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REVIEW

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Efficacy evaluation of *Berberis aristata* and *Silybum marianum* fixed dose combination on glycaemic and insulin resistance parameters in adult population: a systematic review and meta-analysis of randomized controlled trials

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Abstract

Background Diabetes is one of the most prevalent metabolic diseases with high rate of morbidity and mortality. The increased level of blood glucose level and increased insulin resistance is the hallmark of diabetes. Currently, various non-pharmacological and pharmacological therapeutic options are used for lowering the glucose level and improving the insulin activity. The current systematic review and meta-analysis study was conducted to evaluate the efficacy of *Berberis aristata* and *Silybum marianum* fixed dose nutraceutical combination on serum glucose and glycated haemoglobin level and insulin resistance parameters.

Main Body Randomized controlled trials, identified from three online databases, evaluating the efficacy of *Berberis aristata* and *Silybum marianum* fixed dose combination were identified and evaluated as per pre-defined protocol. Quality of studies was evaluated using PEDro scale, and risk of bias was assessed using Cochrane Risk of Bias Tool. Pooled effect was reported as mean difference (MD) and 95% confidence interval, while the complete study was conducted as per PRISMA and Cochrane guidelines. After complete literature screening and evaluation process, seven studies were included in the final analysis. Data of 825 participants (active group: 416 participants and control group: 409 participants) were utilized for the statistical analysis. All included studies (except one) were of good quality. Supplementation of fixed dose combination significantly reduced glucose level (MD: − 5.26 mg/dl; $p = 0.02$) and glycated haemoglobin (HbA1c) level (MD: − 0.69%; $p < 0.0001$) as compared to control therapy, while greater insulin resistance reduction was observed in active group and the difference approached significance (MD: − 0.64 HOMA-IR score; $p = 0.08$). Risk of bias analysis revealed some concerns regarding biasness (mainly due to randomization, outcome measurement and selected reporting biasness). All included studies had moderate risk of biasness. Sensitivity analysis revealed effect of particular study on overall heterogeneity observed, while neither significant publication bias nor any missing study was observed.

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Conclusion The results of current study suggest that *B. aristata* and *S. marianum* fixed dose combination is effective in improving glycaemic and insulin parameters and can be effective in diabetic population. The observed sensitivity of certain studies on overall heterogeneity and the moderate risk of biasness warrants further well-designed clinical studies to strengthen the results of current study.

Keywords *Berberis aristata*, *Silybum marianum*, Diabetes, Glucose level, Insulin resistance, HbA1c, Nutraceutical, Systematic review, Meta-analysis

Background

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by hyperglycaemia resulting from defects in insulin secretion, insulin action, or both. Diabetes is a major and the most prevalent metabolic disease affecting millions of people worldwide [1]. In 2021, around 537 million adult population is estimated to have diabetes and it is estimated to reach 783 million by 2045 [2]. If left untreated, diabetes can lead to serious complications, such as cardiovascular disease [3, 4], chronic kidney disease [5, 6], blindness [7, 8] and lower limb amputations [9, 10].

The consequences of diabetes are far-reaching and can have a significant negative impact on the quality of life of individual. Diabetes is one of the top 10 causes of death globally, with an estimated 4.2 million deaths attributed to the disease in 2019, equivalent to 11.3% deaths from all causes and accountable to eight deaths every minute [11, 12]. In addition to its physical and emotional toll on individuals and families, diabetes also imposes a significant economic burden on healthcare systems and societies. According to the International Diabetes Federation (IDF), the global healthcare expenditure for diabetes was estimated to be $966 billion in 2021 and is projected to reach $1,054 billion by 2045 [13].

Pharmacological and non-pharmacological treatments are available to manage diabetes and reduce the risk of complications. The American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) recommend a patient-centred approach to diabetes care, which includes individualized treatment plans based on patient medical condition and preference [14]. Pharmacological treatments for diabetes include oral hypoglycaemic agents, injectable medications such as insulin and glucagon-like peptide-1 receptor agonists, and other medications that target specific complications of diabetes, such as hypertension and dyslipidaemia, while non-pharmacological interventions such as lifestyle modifications, including diet and exercise, are also recommended to manage diabetes [15, 16]. The use of nutraceutical and herbal supplements in treating DM has raised in recent years due to their better efficacy and less side effects [17]. Nutraceuticals is a broad term which includes botanicals, herbal supplements, probiotics, prebiotics, vitamins, minerals, dietary fibres, polyunsaturated fatty acids, protein and amino acids, and other related substances [17]. Various herbal supplements have been studied for their efficacy in DM, including *Acacia arabica*, *Aegle marmelos*, *Allium cepa*, *Allium sativum*, *Aloe vera*, *Annona squamosa*, *Artemisia pallens*, *Azadirachta indica*, *Andrographis paniculata*, *Biophytum sensitivum*, *Beta vulgaris*, *Brassica juncea*, *Cassia auriculata*, *Boerhavia diffusa*, *Caesalpinia bonducella*, *Citrullus colocynthis*, *Cajanus cajan*, *Coccinia indica*, *Casearia esculenta*, *Catharanthus roseus*, *Camellia sinensis*, *Enicostemma littorale*, *Eugenia jambolana*, *Helicteres isora*, *Ipomoea batatas*, *Morus alba*, *Scoparia dulcis*, *Murraya koenigii*, *Ocimum sanctum*, *Punica granatum*, and many others [17].

Berberis aristata (Berberidaceae family) is a shrub native to the Himalayas and widely used in traditional medicine for its various therapeutic properties [18]. Its roots and stem bark contain several bioactive compounds, including berberine, which has been shown to have antidiabetic effects [18]. The AMP-activated protein kinase pathway (AMPK), that have a key role in glucose and lipid metabolism, is one of the key pathway which is activated by berberine supplementation, leading to improved glucose uptake and insulin sensitivity [19, 20]. Several clinical studies have demonstrated the efficacy of berberine in improving glycaemic control in patients with type 2 diabetes [21].

Silybum marianum (Asteraceae family), also known as milk thistle, is a plant native to the Mediterranean region and widely used for its hepatoprotective effects. The active component of milk thistle is silymarin, a complex mixture of flavonolignans that has been shown to have antioxidant, anti-inflammatory and neuroprotective properties [22]. Silymarin has been found to improve insulin sensitivity of insulin receptors, ameliorates insulin resistance and reduces hepatic glucose production [23, 24]. Silymarin has also been shown to protect against diabetes-related complications, such as diabetic nephropathy, by reducing oxidative stress and inflammation [25]. Clinical studies in humans have demonstrated the potential of silymarin to improve glycaemic control and reduce markers of oxidative stress in patients with type 2 diabetes [26].

