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Lipid-lowering and weight-regulating effects of Triphala aqueous extract in a therapeutic rat model of hypercholesterolemia

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ABSTRACT

Introduction: Triphala, an Ayurvedic polyherbal formulation composed of *Terminalia chebula* Retz., *Terminalia bellirica* (Gaertn.) Roxb., and *Phyllanthus emblica* L., is associated with metabolic regulation. This study evaluated the lipid-lowering effects of Triphala aqueous extract (TPL) in a therapeutic rat model of hypercholesterolemia and explored a potential mechanism involving 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibition.

Methods: Male Wistar rats received cholesterol (2 g/kg, intragastric) in corn oil for 3 weeks to induce hypercholesterolemia. After biochemical confirmation, rats were assigned to six groups (n = 6 each): normal diet, hypercholesterolemic control, atorvastatin (10 mg/kg), or TPL (250, 500, and 1000 mg/kg). Cholesterol administration continued throughout the 6-week treatment period. Serum lipid profiles and body weight were monitored. HMG-CoA reductase inhibition by TPL and individual fruit extracts was assessed.

Results: TPL 250 and 500 mg/kg significantly reduced total cholesterol (TC), triglyceride (TG), and low-density lipoprotein cholesterol (LDL-C), whereas TPL 500 mg/kg significantly increased high-density lipoprotein cholesterol ($P<0.05$). TPL 1000 mg/kg produced lipid-lowering effects comparable to atorvastatin and significantly decreased the atherogenic index of plasma at week 6. *In vitro*, TPL inhibited HMG-CoA reductase by 36.4 ± 1.5% (5 µg/mL), compared with 82.5 ± 2.4% for pravastatin (0.5 µg/mL). Among individual fruit extracts, *P. emblica* exhibited the strongest inhibitory activity, followed by *T. chebula* and *T. bellirica*, while the combined TPL retained appreciable activity. TPL 1000 mg/kg also attenuated diet-induced body weight gain.

Conclusion: TPL exerts significant lipid-lowering and weight-regulating effects under sustained cholesterol challenge, partly mediated by HMG-CoA reductase inhibition, supporting its potential as a natural adjunct for dyslipidemia.

Implication for health policy/practice/research/medical education:
The findings suggest that Triphala may offer a beneficial natural option for improving lipid profiles and moderating weight gain under sustained cholesterol burden, supporting its potential role in promoting cardiometabolic health. This evidence reinforces interest in validated herbal preparations as accessible adjuncts for managing dyslipidemia and related metabolic risks.

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Introduction

In Ayurvedic medicine, Triphala is a well-known polyherbal formulation composed of the fruits of *Terminalia chebula* Retz. (Combretaceae), *Terminalia bellirica* (Gaertn.) Roxb. (Combretaceae), and *Phyllanthus emblica* L. (Euphorbiaceae) (1,2). For centuries, Triphala has been classified as a rasayana (rejuvenative) and is traditionally used to support gastrointestinal and circulatory function (3). Pharmacological investigations report a broad activity profile, including antioxidant, anti-inflammatory, antibacterial, dental care, hepatoprotective, immunomodulatory, and metabolic regulatory effects

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(4-6). Given the rising global burden of lipid disorders, Triphala's hypolipidemic potential has received increasing attention (7-9).

Atherogenic dyslipidemia is characterized by elevated serum total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and triglycerides (TG), together with reduced high-density lipoprotein cholesterol (HDL-C), and is closely linked to atherosclerotic cardiovascular risk (10). Persistent hypercholesterolemia promotes endothelial dysfunction, vascular inflammation, and atherosclerosis progression, culminating in events such as myocardial infarction and stroke (11,12). Cardiovascular diseases were the leading global cause of death in 2021 (approximately 20.5 million deaths) (13). Hypercholesterolemia also aggravates systemic metabolic disorders, including insulin resistance and non-alcoholic fatty liver disease (NAFLD) (14). Consequently, dependable and effective cholesterol management strategies are essential to reduce global cardiovascular disease morbidity and mortality (15).

The mevalonate pathway's rate-limiting enzyme, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, is the primary target of the current pharmacotherapy guideline that inhibits hepatic cholesterol synthesis (16). Statins, the competitive inhibitors of HMG-CoA reductase, remain the basis of lipid-lowering therapy and effectively reduce plasma cholesterol and cardiovascular events (17). However, prolonged administration can be limited by adverse effects, including myopathy, hepatotoxicity, and adverse drug-drug interactions, which may hinder patient compliance and tolerance (18-20).

These therapeutic constraints have intensified the search for safe, natural alternatives with lipid-modulating effects comparable to those of conventional therapies. Polyphenolic compounds, especially gallic acid and ellagic acid, are abundant in Triphala and are documented for their potent antioxidant and metabolic regulatory properties (21,22). Mechanistically, polyphenols can modulate lipid metabolism via non-statin pathways, including transcriptional inhibition of cholesterol synthesis and enhancement of hepatic LDL receptor expression (23,24). Consistent with these mechanisms, Triphala powders and extracts reduce hyperlipidemia in animal models, producing significant decreases in serum TC and LDL-C in rodents fed a high-cholesterol diet (6,25). Despite these encouraging preclinical observations, most studies have employed preventive designs in which Triphala was administered concurrently with the atherogenic diet (6,7). This prophylactic approach does not reflect clinical practice, where treatment typically begins after a diagnosis of established hypercholesterolemia. Consequently, the true therapeutic efficacy of Triphala after the onset of lipid dysregulation remains uncertain. This study therefore evaluates the lipid-lowering and weight-modulating effects of Triphala aqueous extract (TPL) in a therapeutic rat model in which dyslipidemia is verified before treatment initiation, with continued cholesterol supplementation to maintain metabolic stress. In parallel, we compare the *in vitro* HMG-CoA reductase inhibitory activity of TPL with that of its individual component extracts to assess their relative contributions to enzyme inhibition. These complementary approaches aim to clarify Triphala's therapeutic role and mechanistic contribution under conditions that more closely approximate real-world clinical use.

