The Effects of a Fixed Combination of *Berberis aristata* and *Silybum marianum* on Dyslipidaemia – A Meta-analysis and Systematic Review

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The Effects of a Fixed Combination of *Berberis aristata* and *Silybum marianum* on Dyslipidaemia – A Meta-analysis and Systematic Review

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ABSTRACT

A fixed combination of *Berberis aristata* and *Silybum marianum* (Berberol) has been used by patients with dyslipidaemia. The aim of the present meta-analysis was to systematically evaluate the efficacy and safety of a fixed combination of *B. aristata* and *S. marianum* (Berberol) on serum lipid levels compared to placebo in a meta-analysis based on randomised, controlled trials. The meta-analysis was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement, using the PICO (patients, intervention, comparison, outcome) format, and it was registered in the International Prospective Register of Systematic Reviews. The Cochrane Central Register of Controlled Trials, PubMed, Embase, and Web of Science databases were searched for relevant studies. Placebo-controlled clinical studies involving adult patients with a condition of dyslipidaemia and receiving a fixed combination of *B. aristata* and *S. marianum* were included. Four randomised trials, including a total of 491 patients, were pooled in statistical analysis. According to the present meta-analysis, Berberol significantly lowered the low-density lipoprotein level, total cholesterol, fasting plasma glucose levels, and the Homeostatic Model Assessment index compared to placebo; however, its effects on the high-density lipoprotein level, triglyceride level, and body mass index were not statistically significant by the end of a 3-month treatment period. Berberol appeared to be safe, and it did not increase the levels of alanine transaminase, aspartate transaminase, and creatine kinase enzymes. Berberol is an effective and presumably safe complementary therapy for the treatment of dyslipidaemia; however, the evidence supporting its use is very limited. The optimum dose and duration of treatment are unclear. A comprehensive evaluation of efficacy and safety is required in further high-quality clinical studies involving larger patient populations.

Introduction

Dyslipidaemia is one of the leading factors for cardiovascular diseases [1]. Treatment of dyslipidaemia is mostly based on pharmacological therapy and, most often, statins are prescribed to normalise lipid levels. However, a significant proportion of patients treated with statins will eventually develop adverse reactions, such as muscle diseases, abnormal liver function tests, neuropathy, memory loss, changes in mental status, and gastrointestinal complaints [2].

It is well acknowledged that a complex therapeutic approach involving lifestyle changes (e.g., increased physical activity,

ABBREVIATIONS

ALT	alanine transaminase
AST	aspartate transaminase
BMI	body mass index
CI	confidence interval
CK	creatine kinase
FPG	fasting plasma glucose
GRADE	Grading of Recommendations Assessment
HbA_{1c}	glycated haemoglobin, haemoglobin A1c
HDL	high-density lipoprotein
HOMA-IR	Homeostatic Model Assessment of Insulin Resistance
LDL	low-density lipoprotein
MD	difference in means
PICO	P – patient, problem or population; I – intervention; C – comparison, control or comparator; O – outcome
PPG	postprandial plasma glucose
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	International Prospective Register of Systematic Reviews
RCT	randomised controlled clinical trial
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
TC	total cholesterol
TG	triglyceride

weight loss, scientifically proven nutrition) may contribute to normalise lipid levels [3]. While it is debated whether decreasing dietary cholesterol intake can significantly alter serum cholesterol levels or not, several studies unambiguously indicated that the consumption of trans-fatty acids and refined carbohydrates have deteriorating effects on serum lipid parameters and cardiovascular outcomes [1]. Apart from nutrition, patients often consider taking food supplements to substitute or complement pharmacological therapies [3].

Nutraceuticals used in complementary or alternative medicine show great geographical variations, i.e., international and regional disparities are to be expected. In Italy, a fixed combination of extracts from *Berberis aristata* DC (Berberidaceae) and *Silybum marianum* (L.) Gaertn. (Compositae) has been marketed as a food supplement since 2010. The product, named Berberol, is declared to contain standardised extracts of *B. aristata* and *S. marianum*. Each tablet of Berberol contains 105 mg hydro-ethanolic extract of *S. marianum*, standardised for flavonolignans (60–80 %) calculated as silybin, and 588 mg hydroalcoholic extract of *B. aristata*, standardised for berberine (> 85 %) [4].

B. aristata is widely used in Ayurveda and traditional Chinese medicine. All parts of the plant are processed into either pharmaceutical, nutraceutical, or cosmeceutical products [5]. Its main bioactive compounds are alkaloids, and one of the most studied compounds of the plant is berberine. Lipid-lowering effects of the plant and berberine have been studied widely. Based on *in vivo* experiments, the mechanism of action of berberine and its *in vivo* metabolite, berberrubine, involves the upregulation of LDL receptors and PCSK9 expression through the ERK signalling pathway [6]. In a recent meta-analysis, the effects of berberine on lipid levels was evaluated [7]. Sixteen RCTs were pooled for statistical analysis, and it was concluded that berberine lowers plasma lipid levels (TC, LDL, and TG) without increasing the risk for side effects. Although berberine possesses great potential to ameliorate lipid and glycaemic profiles, it has poor oral bioavailability that appears to be due to a P-glycoprotein-mediated efflux mechanism. Apart from structural modifications of the compound, coadministration of P-glycoprotein inhibitors may improve the oral bioavailability of berberine [8].

Based on a meta-analysis of eight RCTs, silymarin lowered the LDL and increased the HDL levels of patients with T2DM, but it had no significant effects on TC or TG levels [9]. During the last decades, several studies have confirmed the P-glycoprotein inhibitory effects of silymarin; hence, the rationale for combining berberine with silymarin is supported by pharmacokinetic reasons [10, 11].

