

RESEARCH

Open Access



Clinical effects of *Emblica officinalis* fruit consumption on cardiovascular disease risk factors: a systematic review and meta-analysis

Paul D. S. Brown¹, Nicole Ketter^{2,3}, Mathew Vis-Dunbar¹ and Brodie M. Sakakibara^{1,3,4*}

Abstract

Background *Emblica officinalis* (EO) fruit consumption has been found to have a beneficial effect on cardiovascular disease (CVD) physiological risk factors in preliminary clinical intervention trials; however, questions remain regarding the overall effectiveness of EO on CVD risk. The purpose of this systematic review and meta-analysis is to: 1) systematically describe the clinical research examining EO; and 2) quantitatively assess the effects of EO on CVD physiological risk factors.

Methods The Pubmed, Embase, Web of Science, and Google Scholar electronic platforms were searched for relevant randomized controlled trials (RCTs) published until April 7, 2021. Studies were included if they involved adults (age ≥ 18 years) ingesting a form of EO fruit; included blood lipids, blood pressure, and/or inflammatory biomarkers as outcomes; had clearly defined intervention and control treatments with pre- and post-intervention data; were peer-reviewed; and were written in English. Studies were excluded if they compared EO with another risk reduction intervention without a usual care control group. RCTs were assessed for methodological quality using the Cochrane risk-of-bias version 2 (ROB2) tool, qualitatively described, and quantitatively evaluated using random and fixed effect meta-analysis models.

Results A total of nine RCTs ($n = 535$ participants) were included for review. Included studies followed parallel-group ($n = 6$) and crossover ($n = 3$) designs, with EO dosage ranging from 500 mg/day to 1500 mg/day, and treatment duration ranging from 14 to 84 days. Meta-analyses revealed EO to have a significant composite effect at lowering low-density lipoprotein cholesterol (LDL-C; Mean difference (MD) = -15.08 mg/dL [95% Confidence interval (CI) = -25.43 to -4.73], $I^2 = 77\%$, prediction interval = -48.29 to 18.13), very low-density lipoprotein cholesterol (VLDL-C; MD = -5.43 mg/dL [95% CI = -8.37 to -2.49], $I^2 = 44\%$), triglycerides (TG; MD = -22.35 mg/dL [95% CI = -39.71 to -4.99], $I^2 = 62\%$, prediction interval = -73.47 to 28.77), and high-sensitivity C-reactive protein (hsCRP; MD = -1.70 mg/L [95% CI = -2.06 to -1.33], $I^2 = 0\%$) compared with placebo.

Conclusions Due to statistical and clinical heterogeneity in the limited number of clinical trials to date, the promising effects of EO on physiologic CVD risk factors in this review should be interpreted with caution. Further research is needed to determine if EO offers an efficacious option for primary or secondary prevention of CVD as either monotherapy or adjunct to evidence-based dietary patterns and/or standard pharmacotherapy.

*Correspondence:

Brodie M. Sakakibara
brodie.sakakibara@ubc.ca

Full list of author information is available at the end of the article



© The Author(s) 2023. **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>. The Creative Commons Public Domain Dedication waiver (<http://creativecommons.org/publicdomain/zero/1.0/>) applies to the data made available in this article, unless otherwise stated in a credit line to the data.

Keywords Meta-analysis, Cardiovascular disease, Cholesterol, Inflammation, *Embllica officinalis*, Chronic disease, Lipids, Amla, *Phyllanthus emblica*, Atherosclerosis

Background

Cardiovascular disease (CVD) is the leading cause of death globally, accounting for ~17.8 million deaths annually [1]. Mortality associated with CVD is expected to increase to >22.2 million per year by 2030 [2]. Due to increasing prevalence, further efforts are required for both primary and secondary prevention of CVD. Aging demographics combined with improved survival post-cardiovascular event contribute to the growing pool of individuals living with established CVD [3]. Secondary prevention of subsequent events via improvement in modifiable CVD risk factors can help reduce morbidity and mortality in this growing population [3].

Modifiable risk factors associated with CVD are both behavioural and physiological. Research indicates a linear progression of risk factors leading to CVD, beginning with unhealthy lifestyle behaviours (e.g., physical inactivity, poor nutritional intake), leading to uncontrolled physiological risk factors, ultimately translating to CVD. Dyslipidemia, inflammation, and hypertension are common physiological risk factors for developing CVD via the progression of atherosclerosis [1]. Evidence-based dietary patterns have been developed to improve CVD physiological risk factors, including the Dietary Approaches to Stop Hypertension (DASH) diet [4] and the Portfolio diet [5, 6]. Although these dietary interventions have been associated with improvement in physiological CVD risk factors, CVD remains a significant global health concern. Therefore, the identification of efficacious, safe, affordable, and convenient options for primary or secondary prevention of CVD as either monotherapy or adjunct to evidence-based dietary patterns and/or standard pharmacotherapy is essential [7]. Furthermore, metabolic syndrome is a multicomponent risk factor for CVD and type 2 diabetes mellitus (T2DM) [1]. Metabolic syndrome is diagnosed when any three or more of the following five cardiometabolic risk factors are present: 1) hypertriglyceridemia, 2) decreased high-density lipoprotein cholesterol (HDL-C), 3) hypertension, 4) hyperglycemia, or 5) central adiposity [1]. Metabolic syndrome increases the risk of CVD mortality and all-cause mortality even for those with metabolic syndrome without T2DM [8]. Therefore, a single agent with the ability to produce beneficial changes in multiple cardiometabolic risk factors would be ideal when treating patients living with metabolic syndrome.

Embllica officinalis (EO)—also known as *Phyllanthus emblica*, Indian gooseberry in English, Amla in Hindi,

and Amalaki in Sanskrit [9]—is a 5–25 m tall deciduous tree, native to tropical and subtropical regions of India, Nepal, Sri Lanka, and throughout South-East Asia to southern China [10]. Although many components of the EO plant (e.g., root bark, stem bark, leaves) are traditionally used in Ayurveda, an Indian indigenous system of medicine, the edible fruit is typically used the most for health reasons [7]. EO berries are spherical and smooth, growing to 2–5 cm in diameter [11]. EO berries are initially pale green in colour, changing to yellow when mature [10]. EO fruit, and formulations incorporating EO fruit, have traditionally been used as dietary supplements to treat an abundance of health ailments, including fever, jaundice, anemia, cough, asthma, headache, dyspepsia, ophthalmic disorders, vomiting, leprosy, diabetes, and menorrhagia [9].

The phytoconstituents of EO fruit include many bioactive compounds including hydrolysable tannins (e.g., chebulinic acid, chebulagic acid, corilagin, punigluconin, pedunculagin, emblicanin A and B), alkaloids, phenols (e.g., gallic acid, ellagic acid, pyrogallol), amino acids, carbohydrates (e.g., pectin), vitamins (e.g., ascorbic acid), flavonoids (e.g., quercetin, kaempferol, rutin), and organic acids (e.g., citric acid) [12]. EO fruit is a rich source of ascorbic acid (vitamin C), with 470–680 mg per 100 g [9]. Vitamin C accounts for ~45–70% of the total antioxidant activity of the EO fruit, along with tannins (particularly punigluconin, pedunculagin, emblicanin A and B), flavonoids, and ellagic acid [11]. Furthermore, experimental research indicates the EO fruit to have antibacterial [13], antidiabetic [14], antidiarrheal [15], antihyperlipidemic [16, 17], antioxidant [18], antipyretic [19], anti-hyperthyroid [20], antitussive [21], antiulcer [22], chemopreventive [23], cognitive enhancing [24], gastroprotective [25], hepatoprotective [26], nephroprotective [27], skin antiaging [28], and wound healing [29] properties, among many others.

Preliminary clinical interventional trials have also shown promising results of EO fruit consumption on a variety of health conditions, including cardiovascular disease [9, 12, 30, 31]. Specifically, significant improvements in participant blood lipids and/or biomarkers of inflammation following consumption of EO fruit in various forms [32–49]. These initial studies have subsequently led to randomized controlled trials (RCTs) investigating the effects of EO on CVD physiological risk factors [50–58]. Thus, a body of evidence

now exists on the effects of EO on physiological risk, however, these effects have not been systematically reviewed or meta-analyzed. The purpose of this systematic review and meta-analysis is to: 1) systematically describe the clinical research examining EO; and 2) quantitatively assess the effects of EO on CVD physiological risk factors, including blood lipids, blood pressure, and biomarkers of inflammation.

Methods

This systematic review and meta-analysis protocol was not registered; however, the reporting in this review follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [59].

