The Efficacy and Safety of *Emblica officinalis* Aqueous Fruit Extract among Adult Patients with Dyslipidemia: A Systematic Review and Meta-analysis

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ABSTRACT

Background. Flavonoids from *Emblica officinalis* effectively reduced serum and tissue lipid levels through their inhibitory effect on the hepatic β-hydroxy-β-methylglutaryl coenzyme A reductase activity. This study aimed to determine the efficacy and safety of *E. officinalis* extract in adults with dyslipidemia.

Methods. We searched the following electronic databases: MEDLINE (PubMed), MEDLINE (Ovid), Google Scholar, EMBASE, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Web of Science, and ClinicalTrials.gov from inception until January 31, 2022. Two reviewers independently screened the abstracts, reviewed full-text papers, and critically appraised the quality of included studies. Meta-analysis was performed using the random-effects model. Our primary outcomes were total cholesterol, LDL-C, serum triglycerides, and HDL-C levels, while secondary outcomes included adverse events.

Results. A total of four randomized trials (N = 227) were included in the final analysis. There were statistically significant decreases in total cholesterol levels (SMD = -21.23 mg/dL, 95% CI: -34.22, -8.25; P = 0.001) and LDL-C levels (SMD = -25.12 mg/dL, 95% CI: -40.24, -10.00; P = 0.001) and significant increase in HDL-C levels (SMD = 4.74 mg/dL, 95% CI: 0.40, 9.07; P = 0.03) after 12 weeks of intervention favoring the use of the *Emblica* extract over placebo. However, there were no statistically significant difference in the serum triglycerides levels following 12 weeks of treatment (SMD = -22.28 mg/dL, 95% CI: -53.33, 8.76; P = 0.16). There was high heterogeneity noted across all outcomes: total cholesterol (P = 0.01, I^2 = 72%), LDL-C (P = 0.0004, I^2 = 83%), HDL-C (P < 0.00001, I^2 = 91%) and serum triglycerides (P < 0.00001, I^2 = 93 %). The intervention was well tolerated and adverse events reported in the three of four studies were all mild: dyspepsia (7 events – treatment), mild diarrhea (3 events – placebo), fever (1 event – placebo), headache (1 event – placebo).

Conclusion. Compared to placebo, *Emblica officinalis* fruit extract resulted in lower total cholesterol and LDL-C levels and increased HDL-C levels but with no effect on serum triglyceride levels based on low certainty of evidence. Trials with a larger sample size that directly compare *E. officinalis* extract to statins, preferably local data, are needed to support its use in patients with dyslipidemia further.

Keywords: dyslipidemia, Emblica officinalis, Phyllanthus emblica, meta-analysis

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INTRODUCTION

Emblica officinalis or *Phyllanthus emblica* Linn, more commonly known as Indian gooseberry or Amla, is an essential medicinal plant in Ayurvedic medicine. It is a medium-sized tree that grows in a geographical zone ranging from India to Southeast Asia and is locally known as *neli* in the Philippines.[1] The most essential component of the plant

is its fruit, which is commonly used as a hair tonic, diuretic, laxative, liver tonic, antipyretic, and anti-inflammatory agent. Preclinical studies have shown that *E. officinalis* possesses antipyretic, analgesic, antitussive, antiatherogenic, cardioprotective, gastroprotective, anti-anemic, anti-hypercholesterolemic, anti-atherosclerotic, hepatoprotective, nephroprotective, and neuroprotective properties.[1] The efficacy of *E. officinalis* in treating hypercholesterolemia is well established in both human and animal studies.[1,2] These studies have also shown that the *Emblica* extract has potent antioxidant activity.[2] Studies conducted in rat models showed that the flavonoids from *E. officinalis* effectively reduced serum and tissue lipid levels through its inhibitory effect on the hepatic β-hydroxy-β-methylglutaryl coenzyme A (HMG-CoA) reductase activity.[2,3]

The cardiovascular effects of *E. officinalis* have been extensively studied and documented in both traditional medicine and modern medical literature.[4-6] Several randomized clinical trials in humans comparing *E. officinalis* fruit extract or Amla to placebo[7-10] and statins[11] showed significant reductions in low-density lipoprotein cholesterol (LDL-C) levels and improvements in high-density lipoprotein cholesterol (HDL-C) levels among adult patients with type 2 diabetes mellitus, dyslipidemia, and metabolic syndrome.

