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Original Research Article

Efficacy and Safety of Black Pepper Supplementation in Adults with Borderline Hypercholesterolemia: A Randomized, Placebo-Controlled Trial

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ABSTRACT

Black pepper (*Piper nigrum*) has long been used in traditional medicine for digestive and metabolic health, and piperine, its primary bioactive compound, has demonstrated lipid-lowering effects in preclinical studies; however, clinical evidence remains limited. This randomized, double-blind, placebo-controlled trial evaluated the efficacy and safety of black pepper capsules on lipid profiles in adults with borderline hypercholesterolemia. Forty-seven participants aged 20–34 years with LDL-C 130–189 mg/dL or 35–60 years with LDL-C 100–130 mg/dL were randomized to receive black pepper capsules (250 mg twice daily, providing approximately 7.16 mg/day of piperine) or a placebo for 12 weeks. Primary outcomes included changes in total cholesterol, LDL-C, HDL-C, triglyceride, non-HDL-C, and VLDL-C, measured at baseline, week 8 and week 12. Safety was assessed via liver and renal function tests at baseline and week 8, with adverse events monitored throughout the study. Black pepper supplementation was safe and well tolerated, with no serious adverse events or clinically significant changes in liver or renal function; minor gastrointestinal side effects were self-limiting. No statistically or clinically significant differences were observed between the black pepper and placebo groups in lipid profile changes over 12 weeks ($p > 0.05$), and age subgroup analyses showed no meaningful LDL-C reductions. In conclusion, black pepper capsules at a dose of 500 mg/day were safe but did not significantly improve lipid profiles in adults with borderline hypercholesterolemia.

Keywords: *Black pepper, Piper nigrum, Piperine, Hypercholesterolemia, Lipid profile.*

Introduction

Hypercholesterolemia is a well-established risk factor for cardiovascular disease (CVD), the leading cause of morbidity and mortality worldwide.[1,2] Borderline hypercholesterolemia, defined as mildly elevated lipid levels, represents a critical clinical window for early lifestyle and therapeutic interventions. Timely intervention in individuals with borderline lipid abnormalities can effectively reduce lipid levels and prevent progression to overt dyslipidemia and related cardiovascular complications.[3] Current treatments focus on lifestyle changes and lipid-lowering drugs such as statins and fibrates, which may cause side effects including myopathy, elevated liver enzymes, and an increased risk of diabetes.[4,5] These limitations have prompted growing interest in complementary and alternative therapies, particularly natural products, for managing cholesterol levels.

Black pepper (*Piper nigrum*), a common culinary spice and traditional herbal remedy, contains piperine as its primary bioactive constituent. Piperine exhibits diverse pharmacological effects, including antioxidant, anti-inflammatory, antihypertensive, immunomodulatory, antidiabetic, antiobesity, cardioprotective, and lipid-modulating activities.[6-8] Previous preclinical studies demonstrated that piperine from black pepper significantly reduces body weight, total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), and fat mass in high-fat diet-fed rats, while increasing high-density lipoprotein cholesterol (HDL-C) levels.[9,10]

The mechanisms underlying these effects are multifaceted. Piperine reduces cholesterol absorption in the intestine by internalizing cholesterol transporter proteins such as Niemann-Pick C1-like 1 (NPC1L1) and scavenger receptor class B type I (SR-BI).[11] Additionally, it inhibits adipogenesis by downregulating key transcription factors, including peroxisome proliferator-activated receptor-γ (PPARγ), sterol regulatory element-binding protein-1c gene (SREBP-1c), and CCAAT/enhancer-binding protein β (C/EBPβ), thereby suppressing the expression of genes involved in fat cell differentiation and lipid storage.[12] Piperine also promotes reverse cholesterol transport by upregulating hepatic SR-B1 and intestinal ATP-binding cassette transporter G8 (ABCG8) transporters, which facilitates cholesterol excretion.[13]

Supporting these mechanistic insights, animal studies have demonstrated that piperine supplementation significantly reduces plasma and tissue lipid accumulation, inhibits Hydroxy-methyl-glutaryl-Coenzyme A (HMG-CoA) reductase activity, and increases bile acid and neutral sterol excretion, thereby exerting a potent hypocholesterolemic effect in high-fat diet-induced hypercholesterolemic rats.[9,14] Regarding safety, subchronic administration of piperine in mice has shown no significant histological damage to the kidney, liver, or lungs,[15] and aqueous extracts of dried black pepper have demonstrated no acute or subchronic toxicity in animal models.[16]

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Despite promising preclinical data, clinical evidence supporting the lipid-lowering efficacy of black pepper in humans remains limited. Therefore, this study is novel in providing one of the first randomized, placebo-controlled clinical trials evaluating black pepper supplementation in adults with borderline hypercholesterolemia. The primary objectives were to assess changes in lipid parameters at baseline, week 8 and week 12, alongside evaluating tolerability and impacts on liver and renal function at baseline and week 8 to establish safety.

Materials and Methods

Study design and ethical statement

This 12-week, randomized, double-blind, placebo-controlled clinical trial was conducted at Mae Fah Luang University Wellness Center and Medical Center with participants diagnosed with borderline hypercholesterolemia. The study protocol was approved by the Mae Fah Luang University Ethics Committee on Human Research (COA: 045/2023, EC-22185-25). The trial was conducted in accordance with the Declaration of Helsinki and the principles of Good Clinical Practice. All participants provided written informed consent after receiving full information about the study's purpose, potential benefits, and risks. Participants retained the right to withdraw at any time for any reason.

