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Does supplementation with pine bark extract improve cardiometabolic risk factors? A systematic review and meta-analysis

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Abstract

Background Supplementation with pine bark extract (PBE) may improve risk factors associated with cardiometabolic syndrome (CMS). The effects of PBE supplementation on cardiometabolic risk factors were evaluated in this systematic review and meta-analysis of randomized controlled trials (RCTs).

Methods A comprehensive search of various databases was performed to identify relevant RCTs published up to September 2024. A random-effects model was employed for the meta-analysis, which included 27 RCTs with 1,685 participants.

Results The findings indicated that PBE supplementation significantly reduced systolic blood pressure (SBP) (weighted mean difference (WMD): -2.26 mmHg, 95% confidence interval (CI): -3.73, -0.79; $P=0.003$), diastolic blood pressure (DBP) (WMD: -2.62 mmHg, 95% CI: -3.71, -1.53; $P<0.001$), fasting blood sugar (FBS) (WMD: -6.25 mg/dL, 95% CI: -9.97, -2.53; $P=0.001$), hemoglobin A1c (HbA1c) (WMD: -0.32%, 95% CI: -0.54, -0.11; $P=0.003$), body weight (WMD: -1.37 kg, 95% CI: -1.86, -0.88; $P<0.001$), and low-density lipoprotein (LDL) cholesterol (WMD: -5.07 mg/dL, 95% CI: -9.21, -0.94; $P=0.016$) in the PBE-treated group compared to their untreated counterparts. However, no significant impact of PBE was observed on waist-to-hip ratio (WHR), body mass index (BMI), waist circumference (WC), or serum levels of insulin, high-density lipoprotein (HDL) cholesterol, triglycerides (TG), and total cholesterol (TC).

Conclusions Supplementation with PBE may ameliorate specific cardiometabolic risk factors, as indicated by reductions in body weight, DBP, SBP, FBS, LDL, and HbA1c levels. This approach can be regarded as an adjunct therapeutic strategy for CMS management. Further high-quality trials with larger sample sizes and longer durations are required to validate these findings.

Keywords Lipid profile, Glycemic parameters, Cardiometabolic syndrome, Oligopin, Pycnogenol, Flavangenol

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Introduction

Cardiometabolic syndrome (CMS), also known as metabolic syndrome (MetS) or insulin resistance syndrome, includes several metabolic dysfunctions [1]. It is characterized by the concurrent presence of at least three medical conditions, including dyslipidemia, hypertension (HTN), impaired glucose tolerance, insulin resistance, and central obesity [2, 3]. Patients with CMS often exhibit elevated levels of inflammation and oxidative stress (OS) [4]. This syndrome is a significant risk factor for cardiovascular disease (CVD) [5]. Patients with CMS are three times more likely to suffer and die from CVDs than individuals without CMS [6]. It is a global public health problem [7–9]. Several factors contribute to CMS-associated complications, including genetics, nutrition, epigenetics, lifestyle choices, and environmental factors [7, 10].

Various pathological procedures are associated with diverse clinical manifestations of CMS [11, 12]. Defective oxidative metabolism significantly contributes to visceral fat accumulation and progression of insulin resistance [11]. Impaired insulin signaling is a fundamental mediator of CMS [13]. In addition, CMS is associated with increased OS and inflammatory marker levels [14]. Chronic low-grade inflammation or metaflammation is a major hallmark of metabolic disorders [11, 15]. This condition is characterized by elevated pro-inflammatory cytokine levels in adipose tissue and is correlated with OS [12, 16, 17].

Patients with MetS may benefit from weight loss and intake of anti-inflammatory nutrients [18]. Supplementation with antioxidants and complementary therapies are recommended for patients with MetS [19]. Antioxidant treatment has shown promise in preventing CMS [20] and obesity-related comorbidities [21]. Reducing OS and inflammation is a therapeutic objective for managing and preventing associated complications [22, 23]. Nutrition plays a crucial role in mitigating OS and inflammation [24]. Dietary antioxidants and polyphenols are effective scavengers of free radicals [25–29]. Antioxidants neutralize free radicals, thereby preserving cellular health and reducing OS, which protects blood vessels and tissues from damage [30]. Furthermore, polyphenols have anti-inflammatory properties that can modulate various inflammatory pathways in the body [31].

The anti-inflammatory and antioxidant properties of pine bark extracts (PBEs) derived from diverse pine species make them active ingredients in dietary supplements and food products [32]. The polyphenolic compounds in these extracts may provide various protective benefits against chronic and degenerative diseases [33]. PBEs have demonstrated cardiovascular benefits, including the inhibition of angiotensin-converting enzyme activity, vasorelaxant effects, and improved microcirculation through enhanced capillary permeability [33]. Oligopin® (OP), Pycnogenol® (PYC), Flavangenol® (FG) (the bark extract of French maritime pine or Pinus pinaster) [34], Pinus massoniana bark extract (PMBE) [35], and Enzogenol® (EZ) (the bark extract of New Zealand Radiata pine) [32], are notable natural antioxidants. These extracts can modulate inflammation or OS [36–38] and protect against pro-oxidants, lipid peroxidation, and peroxynitrite [39]. In addition, PBE stimulates the antioxidative defense system and scavenges free radicals [40] to prevent atherosclerosis progression [41]. Furthermore, PBE helps regenerate and protect vitamins E and C [33]. The anti-inflammatory and antioxidant properties of PBE have been validated through in-vivo and in-vitro studies [33, 42, 43]. It has superior antioxidant [44] and anti-inflammatory [45] properties compared with vitamins E and C.

Limited, inconclusive, and controversial data exist regarding the effects of PBE on cardiometabolic risk factors [20, 39, 46]. In addition, its impact on cardiometabolic risk factors in individuals with different health conditions has not been thoroughly evaluated. This systematic review and meta-analysis of randomized controlled trials (RCTs) examined the effects of PBE supplementation on cardiometabolic risk factors.

Methods

This systematic review and meta-analysis followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [47]. The study protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) under registration number CRD42024529622.

Search strategy

A systematic search was conducted to identify eligible studies published up to September 2024 in multiple databases (Scopus, Medline or PubMed, and Web of Science), without any restrictions on language date. Table S1 provides an overview of the search strategies used in the PubMed database. The search methodology was structured around four PICO elements in the RCTs (population, intervention, comparator, and outcome). The elements included the target population (adults or children), the intervention or exposure (OP, PYC, FG, PBE, PMBE, and EZ supplements), comparator or control group (placebo or no intervention), and specified outcomes (body mass index (BMI), waist circumference (WC), body weight, waist-to-hip ratio (WHR), levels of high-density lipoprotein (HDL) cholesterol, hemoglobin A1c (HbA1c), fasting blood sugar (FBS), low-density lipoprotein (LDL) cholesterol, diastolic blood pressure (DBP), triglycerides (TG), insulin, total cholesterol (TC), and systolic blood pressure (SBP)).

The following search terms were employed in the search strategy: ("Oligopin" OR "PBE" OR "French

maritime pine bark extract" OR "Pinus pinaster" OR "Pycnogenol" OR "Enzogenol" OR "New Zealand Radiata pine bark extract" OR "Flavangenol" OR "Pinus massoniana bark extract" OR "PMBE") AND ("fasting blood sugar" OR "FBS" OR "FBG" OR "fasting blood glucose" OR "HbA1c" OR "Insulin" OR "hemoglobin A1c" OR "lipid profile" OR "TC" OR "TG" OR "HDL" OR "LDL" OR "body mass index" OR "waist circumference" OR "WC" OR "waist-to-hip ratio" OR "body weight" OR "WHR" OR "BMI" OR "blood pressure" OR "systolic blood pressure" OR "diastolic blood pressure" OR" SBP "OR "DBP" OR "high-density lipoprotein" OR "low-density lipoprotein" OR "total cholesterol").

Selection criteria

EndNote reference management software was used to export the identified records. Two investigators (SM and JH) independently evaluated the trials and identified eligible RCTs based on inclusion criteria. Negotiations with a third researcher (TF) resolved any inconsistencies. Eligible RCTs included adults or children and employed a parallel or crossover design with placebo or control groups. A pre-post design was implemented for the trials, which lasted at least two weeks. Outcomes in the PBE-treated and placebo groups were determined at the baseline and after each trial. The effects of PBE supplementation on cardiometabolic parameters were assessed. Trials were excluded based on the following criteria: uncontrolled or non-placebo-controlled trials, studies with a duration of less than two weeks, observational studies or non-RCTs, and trials with inadequate data on specific outcomes.