Berberol is an herbal fixed dose combination containing 588 mg hydro-ethanolic extract from cortex from *B. aristata* standardized to contain at least 85% berberine and 105 mg hydro-ethanolic extract from fruits of *S. marianum* standardized to contain 60–80% flavanol-lignans calculated as silybin. The efficacy of this herbal fixed dose combination supplement has been evaluated in various clinical studies and has been shown to have a range of positive effects on human health, including the management of lipid and glucose metabolism, but no meta-analysis study has been previously conducted to synthesize the results of published clinical studies evaluating the efficacy of the fixed dose combination on markers of diabetes. Hence, the current systematic review and meta-analysis study was conducted to evaluate the effectiveness of a fixed dose combination of *B. aristata* and *S. marianum* supplementation in diabetes condition.

Main text

Study conduct

The current systematic review and meta-analysis study was conducted in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA), Cochrane Handbook for systematic reviews of intervention and the Cochrane statistical method guidelines [27, 28]. The study was conducted based on a pre-designed protocol, and randomized controlled clinical trials were evaluated as per pre-defined inclusion and exclusion criteria. The current study was based on the questions framed as per the PICOS (population, interventions, comparator, outcomes, study design) criteria (Table 1). Based on the PICOS criteria, the study question was as follows: Is *Berberis aristata* and *Silybum marianum* fixed dose combination effective in improving glycaemic index and insulin resistance parameters in participants with impaired glucose level and/or insulin resistance?

Search strategy

The Google scholar, PubMed, and Science Direct online databases were searched independently from the year 2000 until November 2023 by two review authors. The literature search was conducted by using combination of Medical Subject Heading (MeSH) terms along with free-text words related to *B. aristata* and *S. marianum* fixed dose combination supplementation and its effect on glycaemic and insulin parameters. The complete search strategy is as follows: '(Berberol) OR (((*Berberis aristata*) OR (*B.aristata*) OR (*B. aristata*)) AND ((*Silybum marianum*) OR (*S. marianum*) OR (*S.marianum*))) AND ((glucose level) OR (glucose) OR (sugar level) OR (sugar) OR (glycated haemoglobin) OR (glycated haemoglobin) OR (HbA1c) OR (insulin resistance) OR (insulin sensitivity) OR (HOMA)) AND ((clinical trial) OR (clinical study) OR (randomized study) OR (randomized trial) OR (controlled study) OR (controlled trial))'.

Eligibility criteria

The articles were evaluated and screened based on predefined inclusion and exclusion criteria. Articles of randomized controlled clinical studies, available as full-text articles in the English language, evaluating the efficacy of *B. aristata* and *S. marianum* fixed dose combination on the serum glucose level, serum glycated haemoglobin level and insulin resistance parameters were included in the current study. Articles of in vitro studies, pre-clinical animal model studies and clinical studies of study design other than randomized controlled design, evaluating the efficacy of different interventions other than the *B. aristata* and *S. marianum* fixed dose combination on parameters other than the serum glucose level, serum glycated haemoglobin level and insulin parameters and not available as full-text article or available in language other than the English language were excluded from the current study.

Table 1 PICOS criteria for study determination

Parameter	Description
Population	Participants with increased blood glucose and/or insulin resistance level
Intervention	Fixed dose combination of *Berberis aristata* and *Silybum marianum* (either as single therapy or in combination with other therapies)
Comparator	Either placebo, standard therapy alone, or any other supplementation other than the fixed dose combination of *Berberis aristata* and *Silybum marianum*
Outcomes	1. Blood glucose level 2. Glycated haemoglobin (HbA1c) level 3. Insulin resistance level (HOMA-IR score)
Study design	Randomized, controlled clinical study

HOMA-IR homeostatic model assessment for insulin resistance

Study selection and data extraction

After retrieval of articles from online databases and after duplicate removal, two review authors independently screened the title and abstract of the studies for eligibility. Studies deemed eligible after initial screening were evaluated using full-text article evaluation.

Data from included studies were extracted by one review author and independently validated by other review author. Using a pre-designed excel worksheet, the following study characteristics were extracted from the included studies: lead author, publication year, indication, sample size, age, interventions provided and duration of study. Additionally, the data regarding glucose level (in mg/dl), glycated haemoglobin (HbA1c) level (in percentage) and homeostatic model assessment for insulin resistance (HOMA-IR) score were extracted in a separate pre-designed excel worksheet.

Study quality and risk of bias assessment

The Physiotherapy Evidence Database tool (PEDro scale) was used to evaluate the biasness within studies, while the Cochrane Risk of Bias Tool (RoB2) was used to evaluate the biasness between studies as both these scales have demonstrated high validity and inter-rater reliability [29, 30]. The PEDro scale evaluation and the RoB2 assessment were conducted independently by two review authors, and the overall judgment of assessment was discussed among authors. Any discrepancy(s) between the result of assessment were discussed among the authors by joint consensus.

The PEDro scale evaluates the internal and external validity, statistical sufficiency and the overall study quality and categorises the studies into following: high quality (≥ 8 points), moderate quality (4 – 7 points) and low quality (≤ 3 points).The criteria assessed by the tool are as follows: eligibility criteria specified, subject randomisation, allocation concealment, the similarity of baseline prognosis between groups, blinding of subjects, therapists and assessors, a primary outcome measurement on $\geq 85\%$ of initial subjects, use of intention-to-treat analysis, use of variability measures and use of between-group comparison methods [31, 32].

RoB2 tool assesses overall biasness that might have influenced the results of study based on five domains, namely randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome and selection of reported result [33]. As per the study details, the RoB2 tool pre-designed form is filled and based on the tool algorithm, an outcome of low, some concern, or high risk of bias is generated along with the overall judgement. The overall judgement of independent assessment was discussed among authors, and any disagreement was discussed between the authors along with other review authors by considering the full-text of article for final conclusion.