Inclusion/exclusion criteria

Randomized controlled trials were included for review if they involved adults (age ≥ 18 years), with any diagnostic condition, ingesting a form of the EO fruit (no polyherbal formulations); physiological CVD risk factor outcomes used in clinical practice (e.g. blood lipids, blood pressure, and/or inflammatory biomarkers); had clear definitions of intervention and placebo control treatments, such as proprietary extract descriptions and placebo constituents; had pre- and post-intervention data; were published in a peer-reviewed journal; and were written in English. Studies were excluded if they compared EO with another risk reduction intervention without a usual care control group. Cross-over trials were considered appropriate and included in this review due to the temporary effect of EO consumption and the stability of the patient population's health status [60].

Information sources/Search

The Pubmed, Embase, Web of Science, and Google Scholar electronic platforms were searched for relevant literature published up until April 7, 2021 using the search strategy detailed in Appendix A that was collaboratively developed with the university librarian. The Cochrane Database of Systematic Reviews in addition to the electronic platforms were searched for relevant reviews on EO. The reference lists of all relevant papers and reviews were searched for additional studies.

Study selection

All results from the electronic search were imported into a systematic review management program [61]. After duplicates were removed, the title and abstract screening was performed by two study authors independently. If both authors deemed an abstract relevant, it moved on to the full text review; discrepancies in judgement were resolved via discussion and engagement of another reviewer. Full texts of relevant studies were read by two

authors independently. Any discrepancy was discussed to determine final eligibility. Additional papers of interest found in reference lists were obtained and read to determine eligibility.

Data collection process

Data from relevant studies were extracted by the second author and tabulated for comparison. Extracted data included author(s), year, country, study design, sample size, participant characteristics (age, sex, medical diagnoses and medication information relevant to each study's inclusion criteria, and anthropometric and physiological data), details of the intervention and control treatments, outcome measures, and key results. Outcome measures included blood lipids (total cholesterol [TC], triglycerides [TG], LDL-C, HDL-C, and very low-density lipoprotein cholesterol [VLDL-C]), blood pressure (systolic and diastolic), and inflammatory biomarkers (high-sensitivity C-reactive protein [hsCRP]).

Study risk of bias assessment

Methodological quality of each study was completed using version 2 of the Cochrane risk-of-bias tool (ROB2) [62]. The ROB2 tool consists of 5 domains for parallel studies and 6 domains for cross-over studies. These domains include risk of bias arising from the randomization process, due to deviations from intended interventions, due to missing outcome data, in measurement of the outcome, and selection of the reported result. The cross-over tool also includes risk of bias arising from period and carryover effects. For each domain, there is a series of signaling questions and response options include "yes", "probably yes", "probably no", "no", and "no information". Each domain is then given a risk of bias judgement of low, some concern or high using a pre-determined algorithm.

Meta-analyses

Effect sizes were calculated for all outcome measures regardless of dosage. Study data were meta-analyzed using the mean difference (MD) for continuous data. The MD is used as a summary statistic to measure the absolute difference between the mean value in two groups when the outcome measures are made on the same scale [63]. If standard error of the mean was reported, it was converted to standard deviation by multiplying by the square root of the sample size [64]. Forest plots were used to visually display mean differences in outcomes between treatment and control groups for each study. The cross-over trials were analyzed as parallel trials when paired-analyses data and first period only data were not reported, which was the case for all cross-over trials [65].

The main analysis estimates the effect size of all interventions, regardless of dosage of EO on physiological risk factors. In the case where studies had two intervention groups, one receiving 500 mg/day and one receiving 1000 mg/day, the two intervention groups were combined as recommended in the Cochrane handbook [66]. This formula can be found in Appendix B. The meta-analyses estimated the pre-post effects immediately following the completion of the intervention. The I^2 statistic was used to determine statistical heterogeneity. A random effects model was used if the I^2 value was greater than 50%, signifying notable heterogeneity [67], otherwise a fixed effect model was used. Prediction intervals were reported for all random effects models to identify the range of true effect sizes and were calculated using a spreadsheet provided in Borenstein et al. [68]. All analyses were performed using RevMan 5.4 [69], at an alpha set at 0.05.

Results

The search yielded 310 results from Medline, 639 from Embase, and 790 from Web of Science. The PRISMA flow diagram is shown in Fig. 1. Only the first 200 results from Google Scholar were screened for any additional records as recommended by Bramer and colleagues [70]. After 450 duplicates were removed, the remaining 1297 abstracts were screened. Twenty-nine abstracts remained and their full texts were then assessed for eligibility. Nine studies were included in the descriptive synthesis and quantitative meta-analysis.

Study characteristics of the nine RCTs included for review are presented in Table 1. Overall, the sample sizes ranged between 12 [51, 58] and 150 [54] participants. Duration of treatment ranged between 14 [51, 58] and 84 [54–57] days. Seven of the RCTs were from India [50, 51, 54–58], one from Japan [53], and one from Iran [52]. Eight RCTs were double-blinded (i.e., participants and researcher) [50, 51, 53–58] and one RCT was triple-blinded (i.e., participants, researcher, and data analyzer) [52]. Six RCTs were of parallel-group design [50, 52, 54–57], while the remaining three were of crossover design [51, 53, 58]. All nine RCTs recruited adults (age range 20–74 years). Participant recruitment for each RCT were healthy males [51, 58]; healthy males and females [53]; male smokers [50]; males and females with dyslipidemia [55], T2DM [56], metabolic syndrome [57], uncontrolled hypertension [52], and essential hypertension [54].

The methodological quality of all 9 RCTs, including the cross-over studies, were assessed using the ROB2 tool [62]. Of the parallel RCTs, five studies [52, 54–57] had an overall risk of some concern, and one [50] had a high risk of bias arising from the randomization process. All the cross-over studies [51, 53, 58] had an overall risk of

some concern. Figures 2 and 3 show a detailed account of the risk of bias across each domain for the parallel and cross-over studies, respectively. All three cross-over studies [51, 53, 58] showed appropriate cross-over design. Two studies [53, 58] showed proper randomization order, while one study [51] was unclear because they did not describe the randomization method. None of the three cross-over studies explicitly discussed if there were any carry-over effects.

In terms of study outcomes, seven RCTs measured serum TC, TG, HDL-C, and LDL-C [50, 52–57]; four investigated serum VLDL-C [50, 54–56]; five examined systolic and diastolic blood pressure [51–54, 58]; and five reported serum hsCRP [50, 54–57].

Eight RCTs treated participants with an aqueous EO fruit extract [50, 51, 53–58] and the remaining RCT used powdered EO fruit [52]. *Emblica officinalis* was taken orally in capsule form for all nine RCTs. Dosage was 500 mg/day [50, 51, 53, 56, 57], 1000 mg/day [54–58], and 1500 mg/day [52]. *Emblica officinalis* fruit consumption was well-tolerated, with no included RCT reporting any adverse event serious enough to result in premature discontinuation of the study.

Meta-analyses: Effect size by risk factor

The effects of EO ingestion on various CVD risk factors compared with placebo are presented in Fig. 4. *Emblica officinalis* ingestion had significant effects at lowering LDL-C (MD = -15.08 mg/dL [95% CI = -25.43 to -4.73]), $I^2 = 77%$, prediction interval = -48.29 to 18.13, $p = 0.004$), VLDL-C (MD = -5.43 mg/dL [95% CI = -8.37 to -2.94], $I^2 = 44%$, $p = 0.0003$), TG (MD = -22.35 mg/dL [95% CI = -39.71 to -4.99], $I^2 = 62%$, prediction interval = -73.47 to 28.77, $p = 0.01$), and hsCRP (MD = -1.70 mg/L [95% CI = -2.06 to -1.33], $I^2 = 0%$, $p = 0.00001$). EO did not have a significant effect on HDL-C (MD = 2.09 mg/dL [95% CI = -0.91 to 5.08], $I^2 = 86%$, prediction interval = -8.09 to 12.27, $p = 0.17$), SPB (MD = -2.75 mmHg [95% CI = -10.41 to 4.90], $I^2 = 96%$, prediction interval = -30.93 to 25.43, $p = 0.48$) and DPB (MD = -0.83 mmHg [95% CI = -5.87 to 4.21], $I^2 = 89%$, prediction interval = -19.09 to 17.43, $p = 0.75$). Many of the results show high statistical heterogeneity, where an I^2 of 75% to 100% is reported as considerable heterogeneity [74]. The prediction intervals show there is a substantial range of effect size.

