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Curcumin Ameliorates Endothelial Dysfunction Through Attenuation of Oxidative Stress: A Systematic Review and Meta-Analysis of Animal Studies

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Artikel Review

Abstract: *Endothelial dysfunction is an early mechanism in cardiovascular disease and is closely linked to oxidative stress induced impairment of Nitric Oxide (NO) signaling. Curcumin, a bioactive polyphenol from Curcuma longa, exhibits antioxidant and vasoprotective properties. However, its mechanistic effects in preclinical models have not been quantitatively synthesized. This study evaluated the effects of curcumin on endothelial function and oxidative stress–related outcomes in animal models. A systematic search of PubMed, Embase, Scopus, and Web of Science was conducted according to PRISMA 2020 guidelines. Preclinical in vivo and ex vivo studies assessing curcumin monotherapy were included. Pooled standardized mean differences (SMDs) were calculated using a random-effects model. Risk of bias was assessed using SYRCLE, and certainty of evidence was evaluated using GRADE. Sixteen studies were included. Curcumin improved Endothelium-Dependent Vasodilation (EDV) (SMD = 1.44, 95% CI: 1.13 to 1.76, I^2 = 46%), increased endothelial Nitric Oxide Synthase (eNOS) expression or activity (SMD = 1.33, 95% CI: 0.75 to 1.90, I^2 = 68%), and enhanced NO levels (SMD = 1.15, 95% CI: 0.79 to 1.50, I^2 = 0%). It reduced superoxide (SMD = −2.14, 95% CI: −2.88 to −1.41, I^2 = 76%) and Malondialdehyde (MDA) (SMD = −1.65, 95% CI: −2.10 to −1.19, I^2 = 55%). Moderate to substantial heterogeneity was observed. SYRCLE indicated some concerns, and overall certainty was very low. Curcumin may ameliorates endothelial dysfunction via oxidative stress attenuation and restoration of NO signaling. However, these findings require confirmation in rigorously designed clinical studies.*

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Keywords: Curcumin, Endothelium-Dependent Vasodilation, Endothelial Dysfunction, Nitric Oxide, Oxidative Stress

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Abstrak: Disfungsi endotel merupakan mekanisme awal pada penyakit kardiovaskular dan berkaitan erat dengan gangguan sinyal *Nitric Oxide* (NO) yang dipicu oleh stres oksidatif. Kurkumin, suatu polifenol bioaktif yang berasal dari Curcuma longa, memiliki sifat antioksidan dan vasoprotektif. Namun, efek mekanistiknya pada model praklinis belum disintesis secara kuantitatif. Penelitian ini mengevaluasi efek kurkumin terhadap fungsi endotel dan luaran yang berkaitan dengan stres oksidatif pada model hewan. Pencarian sistematis dilakukan pada basis data PubMed, Embase, Scopus, dan Web of Science sesuai dengan pedoman PRISMA 2020. Studi praklinis in vivo dan ex vivo yang menilai monoterapi kurkumin dimasukkan dalam analisis. Perbedaan rerata terstandarisasi (standardized mean differences / SMD) yang digabungkan dihitung menggunakan model efek acak (random-effects model). Risiko bias dinilai menggunakan SYRCLE, dan tingkat kepastian bukti dievaluasi menggunakan GRADE. Sebanyak 16 studi dimasukkan dalam analisis. Kurkumin meningkatkan *Vasodilatasi Dependen Endotel* (EDV) (SMD = 1,44; 95% CI: 1,13 hingga 1,76; I^2 = 46%), meningkatkan ekspresi atau aktivitas endothelial *Nitric Oxide Synthase* (eNOS) (SMD = 1,33; 95% CI: 0,75 hingga 1,90; I^2 = 68%), serta meningkatkan kadar NO (SMD = 1,15; 95% CI: 0,79 hingga 1,50; I^2 = 0%). Kurkumin juga menurunkan kadar superoksida (SMD = −2,14; 95% CI: −2,88 hingga −1,41; I^2 = 76%) dan *Malondialdehyde* (MDA) (SMD = −1,65;

95% CI: −2,10 hingga −1,19; I^2 = 55%). Heterogenitas sedang hingga tinggi ditemukan dalam beberapa analisis. Penilaian SYRCLE menunjukkan adanya beberapa kekhawatiran terhadap risiko bias, dan tingkat kepastian bukti secara keseluruhan dinilai sangat rendah. Kurkumin berpotensi memperbaiki disfungsi endotel melalui penurunan stres oksidatif dan pemulihan jalur pensinyalan NO. Namun, temuan ini masih memerlukan konfirmasi melalui studi klinis yang dirancang secara lebih ketat.