Data extraction

The required information was extracted from the selected full-text articles by two investigators (SM and JH). Any discrepancies were resolved through discussion with a third researcher (TF). The extracted data included study characteristics (e.g., sample size, first author's name, doses of OP, PYC, PBE, and EZ supplements, trial length, setting, and publication year), as well as participants' demographics (e.g., mean age, BMI, and sex). Furthermore, pre- and post-evaluations of selected outcomes (WC, WHR, body weight, BMI, and levels of FBS, insulin, HDL, LDL, HbA1c, TC, TG, SBP, and DBP) were collected at the end and baseline of the RCTs.

Risk of bias evaluation

Two independent reviewers (SM and JH) evaluated the quality of trials using the modified Cochrane risk of bias (RoB 2) tool [48]. They identified probable sources of bias, including reporting bias, attrition bias, detection bias, performance bias, and allocation bias. The RoB for each domain was classified as uncertain, low, or high [48].

Certainty assessment

The GRADE (Grading of Recommendations Assessment, Development, and Evaluation) approach was employed to assess the certainty of evidence. The quality of evidence was classified as very low, moderate, high, or low [49].

Statistical analysis

This meta-analysis was conducted using the STATA statistical software (version 17). The impact of administering PBE on cardiometabolic parameters was evaluated through the analysis of weighted mean differences (WMDs) and 95% confidence intervals (CIs) to identify the overall changes in study outcomes from the start to the end of the trial in the PBE-treated and untreated groups. The results were reported using the mean and standard deviation (SD) as outcome measures. To ascertain the differences in SD from baseline to the intervention endpoints, the following formula was utilized: SD change=$\sqrt{(SD^2_{pre} + SD^2_{post})}$- $(2 \times R \times SD_{pre} \times SD_{post})$ [50]. A random-effects model was applied to compute pooled WMDs [51]. Heterogeneity among trials was evaluated using the I^2 statistic [52] and Cochran's Q test. I^2 values of 50–75%, <25%, and >75% indicated moderate, low, and high heterogeneity among the trials, respectively [53].

Subgroup analyses were performed to determine probable sources of heterogeneity among the included trials. The subgroups examined the dosage of PBE supplements (≥200 mg/d, 101–199 mg/d, and ≤100 mg/d), trial duration (≥10 weeks and <10 weeks), and supplement type (OP, PYC, PBE, and EZ). Leave-one-out sensitivity analyses were performed to determine the effect of each RCT on the overall results. Funnel plots with Begg's [54] and Egger's [55] tests were applied to identify possible publication bias. Statistical significance was set at $P<0.05$.

Results

Study selection

The primary search identified 994 potential citations across multiple databases, of which 542 duplicates were eliminated. After screening abstracts and titles, 411 articles were excluded. The remaining 41 full-text articles were reviewed and 27 relevant articles were included in the meta-analysis. Figure 1 illustrates the flow diagram for the selection of studies.

Study characteristics

This systematic review and meta-analysis included 27 RCTs [46, 56–81]. The trial characteristics are presented in Table 1. These articles were published between 2001 and 2022. The RCTs included 1685 participants (PBE-treated group, $n=880$; untreated group, $n=860$). The mean age of the participants was 10–74 years, and their BMI varied from 18 to 34 kg/m². There were 19 trials with mixed-sex samples [46, 56–60, 62–66, 68, 70, 74,

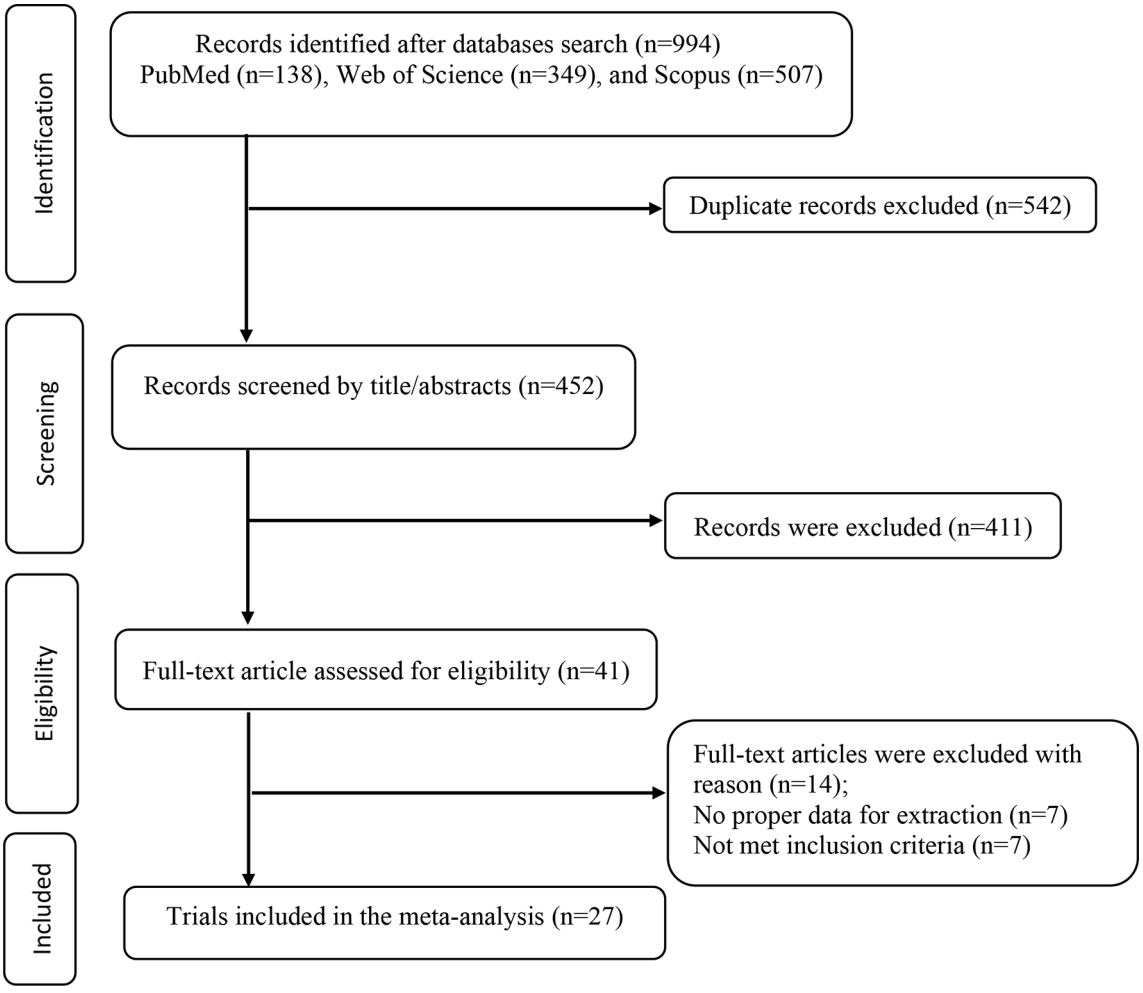

Fig. 1 Flow diagram of study selection

76–78, 80, 81], while six and two RCTs used female-only [67, 69, 72, 73, 75, 79] and male-only [61, 71] samples, respectively. Twenty-four trials employed a parallel design [56–63, 65–81], whereas three used a crossover design [46, 62, 64].

These studies included patients with MetS [56, 78], diabetic microangiopathy [58], CVD risk [60], stable coronary artery disease [62], erectile dysfunction [61], HTN [46, 59, 64], chronic venous insufficiency [66], type 2 diabetes mellitus (T2DM) [68, 73, 81] with microalbuminuria [70], polycystic ovary syndrome (PCOS) [72], depression [76], and vascular retinopathies [77]. In addition, the trials included healthy adults with optimal blood pressure (BP) [63], healthy men [71], perimenopausal women [69, 79] with climacteric syndrome [67], healthy elderly individuals [74], women with obesity [75], chronic smokers [80], individuals recovering from coronavirus disease 2019 (COVID-19) [57], and children with attention deficit hyperactivity disorder (ADHD) [65].

RCTs were conducted in Italy [56–59, 69, 77, 78], the United States (US) [60, 64, 81], the Slovak Republic [61, 76], Switzerland [62], Australia [63, 74], Taiwan [65, 79], Germany [66], Japan [67, 71], China [68], Iran [70, 72, 73, 75], Spain [46], and New Zealand [80]. The duration of the trials varied from 2 to 24 weeks, with daily doses of PBE supplements ranging from 25 mg to 1322 mg.

