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Review

Meta-analysis of the effect and safety of berberine in the treatment of type 2 diabetes mellitus, hyperlipemia and hypertension

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ABSTRACT

Ethnopharmacological relevance: Berberine, extracted from Coptis Root and Phellodendron Chinese, has been frequently used for the adjuvant treatment of type 2 diabetes mellitus, hyperlipidemia, and hypertension in China. Safety and efficacy studies in terms of evidence-based medical practice have become more prevalent in application to Chinese Herbal Medicine. It is necessary to assess the efficacy and safety of berberine in the treatment of type 2 diabetes mellitus, hyperlipidemia and hypertension by conducting a systematic review and meta-analysis of available clinical data.

Materials and methods: We searched the English databases PubMed, ScienceDirect, Cochrane library, EMbase, etc., and Chinese databases including China biomedical literature database (CBM), Chinese Technology Journal Full-text Database, Chinese journal full text database (CNKI), and Wanfang digital periodical full text database. Relevant studies were selected based on the inclusion and exclusion criteria. Meta-analysis was performed with RevMan5.0 software after data extraction and the quality of studies assessment.

Results: Twenty-seven randomized controlled clinical trials were included with 2569 patients. There are seven subgroups in our meta-analysis: berberine versus placebo or berberine with intensive lifestyle intervention versus intensive lifestyle intervention alone; berberine combined with oral hypoglycemic versus hypoglycemic alone; berberine versus oral hypoglycemic; berberine combined with oral lipid lowering drugs versus lipid lowering drugs alone; berberine versus oral lipid lowering drugs; berberine combined with oral hypotensor versus hypotensive medications; berberine versus oral hypotensive medications. In the treatment of type 2 diabetes mellitus, we found that berberine with lifestyle intervention tended to lower the level of FPG, PPG and HbA_{1c} than lifestyle intervention alone or placebo; the same as berberine combined with oral hypoglycaemics to the same hypoglycaemics; but there was no statistical significance between berberine and oral hypoglycaemics. As for the treatment of hyperlipidemia, berberine with lifestyle intervention was better than lifestyle intervention, berberine with oral lipid lowering drugs was better than lipid lowering drugs alone in reducing the level of TC and LDL-C, and raising the level of HDL-C. In the comparative study between berberine and oral lipid lowering drugs, there was no statistical significance in reducing the level of TC and LDL-C, but berberine shows better effect in lowering the level of TG and raising the level of HDL-C. In the treatment of hypertension, berberine with lifestyle intervention tended to lower the level of blood pressure more than the lifestyle intervention alone or placebo did; The same occurred when berberine combined with oral hypotensor was compared to the same hypotensor. Notably, no serious adverse reaction was reported in

Abbreviations: CBM, China biomedical literature database; CNKI, Chinese journal full text database; RCT, randomized controlled trials; IDF, International Diabetes Federation; WHO, World Health Organization; ITT, intention-to-treat; FPG, fasting blood glucose; PPG, postprandial plama glucose; HbA_{1c}, glycosylated hemoglobin; TC, total cholesterol; TG, triglyceride; LDL-C, low density lipoprotein-cholesterol; HDL-C, high density lipoprotein-cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure; RR, risk ratio; MD, mean difference; 95% CI, 95% confidence interval

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the 27 experiments.
Conclusion: This study indicates that berberine has comparable therapeutic effect on type 2 DM, hyperlipidemia and hypertension with no serious side effect. Considering the relatively low cost compared with other first-line medicine and treatment, berberine might be a good alternative for low socioeconomic status patients to treat type 2 DM, hyperlipidemia, hypertension over long time period. Due to overall limited quality of the included studies, the therapeutic benefit of berberine can be substantiated to a limited degree. Better methodological quality, large controlled trials using standardized preparation are expected to further quantify the therapeutic effect of berberine.

Contents

1. Introduction

Diabetes, hyperlipidemia and hypertension are the clinical syndromes caused by the compounding genetic and environmental factors. They are common diseases, frequently occurring on a global scale. According to the International Diabetes Federation (IDF) statistics: the number of diabetes patients worldwide in 2011 has reached 366million, an increase of nearly 30% compared with 285million in 2010 (Ge and Xu, 2013). Type 2 diabetes accounts for the type of diabetes in the vast majority of patients with diabetes (95%). One of the significant features of diabetes mellitus is a malfunctioning of lipid metabolism, which results in hyperlipidemia. Hypertension can be an independent disease or occur with diabetes and hyperlipidemia, another survey by an online medical literature analysis and retrieval system calculates the morbidity, awareness rate, treatment rate, and control rate of hypertension in different regions of world between January1980 and July 2003 (Kearney et al., 2004). The results show dissimilarity in the rate of prevalence of hypertension in different parts of the world, but overall, hypertension prevalence is increasing worldwide (Kearney et al., 2005). Currently, many new varieties of oral hypoglycemic, lipid-lowering drugs and hypotensor have been developed, and have been enlisted as treatment options, but the expensive price places a heavier burden on patients' financial needs. In addition, side effects occurring during the treatment might need to be reviewed to make sure the safety of berberine is evidence based.

At the beginning of the 20th century, berberine (molecular formula, $C_{20}H_{19}NO_5$; molecular weight, 353.36) was extracted from traditional Chinese medicine – Coptis Root (Chinese name, huáng lián) and Phellodendron Chinese (Chinese name, huáng bǎi) by Japanese and German scholars. The brand name is called Compound Berberine Tablets (fù fāng huáng lián sù piàn) (Zhang and Ji, 1999). Dozens of other plants such as Mountain Dragon (Chinese name, gǔ shān lóng), barberry root (Chinese name, sān kē zhēn), and Chinese Mahonia Stem (Chinese name, gōng láo mù) also contain berberine (Ren and Gao, 2009). The plants above are indigenous herbs that have grown in China for thousands of years. The purification of berberine has made this new tablet increasingly prevalent in clinical usage. The main component of this tablet is berberine hydrochloride, and the adjuvant materials are starch, hydroxypropyl cellulose, silica, magnesium stearate, dextrin, sucrose, and talc powder. The purity of berberine varies between plants (Lei, 2010).

Recent studies show that berberine has the clinical effect of controlling arrhythmia, lowering blood lipid, lowering blood pressure and reducing blood sugar. It also effectively promotes regeneration in Islet cells and contributes to recovery of islet function (Zhang, 2006). In terms of traditional Chinese medicine, berberine has the clinical effect of clearing "heat", purging "fire" and removing "dampness". As a traditional, cheap medicine, it is extensively used in the diseases of the digestive system. It is also widely used in the treatment of diabetes, hyperlipidemia and hypertension. Animal experiments have proved that berberine is able to inhibit hepatic gluconeogenesis in order to improve fasting blood sugar levels in diabetic mice without dependence on insulin levels (Xia et al., 2011). It regulates blood lipid through multiple mechanisms: increasing the expression of low density lipoprotein receptors to activate adenosine monophosphates and inhibit lipid synthesis; improving lipoprotein lipase activity; inhibiting the expression of peroxisome proliferator activated by receptor γ to retrain adipocyte differentiation; and reducing the serum free fatty acid (He et al., 2004). Moreover, according to reports in the literature, traditional Chinese medicine berberine has the effect of lowering blood pressure. Its mechanism is the enhancement of acetylcholine and peripheral vasodilatation by anti-cholinesterase (Jiangsu New Medical College, 1997).

Currently, large numbers of medical studies had been done on the treatment of berberine in diabetes, hyperlipidemia and hypertension by clinical scientists. The unique therapeutic effects and decreased side effects of berberine are well presented. But no one has done a systematic evaluation for it. This research uses the Cochrane system evaluation method and evaluates the efficacy and safety of berberine in treating type 2 diabetes, hyperlipidemia and hypertension in several randomized controlled trials. This can provide a critical reference for clinical decision making.

2. Materials and methods

2.1. Object and standard

2.1.1. Inclusion and exclusion criteria

Studies were included if they fulfilled the following criteria: Design of parallel RCT of berberine in treatment of diabetes, hyperlipidemia and hypertension, whether allocation concealment and blinding was used or not; Literature is either Chinese or English literature.

Studies were excluded if: course of treatment lasted less than one week or curative effects could not be judged because of incomplete information. Other specific types of diabetes include gestational diabetes mellitus; Secondary hyperlipidemia; Secondary hypertension. The control group of non oral hypoglycemic drugs, oral hypotensor; Repeated literatures.

2.1.2. Object of study

Type 2 diabetes, hyperlipidemia and hypertension patients, diagnostic criteria: Diagnosis of Diabetes and hypertension was based on WHO formulation and hyperlipidemia was confirmed with diagnostic criteria in "Chinese adult dyslipidemia Prevention Guide" (China Adult Dyslipidemia Prevention Guidelines for Joint Committee, 2007). Patients with serious cardiovascular and cerebrovascular disease were excluded. Patients with obvious abnormality of liver and kidney function were excluded; Patients with severe adverse reactions to drug intervention were excluded; Patients associated with other diseases that may affect blood glucose, blood lipid, blood pressure and other indicators were excluded.

2.1.3. Intervention measures

Berberine group (test group) versus placebo group, lifestyle intervention group or hypoglycemic, lipid-lowering, blood pressure medicine group (control group). Berberine group combined with hypoglycemic, lipid-lowering, blood pressure medicine group (test group) versus hypoglycemic, lipid-lowering, blood pressure medicine group (control group).

2.1.4. Outcome indicators

Fasting plasma glucose (FPG), 2 h postprandial plasma glucose (FPG), glycated hemoglobin (HbA_{1c}), total cholesterol (TC), triglyceride (TG), low density lipoprotein (LDL-C), high density lipoprotein (HDL-C) systolic blood pressure (SBP), diastolic blood pressure (DBP), adverse reaction.