Materials and Methods

Chemicals and plant materials

Analytical-grade organic solvents, reagents, and reference standards of gallic acid, ellagic acid, and chebulagic acid were purchased from Sigma-Aldrich (St. Louis, MO, USA).

Dry fruits of *T. chebula*, *T. bellerica,* and *P. emblica* were obtained from Tong-In traditional drugstore (Maha Sarakham, Thailand). Plant materials were authenticated according to the Thai herbal pharmacopoeia 2018 (26). Voucher specimens of *T. chebula* (MSU.PH-COM-TC02), *T. bellerica* (MSU.PH-COM-TB02), and *P. emblica* (MSU. PH-EUP-PE02) were deposited at the Faculty of Pharmacy, Mahasarakham University, Maha Sarakham, Thailand.

Extract preparations

Seeds were removed from each fruit. The seedless materials were ground and sieved through a mesh No. 14. TPL was prepared by mixing equal masses of powders from *T. chebula, T. bellirica, and P. emblica* (20 g each; total 60 g) and decocting in 1 L of distilled water for 1 hour. The decoction was filtered (Whatman No. 1) and spray-dried to yield a fine powder. Individual aqueous extracts of *T. chebula* (TCh), *T. bellirica* (TB), and *P. emblica* (PE) were prepared using the same protocol as TPL, with 60 g of each powder and 1 L of distilled water. All extracts were stored in light-protected, sealed containers at -20 ºC until analysis.

Total phenolic content (TPC) determination

TPC was determined by modifying a rapid 96-well microplate Folin-Ciocalteu assay (27). Briefly, 20 µL of appropriately diluted sample (or gallic acid standard) was dispensed into each well and mixed with 100 µL of freshly diluted Folin–Ciocalteu reagent (1:10, v/v in water). After 5 minutes at room temperature, 80 µL of 1 M sodium carbonate was added. The plate was incubated for 15 minutes at room temperature. Absorbance was read at 630 nm on a UV spectrophotometer (Varioskan LUX, Thermo Fusher Scientific, USA) against a reagent blank. Gallic-acid standards (10-200 µg/mL) generated the calibration $y= 0.003x+0.0546$ ($R^2 = 0.999$), where y is absorbance and x is gallic acid (µg/mL). Sample concentrations were interpolated and expressed as mg gallic acid equivalents

per g extract (mg GAE/g) with appropriate dilution factors. All measurements were performed in triplicate and reported as mean ± SD.

HPLC quantitative analysis

Gallic acid, ellagic acid, and chebulagic acid served as quality control markers of all extracts. Quantitation was performed on an HPLC system (Shimadzu SCL-10A VP, Kyoto, Japan) using a Phenomenex Luna C18 column (250 × 4.6 mm, 5 μm) with a C18 guard. The experiment followed the method of Sato et al (28). The mobile phase comprised solvent A (water with 0.05% (v/v) trifluoroacetic acid (TFA)) and solvent B (acetonitrile), delivered at 1.0 mL/min. The gradient program was: 0–1 minutes, 5% B; 1–4 minutes, 5–10% B; 4–12 minutes, 10–15% B; 12–32 minutes, 15–35% B; 32–35 minutes, 35–50% B; 35–37 minutes, 50–100% B; 37–40 minutes, 100% B; 40–41 minutes, 100–5% B; 41–45 minutes, 5% B. Injection volume was 20 μL (triplicate injections per sample), and detection was at 270 nm. Marker identification was confirmed by comparing the retention times and UV spectra with the reference standards. Concentrations were calculated from calibration curves: gallic acid, y = 52.804x (R^2=0.995), ellagic acid, y = 206.61x (R^2=0.998), and chebulagic acid, Y = 3096.2x + 0.9341 (R^2=0.992), where y is peak area and x is concentration.

Assay of HMG-CoA reductase inhibition

HMG-CoA reductase activity was quantified spectrophotometrically from the decrease in absorbance at 340 nm due to NADPH oxidation. Reactions were set up using a commercial HMG-CoA reductase assay kit (Sigma-Aldrich, St. Louis, MO, USA) according to the manufacturer's instructions. Pravastatin (Sigma-Aldrich) served as the positive control. The enzyme stock (human recombinant, catalytic domain) was prepared at 0.5-0.75 mg/mL. Each reaction (final volume 200 μL) contained 100 mM potassium phosphate buffer (pH 7.4), 4 μL NADPH, 12 μL HMG-CoA substrate, and was initiated by adding 2 μL enzyme.