Impact of supplementation with PBE on anthropometric parameters

Body weight

Eight trials [46, 56, 63, 65, 70, 75, 79, 80] were included in the meta-analysis to examine the impact of PBE supplementation on body weight in the PBE-treated group compared to the untreated group. Pooled data analysis showed that PBE had a substantial effect on body weight (WMD: -1.37 kg, 95% CI: -1.86, -0.88; $P < 0.001$) (Fig. 2A). Long-term supplementation (≥ 10 weeks) at daily doses of 101–199 mg had a significant lowering effect on body weight (Table 2).

Table 1 Characteristics of the included studies

Author, year	Country	Participants	Study design	Sex	Sample size	Supplement dose (mg/day)	Type of supplement	Duration (weeks)	Mean age (years)		Mean BMI (kg/m^2)	
									IG	CG	IG	CG
Belcaro et al.2013 [56]	Italy	Patients with MetS	P	♂/♀	130	150	PYC	24	45.6 ± 8.2	45.3 ± 3.5	26.7 ± 1.2	26.6 ± 1.4
Belcaro et al. 2022 [57]	Italy	Patients recovering from COVID-19	P	♂/♀	60	150	PYC	12	35–70	35–70	NR	NR
Cesarone et al.2006 [58]	Italy	Patients with diabetic microangiopathy	P	♂/♀	60	150	PYC	4	59	59	NR	NR
Cesarone et al. 2010 [59]	Italy	Patients with HTN	P	♂/♀	55	150	PYC	24	54.3 + 2	53 + 6	< 26	<26
Drieling et al. 2010 [60]	USA	Patients with CVD risk	P	♂/♀	130	200	PBE	12	56.9 ± 9.8	53.9 ± 1	29 ± 2.7	28.4 ± 2.4
Ďuračková et al.2003 [61]	Slovak Republic	Patients with erectile dysfunction	P	♂	21	120	PYC	12	46.5 ± 12.5	46.5 ± 12.5	NR	NR
Enseleit et al. 2012 [62]	Switzerland	Patients with stable coronary artery disease	C	♂/♀	23	200	PYC	8	63.1 ± 7.1	63.1 ± 7.1	27.3 ± 3.3	27.3 ± 3.3
Ferguson et al. 2022 (a) [63]	Australia	Healthy adults with optimal BP	P	♂/♀	20	1322	PBE	12	63.6 ± 3.6	61.7 ± 3.3	23.5 ± 4.4	23.7 ± 2.8
Ferguson et al. 2022 (b) [63]	Australia	Healthy adults with high BP	P	♂/♀	42	1322	PBE	12	66.1 ± 4	64.8 ± 3.6	25. 3 ± 1.7	26 ± 2.1
Hosseini et al.2001 [64]	USA	Patients with mild HTN	C	♂/♀	11	200	PYC	8	50.3 ± 9.3	50.3 ± 9.3	NR	NR
Hsu et al. 2021 [65]	Taiwan	Children with ADHD	P	♂/♀	40	25 or 50	OP	4	10.0 ± 2.1	10.0 ± 2.1	18.1 ± 4.3	18.1 ± 4.3
Koch et al. 2002 [66]	Germany	Patients with chronic venous insufficiency	P	♂/♀	39	360	PYC	4	55.8 ± 7.9	55.8 ± 7.9	NR	NR
Kohama et al. 2013 [67]	Japan	Perimenopausal women with climacteric syndrome	P	♀	156	60	PYC	12	46.4 ± 3.4	46.6 ± 3.0	23.2 ± 3.8	22.4 ± 3.0
Liu et al. 2004 [68]	China	Patients with T2DM	P	♂/♀	77	100	PYC	12	54 ± 12.6	58 ± 14.1	NR	NR
Luzzi et al. 2017 [69]	Italy	Peri-menopausal women	P	♀	70	100	PYC	8	44.3 ± 3.2	44.6 ± 2.5	< 26	<26
Navval-Esfahlan et al. 2021 [70]	Iran	Patients with T2DM & microalbuminuria	P	♂/♀	46	100	OP	8	54.6 ± 7.3	51.3 ± 5.8	30.2 ± 3.8	29.3 ± 5.4
Nishioka et al. 2007 [71]	Japan	Healthy young men	P	♂	16	180	PYC	2	22.4 ± 2.2	22.4 ± 2.2	23.2 ± 2.1	23.2 ± 2.1
Qorbani et al. 2020 [72]	Iran	Patients with PCOS	P	♀	80	50	OP	12	28.3 ± 6.5	27.6 ± 6	27.54 ± 4.8	26.3 ± 6.1
Orouji et al. 2020 [73]	Iran	Women with T2DM	P	♀	30	100	OP	6	57.3 ± 1.7	57.8 ± 1.6	29.7 ± 1.0	28.5 ± 1
Ryan et al. 2008 [74]	Australia	Healthy elderly	P	♂/♀	101	150	PYC	12	66.9 ± 5.3	68.4 ± 5.6	24.3 ± 3.1	25.1 ± 2.5
Sedighiyan et al. 2018 [75]	Iran	Women with OB	P	♀	45	150	PBE	8	37.4 ± 8.8	37.3 ± 8.5	32.6 ± 1.7	32.3 ± 1.9
Smetanka et al. 2019 [76]	Slovak Republic	Patients with depression	P	♂/♀	67	50	PYC	16	42 ± 10.3	44.4 ± 12.5	NR	NR
Spadea et al. 2001 [77]	Italy	Patients with vascular retinopathies	P	♂/♀	40	150	PYC	8	53.1 ± 3.5	59.7 ± 1.8	NR	NR
Stuard et el. 2010 [78]	Italy	Patients with MetS	P	♂/♀	58	150	PYC	24	59.1 ± 8.2	58.2 ± 8.3	26.5 ± 0.9	26.6 ± 1.4
Valls et al. 2016 [46]	Spain	Patients with HTN	C	♂/♀	21	150	OP	5	57.3 ± 11.2	57.3 ± 11.2	26.5 ± 2.7	26.5 ± 2.7
Yang et al. 2007 [79]	Taiwan	Peri-menopausal women	P	♀	155	200	PYC	24	46.7 ± 5.0	47 ± 4.2	24.1 ± 3.07	24 ± 2.8
Young et al. 2006 [80]	New Zealand	Chronic smokers	P	♂/♀	44	480	EZ	12	46 ± 2	46 ± 2	25.9 ± 1.0	27 ± 0.9
Zibadi et al. 2008 [81]	USA	Patients with T2DM	P	♂/♀	48	125	PYC	12	61.3 ± 9.1	58.4 ± 11.5	NR	NR

Abbreviations: NR, not reported; *COVID-19*, coronavirus disease 2019; *PCOS*, polycystic ovary syndrome; *MetS*, Metabolic syndrome; *HTN*, Hypertension; CVD, Cardiovascular disease; *ADHD*, Attention deficit hyperactivity disorder; *T2DM*, type 2 diabetes; *BP*, blood pressure; *PBE*, pine bark extract; *OP*, Oligopin; *PYC*, Pycnogenol; *EZ*, Enzogenol; ♀, female; ♂, male; *CG*, control group; *IG*, intervention group; *OB*, obesity; *BMI*, body mass index; *P*, parallel; *C*, cross-over; *USA*, the United States of America