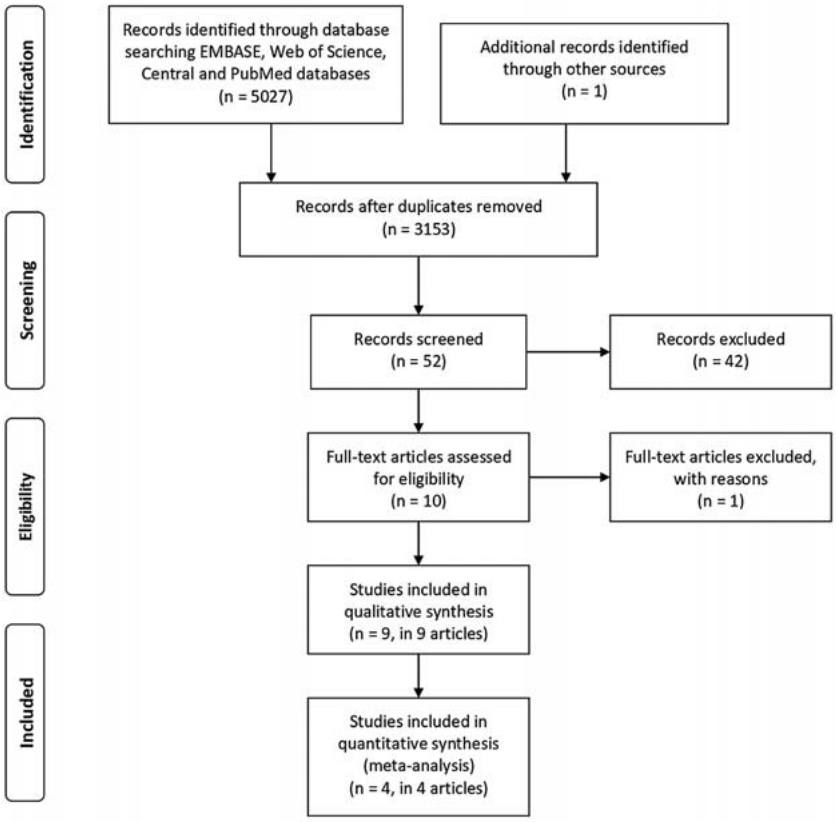
Recently, several RCTs have been conducted to evaluate the efficacy of the fixed combination of the extracts of *B. aristata* and *S. marianum* in dyslipidaemia. Therefore, the aim of the present literature review and meta-analysis was to reassess and synthesise published evidence by systematically reviewing the available literature data on the efficacy and safety of this combination based on RCTs.

Results

Literature searches were conducted through Embase, PubMed, Cochrane Central Register of Controlled Trials, and Web of Science databases. Berberol, *Berberis aristata*, berberine, silymarin, and *Silybum marianum* were used as search terms. After removing duplicates, the search yielded altogether 3153 potentially relevant reports, and the included RCTs were selected according to the flow chart presented below (▶ **Fig. 1**).

After screening the titles and abstracts, ten publications were retrieved for full-text screening. Guarino et al. conducted a placebo-controlled, randomised, double-blind study to assess the effects of Berberol on patients with a condition of T2DM and altered lipid levels [12]. In their study, the verum group received Berberol twice daily for 52 weeks. All the clinically relevant parameters were measured at baseline, and after 24 and 52 weeks of the initiation of the study. The authors concluded that the combination improved several metabolic parameters and body fat distribution. After inspecting the full text, it became clear that there are unresolvable discrepancies in the article regarding the reported parameters at baseline, i.e., the values in ▶ **Tables 1** and **2** are not consistent. Therefore, we could not include this study nor the qualitative or quantitative analysis.

Another study conducted by Guarino et al. assessed the efficacy of berberine combined with silymarin compared to placebo [13]. Patients diagnosed with T2DM and hypercholesterinaemia (TG > 200 mg/dL) were enrolled and administered 500 mg berberine and 150 mg silymarin daily for 6 months. This study did not comply with our PICO (patients, intervention, comparison, outcome) in terms of intervention and therefore, it was not included into the quantitative analysis.



▶ **Fig. 1** PRISMA 2009 flow diagram for identification of relevant studies.

Based on the initial PICO question, studies involving patients with a condition of dyslipidaemia were included in our meta-analysis. In a randomised, placebo-controlled trial, the effects of Berberol were studied in patients with T1DM, and the inclusion criteria for this study did not involve dyslipidaemia and therefore, it was not included in the quantitative analysis [14].

Three studies conducted by Di Pierro et al. were not placebo-controlled. The first study assessing the efficacy of Berberol was uncontrolled [15]. In another study, the effects of Berberol were compared to *B. aristata* [16], whereas in a three-arm study, patients in every group received Berberol [4]. Finally, four placebo-controlled studies with 491 patients were assessed in the quantitative meta-analysis [17–20].

Overall, the methodical quality of the trials included in our final quantitative analysis was reckoned to be acceptable, mostly with a low or unclear risk of bias (**Figs. 1S** and **2S**, Supporting Information). In all the included studies, randomisation of the patients was done by the drawing of envelopes containing randomisation codes prepared by statisticians, thus, the selection bias (i.e., random sequence generation and allocation concealment) was reckoned to be low. Performance bias was also low in all the included studies because both Berberol and placebo were supplied as identical, opaque, white capsules in coded bottles. Therefore, the intervention and the placebo were identical in shape, size, and colour. It is not mentioned in either of the studies whether unblinding occurred before or after data analysis, and if the outcome assessment was performed in a blinded manner or not, hence, all the included studies have an unclear risk of detection bias. All of the studies showed a low risk of attrition and reporting bias and an unclear risk of other types of bias. Due to the low number of studies, publication bias was not assessed by Egger's test, nor by funnel plots.

All the included RCTs were conducted in Italy by the same research group, from 2013 until 2015. ▶ **Table 1** summarises the key characteristics of each included study. Sample size ranged from 98 to 163. In the studies included in the quantitative analysis, the effect of Berberol was investigated in adult, overweight, normotensive patients with a condition of euglycaemia (fasting plasma glucose < 100 mg/dL) and hypercholesterolaemia. In two trials [19, 20], the enrolled patients were intolerant to statins at high dosages. In the trials, patients were not included if they had secondary dyslipidaemia, impaired renal or hepatic function, or GI disorders. Women who were pregnant or breastfeeding or of childbearing potential and not taking adequate contraceptive precautions were also excluded.

In all the included trials, Berberol, a patented nutraceutical food supplement, was investigated. Posology was the same in all trials, two tablets daily: one at lunch, and another at dinner. Berberol contains 588 mg of *B. aristata* extract and 105 mg of *S. marianum* extract. Both extracts are standardised, the former one

▶ **Table 1** Characteristics of the studies (all placebo controlled, randomised trials) included in the final analysis.

First author (year)	Country	Group	Codes used in the manuscript	Sample size		Patient characteristics	Outcome measure(s)
				at baseline	at 3 months		
Derosa, Phytomedicine, 2015	Italy	Berberol	Derosa et al., 2015/1	81	78	Caucasian patients of either sex with a condition of euglycaemia and dyslipidaemia	Changes in blood lipid levels, and liver enzyme levels, HOMA-IR, FPG, BMI
		Placebo		82	77		
Derosa, Atherosclerosis, 2015	Italy	Berberol	Derosa et al., 2015/2	66	65	Caucasian patients of either sex with a condition of euglycaemia and dyslipidaemia	Changes in blood lipid levels, and liver enzyme levels, HOMA-IR, FPG, BMI
		Placebo		62	60		
Derosa, Expert Opin Biol Ther, 2013	Italy	Berberol*	Derosa et al., 2013/1	51	50	Caucasian patients of either sex with a condition of euglycaemia and dyslipidaemia	Changes in blood lipid levels, and liver enzyme levels, HOMA-IR, FPG, BMI
		Placebo*		47	45		
		Berberol**	Derosa et al., 2013/2	48	47		
		Placebo**		45	44		
Derosa, J Biol Regul Homeost Agents, 2013	Italy	Berberol*	Derosa et al., 2013/3	52	51	Caucasian patients of either sex with a condition of euglycaemia and dyslipidaemia	Changes in blood lipid levels, and liver enzyme levels, HOMA-IR, FPG, BMI
		Placebo*		50	49		
		Berberol**	Derosa et al., 2013/4	50	49		
		Placebo**		49	47		

*First 3-month long round. **Second round, after the washout period

contains 85% berberine, and the flavonolignan content of the latter one is not less than 60%. The product is manufactured and traded in Italy.