2.2. Search strategy

We searched PubMed, ScienceDirect, Cochrane library, EMbase and so on. With regard to Chinese databases, China biomedical literature database(CBM), Chinese Technology Journal Full-text Database, Chinese journal full text database (CNKI) and Wanfang digital periodical full text database were searched. The retrieval time is from the establishment of the database to April 2011. Terms used in search are "Berberine", "Huangliansu", "Diabetes", "Hypertension" and "Hyperlipemia". The animal experiments are excluded.

2.3. Literature selecting and data extraction

Literature selecting: read the article title and abstract, eliminated the studies not meeting the inclusion/exclusion criteria. For those that were more ambiguous, full text was accessed and then a choice was made; Data extraction: general data includes published information, patient information, test drug information, the quality information, the index and data of result etc. Literature selecting and data extraction processes were independent, then the results were cross-checked.

2.4. Quality assessment and statistical methods

We used the Jadad Score for randomized controlled studies. The Jadad Score, a well validated and widely used scale, evaluates the quality of reports with a numerical coring system from 0 to 7, 1–3 points is considered low quality, 4–7 points is regarded as a high quality. (Jadad et al., 1996). The quality appraisal of literature includes: stochastic methods, hidden distribution, blind method, quit or lost.

We carried out quantitative and qualitative analyses to corrected data. RevMan5.0 software was downloaded from Cochrane collaboration and used for meta-analysis. Analyzed the clinical and methodological heterogeneity of the included studies, used χ^2 test and I^2 test to judge statistical heterogeneity. When $P > 0.1$, $I^2 < 50\%$, and each study did not show significant heterogeneity, we used the fixed effect model. When $P \leq 0.1$, $I^2 \geq 50\%$, and each study showed significant heterogeneity, we made the subgroup analysis (according to the possible factors of heterogeneity) or sensitivity analysis. If the heterogeneity still existed and data based on the clinical significance view could be merged, we used the random effect model and explain the results cautiously. Categorical variables used the risk ratio (RR) as analysis statistics. Continuous variables used the mean difference (MD) as analysis statistics. 95% confidence interval (95% CI) will be used as effective size for the combined analysis. Hypothesis testing was carried out with u test, which was represented by Z and P. When $P \leq 0.05$, it indicated that there was a significant difference between the two groups. Interval estimation and hypothesis test results were shown in the forest plot.

Table 1
The characteristics of the included studies.

Included trials	Sample size	Testing scheme	Intervention measures (Test group/control group) (1/2/3)			Duration (days)	Outcomes	Jadad scores
Trials of berberine in the treatment of type 2 diabetes mellitus (17 trials)								
Yin et al. (2008)	15/16	RAN	BER, LI		METF, LI	91	ABCDEFGI	5
Gu et al. (2010)	30/30	CEN	BER		PLACEBO	90	ABCDEFGH	5
Zhang et al. (2008)	58/52	CEN	BER, LI		PLACEBO, LI	84	ABCDEFGHI	5
Cao et al. (2012)	38/40	RAN	BER, METF		METF	112	ABCDEFGI	3
Ding et al. (1996)	21/22	UNKN	BER		PHE	60	ABI	2
Liu and Hu (2008)	30/30	NUM	BER, MET, LI		METF, LI	56	ABC	4
Ning et al. (2013)	22/22	BLI	BER, METF, LI		METF, LI	112	ACDEI	4
Ren (2008)	31/30	RAN	BER, LI		LI	84	ABCDEFGI	3
Sheng and Xie (2010)	30/30	RAN	BER, GLIP, METF		GLIP, METF	90	AI	3
Ye (2009)	40/40	RAN	BER, GLIM, MET		GLIM, MET	90	ABCDEFGI	3
Zhang et al. (2011)	30/30	RAN	BER, LI		ROS, LI	90	ACDEF	3
Zhang et al. (2010)	50/26/21	RAN	BER	METF	ROS	60	ACDI	4
Cao (2007)	30/30/30	RAN	LI	METF, LI	BER, LI	90	ABCDEFGI	3
Jin (2014)	40/40/40	RAN	METF	BER	NAT	UNKN	DEFGHI	2
Li and Liu (2007)	50/51/51	RAN	GLIP	BER	GLIP, BER	60	ABCDEFGI	3
Xiang et al. (2011)	20/20/20	RAN	LI	ASP, LI	BER, LI	84	ABCDEFI	3
Zhu et al. (2008)	55/55/50	RAN	BER, LI	BER, MET, LI	METF, LI	90	ABCI	3
Trials of berberine in the treatment of hyperlipidemia (six trials)								
Su et al. (2012)	60/60	RAN	BER, SIM		SIM	56	DEFGI	2
Yu et al. (2007)	50/50	RAN	BER, SIM		SIM	84	DEFI	3
Zhou and Huang (2011)	60/60	RAN	BER, LI		LI	120	DEFG	3
He et al. (2007)	38/38/40	RAN	SIM	BER	SIM, BER	90	DEFGI	3
Wei et al. (2003)	34/16/18	UNKN	BER	SIM	ATO	60	DEFG	2
Zheng et al. (2009)	33/33/33	RAN	SIM	BER	BER, SIM	56	DEFGI	3
Trials of berberine in the treatment of hypertension (four trials)								
Huang (2013)	84/80	NUM	BER, AML		AML	56	DEFGH	4
Sun et al. (2013)	32/32	RAN	BER, AML		AML	56	DEFGH	3
Zhong et al. (1997)	96/96	UNKN	BER		NIT	28	HI	2
Han et al. (1999)	55/50/55	RAN	BER	METO	METO	28	HI	3

Note – BER: berberine; LI: lifestyle intervention; UNKN: unknown; METF: Metformin; ROS: rosiglitazone; SIM: simvastatin; GLIP: glipizide; AML: amlodipine; PHE: phenformin; NIT: nitrendipine; GLIM: glimepiride; NUM: the method of random number; CEN: center randomized double blind; BLI: randomized controlled double blind principle; ASP: aspilin; METO: metoprolol; SIM: simvastatin; ATO: atorvastatin; NAT: nateglinide; A: FPG; B: PPG; C: HbA_{1c}; D: TC; E: TG; F: LDL-C; G: HDL-C; H: BP; I: adverse reactions.

3. Result

3.1. Description of studies

3.1.1. The general characteristics of included studies

After serial selection and evaluation, finally, 27 articles were included in this study, as presented in Table 1. Four articles (Yin et al., 2008; Zhang et al., 2008, 2010; Gu et al., 2010) were published in English and the remaining 23 studies were published in Chinese. A total of 2569 patients met the inclusion criteria and entered the study. The trials (Cao, 2007; Ren, 2008) are graduate theses, the others are journal articles; The 17 articles of berberine research in the treatment of type 2 diabetes mellitus (containing 1366 patients with diabetes). In the study of the treatment of diabetes, 11 trials adopted a two-armed parallel group design and six trials adopted a three-armed group design. Among six articles about hyperlipemia containing 623 patients with hyperlipidemia, three trials adopted a two-armed parallel group design and three trials adopted a three-armed group design. Among four articles about hypertension containing 580 hypertensive patients, three trials adopted a two-armed parallel group design and one trial adopted a three-armed group design. In the 17 trials about the treatment of type 2 diabetes mellitus, there are four trials (Ding et al., 1996; Liu and Hu, 2008; Zhu et al., 2008; Sheng and Xie, 2010) monitored the blood glucose and adverse reaction. The other 13 trials also had monitored cholesterol or blood pressure. In view of the complexity of clinical trial, some patients with diabetes may have both hyperlipidemia and hypertension, but there were not a specific number stated in the vast majority of the literature. In the six hyperlipidemia trials, only blood lipid and adverse reaction were monitored. In four hypertension trials, only blood lipid and adverse reaction were monitored. The duration of interventions in the diabetes trials was different, ranging from 56 days to 112 days, 56 days to 120 days in hyperlipidemia trials and 28 days to 56 days in hypertension trials. The trials (He et al., 2007; Li and Liu, 2007) tested relevant indices in three period, in order to reduce the difference of course of treatment. For data from the trial (Li and Liu, 2007), we chose the index in 60 days. For data from the trial (He et al., 2007), we chose 90 days. The basic information of the literature is shown in Table 1.

3.1.2. Test group and control group

In these 27 trials, there is no obvious difference between the number of most parallel groups, except two trials. In one trial (Zhang et al., 2010), the numbers of three parallel groups were 50, 26 and 21, in another trial (Wei et al., 2003), the numbers of three parallel groups were 34, 16 and 18. The large gap of the number can cause heterogeneity in meta-analysis. We divided them into the subgroup to overcome this gap problem. If the data from the clinical significance view can be merged, we used the random effect model.

The dose of berberine used in the included trials was different. Berberine intake was generally in a range between 0.6 g (Jin, 2014) and 2.7 g (Li and Liu, 2007) per day. There were eight trials (Zhong et al., 1997; Cao, 2007; Yu et al., 2007; Ren, 2008; Zhou and Huang, 2011; Su et al., 2012; Huang, 2013; Sun et al., 2013) used 0.9 g per day eight trials (Wei et al., 2003; He et al., 2007; Yin et al., 2008; Zhu et al., 2008; Ye, 2009; Sheng and Xie, 2010; Cao et al., 2012;

Ning et al., 2013) used 1.5 g per day, three trials (Zhang et al., 2008, 2010; Gu et al., 2010) used 1.0 g per day, two trials (Ding et al., 1996; Liu and Hu, 2008) used 0.9–1.5 g per day, two trials (Zheng et al., 2009; Xiang et al., 2011) used 1.2 g per day, the trial (Han et al., 1999) used 1.2–1.8 g per day and the trial (Zhang et al., 2011) with the dose of berberine 0.02 g per kg.