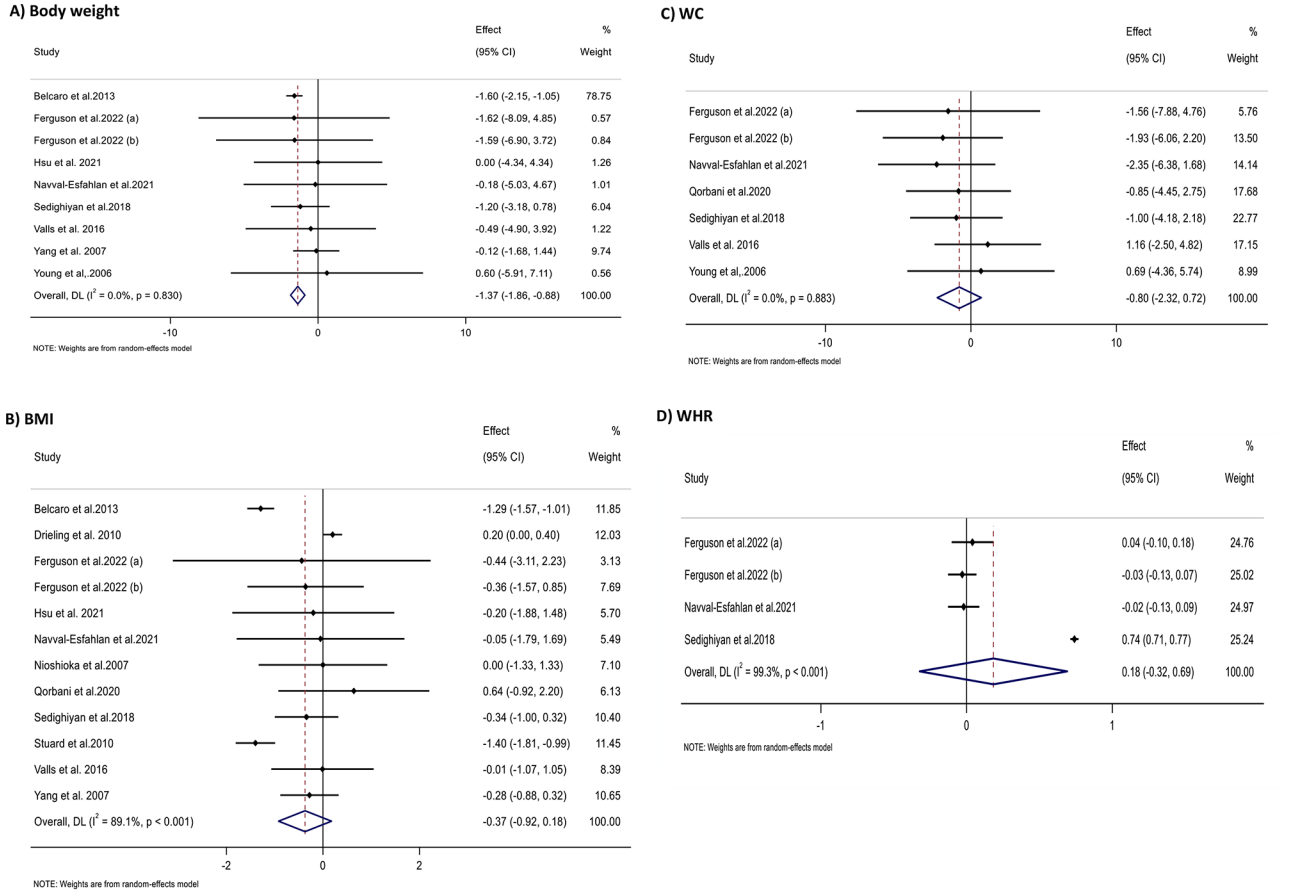

Fig. 2 Forest plots for the effect of supplementation with pine bark extract on anthropometric parameters **A**) body weight (kg), **B**) BMI (kg/m2), **C**) WC (cm), and **D**) WHR

BMI

The effects of PBE supplementation on BMI were examined in 11 studies [46, 56, 60, 63, 65, 70–72, 75, 78, 79]. Meta-analysis revealed no significant changes in BMI following PBE consumption (WMD: -0.37 kg/m^2, 95% CI: -0.92, 0.18; $P = 0.184$). There was also considerable heterogeneity between trials ($I^2 = 89.1\%$, $P < 0.001$) (Fig. 2B). Subgroup analyses indicated that BMI was significantly decreased in trials that administered PYC supplements at daily doses between 101 and 199 mg (Table 2).

WC

A meta-analysis of six RCTs [46, 63, 70, 72, 75, 80] revealed that the consumption of PBE did not significantly alter WC (WMD: -0.80 cm, 95% CI: -2.32, 0.72, $P = 0.301$) (Table 2; Fig. 2C).

WHR

Pooled data analysis of three RCTs [63, 70, 75] revealed no substantial effect of PBE administration on WHR (WMD: 0.18, 95% CI: -0.32, 0.69; $P = 0.477$). Considerable heterogeneity was observed among the studies ($I^2 = 99.3\%$, $P < 0.001$) (Fig. 2D). Subgroup analyses indicated that WHR significantly decreased in trials that administered supplements at daily doses between 101 and 199 mg (Table 2).

Impact of supplementation with PBE on blood pressure

SBP and DBP

The effects of PBE supplementation on SBP and DBP levels were investigated in 20 RCTs [46, 56–60, 62–65, 67, 69, 71, 72, 74–76, 78–80] (Fig. 3A and B). A pooled analysis of the data revealed that supplementation with PBE substantially decreased SBP (WMD: − 2.26 mmHg, 95% CI: -3.73, -0.79; $P = 0.003$) and DBP (WMD: -2.62 mmHg, 95% CI: -3.71, -1.53; $P < 0.001$) in the PBE-treated group compared with their untreated counterparts. However, considerable heterogeneity was observed among the RCTs related to SBP ($I^2 = 81.7\%$, $P < 0.001$) and DBP ($I^2 = 80.7\%$, $P < 0.001$). Subgroup analyses demonstrated consistent results for DBP levels with long-term PYC supplementation (≥ 10 weeks) at daily doses of 101–199 mg, ≤ 100 mg, or ≥ 200 mg (Table 2). A significant SPB-lowering effect was found in short-term and long-term PYC supplementation (< 10 and ≥ 10 weeks) at daily doses of 101–199 mg.

Table 2 Subgroup analyses of the effects of PBE supplementation on cardiometabolic risk factors

Sub-groups	Number of effect sizes	WMD (95%CI)	*P*-value	I^2 (%)	*P*-value heterogeneity
Impact of PBE supplementation on body weight (kg)					
Overall effect	9	-1.37 (-1.86, -0.88)	**<0.001**	0	0.830
Supplement dose (mg/d)					
≤100	2	-0.08 (-3.31, 3.15)	0.961	0	0.957
101-199	3	-1.55 (-2.08, -1.03)	**<0.001**	0	0.830
≥200	4	-0.26 (-1.68, 1.16)	0.716	0	0.917
Trial duration (weeks)					
<10	4	-0.84 (-2.42, 0.73)	0.296	0	0.947
≥10	5	-1.42 (-1.94, -0.91)	**<0.001**	0	0.486
Supplement type					
PYC	2	-1.04 (-2.45, 0.35)	0.143	67.4	0.080
PBE	3	-1.27(-3.06, 0.51)	0.161	0	0.985
OP	3	-0.22 (-2.83, 2.38)	0.867	0	0.988
EZ	1	0.60 (-5.90, 7.10)	0.857	-	-
Impact of PBE supplementation on BMI (kg/m^2)					
Overall effect	12	-0.37 (-0.92, 0.18)	0.184	89.1	<0.001
Supplement dose (mg/d)					
≤100	3	0.15 (-0.79, 1.11)	0.744	0	0.743
101-199	5	-0.81 (-1.33, -0.29)	**0.002**	74.2	0.004
≥200	4	0.12 (-0.07, 0.33)	0.211	1.8	0.383
Trial duration (weeks)					
<10	5	-0.19 (-0.67,0.27)	0.412	0	0.981
≥10	7	-0.49 (-1.25,0.25)	0.197	94	<0.001
Supplement type					
PYC	4	-0.92 (-1.46, -0.38)	**0.001**	77.3	0.004
PBE	4	0.09 (-0.16,0.35)	0.467	7.5	0.356
OP	4	0.08 (-0.62,0.79)	0.818	0	0.885
Impact of PBE supplementation on WC (cm)					
Overall effect	7	-0.80 (-2.32, 0.72)	0.301	0	0.883
Supplement dose (mg/d)					
≤100	2	-1.51 (-4.20, 1.17)	0.269	0	0.587
101-199	2	-0.07 (-2.47, 2.32)	0.953	0	0.382
≥200	3	-1.02 (-3.87, 1.83)	0.483	0	0.721
Trial duration (weeks)					
<10	3	-0.66 (-2.72, 1.39)	0.525	0	0.434
≥10	4	-0.95 (-3.19, 1.28)	0.403	0	0.883
Supplement type					
PBE	3	-1.37 (-3.71, 0.96)	0.249	0	0.939
OP	3	-0.57 (-2.74, 1.58)	0.600	0	0.442
EZ	1	0.69 (-4.36, 5.74)	0.789	-	-
Impact of PBE supplementation on WHR					
Overall effect	4	0.18 (-0.32, 0.69)	0.477	99.3	<0.001
Supplement dose (mg/d)					
≤100	1	-0.02 (-0.12, 0.08)	0.715	-	-
101-199	1	-0.74 (0.71, 0.76)	**<0.001**	-	-
≥200	2	-0.01 (-0.08, 0.07)	0.853	99.3	<0.001
Trial duration (weeks)					
<10 Weeks	2	0.36 (-0.38, 1.10)	0.341	99.4	<0.001
≥10 Weeks	2	-0.01 (-0.08, 0.07)	0.853	0	0.426
Supplement type					
PBE	3	0.25 (-0.34,0.84)	0.404	99.3	<0.001
OP	1	-0.20 (-0.12, 0.08)	0.715	-	-
Impact of PBE supplementation on SBP(mmHg)					