Statistical analysis

The RevMan statistical software (Desktop v5.4) provided by Cochrane collaboration network was used for conducting meta-analysis. Data for individual evaluation parameter were presented separately as mean difference (difference between baseline and final value) and standard deviation (change from baseline) (SD_{change}). The data were evaluated using continuous evaluation method, and the pooled analysis effect was presented as pooled mean difference (MD) with 95% confidence interval (95% CI). SD_{change} for individual parameters was adopted from respective articles, and in case SD_{change} was not provided; then, it was estimated using the following formula adopted as per Cochrane recommendations [34].

$$SD_{\text{change}} = \sqrt{(SD_B^2 + SD_F^2) - (2 \times r \times SD_B \times SD_F)}$$

where "SD_B" and "SD_F" denote standard deviation at baseline and final visit, respectively, while "r" denotes the correlation coefficient, either obtained from other studies or considered to be 0.7 to provide a conservative estimate as undertaken from previous studies [35]. The effect of interventions on individual evaluation parameter was visually presented as forest plots for individual evaluation parameter. The model of effect analysis was decided based on the heterogeneity significance (I^2 value). If the heterogeneity was found to be low ($I^2 \leq 50\%$), the fixed effect model was utilized for the analysis of final data outcome, and if the heterogeneity was found to be high ($I^2 > 50\%$) then random effect model was utilized for the analysis of final data outcome. Sensitivity analysis was conducted by using leave-one-study-out analysis approach using the OpenMeta [Analyst] software. By using the sensitivity analysis, the effect of individual included studies on overall pooled effect and observed heterogeneity was evaluated. The Meta-Essential (v1.5) software package was used for publication bias assessment. Publication bias was statistically assessed using egger regression test and Begg–Mazumdar test, while publication bias was visually assessed using forest plot of individual evaluation parameter. Additionally, the trimming and filling analysis was conducted to identify any missing study(s) and its effect on overall effect size (Cohen's d value). The p-value of < 0.05 was considered to determine significance.

Results and discussion

Study selection process, study characteristics and quality assessment

The initial literature search revealed 811 articles and after duplicate removal, 633 articles were initially screened for eligibility. Eight studies were evaluated completely using full-text screening out of which seven studies [36–42] were included in the study and one study [43] was excluded from the study after the eligibility screening. The complete study selection process is presented in Fig. 1. The data of 825 participants were included in the final analysis, from which 416 participants were allocated to active therapy group, while 409 participants were allocated to control therapy group. The detailed characteristics of individual studies are presented in Table 2.

The quality of included studies was evaluated using PEDro scale, and the overall result is presented in Table 3. Out of seven included studies, one study was of moderate quality [38], while all other studies were of good quality. While all studies reported eligibility criteria,

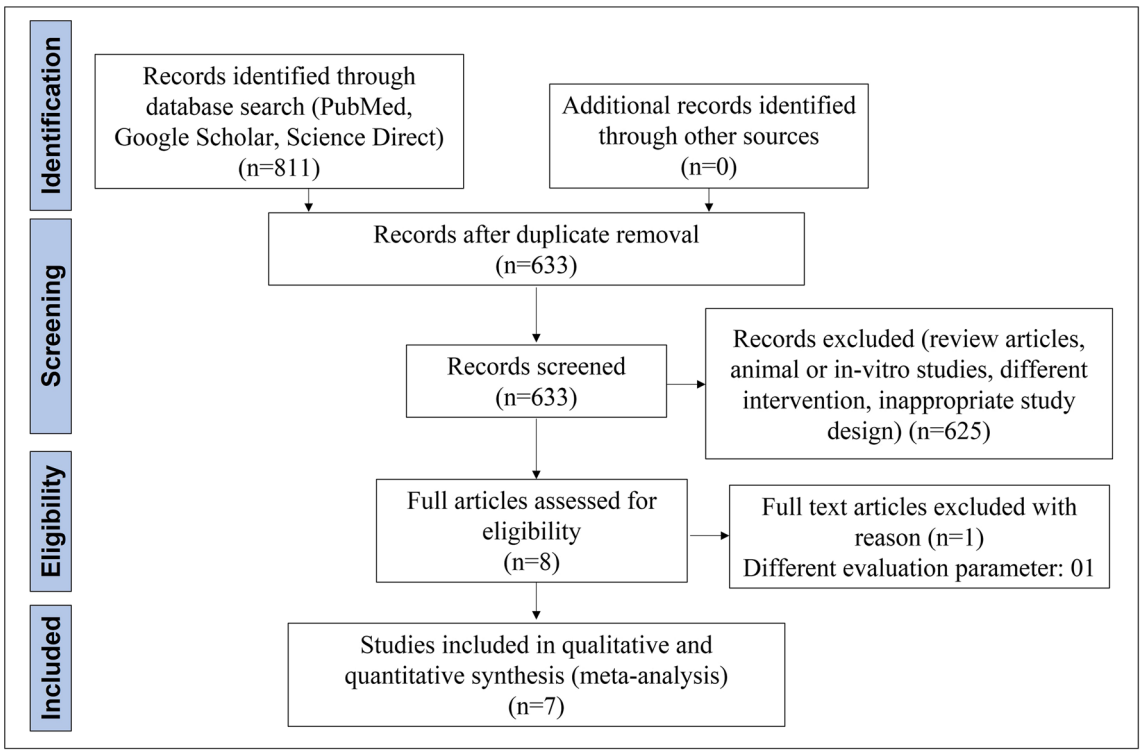

Fig. 1 PRISMA study selection flowchart

Table 2 Characteristics of included studies

Author	Year	Indication	Treatment group		Control group		Control intervention	Study duration
			N	Age	*N*	Age		
Derosa [36]	2013	Dyslipidaemia	51	52 ± 10.5	47	52 ± 10.5	Placebo	3 months
Derosa [37]	2013	Dyslipidaemia	52	51.4 ± 9.5	50	51.4 ± 9.5	Placebo	3 months
Pierro [38]	2013	Type 2 diabetes	32	67.85 ± 10.81	31	66.35 ± 9.8	*B. aristata* supplement	4 months
Derosa [39]	2015	Dyslipidaemia	66	57.8 ± 12.6	62	57.9 ± 12.9	Placebo	3 months
Guarino [40]	2015	Obese + type 2 diabetes	25	54 ± 5	25	56 ± 7	Placebo	6 months
Derosa [41]	2016	Type 1 Diabetes	41	30.7 ± 8.1	44	29.8 ± 7.2	Placebo	6 months
Guarino [42]	2017	Obese + type 2 diabetes	68	56 ± 8	68	55 ± 9	Placebo	52 weeks