Hypercholesterolemia remains a major risk factor for the development of atherosclerosis and is associated with coronary artery disease, stroke, and peripheral vascular disease.[7-13] Therefore, reduction of low-density lipoprotein cholesterol levels has been associated with the improvement of coronary artery disease. Together with intensive lifestyle interventions, diet, exercise, and use of anti-hypercholesterolemic and anti-inflammatory drugs, it is recommended to decrease risk.[12] Statin therapy remains the first-line treatment for patients with elevated LDL-C.[12] However, some patients cannot tolerate the adverse effects of these drugs, especially when given in very high doses, necessitating the use of additional agents as adjuncts.[7-10] For example, side effects of statins, including hepatotoxicity and rhabdomyolysis, may warrant discontinuation.[14]

The hypolipidemic effect of the *Emblica* fruit is brought about by the presence of natural polyphenolic compounds such as flavonoids, tannic acid, and hydrolysable tannins. The amla fruit contains high amounts of ascorbic acid, as well as zeatin, Z-riboside, Z-nucleotide, flavonoids, pectin, and tannins. The tannins present in amla prevent the oxidation of ascorbic acid, while pectin has been reported to decrease serum cholesterol levels in humans.[8] Early animal studies have demonstrated that the flavonoid content of amla has a potent hypolipidemic effect.[3-6] Studies in healthy adults showed significant decreases in total cholesterol and triglycerides and improvement in high-density lipoprotein cholesterol after receiving 1 to 2 grams of *Emblica* fruit extract per day.[14] The exact mechanism by which amla exerts this beneficial effect is presently not clear. Its mechanism of action is likely from a combination of inhibition of HMG-CoA reductase activity, interference with cholesterol absorption, and an increase in lecithin cholesterol acyltransferase activity.[7-11,13,14] All are currently similar in terms of mechanism of action to our hypolipidemic drugs such as statins and ezetimibe, respectively.

Amla, whether in its pure form or in combination with other nutraceuticals, is FDA approved in the Philippines and sold as a supplement in local pharmacies, sports medicine stores, and online marketing. The market formulation and dosage form consist of the aqueous fruit extract in 250 or 500 mg capsules taken twice a day to lower cholesterol levels.[7-10]

In recent years, the use of natural agents as adjuncts in treating common conditions such as dyslipidemia has become increasingly popular to reduce the unwanted adverse effects from very high doses of pharmacologic agents such as statins. With the many available randomized trials comparing *E. officinalis* fruit extracts with placebo in adults, we conducted this meta-analysis and systematic review to determine its efficacy and safety as a possible adjunct for patients with dyslipidemia. This is especially relevant since adverse events are common among patients given very high doses of statins. Specifically, we determined the effect of *E. officinalis* extract on the total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglyceride levels; and evaluated the adverse events associated with the use of *E. officinalis* extract in adults with dyslipidemia.

MATERIALS AND METHODS

Search Strategy

We performed a comprehensive search strategy from inception to January 31, 2022, in the following databases: MEDLINE (PubMed), MEDLINE (Ovid), Google Scholar, EMBASE, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Web of Science, and ClinicalTrials.gov. There was no language restriction on the searches performed. To identify all the relevant studies, we used the following search terms: *Emblica officinalis*, Amla, Amlamax, dyslipidemia, total cholesterol, low-density lipoprotein, among others; terms were combined with the Boolean operators AND and OR. We supplemented our electronic search with manual searches and, by cross-referencing included papers, relevant sections of clinical practice guidelines, and relevant systematic and narrative reviews.

