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The effect of highly bioavailable forms of curcumin on lipoprotein(a) plasma levels: A systematic review and meta-analysis of randomized clinical studies

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ABSTRACT

Curcumin is a bioactive compound derived from the rhizome of *Curcuma longa* (turmeric) that has garnered increasing attention for its potential health benefits. However, its use in clinical practice is limited due to its generally poor bioavailability. This issue can be overcome using novel delivery systems that enhance curcumin's solubility, extend its residence time in plasma, improve its pharmacokinetic profile, and increase its cellular uptake. Novel curcumin formulations with improved bioavailability have been suggested to elevate plasma concentrations of lipoprotein(a) (Lp(a)), but there is no definitive evidence of a causal relationship. To address this, a systematic literature search was conducted in multiple electronic databases to identify relevant randomized placebo-controlled clinical studies published without a time limit. A meta-analysis of data suggested that dietary supplementation with highly bioavailable forms of curcumin significantly reduces Lp(a) levels [Standardized Mean Difference (SMD)= -0.96 (95 % Confidence Interval (CI): −1.82, −0.11)]. The effect size was robust in the leave-one-out sensitivity analysis and was not primarily driven by any single study. Of course, the clinical significance of this observation should be more thoroughly evaluated in longer-term trials, where the combined metabolic and anti-inflammatory effects of curcumin have vascular protective effects.

1. Introduction

Curcumin, chemically known as diferuloylmethane or [1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione], is a bioactive compound derived from the rhizome of *Curcuma longa* (turmeric). It has garnered increasing attention for its potential health benefits, particularly its effects on lipid metabolism [1]. The molecular mechanisms through which curcumin exerts its lipid-lowering effects are numerous and not yet fully understood. Studies has shown that curcumin down-regulates the expression of key enzymes involved in lipid synthesis, such as fatty acid synthase (FAS) and acetyl-CoA carboxylase (ACC). Moreover, it upregulates the expression of the low-density lipoprotein (LDL) receptor (LDLR) on hepatocytes [2]. Curcumin also promotes lipid oxidation by activating peroxisome proliferator-activated receptor gamma (PPAR-γ) and increasing the expression of genes involved in fatty acid β-oxidation [3,4]. Preclinical investigations suggest that curcumin reduces total cholesterol (TC), triglycerides (TG), and LDL cholesterol (LDL-C), while increasing high-density lipoprotein cholesterol (HDL-C) [5]. Similar effects have been observed in humans, although the magnitude of effects varies across clinical studies, depending on the daily dose of curcumin and its bioavailability, which is generally poor due to limited intestinal absorption, extensive reductive and conjugative metabolism in the liver, and biliary excretion [6]. The poor bioavailability is further exacerbated by curcumin binding to

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enterocyte proteins, which can modify its structure [7]. Currently, this issue can be overcome using novel delivery systems that enhance curcumin's solubility, extend its residence in plasma, improve its pharmacokinetic profile, and increase its cellular uptake [8,9]. A meta-analysis of 20 randomized clinical trials, pooling data from 1427 individuals, has recently concluded that curcumin supplementation significantly improves plasma levels of TG (weighted mean difference (WMD): −21.36 mg/dL, 95 % Confidence Interval (CI): −32.18, −10.53, $P < 0.001$) and HDL-C (WMD: 1.42 mg/dL, 95 % CI: 0.03, 2.81, $P < 0.05$), without affecting LDL-C and TC (LDL-C: WMD: −5.82 mg/dL, 95 % CI: −15.80, 4.16, $p = 0.253$; TC: WMD: −9.57 mg/dL, 95 % CI: −20.89, 1.75, $P = 0.098$) [10]. However, according to available evidence, a significant effect on TC and LDL-C has been documented when nanoemulsion delivery systems are used [11]. Further evidence suggests that novel curcumin formulations with improved bioavailability could also improve plasma concentrations of lipoprotein(a) (Lp(a)) [12], whose elevated levels are an independent risk factor for atherosclerotic cardiovascular disease (ASCVD) and calcific valvular aortic stenosis [13]. This is particularly noteworthy because, to the best of current knowledge, lifestyle interventions have minimal effects on Lp(a) [14], with only levocarnitine and coenzyme Q10 (CoQ10) showing the ability to significantly reduce Lp(a) in humans [15,16]. In this context, we conducted a systematic review and meta-analysis of the available double-blind, placebo-controlled randomized clinical trials testing the effect of high-availability curcumin supplementation on plasma Lp(a) levels.

