Chinese**)
- Zhang Y, Hu X, Zhou Y et al (2014) A study of berberine combined with atorvastatin in treatment of patients with cerebral infarction. Pract J Clin Med 11:80–83 (**in Chinese**)
- Zhou Y, Huang S (2011) Clinical observation on 60 cases of hyperlipemia treated by berberine. Chin J Clin Ration Drug Use 4:76– 77 (**in Chinese**)
- Zhou Q, Huang S (2012) Clinical study of berberine combined with metformin in the treatment of obese type 2 diabetes. J Pract Diabetol 8:33–35 (in Chinese)

- Zhou Q, Huang S, Yang X (2016) The effect of comprehensive treatment on inflammatory cytokines in newly diagnosed obesity type 2 diabetes. J Pract Diabetol 12:42–43 (**in Chinese**)
- Zhu J (2010) Effects of berberine hydrochloride combined with irbesartan on middle-aged and elderly patients with early diabetic nephropathy. Clin Educ Gen Pract 8:512–515 (in Chinese)
- Zhu F, Chen L, Zhu J (2015) Influence of berberine combining with atorvastatin on serum high-sensitivity C-reactive protein and adipocyte fatty acid-binding protein in patients with acute ischemic stroke. Chin J Contemp Neurol Neurosurg 15:43–47 (in Chinese)

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.