Discussion

This review estimated the effect of EO consumption on physiological CVD risk factors. *Emblica officinalis* consumption showed statistically significant improvements in LDL-C, VLDL-C, HDL-C, TG, and hsCRP compared with placebo.

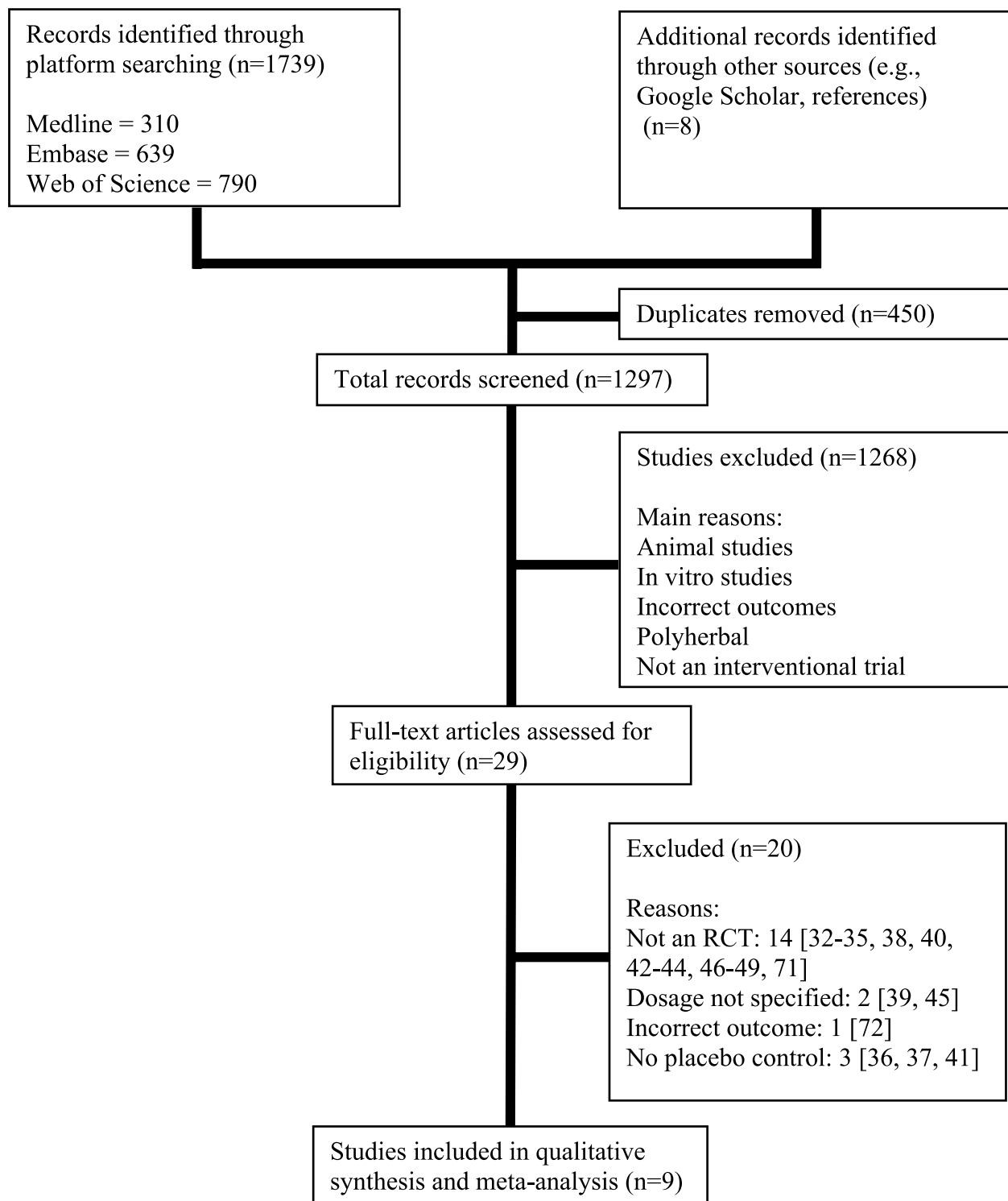


Fig. 1 Selection process of studies examining the effects of EO fruit consumption on CVD risk factors [71, 72]. EO *Emblica officinalis*, CVD Cardiovascular disease, RCT Randomized controlled trial

Table 1 Study characteristics

Author(s), year Study Design Country ROB2 [62] Score	Participants	Intervention/Control Groups	Outcome Measures	Key Results
Biswas et al. 2014 [50] Randomized, double-blind placebo-controlled pilot study Kolkata, India High Risk of Bias	Population: Adult smokers ($n = 30$ total) Sex: 30 Males Age: 20–60 years Characteristics: chronic cough, poor immune status, compromised cardiovascular status, and lipid profile	Intervention: $n = 20$, 250 mg aqueous EO fruit extract (standardized to contain $\geq 60\%$ w/w low molecular weight hydrolysable tannins) capsule b.i.d. PO for 60 days Control: $n = 10$, 250 mg placebo (microcrystalline cellulose, lactose and magnesium stearate) capsule b.i.d. PO for 60 days	TC, LDL-C, HDL-C, TG, hsCRP	Significant decrease in TC, LDL-C, TC/HDL-C ratio, LDL-C/HDL-C ratio, hsCRP, and significant increase in HDL-C after EO compared with baseline
Fatima et al. 2014 [51] Randomized, double-blind, placebo-controlled crossover study Hyderabad, India Some Concern of Bias	Population: Healthy adults ($n = 12$ total) Sex: 12 males Age: 20–30 years, mean of 25.62 ± 2.32 years Characteristics: mean BMI 22.42 ± 2.32 kg/m ²	Intervention: $n = 12$, 250 mg aqueous EO fruit extract (standardized to contain $\geq 60\%$ w/w low molecular weight hydrolysable tannins) capsule b.i.d. PO for 14 days 14-day washout period Control: $n = 12$, placebo capsule contains microcrystalline cellulose (49.7% w/w), lactose (49.5% w/w) and magnesium stearate (0.69% w/w) b.i.d. PO for 14 days	Automated, radial and aortic SBP and DBP using non-invasive software (SphygmoCor; AtCor Medical, Australia)	Significant decrease in cold pressor stress test induced changes on aortic wave reflections after EO compared with baseline and placebo
Ghaffari et al. 2020 [52] Randomized, triple-blind, placebo-controlled add-on clinical trial Tabriz, Iran Some Concern of Bias	Population: Adults with uncontrolled hypertension ($n = 81$ total) Sex: 45 males, 36 females Age: 35–74 years, mean of 53.64 ± 10.01 years Characteristics: BMI < 30 , SBP ≥ 140 mm Hg, DBP ≥ 90 mm Hg or both, and SBP ≥ 150 mm Hg for patients older than 60 years, maximum of 2 antihypertensive drugs for at least 8 weeks, a minimum of one month must have elapsed from the start of medication	Intervention: $n = 41$, 500 mg EO fruit powder (fresh EO fruit dried then powdered) capsule t.i.d. PO after meal for 8 weeks Control: $n = 40$, placebo (wheat starch powder) capsule t.i.d. PO after meal for 8 weeks	Automated, brachial SBP and DBP TC, LDL-C, HDL-C, TG	Significant decrease in SBP and DBP after EO compared with baseline and control group

Table 1 (continued)