Studies published in 2015 lasted 6 months, while those studies that were published in 2013 evaluated the effects of Berberol for 3 months twice, i.e., in these studies patients had received Berberol for 3 months, and after a 2-month washout period, it was readministered to the same patients for another 3-month period. Both results of these studies were included in the statistical analysis. Extracted outcomes are listed in ▶ **Table 2**.

In two studies [19, 20], patients took a half dose of statins compared to what they had been taking prior to the trials. Unfortunately, in the other two studies [17, 18], the administered concomitant lipid-lowering drugs were not clearly indicated.

Although studies that did not comply with our PICO question were excluded from the quantitate analysis, the results of these studies may also contribute to the whole picture of the clinical efficacy of Berberol. Derosa et al. studied the effects of Berberol in 85 T1DM patients for 6 months in a randomised, double-blind, placebo-controlled setting [14]. The primary aim was to evaluate whether the addition of *B. aristata*/*S. marianum* to insulin therapy could lead to a decrease of the insulin dose requirement of the patients, and whether the combination of Berberol with reduced doses of insulin offered better glycaemic control to the patients. Furthermore, the study aimed to assess the possible lipid profile changes. Patients in the Berberol group were advised to take 1 tablet at lunch and 1 tablet at dinner. Among other parameters, patients' BMI, lipid profile, glycaemic parameters, and liver enzyme levels were measured at baseline and 6 months after randomisation. It was observed that in the Berberol group, both total and postprandial insulin requirements were reduced compared to baseline and placebo. Moreover, Berberol improved some glycaemic (FPG, PPG) and lipid parameters (LDL, HDL) without altering liver and kidney function levels.

A three-arm study assessed the efficacy of Berberol as a single and as an add-on therapy to statins and ezetimibe. This study was not included in the meta-analysis, since it was carried out in a non-randomised, active controlled setting. Nevertheless, it was concluded that Berberol may improve the lipid profile and glycaemic control in T2DM patients intolerant to statins [4].

In a single-blind, randomised, controlled study, Di Pierro et al. compared the efficacy and safety of Berberol and *B. aristata*, and this study shed light on the benefits of combining *B. aristata* with *S. marianum* [16]. Patients in either group received 1000 mg berberine daily, but patients in the Berberol group received berberine in combination with 210 mg of *S. marianum* extract. Therefore, the differences in the outcomes were presumably attributable only to the coadministration of *S. marianum*. A significant reduction in TC and TG levels was observed in both groups, but LDL and HbA_{1c} levels decreased significantly only in the Berberol group. These results indicate that Berberol is equally safe and more effective than the extract of *B. aristata* in patients with T2DM.

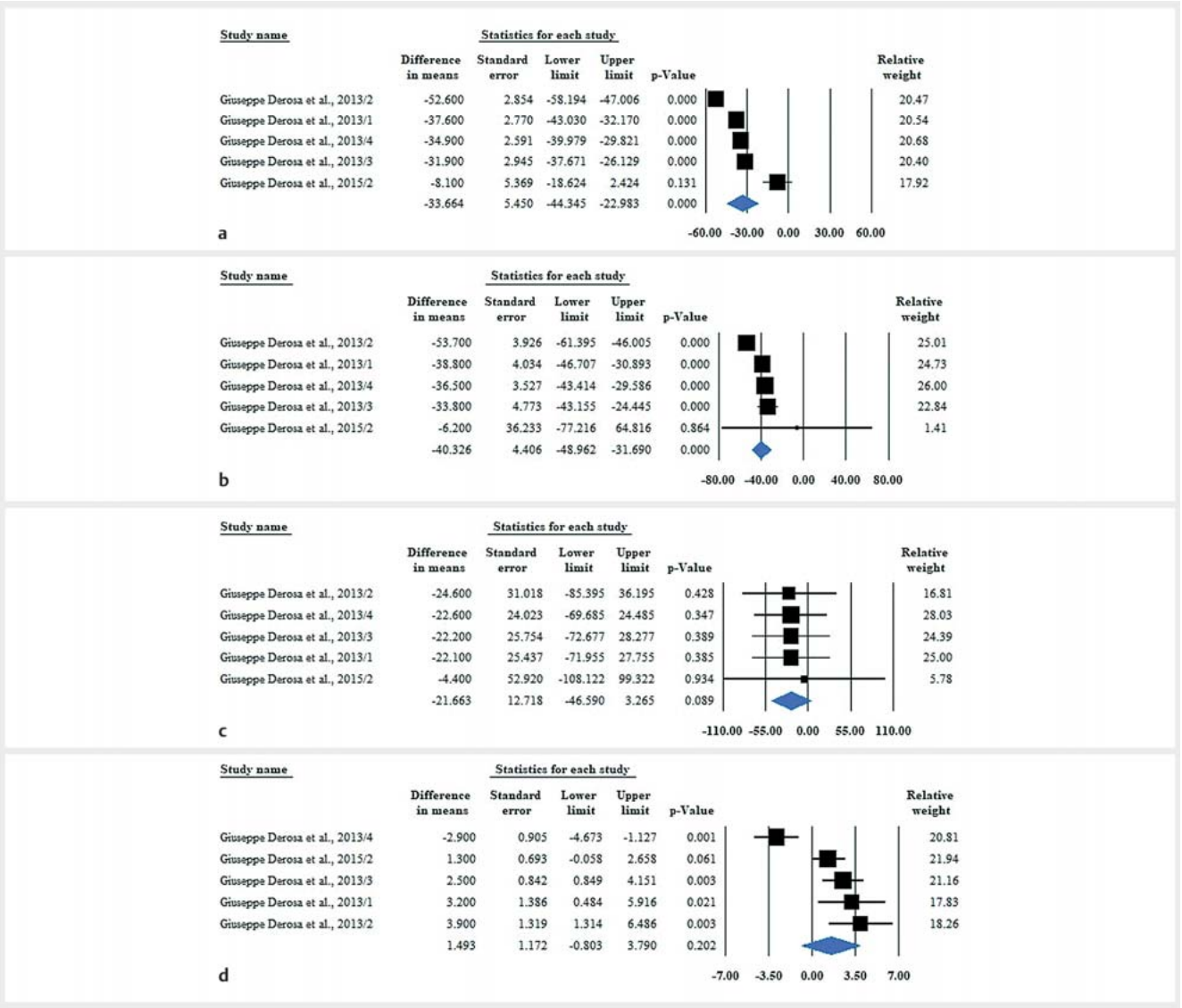
The first study that evaluated the efficacy and safety of Berberol was a noncontrolled pilot study involving 26 T2DM patients. After 90 days of treatment, a significant reduction was observed in the glycaemic (HbA_{1c}, basal insulin level, HOMA-IR) and lipid profile (TC, LDL, TG), whereas no adverse events attributable to the product were detected [15].