Kata kunci: Disfungsi Endotel, Kurkumin, Nitric Oxide (NO), Stres Oksidatif, Vasodilatasi Dependen Endotel

Introduction

Endothelial dysfunction is a pivotal early event in the development and progression of cardiovascular disease (CVD) and is strongly associated with increased global morbidity and mortality (1-4). Under physiological conditions, the endothelium preserves vascular homeostasis by regulating vascular tone, platelet aggregation, leukocyte adhesion, and smooth muscle cell proliferation through a balanced release of vasodilatory and vasoconstrictive mediators (5, 6). Among these factors, nitric oxide (NO), synthesized by endothelial nitric oxide synthase (eNOS), plays a central role in endothelium-dependent vasodilation (EDV) and exerts critical vasoprotective effects (7, 8).

Oxidative stress is a central driver of endothelial dysfunction. Excessive production of reactive oxygen species (ROS), particularly superoxide anions, diminishes NO bioavailability through direct scavenging and promotes eNOS uncoupling, ultimately disrupting endothelial signaling pathways (9-13). In addition, lipid peroxidation byproducts such as malondialdehyde (MDA) aggravate endothelial injury and vascular inflammation, thereby perpetuating a self-amplifying cycle between oxidative stress and endothelial impairment (14). Accordingly, therapeutic approaches aimed at reducing oxidative stress and restoring NO signaling have emerged as promising strategies for the prevention and management of vascular diseases (15).

Curcumin, a bioactive polyphenolic compound isolated from *Curcuma longa*, has been widely investigated for its antioxidant, anti-inflammatory, and vasoprotective effects (16, 17). Preclinical studies indicate that curcumin exerts potent antioxidant activity by scavenging ROS, suppressing lipid peroxidation, and modulating redox-sensitive signaling pathways involved in endothelial homeostasis, notably nuclear factor-κB (NF-κB) and nuclear factor erythroid 2–related factor 2 (Nrf2) pathways (9, 18, 19). Furthermore, curcumin has been reported to upregulate eNOS expression and/or activity, thereby enhancing NO bioavailability and improving vascular reactivity (20).

Several systematic reviews and meta-analyses of randomized controlled trials (RCTs) indicate that curcumin supplementation improves flow-mediated dilation (FMD), although its effects on other vascular markers remain inconsistent (21-23). Umbrella reviews also report favorable modulation of oxidative stress biomarkers, including reduced MDA levels (24). However, these findings rely mainly on surrogate clinical endpoints and do not clarify tissue-level endothelial mechanisms (25). Moreover, heterogeneity in study design and curcumin formulations limits causal interpretation (26, 27). Consequently, the mechanistic and translational significance of curcumin's vascular effects remains insufficiently established without a comprehensive synthesis of preclinical evidence.

Preclinical studies provide a controlled framework to investigate the mechanistic effects of curcumin on endothelial dysfunction; however, heterogeneity in experimental designs has limited definitive conclusions. To date, no systematic review and meta-analysis has quantitatively synthesized preclinical evidence focusing on oxidative stress–related mechanisms. Therefore, this study aimed to systematically review and meta-analyze preclinical animal data to evaluate the effects of curcumin on endothelial function, nitric oxide signaling, and oxidative stress markers, thereby clarifying its mechanistic and translational relevance.

Methods

Literature Search Strategy

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines (Supplementary Table 1), and was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO) under registration number CRD420251237662 (28). A comprehensive literature search was performed in PubMed, Embase, Scopus, and Web of Science to identify relevant studies published up to October 2025. The search strategy was designed to capture preclinical animal studies evaluating the effects of curcumin on endothelial dysfunction. Free-text keywords were used without applying Medical Subject Headings (MeSH) or other controlled vocabulary terms. The search query was as follows : ("Curcumin" OR "curcumin" OR "diferuloylmethane") AND ("Endothelium, Vascular" OR "Endothelial Cells" OR "Endothelial Dysfunction" OR "endothelial function" OR "vascular function" OR "endothelium-dependent vasodilation") AND ("Animals" OR "animal") (Supplementary Table 2). Grey literature sources were not included, and no manual screening of reference lists from eligible studies or relevant reviews was conducted.

Inclusion and Exclusion Criteria

All studies retrieved through the literature search were imported into the Rayyan web-based systematic review tool for duplicate removal and study screening (29). Study selection was conducted according to predefined eligibility criteria in Table 1. Only original English-language preclinical animal studies investigating the effects of curcumin on endothelial dysfunction were considered.

Table 1. Inclusion and Exclusion Criteria

Component	Inclusion Criteria	Exclusion Criteria
Population	Animal models with induced endothelial dysfunction (in vivo or ex vivo)	Human subjects or in vitro cell models
Intervention	Curcumin administered as a single compound	Combination therapy or modified formulations of curcumin
Comparator	Any control group (placebo, vehicle, untreated)	No appropriate control group
Outcomes	Endothelial function–related parameters (EDV, eNOS, NO, oxidative stress markers)	No direct assessment of endothelial function
Study Design	Original experimental studies	Reviews, conference abstracts, editorials
Language	English	Non-English publications
Data Availability	Quantitative data sufficient for meta-analysis	Insufficient extractable data

Data Extraction

Data extraction was independently performed by two reviewers. The collected data comprised publication year and country, baseline animal characteristics, animal weight, disease model, intervention details (including control conditions), and treatment duration. Outcome variables, along with mean values, measures of dispersion (e.g., SD or SEM), and p-values, were also recorded for meta-analytic purposes. When numerical data were not explicitly reported, values were obtained by digitizing graphical data using the figure calibration plugin in ImageJ and subsequently incorporated into the meta-analysis.