The category of drug in the control group is extensive, there is metformin, phenformin, glipizide, rosiglitazone etc. as a hypoglycemic western drug; simvastatin and atorvastatin as lipid-lowering drug and nitrendipine, amlodipine and metoprolol as hypotensor. The dose in the test group and control group is the same, for example, in the trial (Cao et al., 2012), the dose of metformin in test group is 1.5 g and the same in the control group. In the trial (Han et al., 1999), both of the control groups used Metoprolol, but the dose was different, the dose of metoprolol in group 2 was 100–200 mg per day and 50–100 mg per day in group 3. Both the trials (Zhang et al., 2008; Gu et al., 2010) used placebo which were not described in detail.

In these 27 trials, some studies randomized participants to receive berberine with a co-intervention of lifestyle intervention versus a control of lifestyle intervention alone and/or plus placebo. Some trials compared berberine with one kind of oral western medicine. Some trials compared a co-intervention of berberine and one or two types of oral western medicine with control of the same drugs. The design of these trials is different and this is the basis of subgroup classification.

The trials (Han et al., 1999; Zhang et al., 2010; Jin, 2014) contained two control groups, so we divided them into two groups. They are Han et al. (1999) – A and B, Zhang et al. (2010) – A and B, Jin (2014) – A and B.

3.1.3. Quality of studies

In the included 27 articles, the methodological quality of most trials in this meta-analysis was low. The trials (Zhang et al., 2008; Gu et al., 2010) used center randomized double blind, the trials (Liu and Hu, 2008; Huang, 2013) used the method of random number tables, the trial (Ning et al., 2013) used the randomized double blind principle, the trials (Zhong et al., 1997; Wei et al., 2003) did not clearly define the test scheme, the rest of the studies only mentioned randomized controlled. All studies are unclear in allocation concealment. The trials (Zhang et al., 2008) have lost participants, and used intention-to-treat (ITT)analysis, the rest experience had not lost participant. In the Jadad scale, 15 studies got 3 points and five studies got 2 points (low quality), three studies got 5 points and four studies got 4 points (high quality) as shown in Table 1.

3.2. Intervention measures

The 27 included trials differed in the type of the disease and treatment measures, therefore, subgroup analyses were performed on intervention type of the treatment group, which is shown in Table 1. specific forms in different subgroup lied in the following:

(1) Berberine versus placebo or berberine with intensive lifestyle intervention versus intensive lifestyle intervention. The aim is to understand if the effect of berberine treatment is superior to that of the placebo or intensive lifestyle intervention.
(2) Berberine combined with oral hypoglycaemics versus the same hypoglycaemics alone. The aim is to understand if the basic hypoglycemic western medicine plus berberine is better than single western medicine.
(3) Berberine versus oral hypoglycaemics. Aim to understand if the effect of berberine therapy in patients with type 2 diabetes is superior to hypoglycemic western medicine.
(4) Berberine combined with oral lipid lowering drugs versus the same lipid lowering drugs. The aim is to understand if the basis of lipid-lowering western medicine plus berberine is better than western medicine alone.
(5) Berberine versus oral lipid lowering drugs. The aim is to understand if the berberine in treatment of hyperlipidemia is superior to lipid-lowering western medicine.
(6) Berberine combined with oral hypotensor versus the same hypotensor. The aim is to understand if oral hypotensor plus berberine is superior to oral hypotensor.
(7) Berberine versus oral hypotensor. The aim is to understand whether berberine treatment in patients with hypertension is superior to hypotensor medicine.

3.3. Outcome indicators

3.3.1. Berberine with lifestyle intervention versus lifestyle intervention alone or berberine versus placebo

3.3.1.1. Effect on blood glucose and glycosylated hemoglobin. As shown in Fig. 1, five trials (Cao, 2007; Ren, 2008; Zhang et al., 2008; Gu et al., 2010; Xiang et al., 2011) were used for comparing with the effect of berberine group with control group on the blood glucose and glycosylated hemoglobin. Berberine group contained 169 patients and control group 162 patients. No significant heterogeneity was shown between the results (FPG: $I^2=35\%$, $P=0.19$; PPG: $I^2=0\%$, $P=0.45$; HbA_{1c}: $I^2=19\%$, $P=0.3$), so we use the fixed effect model for meta-analysis. The results showed that berberine group was more effective in reducing blood glucose and glycated hemoglobin levels than the control group [FPG: MD$=-0.86$ mmol/L, 95% CI (-1.14, -0.57), $P<0.00001$; PPG: MD$=-1.91$ mmol/L, 95% CI (-2.45, -1.36), $P<0.00001$; HbA_{1c}: -0.71%, 95% CI (-0.94, -0.49), $P<0.00001$].

3.3.1.2. Effect on blood lipids (TC, TG, LDL-C, HDL-C). Six trials (Cao, 2007; Zhang et al., 2008; Ren, 2008; Gu et al., 2010; Xiang et al., 2011; Zhou and Huang, 2011) were used to compare the effect of berberine group with control group on blood lipids. The berberine group contained 229 patients and the control group 222 patients. The trial (Xiang et al., 2011) did not compare the effects on the level of HDL-C. For the study on TC and TG, the results have statistical heterogeneity (TC: $I^2=83\%$, $P<0.0001$; TG: $I^2=60\%$, $P=0.03$). Each study demonstrated clinical homogeneity (divided into the subgroups with patient's age, sex, course of treatment being similar at baseline between the two groups), therefore, a random effects model was used for meta-analysis. No statistical heterogeneity was shown in research results of LDL-C and HDL-C (LDL-C: $I^2=38\%$, $P=0.15$; HDL-C: $I^2=0\%$, $P=0.97$), so we used the fixed effect model for meta-analysis. Through the comparative study of berberine and lifestyle intervention or placebo, the results indicated that the berberine group can more effectively reduce blood lipid level than the control group [TC: MD$=-0.66$ mmol/L, 95% CI (-1.02, -0.31), $P=0.0002$; TG: MD$=-0.39$ mmol/L, 95% CI (-0.59, -0.19), $P=0.0001$; LDL-C: -0.65 mmol/L, 95% CI (-0.75, -0.56), $P<0.00001$; HDL-C: 0.07 mmol/L, 95% CI (0.04, 0.1), $P<0.00001$] as shown in Fig. 1.

3.3.1.3. Effect on blood pressure (SBP, DBP). Three trials (Zhang et al., 2008; Gu et al., 2010; Jin, 2014) were used in comparing the effect of the berberine group and the control group on blood pressure. The trial (Jin, 2014) adopted two blank control groups; it actually has four comparative research components as shown in Fig. 1. The berberine group contained 168 patients and the control group contained 162 patients. No significant heterogeneity was shown among the results of research, (SBP: $I^2=0\%$, $P=0.92$; DBP: $I^2=0\%$, $P=0.88$), so we used the fixed effect model for meta-analysis. The results showed that berberine group can be more effective in reducing blood pressure than the control group [SBP:

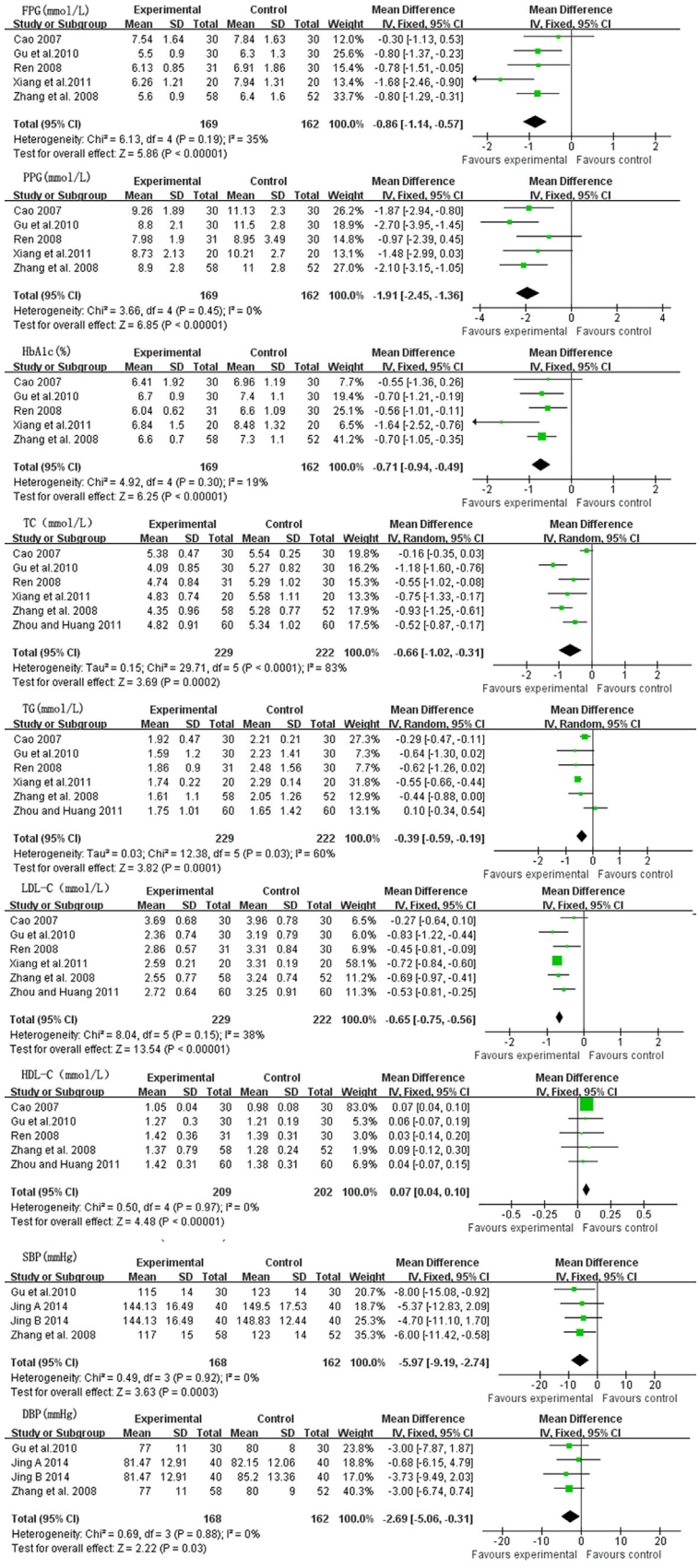

Fig. 1. Berberine versus placebo or berberine with lifestyle intervention versus lifestyle.