Inclusion and Exclusion Criteria

The eligibility criteria for each trial included in the analysis were as follows: 1) Randomized controlled trial; 2) The study compared the efficacy of *E. officinalis* extract to placebo on patients with dyslipidemia; 3) The formulation must be in tablet or capsule form; 4) The outcomes included total serum cholesterol, low-density lipoprotein, high-density lipoprotein, triglycerides, and safety data; and 5) The study

was published as a full text with complete outcomes. We excluded all studies that did not fulfill the eligibility criteria.

Data Extraction and Analysis

Two investigators (LTA and HCC) independently screened for citations from the electronic search, reviewed full-text papers for inclusion, critically appraised the quality of studies, and extracted data. A consensus was achieved for the inclusion of studies and abstracted data by a discussion among reviewers; a third reviewer (RBL) and clinical content experts (AES and MCAC) were consulted in the event of any discrepancies that we could not be resolve by reviewer discussion. We evaluated each study for its risk of bias using the Risk of Bias evaluation tool developed by the Cochrane Collaboration (ROB 2.0) and reported our outcomes according to PRISMA standards.

Our primary outcomes were total cholesterol, LDL-C levels, serum triglycerides, and HDL-C, while adverse events were our secondary outcomes. We reported continuous data for total cholesterol and LDL-C as means and standard deviations. We presented adverse events narratively. We performed a random-effects model meta-analysis since our outcomes of interest (serum cholesterol, LDL-C, HDL-C, and triglycerides) are variables that change at a constant rate over time. We estimated serum total cholesterol, LDL-C, HDL-C, and triglyceride levels using a 95% confidence interval using the Review Manager Software Version 5.3 (Revman 5.3).

RESULTS

Search Results

We retrieved the titles and abstracts of a total of 733 articles. There was a total of 86 duplicate studies. Among the 644 articles retrieved, only 19 studies fulfilled the inclusion criteria. Fifteen articles were further excluded after a thorough evaluation of the full manuscripts, with reasons for exclusion outlined below. Finally, we included four studies in this systematic review (Figure 1).

Characteristics of Individual Studies

The characteristics of the articles included in this meta-analysis are summarized in Table 1. All studies were carried out in India and were published from 2008 to 2019. The study designs were randomized controlled trials comparing *Emblica officinalis* extract to placebo. Overall, all four studies yielded a total of 227 participants. The mean age of the participants ranged from 35 to 68 years.

All four studies[7-10] showed an overall low risk for bias except for the study of Antony[7] and colleagues that had a high risk for bias due to the lack of blinding of participants and outcome assessors. However, this only had a minimal effect on the primary outcome measures, which were quantitative lipid profile parameters. A summary of the risk of bias in included trials is shown in Figure 2.

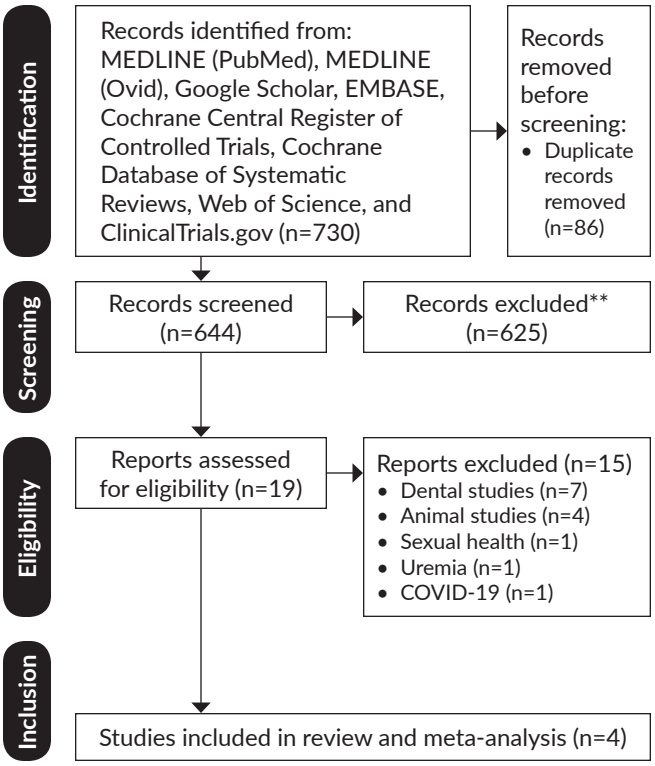

Figure 1. PRISMA study flow diagram for identification of studies via databases and registers.