Author(s), year Study Design Country ROB2 [62] Score	Participants	Intervention/Control Groups	Outcome Measures	Key Results
Kapoor et al. 2020 [53] Randomized, double-blind, placebo-controlled crossover study Japan Some Concern of Bias	Population: Healthy adults ($n = 13$ total) Sex: 6 males, 7 females Age: 36–67 years, mean of 51.9 ± 2.8 years Characteristics: Mean BMI 25.1 ± 0.63 kg/m ² , with elevated TG, lower HDL-C, and average blood fluidity	Intervention: $n = 13$, 125 mg aqueous EO fruit extract powder (EO fruit pulp hydrolysed with pectinase followed by centrifugation with the supernatant spray dried) capsule q.i.d. PO (2 capsules after breakfast + 2 after dinner) for 4 weeks (each capsule contained 125 mg EO + 125 mg dextrin) 3-week washout period Control: $n = 13$, 250 mg dextrin capsule q.i.d. PO (2 capsules after breakfast + 2 after dinner every day) for 4 weeks	Automated, brachial SBP and DBP TC, LDL-C, HDL-C, TG	Significant increase in HDL-C after 2 weeks (but not 4 weeks) of EO compared with baseline
Shanmugarajan et al. 2021 [54] Randomized, double-blind, placebo-controlled clinical trial Puducherry, India Some Concern of Bias	Population: Adults with essential hypertension ($n = 150$ total) Sex: 119 males, 31 females Age: Intervention: mean of 58.8 ± 8.68 years, control: mean of 60.0 ± 9.42 years Characteristics: Essential hypertension on amlodipine 5 mg or enalapril 5 mg and had not yet attained target blood pressure goals (130 mmHg of systolic and 80 mmHg of diastolic blood pressure)	Intervention: $n = 75$, 500 mg aqueous EO dried fruit extract powder capsule b.i.d. PO for 12 weeks Control: $n = 75$, 500 mg maize starch IP grade capsule b.i.d. PO for 12 weeks	SBP, DBP TC, LDL-C, VLDL-C, HDL-C, TG, hsCRP	NS change in SBP, DBP, TC, LDL-C, VLDL-C, HDL-C, TG, or hsCRP after EO compared with placebo
Upadaya et al. 2019 [55] Randomized, double-blind, placebo-controlled, multicenter clinical trial Southern India Some Concern of Bias	Population: Adults with dyslipidemia ($n = 98$ total) Sex: 45 males, 53 females Age: 30–65 years, intervention: mean of 40.7 ± 10.13 years, control: mean of 42.2 ± 9.20 years Characteristics: TG > 200 mg/dL, LDL-C > 130 mg/dL, TC > 200 mg/dL and HDL-C < 40 mg/dL for men and < 50 mg/dL for women Patients were not taking any medication (including herbal product) for management of dyslipidemia in past 4 weeks	Intervention: $n = 49$, 500 mg aqueous EO fruit extract powder (fresh, whole EO fruit extracted with ethyl acetate, standardized to contain $\geq 35\%$ polyphenols, 8% triterpenoids, and 10% EO oil) capsule b.i.d. PO (1 capsule after breakfast + 1 after dinner) for 12 weeks Control: $n = 49$, 500 mg roasted rice powder capsule b.i.d. PO (1 capsule after breakfast + 1 after dinner) for 12 weeks	TC, LDL-C, VLDL-C, HDL-C, TG, hsCRP	Significant decrease in TC, LDL-C, VLDL-C, and TG after EO compared with placebo

Table 1 (continued)

Author(s), year Study Design Country ROB2 [62] Score	Participants	Intervention/Control Groups	Outcome Measures	Key Results
Usharani et al. 2013 [56] Randomized, double-blind, placebo-controlled study Hyderabad, India Some Concern of Bias	Population: Adults with T2DM (n = 80 total) Sex: 53 males, 27 females Age: 30–68 years, intervention 1: mean of 57.60 ± 9.67 years, intervention 2: mean of 57.75 ± 9.86 years, intervention 3: mean of 56.95 ± 8.04 years, control: mean of 56.90 ± 9.17 years Characteristics: Fasting blood glucose of 110–126 mg/dL, glycosylated hemoglobin of 7%–9%, on stable antidiabetic medication (metformin 1,500–3,000 mg) for the 8 weeks prior to the screening visit, and endothelial dysfunction	Intervention 1: n = 20, 250 mg aqueous EO extract (standardized to contain ≥ 60% w/w low molecular weight hydrolysable tannins) capsule b.i.d. PO for 12 weeks Intervention 2: n = 20, 500 mg aqueous EO extract capsule b.i.d. PO for 12 weeks Intervention 3: n = 20, 10 mg atorvastatin capsule o.d. PO at bedtime + matching placebo capsule o.d. PO in the morning for 12 weeks Control: n = 20, placebo capsule b.i.d. PO for 12 weeks. Matching placebo capsules contained microcrystalline cellulose (49.7% w/w), lactose (49.5% w/w), and magnesium stearate (0.69% w/w) as excipients	TC, LDL-C, VLDL-C, HDL-C, TG, hsCRP	Significant decrease in TC, LDL-C, TG, hsCRP and significant increase in HDL-C after both EO dosages and atorvastatin compared with baseline and placebo Significant decrease in VLDL-C after both EO dosages compared with baseline but not placebo Significant decrease in VLDL-C after atorvastatin compared with baseline and placebo
Usharani et al. 2019 [57] Prospective, randomised, double-blind and placebo-controlled clinical study Hyderabad, India Some Concern of Bias	Population: Adults with metabolic syndrome (n = 59 total) Sex: 43 males, 16 females Age: 30–68 years, intervention 1: mean of 57.45 ± 7.44 years, intervention 2: mean of 57.24 ± 8.94 years, control: mean of 56.89 ± 7.39 years Characteristics: Endothelial dysfunction	Intervention 1: n = 20, 250 mg aqueous EO fruit extract (standardized to contain ≥ 60% w/w low molecular weight hydrolysable tannins) capsule b.i.d. PO for 12 weeks Intervention 2: n = 21, 500 mg aqueous EO fruit extract capsule b.i.d. PO for 12 weeks Control: n = 18, placebo (microcrystalline cellulose, lactose and magnesium stearate) capsule b.i.d. PO for 12 weeks	TC, LDL-C, HDL-C, TG, hsCRP	Significant decrease in TC, LDL-C, HDL-C, TG, and hsCRP after both EO dosages compared with baseline and placebo
Usharani et al. 2017 [58] Randomized, double-blind, placebo-controlled, crossover study Hyderabad, India Some Concern of Bias	Population: Healthy adults (n = 12 total) Sex: 12 males Age: 20–30 years, mean of 24.75 ± 2.01 years Characteristics: BMI between 18–24.9 kg/m ² and non-smokers	Intervention: n = 12, 250 mg aqueous EO fruit extract (standardized to contain ≥ 60% w/w low molecular weight hydrolysable tannins) capsule q.i.d. PO (2 capsules b.i.d. PO) for 14 days 14-day washout period Control: n = 12, 250 mg placebo (microcrystalline cellulose, croscarmellose sodium, silicon dioxide, talc and magnesium stearate) capsule q.i.d. PO (2 capsules b.i.d. PO) for 14 days	Automated, radial and aortic SBP and DBP using non-invasive software (SphygmoCor; AtCor Medical, Australia)	Significant decrease in mental stress test induced changes on aortic wave reflections after EO compared with baseline and placebo

b.i.d. Twice daily, BMI Body mass index, DBP Diastolic blood pressure, EO *Embilica officinalis*, HDL-C High-density lipoprotein cholesterol, hsCRP High-sensitivity C-reactive protein, LDL-C Low-density lipoprotein cholesterol, o.d. Once daily, PO Orally, q.i.d. Four times daily, SBP Systolic blood pressure, t.i.d. Three times daily, T2DM Type 2 diabetes mellitus, TC Total cholesterol, TG Triglycerides, VLDL-C Very low-density lipoprotein cholesterol

Study	Risk of bias domains					
	D1	D2	D3	D4	D5	Overall
Biswas et al.	⊗	⊖	⊖	⊕	⊖	⊗
Ghaffari et al.	⊕	⊖	⊕	⊕	⊕	⊖
Shanmugarajan et al.	⊕	⊖	⊕	⊕	⊕	⊖
Upadya et al.	⊕	⊖	⊕	⊕	⊖	⊖
Usharani et al. 2013	⊖	⊖	⊕	⊕	⊖	⊖
Usharani et al. 2019	⊕	⊖	⊕	⊕	⊖	⊖

Domains:
D1: Bias arising from the randomization process.
D2: Bias due to deviations from intended intervention.
D3: Bias due to missing outcome data.
D4: Bias in measurement of the outcome.
D5: Bias in selection of the reported result.