2. Materials and methods

This systematic review and meta-analysis were conducted in accordance with the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [17] (see the Supplementary Material for the PRISMA Checklist). The study protocol was prospectively registered in the PROSPERO database (CRD42023138724). Ethical approval was not required, as no new participants were recruited, and only previously published data were analyzed.

2.1. Search strategy

Web of Science, PubMed-MEDLINE, and Scopus were systematically searched without applying any filters (e.g., no date restriction) from inception to October 30, 2023. Google Scholar was also included to capture a broader range of relevant studies, including those that may not be indexed in other databases. Although it has limitations compared to Web of Science, PubMed-MEDLINE, and Scopus -such as the lack of advanced filtering options and inconsistent indexing- its inclusion ensured a more comprehensive search and reduced the risk of missing relevant studies.

To minimize language bias, no language restrictions were applied during the search process. As a result, both English and non-English studies were considered for inclusion in the meta-analysis. However, for studies published in languages other than English, only those with accessible abstracts or full texts available in English were included to ensure accurate data extraction and analysis.

The following search terms were used in various combinations: "curcumin", "turmeric", "curcuma", "Curcuma longa", "C. longa", "curcuminoids", "lipoprotein(a)", "Lp(a)", "intervention", "clinical trial" and "clinical study". Truncation and Boolean operators ("AND", "OR", "*") were employed to enhance the sensitivity of the search strategy (the exact search strings used for each database are provided in the supplementary materials). The reference list of all included studies was manually checked for additional relevant articles. All abstracts were independently screened by two authors (F.F. and M.G.) to exclude ineligible studies, and the remaining full-text articles were assessed by the same authors, who also conducted data extraction and quality assessment. Any disagreements were initially resolved through discussion between F.F. and M.G., and if consensus could not be reached, the Principal Investigator (A.F.G.C.) was consulted to make the final decision.

2.2. Criteria for studies eligibility

The comprehensive Population, Intervention, Comparison, Outcomes and Study (PICOS) selection criteria are presented in Table 1.

Original studies were included if they met the following criteria: (i) they were double-blind clinical trials with either a multicenter or single-center design; (ii) they were conducted in accordance with the Helsinki Declaration and its amendments; (iii) they employed an appropriate controlled design for dietary curcumin supplementation; and (iv) they investigated the effect of curcumin on Lp(a). Studies were excluded if they lacked of sufficient information on Lp(a) levels at baseline and/or follow-up, as these data were necessary to calculate effect sizes.

2.3. Data extraction

The data extracted from the eligible studies included the following: (i) first author's name; (ii) year of publication; (iii) study design; (iv) study location; (v) main inclusion and exclusion criteria; (vi) curcumin formulation and daily dose tested; (vii) duration of dietary supplementation; (viii) number of participants enrolled; (ix) sex distribution; and (x) mean age of participants.

2.4. Risk of bias assessment

The risk of bias in the included randomized controlled trials was systematically assessed using Version 2 of the Cochrane Risk of Bias tool for randomized trials (RoB 2), which evaluates the following domains: randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result [18]. Two authors (F.F. and M.G.) independently performed the risk-of-bias assessment [19]. Any disagreements were resolved by consensus, which involved discussing the rationale behind each author's judgment and reviewing the study's methodology in detail. If consensus could not be reached, the Principal Investigator (A.F.G.C.) was consulted to make the final decision.

2.5. Data synthesis

Data were pooled and analyzed using Comprehensive Meta-Analysis (CMA) Version 4 (Biostat, NJ) [20], considering the intention-to-treat

Table 1
The PICOS framework summarizes the rationale behind the meta-analysis and outlines the criteria for the included clinical trials.

Category	Inclusion criteria	Exclusion criteria
Population	• Adult participants (aged ≥18 years)	
Intervention	• Dietary supplementation with highly bioavailable forms of curcumin	
Comparison	• Placebo	
Outcome measure	• Change in Lp(a) levels	• Lack of sufficient information about Lp(a) at baseline and/or at follow-up
Study type	• Randomized, double-blind clinical studies with either multicentre or single-centre design • Trials conducted in accordance with the Helsinki Declaration and its amendments*	

Lp(a)= Lipoprotein(a).
* This was ensured by reviewing the ethical approval statements provided in the included studies.

(ITT) population. Change scores were calculated accordingto the protocol registered in the PROSPERO database [21]. The study findings were combined using a random-effects model [22]. The inter-study heterogeneity was quantitatively assessed using the Higgins' I^2 index, and it was considered high when exceeding 50 % [23]. To explore potential sources of heterogeneity and evaluate the robustness of the results, a sensitivity analysis was performed [24].