Participants

Eligible participants were adults aged 20–34 years with LDL-C levels of 130–189 mg/dL, or adults aged 35–60 years with LDL-C levels of 100–130 mg/dL, and a body mass index (BMI) between 18 and 35 kg/m². All were newly diagnosed with hypercholesterolemia by a clinician and had a 10-year CVD risk score below 10%, based on the Thai CV Risk Score.

Exclusion criteria included secondary hypercholesterolemia (e.g., hypothyroidism, nephrotic syndrome), use of lipid-lowering medications or supplements, blood pressure ≥130/80 mmHg, use of antihypertensive or cardiovascular drugs, known allergies to black pepper or herbal products, use of weight-loss medication in the past six months, participation in intense physical activity or strict dietary regimens, and pregnancy or lactation.

Sample size

The primary outcome of this study was serum lipid levels, which are continuous variables. The F-test with ANOVA repeated-measures between factors was used to calculate the required sample size. Based on prior literature, the effects of *Hibiscus sabdariffa* extract and simvastatin on lipid levels in hyperlipidemic patients, we assumed mean LDL-C levels were 144.2 ±16.8 mg/dL and 123.7 ± 24.4 mg/dL for the two groups, respectively.[17] Using a Type I error rate (α) of 0.05 and Type II error rate (β) of 0.1, a minimum of 20 participants per group was required. Considering a potential 20% attrition rate and funding constraints, the total sample size was set at 48 participants (24 per group).

Randomization and intervention

Participants were stratified by age and randomly assigned to the intervention group (n = 23) or control group (n = 24). The intervention group received 250 mg of black pepper capsules twice daily before meals, while the control group received a placebo at the same frequency for 12 weeks. Both groups received identical dietary and lifestyle recommendations. All participants and investigators were blinded to group assignments.

The black pepper capsules contained standardized piperine extract, manufactured under Good Manufacturing Practice (GMP) conditions at the Medicinal Plant Innovation Center, Mae Fah Luang University, Thailand. Finely ground 100% natural Chanthaburi black pepper powder was purchased from Khataiku Co. Ltd. The black pepper was formulated into capsule form (250 mg/capsule) with the addition of excipients. The piperine content was determined to be 3.58 ± 0.03 mg/capsule using High-Performance Liquid Chromatography with Diode-Array Detection (HPLC-DAD, Agilent 1260 Infinity II, Agilent Technologies, USA), following a validated method.[18] The placebo capsules contained inert microcrystalline cellulose (food grade, Thailand) and were identical in appearance, weight, and packaging.

Outcome measures

Primary outcomes included changes in serum lipid profiles, including TC, TG, LDL-C, HDL-C, non-HDL-C, very low-density lipoprotein cholesterol (VLDL-C), the LDL/HDL ratio, and the TC/HDL ratio, measured at baseline, week 8 and week 12. All biochemical parameters were analyzed using an automated clinical chemistry analyzer (cobas Integra *400* plus; Roche Diagnostics, Germany).

Secondary outcomes included safety assessments based on liver function tests (Aspartate Aminotransferase [AST], Alanine Aminotransferase [ALT], and Alkaline Phosphatase [ALP]) and renal function tests (Blood Urea Nitrogen [BUN], creatinine, and Estimated Glomerular Filtration Rate [eGFR]). All measurements were performed at baseline and week 8 using the same analyzer under standardized laboratory protocols. Adverse events were monitored throughout the study.

Statistical analysis

Statistical analyses were performed using SPSS Statistics, version 26.0 (IBM Corp., 2019). Categorical variables were compared with the chi-square test. For efficacy, normally distributed lipid data were analyzed using repeated-measures ANOVA to assess differences within and between groups. Safety data with normal distribution were compared between groups using independent t-tests and within groups using paired t-tests. For non-normally distributed data, between-group comparisons used the Mann–Whitney U test, and within-group comparisons employed the Wilcoxon signed-rank test. A p-value of <0.05 was considered statistically significant.

Results and Discussion

Participant recruitment and follow-up

A total of 61 participants were screened for eligibility. Forty-seven participants were randomized into the intervention (n = 23) and placebo (n = 24) groups between August 2023 and January 2024. Participants were recruited from Mae Fah Luang University Medical Center Hospital and followed up for 12 weeks. During the follow-up period, three participants in the black pepper group and two in the placebo group withdrew, resulting in an overall attrition rate of 10.64%. There were no significant differences in the attrition rate or reasons for withdrawal between the two groups ($p > 0.05$). All participants attended at least one visit after randomization, ensuring that the full analysis set was based on the intention-to-treat principle. The CONSORT flow diagram is presented in Figure 1.

Baseline characteristics

Baseline demographics and clinical parameters were similar between groups. The black pepper group had a mean age of 37.96 ± 6.98 years compared to 36.21 ± 6.21 years in the placebo group, with 56.5% and 62.5%, respectively, aged over 35 years. Male participants accounted for 30.4% of the black pepper group and 16.7% of the placebo group. Anthropometric measures, including BMI, waist circumference (WC), hip circumference (HC), and waist-to-hip ratio, were not significantly different between groups.