Table 2 (continued)

Sub-groups	Number of effect sizes	WMD (95%CI)	*P*-value	I^2 (%)	*P*-value heterogeneity
Overall effect	21	-2.26 (-3.73, -0.79)	**0.003**	81.7	<0.001
Supplement dose (mg/d)					
≤100	5	-1.35 (-4.96, 2.25)	0.462	80.1	<0.001
101-199	9	-4.10 (-5.90, -2.31)	**<0.001**	81.1	<0.001
≥200	7	-0.24 (-2.58,2.10)	0.840	47.3	0.077
Trial duration (weeks)					
<10	8	-3.29 (-6.52, -0.06)	**0.046**	79.8	<0.001
≥10	13	-1.79 (-3.53, -0.05)	**0.043**	83	<0.001
Supplement type					
PYC	13	-3.12 (-4.60, -1.63)	**<0.001**	78.9	**<0.001**
PBE	4	-3.50 (-10.30,3.29)	0.312	87.1	**<0.001**
OP	3	0.70 (-2.01,3.42)	0.611	0	0.527
EZ	1	4 (-1.27,9.27)	0.137	-	-
Impact of PBE supplementation on DBP (mmHg)					
Overall effect	21	-2.62 (-3.71, -1.53)	**<0.001**	80.7	<0.001
Supplement dose (mg/d)					
≤100	5	-2.83 (-5.28, -0.39)	**0.023**	70.1	0.009
101-199	9	-3.67 (-5.51, -1.83)	**<0.001**	89.9	<0.001
≥200	7	-1.18 (-2.22, -0.14)	**0.026**	0	0.981
Trial duration (weeks)					
<10	8	-2.34 (-4.77,0.08)	0.059	82.5	<0.001
≥10	13	-2.69 (-3.92, -1.45)	**<0.001**	79.5	<0.001
Supplement type					
PYC	13	-3.39 (-4.74, -2.03)	**<0.001**	86	<0.001
PBE	4	-1.87 (-4.40,0.66)	0.148	54.6	0.086
OP	3	-0.03 (-2.11,2.03)	0.973	0	0.545
EZ	1	-1.00 (-4.51,2.51)	0.577	-	-
Impact of PBE supplementation on FBS (mg/dL)					
Overall effect	13	-6.25 (-9.97, -2.53)	**0.001**	89	<0.001
Supplement dose (mg/d)					
≤100	4	-9.08 (-17.32, -0.84)	**0.031**	89	<0.001
101-199	8	-5.86 (-10.55, -1.17)	**0.014**	89.1	<0.001
≥200	1	-1.80 (-10.73,7.13)	0.693	-	-
Trial duration (weeks)					
<10	8	-4.97 (-8.70, -1.23)	**0.009**	75.5	<0.001
≥10	5	-8.39 (-16.22, -0.56)	**0.036**	94.7	<0.001
Supplement type					
PYC	9	-7.14 (-10.94, -0.35)	**<0.001**	85.6	<0.001
PBE	1	-7.90 (-15.99,0.19)	0.056	-	-
OP	3	-2.28 (-9.93,5.36)	0.559	79.1	0.008
Impact of PBE supplementation on Insulin (μU/mL)					
Overall effect	3	-0.11 (-1.31,1.08)	0.852	51.8	0.126
Supplement dose (mg/d)					
≤100	2	-0.97 (-2.30,0.34)	0.147	51.8	0.126
101-199	1	0.43 (-0.11,0.97)	0.118	-	-
Trial duration (weeks)					
<10	2	0.42 (-0.10,0.96)	0.116	0	0.982
≥10	1	-1.12 (-2.51,0.27)	0.115	-	-
Supplement type					
OP	3	-0.11(-1.31,1.08)	0.852	51.8	0.126
Impact of PBE supplementation on HbA1c (%)					
Overall effect	6	-0.32 (-0.54, -0.11)	**0.003**	75.9	<0.001
Supplement dose (mg/d)					

Table 2 (continued)

Sub-groups	Number of effect sizes	WMD (95%CI)	*P*-value	I^2 (%)	*P*-value heterogeneity
≤100	3	-0.21 (-0.53, 0.11)	0.241	77.6	0.011
101-199	3	-0.41 (-0.53, -0.29)	**<0.001**	0	0.659
Trial duration (weeks)					
<10	2	-0.60 (-1.15, -0.06)	**0.003**	61.8	0.106
≥10	4	-0.23 (-0.49, 0.02)	0.076	78.4	0.003
Supplement type					
PYC	4	-0.35 (-0.49, -0.20)	**<0.001**	42.8	0.155
OP	2	-0.41 (-1.45,0.61)	0.429	87.9	0.004
Impact of PBE supplementation on TC (mg/dL)					
Overall effect	15	-5.23 (-10.56,0.11)	0.055	77.5	<0.001
Supplement dose (mg/d)					
≤100	5	-3.98 (-11.30,3.33)	0.286	67.9	0.014
101-199	7	-2.27 (-8.34,3.79)	0.463	63.9	0.011
≥200	3	-15.80 (-44.24,12,62)	0.276	93.1	<0.001
Trial duration					
<10	8	-11.40 (-19.73, -3.06)	**0.007**	79.6	<0.001
≥10	7	1.45 (-1.79,4.70)	0.381	2.6	0.406
Supplement type					
PYC	10	-7.62 (-14.43, -0.82)	**0.028**	82.3	<0.001
OP	4	-2.04 (-10.98,6.90)	0.655	56.8	0.074
EZ	1	7.70 (-5.30,20.70)	0.055	-	-
Impact of PBE supplementation on TG (mg/dL)					
Overall effect	13	-4.19 (-15.58,7.19)	0.471	95	<0.001
Supplement dose (mg/d)					
≤100	5	-2.02 (-14.82,10.77)	0.756	82.5	<0.001
101-199	5	-9.93 (-30.32,10.46)	0.340	95.8	<0.001
≥200	3	2.20 (-4.90,9.13)	0.543	0	0.877
Trial duration (weeks)					
<10	7	-4.78 (-13.17,3.60)	0.264	67.1	0.006
≥10	6	-3.32 (-23.86,17.21)	0.751	97	<0.001
Supplement type					
PYC	7	-5.46 (-20.78,9.86)	0.485	96.6	<0.001
PBE	1	-14.40 (-29.92,1.12)	0.069	-	-
OP	4	0.31 (-8.54,9.18)	0.944	27.9	0.245
EZ	1	3.90 (-9.10,16.90)	0.471	-	-
Impact of PBE supplementation on HDL (mg/dL)					
Overall effect	17	0.54 (-4.60,5.69)	0.837	98.4	<0.001
Supplement dose (mg/d)					
≤100	5	0.77 (1.35, 2.90)	**0.047**	63.3	0.028
101-199	8	3.52 (-0.05, 6.98)	0.604	91.1	<0.001
≥200	4	-5.31 (-25.38,14.76)	0.476	99.5	<0.001
Trial duration (weeks)					
<10	9	4.20 (1.68,6.27)	**0.001**	83.1	<0.001
≥10	8	-3.28 (-11.92,5.36)	0.457	98.9	<0.001
Supplement type					
PYC	10	-0.45 (-8.49,7.58)	0.912	99	<0.001
PBE	1	5.70 (2.64,8.75)	**<0.001**	-	-
OP	5	1.82 (-0.54,4.10)	0.131	65	0.022
EZ	1	-0.80 (-6.45,4.85)	0.782	-	-
Impact of PBE supplementation on LDL (mg/dL)					
Overall effect	14	-5.07 (-9.21, -0.94)	**0.016**	78.5	<0.001
Supplement dose (mg/d)					
≤100	5	-2.54 (-5.91,0.82)	0.139	43.1	0.134

Table 2 (continued)