The standardization of Lp(a) measurements across studies was achieved by expressing the effect size as the standardized mean difference (SMD) with 95 % CI [25]. This approach was used to account for variability in Lp(a) measurements, as different assays were used across the studies [26]. Furthermore, plasma samples were sometimes fresh, while in other times they had been frozen for extended periods before measurement [27].

Two-sided P-values < 0.05 were considered statistically significant.

2.6. Publication biases

Rosenthal's fail-safe N test was conducted to estimate the number of additional "negative" studies required to raise the P-value of the meta-analysis above 0.05 [28].

2.7. Certainty of evidence

The certainty of the current evidence regarding the effect of highly bioavailable forms of curcumin on Lp(a) (that is, the likelihood that the true effect lies within the 95 %CI) was assessed using the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) approach [29]. The following domains were considered: study limitations, indirectness, imprecision, inconsistency, and publication bias.

3. Results

3.1. Flow of literature and characteristics of the included studies

After conducting database searches and assessing eligible studies, 3 articles were included in the meta-analysis. The study selection process is illustrated in the PRISMA flow chart (Fig. 1).

Data were pooled from 3 clinical trials comprising 6 treatment arms (3 with active treatment and 3 with placebo), including a total of 264 participants (132 in the active treatment arms and 132 in the control arms).

The eligible studies were published between 2014 and 2023 and evaluated various curcumin formulations with enhanced bioavailability.

Follow-up durations ranged from 8 to 12 weeks. The main characteristics of the included studies are summarized in Table 2.

3.2. Risk of bias assessment

All the studies included in the meta-analysis provided sufficient information regarding the randomization process, deviations from