Quality Assessment

The risk of bias and methodological quality of the included studies were assessed using the SYRCLE risk of bias tool, which evaluates ten domains specific to preclinical animal research, including sequence generation, allocation

concealment, blinding, incomplete outcome data, and selective reporting. Each domain was judged as "low risk," "high risk," or "some concerns" based on predefined signaling questions. These assessments informed the overall methodological quality of the included studies (30). The certainty of evidence for each meta-analytic outcome was evaluated using the GRADE approach. As all included studies were randomized preclinical animal experiments, the certainty was initially rated as high and subsequently downgraded according to predefined domains, including risk of bias, inconsistency, indirectness, imprecision, and publication bias (31).

Meta-Analysis

This meta-analysis evaluated the effects of curcumin on endothelial dysfunction in preclinical animal models, focusing on functional endothelial outcomes and relevant biochemical markers. Studies were eligible if they reported within-group comparisons or provided baseline and post-intervention data. Effect sizes were calculated using a random-effects model with the inverse variance method, and pooled standardized mean differences (SMDs) with 95% confidence intervals (CIs) were derived from pre- and post-treatment change scores. All statistical analyses were conducted using Review Manager (RevMan) version 5.4 (Nordic Cochrane Centre, The Cochrane Collaboration) (32). Heterogeneity was assessed using the I^2 statistic (33). Leave-one-out sensitivity analyses were performed to evaluate the robustness of pooled estimates by sequentially excluding individual studies (34). Publication bias was assessed through visual inspection of funnel plot asymmetry and further evaluated using statistical tests, with funnel plots generated using the Metafor package in RStudio (version 2025.09.2 Build 418) (35, 36).

For studies including multiple curcumin treatment arms with different doses or durations, each treatment arm and its corresponding control group were treated as independent comparisons. Subgroup analyses were conducted to explore sources of heterogeneity based on dosage (low ≤100 mg/kg vs. high >100 mg/kg) and treatment duration (short ≤30 days vs. long >30 days), provided that at least three comparisons were available per subgroup. Meta-regression analyses were performed using the Metafor package to examine dose response relationships. Standard errors were derived from reported 95% CIs. In accordance with methodological recommendations, meta-regression was conducted only for outcomes with at least ten comparisons to reduce the risk of spurious associations.

Results

Study Selection

A total of 2,723 records were identified through the systematic database search. After removing 1,183 duplicates, 1,540 records remained for title and abstract screening, of which 1,497 were excluded. The full texts of 43 articles were subsequently assessed for eligibility, and 16 studies met the inclusion criteria and were included in the final systematic review and meta-analysis. The detailed study selection process is illustrated in Figure 1.

Characteristics of Included Studies

This systematic review and meta-analysis included 16 preclinical ex vivo and in vivo animal studies published between 2005 and 2023. The studies were conducted across multiple geographical regions, including Thailand (37-42), China (43-45), Italy (46), Portugal (47), the United States (48), India (49, 50), Bahrain (51), and Saudi Arabia (52). Various rodent models were utilized, predominantly Sprague–Dawley rats (37, 39, 42, 45, 49, 51) and Wistar rats (40, 43, 47, 50, 52), as well as SHRsp rats (44), ICR mice (38, 41), C57BL/6N mice (48) and MeCP2+/− mice (46), to investigate endothelial dysfunction under diverse pathological conditions.