Besides Berberol, another combined product containing berberine and silymarin was investigated in a randomised, placebo-controlled trial [13]. Based on their results, this combination was also effective in reducing the patients' HOMA index and TC level ($p < 0.05$) without significant side effects.

▶ **Table 2** Outcomes of the RCTs included in the meta-analysis.

Parameter		Group											
		Derosa et al., 2015/1		Derosa et al., 2015/2		Derosa et al., 2013/1		Derosa et al., 2013/2		Derosa et al., 2013/3		Derosa et al., 2013/4	
		Berberol	Placebo	Berberol	Placebo	Berberol	Placebo	Berberol	Placebo	Berberol	Placebo	Berberol	Placebo
LDL (mean ± SD, mg/dL)	before	n. n.d*	n. n. d.*	129.2 ± 11.5	124.6 ± 10.6	151.0 ± 9.3	151.5 ± 9.3	156.1 ± 10.4	141.5 ± 7.8	151.3 ± 9.6	151.3 ± 9.7	148.3 ± 9.3	139.4 ± 8.2
	after	n. n. d.*	n. n. d.*	138 ± 14.6	141.5 ± 14.8	102.2 ± 5.8	140.3 ± 7.5	102.3 ± 5,8	140.3 ± 7.5	104.1 ± 6.9	136.0 ± 7.8	103.6 ± 6.9	129.6 ± 6.9
TC (mean ± SD, mg/dL)	before	n. n. d.*	n. n. d.*	188.6 ± 30.9	184.5 ± 28.3	212.0 ± 11.2	212.4 ± 11.5	218.0 ± 12.2	204.1 ± 9.3	214.2 ± 12.8	214.4 ± 13.0	201.4 ± 11.4	201.3 ± 9.8
	after	n. n. d.*	n. n. d.*	203.5 ± 35.7	205.6 ± 39.2	163.1 ± 6.7	202.3 ± 8.9	162.7 ± 6.5	202.5 ± 8.9	164.3 ± 7.1	198.3 ± 9.6	163.4 ± 7.0	190.8 ± 8.0
TG (mean ± SD, mg/dL)	before	n. n. d.*	n. n. d.*	92.8 ± 36.7	95.3 ± 38.02	99.6 ± 26.5	97.8 ± 24.9	105.5 ± 29.9	105.6 ± 28.1	102.7 ± 27.8	102.3 ± 27.4	99.9 ± 29.7	94.3 ± 24.3
	after	n. n. d.*	n. n. d.*	109.4 ± 43.6	116.3 ± 44.2	80.1 ± 19.8	100.4 ± 26.6	79.6 ± 19.1	104.3 ± 27.7	77.6 ± 17.9	99.4 ± 26.7	75.1 ± 16.8	92.1 ± 23.7
HDL (mean ± SD, mg/dL)	before	n. n. d.*	n. n. d.*	40.8 ± 4.6	40.3 ± 4.4	41.1 ± 5.0	41.3 ± 5.2	40.8 ± 4.6	41.5 ± 5.5	42.4 ± 4.2	42.6 ± 4.4	42.1 ± 4.0	43.0 ± 4.6
	after	n. n. d.*	n. n. d.*	42.6 ± 5.1	40.8 ± 4.5	44.9 ± 6.9	41.9 ± 5.7	44.5 ± 6.5	41.3 ± 5.2	44.7 ± 5.3	42.4 ± 4.4	44.8 ± 5.5	42.8 ± 4.5
AST (mean ± SD, U/L)	before	24.1 ± 12.2	25.1 ± 12.8	24.5 ± 12.4	25.1 ± 12.8	24.1 ± 12.1	24.3 ± 12.0	23.0 ± 11.1	24.3 ± 12.0	23.6 ± 11.6	23.4 ± 11.4	24.2 ± 12.0	24.4 ± 12.4
	after	23.9 ± 11.9	25.9 ± 13.2	24.8 ± 12.1	25.9 ± 13.2	24.9 ± 12.8	25.0 ± 12.4	24.7 ± 12.5	25.8 ± 13.3	24.6 ± 12.2	23.8 ± 11.7	24.2 ± 12.0	24.9 ± 12.8
ALT (mean ± SD, U/L)	before	20.6 ± 9.6	18.5 ± 7.8	19.8 ± 9.1	18.5 ± 7.8	20.2 ± 8.6	20.4 ± 8.8	21.3 ± 9.6	21.9 ± 9.9	19.7 ± 9.0	19.5 ± 8.8	20.9 ± 9.9	21.0 ± 10.2
	after	20.1 ± 9.4	19.3 ± 8.7	20.4 ± 9.8	19.3 ± 8.7	21.6 ± 9.8	22.3 ± 9.9	21.4 ± 9.6	22.6 ± 10.5	20.5 ± 9.6	20.8 ± 9.8	21.4 ± 10.4	21.7 ± 10.8
CK (mean ± SD, U/L)	before	161.9 ± 44.8	155.9 ± 40.2	158.2 ± 42.5	155.9 ± 40.2	112.2 ± 28.3	112.4 ± 28.4	114.2 ± 28.7	115.3 ± 29.7	122.4 ± 29.7	122.8 ± 30.1	124.4 ± 30.3	125.8 ± 31.4
	after	163.9 ± 45.2	159.4 ± 43.5	163.4 ± 44.3	159.4 ± 43.5	117.4 ± 29.9	116.5 ± 30.2	116.2 ± 29.5	120.1 ± 33.4	125.2 ± 30.9	127.8 ± 32.4	124.6 ± 30.5	122.9 ± 30.3
BMI (kg/m^2)	before	29.6 ± 1.2	29.6 ± 1.3	28.8 ± 1.1	29.5 ± 1.3	26.2 ± 1.7	27.0 ± 1.5	26.2 ± 1.6	26.9 ± 1.4	27.4 ± 1.1	27.1 ± 1.0	27.3 ± 1.1	26.6 ± 0.8
	after	29.2 ± 1.0	29.4 ± 1.1	28.6 ± 1.0	29.3 ± 1.1	25.9 ± 1.2	26.8 ± 1.4	25.9 ± 1.2	26.6 ± 1.2	27.3 ± 1.1	27.0 ± 0.9	27.1 ± 1.1	26.9 ± 0.8
HOMA-IR	before	n. n. d.*	n. n. d.*	2.06 ± 0.46	2.10 ± 0.48	n. n. d.*	n. n. d.*	n. n. d.*	n. n. d.*	2.10 ± 0.7	2.05 ± 0.5	2.05 ± 0.5	1.99 ± 0.5
	after	n. n. d.*	n. n. d.*	1.87 ± 0.38	2.00 ± 0.44	n. n. d.*	n. n. d.*	n. n. d.*	n. n. d.*	1.70 ± 0.3	1.93 ± 0.4	1.71 ± 0.3	2.01 ± 0.5
FPG (mg/dL)	before	n. n. d.*	n. n. d.*	92.8 ± 6.1	91.7 ± 5.9	84.1 ± 8.2	83.8 ± 7.9	84.4 ± 8.4	86.2 ± 10.3	84.1 ± 8.6	83.7 ± 8.2	83.7 ± 8.2	84.0 ± 8.4
	after	n. n. d.*	n. n. d.*	88.6 ± 5.8	90.9 ± 5.4	82.2 ± 6.9	82.8 ± 7.1	85.2 ± 9.3	85.4 ± 9.6	83.2 ± 7.8	83.1 ± 7.8	83.5 ± 8.1	83.1 ± 8