LDL-C inclusion criteria were stratified by age to reflect differing cardiovascular risk profiles: participants aged 20–34 years were required to have LDL-C levels between 130 and 189 mg/dL, while those aged 35–60 years qualified with LDL-C between 100 and 130 mg/dL. Although these thresholds differ, both are within the borderline or near-optimal range for hypercholesterolemia, especially when considering age-related risk factors.[19,20] This approach aligns with the Thai CV Risk Score, which incorporates age as a key determinant and supports early intervention.[21]

Baseline lipid profiles (TC, TG, LDL-C, HDL-C) were similar across groups and consistent with borderline hypercholesterolemia criteria.[22] The mean LDL-C level was 139.57 ± 27.35 mg/dL in the black pepper group and 134.96 ± 21.73 mg/dL in the placebo group. No significant differences were observed for TC, TG, HDL-C, or blood pressure. The only exception was the Thai Cardiovascular Risk Score, which was significantly higher in the black pepper group (2.03 ± 1.20%) compared with the placebo group (1.32 ± 0.74%; $p = 0.022$).

Lifestyle factors, including smoking status, alcohol consumption, and physical activity, were evenly distributed between the groups. Dietary

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preferences for high-fat or high-energy foods were also similar. Detailed baseline characteristics are shown in Table 1.

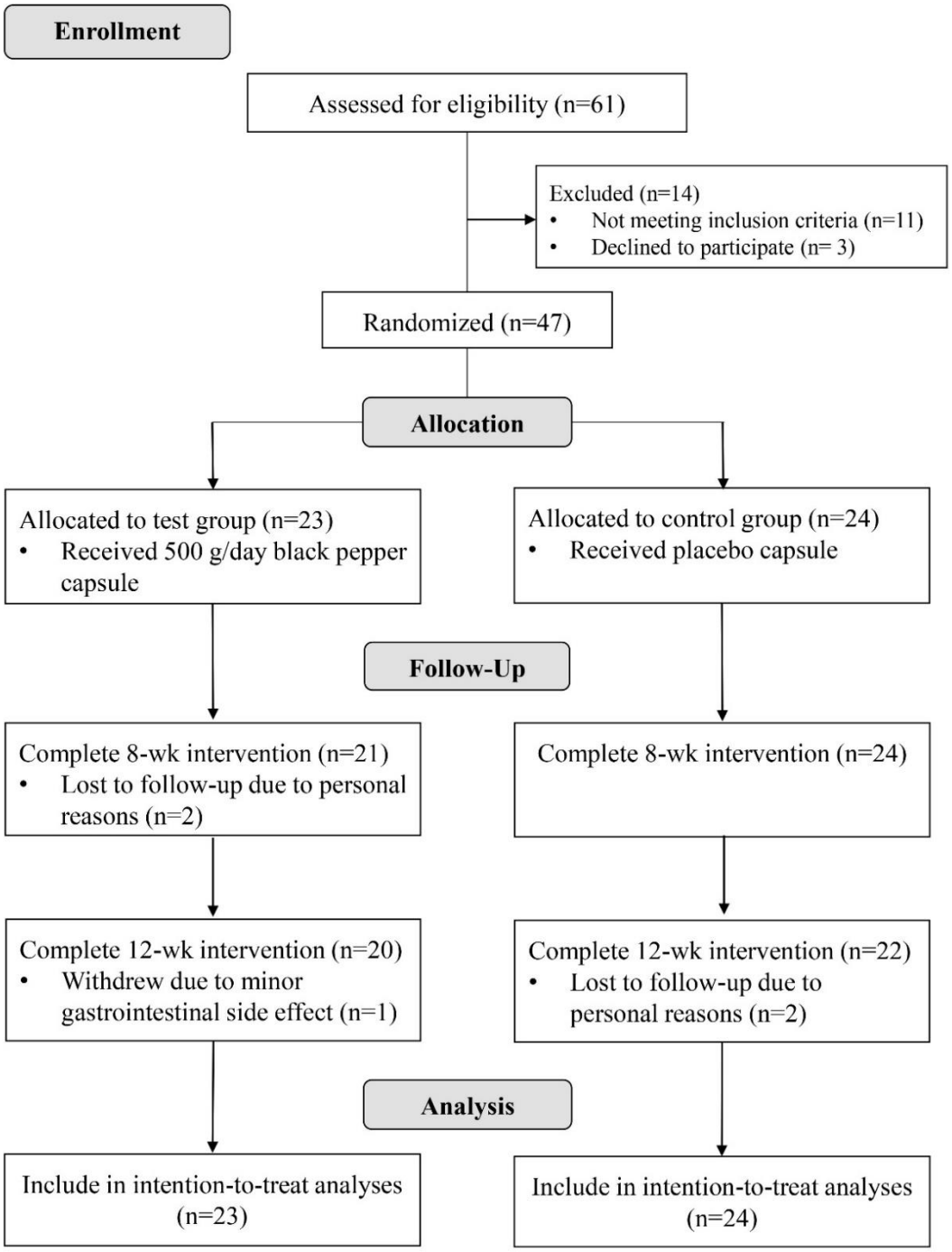

Figure 1: The CONSORT Diagram of study participants.

A total of 47 adults with borderline hypercholesterolemia were screened, randomized, and allocated to either the black pepper (*Piper nigrum*) supplementation group or placebo group. The diagram illustrates participant flow through the study, including exclusions, dropouts, and the number of participants completing the 12-week intervention.

Table 1: Baseline characteristics of the study participants.