Age presented as mean ± standard deviation

N number of participants

Table 3 Quality assessment of included studies as per PEDro scale

Parameters	Study						
	Derosa [36]	Derosa [37]	Pierro [38]	Derosa [39]	Guarino [40]	Derosa [41]	Guarino [42]
Eligibility criteria specified	1	1	1	1	1	1	1
Random allocation	1	1	1	1	1	1	1
Concealed allocation	1	1	0	1	1	1	1
Groups similar at baseline	1	1	1	1	1	1	1
Subject blinding	1	1	1	1	1	1	1
Therapist blinding	1	1	0	1	1	1	1
Assessor blinding	0	0	0	0	0	0	0
Less than 15% dropouts	1	1	1	1	1	1	1
Intention-to-treat analysis	1	1	0	1	1	1	1
Between-group statistical comparison	1	1	1	1	1	1	1
Point measures and variability	1	1	1	1	1	1	1
Overall score	10	10	7	10	10	10	10

randomization allocation, groups similarity at baseline, subject blinding, low dropout rate (below 15%), point and variable measures, and statistical comparison between the intervention groups, none of the included studies provided details of assessor blinding. While the assessor blinding may have significant impact on the overall result of clinical study, the major outcome parameters of current study are laboratory-evaluated parameters, and the influence of assessor biasness might be negligible in the current study context. The overall detailed quality evaluation and criteria for judgement are provided as Additional file 1.

Risk of bias assessment

Among the seven included studies, all the studies were found to have moderate level of biasness. All included studies had risk of biasness regarding randomization process, while moderate biasness regarding measurement of outcome parameter was observed in three studies [37, 38, 41], and biasness regarding reported result selection was observed in three studies [40–42]. The result of risk of biasness assessment of individual studies is presented in Fig. 2A, while the result of overall assessment is provided as Fig. 2B.

Meta-analysis

Among the included studies, the efficacy of interventions on plasma glucose level was evaluated in five studies [36–39, 41], and data of 470 participants (237 participants in active group and 233 participants in control group) were used for final analysis. Supplementation of *B. aristata* and *S. marianum* combination showed significant reduction in plasma glucose level (MD: − 5.30 mg/dl; 95% CI − 9.91 to − 0.70; $p=0.02$; Fig. 3) as compared to control group. Significant heterogeneity was observed among included studies ($I^2=90\%$). Sensitivity analysis revealed no significant effect of any included studies on overall observed heterogeneity (Table 4), while removal of two studies [39, 41] individually made the observed pooled effect insignificant (Fig. 6A).

The effect of interventions on HbA1c level was evaluated in four studies [38, 40–42], and data of 328 participants (161 participants in active group and 167 participants in control group) were included in final analysis. Supplementation of *B. aristata* and *S. marianum* showed significant reduction in HbA1c level (MD: − 0.69%; 95% CI − 1.02 to − 0.37; $p<0.0001$; Fig. 4) as compared to control therapy. Random effect model was used for pooled effect estimate due to significant heterogeneity among included studies ($I^2=90\%$). Sensitivity analysis revealed no significant effect of individual studies on overall pooled estimate (Fig. 6B), while removal of one particular study [42] reduced the observed heterogeneity to a non-significant range ($I^2=39\%$) as detailed presented in Table 4.

Among the included studies, the effect of interventions on reducing insulin resistance parameter (HOMA-IR score) was evaluated in four studies [37, 39, 40, 42]. Data of 416 participants (active group: 211 participants; control group: 205 participants) were analysed that showed that supplementation of *B. aristata* and *S. marianum* combination reduced HOMA-IR score compared to control group, while the difference approached significance (MD: − 0.64; 95% CI − 1.36 to 0.07; $p=0.08$; Fig. 5). Significant heterogeneity was observed among included studies ($I^2=99\%$); hence, random-effect model was used for pooled analysis. Sensitivity analysis revealed removal of one particular study [42] reduced the overall