Judgement
⊗ High
⊖ Some concerns
⊕ Low

Fig. 2 Cochrane Risk of Bias Assessments for parallel RCTs. Figure is generated using robvis [73]






















		Risk of bias domains						
		D1	D1b	D2	D3	D4	D5	Overall
Study	Fatima et al.							
	Kapoor et al.							
	Usharani et al. 2017							

Fig. 3 Cochrane Risk of Bias Assessments for cross-over RCTs. Figure is generated using robvis [73]

Limitations

Considerable heterogeneity exists in the RCTs examining the effect of EO extract on CVD risk factors that have been published so far. There are marked variations in the participant inclusion criteria, baseline biochemical values, study design, and duration of treatment. The potential variation in proprietary extract preparation techniques between studies may have also influenced the findings. One RCT [52] did not use an extract but the dried raw EO fruit itself, which may exert a different effect at equal dosage relative to an extract. Commercial interest may limit the submission and subsequent publication of non-significant or opposing data regarding the alleged health benefits of EO. Relatively small sample sizes must also be taken into consideration, with three of the nine included RCTs containing only 12 [51, 58] or 13 [53] participants. There is also a limited number of included RCTs and neither funnel plots nor Eggar regression tests were completed due to insufficient sample size. Prediction intervals, which signify an absolute measure of heterogeneity, were provided for all random effects models to aid in the interpretation of the heterogeneity [68]. There is a limitation in the analysis of the cross-over trials given the limited availability of reported data. The

analysis of cross-over trials as parallel trials does give rise to a unit-of-analysis error [65]. However, this analysis is conservative, and consequently the cross-over studies are underweighted [65]. According to the Friedewald equation, LDL-C is calculated as TC minus HDL-C minus VLDL-C [75]. Clinically, VLDL is often estimated as TG divided by 2.2 (if values are in mmol/L) or 5 (if values are in mg/dL) [75]. Although a higher serum HDL-C is considered protective against CVD, a higher HDL-C would contribute to a higher serum TC based on this equation, which is considered a risk factor for CVD. Therefore, the individual components of TC (e.g., LDL-C, HDL-C, VLDL-C, TG) may be more informative when assessing CVD risk compared with TC alone. Therefore, TC was not included in this review. Excluding non-English articles and not investigating safety in this review are additional limitations.

Dyslipidemia is a primary causal factor for the development of atherosclerosis and CVD [1]. Dyslipidemia refers to abnormally high serum TC (≥ 5.2 mmol/L or ≥ 200 mg/dL), LDL-C (≥ 3.4 mmol/L or ≥ 130 mg/dL), TG (≥ 1.7 mmol/L or ≥ 150 mg/dL), or low serum HDL-C (< 1.0 mmol/L or < 40 mg/dL) [1]. For every 1.0 mmol/L (38.67 mg/dL) reduction in LDL-C there is a 20–22%

relative risk reduction for the development of CVD [76]. High-density lipoprotein cholesterol is thought to counteract the atherosclerotic process by inhibiting the oxidation of LDL-C and removing cholesterol from foam cells (i.e., lipid-laden macrophages within the arterial tunica intima) for transportation back to the liver [50]. Non-HDL-C includes chylomicron remnants, VLDL-C, intermediate-density lipoprotein cholesterol, lipoprotein(a), and LDL-C [76]. The components of non-HDL-C are atherogenic, apolipoprotein B-100 (Apo B) containing lipoproteins [76]. *Emblica officinalis* showed improvements in components of non-HDL-C in this review.

The mechanisms of how EO may exert its beneficial effects on lipid profile are not fully elucidated. Proposed mechanisms include interference of cholesterol absorption [77]; inhibition of hepatic 3-hydroxy-3-methylglutaryl coenzyme-A (HMG-CoA) reductase activity, resulting in decreased cholesterol synthesis [78]; and increase in lecithin-cholesterol acyltransferase (LCAT) activity, resulting in greater cholesterol transfer to HDL for transport to liver for hepatic degradation and biliary excretion [78]. Increased transfer of cholesterol to HDL from other sources (e.g., LDL) via upregulation of lipoprotein transfer enzymes and/or proteins may partially explain the tendency for EO to increase HDL-C with a concurrent decrease in non-HDL-C components [33]. *Emblica officinalis* may be an addition to established dietary interventions to combat dyslipidemia such as the Portfolio diet, or adjunct to standard pharmacotherapy such as HMG-CoA reductase inhibitors.

HMG-CoA reductase inhibitors, also known as statins, are a class of medication widely prescribed to treat dyslipidemia, especially to lower serum LDL-C [1]. Statins lower cholesterol via inhibition of hepatic HMG-CoA reductase, the rate-limiting enzyme of cholesterol biosynthesis [76]. Reported side effects of statin use include myopathy, hepatotoxicity, and cephalgia [56]. Several clinical trials have compared the effect of EO and statins on blood lipids [35, 36, 56]. These trials reported similar improvements in lipids after a 500–1000 mg/day dose of EO and an initial dose (10–20 mg/day) of standard statin pharmacotherapy. However, only Usharani and colleagues [56] met inclusion criteria for this review (Table 1). No serious adverse events were reported in the EO or statin groups for the duration of these clinical trials.

C-reactive protein (CRP) is a non-specific biomarker of inflammation. Elevated hsCRP (≥ 2 mg/L) has been associated with atherosclerosis and CVD [1, 76]. However, it remains uncertain whether CRP is directly involved in the progression of atherosclerosis or simply a consequence of the atherosclerotic process [56]. Oxidative stress via accumulation of reactive oxygen species (ROS) may reduce the bioavailability of nitric oxide and result in endothelial dysfunction and vascular inflammation. Excess ROS may also increase the conversion of LDL-C to oxidized LDL-C, further exacerbating the inflammatory cascade [57]. The anti-inflammatory properties of EO—as demonstrated by the significant reduction in hsCRP in this meta-analysis—may be explained by the large antioxidant capacity and ROS scavenging ability of the fruit [56]. This antioxidant capacity is partially attributed to the relatively high ascorbic acid and ellagitannin content [53]. The EO fruit is rich source of ellagitannins—such as chebulagic acid, pedunculagin, geraniin, corilagin, elaeocarpusin—which are hydrolysable to ellagic acid and gallic acid [53]. The complex and potentially synergistic interactions between the various EO phytochemicals may also enhance the antioxidant capacity of the fruit [53].

Conclusions

Emblica officinalis has beneficial effects on LDL-C, VLDL-C, HDL-C, TG, and hsCRP that are statistically significant; however, due to small sample size and heterogeneity (clinical and statistical), these results should be interpreted with caution. Further research on the clinical effects of EO is necessary. Additional large RCTs are required to confirm these results and identify the most efficacious dose and form of EO in various patient populations. Potential sex differences should also be explored. The mechanism of action requires further investigation as the many bioactive phytochemicals of the fruit appear to exert individual beneficial effects and the potential to interact synergistically. These complex, potentially synergistic interactions may favour consumption of the whole EO fruit as opposed to proprietary extracts of the fruit, where some of the bioactive phytochemicals may be lost or altered during the extraction process. However, this is speculative and requires clinical validation involving minimally processed preparations of EO that can

(See figure on next page.)

Fig. 4 **a** Forest plot of seven studies comparing mean difference of LDL-C (mg/dL) between two groups. **b** Forest plot of three studies comparing mean difference of VLDL-C (mg/dL) between two groups. **c** Forest plot of seven studies comparing mean difference of HDL-C (mg/dL) between two groups. **d** Forest plot of six studies comparing mean difference of TG (mg/dL) between two groups. **e** Forest plot of four studies comparing mean difference of hsCRP (mg/L) between two groups. **f** Forest plot of five studies comparing mean difference of SBP (mmHg) between two groups. **g** Forest plot of five studies comparing mean difference of DBP (mmHg) between two groups. *EO* *Emblica officinalis*, *LDL-C* Low-density lipoprotein cholesterol, *VLDL-C* Very low-density lipoprotein cholesterol, *HDL-C* High-density lipoprotein cholesterol, *TG* Triglycerides, *hsCRP* High-sensitivity C-reactive protein, *SBP* Systolic blood pressure, *DBP* Diastolic blood pressure