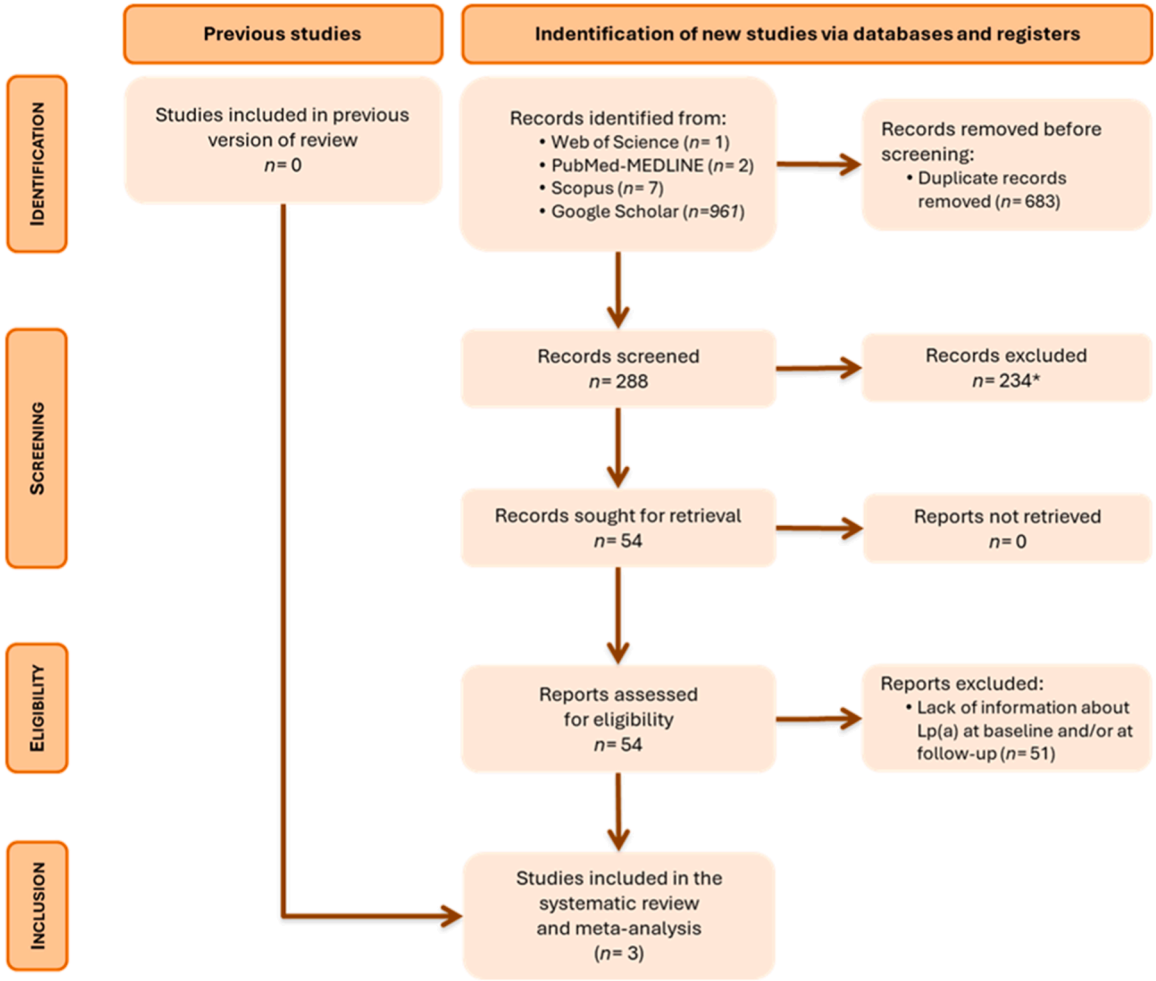

Fig. 1. PRISMA flow chart showing the number of studies identified and included into the meta-analysis. * 234 records screened were excluded after abstract review because the data did not meet the search criteria.

Table 2
Key characteristics of the studies included in the meta-analysis.

First author, year	Study design	Location	Main inclusion criteria	Curcumin formulation (daily dose)	Duration of dietary supplementation	Study groups	Number of enrolled individuals (n.)	Sex (Men / Women)	Age (years; mean ± SD)	BMI (Kg/m2; mean ± SD)
Dastani, 2023 [30]	Randomized, double-blind, placebo-controlled, clinical study	Iran	– Type 2 Diabetes – Mild to moderate CAD (<70 % stenosis in angiography)	Nano micelles containing curcumin (80 mg)	90 days	Curcumin	32	11 / 21	60 ± 7.2	26.2 ± 3.9
						Placebo	32	14 / 18	60.5 ± 10.6	26.7 ± 3.9
Panahi, 2017 [31]	Randomized, double-blind, placebo-controlled clinical study	Iran	– 18–65 years of age – Type 2 Diabetes Mellitus	Curcuminoids (1000 mg) + piperine (10 mg biopiperine®)	12 weeks	Curcumin	50	25 / 25	43 ± 8	26.5 ± 2.3
						Placebo	50	26 / 24	41 ± 7	27.3 ± 1.6
Panahi, 2014 [32]	Randomized, double-blind, placebo-controlled clinical study	Iran	– 25–75 years of age – Metabolic Syndrome (based on NCEP-ATP III guidelines)	Curcuminoids (1000 mg) + piperine (10 mg biopiperine®)	8 weeks	Curcumin	50	23 / 27	44.8 ± 8.7	25.5 ± 2.5
						Placebo	50	27 / 23	43.5 ± 9.7	22.8 ± 5.4

*the standard deviation is not available. BMI= Body mass index; CAD= Coronary artery disease; *n.*= Number of individuals; NCEP-ATP III= National Cholesterol Education Program Adult Treatment Panel III; SD= Standard deviation.

intended interventions, missing outcome data, and outcome measurement (Table 3).

Other potential sources of bias were identified concerning pre-analytical sample handling (i.e., sample collection and storage) and Lp(a) measurement methods. In particular, variability in assays and plasma sample conditions could introduce bias into the results. Different assays used across studies may have varying sensitivities, specificities, and measurement techniques, which could affect the consistency of Lp(a) data [26]. Additionally, the condition of plasma samples—whether they were fresh or had been frozen for extended periods before measurement—could influence the accuracy and reliability of Lp(a) measurements [27]. To address these concerns and standardize Lp(a) measurements across studies, the effect size was expressed as the SMD with 95 % CI [25]. This helped mitigate the impact of assay variability and sample conditions on the overall analysis. Despite these efforts, some residual risk of bias may still remain due to the inherent differences in the methods used in the included studies.

3.3. Impact of curcumin on Lp(a)

The pooled analysis indicated that dietary supplementation with curcumin significantly reduced Lp(a) [SMD= -0.96 (95 %CI: −1.82, −0.11); I^2= 90.6 %] (Fig. 2).

The true effect size varied across studies, ranging from −11.6–9.7 for each study (Fig. 3).

Moreover, the effect size was robust in the leave-one-out sensitivity analysis and was not primarily influenced by a single study (Fig. 4).

Rosenthal's fail-safe N test suggested that 38 studies with negative results would be needed to bring the estimated effect size to a non-significant level ($P > 0.05$).

The certainty of the evidence was assessed as moderate to high despite the presence of some concerns regarding study limitations (Table 4).