Effects of Intervention

Effect on LDL-C levels

There was a significant difference in LDL-C levels after 12 weeks of intervention (pooled SMD = -25.12 mg/dL, 95% CI: -40.24, -10.00; P = 0.001) favoring the use of the *Emblica* extract over placebo. However, there was significant heterogeneity noted (P = 0.0004, I^2 = 83%) (Figure 3).

Effect on Total Cholesterol Levels

There was a significant difference in total cholesterol levels at 12 weeks (SMD = -21.23 mg/dL, 95% CI: -34.22, -8.25; P = 0.001) favoring the use of *Emblica* extract over placebo. There was significant heterogeneity (P = 0.01, I^2 = 72%) (Figure 4).

Effect on Serum Triglyceride Levels

Although there was a trend towards benefit in the use of *Emblica* extract, there was no statistically significant difference in serum triglycerides levels at 12 weeks following intervention (SMD = -22.28 mg/dL, 95% CI: -53.33, 8.76; P = 0.16). There was significant heterogeneity (P < 0.00001, I^2 = 93%) (Figure 5).

Effect on HDL-C

There was a statistically significant increase in HDL-C levels at 12 weeks for *Emblica* extract compared to placebo

Table 1. Characteristics of included studies

Author (Year)	Study Design	Sample Size	Mean Age, years (SD)	Patient Profile and Comorbidities	Mean baseline LDL-C levels in mg/dL (SD)	Intervention and Comparator	Outcomes
Antony (2008)	RCT	30	I: 35-45 C: 35-45	Adults with dyslipidemia	I: 202.1 (5.8) C: 170.8 (18.2)	Intervention: Amla (*Emblica officinalis*) extract in tablet form Dose: 500 mg/tab twice daily Comparator: Dietary restriction and exercise only	Total cholesterol, triglycerides, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol before treatment and at 12 weeks post-treatment
Fatima (2013)	RCT	40	I: 57.75 (9.86) C: 56.9 (9.17)	Adults with dyslipidemia and fasting glucose of 110-126 mg/dL or HbA1c of 7-9% and on oral diabetes medications only	I: 116.9 (28.24) C: 126.2 (39.45)	Intervention: Amla (*Emblica officinalis*) extract in tablet form Dose: 500 mg/tab twice daily Comparator: Identical placebo tablet	Total cholesterol, triglycerides, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol before treatment and at 12 weeks post-treatment
Upadya (2019)	RCT	98	I: 40.7 (10.13) C: 42.2 (9.20)	Adults with dyslipidemia	I: 140.0 (19.66) C: 132.2 (20.82)	Intervention: Amla (*Emblica officinalis*) extract in tablet form Dose: 500 mg/tab twice daily Comparator: Identical placebo tablet	Total cholesterol, triglycerides, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol before treatment and at 12 weeks post-treatment
Usharani (2019)	RCT	59	C: 56.89 (7.39) I: 57.24 (8.94)	Adults with dyslipidemia	C: 136.7 (16.02) I: 134.86 (12.24)	Intervention: Amla (*Emblica officinalis*) extract in tablet form Dose: 500 mg/tab twice daily Comparator: Identical placebo capsule	Total cholesterol, triglycerides, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol before treatment and at 12 weeks post-treatment

RCT, Randomized controlled trial; I, intervention; C, comparator

(SMD = 4.74 mg/dL, 95% CI: 0.40, 9.07; P = 0.03). However, there was significant heterogeneity (P < 0.00001, I^2 = 91%) (Figure 6).