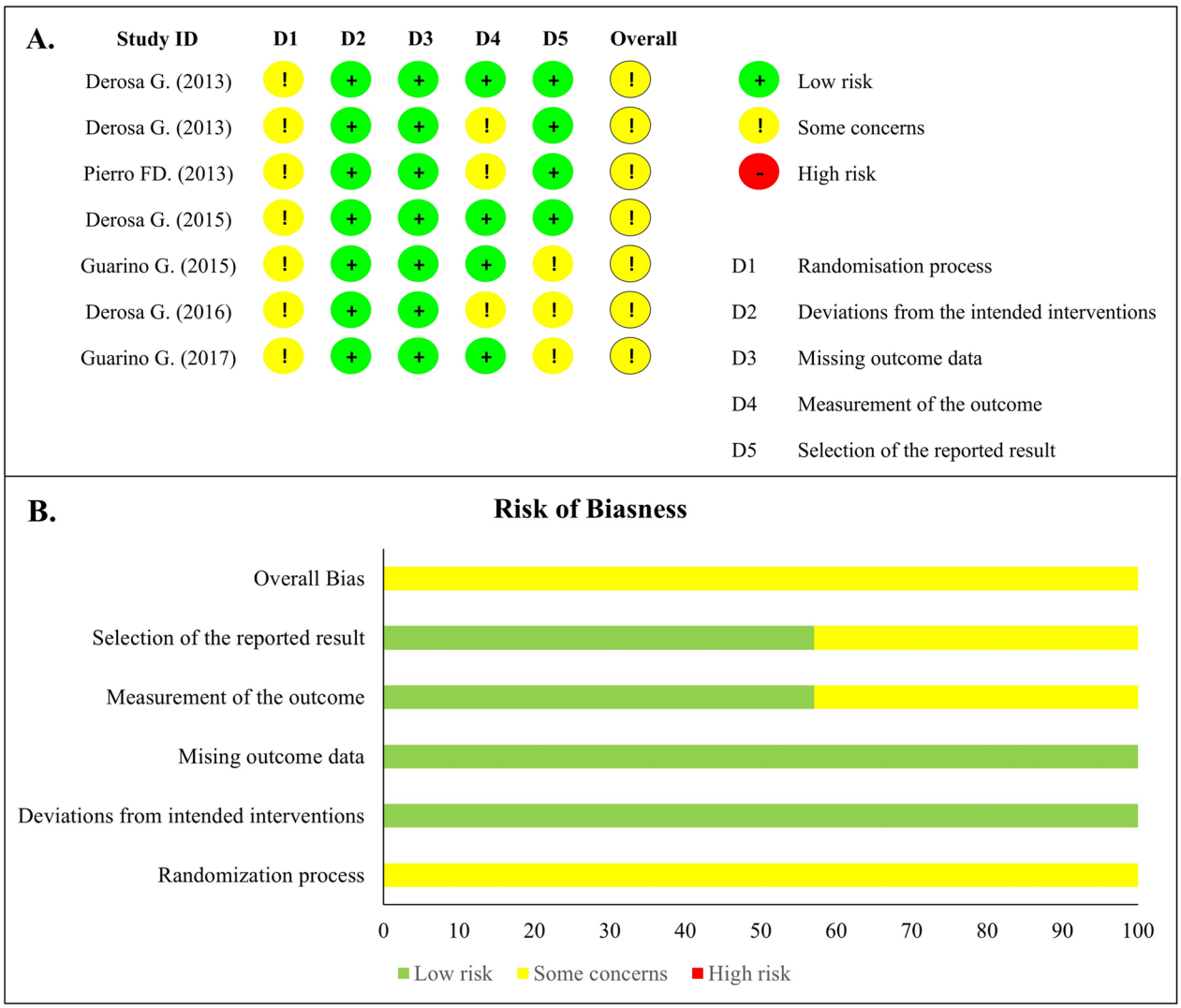

Fig. 2 Risk of bias assessment of (**A**) individual included studies and (**B**) overall risk of bias assessment

observed heterogeneity to non-significant range ($I^2 = 0\%$) and reduced the overall pooled estimate, with the difference compared to control therapy reaching significance ($p < 0.001$) as presented in Table 4 and Fig. 6C.

Publication bias

Egger test and Begg test were used to identify any publication bias among the included studies. From the data presented in Table 5, it was concluded that no publication bias was found for glucose level (Egger test $p = 0.570$; Begg–Mazumdar test $p = 0.624$), HbA1c level (Egger test $p = 0.795$; Begg–Mazumdar test $p = 0.497$) and HOMA-IR score (Egger test $p = 0.375$; Begg test $p = 0.174$) parameters. The funnel plots evaluating publication bias for glucose level, HbA1c level and HOMA-IR score are presented as Fig. 7A–C, respectively. The trimming and filling method showed the absence of any missing study.

Findings and interpretations

The current meta-analysis study aimed to evaluate the efficacy of a nutraceutical composition composed of fixed dose combination of *B. aristata* and *S. marianum* on glycaemic indices and marker of insulin resistance. The studies included in the analysis were conducted on subjects suffering from diabetes and dyslipidaemia. The result of the present study shows that the nutraceutical composition is effective in reducing the level of glucose and glycated haemoglobin, while effect on insulin resistance was not significant.

Previous research has demonstrated the mechanism of action of *B. aristata* and *S. marianum* in reducing glucose level and provides improvement in diabetic condition. Berberine, the active constituent of *B. aristata*, has demonstrated to reduce the insulin level in type 2 DM patients by improving insulin sensitivity,

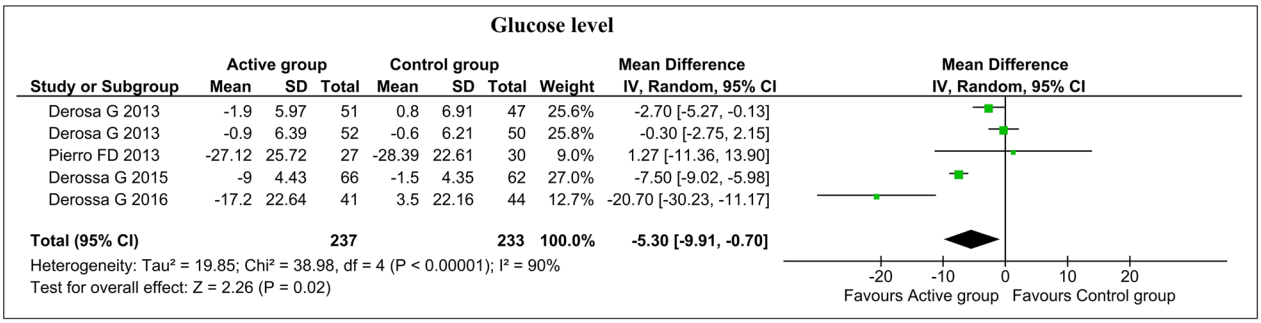

Fig. 3 Efficacy of *B. aristata* and *S. marianum* fixed dose combination in improving blood glucose level: meta-analysis result

while in end-stage type 2 DM and in newly diagnosed type 1 DM patients berberine has shown to increase the insulin secretion by protecting the pancreatic ß-cells because of the antioxidant and anti-lipid peroxidation activity of berberine [44]. This dual effect of berberine is due to its various mechanism of action. Berberine is shown to directly activate the AMPK pathway (action similar to metformin) by increasing the phosphorylation of Thr-172 unit of AMPK-α sub-unit, the catalytic domain of AMPK, which results to the downstream signalling activation, and thereby increasing the insulin sensitivity and glucose consumption [44, 45]. Additionally, berberine is shown to indirectly activate the AMPK pathway by inhibiting the mitochondrial oxidative respiration, by inhibiting the monoamine oxidase enzyme and the electron transporter chain complex-I, which reduces the oxidative ATP production by mitochondria and increases the AMP/ATP level, which ultimately initiates the AMPK-signalling pathway [44, 45]. Because of this dual effect, certain studies have claimed berberine activity to be similar to metformin and rosiglitazone [44]. In liver, berberine reduces gluconeogenesis by inhibiting various gluconeogenic genes, namely phosphoenolpyruvate carboxykinase (PEPCK), glucose-6-phosphatase (G6Pase), Forkhead transcription factor-1 (FoxO1), sterol regulatory element-binding protein 1c (SREBP1), and carbohydrate-responsive element-binding protein (ChREBP), while increases hepatic glycolysis by increasing the mRNA expression of hepatic nuclear factor-4α (HNF-4α) [44, 45]. Berberine also inhibits various gastrointestinal enzymes including α-glucosidase, disaccharidase, sucrase-isomaltase complex and ß-glucuronidase, thereby reducing the intestinal absorption of dietary carbohydrates, action similar to acarbose [44, 45]. Because of these myriad of activities, berberine supplementation has clinically proven hypoglycaemic and insulin sensitization activity [46]. Silymarin, the active constituent of *S. marianum*, includes four structurally similar isoforms, namely silybin, isosilybin, silychristin and silydianin [47]. Various studies have demonstrated that silymarin exerts potent antioxidant activity through various different mechanisms, including inhibition of reactive oxygen species (ROS)-producing enzymes, thereby preventing free radicals formation, improving mitochondrial membrane integrity in stressful conditions, reducing inflammatory responses by inhibiting nuclear factor kappa-B (NF-κB) signalling pathway, maintaining optimal redox balance in cell by activating range of antioxidant enzymes and activation of nuclear factor-erythroid two-related factor (Nrf-2), thereby causing increase in non-enzymatic antioxidant