Test samples were 1 μL aliquots of extract solutions added immediately before initiation. Assays were incubated at 37 °C, monitored at 20 s intervals for 15 minutes using a UV spectrophotometer (Varioskan LUX, Thermo Fusher Scientific, USA). Reaction rates were obtained from the linear region of the time–absorbance traces. The enzyme activity was calculated as follows:

$$\text{Unit/mg Protein} = \frac{(\Delta A_{340} / \min_{\text{sample}}) - (\Delta A_{340} / \min_{\text{blank}})}{12.44 \times V \times 0.6 \times LP} \times 0.2$$

V= Volume of enzyme used in the assay (0.2 mL)
LP= Light path (0.55 cm for plates)

The inhibition of enzyme activity was calculated using the following equation:

$$\%\ \text{enzyme inhibition} = \frac{(\text{Activity}_{\text{enzyme}} - \text{Activity}_{\text{sample}})}{\text{Activity}_{\text{enzyme}}} \times 100$$

Animal experimental protocol

All animal procedures were conducted in 2012, prior to the establishment of the Institutional Animal Care and Use Committee (IACUC) at Mahasarakham University. At that time, protocols were reviewed and authorized by the University Research Committee; consequently, no IACUC approval number is available, and retrospective approval is not applicable. All procedures complied with the Guide for the Care and Use of Laboratory Animals ((National Research Council)) and the 3Rs principle (Replacement, Reduction, Refinement), with housing, handling, and monitoring performed by trained staff under veterinary oversight.

Thirty-six male Wistar rats (150-200 g) were obtained from the National Laboratory Animal Center, Mahidol University (Nakhon Pathom, Thailand). Animals were housed under standard laboratory conditions (12-hour light/dark, 22–25 °C, 40–70% relative humidity) with ad libitum access to chow and water. After a one-week acclimatization period, rats were randomly allocated to either a normal diet (ND) group or a hypercholesterolemic (HC) induction group.

Hypercholesterolemia was induced in the HC group by once-daily intragastric gavage of cholesterol (2 g/kg) suspended in 2 mL of corn oil for 3 weeks. Following a 14-hour fast, tail-vein blood was collected to confirm induction, and serum TC, TG, and HDL-C were quantified using enzymatic assay kits (Abcam, Cambridge, MA, USA). LDL-C was calculated using the Friedewald equation (29):

LDL = TC – HDL – TG/5

Rats were considered successfully induced if TC ≥ 200 mg/dL. Confirmed HC rats were then randomized into six groups (n = 6 per group) and treated as follows:

1. ND: normal diet + 2 mL of double-distilled water
2. DW: HC + 2 mL of double-distilled water
3. ATV: HC + atorvastatin (10 mg/kg)
4. TPL 250: HC + Triphala aqueous extract (250 mg/kg)
5. TPL 500: HC + Triphala aqueous extract (500 mg/kg)
6. TPL 1000: HC + Triphala aqueous extract (1000 mg/kg)

All treatments were administered once daily by gavage for 6 weeks. To maintain metabolic pressure, all HC groups continued receiving daily cholesterol in corn oil throughout the treatment period, whereas ND rats received water only. Fasting serum TC, TG, LDL-C, and HDL-C were quantified at predetermined intervals. The atherogenic index of plasma (AIP) was calculated at each time point as AIP = $\log_{10}$(TG/HDL-C).

Although a formal IACUC system was not yet in place during the time of the experiment, all procedures adhered to internationally accepted standards for the humane care and use of laboratory animals, including appropriate housing, handling, and minimization of discomfort, in

accordance with the principles outlined in the National Research Council's Guide for the Care and Use of Laboratory Animals.

Statistical analysis

HMG-CoA reductase inhibition data were reported as mean ± standard deviation (SD). Rat lipid profile data and AIP were presented as mean ± standard error of the mean (SEM). Analyses were performed in IBM SPSS Statistics v29 (IBM Corp., Armonk, NY, USA). $P<0.05$ was considered statistically significant.

Results

Extraction and phytochemical analysis

All extracts were obtained as brownish dry powders, with extraction yields ranging from 24.31% to 36.93% (Table 1). TPC, determined by the Folin-Ciocalteu method and expressed as gallic acid equivalents (GAE) per gram of extract, was 349.6 ± 17.93 mg GAE/g for TPL. Among the individual fruit extracts, TPC values ranged from 276.6 to 440.3 mg GAE/g, with TB aqueous extract exhibiting a significantly higher TPC than the other single fruit extracts ($P<0.05$).

For quantitative phytochemical profiling, HPLC analysis was performed on TPL and the individual fruit extracts (Figure 1). Marker identification was confirmed by comparing retention times and UV spectra with authenticated reference standards. In TPL, gallic acid and ellagic acid were quantified at 136.32 ± 5.070 mg/g and 26.85 ± 0.861 mg/g of extract, respectively. The contents of gallic acid and ellagic acid did not differ significantly between TPL and the individual fruit extracts ($P>0.05$), despite the variation observed in TPC.

Chebulagic acid, a representative ellagitannin of Triphala, was also quantified. The results showed that TB extract contained a significantly higher amount of chebulagic acid than TPL, TCh, and PE ($P<0.05$), whereas no significant differences were observed among TPL, TCh, and PE.

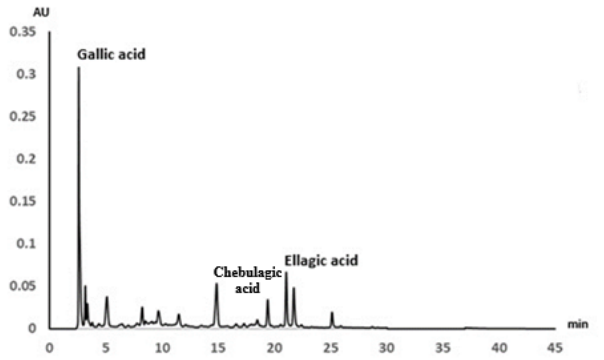

Figure 1. High-performance liquid chromatography chromatogram of Triphala aqueous extract (TPL). Gallic acid, ellagic acid, and chebulagic acid were used as marker compounds for quantitative analysis. Peaks were identified by comparing retention times and UV spectra with authenticated standards.