Sub-groups	Number of effect sizes	WMD (95%CI)	*P*-value	I^2 (%)	*P*-value heterogeneity
101-199	5	-5.05 (-14.02,3.91)	0.269	68.3	0.013
≥200	4	-8.52 (-18.91,1.86)	0.108	85.7	<0.001
Trial duration					
<10	7	-6.50 (-12.23, -0.78)	**0.026**	80.3	<0.001
≥10	7	-3.52 (-10.63,3.58)	0.331	78.1	<0.001
Supplement type					
PYC	8	-9.05 (-15.95, -2.14)	**0.010**	81.4	<0.001
OP	5	-2.40 (-6.13,1.33)	0.207	42.6	0.138
EZ	1	11.60 (-1.42,24.62)	0.081	-	-

Abbreviations: BMI, body mass index; *HDL*, high-density lipoproteins; *TG*, triglycerides; *FBS*, fasting blood sugar; *SBP*, systolic blood pressure; *LDL*, low-density lipoproteins; *TC*, total cholesterol; *DBP*, diastolic blood pressure; *WC*, waist circumference; *WHR*, waist to hip ratio; *PBE*, pine bark extract; *OP*, Oligopin; *PYC*, Pycnogenol; *EZ*, Enzogenol; *WMD*, weighted mean difference; *CI*, confidence interval

Impact of supplementation with PBE on glycemic parameters

FBS

A meta-analysis of 13 RCTs [46, 56, 58, 62, 68–72, 75, 77, 78, 81] revealed a remarkable fall in serum FBS levels in the PBE-treated group (WMD: -6.25 mg/dL, 95% CI: -9.97, -2.53; $P = 0.001$) compared with the placebo group (Fig. 4A). In addition, there was significant heterogeneity among RCTs (I^2 = 89%, $P < 0.001$). Subgroup analyses revealed consistent findings for short- or long-term supplementation with PYC (< 10 or ≥ 10 weeks) at daily dosages of 101–199 mg or ≤ 100 mg (Table 2).

Insulin

A pooled analysis of three trials [46, 70, 72] revealed that PBE had no significant effect on serum insulin concentrations (WMD: -0.11 µU/mL, 95% CI: -1.31, 1.08, $P = 0.852$) (Table 2; Fig. 4B).

HbA1c

A meta-analysis of six trials [58, 68, 70, 72, 78, 81] indicated a remarkable decrease in serum HbA1c levels following PBE intake (WMD: -0.32%, 95% CI: -0.54, -0.11; $P = 0.003$) compared to the placebo group (Fig. 4C). However, the degree of heterogeneity among the studies was considerable (I^2 = 75.9, $P < 0.001$). Similar outcomes were found in subgroup analyses for short-term PYC supplementation (< 10 weeks) at daily doses of 101–199 mg (Table 2).

Impact of supplementation with PBE on lipid profile

TC

A meta-analysis of 15 studies [46, 58, 59, 61, 62, 65–67, 69–72, 74, 78, 80] revealed that PBE did not significantly change serum TC concentrations in the intervention group compared to the control group (WMD: -5.23 mg/dL, 95% CI: -10.56, 0.11; $P = 0.055$) (Fig. 5A). However, considerable heterogeneity was observed among the trials ($I^2 = 77.5\%$, $P < 0.001$). Subgroup analyses revealed a substantial decrease in serum TC levels following short-term PYC supplementation (< 10 weeks) (Table 2).

TG

A pooled analysis of 13 RCTs [46, 56, 62, 65, 67, 69–72, 74, 75, 79, 80] revealed no significant impact of PBE on serum TG concentrations in the PBE group (WMD: -4.19 mg/dL, 95% CI: -15.58, 7.19; $P = 0.471$) compared with the control group (Table 2; Fig. 5B). Substantial heterogeneity was found among the trials (I^2 = 95%, $P < 0.001$).

HDL

The impact of PBE supplementation on serum HDL concentrations was evaluated in 17 studies [46, 58, 59, 61, 62, 65–67, 70–75, 78–80] (Fig. 5C). Pooled data analysis showed no substantial differences in serum HDL levels between the two groups (PBE vs. placebo) (WMD: 0.54 mg/dL, 95% CI: -4.60, 5.69; $P = 0.837$), with high heterogeneity among the RCTs (I^2 = 98.4%, $P < 0.001$). Subgroup analyses revealed a substantial increase in serum HDL levels following short-term PBE supplementation (< 10 weeks) at daily doses ≤ 100 mg (Table 2).

LDL

A pooled analysis of 14 trials [46, 61, 62, 65–67, 70–74, 79–81] indicated substantial changes in serum levels of LDL following the consumption of PBE in the experimental group compared to the placebo group (WMD: -5.07 mg/dL, 95% CI: -9.21, -0.94; $P = 0.016$) (Fig. 5D). Furthermore, there was noticeable heterogeneity among the trials (I^2 = 78.5%, $P < 0.001$). Subgroup analysis revealed that short-term PYC supplementation (< 10 weeks) significantly decreased the serum LDL levels (Table 2).

Risk of bias assessment

The RoB assessment of the included trials is presented in Table S2. Nine studies [56–59, 62, 66, 69, 76, 78] exhibited a high risk of bias, primarily related to randomization

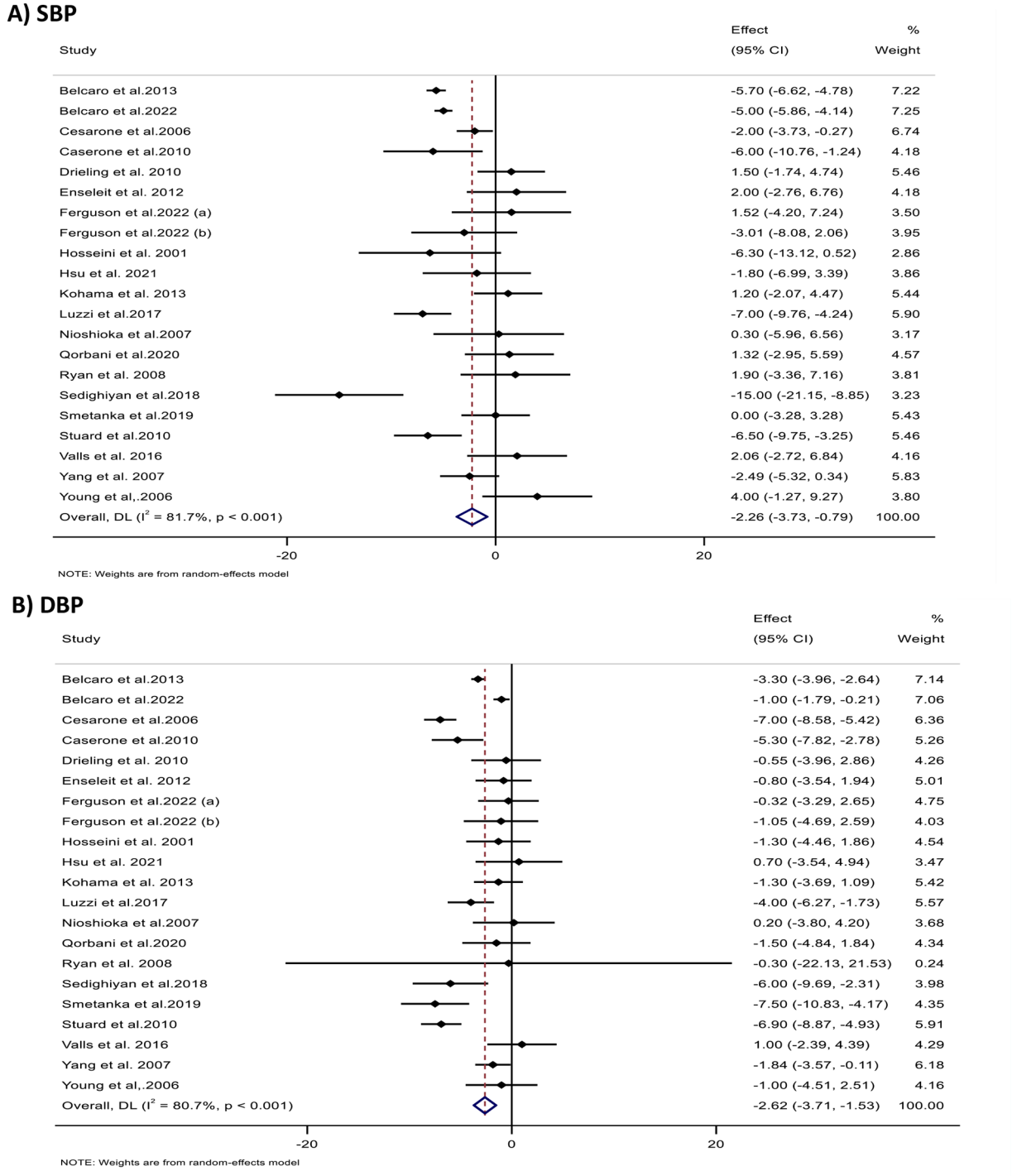

Fig. 3 Forest plots for the effect of supplementation with pine bark extract on blood pressure **A**) SBP (mmHg) and **B**) DBP (mmHg)

procedures and missing outcome data. Sixteen trials were classified as having low RoB [46, 60, 61, 63–65, 67, 68, 70–74, 77, 80, 81], while two trials [75, 79] raised concerns due to missing outcome data or deviations from the intended intervention.