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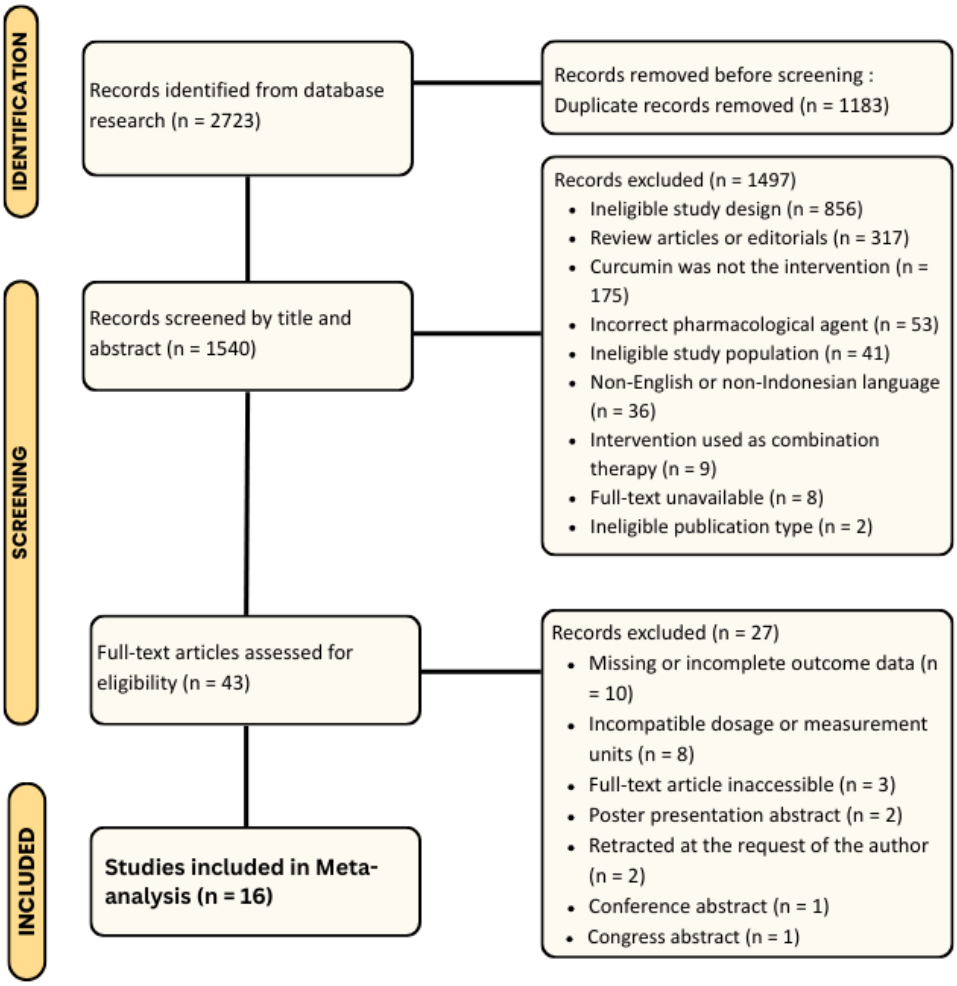

Figure 1. PRISMA flowchart of the study selection process

The animal models represented a wide range of etiologies associated with endothelial dysfunction, including diabetes mellitus (40, 49), hypertension (37, 44), type 2 diabetes mellitus (47), natural aging (45, 48), genetic mutation–related endothelial dysfunction (46), nitric oxide–deficiency–induced endothelial dysfunction (39), high-fat-diet–induced endothelial dysfunction (51), pressure overload (43), heavy metal exposure (42), lipopolysaccharide (LPS)–induced vascular injury (41), cadmium-induced vascular toxicity (38), methotrexate-induced endothelial injury (50), and metabolic syndrome (52). This diversity of models reflects the contribution of both metabolic and non-metabolic factors to endothelial dysfunction.

The duration of curcumin administration varied considerably across studies, ranging from 1 day to 168 days. Most studies administered curcumin via the oral route (37-39, 41-46, 48-51), whereas others used intravenous (40), subcutaneous (47), or intraperitoneal administration (52). Curcumin dosage regimens also differed substantially, with doses ranging from 5 to 400 mg/kg, depending on the experimental design and disease model.

Endothelial function was primarily assessed using EDV as the main functional outcome. Molecular and biochemical markers related to endothelial function and oxidative stress, including eNOS, NO, superoxide, and MDA, were also evaluated, enabling a comprehensive assessment of vascular responses and oxidative stress–related mechanisms. A detailed summary of study characteristics and extracted outcomes is presented in Table 2.