4. Discussion

The use of curcumin in the prevention and management of various diseases in humans faces several challenges that hinder its widespread application in clinical practice. One of the main obstacles is its high hydrophobicity and limited water solubility, which significantly affect its bioavailability. The poor solubility of curcumin reduces its absorption into plasma and target tissues, thereby limiting its effectiveness. Furthermore, curcumin undergoes rapid metabolism, further decreasing its bioavailability and shortening its half-life. Curcumin is highly sensitive to light and has limited chemical stability during both manufacturing and storage processes [33]. It exhibits keto-enol tautomerism, which is pH-dependent. At pH values below 7, the keto form predominates, while at pH above 7, the enol form is more prevalent [34]. Curcumin's molecular behavior is characterized by three distinct pKa values: the first (pKa 7.7–8.5) and second (pKa 8.5–10.4) values are associated with the phenolic hydroxy groups, while the third (pKa 9.5–10.7) corresponds to the enolic proton [35]. Although curcumin remains chemically within the pH range of 1–6, its solubility in water is virtually nonexistent in this range. Autoxidation reactions occurring at physiological pH levels result in the formation of bicyclopentadione products, where the 7-carbon chain undergoes oxygenation and double cyclization [36]. Another, albeit minor, degradation pathway occurs in alkaline environments, where curcumin transforms into

Table 3
Outcomes of the RoB-2 assessment of the included studies.

First author, year	Bias arising from the randomization process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported results
Dastani, 2023 [30]	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	Unclear risk of bias
Panahi, 2017 [31]	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	High risk of bias
Panahi, 2014 [32]	Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	High risk of bias

RoB-2= Risk-of-bias 2.

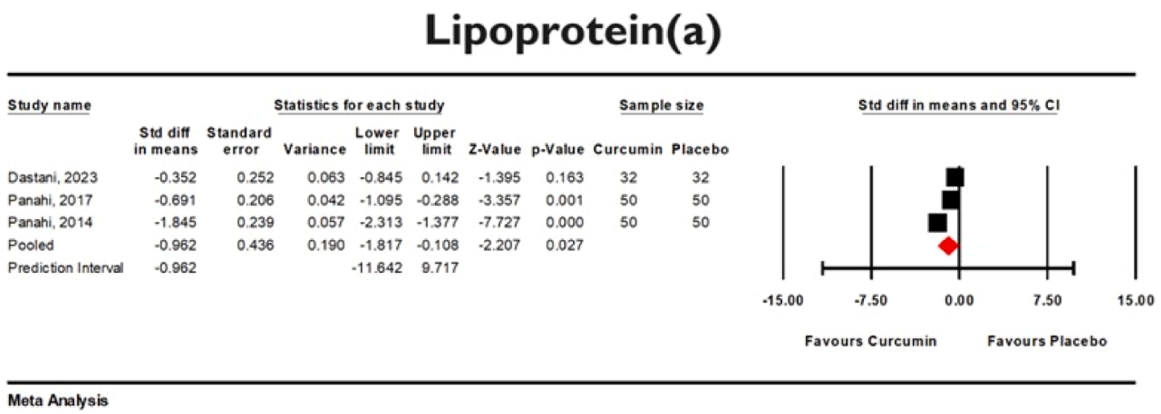

Fig. 2. Forest plot displaying the SMD and 95 %CI for the impact of dietary curcumin supplementation on serum Lp(a) concentrations. The plot shows a significant effect of curcumin in reducing Lp(a) levels, with high heterogeneity observed among the included studies.