*n. n. d.: no numerical data

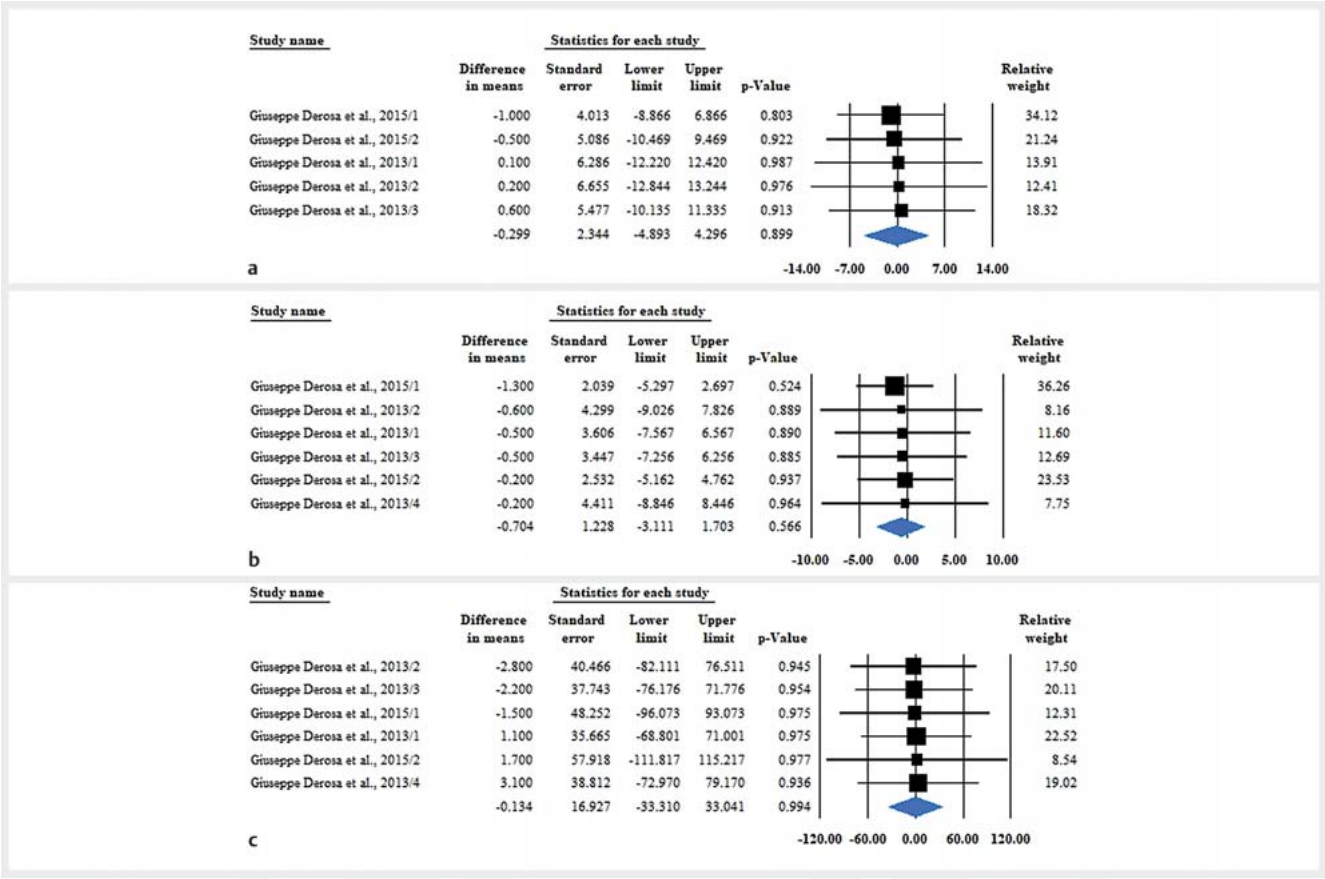


▶ **Fig. 2** Effects of Berberol on lipid levels in a random effects meta-analysis. **a** Effect of Berberol (MD with CI) on LDL level in mg/dL (n = 5). **b** Effect of Berberol (MD with CI) on TC level in mg/dL (n = 5). **c** Effect of Berberol (MD with CI) on TG level in mg/dL (n = 5). **d** Effect of Berberol (MD with CI) on HDL level in mg/dL (n = 5).

Altogether four trials assessing the effects of Berberol on the lipid profile was included in our meta-analysis. Two of the included trials published in 2015 were 6 months long [19, 20], and two studied the effects of Berberol for 3 months in two rounds [17, 18]. Unfortunately, in one of the articles, the authors failed to report some of the results numerically. The majority of the outcomes were shown only graphically in a figure. Therefore, we could not include the results of this trial in the quantitative analysis [20]. Hence, the results of three articles were pooled for statistical analysis. In two trials, Berberol had been administered for 3 months, and after a 2-month long washout period, it was readministered to the same groups. Results of the second 3-month periods were also taken into account because it is highly unlikely that the washout period was not long enough to reach pretreatment condition. Indeed, after 2 months, the lipid parameters of the patients returned to their initial levels. Therefore, in cases of LDL, HDL, TG, and TC, five results were analysed regarding the effects of Berberol in a 3-month period, even though this meant only three different groups of patients.

After 3 months, Berberol had significant effects on LDL and TC levels compared to the placebo. In case of the LDL level, the pooled MD was − 33.664 mg/dL (favouring Berberol; 95% CI: [− 44.345; − 22.983], p < 0.001) with a random effect model (p < 0.001, I^2 = 93.6%) (▶ **Fig. 2 a**). For the TC level, a random effect model was applied as well (p = 0.002, I^2 = 74.3%), and the MD was − 40.326 mg/dL (favouring Berberol; 95% CI: [− 48.962; − 31.690], p < 0.001) (▶ **Fig. 2 b**).