MD = −5.97 mmHg, 95% CI (−9.19, −2.74), P=0.0003; DBP: MD = −2.69 mmHg, 95% CI (−5.06, −0.31), P=0.03].

3.3.2. Berberine combined with oral hypoglycaemics versus the same hypoglycaemics (compared the level of FPG, PPG and HbA_{1c})

There were seven trials (Li and Liu, 2007, 2008; Zhu et al., 2008; Ye, 2009; Sheng and Xie, 2010; Cao et al., 2012; Ning et al., 2013) compared the effect of berberine combined with oral hypoglycemic drug group and hypoglycemic drug group on blood glucose and glycosylated hemoglobin. For the contrastive research of FPG, there were 266 patients in berberine group and 263 patients in control group. The trials (Sheng and Xie, 2010) only compared FPG level and the trial (Ning et al., 2013) compared the level of FPG and HbA_{1c}, for the contrastive research of PPG, there were 214 patients in berberine group and 211 patients in control group. HbA_{1c} was 236–233. No significant heterogeneity between the results of FPG (I^2=30%, P=0.2), so we used the fixed effect model for meta-analysis. There was a significant heterogeneity between the results of PPG and HbA_{1c} (PPG: I^2=63%, P=0.03; HbA_{1c}: I^2=70%, P=0.0005), so we used the fixed effect model for meta-analysis. Each study had clinical homogeneity (divided into the subgroup and the patient's age, sex, course of treatment were similar at baseline between the two groups), therefore, we used a random effects model for meta-analysis. The results of three groups all showed that berberine group can be more effective in lowering blood glucose levels than in the control group [FPG: MD = −0.67 mmol/L, 95% CI (−0.85, −0.49), P<0.00001; PPG: MD = −0.98 mmol/L, 95% CI (−1.54, −0.42), P=0.0006; HbA_{1c}: MD = −0.58%, 95% CI (−0.96, −0.21), P=0.002] (Fig. 2).

3.3.3. Berberine versus oral hypoglycaemics (compared the level of FPG, PPG and HbA_{1c})

As shown in Fig. 3, the effect of the berberine group and the oral hypoglycemic group on blood glucose and glycosylated hemoglobin was compared. For the comparative study of FPG, seven trials were involved (Ding et al., 1996; Cao, 2007; Li and Liu, 2007; Yin et al., 2008; Zhu et al., 2008; Zhang et al., 2010, 2011). The trial (Zhang et al., 2010) contained two control groups of hypoglycemic, so we divided it into Zhang et al. (2010) – A and B. 302 patients were included in the berberine group and 245 in the control group. In the comparison of PFG study, among the seven trials, the trial (Ding et al., 1996) did not compare HbA_{1c} level and the trials (Zhang et al., 2010, 2011) without the level of PPG. For the comparative research of PPG, berberine group involved 172 patients and 168 patient in control group and HbA_{1c} was 281 to 223. The results of the three indexes showed a statistical heterogeneity (FPG: I^2=49%, P=0.06; PPG: I^2=92%, P<0.00001; HbA_{1c}: I^2=77%, P=0.0002). Each study had clinical homogeneity (divided into the subgroup and the patient's age, sex, course of treatment were similar at baseline between the two groups), therefore, a random effects model can be used for meta-analysis. Results from three groups were presented to show the effects of berberine group and oral medicine on blood glucose and HbA_{1c} had no statistical significance [FPG: MD=0.2 mmol/L, 95% CI (−0.00, 0.4), P=0.05; PPG:

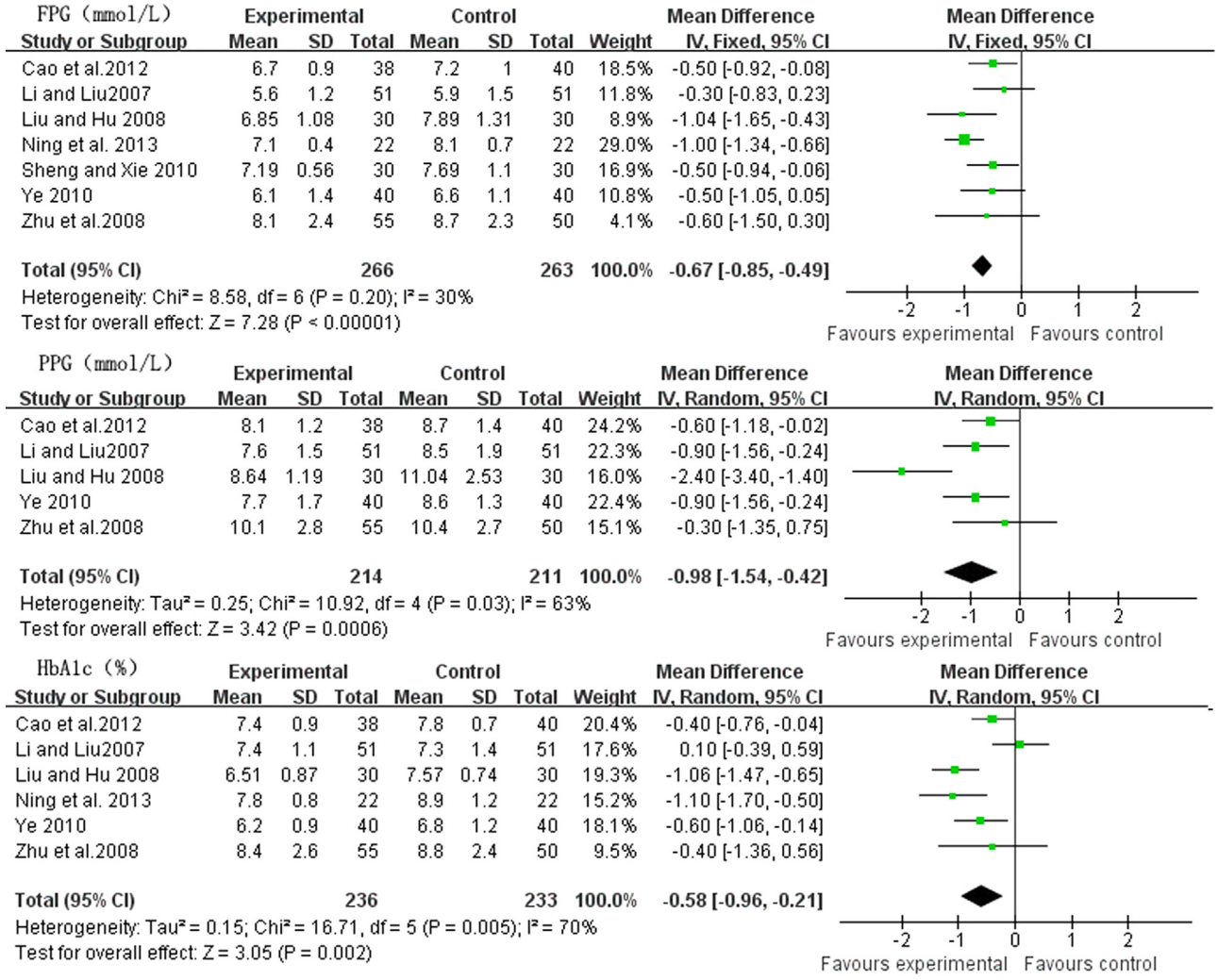

Fig. 2. Berberine combined with oral hypoglycaemics versus the same hypoglycaemics.