GRADE evaluation

Table S3 presents the GRADE assessments of the evaluated outcomes. High certainty was observed for outcomes related to body weight. Moderate quality evidence was considered for BMI, WC, insulin, and HBA1c. In addition, the WHR, DBP, FBS, TC, HDL, and LDL outcomes were downgraded to low-quality evidence because

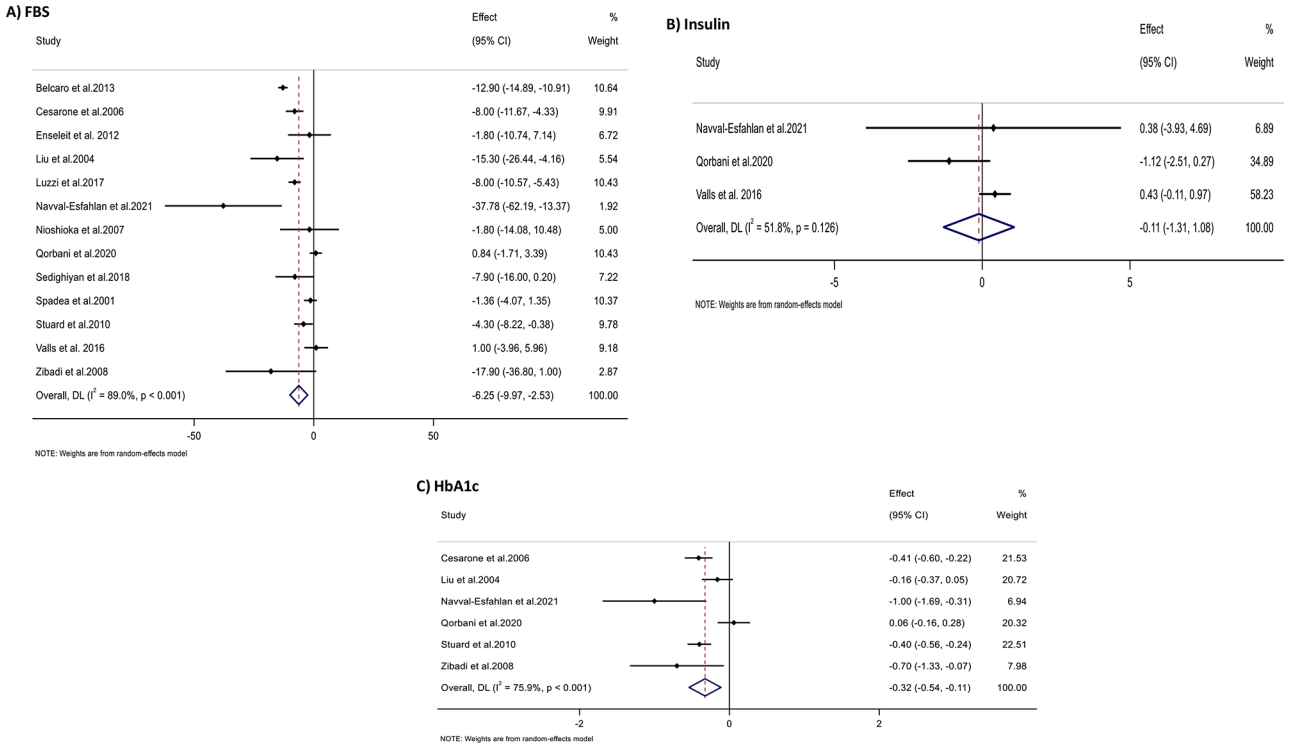

Fig. 4 Forest plots for the effect of supplementation with pine bark extract on glycemic parameters **A**) FBS (mg/dL), **B**) Insulin (μU/mL), and **C**) HbA1c (%)

of serious inconsistency and imprecision. Furthermore, the quality of evidence supporting the effects of PBE on SBP and TG was rated very low.

Sensitivity analysis

Sensitivity analyses demonstrated that the outcomes remained consistent, even when specific RCTs related to WC, WHR, SBP, DBP, FBS, HBA1c, insulin, TG, HDL, and LDL were excluded. However, the results were significantly changed by the elimination of one trial related to BMI [60], one related to body weight [56], and six RCTs associated with TC [46, 59, 65, 67, 74, 80].

Publication bias

Visual inspection of the funnel plots used to assess publication bias in the meta-analysis revealed asymmetrical patterns (Fig. S1). Egger's test indicated a significant publication bias in the studies concerning TG, SBP, and WHR outcomes. No substantial publication bias was detected in trials related to the other outcomes evaluated using Egger's and Begg's tests.

Discussion

This systematic review and meta-analysis of 27 RCTs indicated that supplementation with PBE significantly reduced body weight, SBP, DBP, LDL, FBS, and HbA1c in the PBE-treated group compared to the untreated control group. No significant effects of PBE were observed on BMI, WC, WHR, serum insulin, HDL, TG, and TC. In addition, a high degree of certainty was noted in the outcomes related to body weight. A moderate quality of evidence was assessed for BMI, WC, insulin, and HbA1c levels. The quality of evidence for WHR, DBP, FBS, TC, HDL, and LDL outcomes was classified as low, while it was rated very low for TG and SBP.

Subgroup analyses indicated that the BMI significantly decreased with moderate daily doses of PYC supplements (101–199 mg). In addition, a notable reduction in body weight was observed in studies involving long-term supplementation (≥ 10 weeks) with moderate daily doses. Furthermore, the WHR was substantially reduced in trials that provided moderate daily doses of PBE supplements. Long-term PYC supplementation was associated with a significant decline in DBP across various dosage categories including moderate (101–199 mg), low (≤ 100 mg), and high (≥ 200 mg) daily doses. A considerable decrease in SBP was observed after short- and long-term supplementation with moderate daily doses of PYC. Short-term PYC supplementation (< 10 weeks) also substantially reduced the serum TC and LDL levels. Furthermore, a considerable increase in serum HDL levels was observed after short-term supplementation with low daily doses of PBE. Serum FBS levels were significantly reduced following short- and long-term supplementation