Table 2. Characteristics of the Studies Included in the Meta-Analysis

Year (Reference)	Country	Animal	Animal Model	Number (M/F)	Duration (days)	Administration Route	Dose (mg/kg)	Reported Outcomes
2010(40)	Thailand	Wistar rats	Diabetes-induced endothelial dysfunction	20/0	40	Intravenous	30, 300	EDV, Superoxide
2013(46)	Italy	MeCP2+/– mice	Endothelial dysfunction secondary to MeCP2 mutation	0/18	21	Oral	365	EDV, eNOS,Superoxide, MDA
2018(44)	China	SHRsp rats	Hypertension and endothelial dysfunction	16/0	40	Oral	100	EDV, NO, eNOS, MDA
2014(37)	Thailand	Sprague-Dawley rats	hypertension-induced endothelial dysfunction	20/0	42	Oral	50, 100	EDV, NO, eNOS, Superoxide, MDA
2022(47)	Portugal	Wistar rats	Type 2 diabetes impaired endothelial function	14/0	14	Subcutanous	40	EDV, Superoxide
2013(45)	China	Sprague-Dawley rats	Natural aging causing cerebrovascular endothelial dysfunction	12/0	30	Oral	150	EDV, eNOS, Superoxide
2013(48)	USA	C57BL/6N mice	Aging-associated endothelial dysfunction	20/0	28	Oral	225	EDV, eNOS, Superoxide
2009(41)	Thailand	ICR mice	LPS-induced vascular dysfunction	20/0	1	Oral	50, 100	EDV, NO, Superoxide, MDA
2014(38)	Thailand	ICR mice	Cadmium-induced vascular dysfunction and hypertension	20/0	56	Oral	50, 100	EDV, NO, eNOS, Superoxide, MDA
2017(43)	China	Wistar rats	Pressure-overload–induced endothelial dysfunction	20/0	70	Oral	50	EDV, eNOS
2005(49)	India	Sprague-Dawley rats	Diabetes-induced endothelial dysfunction	16/0	168	Oral	200	EDV, NO, MDA
2011(39)	Thailand	Sprague-Dawley rats	NO-deficiency–induced endothelial dysfunction and hypertension	20/0	21	Oral	50, 100	EDV, NO, eNOS, Superoxide, MDA
2023(51)	Bahrain	Sprague-Dawley rats	High-fat–diet–induced endothelial dysfunction	35/0	140	Oral	88.65	EDV, NO
2021(42)	Thailand	Sprague-Dawley rats	Heavy metal–induced hypertension with endothelial dysfunction	16/0	112	Oral	100	EDV, NO, eNOS, Superoxide, MDA
2015(50)	India	Wistar rats	Methotrexate (MTX)-induced vascular endothelial dysfunction	12/0	28	Oral	100, 200, 400	EDV, Superoxide, MDA
2014(52)	Saudi Arabia	Wistar rats	Metabolic syndrome with endothelial dysfunction	16/0	42	Intraperitoneal	5	EDV, NO

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Quality Assessment

The risk of bias was assessed using the SYRCLE tool, which evaluates internal validity across ten domains specific to in vivo studies (Figure 2). Domains related to baseline characteristics and completeness of outcome data were generally judged to be at low risk of bias. By contrast, several methodological domains, including random sequence generation, allocation concealment, random housing, and blinding procedures, were predominantly rated as some concerns because of insufficient reporting. These assessments reflect variability in the reporting quality of methodological details across the included studies.

The quality of evidence for each outcome was assessed using the GRADE approach. The certainty of evidence for all outcomes was rated as very low, primarily due to indirectness associated with the exclusive use of animal models. Inconsistency and imprecision further contributed to the low certainty of evidence, as indicated by substantial heterogeneity across studies, wide confidence intervals, and relatively small sample sizes (Supplementary Table 3). Publication bias was assessed using Egger's regression test, Begg's rank correlation test, and visual inspection of funnel plots. Significant small-study effects were detected for EDV (Egger's $p < 0.0001$, Begg's $p < 0.0001$), eNOS (Egger's $p = 0.0031$, Begg's $p = 0.0032$), MDA (Egger's $p < 0.0001$, Begg's $p = 0.0005$), and superoxide (Egger's $p < 0.0001$, Begg's $p < 0.0001$). Visual inspection of the funnel plots for these outcomes showed asymmetry, suggesting potential publication bias. In contrast, no significant publication bias was observed for NO (Egger's $p = 0.5411$, Begg's $p = 0.4767$), and the corresponding funnel plot appeared symmetrical (Supplementary Figure 9).

Effect of Curcumin on Endothelial Function

The impact of curcumin on endothelial function was evaluated across included preclinical studies using established functional and biochemical assessments of vascular endothelial integrity. Endothelial function was assessed using three key outcome measures: EDV, eNOS expression or activity, and NO levels. These outcomes provide complementary functional, biochemical, and molecular indicators of endothelial integrity. The assessment of eNOS expression or activity provides a molecular indicator of endothelial function, as eNOS is the primary enzymatic source of endothelial NO production. Together, these complementary outcomes enable an integrated evaluation of endothelial function at functional, biochemical, and molecular levels.

A total of 24 comparisons were included in the meta-analysis of EDV, comprising 204 animals in the curcumin-treated group and 210 animals in the negative control group. The pooled analysis demonstrated a statistically significant difference favoring curcumin (SMD = 1.44, 95% CI: 1.13 to 1.76, $p < 0.00001$, $I^2 = 46\%$) (Figure 3A).

Subgroup analysis stratified by curcumin dosage showed that in the low-dose subgroup (≤100 mg/kg body weight), 17 comparisons involving 150 curcumin-treated animals and 156 control animals were included. Meta-analysis revealed a significant effect of curcumin (SMD = 1.30, 95% CI: 0.95 to 1.65, $p < 0.00001$, $I^2 = 43\%$). In the high-dose subgroup (>100 mg/kg body weight), comprising 7 comparisons with 54 animals in each group, the meta-analysis also demonstrated a significant effect (SMD = 1.85, 95% CI: 1.20 to 2.50, $p < 0.00001$, $I^2 = 43\%$). However, no statistically significant difference was observed between the low- and high-dose subgroups ($Chi^2 = 2.14$, $p = 0.14$, $I^2 = 53.2\%$) (Supplementary Figure 1). Subgroup analysis based on intervention duration indicated that in the short-duration subgroup (≤30 days), 11 comparisons including 83 curcumin-treated animals and 88 control animals were analyzed, yielding a pooled effect (SMD = 1.67, 95% CI: 1.30 to 2.04, $p < 0.00001$, $I^2 = 0\%$). In the long-duration subgroup (>30 days), which comprised 13 comparisons with 121 animals in the curcumin group and 122 animals in the control group, the pooled effect was also significant (SMD = 1.26, 95% CI: 0.81 to 1.71, $p < 0.00001$, $I^2 = 57\%$). No statistically significant difference was detected between the short- and long-duration subgroups ($Chi^2 = 1.88$, $p = 0.17$, $I^2 = 46.8\%$) (Supplementary Figure 4).