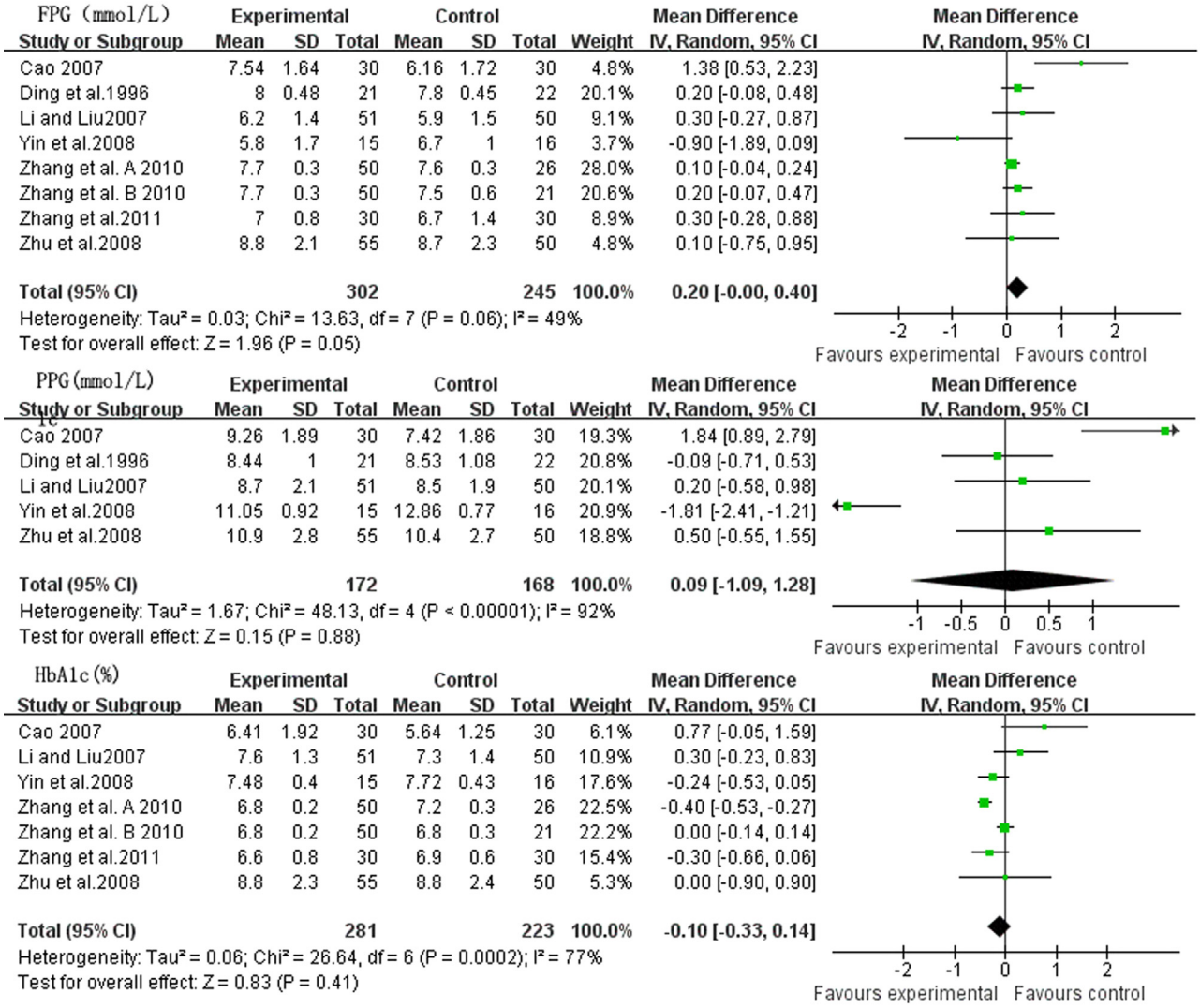

Fig. 3. Berberine versus oral hypoglycaemics.

MD = 0.09 mmol/L, 95% CI (−1.09, 1.28), $P = 0.88$; HbA_{1c}: MD = −0.1%, 95% CI (−0.33, 0.14), $P = 0.41$].

3.3.4. *Berberine combined with lipid lowering drugs versus lipid lowering drugs (compared the level of TC, TG, LDL-C and HDL-C)*

As shown in Fig. 4, four trials (He et al., 2007; Yu et al., 2007; Zheng et al., 2009; Su et al., 2012) were used to compare the effect of berberine combined with lipid-lowering drug to lipid-lowering drug on lipid levels. 183 patients were included in the test group and 181 patients in control group. The trial (Yu et al., 2007) did not compare the HDL-C level, so on the research of HDL-C, 133 patients in test group and 131 patients in control group. The results of TC and TG showed a statistical heterogeneity (TC: $I^2 = 62\%$, $P = 0.05$; TG: $I^2 = 86\%$, $P = 0.0001$). Each study had clinical homogeneity (divided into the subgroup and the patient's age, sex, course of treatment were similar at baseline between the two groups), therefore, a random effect model was used for meta-analysis. No statistical heterogeneity was shown in the result of LDL-C and HDL-C (LDL-C: $I^2 = 0\%$, $P = 0.5$; HDL-C: $I^2 = 15\%$, $P = 0.31$), so we use the fixed effect model for meta-analysis. The chart shows berberine group can reduce the TC and LDL-C levels and rise HDL-C level more than the control group [TC: MD = −0.27 mmol/L, 95% CI (−0.45, −0.09), $P = 0.003$; LDL-C: MD = −0.11 mmol/L, 95% CI (−0.14, −0.07), $P < 0.00001$; HDL-C: MD = 0.2 mmol/L, 95% CI (0.19, 0.21), $P < 0.00001$], but there was no statistical significance on TG, [TG: MD = −0.32 mmol/L, 95% CI (−0.65, 0.02), $P = 0.07$].

3.3.5. *Berberine versus lipid lowering drugs (compared the level of TC, TG, LDL-C and HDL-C)*

Three trials (Wei et al., 2003; He et al., 2007; Zheng et al., 2009) compared the effect of berberine group and oral medicine group on lipid levels. The trial (Wei et al., 2003) contained two control group of western medicine, we divided it into Wei et al. (2003) – A and B in this meta-analysis. Test group contained 141 patients and control group contained 105 patients. No significant heterogeneity between the results of TG (TG: $I^2 = 30\%$, $P = 0.32$), so we used the fixed effect model of meta-analysis. The results of TC, LDL-C and HDL-C had statistically significant heterogeneity, (TC: $I^2 = 98\%$, $P < 0.00001$; LDL-C: $I^2 = 97\%$, $P < 0.00001$; HDL-C: $I^2 = 66\%$, $P = 0.03$). We divided into the subgroup for each study and the patient's age, sex, course of treatment were similar at baseline between the two groups, therefore, a random effects model was used for meta-analysis. The chart showed that berberine can decrease TG, increase HDL-C level more than western medicine [TG:MD = −0.2 mmol/L, 95% CI (−0.21, −0.19), $P < 0.00001$; HDL-C: MD = 0.12 mmol/L, 95% CI (0.01, 0.22), $P = 0.04$]. No statistical significance on TC and LDL-C [TC: MD = −0.45 mmol/L,

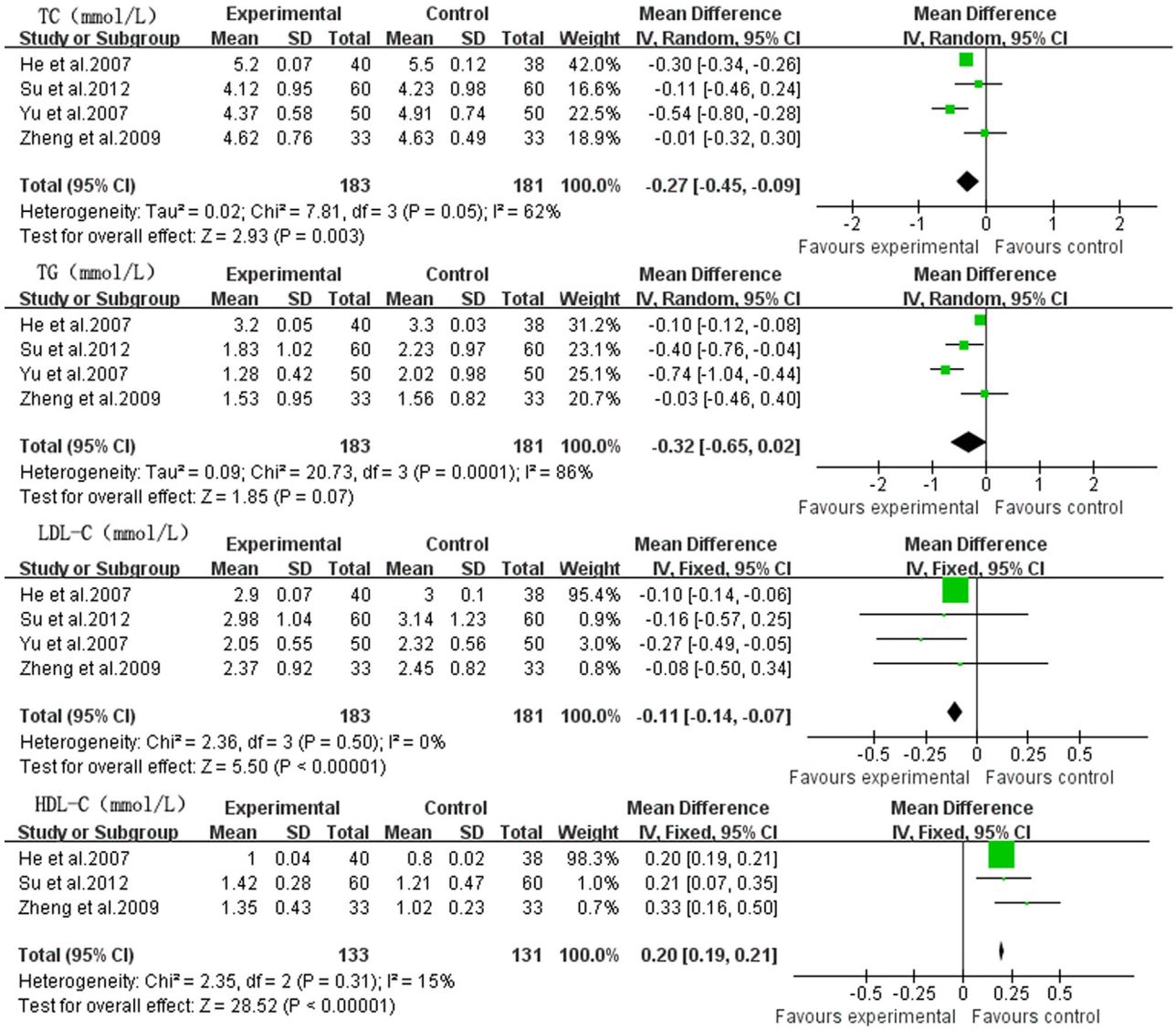

Fig. 4. Berberine combined with lipid lowering drugs versus lipid lowering drugs.