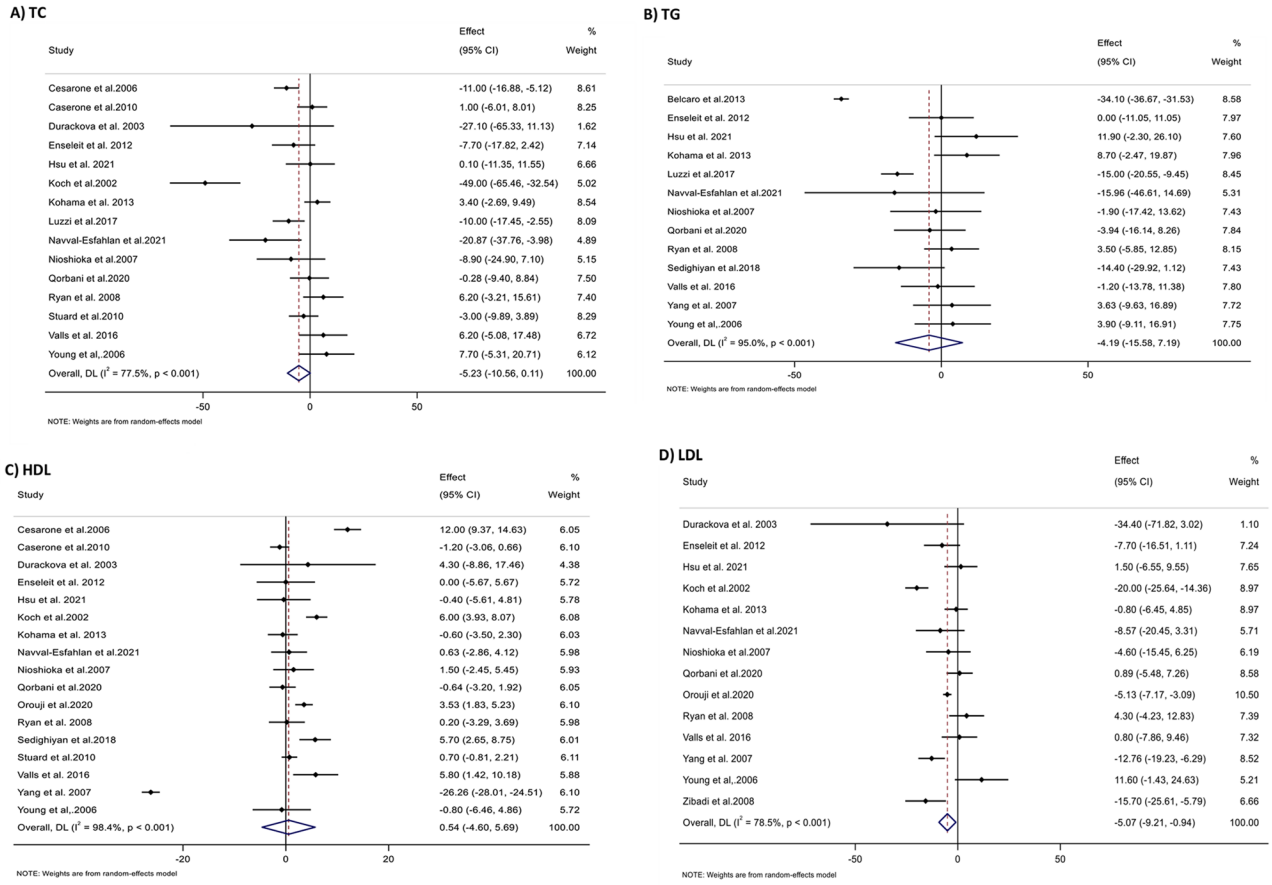

Fig. 5 Forest plots for the effect of supplementation with pine bark extract on lipid profile **A**) TC (mg/dL), **B**) TG (mg/dL), **C**) HDL (mg/dL), and **D**) LDL (mg/dL)

with moderate or low daily doses of PYC. After short-term supplementation with moderate daily PYC doses, the serum HbA1c levels were significantly reduced.

Previous meta-analyses have indicated that supplementation with PYC significantly increased HDL levels [20] and reduced BP [20, 82–84], LDL [20], BMI [20], HbA1c [20], and FBS [20]. In addition, a meta-analysis revealed that PBE supplementation increased levels of HDL [85]. However, changes in serum levels of TG, TC, and LDL were not statistically significant [85]. It has been reported that PBE may enhance insulin resistance and MetS [86]. Furthermore, PBE alleviated symptoms related to insulin resistance and abnormal glucose metabolism in a mouse model [87]. The hypoglycemic effects of PBE can be attributed to its oligomeric compounds, particularly procyanidin, which suppress the activity of the α-glycosidase enzyme and reduce intestinal glucose absorption [81, 88]. The administration of PBE significantly reduced the levels of endothelin-1, a substance secreted by the endothelium that plays a crucial role in regulating vascular pressure and blood pressure [68]. The observed reduction in BP is associated with a decrease in composite CVD risk [89]. It has been proposed that PBE influences cardiovascular risk factors by reducing OS, increasing nitric oxide (NO) production, decreasing blood vessel vasoconstriction, and enhancing antiplatelet effects [90]. These changes may improve BP, lipid profiles, and glycemic parameters [90].

PBE is a dietary antioxidant with low acute and chronic toxicity [33]. It mitigates excessive OS in various cellular systems by promoting intracellular synthesis of antioxidant enzymes and neutralizing free radicals [91]. This antioxidant effect contributes to the reduction in OS, which is associated with LDL oxidation, a critical factor in the development of atherosclerosis [92]. In animal studies, PBE reduced the serum TC levels, indicating a direct hypolipidemic effect [92, 93]. Multiple biological pathways influence weight management by inhibiting lipid absorption [94, 95], modulating adipogenic gene expression [96, 97], and reducing risk factors [75]. However, the specific mechanisms underlying the significant physiological functions of PBE components remain poorly understood [91]. PBE supplements may be advantageous in managing several diseases, such as CVDs or CMS, and may serve as a complementary therapeutic approach [36]. In addition to their antioxidant properties,

PBEs induce inflammation [41, 42, 45, 98]. PYC has been proposed as a natural antihypertensive supplement [83, 84] that contributes to cardiovascular health [90]. PBE supplementation results in lower levels of FBS and HbA1c, indicating improved glycemic control in patients with diabetes [90]. Therefore, PBEs can be incorporated into food ingredients and may represent a promising avenue for nutraceutical and pharmaceutical applications [91].

There have been no documented cases of severe adverse effects associated with PBE use, although the available toxicological data are limited [91]. Following oral administration of PYC, no toxic or mutagenic effects were observed, indicating its safety as a dietary supplement [99]. A review of 104 clinical studies revealed that the incidence of adverse effects among participants who consumed PYC was 1.66% [99]. PBEs have been extensively studied, and are generally considered safe for human consumption [38, 100, 101]. No serious adverse effects were detected with PYC supplementation in 39 RCTs [100]. Despite its overall safety, caution is advised regarding its potential interactions with medications, particularly in postmenopausal women [102].

The results of this meta-analysis suggest that PBE supplementation is an effective strategy for managing obesity and MetS. These findings have substantial implications for clinical practice and the development of RCTs. This systematic review did not restrict the timeframe or language of the included RCTs.

This meta-analysis had several limitations. The included trials showed considerable variations in health status, duration of supplementation, dosage or type of supplements, and participant age. Eleven RCTs had a high RoB and raised concerns of potential bias. Half of the evaluated outcomes displayed low or very low certainty. The trials were conducted across diverse geographical and ethnic groups. In addition, various non-intervention or control groups were included in these trials. These studies exhibited considerable variability and underscored the dearth of comprehensive clinical trials that evaluated parameters such as WHR and insulin levels. The methods used to prepare or deliver PBE supplements varied across studies, including powdered, hydroalcoholic, and alcoholic extracts, which affect the concentration of the active constituents in the supplements. The long-term effects of PBE supplementation, its underlying mechanisms of action, and its potential interactions with other pharmacological agents warrant further investigation through additional RCTs.

Conclusions

This meta-analysis showed that PBE supplementation reduced certain cardiometabolic risk factors, as indicated by reductions in body weight, SBP, LDL, DBP, FBS, and HbA1c. However, it did not exhibit remarkable effects on BMI, WC, WHR, or serum levels of insulin, HDL, TG, and TC. PBE supplementation can be considered an adjunct therapeutic strategy for managing CMS. This treatment may have a significant effect on the management and prevention of cardiometabolic disorders. Further RTCs with longer durations and larger sample sizes are required to confirm these outcomes.

Abbreviations

RCT	Randomized controlled trial
SBP	Systolic blood pressure
DBP	Diastolic blood pressure
BP	Blood pressure
FBS	Fasting blood sugar
WMD	Weighted mean difference
HbA1c	Hemoglobin A1c
WC	Waist circumference
BMI	Body mass index
WHR	Waist-to-hip ratio
TC	Total cholesterol
TG	Triglycerides
HDL	High-density lipoprotein (HDL) cholesterol
LDL	Low-density lipoprotein (LDL) cholesterol
CMS	Cardiometabolic syndrome
MetS	Metabolic syndrome
HTN	Hypertension
OS	Oxidative stress
CVD	Cardiovascular disease
PBE	Pine bark extract
OP	Oligopin
PYC	Pycnogenol
FG	Flavangenol
EZ	Enzogenol
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RoB	Risk of bias
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
T2DM	Type 2 diabetes mellitus
NO	Nitric oxide
PROSPERO	Prospective Register of Systematic Reviews
CIs	Confidence intervals
PICO	Population, Intervention, Comparator and Outcome
COVID-19	Coronavirus disease 2019
PCOS	Polycystic ovary syndrome
ADHD	Attention deficit hyperactivity disorder
USA	the United States of America

Supplementary Information

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Supplementary Material 1

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Author contributions

S. M. and J. H. developed the study protocol. S. M., T. F., A. K., S. E., M. H., S. Z., F. F., E. M., M.A., and J. H. participated in data extraction, search, and screening. S.M. performed data analysis and prepared the first draft of the manuscript. All authors reviewed and approved the final version of the manuscript.

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Data availability
All data supporting the findings of this study are available within the paper and its Supplementary Information.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
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Competing interests
The authors declare no competing interests.

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