Table 4 Result of sensitivity analysis using leave-one-study-out method

Studies (removed from analysis)	I^2 value (%)	Estimate	95% CI	*p*-value
Glucose level				
Overall	90	− 5.302	− 9.905 to − 0.698	0.024
Derosa [36]	91	− 6.433	− 12.799 to − 0.067	0.048
Derosa [37]	85	− 6.980	− 12.078 to − 1.882	0.007
Pierro [38]	92	− 5.969	− 10.836 to − 1.102	0.016
Derosa [39]	83	− 4.498	− 9.906 to 0.909	0.103
Derosa [41]	89	− 3.158	− 7.518 to 1.203	0.156
HbA1c level				
Overall	90	− 0.693	− 1.017 to − 0.370	< 0.001
Pierro [38]	91	− 0.776	− 1.133 to − 0.420	< 0.001
Guarino [40]	93	− 0.686	− 1.156 to − 0.215	0.004
Derosa [41]	92	− 0.754	− 1.136 to − 0.372	< 0.001
Guarino [42]	39	− 0.563	− 0.732 to − 0.394	< 0.001
HOMA-IR score				
Overall	99	− 0.644	− 1.358 to 0.07	0.077
Derosa [37]	99	− 0.765	− 1.693 to 0.163	0.106
Derosa [39]	99	− 0.763	− 1.701 to 0.175	0.111
Guarino [40]	99	− 0.724	− 1.614 to 0.166	0.111
Guarino [42]	0	− 0.303	− 0.394 to − 0.211	< 0.001

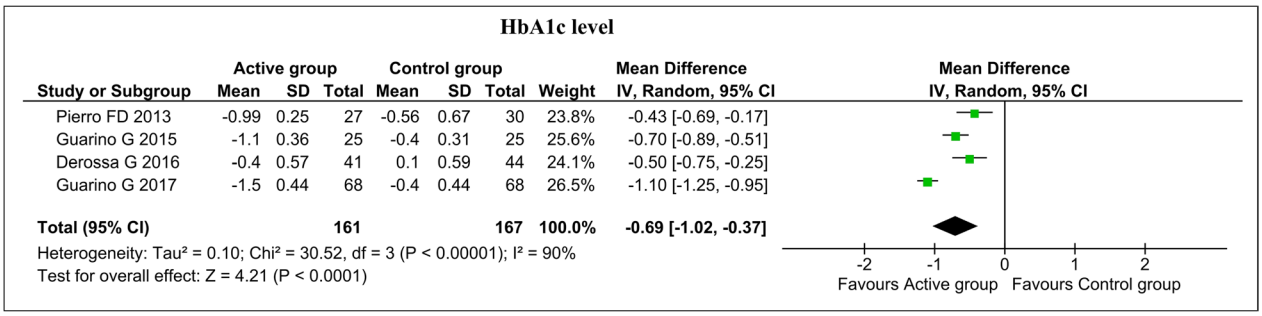

Fig. 4 Efficacy of *B. aristata* and *S. marianum* fixed dose combination in improving HbA1c level: meta-analysis result

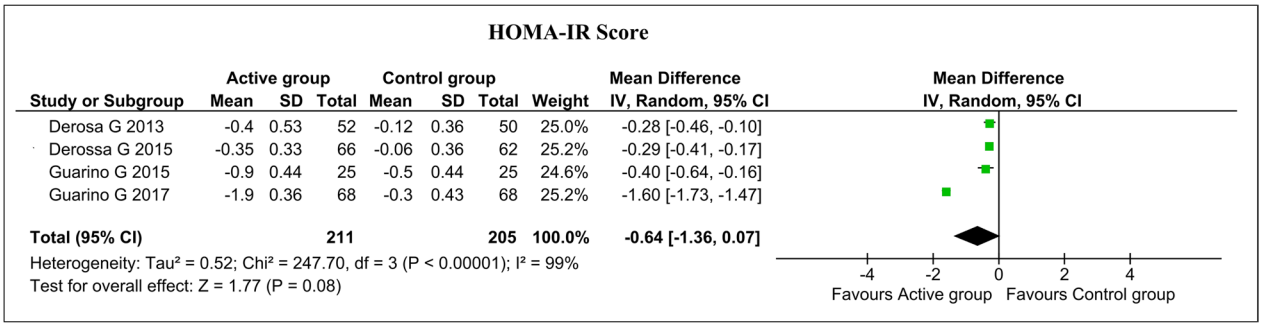

Fig. 5 Efficacy of *B. aristata* and *S. marianum* fixed dose combination in improving HOMA-IR score: meta-analysis result

potential [47]. This activity of silymarin is largely due to the presence of β-catechol group, which is capable of donating hydrogen ions and thereby stabilizing free radical species, and by the presence of 2,3-unsaturation along with 4-oxo functional group and other functional groups which are capable of forming bonds with metal ions and stabilize them [48]. Due to these antioxidant and anti-inflammatory mechanisms, silymarin is found to be effective in reducing the diabetic complications including diabetic nephropathy, diabetic neuropathy and diabetic retinopathy [47]. The effects of silymarin on glucose metabolism and insulin activity are largely unexplored with very few studies identifying the exact mechanistic role. In liver, silymarin is found to reduce the activity of pyruvate kinase enzyme which leads to reduction in dihydroxyacetone phosphorylation and decrease in glucose-6-phosphate hydrolysis, ultimately causing reduction in hepatic gluconeogenesis [48]. In conditions of reduced insulin-producing capacity, silymarin supplementation is associated with increased Pdx1 transcription leading to increase in insulin gene expression and ultimately production, while by increasing the expression of Nkx61, a key transcription factor for maintenance of pancreatic β-cells health, silymarin supplementation improves the overall health of pancreatic β-cells and thus improves insulin secretion [23]. Additionally, silymarin supplementation is associated with improved insulin sensitivity by reducing the tumour necrosis factor-alpha (TNF-α)-mediated insulin resistance [23]. In normal condition, the binding of insulin to insulin receptors causes activation of insulin receptor substrate-1 (IRS-1) complex, which in turn activates the phosphatidylinositol 3-kinase-protein kinase B (PI3K)/Akt pathway leading to increased expression of glucose transporter type-4 (GLUT-4) on the cellular surface and thereby increases glucose consumption. As diabetes is associated with chronic inflammation, high TNF-α level causes activation of c-Jun N-terminal kinase (JNK) and I-kappa B-kinase (IKK) complex, which directly inhibits the activation of IRS-1 complex, which thereby reduces insulin-mediated activity and leads to insulin resistance [23]. Silymarin supplementation inhibits the TNF-α, JNK and