95% CI (−1.33, 0.44), P=0.32; LDL-C: MD=−0.24 mmol/L, 95% CI (−.05, 0.56), P=0.55], as shown in Fig. 5.

3.3.6. *Berberine combined with hypotensor versus hypotensor (compared the level of SBP and DBP)*

The trials (Huang, 2013; Sun et al., 2013) compared the effect of berberine group and control group on the level of blood pressure, there were 116 patients in berberine group and 112 in control group. No significant heterogeneity was shown among study results (SBP: I^2=0%, P=0.78; DBP: I^2=0%, P=1), so we use the fixed effect model for meta-analysis. The chart shows berberine combine with hypotensor can reduce blood pressure more than hypotensor alone [SBP: MD=−4.91 mmHg, 95% CI (−8.72, −1.1), P=0.01; DBP: MD=−2, 95% CI (−3.76, −0.24), P=0.03] (Fig. 6).

3.3.7. *Berberine versus hypotensor (compared the level of SBP and DBP)*

The trials (Zhong et al., 1997; Han et al., 1999) compared the effect of berberine group with control group on the level of blood pressure, there were 152 patients in berberine group and 147 patients in control group. The trial (Han et al., 1999) contained two hypotensor control group, so we divided it into two subgroups named as Han et al. (1999) –A and B for this meta-analysis. Research results have showed a statistical heterogeneity (SBP: I^2=76%, P=0.01; DBP: I^2=61%, P=0.08), we divided them into the subgroup for each study and the patient's age, sex, course of treatment were similar at baseline between the two groups, therefore, a random effect model was used for meta-analysis. The chart shows the effect of berberine with hypotensor had no statistical significance [SBP: MD=0.1 kPa, 95% CI (−0.89, 1.1), P=0.84; DBP: MD=0.15 kPa, 95% CI (−0.4, 0.7), P=0.59] as shown in Fig. 7.

3.3.8. *Adverse reactions*

Twenty articles reported the adverse drug reactions and side effects of berberine or control drugs, the remaining seven articles are unspecified clearly as shown in Table 1. In these 20 articles, 12 trials reported the number of adverse reactions and the other eight articles only stated a slight adverse reactions of berberine without clear data. We sorted out the data and listed into a figure (Fig. 8). Our statistical data shows that the incidence of toxic side effect is related to the doses of berberine, as the dose of berberine increases, the risk of toxic side effect also increases. The current studies about the adverse

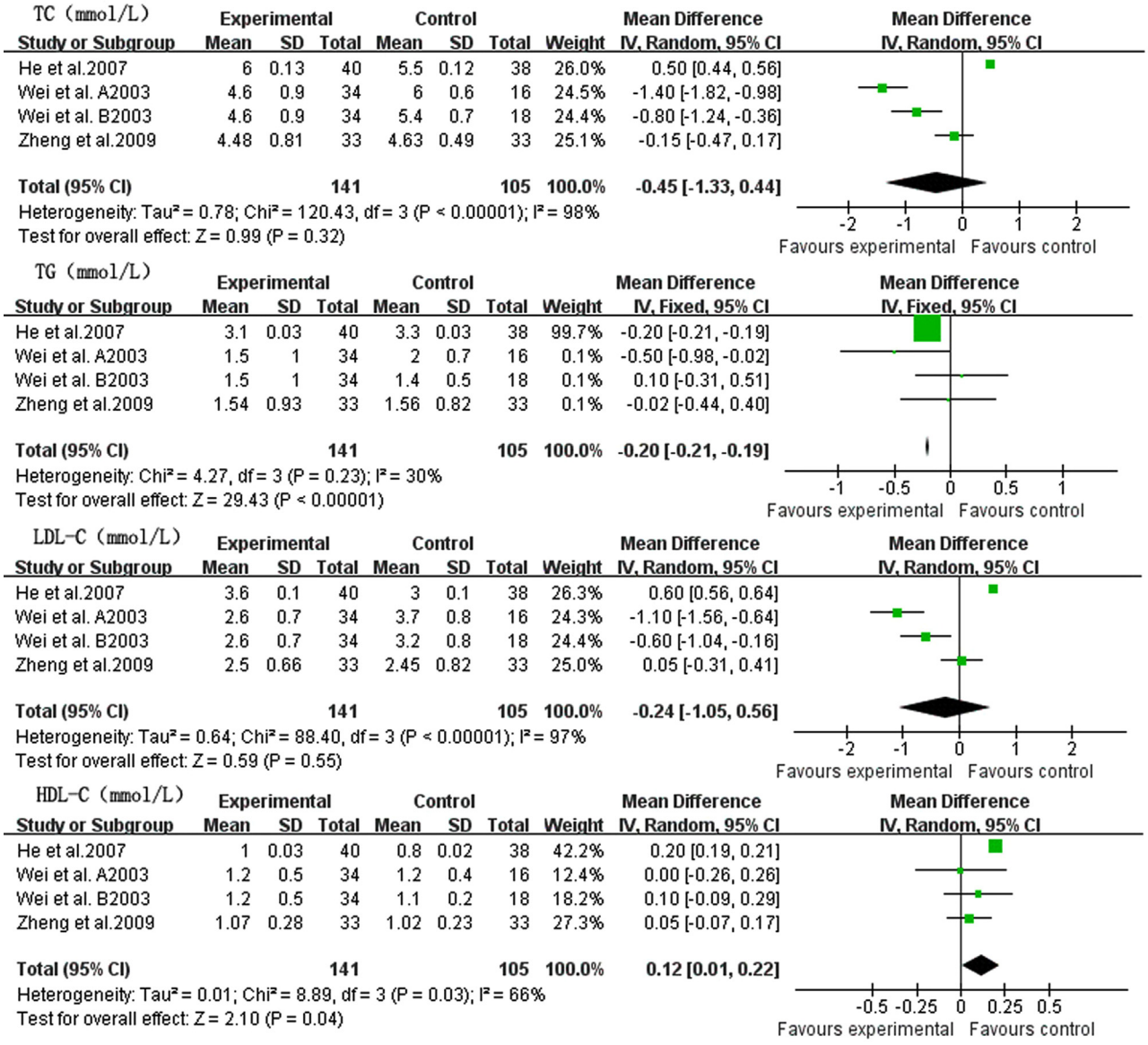

Fig. 5. Berberine versus lipid lowering drugs.

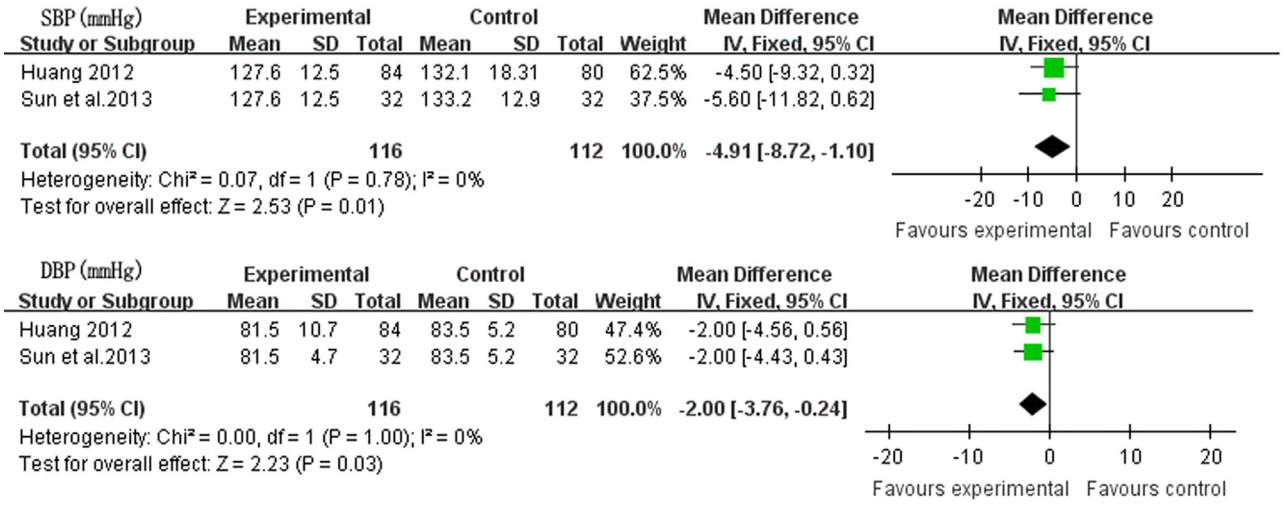

Fig. 6. Berberine combined with hypotensor versus hypotensor.