Characteristics	Black pepper (n=23)	Placebo (n=24)	*p*-value
Age (years)			0.449
Mean ± SD	37.96 ± 6.98	36.21 ± 6.21	
>35 years, No. (%)	13 (56.52%)	15 (62.50%)	
Sex, No. (%)			0.441
Male	7 (30.40%)	4 (16.70%)	
Female	16 (69.60%)	20 (83.30%)	
BMI (kg/m²)	25.16 ± 4.69	23.52 ± 4.56	0.217
TC (mg/dL)	213.48 ± 29.61	204.25 ± 26.74	0.268
LDL-C (mg/dL)	139.57 ± 27.35	134.96 ± 21.73	0.749
HDL-C (mg/dL)	62.04 ± 15.78	59.67 ± 10.30	0.542
TG (mg/dL)	133.22 ± 76.27	113.67 ± 57.02	0.389
CV Risk Score (%)	2.03 ± 1.20	1.32 ± 0.74	0.022
SBP (mmHg)	115.87 ± 11.43	119.88 ± 13.48	0.279
DBP (mmHg)	69.09 ± 10.40	74.92 ± 10.94	0.068
WC (cm)	84.61 ± 12.39	80.67 ± 11.95	0.273
HC (cm)	100.65 ± 10.13	96.79 ± 9.58	0.186
WC/HC ratio	0.84 ± 0.06	0.83 ± 0.06	0.658
Smoking, No. (%)			1.000
Do not smoke	23 (100.00%)	24 (100.00%)	
Alcohol Consumption, No. (%)			1.000
Do not drink	12 (52.20%)	12 (50.00%)	
Drink	11 (47.80%)	10 (50.00%)	
Physical Activity/Sports, No. (%)			0.372
Do not exercise at all	12 (60.90%)	13 (54.20%)	
Exercise < 3 times/week	3 (13.00%)	6 (25.00%)	
Exercise ≥ 3 times/week	4 (17.40%)	5 (20.80%)	
Exercise daily (≥30 min)	2 (8.70%)	0 (0%)	
Eating Preferences (High-Fat and High-Energy Foods and drinks), No. (%)			1.000
Dislikes	3 (13.00%)	3 (12.50%)	
Likes	20 (87.00%)	21 (87.50%)	

Data are represented as number (%) or mean ± standard deviation (SD).
Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; WC, waist circumference; HC, hip circumference; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; VLDL-C, very low-density lipoprotein cholesterol.

Table 2: Comparison of blood lipid parameters between black pepper and placebo groups.

Variables	Tested group		*p*-value (repeated measurement)		
	Black pepper (n=23)	Placebo (n=24)	Time	Group	Time × Group
TC (mg/dL)					
Baseline	213.48 ± 29.61	204.25 ± 26.74	0.040	0.390	0.300
Week 8	206.65 ± 28.91	204.79 ± 29.54			
Week 12	217.70 ± 30.53	208.13 ± 30.59			
LDL-C (mg/dL)					
Baseline	139.57 ± 27.35	134.96 ± 21.73	0.252	0.726	0.376
Week 8	137.35 ± 30.95	139.38 ± 27.61			
Week 12	144.48 ± 30.35	139.29 ± 26.84			
HDL-C (mg/dL)					
Baseline	62.04 ± 15.78	59.67 ± 10.30	0.043	0.484	0.171
Week 8	60.61 ± 16.45	59.08 ± 10.22			
Week 12	64.00 ± 17.62	59.63 ± 10.21			
TG (mg/dL)					
Baseline	133.22 ± 76.27	113.67 ± 57.02	0.732	0.246	0.949
Week 8	130.26 ± 79.88	107.38 ± 57.33			
Week 12	132.22 ± 61.70	112.96 ± 53.10			
Non-HDL-C (mg/dL)					
Baseline	151.43 ± 29.68	144.58 ± 25.66	0.152	0.615	0.452
Week 8	146.04 ± 30.23	145.71 ± 30.70			
Week 12	153.70 ± 30.52	148.50 ± 32.09			
VLDL-C (mg/dL)					
Baseline	26.64 ± 15.25	22.73 ± 11.40	0.732	0.246	0.949
Week 8	26.05 ± 15.98	21.48 ± 11.47			
Week 12	26.44 ± 12.34	22.59 ± 10.62			
LDL/HDL ratio					
Baseline	2.40 ± 0.75	2.34 ± 0.64	0.427	0.987	0.674
Week 8	2.42 ± 0.80	2.45 ± 0.77			
Week 12	2.42 ± 0.80	2.43 ± 0.76			
TC/HDL ratio					
Baseline	3.63 ± 0.91	3.51 ± 0.70	0.822	0.825	0.609
Week 8	3.62 ± 0.98	3.57 ± 0.84			
Week 12	3.60 ± 0.95	3.60 ± 0.88			

Data are represented as mean ± standard deviation (SD).

Abbreviations: TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; VLDL-C, very low-density lipoprotein cholesterol. Statistical analysis was conducted using Repeated measure ANOVA.

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Table 3: Changes of blood lipid parameters in pepper and placebo groups.

Parameters	Black pepper (n=23)		Placebo (n=24)		*p*-value	
	Δ1	Δ2	Δ1	Δ2	Δ1	Δ2
TC (mg/dL)	-6.83 (-21.57, 7.92)	4.22 (-8.04, 16.47)	0.54 (-7.27, 8.36)	3.88 (-3.89, 11.64)	0.828	0.289
LDL-C (mg/dL)	-2.22 (-17.83, 13.40)	4.91 (-8.44, 18.26)	4.42 (-2.71, 11.55)	4.33 (-3.49, 12.16)	0.814	0.425
HDL-C (mg/dL)	-1.44 (-3.96, 1.09)	1.96 (-1.41, 5.32)	-0.58 (-3.66, 2.49)	-0.04 (-2.75, 2.67)	0.703	0.757
TG (mg/dL)	-2.96 (-20.16, 14.25)	-1.00 (-23.39, 21.39)	-6.29 (-26.99, 14.40)	-0.71 (-26.97, 25.55)	0.154	0.257
Non-HDL-C (mg/dL)	-5.39 (-19.37, 8.59)	2.26 (-9.70, 14.23)	1.13 (-5.74, 7.99)	3.92 (-3.78, 11.62)	0.970	0.573
VLDL-C (mg/dL)	-0.59 (-4.03, 2.85)	-0.20 (-4.68, 4.28)	-1.26 (-5.40, 2.88)	-0.14 (-5.39, 5.11)	0.154	0.257
LDL/HDL ratio	0.02 (-0.27, 0.32)	0.02 (-0.26, 0.31)	0.12 (-0.03, 0.26)	0.09 (-0.08, 0.26)	0.907	0.932
TC/HDL ratio	-0.01 (-0.28, 0.26)	-0.02 (-0.29, 0.25)	0.06 (-0.11, 0.24)	0.09 (-0.10, 0.29)	0.866	0.975