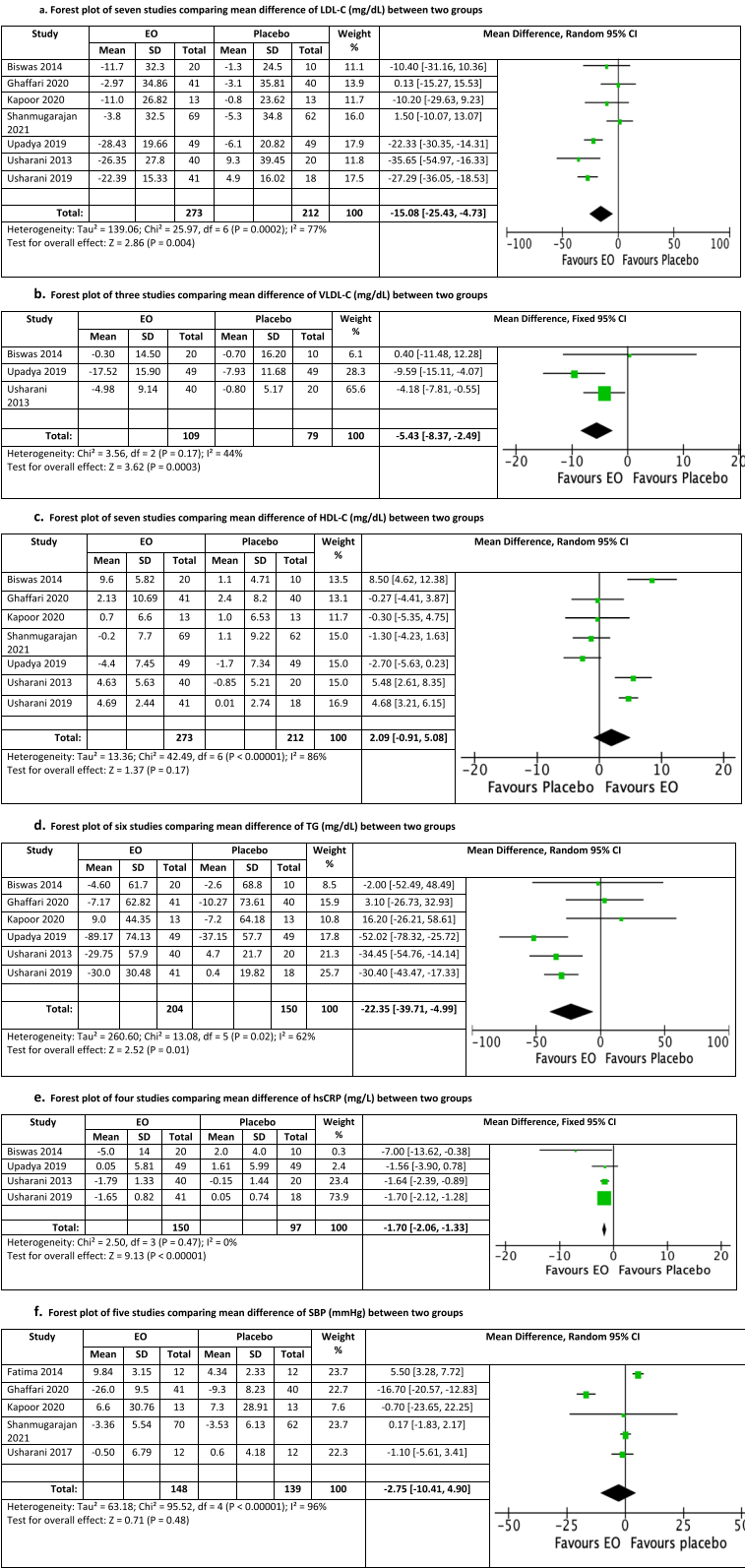


Fig. 4 (See legend on previous page.)

still be effectively blinded and placebo controlled. For example, dried EO fruit powder ingested via capsule. *Emblica officinalis* may offer an efficacious, affordable, and convenient option for primary or secondary prevention of CVD as either monotherapy or adjunct to evidence-based dietary patterns and/or standard pharmacotherapy.

Abbreviations

Apo B	Apolipoprotein B-100
CRP	C-reactive protein
CVD	Cardiovascular disease
DASH	Dietary Approaches to Stop Hypertension
EO	<i>Emblica officinalis</i>
HDL-C	High-density lipoprotein cholesterol
HMG-CoA	Hepatic 3-hydroxy-3-methylglutaryl coenzyme-A
hsCRP	High-sensitivity C-reactive protein
LCAT	Lecithin-cholesterol acyltransferase
LDL-C	Low-density lipoprotein cholesterol
MD	Mean difference
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCTs	Randomized controlled trials
ROB2	Risk of Bias 2 Assessment Tool
ROS	Reactive oxygen species
T2DM	Type 2 diabetes mellitus
TC	Total cholesterol
TG	Triglycerides
VLDL-C	Very low-density lipoprotein cholesterol

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12906-023-03997-8>.

Additional file 1. Appendix A and B.

Acknowledgements

Not applicable.

Authors' contributions

PDB conceptualized the study, analyzed and interpreted the data, and wrote the first draft of the manuscript. NK helped analyze and interpret the data and prepare the manuscript. MV-D helped prepare the search strategy, interpret the data, and prepare the manuscript. BMS conceptualized the study, analyzed and interpreted the data, and helped prepare the manuscript. All authors read and approved the final manuscript.

Funding

This research was supported by a Michael Smith Foundation for Health Research Scholar Award to BMS. The funding body was not involved in the design of the study; collection, analysis, and interpretation of data; or writing of the manuscript.

Availability of data and materials

All data supporting this systematic review and meta-analysis are from published randomized controlled trials that have been cited in this article.

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.

Author details

¹Southern Medical Program, Faculty of Medicine, University of British Columbia Okanagan Campus, 1088 Discovery Avenue, Kelowna, BC V1V 1V7, Canada. ²Department of Biology, Irving K. Barber Faculty of Science, University of British Columbia Okanagan Campus, 3187 University Way, ASC 413, Kelowna, BC V1V 1V7, Canada. ³Centre for Chronic Disease Prevention and Management, University of British Columbia Okanagan Campus, 1088 Discovery Avenue, Kelowna, BC V1V 1V7, Canada. ⁴Department of Occupational Science and Occupational Therapy, University of British Columbia, T325 - 2211, Westbrook Mall, Vancouver, BC V6T 2B5, Canada.

Received: 9 September 2021 Accepted: 13 May 2023

Published online: 09 June 2023

References

- Virani SS, Alonso A, Benjamin EJ, Bittencourt MS, Callaway CW, Carson AP, et al. Heart disease and stroke statistics-2020 update: A report from the American Heart Association. *Circulation*. 2020;141:e139–596.
- World Health Organization. Global Status Report on Noncommunicable Diseases. 2014. <https://www.who.int/nmh/publications/ncd-status-report-2014/en/>. Accessed June 2, 2021.
- Bansilal S, Castellano JM, Fuster V. Global burden of CVD: focus on secondary prevention of cardiovascular disease. *Int J Cardiol*. 2015;201(S1):S1–7.
- Filippou CD, Tsioufis CP, Thomopoulos CG, Mihos CC, Dimitriadis KS, Sotiropoulou LI, et al. Dietary approaches to stop hypertension (DASH) diet and blood pressure reduction in adults with and without hypertension: a systematic review and meta-analysis of randomized controlled trials. *Adv Nutr*. 2020;11(5):1150–60.
- Chiavaroli L, Nishi SK, Khan TA, Braunstein CR, Glenn AJ, Mejia SB, et al. Portfolio dietary pattern and cardiovascular disease: a systematic review and meta-analysis of controlled trials. *Prog Cardiovasc Dis*. 2018;61(1):43–53.
- Jenkins DJA, Jones PJH, Lamarche B, Kendall CWC, Faulkner D, Cermakova L, et al. Effect of a dietary portfolio of cholesterol-lowering foods given at 2 levels of intensity of dietary advice on serum lipids in hyperlipidemia: a randomized controlled trial. *JAMA*. 2011;306(8):831–9.
- Khan KH. Roles of *Emblica officinalis* in medicine - a review. *Botany Research International*. 2009;2(4):218–28.
- Mottillo S, Filion KB, Genest J, Joseph L, Poirier P, et al. The metabolic syndrome and cardiovascular risk: a systematic review and meta-analysis. *J Am Coll Cardiol*. 2010;56(14):1113–32.
- Yadav SS, Singh MK, Singh PK, Kumar V. Traditional knowledge to clinical trials: a review on therapeutic actions of *Emblica officinalis*. *Biomed Pharmacother*. 2017;93:1292–302.
- Lim TK. *Phyllanthus emblica*. In: *Edible Medicinal and Non-Medicinal Plants: Volume 4, Fruits*. Springer; 2012. p. 258–96.
- Pareek S, Shikov AN, Pozharitskaya ON, Makarov VG, González-Aguilar GA, Ramalho SA, et al. Indian Gooseberry (*Emblica officinalis* Gaertn.). In: Yahia EM, editor, et al., *Fruit and Vegetable Phytochemicals: Chemistry and Human Health*. 2nd ed. Hoboken, NJ: John Wiley & Sons Ltd; 2018. p. 1077–105.
- Hashem-Dabaghian F, Ziaee M, Ghaffari S, Nabati F, Kianbakht S. A systematic review on the cardiovascular pharmacology of *Emblica officinalis* Gaertn. *J Cardiovasc Thorac Res*. 2018;10(3):118–28.
- Saini A, Sharma S, Chhibber S. Protective efficacy of *Emblica officinalis* against *Klebsiella pneumoniae* induced pneumonia in mice. *Indian J Med Res*. 2008;128(2):188–93.
- Krishnaveni M, Mirunalini S, Karthishwaran K, Dhamodharan G. Antidiabetic and antihyperlipidemic properties of *Phyllanthus emblica* Linn. (Euphorbiaceae) on streptozotocin induced diabetic rats. *Pak J Nutr*. 2010;9(1):43–51.
- Mehmood MH, Siddiqi HS, Gilani AH. The antidiarrheal and spasmolytic activities of *Phyllanthus emblica* are mediated through dual blockade of muscarinic receptors and Ca²⁺ channels. *J Ethnopharmacol*. 2011;133(2):856–65.