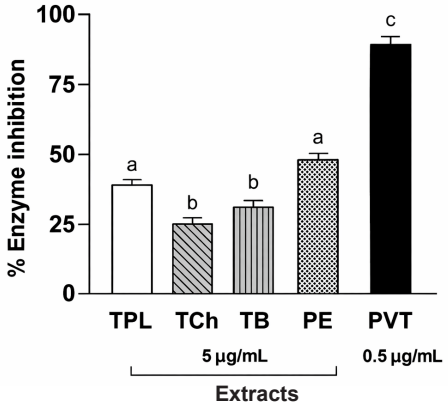

Figure 2. Inhibition of 3-hydroxy-3-methylglutaryl–coenzyme A (HMG-CoA) reductase activity of Triphala aqueous extract (TPL) and its individual fruit extract. TCh: *Terminalia chebula* aqueous extract, TB: *T. bellirica* aqueous extract, PE: *Phyllanthus emblica* aqueous extract. Sample extracts (TPL, TCh, TB and PE) were tested at 5 µg/mL pravastatin (PVT), and 0.5 µg/mL served as the positive control. Data are represented as mean ± SD (n = 4). Bars not sharing a superscript letter (*a, b, c*) indicate statistically significantly different (one-way ANOVA followed by Dunnett's post hoc test, $P \leq 0.01$).

HMG CoA reductase inhibition of Triphala and its individual fruit extracts

The 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitory activity of TPL and its individual fruit extracts (TCh, TB, PE) was quantified using an *in vitro* enzyme assay (Figure 2). Under the assay conditions, the positive control, pravastatin (PVT), at 0.5 µg/mL produced 82.5 ± 2.4% inhibition and served as the benchmark, while the sample extracts (TPL, TCh, TB, and PE) were at 5 µg/mL. Among the sample extracts, PE

Table 1. Extraction yield, total phenolic content, and marker compound contents of Triphala aqueous extract and its individual fruit extracts

Triplala and its individual fruit extracts	% Yield of extracts	Total phenolic content (mg GAE /g of extract)	Marker contents (mg/g of extract)		
			Gallic acid	Ellagic acid	Chebulagic acid
TPL	25.87	349.6±17.93 [a]	136.32 ± 5.070	26.85 ± 0.861	34.48 ± 0.814 [a]
TCh	36.93	276.6± 6.31 [a]	143.30 ± 9.155	26.97 ± 0.638	18.71 ± 0.853 [a]
TB	24.31	440.3±17.26 [b]	98.74 ± 1.870	29.50 ± 0.143	112.42 ± 1.912 [b]
PE	27.09	317.6± 9.22 [a]	96.85 ± 1.833	19.25 ± 0.093	24.42 ± 0.742 [a]

TPL: Triphala aqueous extract, TCh: *Terminalia chebula* aqueous extract, TB: *T. bellirica* aqueous extract, PE: *Phylanthus emblica* aqueous extract, GAE: Gallic acid equivalent. The contents of total phenolic, gallic acid, ellagic acid, and chebulagic acid are expressed as mean ± SD (n = 3). Within the same column, values not sharing a superscript letter (*a, b*) differ significantly (one-way ANOVA followed by Dunnett's post hoc test, $P < 0.05$).

showed the highest inhibition (41.3 ± 2.3%), followed by TPL (36.4 ± 1.5%). The difference between PE and TPL was not statistically significant ($P > 0.01$). TCh and TB displayed lower inhibitory effects than TPL.

Lipid-lowering effect of TPL in hypercholesterolemic rats

Induction of hypercholesterolemia

Oral administration of cholesterol (2 g/kg/day) for three weeks successfully induced hypercholesterolemia in rats. As shown in Figure 3, serum TC, TG, and LDL-C levels were significantly elevated in the HC group compared with the ND group ($P < 0.01$), confirming successful model establishment. HDL-C level did not differ significantly between ND and HC ($P > 0.05$).

Body weight

Body weight changes for all groups are shown in Figure 4A. At the start of the treatment period (week 0), no significant differences were observed among groups, indicating comparable baseline weights. By week 4, rats in the hypercholesterolemic distilled-water (DW) group exhibited significantly greater body weight gain than those in the ND group ($P < 0.05$), reflecting the effect of continuous cholesterol feeding. In contrast, rats treated with atorvastatin 10 mg/kg (ATV10) or TPL at doses 250, 500, and 1000 mg/kg (TPL250, TPL500, and TPL1000) showed a tendency toward reduced weight gain compared to the DW group. At week 6, body weights remained significantly elevated in the DW group compared with ND ($P < 0.05$). Rats receiving TPL1000 mg/kg displayed body weight values that were comparable to those of ND rats, indicating effective attenuation of cholesterol-induced weight gain. These findings suggest that higher doses of TPL may modulate weight gain under continued cholesterol challenge.

Total caloric intake data are presented in Figure 4B. Caloric intake increased progressively throughout the 6-week experimental period in all groups. Hypercholesterolemic rats exhibited significantly higher caloric intake than ND controls ($P < 0.05$), reflecting the additional energy contribution from cholesterol and corn oil gavage. No significant differences in caloric intake were observed among hypercholesterolemic rats receiving distilled water, atorvastatin, or TPL at any dose ($P > 0.05$), and no significant time × group interaction was detected. These findings indicate that differences in body weight gain were not attributable to variations in caloric intake.

Serum lipid profiles

Total cholesterol (TC)

As shown in Figure 5A, baseline TC levels were significantly higher in all HC groups (DW, ATV10, TPL250, TPL500, and TPL1000) compared with the ND group ($P < 0.05$). By week 4, ATV10 and all TPL doses produced significant reductions in TC relative to DW ($P < 0.05$), with a clear dose-dependent pattern. TPL500 and TPL1000 showed the most pronounced decreases. By week 6, TC levels in TPL500 and TPL1000 remained significantly lower than DW ($P < 0.05$) and were comparable to those observed in the atorvastatin-treated group.