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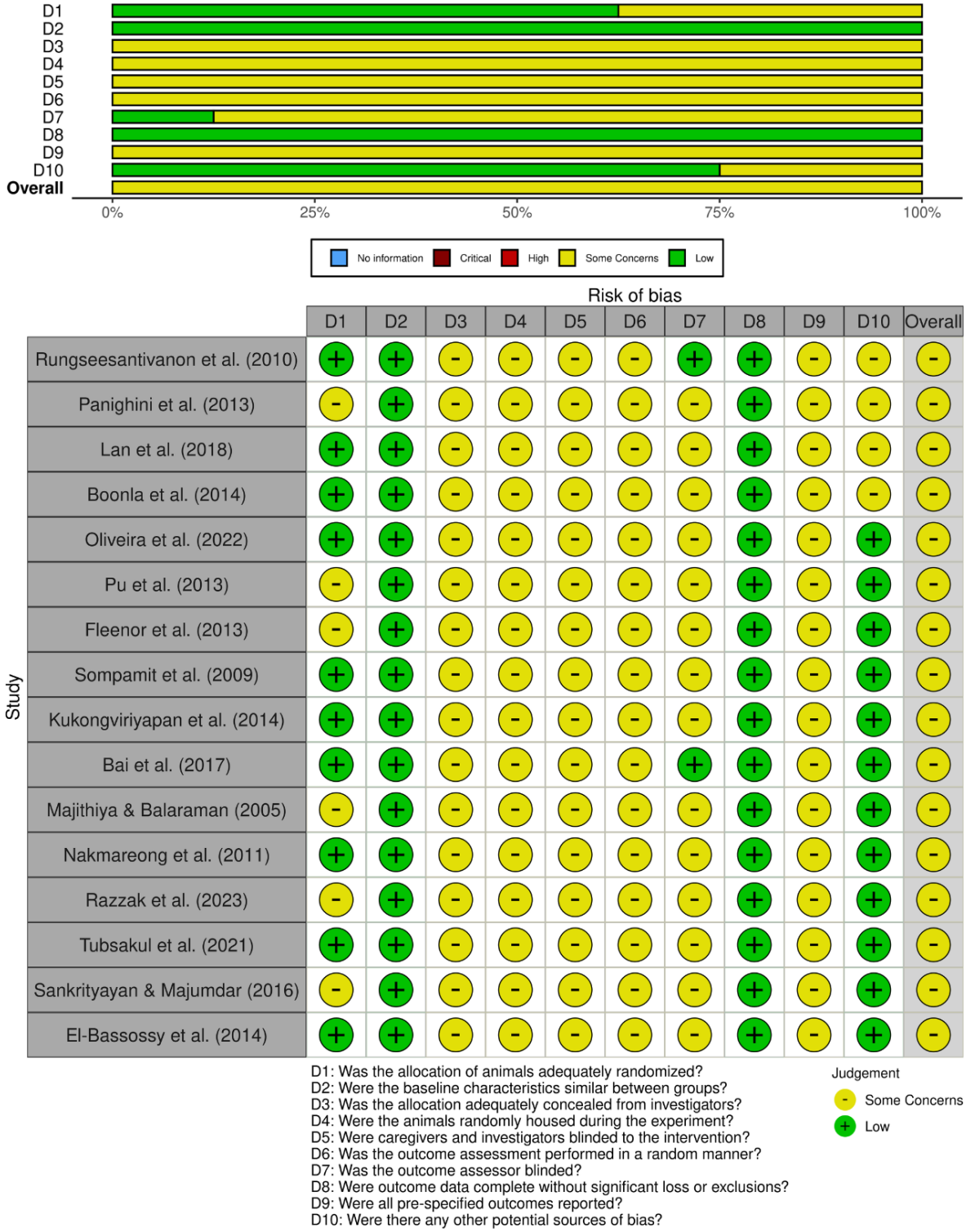
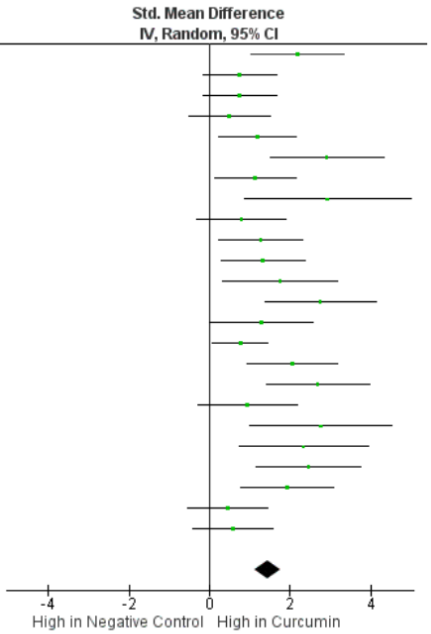