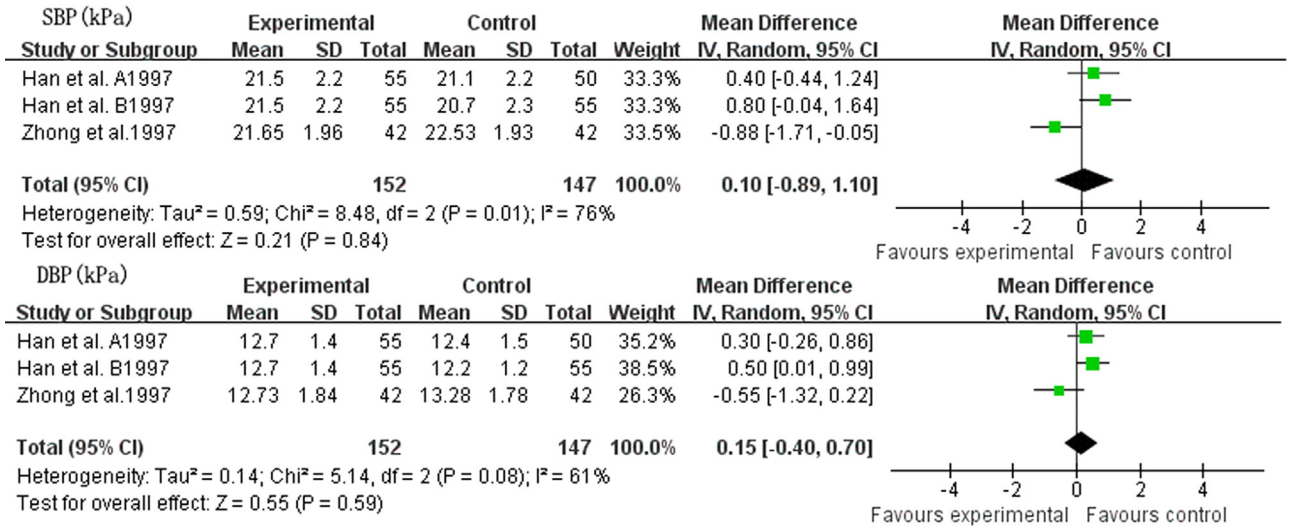

Fig. 7. Berberine versus hypotensor.

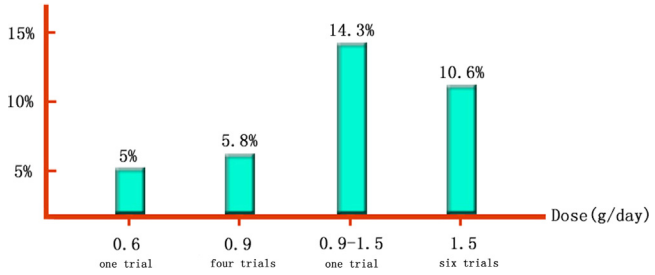

Fig. 8. The incidence of adverse reactions of berberine in different doses.

reactions and side effects of berberine found toxicity reaction occur in the large dose (Lei, 2010). In most of the articles without clear data showed that the berberine is safe in the treatment process and the incidence of adverse reactions and side effects is low, without occurrence or no serious adverse reactions that effects important organs occurred in the course of the experiment (Yin et al., 2008; Zhu et al., 2008; Xiang et al., 2011). In contrast with the side effect of berberine and western medicine, there was no statistical significance, the statistic of the trial (Cao et al., 2012) toward the side effect of berberine group and control group showed $\chi^2 = 0.158$, $P = 0.691$. Some minor adverse reactions occurred in the digestive system, such as nausea, diarrhea, constipation, abdominal distension, abdominal pain (Ding et al., 1996; Cao, 2007; Sheng and Xie, 2010; Cao et al., 2012), others such as hypoglycemia is rare. Patient can tolerate these side effects, without stopping drug, or reducing the dose of berberine to 0.6 g per day (Ren, 2008),

4. Discussion

There have been a lot of clinical studies or reports about the berberine in the treatment of type 2 diabetes, hyperlipidemia and hypertension. However, the quality of study varies. We would ask questions about the clinical studies involving berberine. What is the accurate effect of berberine? How safe it is? How strong is the evidence? Can it benefit patients or not? meta-analysis or systematic reviews are needed to answer these questions.

At present, no meta-analysis of the efficacy and safety of berberine in type 2 diabetes, hyperlipidemia and hypertension has been done. The trials (Na et al., 2012; Dong et al., 2012) used meta-analysis of treatment effect and safety of berberine in type 2 diabetes. The study (Na et al., 2012) was published in November 2012. Patients were divided into two groups: (a) berberine versus placebo or lifestyle modification or hypoglycemic; (b) berberine combined with hypoglycemic versus the same hypoglycemic, compared with this index: FPG, PPG, HbA_{1c}, LDL-C, HDL-C, TC, TG and adverse reaction. The study (Dong et al., 2012) (adopted 14 trials and involved 1068 patients) was also published in 2012 in Evidence-Based Complementary and Alternative Medicine (USA), the study (Dong et al., 2012) added a subgroup (berberine versus hypoglycemic) compared to the study (Na et al., 2012). Due to the distinction of disease (our study adds hyperlipidemia and hypertension), our study divided into seven subgroups. They added fasting insulin (FINS) based on the study (Na et al., 2012). At last, the conclusion of the study (Dong et al., 2012) is that berberine has beneficial effects on blood glucose control in the treatment of type 2 diabetic patients and exhibits efficacy comparable with that of conventional oral hypoglycaemics. The anti-dyslipidemic effect of berberine needs to be further confirmed.

There is something unreasonable in the two papers mentioned above, for example, in the subgroup (berberine combined with oral hypoglycaemics versus the same hypoglycaemics, berberine versus oral hypoglycaemics), they adopted a lipids index, but hypoglycaemic has no direct regulatory effect on blood lipid, and not all diabetic patients have hyperlipidemia at the same time. We adopted six trials on hyperlipidemia, thereby solving these problems. We adopted four hypertension trials to assess the impact of berberine on blood pressure in hypertensive patients, and thus raise a level in the literature significance and reference value.

Our meta-analysis showed: in the treatment of type 2 diabetes mellitus, berberine with lifestyle intervention lowered the level of FPG, PPG and HbA_{1c} more than lifestyle intervention alone or placebo. The same happened in comparing berberine combined with oral hypoglycaemics to the same hypoglycaemics. There was no statistical significance between treatment of berberine and oral hypoglycaemics. In the treatment of hyperlipidemia, berberine with lifestyle intervention was better than lifestyle intervention. Berberine with oral lipid lowering drugs was better than lipid lowering drugs alone in reducing the level of TC and LDL-C and rising the level of HDL-C, but in two subgroups, there was no statistical significance in reducing the level of TG, in the comparative study between berberine and oral lipid lowering drugs; there was no statistical significance in reducing the level of TC and LDL-C, which berberine shows better effects lowering in TG and rising HDL-C. In the treatment of hypertension, berberine with lifestyle intervention tended to lower the level of blood pressure more than lifestyle intervention alone or

placebo. The same occurred when berberine combined with oral hypotensor was compared to the same hypotensor. Therefore, based on the results of our meta-analysis, in the treatment of type 2 DM, berberine can reduce the FPG, PPG and HbA1c; Lower the TC, TG and LDL-C levels of hyperlipemia patients, elevate HDL-C levels; Has antihypertensive effect on patients with hypertension.

Similarly, berberine also shows its therapeutic effect in non-clinical trials, the experts in the first hospital of Nanjing city (China) had explored the mechanism of berberine in reducing blood lipids in the molecular level by using human hepatoma cells and hyperlipidemic hamsters. These findings strongly suggest that berberine is a promising new hypolipidemic drug that acts through pathways distinct from those of statins. They postulated that berberine can be used as a monotherapy to treat hypercholesterolemic patients or it may be explored in combination therapy with statins (Kong et al., 2004).

In terms of toxic and side effect of berberine, our statistical data shows that the incidence of toxic side effects is related to the doses of berberine. When the dose of berberine increases, the risk of toxic side effect also increases. Currently, the dispute about drug toxicity of berberine has not been resolved. Studies on the toxicity of berberine also lacks systematic and complete research, so a conclusion as to whether berberine is toxic or non-toxic cannot be made (Lei, 2010). Based on the included 27 trials, berberine can produce certain side effects. The incidence of adverse reactions is low, without occurrences or serious adverse reactions that affect important organs occurred in the course of treatment. Berberine is relatively safe for diabetes, hyperlipidemia, hypertension.

5. Study strengths and limitations

This study is the first meta-analysis of the effect and safety of berberine in the treatment of type 2 diabetes mellitus, hyperlipidemia, and hypertension. Twenty-seven articles were included in this study with a total of 2569 patients, the sample size is relatively large. In the methodology, we used a subgroup analysis, thereby reducing the heterogeneity and making the conclusion clearer. The results of meta-analysis will be relatively accurate. As for the results of study, it is a positive conclusion, our meta-analysis shows that berberine has a therapeutic effect on type 2 DM, hyperlipidemia and hypertension and has less side-effects.

However, each meta-analysis has the limitations of methodology or research object. In our study, the result of system review has the possibility of selection bias, detection bias, implementation bias and publication bias. These biases may result in a declinational estimation to the true treatment effect in meta-analysis. Due to the discordance of the course of the disease, course of treatment, drug and dose of the control group, we did not do a pooling analysis. To get more accurate results, a pooling analysis based on the progress of the disease, course of drug treatment, and dose of the control group is needed. The trials of this study are all RCT. However, the literature rarely described research design, random method and concealment of the random scheme. Only the randomization method was mentioned without detailed information as to whether the test design meets all standards. At the same time, most trials did not use concealing procedure, which may result in implementation bias or measurement bias.

6. Conclusion

This study indicates that berberine has comparable therapeutic effect on type 2 DM, hyperlipidemia and hypertension with no serious side effect. Considering the relatively low cost compared with other first-line medicine and treatment, berberine might be a good alternative for low socioeconomic status patients to treat type 2 DM, hyperlipidemia, hypertension over long time period. Due to overall limited quality of the included studies, the therapeutic benefit of berberine can be substantiated to a limited degree. Our data also provide supportive evidence for initiating more efforts on investigation of the role of berberine in the treatment of type 2 DM, hyperlipidemia and hypertension. Better methodological quality, large controlled trials using standardized preparation are expected to further quantify the therapeutic effect of berberine.