Data are presented as mean difference (95% confidence interval).

Abbreviations: TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; VLDL-C, very low-density lipoprotein cholesterol. Statistical analysis was conducted using Independent-samples t-test or Mann-Whitney Test. Δ1: the score changes between baseline and the 8th week after treatment.; Δ2: the score changes between baseline and the 12th week after treatment.

Table 4: Comparison of LDL-C between sub-group of black pepper and placebo groups.

LDL-C (mg/dL)	Tested group		*p*-value (repeated measurement)		
	Black pepper	Placebo	Time	Group	Time × Group
20–24 years (n = 19)					
Baseline	165.50 ± 20.02	157.22 ± 18.25	0.770	0.883	0.142
Week 8	153.80 ± 23.93	165.67 ± 23.43			
Week 12	163.10 ± 23.57	163.56 ± 29.05			
35–60 years (n = 28)					
Baseline	119.62 ± 8.87	121.60 ± 8.71	0.167	0.796	0.504
Week 8	124.69 ± 30.45	123.60 ± 15.08			
Week 12	130.15 ± 27.57	124.73 ± 9.77			

Data are represented as mean ± standard deviation (SD).

Abbreviations: LDL-C, low-density lipoprotein cholesterol. Statistical analysis was conducted using Repeated measure ANOVA.

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Table 5: Changes of LDL-C in sub-group of black pepper and placebo groups.

LDL-C (mg/dL)	Tested group		*p*-value
	Black pepper	Placebo	
20–24 years (n = 19)			
Δ1	-11.7 (-36.81, 13.41)	8.44 (-3.87, 20.76)	0.291
Δ2	-2.40 (-21.35, 16.55)	6.33 (-15.56, 28.23)	0.970
35–60 years (n = 28)			
Δ1	5.08 (-17.39, 27.54)	2.00 (-7.88, 11.88)	0.903
Δ2	10.54 (-10.25, 31.33)	3.13 (-3.41, 9.68)	0.482

Data are represented as mean ± standard deviation (SD).
Abbreviations: LDL-C, low-density lipoprotein cholesterol. Statistical analysis was conducted using Independent-samples t-test. Δ1: the score changes between baseline and the 8th week after treatment.; Δ2: the score changes between baseline and the 12th week after treatment.

Table 6: Liver and renal function tests in black pepper and placebo groups.

Variables	Tested group		Mean difference	*p*-value[a]
	Black pepper (n=23)	Placebo (n=24)		
Liver function test				
AST (U/L)				
Baseline	23.52 ± 7.13	20.21 ± 8.74	3.31 (-1.38, 8.01)	0.038*
Week 8	24.09 ± 8.02	20.63 ± 7.45	3.45 (-1.09, 8.00)	0.065
Mean change	0.57 (-1.04, 2.17)	0.43 (-2.83, 3.68)		
p-value[b]	0.443	0.749		
ALT (U/L)				
Baseline	32.13 ± 23.00	19.88 ± 15.28	12.26 (0.83, 23.68)	0.036*
Week 8	34.43 ± 26.50	19.38 ± 14.32	15.06 (2.62, 27.50)	0.016*
Change	2.30 (-2.16, 6.76)	-0.50 (-4.83, 3.83)		
p-value[b]	0.259	0.260		
ALP (U/L)				
Baseline	65.00 ± 15.17	67.38 ± 17.93	-2.38 (-12.15, 7.40)	0.898
Week 8	65.39 ± 16.58	65.50 ± 13.66	-0.11 (-9.02, 8.80)	0.981
Change	0.39 (-2.54, 3.32)	-1.88 (-5.80, 2.05)		
p-value[b]	0.784	0.537		
Renal function test				
BUN (mg/dL)				
Baseline	12.05 ± 3.40	11.45 ± 2.38	0.61 (-1.11, 2.32)	0.725
Week 8	12.07 ± 2.73	11.31 ± 2.64	0.77 (-0.81, 2.34)	0.334
Change	0.02 (-0.69, 0.74)	-0.14 (-1.17, 0.89)		
p-value[b]	0.760	0.785		
Cr (mg/dL)				
Baseline	0.81 ± 0.21	0.75 ± 0.15	0.06 (-0.05, 0.16)	0.304
Week 8	0.82 ± 0.21	0.74 ± 0.14	0.08 (-0.03, 0.18)	0.277
Change	0.01 (-0.02, 0.03)	-0.01 (-0.04, 0.01)		
p-value[b]	0.669	0.310		
eGFR (mL/min/1.73 m²)				
Baseline	100.94 ± 15.43	105.15 ± 12.69	-4.21 (-12.49, 4.07)	0.311
Week 8	100.62 ± 15.21	106.47 ± 11.12	-5.85 (-13.66, 1.95)	0.138
Change	-0.32 (-2.39, 1.75)	1.32 (-1.31, 3.96)		
p-value[b]	0.750	0.363		

Data are represented as mean ± standard deviation (SD) or mean difference (95% confidence interval).
Abbreviations: AST, aspartate aminotransferase levels; ALT, alanine aminotransferase levels; ALP, Alkaline phosphatase; BUN, blood urea nitrogen levels; Cr, creatinine levels; eGFR, estimated glomerular filtration rate. [a]: Statistical analysis was conducted using Independent-samples t-test or Mann-Whitney Test. [b]: Statistical analysis was conducted using Paired t-test or Wilcoxon Signed Ranks Test. **p*-value < 0.05.