Figure 2. SYRCLE's Risk of Bias Tool for Animal Studies

(A)

Study or Subgroup	Curcumin Mean	SD	Total	Negative Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Bai Xiao Jie et al. 2017 (50)	54.02	9.78	10	34.78	6.85	10	4.2%	2.18 [1.03, 3.34]
Boonla O et al. 2014 (100)	72.89	18.04	10	59.06	17.36	10	5.3%	0.75 [-0.17, 1.66]
Boonla O et al. 2014 (50)	69.67	7.95	10	59.06	17.36	10	5.3%	0.75 [-0.16, 1.67]
El-Bassossy H M et al. 2014 (5)	64.58	20.1	8	54.65	17.8	8	4.9%	0.49 [-0.51, 1.49]
Fleenor B S et al. 2013 (225)	93.15	14.82	10	78.49	7.6	10	5.0%	1.19 [0.22, 2.16]
Kukongviriyapan U et al. 2014 (100)	42.91	2.64	9	30.79	4.94	9	3.3%	2.91 [1.50, 4.33]
Kukongviriyapan U et al. 2014 (50)	38.27	7.41	9	30.79	4.94	9	4.8%	1.13 [0.12, 2.15]
Lan C et al. 2018 (100)	47.6	8.56	5	25	4.85	5	1.9%	2.93 [0.87, 5.00]
Majithiya J B et al. 2005 (200)	64.04	6.66	7	55.54	12.49	7	4.4%	0.80 [-0.31, 1.90]
Nakmareong S et al. 2011 (100)	39.18	8.56	9	28.7	7.02	9	4.7%	1.28 [0.24, 2.31]
Nakmareong S et al. 2011 (50)	36.96	4.52	9	28.7	7.02	9	4.7%	1.33 [0.29, 2.38]
Oliveira S et al. 2022 (40)	62.22	10.18	4	44.16	9.33	9	3.2%	1.76 [0.33, 3.18]
Panighini A et al. 2013 (365)	30.85	7.85	9	10.73	5.89	9	3.4%	2.76 [1.38, 4.14]
Pu Yunfei et al. 2013 (150)	84.88	10.46	6	71.17	9.15	6	3.7%	1.29 [-0.01, 2.58]
Razzak R A et al. 2023 (88.65)	80.89	21.4	17	66.41	15.02	18	6.5%	0.77 [0.08, 1.46]
Rungseesantivanon S et al. 2010 (30)	10.59	0.56	10	8.09	1.55	10	4.3%	2.05 [0.93, 3.18]
Rungseesantivanon S et al. 2010 (300)	11.9	1.13	10	8.09	1.55	10	3.7%	2.69 [1.41, 3.97]
Sankrityayan H et al. 2015 (100)	44.84	8.06	6	37.29	6.59	6	3.9%	0.95 [-0.28, 2.17]
Sankrityayan H et al. 2015 (200)	59.42	8.06	6	37.29	6.59	6	2.4%	2.77 [1.01, 4.54]
Sankrityayan H et al. 2015 (400)	62.78	12.63	6	37.29	6.59	6	2.8%	2.34 [0.73, 3.94]
Sompamit K et al. 2009 (100)	37.7	9	9	20.9	1.8	9	3.7%	2.47 [1.17, 3.76]
Sompamit K et al. 2009 (50)	33.6	8.7	9	20.9	1.8	9	4.2%	1.93 [0.76, 3.09]
Tubsakul A et al. 2021 (100) Cd	50.22	5.57	8	47.77	4.48	8	4.9%	0.46 [-0.54, 1.46]
Tubsakul A et al. 2021 (100) Pb	50.17	5.84	8	47.15	3.8	8	4.8%	0.58 [-0.43, 1.59]
Total (95% CI)			**204**			**210**	**100.0%**	**1.44 [1.13, 1.76]**

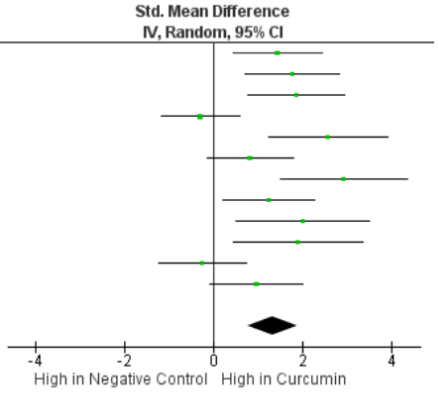
Heterogeneity: Tau² = 0.28; Chi² = 42.54, df = 23 (P = 0.008); I² = 46%
Test for overall effect: Z = 8.92 (P < 0.00001)