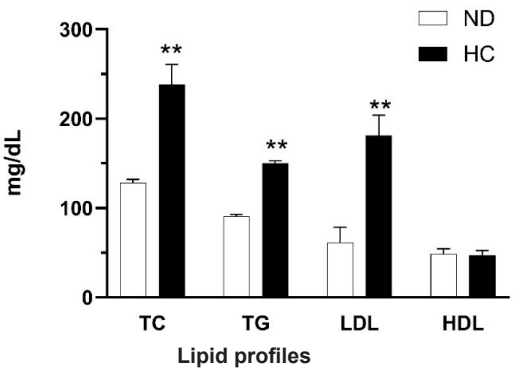

Figure 3. Serum lipid profiles following induction of hypercholesterolemia. Total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) levels in normal diet (ND) rats and hypercholesterolemic (HC) rats after 3 weeks of cholesterol administration (2 g/kg/day). Data are presented as mean ± SEM (n = 6). The symbol (**) represents a statistical significance vs. ND group (Student's t-test, $P \leq 0.01$).

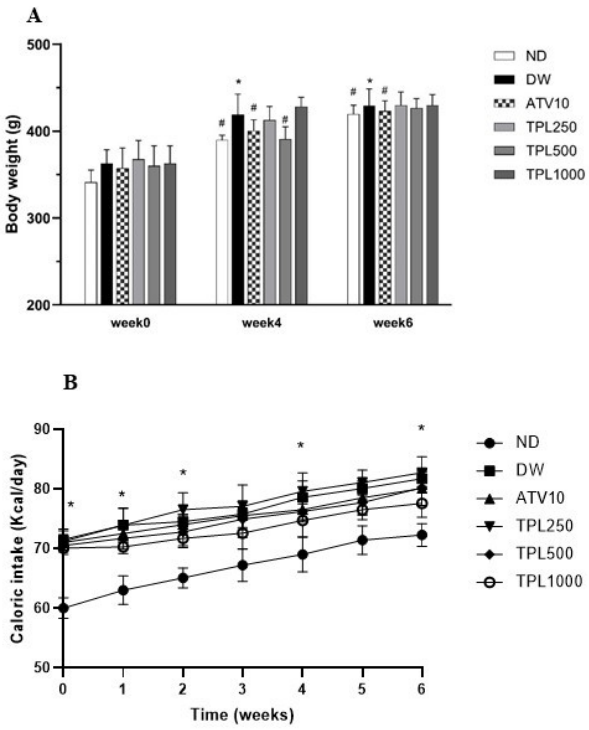

Figure 4. Effects of treatments on body weight (A) and caloric intake (B) in rats receiving a normal diet (ND) or a hypercholesterolemic diet with treatments during the 6-week experimental period. Hypercholesterolemic (HC) rats received distilled water (DW), atorvastatin 10 mg/kg (ATV10), or TPL at 250, 500, and 1,000 mg/kg (TPL250, TPL500, and TPL1000) for 6 weeks. Data are presented as mean±SEM (n = 6). The symbol *represents a statistical significance vs. the ND group and # indicates a statistical significance vs. the HC +DW group (one-way ANOVA followed by Dunnett's post hoc test, $P \leq 0.05$).

Low-density lipoprotein cholesterol (LDL-C)

At baseline, LDL-C levels were significantly elevated in all HC groups compared with the ND group ($P<0.05$), with no differences among HC groups prior to treatment. After 4 weeks, LDL-C levels remained high in DW rats, whereas atorvastatin and all TPL doses significantly reduced LDL-C ($P<0.05$). A dose-response effect was observed, and by week 6, both TPL500 and TPL1000 achieved LDL-C reductions comparable to atorvastatin.

Triglycerides (TG)

A similar trend was observed for triglycerides (Figure 5B). At week 0, TG levels were significantly higher in all HC groups compared with ND ($P<0.05$). By week 4, TG levels were significantly decreased in all treated groups compared with DW ($P<0.05$), with larger reductions observed in TPL500 and TPL1000. These improvements were sustained through week 6, at which point TG levels in TPL500 and TPL1000 were significantly lower than in DW ($P<0.05$) and comparable to those in the ATV10 group.

High-density lipoprotein cholesterol (HDL-C)

HDL-C levels were similar across all groups at baseline (Figure 5D). By week 4, atorvastatin significantly increased HDL-C compared with DW ($P<0.05$). TPL500 and TPL1000 also produced significant increase in HDL-C levels ($P<0.05$). These improvements persisted through week 6, with both higher TPL doses maintaining HDL-C levels significantly above those in the DW group ($P<0.05$).

Atherogenic index of plasma (AIP)

At baseline (week 0), AIP values were similar across groups (-0.08 to 0.22) as shown in Table 2. By week 4, ND exhibited significantly lower AIP values compared with DW ($P<0.05$), whereas no significant differences were observed between DW and the treatment groups at this time point. At week 6, AIP increased further in DW (0.25 ± 0.015), indicating progression of atherogenic risk. In contrast, ATV10 and TPL1000 significantly reduced AIP to -0.35 ± 0.010 and -0.28 ± 0.001, respectively. Both values were significantly lower than that of DW ($P<0.05$) and also represented significant within group reduction from baseline. ND likewise maintained significantly lower AIP values compared with DW at week 6. Although TPL500 (-0.12 ± 0.003) and TPL250 (0.00 ± 0.006) showed numerically favorable trends toward AIP reduction, these changes did not reach statistical significance compared with the DW or relative to baseline after adjustment for multiple comparisons.