Table 5 Outcome indicators and publication bias of studies on effects of combination therapy supplementation

Outcome	I^2 (%)	I^2 *p*-value	Egger test *p*-value	Begg–Mazumdar test *p*-value
Glucose level	90	< 0.00001	0.570	0.624
HbA1c level	90	< 0.00001	0.795	0.497
HOMA-IR Score	99	< 0.00001	0.375	0.174

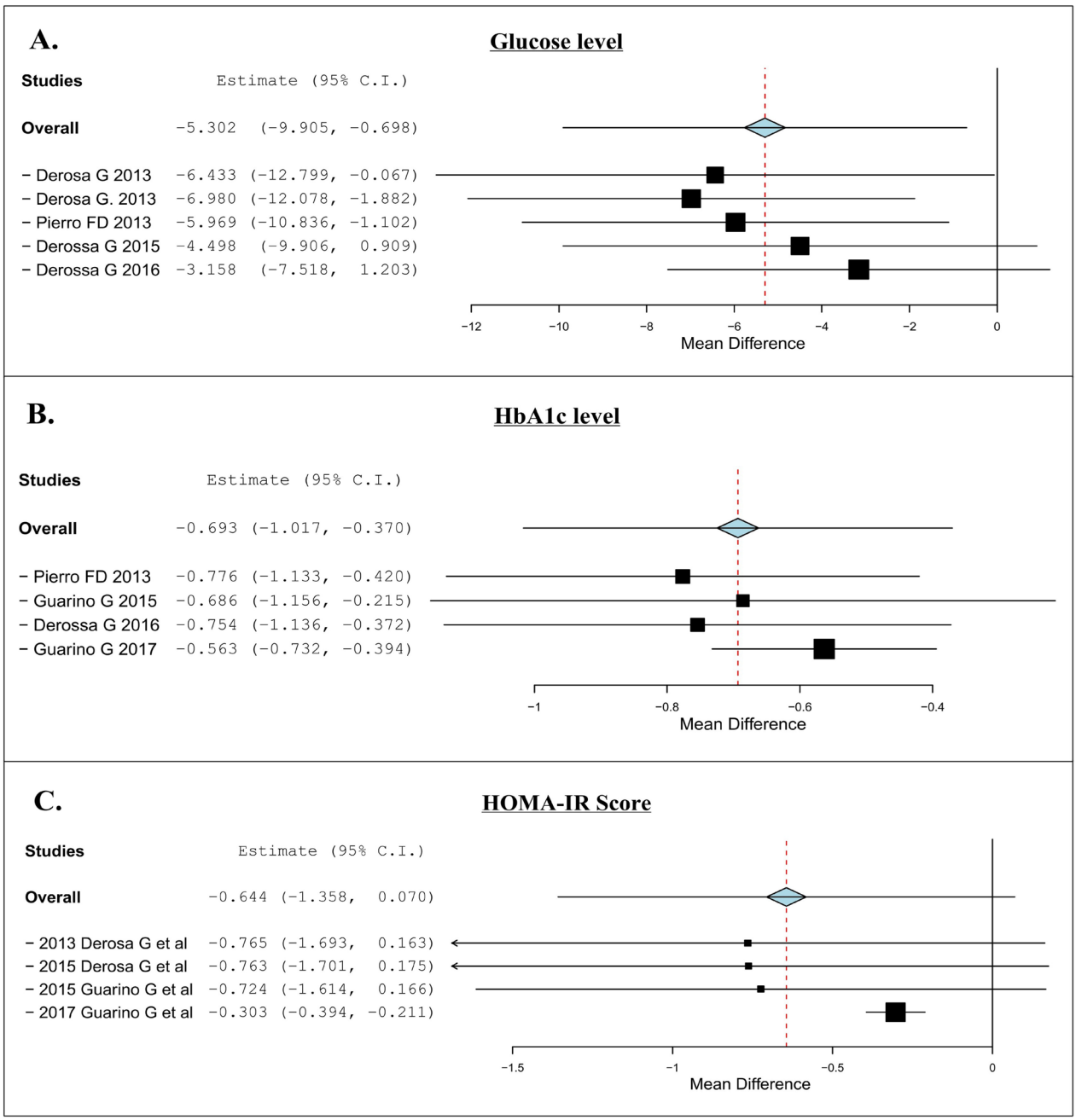

Fig. 6 Result of sensitivity analysis using leave-one-study-out analysis for parameters of (**A**) blood glucose level, (**B**) HbA1c level and (**C**) HOMA-IR score

IKK phosphorylation and activation, which ultimately leads to improved insulin sensitivity and reduced insulin resistance [23]. Due to these myriad of mechanisms, various studies have demonstrated that silymarin supplementation is associated with improved glucose metabolism and reduced insulin resistance [48].

In the current study, the sensitivity analysis revealed that study conducted by Giuseppe Derosa [39] and Giuseppe Derosa [41] has potential effect on the overall effect estimate of glucose level. The former study included patients with dyslipidaemia who were intolerant to high doses of statins, while subjects with type-I diabetes were included in the latter study. As the analysis revealed no publication bias in the evaluated parameters, it can be postulated that the effect of this nutraceutical composition is greater in these patient population, and