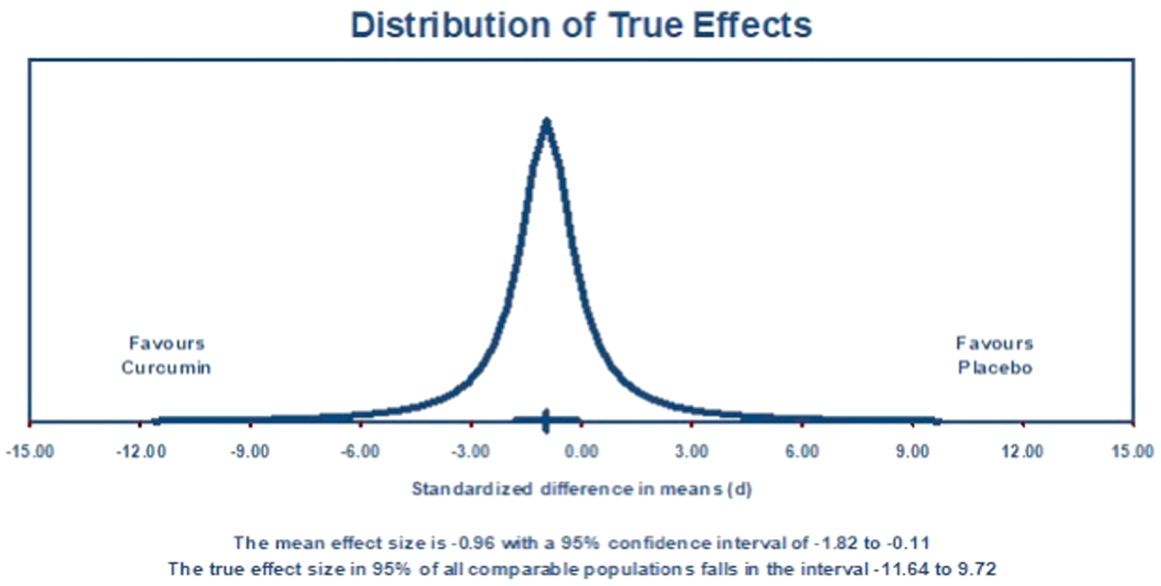

Fig. 3. Distribution of the true effect sizes across individual studies. The plot illustrates the range of effect sizes, which varied from −11.6–9.7, highlighting the variability in the impact of curcumin supplementation on Lp(a) levels among the studies included in the meta-analysis.

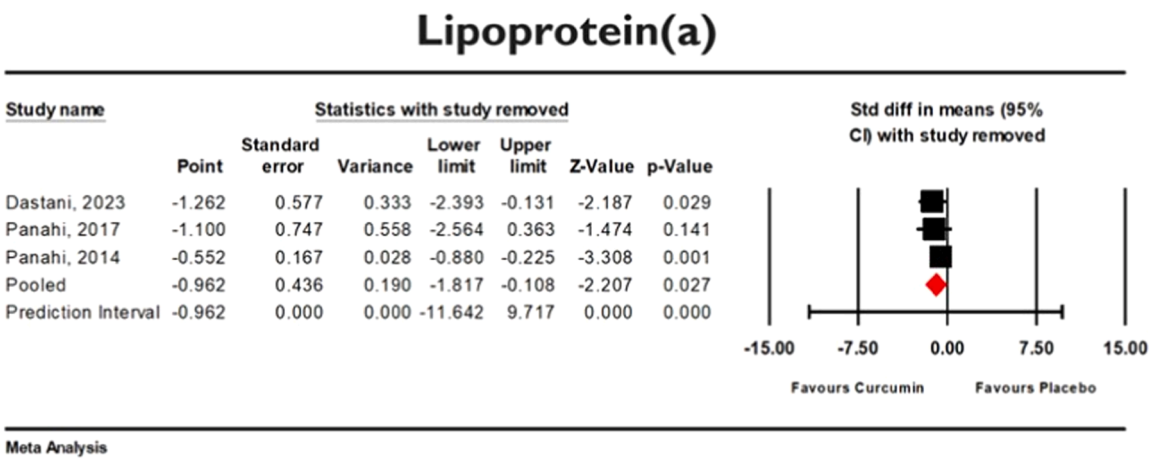

Fig. 4. Leave-one-out sensitivity analysis showing the robustness of the overall effect size. The plot illustrates that the effect size remains consistent even when each individual study is excluded, suggesting that no single study had a disproportionate influence on the results of the meta-analysis.

Table 4
Grading the quality of studies for assessment using the standardized GRADE approach.

Domains	Risk of bias	Imprecision	Incostistency	Indirectness	Publication bias
Level of initial evidence certainty	Moderate	High	High	High	Moderate

trans-6-(4'-hydroxy-3'-methoxyphenyl)-2,4-dioxo-5-hexenal, which subsequently degrades into vanillin, ferulic acid, and feruloyl-methane. The stability of curcumin is closely lied to the undissociated form of its hydroxy groups [37]. Furthermore, its poor bioavailability is further compromised by its binding to enterocyte proteins, which can alter its structure [38]. Curcumin undergoes an alternative metabolic pathway mediated by intestinal microbiota, including *Escherichia coli* and *Blautia* sp. Specifically, *Escherichia coli* exhibits activity through an NADPH-dependent reductase, catalyzing a two-step reduction process that converts curcumin to dihydrocurcumin, and subsequently to tetrahy-drocurcumin [39]. Additionally, oxidative degradation and modifications can be induced by light absorption, leading to photo-degradation reactions that significantly alter curcumin's structure and properties, thereby impacting its pharmacokinetic and pharmacody-namic characteristics [40]. To address these challenges, researchers have turned to nanotechnology, utilizing various types of nanoparticles (NPs) such as liposomes, niosomes, and gold nanoparticles, to enhance curcumin's solubility and bioavailability [41]. Various nanocarriers based on chitosan, each with unique characteristics for curcumin de-livery, have been developed. These carriers include, but are not limited to, self-assembled nanoparticles, nanocomposites, nanoemulsions, nanotubes, and nanofibers [42]. Some researchers have also explored the use of exosomes to enhance curcumin bioavailability [43]. Piperine, a natural alkaloid found in black pepper (*Piper nigrum*), is known for its ability to modify the disposition and bioavailability of curcumin. It acts as a potent inhibitor of biotransformation, particularly glucuronidation. When combined with curcumin, a synergistic effect was observed, with a 2 g dose of curcumin plus 5 mg of piperine resulting in a remarkable three-fold increase in bioavailability compared to pure curcumin [44]. For these reasons, we focused on studies testing only highly bioavailable forms of curcumin.