Adverse Events

All three studies[8-10] except the one by Antony et al.[7] reported the number of patients who experienced adverse events from the *Emblica* extract and the placebo. The adverse events reported in the three studies[8-10] were all mild and summarized as follows: dyspepsia (7 events – treatment), mild diarrhea (3 events – placebo), fever (1 event – placebo),

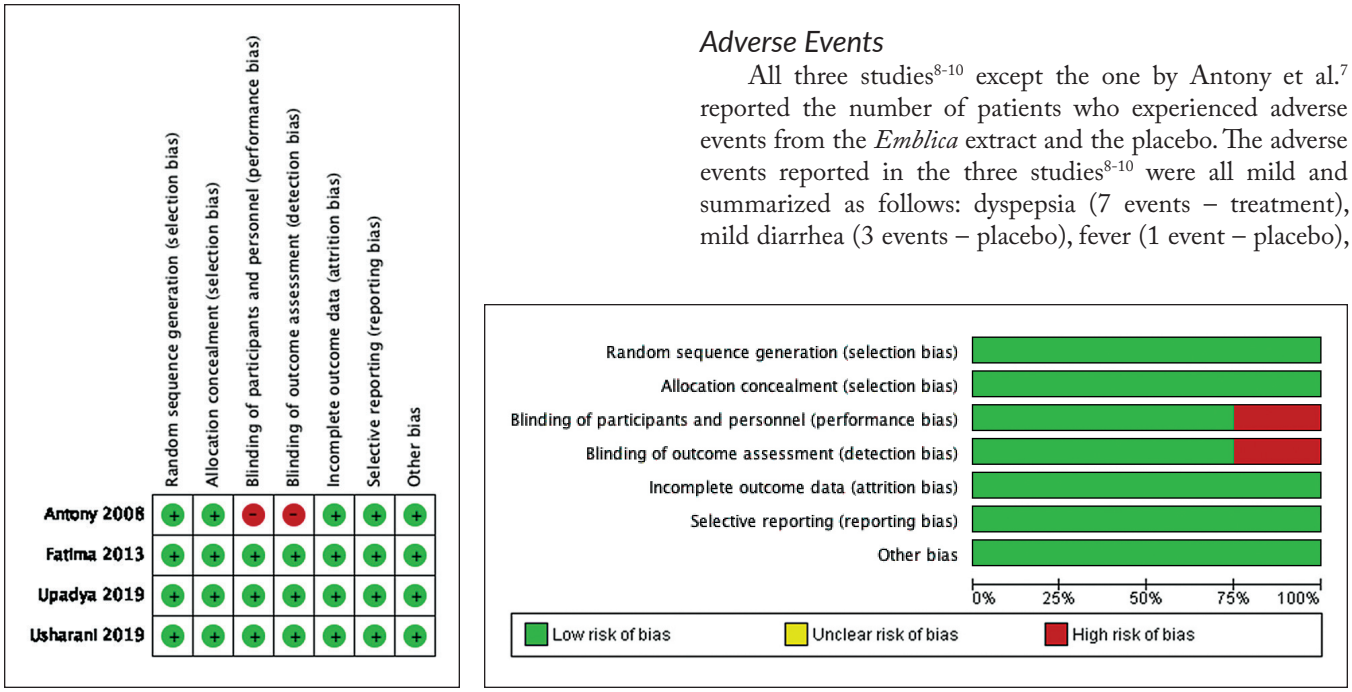

Figure 2. Risk of bias graph and summary of included studies.