Discussion

This study demonstrated that TPL exerted therapeutic lipid-modifying activity and moderates body weight gain in a rat model of hypercholesterolemia in which

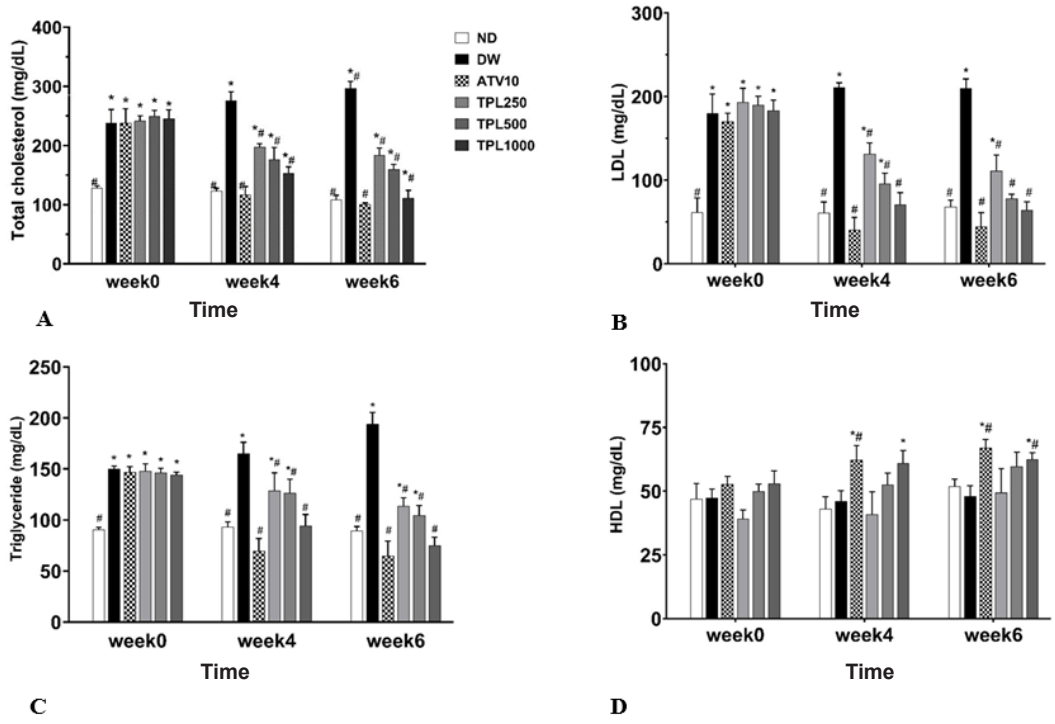

Figure 5. Serum lipid profiles over the 6-week treatment period: (A)Total cholesterol (TC), (B) triglycerides (TG), (C) low-density lipoprotein cholesterol (LDL-C), and (D) high-density lipoprotein cholesterol (HDL-C) in rats fed a normal diet (ND) or rendered hypercholesterolemic (HC) and treated with atorvastatin 10 mg/kg (ATV10) or TPL at 250, 500, or 1,000 mg/kg (TPL250, TPL500, TPL1000). Values are presented as mean±SEM (n = 6). Statistical analysis was performed using one-way ANOVA followed by Dunnett's post hoc test. The symbol * indicates $P \leq 0.05$ vs. ND; # indicates $P \leq 0.05$ vs. HC receiving distilled water (DW).

Table 2. Atherogenic index of plasma (AIP, $\log_{10}$[TG/HDL-C], mmol/L) across treatment groups and timepoints

Treatment period	Atherogenic index of plasma (mmol/L)					
	ND	DW	ATV10	TPL250	TPL500	TPL1000
Week 0	-0.08±0.004	0.14±0.013	0.08±0.005	0.22±0.013	0.11±0.008	0.07±0.009
Week 4	-0.02±0.007#	0.19±0.014	-0.31±0.030	0.14±0.003	0.02±0.004	-0.17±0.003
Week 6	-0.12±0.002#	0.25±0.015	-0.35±0.010#*	0.00±0.006	-0.12±0.003	-0.28±0.001#*

Hypercholesterolemic (HC) rats received distilled water (DW), atorvastatin 10 mg/kg (ATV10), or Triphala aqueous extract (TPL) at 250, 500, or 1,000 mg/kg (TPL250, TPL500, TPL1000) for 6 weeks. Data are presented as mean±SEM (n=6). Statistics: between-group comparisons versus HC +DW at each week used one-way ANOVA with Dunnett's post hoc test ($P \leq 0.05$), within-group comparisons used paired tests from Week 0 to Week 6 ($P \leq 0.05$). The symbol # represents a statistical difference from HC+DW at the same week (between groups), and * indicates a statistical difference from baseline (Week 0) within the same group.

dyslipidemia was first established and cholesterol feeding was maintained throughout treatment. After biochemical confirmation of hypercholesterolemia, TPL produced dose-related reductions in TC, TG, and LDL-C, and at 500 mg/kg increased HDL-C. At 1000 mg/kg, the overall lipid-lowering magnitude approached that of atorvastatin (10 mg/kg). These outcomes indicate treatment efficacy under continued metabolic challenge, rather than a purely prophylactic effect.