Lipid profile outcomes

Changes in serum lipid parameters, including TC, TG, LDL-C, HDL-C, non-HDL-C, and VLDL-C, were assessed. Black pepper supplementation did not result in statistically significant lipid-lowering effects compared with the placebo at week 8 or week 12 ($p > 0.05$). Minor reductions in TC, TG, LDL-C, non-HDL-C, VLDL-C, and the TC/HDL-C ratio were observed in the black pepper group at week 8; however, these changes were not statistically significant and were not sustained at week 12. Changes in HDL-C were also modest and not statistically significant (Tables 2 and 3).

Subgroup analysis revealed a greater LDL-C reduction at week 8 (−11.7 mg/dL) among participants aged 20–34 years; however, these changes were not statistically significant compared to placebo in any age subgroup ($p > 0.05$) (Tables 4 and 5).

Our results showed no statistically significant differences in all lipid outcomes between groups. These findings are consistent with several previous studies of humans showing limited or no effect of black pepper or isolated piperine on lipid profiles. Although some clinical studies, particularly those in populations with metabolic syndrome or using curcumin-piperine combination therapies, have reported improved lipid levels, these findings may be dependent on the study population or treatment protocol and are not broadly generalizable.[23,24] In contrast, animal and in vitro studies consistently demonstrate that piperine can lower TC, TG and LDL-C, and increase HDL-C by modulating cholesterol transporters, fat metabolism, and gene expression.[8-13,25,26] Notably, black pepper powder has been shown to significantly improve lipid profiles in patients with non-alcoholic fatty liver disease, reducing TC, TG and LDL-C while modestly increasing HDL-C.[27]

Experimental evidence suggests that piperine regulates lipids by reducing cholesterol uptake via internalization of transporter proteins such as NPC1L1 and SR-BI, as well as by modulating enzymes and transcription factors involved in lipid metabolism, adipogenesis, and cholesterol efflux.[11-13,26] Despite these mechanisms, no clinical efficacy was observed in the present study.

Differences in dosage, formulation, intervention duration, and participant characteristics may explain the discrepancy between preclinical and clinical results. In this study, the piperine dose (~7.16 mg/day) was likely too low to produce a significant therapeutic effect, particularly given its poor oral bioavailability and systemic absorption without bioenhancement.[28,29] The 12-week intervention may have been too short to observe long-term lipid or metabolic improvements. Certain clinically tested lipid-lowering nutraceuticals are safe and effective for improving plasma lipid levels in individuals with mild-to-moderate dyslipidemia and low cardiovascular risk.[30] Finally, modest changes in lipid parameters likely reflect natural physiological variation or lifestyle factors rather than treatment effects.[3,31,32]

In traditional Thai medicine, black pepper is rarely used alone, but more commonly included in polyherbal formulations as a bioenhancer by inhibiting cytochrome P*450* enzymes and P-glycoprotein to improve absorption of other herbs or drugs.[33] The limited efficacy observed in this study may therefore reflect its use as monotherapy rather than in combination with other herbs or compounds.

Safety and adverse events

The black pepper capsules were generally well tolerated, with no serious adverse events reported in either group during the 12-week study period. Minor side effects in the black pepper group included belching with a peppery odor (n = 2), abdominal warmth (n = 2), excessive sweating (n = 2), throat warmth (n = 1), generalized body warmth (n = 1), increased appetite (n = 1), and increased thirst (n = 1), which is consistent with the thermogenic and pungent properties of piperine.[34] One participant discontinued treatment at week 8 due to a persistent burning sensation in the throat and chest, which interfered with daily activities. The symptoms were assessed by clinicians as related to the intervention and resolved after discontinuation of the black pepper capsules, without the need for medication or medical treatment.

Liver and renal function markers remained within normal limits in both groups. Although AST and ALT levels were occasionally higher in the black pepper group, no significant changes from the baseline were observed. Renal function parameters, including BUN, creatinine, and eGFR, also remained stable (Table 6). These findings are consistent with previous research that found no notable hepatic or renal toxicity at moderate doses of piperine.[27,35] High doses of piperine (≥35–140 mg/kg) have demonstrated hepatotoxicity and nephrotoxicity in rodent models.[15]

Conclusion

Black pepper capsules at a dose of 500 mg/day (≈7.16 mg/day piperine) were safe and well tolerated, with no serious adverse events observed. Over the 12-week intervention, however, supplementation did not result in statistically significant improvements in lipid profiles compared to the placebo. These findings should be interpreted considering the study's limitations, including the small sample size, short duration, focus on adults with borderline hypercholesterolemia and low cardiovascular risk, and limited monitoring of diet and physical activity. Future studies with larger cohorts, longer follow-up periods, higher-risk populations, and varied piperine doses or combination regimens are warranted to better clarify the lipid-modulating potential of black pepper.