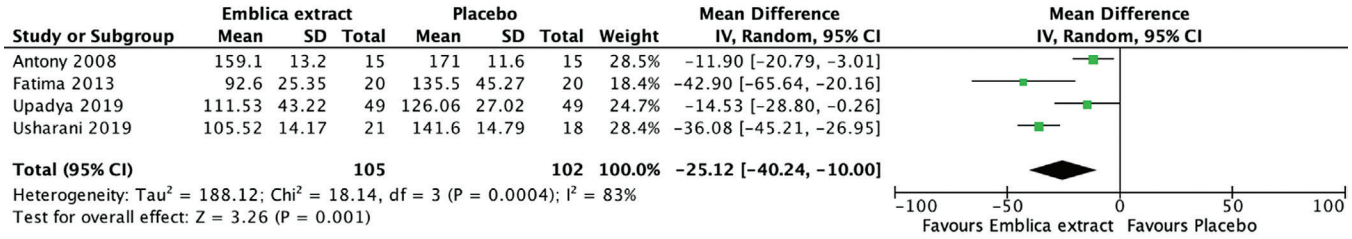

Figure 3. Forest plot showing the effect of Amla (*Emblica officinalis*) on LDL-C levels.

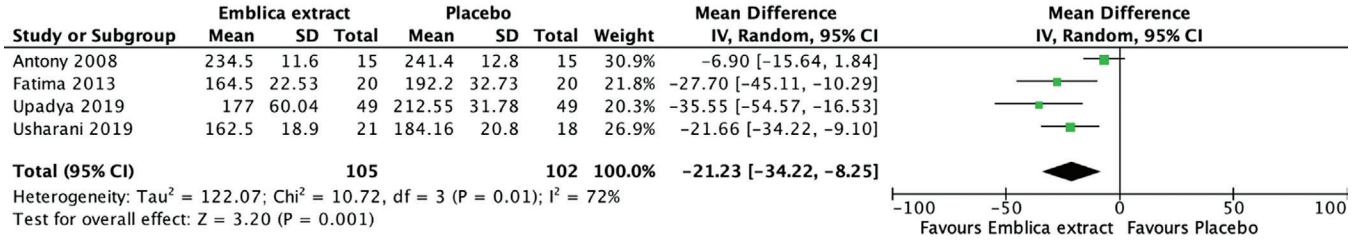

Figure 4. Forest plot showing the effect of Amla (*Emblica officinalis*) on total cholesterol.

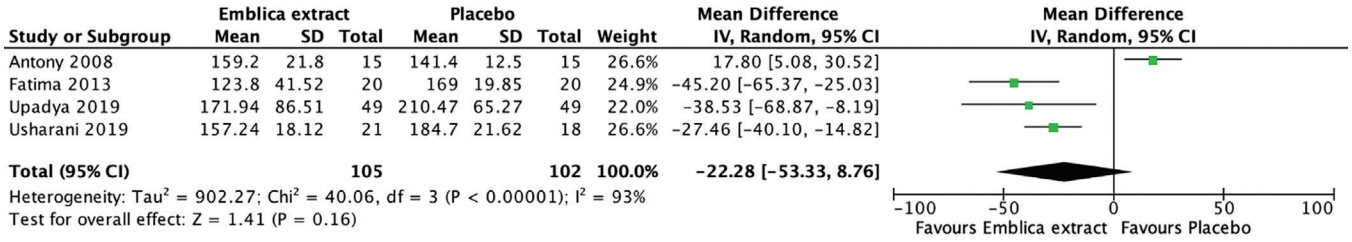

Figure 5. Forest plot showing the effect of Amla (*Emblica officinalis*) on serum triglyceride levels.

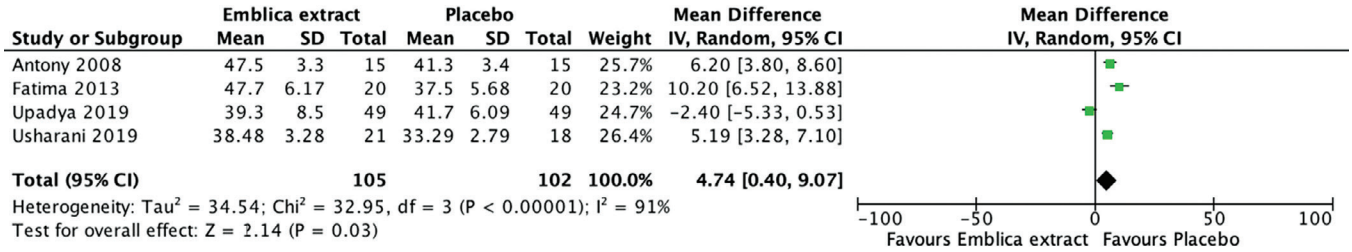

Figure 6. Forest plot showing the effect of Amla (*Emblica officinalis*) on HDL-C levels.