16. Kim HJ, Yokozawa T, Kim HY, Tohda C, Rao TP, Juneja LR. Influence of amla (*Embolica officinalis* Gaertn.) on hypercholesterolemia and lipid peroxidation in cholesterol-fed rats. *J Nutri Sci Vitaminol*. 2005;51(6):413–8.
17. Santoshkumar J, Manjunath S, Pranavkumar MS. A study of anti-hyperlipidemia, hypolipidemic and anti-atherogenic activity of fruit of *Embolica officinalis* (amla) in high fat fed albino rats. *Int J Med Res Health Sci*. 2013;2(1):70–7.
18. Prakash D, Upadhyay G, Gupta C, Pushpangadan P, Singh KK. Antioxidant and free radical scavenging activities of some promising wild edible fruits. *Int Food Res J*. 2012;19(3):1109–16.
19. Perianayagam JB, Sharma SK, Joseph A, Christina AJM. Evaluation of anti-pyretic and analgesic activity of *Embolica officinalis* Gaertn. *J of Ethnopharmacol*. 2004;95(1):83–5.
20. Panda S, Kar A. Fruit extract of *Embolica officinalis* ameliorates hyperthyroidism and hepatic lipid peroxidation in mice. *Pharmazie*. 2003;58(10):753–5.
21. Nosál'ová G, Mokry J, Tareq Hassan KM. Antitussive activity of the fruit extract of *Embolica officinalis* Gaertn. (*Euphorbiaceae*). *Phytomedicine*. 2003;10(6–7):583–9.
22. Chatterjee A, Chattopadhyay S, Bandyopadhyay SK. Biphasic effect of *Phyllanthus emblica* L. extract on NSAID-induced ulcer: An antioxidative trail weaved with immunomodulatory effect. *Evid Based Complement Alternat Med*. 2011; <https://doi.org/10.1155/2011/146808>.
23. Krishnaveni M, Mirunalini S. Chemopreventive efficacy of *Phyllanthus emblica* L. (amla) fruit extract on 7,12-dimethylbenz(a)anthracene induced oral carcinogenesis - a dose-response study. *Environ Toxicol Pharmacol*. 2012;34(3):801–10.
24. Uddin MS, Mamun A al, Hossain MS, Akter F, Iqbal MA, Asaduzzaman M. Exploring the effect of *Phyllanthus emblica* L. on cognitive performance, brain antioxidant markers and acetylcholinesterase activity in rats: promising natural gift for the mitigation of Alzheimer's disease. *Ann Neurosci*. 2016;23(4):218–29.
25. Al-Rehaily AJ, Al-Howiriny TA, Al-Sohaibani MO, Rafatullah S. Gastro-protective effects of "Amla" *Embolica officinalis* on in vivo test models in rats. *Phytomedicine*. 2002;9(6):515–22.
26. Huang CZ, Tung YT, Hsia SM, Wu CH, Yen GC. The hepatoprotective effect of *Phyllanthus emblica* L. fruit on high fat diet-induced non-alcoholic fatty liver disease (NAFLD) in SD rats. *Food Funct*. 2017;8(2):842–50.
27. Yokozawa T, Kim HY, Kim HJ, Tanaka T, Sugino H, Okubo T, et al. Amla (*Embolica officinalis* Gaertn.) attenuates age-related renal dysfunction by oxidative stress. *J Agric Food Chem*. 2007;55(19):7744–52.
28. Fujii T, Wakaizumi M, Ikami T, Saito M. Amla (*Embolica officinalis* Gaertn.) extract promotes procollagen production and inhibits matrix metalloproteinase-1 in human skin fibroblasts. *J Ethnopharmacol*. 2008;119(1):53–7.
29. Sumitra M, Manikandan P, Gayathri VS, Mahendran P, Suguna L. *Embolica officinalis* exerts wound healing action through up-regulation of collagen and extracellular signal-regulated kinases (ERK1/2). *Wound Repair Regen*. 2009;17(1):99–107.
30. Teimouri E, Rainey-Smith SR, Bharadwaj P, Verdile G, Martins RN. Amla therapy as a potential modulator of Alzheimer's disease risk factors and physiological change. *J Alzheimers Dis*. 2020;74(3):713–33.
31. Variya BC, Bakrania AK, Patel SS. *Embolica officinalis* (Amla): a review for its phytochemistry, ethnomedicinal uses and medicinal potentials with respect to molecular mechanisms. *Pharmacol Res*. 2016;111:180–200.
32. Akhtar MS, Ramzan A, Ali A, Ahmad M. Effect of amla fruit (*Embolica officinalis* Gaertn.) on blood glucose and lipid profile of normal subjects and type 2 diabetic patients. *Int J Food Sci Nutr*. 2011;62(6):609–16.
33. Antony B, Merina B, Sheeba V. Amlamax™ in the management of dyslipidemia in humans. *Indian J Pharm Sci*. 2008;70(4):504–7.
34. Antony B, Benny M, Kaimal TNB. A pilot clinical study to evaluate the effect of *Embolica officinalis* extract (Amlamax™) on markers of systemic inflammation and dyslipidemia. *Indian J Clin Biochem*. 2008;23(4):378–81.
35. Gopa B, Bhatt J, Hemavathi KG. A comparative clinical study of hypolipidemic efficacy of Amla (*Embolica officinalis*) with 3-hydroxy-3-methylglutaryl-coenzyme-A reductase inhibitor simvastatin. *Indian J Pharmacol*. 2012;44(2):238–42.
36. Sinha RR, Sharma N, Advani U, Dadheech G, Kulshreshtha S, Parakh R. Comparative study of hypolipidemic effects of atorvastatin with *Embolica officinalis* (Amla) in patients of type II hyperlipidemia. *World J Pharm Res*. 2014;3(2):2799–810.
37. Fatima N, Usharani P, Muralidhar N. Study of pharmacodynamic interaction of *Phyllanthus emblica* extract with clopidogrel and ecosprin in patients with type II diabetes mellitus. *Phytomedicine*. 2014;21(5):579–85.
38. Khanna S, Das A, Spieldenner J, Rink C, Roy S. Supplementation of a standardized extract from *Phyllanthus emblica* improves cardiovascular risk factors and platelet aggregation in overweight/class-1 obese adults. *J Med Food*. 2015;18(4):415–20.
39. Gupta M, Mathur KC, Yadav K, Sharma P, Tilwani K, Narnolia PK, et al. Effect of Amla (*Embolica officinalis*) on various physiological and biochemical parameters of metabolic syndrome. *Scholars Journal of Applied Medical Sciences*. 2016;4(2C):469–75.
40. Walia K, Boolchandani R, Dhand S, Antony B. Improving glycemic & lipidemic profile with Amla powder (*Embolica officinalis*) supplementation in adults with type 2 diabetes mellitus. *International Journal of Basic and Applied Medical Sciences*. 2015;5(2):251–8.
41. Usharani P, Kishan PV, Fatima N, Uday KC. A comparative study to evaluate the effect of highly standardised aqueous extracts of *Phyllanthus emblica*, *Withania somnifera* and their combination on endothelial dysfunction and biomarkers in patients with type II diabetes mellitus. *Int J Pharm Sci Res*. 2014;5(7):2687–97.
42. Tayyab F, Lal SS. Comparative study on supplementation effect of *Momordica charantia* Linn. and *Embolica officinalis* Gaertn. on lipid profile of type II diabetic patients in Allahabad, Uttar Pradesh India. *Ann Phytomed*. 2016;5(1):40–2.
43. Iyer U, Joshi A, Dhruv S. Impact of Amla (*Embolica officinalis*) supplementation on the glycemic and lipidemic status of type 2 diabetic subjects. *Journal of Herbal Medicine and Toxicology*. 2009;3(2):15–21.
44. Chandra RH, Veeresham C, Asres K. Effects of *Embolica officinalis* commercial formulation in type 2 diabetic patients. *Indian J Pharm Sci*. 2004;66(6):735–8.
45. Kavita MB, Mallika KJ, Poornima B. A clinical study on effect of Amalaki (Indian gooseberry) as food supplement in dyslipidemia. *Int J Res Ayurveda Pharm*. 2016;7(4):59–64.
46. Sri KVS, Kumari DJ, Sivannarayana G. Effect of Amla, an approach towards the control of diabetes mellitus. *Int J Curr Microbiol Appl Sci*. 2013;2(9):103–8.
47. Chen T-S, Liou S-Y, Chang Y-L. Supplementation of *Embolica officinalis* (Amla) extract reduces oxidative stress in uremic patients. *Am J Chin Med*. 2009;37(1):19–25.
48. Nilkanthrao KD, Shandilya MK. Evaluation of rasayana (rejuvenative) effect of Amalaki (*Embolica officinalis*) in healthy volunteers. *Int J Res Ayurveda Pharm*. 2015;6(1):18–21.
49. Jacob A, Pandey M, Kapoor S, Saroja R. Effect of the Indian gooseberry (amla) on serum cholesterol levels in men aged 35–55 years. *Eur J Clin Nutr*. 1988;42(11):939–44.
50. Biswas TK, Chakrabarti S, Pandit S, et al. Pilot study evaluating the use of *Embolica officinalis* standardized fruit extract in cardio-respiratory improvement and antioxidant status of volunteers with smoking history. *J Herb Med*. 2014;4(4):188–94.
51. Fatima N, Usharani P, Pilli R. Evaluation of *Phyllanthus emblica* extract on cold pressor induced cardiovascular changes in healthy human subjects. *Pharmacognosy Res*. 2014;6(1):29–35.
52. Ghaffari S, Navabzadeh M, Ziaee M, Ghobadi A, Ghods R, Hashem-Dabaghian F. A randomized, triple-blind, placebo-controlled, add-on clinical trial to evaluate the efficacy of *Embolica officinalis* in uncontrolled hypertension. *Evid Based Complement Alternat Med*. 2020. <https://doi.org/10.1155/2020/8592869>.
53. Kapoor MP, Suzuki K, Derek T, Ozeki M, Okubo T. Clinical evaluation of *Embolica officinalis* Gaertn (Amla) in healthy human subjects: health benefits and safety results from a randomized, double-blind, crossover placebo-controlled study. *Contemp Clin Trials Commun*. 2020. <https://doi.org/10.1016/j.conctc.2019.100499>.
54. Shanmugarajan D, Girish C, Harivenkatesh N, Chanaveerappa B, Prasanna Lakshmi NC. Antihypertensive and pleiotropic effects of *Phyllanthus emblica* extract as an add-on therapy in patients with essential hypertension—a randomized double-blind placebo-controlled trial. *Phytother Res*. 2021. <https://doi.org/10.1002/ptr.7043>.
55. Upadya H, Prabhu S, Prasad A, Subramanian D, Gupta S, Goel A. A randomized, double blind, placebo controlled, multicenter clinical trial