Acknowledgments

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References

Cao, Y., 2007. Clinical Research on Multiple Factor Intervention of Improving the Insulin Resistance (M.S. thesis). Shandong University of Traditional Chinese Medicine (in Chinese).

Cao, Y.F., Cai, W.W., Zhang, L.L., Fang, Y., 2012. Clinical observation of berberine combined with metformin in the treatment of diabetes mellitus accompany with non alcoholic fatty liver. Modern Preventive Medicine 39, 4885–4889.

China Adult Dyslipidemia Prevention Guidelines for Joint CommitteeChinese adult dyslipidemia prevention guide. Chinese Journal of Cardiovascular Disease 35, 390–413.

Ding, C.P., Zhang, R.L., Pan, C.S., Jie, Y.Q., Yuan, F., 1996. Clinical observation of 21 cases of berberine in treatment of non insulin dependent diabetes mellitus. Chinese Rural Medical 24, 19–20 (in Chinese).

Dong, H., Wang, N., Zhao, L., Lu, F.E., 2012. Berberine in the treatment of type 2 diabetes mellitus: a systemic review and meta-analysis. Evidence-Based Complementary and Alternative Medicine 10, 1–12.

Ge, J.B., Xu, Y.J., 2013. Internal Medicine 8, 733.

Gu, Y., Zhang, Y.F., Shi, X.Z., Li, X.Y., Hong, J., Chen, J., Gu, W.Q., Lu, X., Xu, G.W., Ning, G., 2010. Effect of traditional Chinese medicine berberine on type 2 diabetes based on comprehensive metabonomics. Talanta 81, 766–772.

Han, Z.X., Huang, J.X., Zhang, Z.S., Ji, S.J., Xu, J., 1999. Elderly hypertensive disease observation of Betaloc treated with Berberine. Medical Research Communications 28, 43 (in Chinese).

He, J.J., Xu, X.G., Zheng, X., 2007. Effect of simvastatin and berberine in treating hyperlipidemia and carotid atherosclerosis. Tianjin Medical 35, 539–541 (in Chinese).

He, M.K., Lu, F.E., Wang, K.F., Leng, S.H., Xu, L.J., Zou, X., 2004. Effects of berberine on glucose and lipid metabolism hyperlipidemia accompany insulin resistance in rats. Chinese Journal of Hospital Pharmacy 24, 389–391 (in Chinese).

Huang, G.L., 2013. therapeutic evaluation in the treatment of Amlodipine combined with berberine on light, moderate hypertension complicated with gout. China Pharmaceuticals 22, 32–33 (in Chinese).

Jadad, A.R., Moor, R.A., Carroll, D., Jenkinson, C., Reynolds, D.J., Gavaghan, D.J., McQuay, H.J., 1996. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Controlled Clinical Trials 17, 1–12.

Jiangsu New Medical College, 1997. The Dictionary of Traditional Chinese Medicine. Shanghai People's Publishing House, p. 2024 (in Chinese).

Jin, J.D., 2014. To observe the clinical curative effect of application of berberine in treatment of type 2 diabetes. Contemporary Medicine Forum 12, 286 (in Chinese).

Kearney, P.M., Whelton, M., Reynolds, K., Whelton, P.K., He, J., 2004. Worldwide prevalence of hypertension: a systematic review. Journal of Hypertension 22, 21–24.

Kearney, P.M., Whelton, M., Reynolds, K., Muntner, P., Whelton, P.K., 2005. Global burden of hypertension: analysis of worldwide data. Lancet 365, 217–223.

Kong, W.J., Wei, J., Abidi, P., Lin, M.H., Inaba, S., Li, C., Wang, Y.L., Wang, Z.Z., Si, S.Y., Pan, H.N., Wang, S.K., Wu, J.D., Wang, Y., Li, Z.R., Liu, J.W., Jiang, J.D., 2004. Berberine is a novel cholesterol lowering drug working through a unique mechanism distinct from statins. Nature Medicine 10, 1344–1351.

Lei, Z.Y., 2010. Drug safety of *Coptis chinensis* and berberine. China Pharmaceuticals 19, 84–86.

Liu, H.Y., Hu, Q.M., 2008. Effect of berberine on islet β-cell function in type 2 diabetes mellitus (damp-heat type). Chinese Journal of Information on TCM 15, 12–14.

Li, Z., Liu, L.H., 2007. Therapeutic efficacy of combined berberine and glipizide on type 2 diabetes. Journal of Clinical Research 24, 61–64.
Na, Qimuge, Zhao, T.Y., He, M., Tian, C., 2012. Effectiveness and safety of berberine in the treatment of type2 diabetes: a systematic review. Chinese Journal of Evidence-Based Medicine 12, 81–91.
Ning, J., Zhang, H.T., Liu, D.X., Wang, X.Q., 2013. To investigate the effect of berberine combined with metformin in the treatment of type 2 diabetic patients with non alcoholic fatty liver. China Modern Drugs 7, 155–156 (in Chinese).
Ren, Y.J., Gao, F.X., 2009. Research progress of berberine. Journal of Liaoning University of Traditional Chinese Medicine 11, 50–51.
Ren, Y., 2008. Effect of Berberine on Blood Glucose, Blood Lipid and Serum Adiponect in of Primary Type 2 Diabetes Mellitus Patients (M.S. thesis). Shanxi Medical University.
Sheng, Z.X., Xie, D.H., 2010. Therapeutic effect of berberine on the levels of in flammatory factors in type 2 diabetic patients. New Medicine 41, 177–180.
Su, X.Y., Xing, J.W., Ju, J., Qian, C.F., 2012. Sixty cases of treatment of simvastatin combined with berberine in hyperlipidemia. Chinese Medicine Modern Distance Education of China 10, 41–42 (in Chinese).
Sun, S.P., Huang, Z.S., Ruan, W.J., 2013. Effect observation of combination therapy in the treatment of elderly hypertensive patients with gout. Forefront of Medicine 35, 394–395 (in Chinese).
Wei, J., Jiang, J.D., Wu, J.D., Wang, S.K., Wang, Z.Z., Pan, W.N., Dai, S.Q., 2003. Study of lipid regulating effects of berberine hydrochloride. Chinese Journal of Diabetes 13, 49-51 in Chinese.
Xia, X., Yan, J., Shen, Y., Tang, K., Yin, J., Zhang, Y., Yang, D., Liang, H., Ye, J., Weng, J., 2011. Berberine Improves glucose metabolism in diabetic rats by inhibition of hepatic gluconeogenesis. PLoS One 6, e16556.
Xiang, W., Huang, X.J., Huang, G.X., 2011. Research on the therapeutic effect of two kinds of anti-inflammatory drugs in newly diagnosed type 2 diabetic patients. Journal of Practical Diabetology 7, 51–52.
Ye, W.P., 2009. Clinical efficacy of berberine treatment of diabetes. Modern Hospital 10, 9–10.
Yin, J., Xing, H., Ye, J., 2008. Efficacy of berberine in patients with type 2 diabetes mellitusMetabolism 57, 712–717.
Yu, J.Y., Li, Z., Wang, Q.Z., 2007. The combination therapy of small dose simvastatin and berberine in hyperlipidemia of fifty patients. Shandong Medical 47, 39 (in Chinese).
Zhang, E.L., 2006. New clinical application of berberine. Lishizhen Medicine and Materia Medica Research 17, 1085 (in Chinese).
Zhang, H., Wei, J., Xue, R., Wu, J.D., Zhao, W., Wang, Z.Z., Wang, S.K., Zhou, Z.X., Song, D.Q., Wang, Y.M., Pan, H.N., Kong, W.J., Jiang, J.D., 2010. Berberine lowers blood glucose in type 2 diabetes mellitus patients through increasing insulin receptor expression. Metabolism 59, 285–292.
Zhang, L.Z., Ji, Y.F., 1999. Application of berberine in the treatment of diabetes. Journal of Practical Medicine Department of Internal Medicine 13, 22 (in Chinese).
Zhang, R.D., Bai, R.M., Wei, J., 2011. The therapeutic effects of berberine on 24 h urinary albumin of type II diabetes mellitus. Chinese Journal of Integrated Traditional and Western Nephrology 12, 28–30.
Zhang, Y.F., Li, X.Y., Zou, D.J., Zhu, N., Huo, L., Wang, M., Hong, J., Wu, P.H., Ren, G.G., Ning, G., 2008. Treatment of type 2 diabetes and dyslipidemia with the natural plant alkaloid berberine. Journal of Clinical Endocrinology and Metabolism 93, 2559–2565.
Zheng, B.B., Wei, J., Jiang, J.D., Gong, H.H., Zhang, R.S., 2009. Evaluate the efficacy of statins combined with berberine for the treatment of hyperlipidemia. Acta Universitis Medicinalis Nanjing (Natural Science) 29, 1493–1497 (in Chinese).
Zhong, S.L., Zhou, Y.S., Chen, H.M., Yang, G.S., 1997. Clinical observation on 96 cases of elderly patients with hypertension of berberine treatment. China Journal of Gerontology 17, 349–350 (in Chinese).
Zhou, Y.F., Huang, S.J., 2011. Clinical observation on hyperlipidemia of sixty cases of berberine treatment. Chinese Journal of Clinical Rational Drug Use 4, 76–77 (in Chinese).
Zhu, G.C., Zhang, C.S., Kang, S.K., 2008. Observing the effect of berberine combined with metformin in type II diabetes. Journal of China Misdiagnostics 9, 788–789 (in Chinese).