Conflicts of interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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References

1. Goff DC, Lloyd-Jones DM, Bennett G, Coady S, D'agostino RB, Gibbons R, Greenland P, Lackland DT, Levy D, O'donnell CJ, Robinson JG, Schwartz JS, Shero ST, Smith SC, Sorlie P, Stone NJ, Wilson PWF. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014;63(25 Pt B):2935-2959. Doi: 10.1016/j.jacc.2013.11.005
2. Gallo A, Le Goff W, Santos RD, Fichtner I, Carugo S, Corsini A, Sirtori C, Ruscica M. Hypercholesterolemia and inflammation—cooperative cardiovascular risk factors. Eur J Clin Invest. 2025;55(1):e14326. Doi: 10.1111/eci.14326
3. Castela Forte J, Gannamani R, Folkertsma P, Kumaraswamy S, Mount S, van Dam S, Hoogsteen J. Changes in blood lipid levels after a digitally enabled cardiometabolic preventive health program: pre-post study in an adult Dutch general population cohort. JMIR Cardio. 2022;6(1):e34946. Doi: 10.2196/34946
4. Feingold KR. Cholesterol lowering drugs. [Updated 2024 Feb 12]. In: Feingold KR, Ahmed SF, Anawalt B, Boyce A, Chushkin MI, Dungan K, Grossman A, Kalra S, McDermott MT, Pantalone KM, Sawka AM, Usher-Smith J, Witchel SF, editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK395573/

5. Zeng W, Deng H, Luo Y, Zhong S, Huang M, Tomlinson B. Advances in statin adverse reactions and the potential mechanisms: A review. J Adv Res. 2024;76:781-797. Doi: 10.1016/j.jare.2024.12.020
6. Wang D, Zhang L, Huang J, Himabindu K, Tewari D, Horbańczuk JO, Xu S, Chen Z, Atanasov AG. Cardiovascular protective effect of black pepper (*Piper nigrum* L.) and its major bioactive constituent piperine. Trends Food Sci Technol. 2021;117:34-45. Doi: 10.1016/j.tifs.2020.11.024
7. Haq IU, Imran M, Nadeem M, Tufail T, Gondal TA, Mubarak MS. Piperine: A review of its biological effects. Phytother Res. 2021; 35(2):680-700. Doi: 10.1002/ptr.6855
8. Konsue A, Taepongsorat L. Phytochemical screening and antioxidant activity of longevity remedy from national Thai traditional medicine scripture (formulary special edition). Trop J Nat Prod Res. 2022;6(6):868-871. Doi: 10.26538/tjnpr/v6i6.6
9. Shah SS, Shah GB, Singh SD, Gohil PV, Chauhan K, Shah KA, Chorawala M. Effect of piperine in the regulation of obesity-induced dyslipidemia in high-fat diet rats. Indian J Pharmacol. 2011;43(3):296-299. Doi: 10.4103/0253-7613.81516
10. Emmanuel FD, Obia O, Charles C, Okari KA, Otto JB, Reuben E, Onyeso G. Comparative assessment of red, green and black pepper species on plasma and fecal lipid profile of high-fat diet fed wistar rats. Int J Biochem Res Rev. 2025;34(1):153-163. Doi: 10.9734/ijbcrr/2025/v34i1956
11. Duangjai A, Ingkaninan K, Praputpittaya C, Limpeanchob N. Black pepper and piperine reduce cholesterol uptake and enhance translocation of cholesterol transporter proteins. J Nat Med. 2013;67(2):303-310. Doi: 10.1007/s11418-012-0682-7
12. Park UH, Jeong HS, Jo EY, Park T, Yoon SK, Kim EJ, Jeong JC, Um SJ. Piperine, a component of black pepper, inhibits adipogenesis by antagonizing PPARγ activity in 3T3-L1 cells. J Agric Food Chem. 2012;60(15):3853-3860. Doi: /10.1021/jf204514a
13. Hou X, Zhang C, Wang L, Wang K. Natural piperine improves lipid metabolic profile of high-fat diet-fed mice by upregulating SR-B1 and ABCG8 transporters. J Nat Prod. 2021;84(2):373-381. Doi: 10.1021/acs.jnatprod.0c01018
14. Vijayakumar RS, Nalini N. Lipid-lowering efficacy of piperine from *Piper nigrum* L. in high-fat diet and antithyroid drug-induced hypercholesterolemic rats. J Food Biochem. 2006;30(4):405-421.
15. Makiyah SN, Tasminatun S, Arsito PN, Fauziah KN, Nugrahanti DR, Putriani A. Subchronic toxicity of piperine in *Piper nigrum* on the histology of the kidney, liver, and lungs of mice (*Mus musculus* L.). Bali Med J. 2021;10(3):1161-1117. Doi: 10.15562/bmj.v10i3.2837
16. Chunlaratthanaphorn S, Lertprasertsuke N, Ngamjariyawat US, Jaijoy K. Acute and subchronic toxicity study of the water extract from dried fruits of *Piper nigrum* L. in rats. J Health Spec. 2007;29:109-124.
17. Intarit P, Pava KK, Itharat A, Chinsoi P. Comparative study on the efficacy and side effects of *Hibiscus sabdariffa* Linn. (*Capsicum annum*) against diverse metabolic complications. Molecules. 2023;28(18):6569. Doi: 10.3390/molecules28186569
27. Beenish B, Saxena S, Kifayat M, Shruti S. Impact of black pepper (*Piper nigrum*) powder on lipid profile parameters among subjects with non-alcoholic fatty liver disease (NAFLD). BIO Web Conf. 2025;178:02011. Doi: 10.1051/bioconf/202517802011
28. Li J, Leung SSY, Chan EHY, Jiang C, Ho ETY, Zuo Z. Significantly increased aqueous solubility of piperine via nanoparticle formulation serves as the most critical factor for its brain uptake enhancement. Int J Nanomedicine. *2025*;*20:3945-3959.* Doi: *10.2147/*IJN.S*506827*