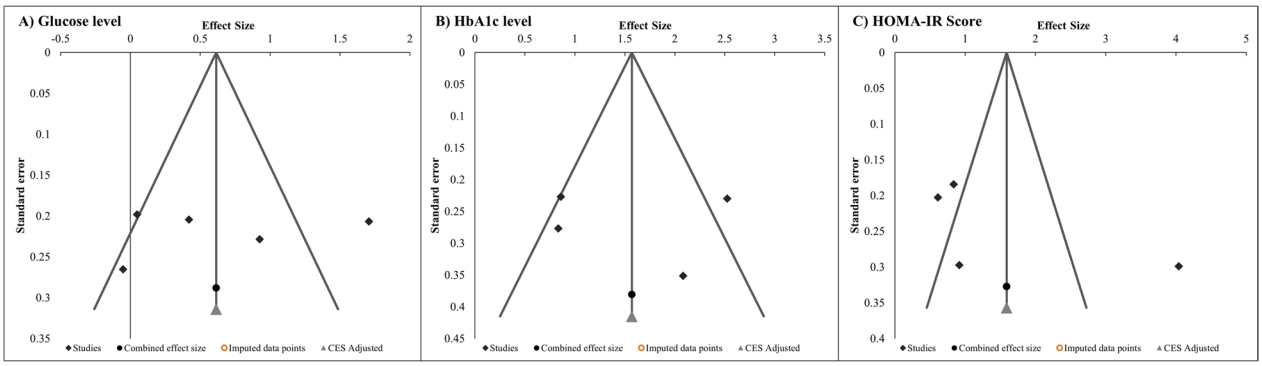

Fig. 7 Funnel plot for publication bias assessment of (**A**) blood glucose level, (**B**) HbA1c level and (**C**) HOMA-IR score

this hypothesis would need to be examined by more clinical trials including similar patient population. Similarly, observation was seen in HOMA-IR parameter, where study conducted by Guarino et al. [42] had significant impact on overall effect-estimate. But, since the pooled estimate had *p*-value of 0.08 (approaching significance), and the absence of any publication bias, the difference observed from the study may be negligible.

The results of the current study are novel as no previous studies have evaluated the efficacy of *B. aristata* and *S. marianum* fixed dose combination on glycaemic and insulin resistance parameters using a systematic review and meta-analysis approach. A previous meta-analysis study included data from four clinical trials involving 491 participants evaluated the effect of *B. aristata* and *S. marianum* combination on markers of dyslipidaemia [49]. The study included data of subjects with dyslipidaemia, and the effect of supplementation was evaluated on low-density lipoprotein level, high-density lipoprotein level, total cholesterol level, and triglycerides level. In the current study, data of patients with diabetes and dyslipidaemia were included, and the markers evaluated were related to blood glucose and insulin resistance.

Strengths and limitations of current study

The current study has various strengths. Firstly, the current study is novel, and the results of the current study are in line with the results observed in individual clinical studies evaluating the effect of *B. aristata* and *S. marianum* fixed dose combination on glycaemic and insulin resistance parameters. Secondly, the transparency of the study is one of the strengths of the current study which was maintained by following the guidelines provided by PRISMA. The current study has few limitations too. Firstly, the significant heterogeneity and moderate level of biasness observed among included studies. While the feasibility of conducting meta-analysis in such scenario is questionable, the current study was entirely conducted as per a pre-designed and finalized protocol that was developed before the initiation of the first step of review process (i.e. literature mining). In order to identify the cause of significant heterogeneity, sensitivity analysis was conducted using the leave-one-study-out method, and the individual studies having significant effect on the overall heterogeneity were determined for few outcome parameters, but more statistical correlation research is required for further identifying the exact cause of heterogeneity, which was not covered in the current study due to limited statistical scope. Secondly, the absence of assessor blinding in all of the included studies is one of the major limitations of the included studies. While the evaluation parameters of current study are laboratory evaluated parameters, the influence of assessor might reduce the reliability the results of the current study. Hence more clinical studies with true blinding of the subjects, the therapist and the assessors are required to validate the results of current analysis. Thirdly, the current study included adult population with impaired glucose metabolism and insulin resistance with no limitations on any particular disease indications; the results of the current study needs to be considered with caution, as impaired glucose metabolism and insulin resistance are observed in various conditions like metabolic complications (including diabetes, obesity, dyslipidaemia and non-alcoholic fatty liver disease), cardiovascular complications including hypertension, and gynaecological complications like polycystic ovarian syndrome as well. Hence, the results of the current study do not justify the use of this fixed dose combination nutraceutical supplement in disease indications other than diabetes, dyslipidaemia and obesity in which the clinical studies have been conducted. Lastly, the limited number of studies with a smaller number of participants utilized in the current study warrants further clinical studies.

Conclusion

The results of the current study suggest that the supplementation of *Berberis aristata* and *Silybum marianum* fixed dose combination is effective in improving glycaemic indices by reducing insulin resistance. However, in light of the study limitations including the low number of available studies, the high heterogeneity observed and the moderate risk of biasness, further well-designed clinical studies are warranted.

Abbreviations

DM	Diabetes mellitus
IDF	International Diabetes Federation
ADA	American Diabetes Association
EASD	European Association for the Study of Diabetes
AMPK	AMP-activated protein kinase pathway
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analyses
PICOS	Population, interventions, comparator, outcomes, study design
MeSH	Medical subject heading
HbA1c	Glycated haemoglobin
HOMA-IR	Homeostatic model assessment for insulin resistance
PEDro	Physiotherapy evidence database tool
RoB2	Risk of bias tool
SD_{change}	Standard deviation (change from baseline)
MD	Mean difference
95% CI	95% Confidence interval
PEPCK	Phosphoenolpyruvate carboxykinase
G6Pase	Glucose-6-phosphatase
FoxO1	Forkhead box protein O1
SREBP1	Sterol regulatory element-binding protein-1
ChREBP	Carbohydrate response element-binding protein
HNF-4α	Hepatocyte nuclear factor 4 alpha
ROS	Reactive oxygen species
NF-κB	Nuclear factor kappa B
Nrf-2	Nuclear factor erythroid 2–related factor 2
TNF-α	Tumour necrosis factor-α
IRS-1	Insulin receptor substrate 1
PI3K/Akt	Phosphoinositide-3-kinase–protein kinase B
GLUT-4	Glucose transporter type 4
JNK	C-Jun N-terminal kinase
IKK	I-kappa B-kinase

Supplementary Information

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Additional file 1. Details of PEDro scale judgment and supporting data for the judgment for individual study included in the review.

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Author contributions

All authors have studied and permitted the final manuscript for communication. VD was responsible for study conceptualization and ideation, protocol development, complete literature search, formal analysis and investigation, statistical analysis and development of initial manuscript. JK, DK and VS worked together with VD for the screening of literature searches and selection of eligible studies. JK, DK and VS worked together with VD in organizing the manuscript in proper format. VD and JK worked together in proper formatting the references and updating them regularly. The authors have read and approved the final version of manuscript.

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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