After a 3-month treatment, Berberol lowered the patients' TG level and increased their HDL level, but the results of our meta-analysis failed to show significant differences between Berberol and placebo within the 3-month treatment period. In both cases, a random effect model was applied (p = 0.802, I^2 = 0% for the TG



▶ **Fig. 3** Effects of Berberol on enzyme levels in a random effects meta-analysis. **a** Effect of Berberol (MD with CI) on AST level in U/L (n = 5). **b** Effect of Berberol (MD with CI) on ALT level in U/L (n = 6). **c** Effect of Berberol (MD with CI) on CK level in U/L (n = 6).

level; p = 0.202, I^2 = 86.292% for the HDL level). The MD was − 22.1663 mg/dL (favouring Berberol; 95% CI: [− 46.590; + 3.265], p = 0.089) for the TG level (▶ **Fig. 2c**) and + 1.493 mg/dL (favouring Berberol; 95% CI: [− 0.803; + 3.790], p = 0.202) for HDL (▶ **Fig. 2d**).

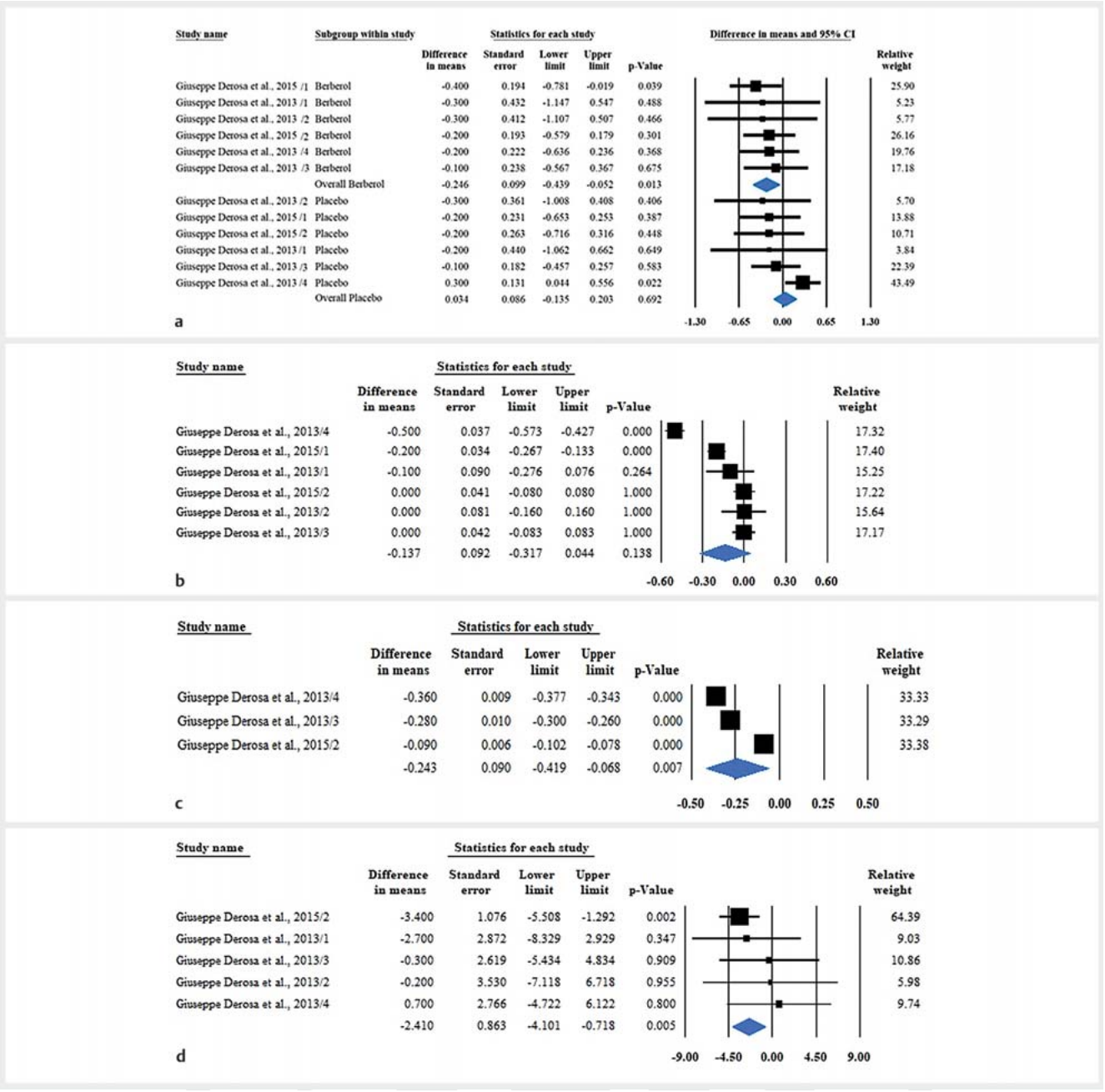
Enzymes indicating side effects involving the liver (AST, ALT) or musculoskeletal system (CK) were measured in all the included studies. In all cases, a random effect model was applied. All three enzyme levels seemed to be slightly lower after administering Berberol, however, the differences were not statistically significant. Based on the pooled results, for the AST level, the MD was − 0.299 U/L (favouring Berberol; 95% CI: [− 4.893; + 4.296], p = 0.899; with a heterogeneity of p = 0.992, I^2 = 0%) (▶ **Fig. 3a**). In the case of the ALT level, the MD was − 0.704 U/L (favouring Berberol; 95% CI: [− 3.111; + 1.703], p = 0.566; with a heterogeneity of p = 0.953, I^2 = 0%) (▶ **Fig. 3b**). Whereas, in the case of the CK level, the MD was even smaller between the two groups, and in this case, the MD was − 0.134 U/L (favouring Berberol; 95% CI: [− 33.310; + 33.041], p = 0.994; with a heterogeneity of p = 0.999, I^2 = 0%) (▶ **Fig. 3c**).

BMI values at baseline and 3 months after initiating the studies were given in each article, and altogether six results were available. Based on the pooled results, the BMI value was reduced significantly in patients receiving Berberol from baseline to 3 months after initiating the study (MD = − 0.246 kg/m^2, 95% CI: [− 0.439; − 0.052], p = 0.013; I^2 = 0%) and did not change in the placebo group (MD = + 0.034 kg/m^2, 95% CI: [− 0.135; + 0.203], p = 0.692; I^2 = 34.5%).

When the result of Berberol was compared to placebo at 3 months, the difference between the two groups diminished, and it was not significant (MD = − 0.137 kg/m^2, favouring Berberol; 95% CI: [− 0.317; + 0.044], p = 0.138; I^2 = 95.7%). In each case, a random effect model was applied (▶ **Fig. 4a, b**).

The HOMA index was given in two articles, yielding three results suitable for statistical analysis. A meta-analysis using a random effect model (p = 0.002, I^2 = 99.7%) revealed that Berberol lowered the HOMA index compared to placebo (MD = − 0.243, favouring Berberol; 95% CI: [− 0.419; − 0.068], p = 0.007) (▶ **Fig. 4c**). According to the combined meta-analysis, Berberol lowered the FPG level as well. In this case, using a random effect model (p = 0.757, I^2 = 0%), the pooled MD was − 2.410 mg/dL (favouring Berberol; 95% CI: [− 4.101; − 0.718], p = 0.005) (▶ **Fig. 4d**).