extract versus simvastatin in reducing blood lipid levels in hyperlipidemic patients (phase II clinical trial). Thammasat Med J. 2012;12(3):506-517.
18. Santosh MK, Shaila D, Rajyalakshmi I, Rao IS. RP-HPLC method for determination of piperine from *Piper longum* Linn. and *Piper nigrum* Linn. J Chem. 2005;2(2):131-135.
19. Anderson TJ, Grégoire J, Pearson GJ, Barry AR, Couture P, Dawes M, Francis GA, Genest Jr J, Grover S, Gupta M, Hegele RA. 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):1263-1282. Doi: 10.1016/j.cjca.2016.07.510
20. Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, Goldberg AC, Gordon D, Levy D, Lloyd-Jones DM, McBride P, Schwartz JS, Shero ST, Smith SC, Watson K, Wilson PWF. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association task force on practice guidelines. J Am Coll Cardiol. 2014;63(25 Pt B):2889-2934. Doi: 10.1016/j.jacc.2013.11.002
21. D'Agostino Sr RB, Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, Kannel WB. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. Circulation. 2008;117(6):743-753. Doi: 10.1161/CIRCULATIONAHA.107.699579
22. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III) final report. Circulation. 2002;106(25):3143-421.
23. Hosseini H, Bagherniya M, Sahebkar A, Iraj B, Majeed M, Askari G. The effect of curcumin-piperine supplementation on lipid profile, glycemic index, inflammation, and blood pressure in patients with type 2 diabetes mellitus and hypertriglyceridemia. Phytother Res. 2024;38(11):5150-5161. Doi: 10.1002/ptr.8304
24. Hosseini H, Ghavidel F, Panahi G, Majeed M, Sahebkar A. A systematic review and meta-analysis of randomized controlled trials investigating the effect of the curcumin and piperine combination on lipid profile in patients with metabolic syndrome and related disorders. Phytother Res. 2023;37(3):1212-1224. Doi: 10.1002/ptr.7730
25. Du Y, Chen Y, Fu X, Gu J, Sun Y, Zhang Z, Xu J, Qin L. Effects of piperine on lipid metabolism in high-fat diet induced obese mice. J Funct Foods. 2020;71:104011. Doi: 10.1016/j.jff.2020.104011
26. Dludla PV, Cirilli I, Marcheggiani F, Silvestri S, Orlando P, Muvhulawa N, Moetlediwa MT, Nkambule BB, Mazibuko-Mbeje SE, Hlengwa N, Hanser S, Ndwandwe D, Marnewick JL, Basson AK, Tiano L. Bioactive properties, bioavailability profiles, and clinical evidence of the potential benefits of black pepper (*Piper nigrum*) and red pepper

29. Cho S, Jung Y, Rho SJ, Kim YR. Stability, bioavailability, and cellular antioxidant activity of piperine complexed with cyclic glucans. Food Sci Biotechnol. *2025*;*34(11):2475-2488.* Doi: *10.1007/*s*10068-025-01884-1*
30. Cicero AF, Fogacci F, Stoian AP, Vrablik M, Al Rasadi K, Banach M, Toth PP, Rizzo M. Nutraceuticals in the management of dyslipidemia: which, when, and for whom? Could nutraceuticals help low-risk individuals with non-optimal lipid levels? Curr Atheroscler Rep. 2021;23(10):57. Doi: 10.1007/s11883-021-00955-y
31. Feingold KR. The effect of diet on cardiovascular disease and lipid and lipoprotein levels. [Updated 2024 Mar 31]. In: Feingold KR, Ahmed SF, Anawalt B, Boyce A, Chrousos G, Dungan K, Grossman A, Hershman JM, Hofland J, Kaltsas

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G, Kopp P, Korbonits M, McLachlan R, Morley JE, Newell-Price J, Purnell J, Sahay R, Stratakis CA, Trence DL, Vinik A, Wilson JD, editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK570127/

32. Teekaput C, Thiankhaw K, Wongcharoen W, Prasertwitayakij N, Gunaparn S, Phrommintikul A. Visit-to-visit lipid variability on long-term major adverse cardiovascular events: a prospective multicentre cohort from the CORE-Thailand registry. Sci Rep. 2025;15(1):1953. Doi: 10.1038/s41598-025-85453-w
33. Bhardwaj RK, Glaeser H, Becquemont L, Klotz U, Gupta SK, Fromm MF. Piperine, a major constituent of black pepper, inhibits human P-glycoprotein and CYP3A4. J Pharmacol Exp Ther. 2002;302:645–650. Doi: 10.1124/jpet.102.034728
34. Zou R, Zhou Y, Lu Y, Zhao Y, Zhang N, Liu J, Zhang Y, Fu Y. Preparation, pungency and bioactivity transduction of piperine from black pepper (*Piper nigrum* L.): a comprehensive review. Food Chem. 2024;456:139980. Doi: 10.1016/j.foodchem.2024.139980
35. Nouri-Vaskeh M, Hashemi P, Hataminia N, Yazdani Y, Nasirian M, Alizadeh L. The impact of piperine on the metabolic conditions of patients with NAFLD and early cirrhosis: a randomized double-blind controlled trial. Sci Rep. 2024;14(1):1053. Doi: 10.1038/s41598-024-51726-z