The present findings extend prior work on Triphala's hypolipidemic properties, particularly the preventive co-administration paradigm reported by Rana et al (7), which compared 1:1:1 versus 1:2:4 ratios of *T. chebula*, *T. bellirica*, *P. emblica*. In that setting, Triphala reduced TC and TG and increased HDL-C, with the 1:2:4 formulation performing superior outcomes at 1000 mg/kg and improving hepatic lipid peroxidation and atherogenic index. In contrast, the present study employed a therapeutic design in which Triphala administration was initiated only after hypercholesterolemia and cholesterol challenge was maintained throughout the treatment period. Demonstrating lipid correction in this stricter therapeutic context strengthens translational relevance and complements the preventive evidence.

Mechanistically, our *in vitro* assay indicated partial inhibition of HMG-CoA reductase by TPL (36.4 ± 1.5% inhibition at 5 μg/mL), whereas pravastatin achieved 82.5 ± 2.4% at 0.5 μg/mL. Although gallic acid and ellagic acid were present at comparable levels in TPL and in all individual fruit extracts, HMG-CoA reductase inhibition was significantly greater for TPL and PE than the other single fruit extracts. Together with our preliminary tests showing low inhibition by gallic acid and ellagic acid standards (<10% inhibition at 0.5 μg/mL) relative to TPL and the individual fruit extracts (data not shown). These observations suggest that gallic acid and ellagic acid are unlikely to be the principal HMG-CoA reductase active constituents under our conditions.

Additional insight was obtained from quantitative analysis of chebulagic acid, a major ellagitannin frequently implicated in the Triphala bioactivity (30). Although TB contained significantly higher levels of chebulagic acid than TPL, TCh, or PE, it did not exhibit proportionally stronger HMG-CoA reductase inhibition. In contrast, TPL and PE showed greater inhibitory activity despite containing lower amounts of chebulagic acid. This lack of concordance between chebulagic acid abundance and enzyme inhibition suggests a multicomponent mechanism of action. Consistent with Prasad and Srivastava (31), total antioxidant capacity follows *T. chebula* > *T. bellirica* > *P. emblica*, paralleling their flavonoid content. This pattern suggests a functional 'division of labor', whereby PE contributes more to direct HMG-CoA reductase engagement, while TC contributes disproportionately to flavonoid-driven antioxidant/antiperoxidative buffering that complements LDL receptor regulation and bile acid/intestinal lipid handling. Accordingly, future optimization should standardize to a marker panel (e.g., chebulagic/chebulinic/gallic/ellagic acids plus a flavonoid index) and evaluate both enzyme inhibition and oxidative stress biomarkers in the same therapeutic, continued challenge paradigm.

Consistent with docking, ten Triphala phytochemicals with putative HMG-CoA reductase activity cluster into four chemotype classes as phytosterols, polyphenols, tannins (ellagitannins), and flavonoids, with β-sitosterol exhibiting the highest predicted binding affinity to the enzyme (25). Thus, more plausible contributors to direct enzyme engagement include ellagitannins (e.g., chebulagic/chebulinic acids), phytosterols (e.g., β-sitosterol/7-dehydrosigmasterol), and other co-extracted phenolics, acting alone or collectively within the Triphala matrix. The disparity between the moderate single-point enzyme inhibition observed *in vitro* and the robust lipid-lowering effects seen *in vivo* likely reflects the contribution of non-gallic acid and non-ellagic acid constituents that directly target HMG-CoA reductase, as well as multitarget mechanisms operating in parallel. These may include LDL receptor regulation (32), antioxidant protection (31), bile acid and intestinal lipid handling (33), and modulation of AKT1/PPARG signaling pathways (34), all acting synergistically alongside partial HMG-CoA reductase inhibition. Microbiota-derived urolithins from ellagitannins may further facilitate TG turnover and cholesterol efflux (35). Collectively, these pathways provide a coherent basis for the *in vivo* phenotype under sustained cholesterol load.

To complement LDL-centric readouts, we assessed the

atherogenic index of plasma (AIP; $\log_{10}$[TG/HDL-C], mmol/L) as a composite of triglyceride burden relative to HDL-C. In this continued challenge model, atorvastatin (ATV10) and TPL1000 produced the largest AIP reductions by week 6, each significantly lower than the vehicle control, with within-group decrease evident from week 4. These AIP improvements mirror TG lowering and HDL behavior and are consistent with a multifactorial mechanism in which partial HMG-CoA reductase inhibition acts alongside polyphenol-mediated effects on hepatic LDL receptor activity, oxidative stress, and intestinal/bile acid handling.

The individual fruit extract comparison provided insight into the relative contribution of individual fruit extracts to HMG-CoA reductase inhibition. PE displayed the highest HMG-CoA reductase inhibition among individual fruit extracts under our assay conditions, while the composite TPL retained appreciable activity. This pattern is consistent with the combined contribution of multiple fruit-derived constituents rather than dominance by a single compound and aligns with prior observations that increasing the *P. emblica* proportion (1:2:4 ratio) can strengthen lipid outcomes *in vivo* (7). Formal concentration-response studies normalized to phytochemical markers would help verify relative contributions and determine whether ratio optimization could enhance therapeutic effect.

An additional observation was the selective rise in HDL-C at TPL 500 mg/kg, without further elevation at 1000 mg/kg despite stronger reductions in TC, TG, and LDL-C. This pattern is biologically plausible for polyphenol-rich extracts, which often exhibit biphasic gene regulatory responses (36). Intermediate exposure may best stimulate apolipoprotein A-I expression and ABCA1/ABCG1-mediated reverse cholesterol transport (37-39), whereas higher exposure shifts flux toward LDL-C clearance, fatty acid oxidation, and bile-acid-linked disposal, plateauing HDL-C even as overall lipid control improves (40,41). Activation of PPAR-α and AMPK reported for *P. emblica* and gallic acid provides a mechanistic rationale for this dose-contingent redistribution of lipid metabolism (42,43).