This meta-analysis synthesizes data from three randomized, double-blind, controlled clinical studies, providing evidence that dietary sup-plementation with curcumin can lead to a reduction in Lp(a) plasma levels. Observational studies suggest that only reductions of Lp(a) by 80–90 % are likely to result in a meaningful improvement in the risk of ASCVD [45]. Therefore, the prognostic significance of our findings re-mains uncertain. Nonetheless, our results open up promising avenues for the development of novel Lp(a)-targeted therapies with innovative mechanisms of action.

To date, managing individuals with elevated Lp(a) levels remains challenging. Adherence to a healthy lifestyle has been shown to have a minimal impact on blood Lp(a) concentrations, although it is associated with improved cardiovascular health (CVH) out-comes, even in patients with elevated plasma Lp(a) levels [46,47]. In this context, a dose-response relationship was observed between plasma Lp(a) con-centrations and physical activity in a large multicenter study of Finnish children and young adults (n = 2464) [48].

There is insufficient evidence to support the use of nutraceuticals or functional foods to alter Lp(a). A low carbohydrate, high fat diet may decrease Lp(a) levels by 10–15 %, despite raising LDL-C, according to findings from the DELTA (Dietary Effects on Lipoproteins and Throm-bogenic Activity) Program [49,50]. These observations have been further corroborated by several reports, which show that increases in Lp (a) occur when saturated fatty acids (SFA) are replaced with mono-unsaturated fatty acids (MUFA) or a combination of MUFA and poly-unsaturated fatty acids (PUFA) [51,52]. Moreover, plasma Lp(a) levels are likely influenced by coffee consumption, with significant interindi-vidual variability depending on the coffee source, preparation method, and the dose and duration of consumption [53]. Short-term coffee consumption tends to reduce Lp(a), while habitual coffee drinking is associated with increased Lp(a) levels [53]. Dietary supplementation with L-carnitine and coenzyme Q10 (CoQ10) has also been shown to mildly improve Lp(a) levels [54]. However, prolonged-release (PR) nicotinic acid remains the only agent proven to reduce Lp(a) by 20–30 %, although its use in clinical practice is limited by poor tolera-bility and the lack of clear evidence that it reduces long-term ASCVD burden [55,56]. The antisense oligonucleotide Mipomersen can also reduce Lp(a), but concerns about its liver safety have been raised [57]. Additionally, Lp(a) levels can be reduced by cholesterol ester transfer protein (CETP) inhibitors [58], although none of these drugs have been associated with ASCVD risk reduction.

The effect of curcumin supplementation on plasma Lp(a) levels can be explained by its regulation of several key targets involved in lipid metabolism and homeostasis, including LDLR, Niemann-Pick C1-Like 1 protein (NPC1L1), sterol regulatory element-binding protein 1 (SREBP-1), apolipoprotein B-100, peroxisome proliferator-activated receptor-α (PPAR-α), and fatty acid synthase (FAS) [59]. Curcumin also enhances cell-surface LDLR expression and promotes LDL uptake by down-regulating the proprotein convertase subtilisin/kexin type 9 (PCSK9) gene expression through a sterol-responsive element binding protein (SREBP)-independent pathway [60], ultimately reducing Lp(a) in a manner similar to the PCSK9 inhibitors Evolocumab and Alirocumab [12,20]. Furthermore, it should be acknowledged that in both the FOURIER (Further Cardiovascular Outcomes Research with PCSK9 In-hibition in Subjects with Elevated Risk) and the ODYSSEY OUTCOMES (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syn-drome During Treatment With Alirocumab) trials, improvements in Lp (a) plasma levels were associated with significant reductions in ASCV events regardless of LDL-C levels [61].