headache (1 event – placebo).[8-10] No study subject prematurely dropped out or prematurely terminated their participation in the study because of the adverse events reported. There were no mortalities during the trial period for all the studies.[8-10]

DISCUSSION

This is the first systematic review and meta-analysis on the efficacy and safety of *Emblica officinalis* aqueous fruit extract versus placebo on patients with dyslipidemia. Our analysis showed a statistically significant decrease in the levels of total cholesterol and low-density lipoprotein cholesterol; a statistically significant increase in the levels of high-density lipoprotein cholesterol levels, and no significant differences in the serum triglyceride levels as compared to placebo seen after 12 weeks of treatment. Adverse events did not differ between the intervention and placebo groups. The events were few and mild in severity, with dyspepsia being the most common for the intervention group and diarrhea for the placebo group. However, there was high heterogeneity noted across all outcomes, which may be attributed to differences in each participant in terms of baseline lipid profile parameters and, more importantly, the different methods, assays, and

instrumentation used for the measurement of the outcomes of interest as these trials were conducted in various centers.

The reduction in serum cholesterol and LDL-C levels can be explained by the inhibition of the HMG-CoA reductase enzyme, thereby preventing cholesterol synthesis. Additionally, *E. officinalis* fruit extracts increased cholesterol uptake through increased LDL-receptor expressions on hepatocytes and decreased LDL-receptor degradation due to reduced proprotein convertase subtilisin/kexin type 9 expression. The increase in HDL-C cholesterol levels is due to the upregulation of enzymes responsible for transferring cholesterol from low-density lipoprotein to high-density lipoproteins.[6] The three studies[8-10] demonstrated a more significant decrease in serum triglyceride levels due to *E. officinalis* fruit extract compared to the study of Antony et al.[7] This may be due to increased peroxisome proliferator-activated receptors-α expression and increased activity of lipid oxidation through carnitine palmitoyl transferase. There may also be decreased activity of hepatic lipogenic enzymes such as glucose-6-phosphate dehydrogenase, fatty acid synthase, and malic enzyme.[6-10]

However, our study has several limitations. First, although all included studies were randomized trials, the sample size of each study was relatively small compared to clinical trials of statins, and this could lead to imprecision. Second, the study of Fatima and colleagues[8] included patients with controlled diabetes on top of dyslipidemia, while the rest only included patients with dyslipidemia alone. Third, although the interventions were similar, the comparators were not uniform, with one study using diet and exercise[7] while the rest used a placebo. All have resulted in high heterogeneity across all outcomes, for which the results must therefore be interpreted with caution. In addition, the follow-up period was relatively short at 12 weeks and no long-term follow-up on lipid levels and adverse events were conducted, failing to simulate how we give and monitor statin therapy on a long-term basis. Lastly, we do not have local studies and additional international data to support and validate the currently published results.

CONCLUSION

In summary, *Emblica officinalis* aqueous fruit extract resulted in lower total cholesterol and LDL-C, increased HDL-C but no effect on serum triglyceride levels at 12 weeks, with only low certainty evidence. We cannot yet recommend its use as an alternative treatment to statins. However, trials with larger sample sizes with direct comparison to statins and local data are needed to support further it use in patients with dyslipidemia.

Statement of Authorship

All authors contributed in the conceptualization of work, acquisition and analysis of data, drafting and revising and approved the final version submitted.

Author Disclosure

All authors have declared no conflicts of interest.

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