- to assess the efficacy and safety of Emblica officinalis extract in patients with dyslipidemia. *BMC Complement Altern Med*. 2019. <https://doi.org/10.1186/s12906-019-2430-y>.
56. Usharani P, Fatima N, Muralidhar N. Effects of Phyllanthus emblica extract on endothelial dysfunction and biomarkers of oxidative stress in patients with type 2 diabetes mellitus: A randomized, double-blind, controlled study. *Diabetes Metab Syndr Obes*. 2013;6:275–84.
 57. Usharani P, Merugu PL, Nuttalapati C. Evaluation of the effects of a standardized aqueous extract of Phyllanthus emblica fruits on endothelial dysfunction, oxidative stress, systemic inflammation and lipid profile in subjects with metabolic syndrome: A randomised, double blind, placebo controlled clinical study. *BMC Complement Altern Med*. 2019. <https://doi.org/10.1186/s12906-019-2509-5>.
 58. Usharani P, Sudha Rani E, Kiran Kishore K, Raveendranath P. Evaluation of the effect of a standardized aqueous extract of the fruits of Emblica officinalis on mental stress induced cardiovascular changes in healthy human subjects. *Int J Pharm Sci Res*. 2017;8(10):4138–46.
 59. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372: n71.
 60. Elbourne DR, Altman DG, Higgins JPT, Curtin F, Worthington HV, Vail A. Meta-analysis involving cross-over trials: methodological issues. *Int J Epidemiol*. 2002;32(1):140–9.
 61. Covidence Systematic Review Software [Computer program]. Melbourne, Australia: Veritas Health Innovation; 2021
 62. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomized trials. *BMJ*. 2019;366:14898.
 63. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editors. *Cochrane handbook for systematic reviews of interventions*. Version 6.2. Cochrane; 2021. www.training.cochrane.org/handbook. Accessed June 2, 2021.
 64. Higgins JPT, Green S. Chapter 7: selecting studies and collecting data. In: Higgins JPR, Green S, editors. *Cochrane handbook for systematic reviews of interventions*. Version 5.1.0. Cochrane; 2011. https://handbook-5-1.cochrane.org/chapter_7/7_selecting_studies_and_collecting_data.htm. Accessed June 2, 2021.
 65. Higgins JPT, Eldridge S, Tianjing L. Chapter 23: Including variants on randomized trials. In: Higgins JPR, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editors. *Cochrane handbook for systematic reviews of interventions*. Version 6.3. Cochrane; 2022. Available from: <https://training.cochrane.org/handbook/current/chapter-23>.
 66. Higgins JPT, Green S. Chapter 16: special topics in statistics. In: Higgins JPR, Green S, editors. *Cochrane handbook for systematic reviews of interventions*. Version 5.1.0. Cochrane; 2011. https://handbook-5-1.cochrane.org/chapter_16/16_special_topics_in_statistics.htm. Accessed June 2, 2021.
 67. Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med*. 2002;21(11):1539–58.
 68. Borenstein M, Higgins JP, Hedges LV, Rothstein HR. Basics of meta-analysis: I2 is not an absolute measure of heterogeneity. *Res Synth Methods*. 2017;8(1):5–18.
 69. Review Manager (RevMan) [Computer program]. Version 5.4. The Cochrane Collaboration. 2020.
 70. Bramer WM, Rethlefsen ML, Kleijnen J, Franco OH. Optimal database combinations for literature searches in systematic reviews: a prospective exploratory study. *Syst Rev*. 2017;6:245.
 71. Srivastava R. Efficacy of amla powder (emblica officinalis) and nutrition counselling on hyperlipidemic and hypertensive subject". Punjab Agricultural University: Independently Published; 2018. p. 1–119.
 72. Chepulis L, Al-Aubaidy H, Page R. Effects of selected antioxidant food extracts on postprandial glucose responses in healthy individuals. *Functional Foods in Health and Disease*. 2016;6(8):493–505.
 73. McGuinness LA, Higgins JPT. Risk-of-bias Visualization (robvis): An R package and Shiny web app for visualizing risk-of-bias assessments. *Research Synthesis Methods*. 2020.
 74. Higgins JPT, Green S. Chapter 9: Analysis data and undertaking meta-analyses. In: Higgins JPR, Green S, editors. *Cochrane handbook for systematic reviews of interventions*. Version 5.1.0. Cochrane; 2011. https://handbook-5-1.cochrane.org/chapter_9/9_analysing_data_and_under-taking_meta_analyses.htm. Accessed Jan 23, 2022.
 75. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem*. 1972;18(6):499–502.
 76. Anderson TJ, Grégoire J, Pearson GJ, Barry AR, Couture P, Dawes M, et al. 2016 Canadian Cardiovascular Society guidelines for the management of dyslipidemia for the prevention of cardiovascular disease in the adult. *Can J Cardiol*. 2016;32(11):1263–82.
 77. Mathur R, Sharma A, Dixit VP, Varma M. Hypolipidaemic effect of fruit juice of Emblica officinalis in cholesterol-fed rabbits. *J Ethnopharmacol*. 1996;50(2):61–8.
 78. Anila L, Vijayalakshmi NR. Flavonoids from Emblica officinalis and Mangifera indica—effectiveness for dyslipidemia. *J Ethnopharmacol*. 2002;79(1):81–7.

Publisher's Note

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

Ready to submit your research? Choose BMC and benefit from:

- fast, convenient online submission
- thorough peer review by experienced researchers in your field
- rapid publication on acceptance
- support for research data, including large and complex data types
- gold Open Access which fosters wider collaboration and increased citations
- maximum visibility for your research: over 100M website views per year

At BMC, research is always in progress.

Learn more biomedcentral.com/submissions