Beyond plasma lipids, TPL at 1000 mg/kg attenuated body weight gain to levels comparable to those of the normal diet group, despite continued cholesterol feeding. This weight-regulating effect is biologically plausible in light of Triphala's phytochemical profile. Triphala has been reported to contain a predominance of hydrolysable tannins and their subclass ellagitannins, together with lower amounts of simple phenolics and other polyphenols (44). Hydrolysable tannins have been linked to reductions in body weight, weight gain, serum cholesterol, LDL, and TG in animal models (45), while ellagitannins have demonstrated inhibitory activity on carbohydrate-digesting enzymes, a mechanism relevant to obesity and metabolic control (46). In addition, phenolic constituents present in Triphala are likely to contribute to its metabolic profile. Gallic acid has been reported to suppress lipogenesis and enhance fatty-acid β-oxidation through AMPK-related pathways (47,48), while ellagic acid has been associated with improvements in lipid and glucose metabolism and inhibition of adipocyte differentiation (49,50).

Phenolic constituents have been implicated in anti-obesity mechanisms through modulation of lipid handling and adipogenesis (51). During digestion, they may also inhibit pancreatic lipase, promote aggregation of fat globules, and alter the generation and absorption of long-chain fatty acids, thereby limiting fat uptake (52). Complementing these mechanisms, Kwandee et al showed that Triphala enhanced phenylalanine, tyrosine, and tryptophan biosynthesis in fecal batch-culture fermentations from obese adults, with these aromatic amino acids identified as key metabolites linked to energy-metabolism regulation (53). Taken together, the tannin-rich composition, phenolic-driven modulation of lipid handling, and microbiota-associated shifts in energy-related amino acid metabolism provide a coherent explanation for the attenuated weight gain observed in TPL-treated hypercholesterolemic rats and support a broader role for Triphala in integrated regulation of lipid and energy balance.

Concordant cell-based data indicate that Triphala can restrain lipid accrual in adipocytes by down-regulating adipogenic genes, including PPARG, C/EBPα, FAS, and GLUT4, and by shifting transcriptional programs governing triglyceride synthesis and storage (54). In line with these observations, network pharmacology and molecular docking analyses have identified several Triphala constituents, namely β-sitosterol, 7-dehydrosigmasterol, peraksine, α-amyrin, luteolin, quercetin, kaempferol, ellagic acid, and phyllanthin, as exhibiting favorable binding interactions with AKT1 and PPARG, central regulators at the intersection of insulin signaling, lipid metabolism, and inflammation (55). These compound-target relationships provide a mechanistic bridge between polyphenolic chemistry and the observed weight-regulatory and lipid-modifying effects *in vivo*.

Translational observations align with this profile. Clinical studies have reported that Triphala supplementation is associated with reduction in body weight and central adiposity in obese individuals, together with improvements in lipid parameters. In addition, small scale human studies have also described increases in HDL-C and modest glycemic benefits, while reductions in serum lipid levels have also been observed in hypercholesterolemic patients (56,57). Collectively, these clinical signals, together with adipocyte gene expression data, and AKT1/PPARG-centered docking results, support a coherent model in which Triphala modulates lipid flux and energy handling, complementing partial HMG-CoA reductase inhibition to produce the integrated metabolic benefits observed in the present study.

As expected for a direct HMG-CoA reductase inhibitor, atorvastatin produced the largest lipid changes overall. Nevertheless, high-dose TPL achieved near comparable improvements across several parameters despite continued cholesterol exposure. These findings support Triphala as a potential adjunct in dyslipidemia management. However, substitutability for statins cannot be inferred from the present preclinical data. To delineate mechanism and translational potential, future work should quantify effects on energy expenditure, fatty acid oxidation, and gut microbiota-dependent metabolism, and undertake long-term efficacy and safety evaluations in well-controlled studies.

Conclusion

TPL produced statistically significant lipid-lowering and weight-modulating effects in hypercholesterolemic rats under continuous cholesterol challenge, indicating true therapeutic efficacy accompanied by improvements in standard lipid indices; atherogenic index in plasma provided a supportive TG-HDL context. The profile is partly attributable to HMG-CoA reductase inhibition. In contrast to preventive co-administration models, our post-induction design shows that Triphala retains lipid-modifying activity in a treatment setting. Among the doses tested, TPL 1000 mg/kg yielded the largest and most consistent effects (approaching those of atorvastatin), making it the optimal dose in this model. To define clinical utility, future work should map molecular pathways, optimize fruit ratios, and include comprehensive pharmacokinetic and safety evaluations in rigorously controlled studies of dyslipidemia.

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Authors' contribution

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Software: All authors.
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Writing–review & editing: All authors.

Conflict of interests

The authors declare no conflicts of interest.

Ethical considerations

This study was conducted in 2012, before the establishment of the institutional Animal Care and Use Committee (IACUC) at Mahasarakham University. Animal protocols were reviewed and authorized by the University Research Committee; therefore, no IACUC approval number is available and retrospective approval is not applicable. Procedures adhered to internationally accepted standards, including the Guide for the Care and Use of Laboratory Animals (National Research Council) and the 3Rs principles (Replacement, Reduction, Refinement), with animals housed and monitored by trained personnel under veterinary oversight and measures taken to minimize pain and distress (appropriate handling, monitoring, and humane endpoints). The authors also affirm that ethical issues, including plagiarism, data falsification, and redundant publication, were carefully considered throughout the research and publication process.

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