Apart from its direct effects on lipid metabolism, curcumin's anti-inflammatory and antioxidant properties may indirectly contribute to improved lipid profiles [62]. Chronic inflammation and oxidative stress are implicated in lipid dysregulation, and curcumin's ability to mitigate these factors may play a role in its lipid-lowering effects [63]. Unfor-tunately, a significant drawback is curcumin's low oral bioavailability, although several strategies have been attempted to overcome this issue [64]. These include the use of adjuvants and liposomal formulations, phospholipid complexes, and curcumin nanoparticles [65]. Addition-ally, in humans, the co-administration of curcumin and piperine en-hances curcumin's oral bioavailability of curcumin by 2000 % within 45 minutes [66]. Piperine has several molecular targets, including PPAR-γ, nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), adenosine monophosphate-activated protein kinase (AMPK), c-Jun N-terminal kinase (JNK) and inflammatory cytokines [67]. Furthermore, piperine inhibits intestinal and hepatic glucuronidation, increases intestinal perfusion and enterocyte permeability, and reduces the activity of glucuronidase enzymes without any adverse effects [68].

However, the interpretation of outcomes is limited by the presence of heterogeneity across studies. Based on the pre-specified selection criteria, the meta-analysis included relatively few clinical trials with small sample sizes. This is because, although a large number of ran-domized clinical trials have investigated the effects of curcumin on plasma lipids, Lp(a) has almost never been assessed. The studies inves-tigating the effect of curcumin on Lp(a) plasma levels were largely ho-mogenous in terms of the types of pharmaceutical formulations tested. It must also be noted that all the studies included in the present meta-analysis enrolled individuals from Iran, limiting the generalizability of the conclusions to other populations. However, this homogeneity may reduce variability due to differences in behavioral habits or genetic

polymorphisms that could influence the effect of curcumin on Lp(a) levels. Another limitation is that the studies did not report data by sex, making the final observations harder to interpret. Evidence suggests that sex can impact the pharmacokinetics of curcumin [69,70], which factors such as enhanced clearance in men due to increased liver drug efflux transporter activity, and higher body fat levels in women [71]. Nevertheless, both sexes were equally represented in the trials considered, so no significant sex-related unbalance is expected. Finally, it is important to note that the clinical studies included in this meta-analysis were predominantly short-term in nature. As a result, the observed effects of highly bioavailable curcumin supplementation on Lp(a) cannot be definitively linked to any clinical outcomes, such as reductions in cardiovascular events or mortality. The relatively brief duration of these studies limits the ability to assess the long-term benefits or potential risks of curcumin supplementation. While curcumin shows promise in lowering Lp(a) levels, further long-term studies are required to determine whether this translates into meaningful clinical improvements. Notably, despite extensive research, no dietary supplement or pharmaceutical intervention has yet been conclusively proven to improve cardiovascular outcomes by reducing Lp(a) levels. This highlights the need for continued exploration of novel Lp(a)-targeted therapies, particularly those that could offer sustained benefits over time and address the limitations of current treatments. Our findings point to new avenues for research aimed at developing Lp(a)-lowering drugs that do not target LPA messenger ribonucleic acid (mRNA).

5. Conclusions

Dietary supplementation with highly bioavailable curcumin has shown potential in reducing Lp(a) plasma levels in humans. Although these findings are promising, clinical relevance remains uncertain, as the long-term effects have not been fully explored. Many studies conducted thus far have been short-term, limiting the ability to establish a direct link between Lp(a) reduction and clinical outcomes such as cardiovascular events or mortality. Therefore, further investigation through long-term clinical trials is necessary to determine whether curcumin supplementation can yield lasting clinical benefits. Despite these uncertainties, the current evidence raises intriguing possibilities for the development of novel Lp(a)-targeted therapies. If curcumin proves effective in reducing Lp(a) levels, it could offer a new approach to managing cardiovascular risk, especially since current treatments for elevated Lp(a) are limited. Further research is crucial to better understand the mechanisms behind curcumin's effects and to assess its potential as a therapeutic option for cardiovascular disease.

CRediT authorship contribution statement

Cicero Arrigo Francesco Giuseppe: Writing – original draft, Supervision, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Cesaro Arturo:** Writing – review & editing, Methodology, Investigation, Data curation. **Bernardi Marco:** Writing – review & editing, Visualization, Investigation, Data curation. **Perone Francesco:** Writing – review & editing, Methodology, Investigation, Data curation. **Giovannini Marina:** Writing – original draft, Methodology, Investigation, Data curation. **Fogacci Federica:** Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Avagimyan Ashot:** Writing – original draft, Visualization, Investigation, Data curation.

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Declaration of Competing Interest

The authors declare no conflict of interest.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.prostaglandins.2025.106994.

Data availability

Data will be made available on request.

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