Both *B. aristata* and *S. marianum* have been safely used for a long time [5, 21]. Including the most recent RCTs, no serious adverse events attributable to either plant were reported. In the included four trials, none of the patients reported side effects after given Berberol [22, 23]. Changes in enzyme levels (ALT, AST, CK) were not significant in the trials, and our meta-analysis also confirmed that Berberol does not alter the level of these enzymes.



▶ **Fig. 4** Effect of Berberol on metabolic parameters in a random effects meta-analysis. **a** Three-month effect of Berberol (MD with CI) and placebo on BMI compared to baseline in kg/m^2 (n = 6). **b** Effect of Berberol (MD with CI) on BMI compared to placebo at 3 months in kg/m^2 (n = 6). **c** Effect of Berberol (MD with CI) on HOMA-IR (n = 3). **d** Effect of Berberol (MD with CI) on FPG in mg/dL (n = 5).

The grade of evidence of our statements was quantified with the GRADE approach (▶ **Table 3**). In our meta-analysis only, randomised controlled studies were included. Therefore, the baseline, the grade of evidence, was considered high. However, a bias-free high grade of evidence is only obtainable when analysing a large number of high-quality, randomised, controlled studies. To assess the grade of evidence, we considered five downgrading items (i.e., limitations in the design and implementation, indirectness, heterogeneity, imprecision, and publication bias).

Publication bias is suspected due to the fact that published evidence includes only a few small trials. Moreover, the authors list of the included trials overlaps. In addition, because of the wide range of CIs, imprecision is suspected, and its indirectness is also assumed, hence, the involved patient populations were not homogeneous (i.e., the response to certain lipid-lowering drugs may vary depending on the patients' tolerance to statins), and the concomitant therapies are not fully described in the articles. Overall, the lipid-lowering effects of Berberol and the finding that Berberol improves the lipid profile and may possess beneficial effects on

▶ **Table 3** Summary of findings. Population: adult patients with a condition of dyslipidaemia; intervention: Berberol; comparison: placebo; outcome: changes in lipid profile, enzyme levels, and metabolic parameters.

Outcomes	No. of studies included in the qualitative analysis (patients*)	Difference in means (95% confidence interval; p value)	Quality of evidence	Comments
LDL	3 (328)	**−33.664** (CI: [− 44.345; − 22.983], p < 0.001)	⊕⊕⊕⊕◯ very low	Downgraded for risk of bias, publication bias, imprecision, and indirectness.
TC		**−40.326** (CI: [− 48.962; − 31.690], p < 0.001)	⊕⊕⊕⊕◯ very low	Downgraded for risk of bias, publication bias, imprecision, and indirectness.
TG		**−21.663** (CI: [− 46.590; + 3.265], p = 0.089)	⊕⊕⊕⊕◯ very low	Downgraded for risk of bias, publication bias, imprecision, and indirectness.
HDL		**+1.493** (CI: [− 0.803; + 3.790], p = 0.202)	⊕⊕⊕⊕◯ very low	Downgraded for risk of bias, publication bias, imprecision, and indirectness.
FPG		**−2.410** (CI: [− 4.101; − 0.718], p = 0.005)	⊕⊕⊕⊕◯ very low	Downgraded for risk of bias, publication bias, imprecision, and indirectness.
HOMA-IR	2 (230)	**−0.243** (CI: [− 0.419; − 0.068], p = 0.007)	⊕⊕⊕⊕◯ very low	Downgraded for risk of bias, publication bias, imprecision, and indirectness.
AST	4 (491)	**−0.299** (CI: [− 4.893; + 4.296], p = 0.899)	⊕⊕⊕⊕◯ very low	Downgraded for risk of bias, publication bias, imprecision, and indirectness.
ALT		**−0.704** (CI: [− 3.111; + 1.703], p = 0.566)	⊕⊕⊕⊕◯ very low	Downgraded for risk of bias, publication bias, imprecision, and indirectness.
CK		**−0.134** (CI: [− 33.310; + 33.041], p = 0.994)	⊕⊕⊕⊕◯ very low	Downgraded for risk of bias, publication bias, imprecision, and indirectness.
BMI		**−0.137** (CI: [− 0.317; + 0.044], p = 0.138)	⊕⊕⊕⊕◯ very low	Downgraded for risk of bias, publication bias, imprecision, and indirectness.

*The number of patients at randomisation is given; ⊕⊕⊕⊕◯ means very low quality of evidence.

certain glycaemic parameters (HOMA-IR and FPG) without altering enzyme levels (AST, ALT, CK) and BMI in patients with a condition of dyslipidaemia is supported by very low-quality evidence, i.e., further research is very likely to change the estimate.

Discussion

Both *B. aristata* and *S. marianum* have proven beneficial effects in patients with metabolic syndrome and dyslipidaemia [5, 24]. The fixed combination of the aforementioned two plants is marketed as a food supplement in Italy. The present meta-analysis was designed to synthesise the currently available evidence on this product.

In a recent meta-analysis on a similar topic, the metabolic effects of the combination of berberine-silymarin were assessed [25]. Compared to that meta-analysis, the present study has certain strengths. One of these is transparency: our meta-analysis was registered in the PROSPERO register, and we predefined a question to be answered, as well as the population, the comparator, and the outcomes. The PICO question of the previous meta-analysis in unclear regarding the patient population. Using explicit eligibility criteria led to the exclusion of two trials that had been included in the previous meta-analysis [12, 13]. One of these publications contained unresolvable discrepancies in the published data, therefore, we decided not to include the results of this trial in our statistical analysis [12]. Another study included in the previous meta-analysis did not study the effects of Berberol, but a combination of berberine and silymarin in different doses compared to Berberol, therefore, this study did not comply with our PICO question [13]. A comprehensive search yielded two more eligible trials that were not included in the previous meta-analysis [18, 20]. Hence, data sets that are used in our meta-analysis differ significantly from that of the previous meta-analysis. Moreover, two further outcomes (i.e., HOMA index and BMI) were extracted and analysed in our meta-analysis. Further major strengths of the present paper are that studies with different treatment durations were not analysed together and we used the GRADE approach to estimate the quality of evidence of all outcomes assessed.

Based on a comprehensive literature search, four RCTs were identified, which included 491 patients with dyslipidaemia. The effects of Berberol on the outcomes tested in RCTs are summarised in ▶ **Table 2**. For the evaluation of the effects of a natural product, it is indispensably necessary to describe the applied product properly. In our meta-analysis, the effects of a well-described product were assessed. In the included trials the posology of the study drug was uniform, and even though almost all the publications reported on the same outcomes, the concomitant lipid-lowering medications taken simultaneously with the study drug were not described in two articles [17, 18]. However, due to the limited number of included trials, the forest plots are short, and it was not possible to properly assess publication bias by the Egger's tests or by funnel plots. Based on the LDL and TC results, the combined preparation is confirmed to ameliorate dyslipidaemia, but its effects on TG and HDL levels are not significant. Based on our meta-analysis, the superiority of Berberol over placebo in the treatment of dyslipidaemia is not unambiguous. These results are in line with the expectations reasoned by the low number of trials focusing on Berberol.

Berberol seems to be safe and effective as a complementary therapy for dyslipidaemia. Nevertheless, the optimum duration of the treatment is still unclear, since we could only assess the results obtained at 3 months statistically. In the studies lasting for 6 months, the superiority of Berberol over placebo was reported. In these studies, where Berberol was combined with reduced doses of statins, worsening of patients' lipid profile was observable in the placebo groups, and despite the reduction of the statin dosage, patients' TC, LDL, and TG levels did not increase significantly in the Berberol groups [19, 20]. The available numerical data for the 6-month long administration was not sufficient to perform a statistical analysis.

Limitations of our literature review and meta-analysis are largely related to the original studies. All the included trials were carried out in Italy, and there is a clear overlap between the authors of the papers. All of the quantitatively analysed trials were published within a relatively short time period, between 2013 and 2015. We have contacted the corresponding author of the included studies to obtain individual patient data and to clarify the concomitant drugs that the patients had been receiving in the trials published in 2013. Up until now, we have received no answers to our concerns.

In summary, Berberol improves the lipid profile and glycaemic parameters of patients with a condition of dyslipidaemia by lowering LDL, TC, HOMA-IR, and FPG levels. Moreover, it has beneficial, but not statistically significant, effects on the patients' BMI, HDL, and TG levels. However, the optimum dose and duration of treatment is still unclear. Involving larger patient populations probably would allow for the analysis of the effects of Berberol in dose- and duration-based subgroups. In the included studies, Berberol was well tolerated and its adverse effect profile did not differ from that of the placebo. Based on our results, Berberol provides a safe complementary therapy for patients with dyslipidaemia. Nevertheless, considering the limitations, our conclusion is that further and larger trials performed by independent research groups are needed to assess the efficacy of Berberol with a lower risk of bias. Our meta-analysis supports the use of Berberol, yet highlights the lack of clinical data regarding natural products.

Methods

This meta-analysis was reported according to the PRISMA statement, and it was registered in PROSPERO *a priori* with the registration number CRD42019137349.

The following PICO (patients, intervention, comparison, outcome) format was applied: P – patients diagnosed with dyslipidaemia; I – fixed combination of *B. aristata* and *S. marianum* (Berberol); C – placebo; and O – changes in LDL, TG, TC, and HDL levels, liver enzyme levels (ALT, AST), CK level, and other metabolic parameters (BMI, HOMA-IR, FPG).

Information sources and search strategy

A literature search was conducted until April 10, 2019 by using the following search strategy: [*berberol OR 'berberis aristata'/exp OR 'berberis aristata' OR (('berberis'/exp OR berberis) AND aristata) OR (('berberine'/exp OR berberine) AND ('silymarin'/exp OR silymarin)) OR 'silybum marianum'/exp OR 'silybum marianum' OR (('silybum'/exp OR silybum) AND marianum)] for EMBASE; [berberol[All Fields] OR (("berberis"[MeSH Terms] OR "berberis"[All Fields]) AND aristata [All Fields]) OR (("berberine"[MeSH Terms] OR "berberine"[All Fields]) AND ("silymarin"[MeSH Terms] OR "silymarin"[All Fields])) OR ("milk thistle"[MeSH Terms] OR ("milk"[All Fields] AND "thistle"[All Fields]) OR "milk thistle"[All Fields] OR ("silybum"[All Fields] AND "marianum"[All Fields]) OR "silybum marianum"[All Fields])]* for MEDLINE (via PubMed); *berberol OR (berberis aristata) OR (berberine AND silymarin) OR (silybum marianum)* in Title Abstract Keyword for Cochrane Central Register of Controlled Trials (CENTRAL); *and [((((berberol OR berberis aristata) OR (berberine AND silymarin)) OR silybum marianum)* Timespan: All years. Indexes: SCI-EXPANDED, SSCI, A&HCI, ESCI.] for Web of Science. No language, publication date, or publication status restrictions were applied. The reference lists of all identified articles were inspected for further possible eligible studies.

Eligibility criteria and study selection

Randomised, placebo-controlled trials evaluating the effects of the combination of *B. aristata* and *S. marianum* in adult patients with a condition of dyslipidaemia were included. Abstracts, case series, and case reports were excluded. For reference management, Mendeley 1.17.9 was used. After removing duplicates, the remaining records were screened for eligibility based on the abstracts. The eligibility of the full texts of the resulting records was assessed by two reviewers (V. V., B. T.) independently. In case of disagreement between reviewers, a third reviewer (D. C.) was consulted.

Data extraction and synthesis of results

Study characteristics and results were extracted by the two reviewers (V. V., B. T.) independently. The following data items were extracted from the included papers: study design, characteristics of the patient population and sample size, intervention details, type of comparator(s), outcome measures, and overall results. LDL, HDL, TG, TC, ALT, AST, CK, and FPG levels, BMI, and HOMA-IR were extracted as outcome measures.

Risk of bias

The risk of bias was analysed by two of the authors (D. C., V. V.), using the Cochrane Risk of Bias Tool, which includes the following domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other scores of bias. For each domain, studies were judged to have a high (red), unclear (yellow), or low (green) risk of bias (**Fig. 1S**, Supporting Information). Disagreements were resolved by consensus. Risk of bias figures were prepared by using the RevMan 5 statistical program [26].

Statistical analyses

To compare mean data, MD with 95 % CIs were computed. Pooled estimates were calculated with a random effects model by using the DerSimonian-Laird method. A two-tailed $p < 0.05$ was considered statistically significant. Data were visualised using forest plots.

Heterogeneity was tested by both performing Cochran's *Q* test and calculating Higgins' I^2 indicator [26, 27]. The *Q* statistics were computed as the weighted sum of individual study effects' squared deviations from the pooled effect, with the weights being used in the pooling method. P values were obtained by comparing the test statistics with a chi-square with *k*-1 degrees of freedom (where *k* was the number of studies). A p value of less than 0.1 was considered suggestive of significant heterogeneity. The I^2 index corresponds to the percentage of the total variability across studies that is due to heterogeneity. Based on Cochrane's handbook, a rough classification of its value is as follows: low (0–40 %), moderate (30–60 %), substantial (50–90 %), and considerable (75–100 %) [28]. All statistical analyses were performed using Comprehensive Meta-Analysis (version 3, Biostat Inc.).

Quality of evidence

GRADE was used for estimating the quality of evidence of all outcomes assessed [29].

Supporting information

A risk of bias summary and graph are available as Supporting Information.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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