(B)

Study or Subgroup	Curcumin Mean	SD	Total	Negative Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Bai Xiao Jie et al. 2017 (50)	0.1	0.02	10	0.07	0.02	10	9.0%	1.44 [0.43, 2.44]
Boonla O et al. 2014 (100)	82.88	16.73	10	49.49	19.25	10	8.7%	1.77 [0.70, 2.84]
Boonla O et al. 2014 (50)	79.24	9.89	10	49.49	19.25	10	8.6%	1.86 [0.77, 2.95]
Fleenor B S et al. 2013 (225)	0.5	0.32	10	0.6	0.32	10	9.6%	-0.30 [-1.18, 0.58]
Kukongviriyapan U et al. 2014 (100)	80.75	21	9	30.5	15.75	9	7.5%	2.58 [1.25, 3.91]
Kukongviriyapan U et al. 2014 (50)	46.42	21	9	30.5	15.75	9	9.2%	0.82 [-0.16, 1.79]
Nakmareong S et al. 2011 (100)	103.22	25.6	9	47.28	2.75	9	7.1%	2.93 [1.50, 4.35]
Nakmareong S et al. 2011 (50)	58.78	12.22	9	47.28	2.75	9	8.9%	1.24 [0.21, 2.27]
Panighini A et al. 2013 (365)	0.17	0.03	6	0.08	0.05	6	6.7%	2.01 [0.52, 3.51]
Pu Yunfei et al. 2013 (150)	0.93	0.14	6	0.61	0.17	6	6.9%	1.90 [0.43, 3.36]
Tubsakul A et al. 2021 (100) Cd	36.77	6.5	8	39.63	13.18	8	9.1%	-0.26 [-1.25, 0.73]
Tubsakul A et al. 2021 (100) Pb	80.62	17.3	8	64.97	13.09	8	8.8%	0.96 [-0.09, 2.02]
Total (95% CI)			**104**			**104**	**100.0%**	**1.33 [0.75, 1.90]**

Heterogeneity: Tau² = 0.69; Chi² = 34.80, df = 11 (P = 0.0003); I² = 68%
Test for overall effect: Z = 4.53 (P < 0.00001)



(C)

Study or Subgroup	Curcumin Mean	SD	Total	Negative Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Boonla O et al. 2014 (100)	15.5	5.38	10	9.3	2.85	10	12.7%	1.38 [0.38, 2.38]
Boonla O et al. 2014 (50)	13.7	3.48	10	9.3	2.85	10	12.9%	1.32 [0.34, 2.31]
Lan C et al. 2018 (100)	9.91	3.39	8	5.11	3.9	8	10.5%	1.24 [0.14, 2.34]
Majithiya J B et al. 2005 (200)	12.13	2.23	7	12.4	2.43	7	11.5%	-0.11 [-1.16, 0.94]
Nakmareong S et al. 2011 (100)	9.15	1.41	9	6.43	1.55	9	10.0%	1.75 [0.62, 2.88]
Nakmareong S et al. 2011 (50)	8.18	1.15	9	6.43	1.55	9	12.0%	1.22 [0.19, 2.25]
Razzak R A et al. 2023 (88.65)	61.9	25	7	24.47	20.69	7	8.2%	1.53 [0.28, 2.77]
Tubsakul A et al. 2021 (100) Cd	9.4	3.11	8	6	2.26	8	10.7%	1.18 [0.09, 2.27]
Tubsakul A et al. 2021 (100) Pb	9.3	2.83	8	6.7	2.26	8	11.4%	0.96 [-0.09, 2.01]
Total (95% CI)			**76**			**76**	**100.0%**	**1.15 [0.79, 1.50]**

Heterogeneity: Tau² = 0.00; Chi² = 7.46, df = 8 (P = 0.49); I² = 0%
Test for overall effect: Z = 6.32 (P < 0.00001)

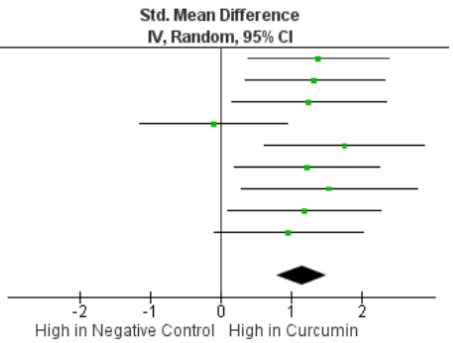


Figure 3. Meta-analysis results of endothelial function related outcomes : (A) EDV, (B) eNOS, and (C) NO

Twelve comparisons involving 208 animals were included in the meta-analysis of eNOS, with equal allocation to the curcumin-treated and negative control groups (n = 104 each). The pooled results indicated a significant improvement following curcumin treatment (SMD = 1.33, 95% CI: 0.75 to 1.90, $p < 0.00001$, I^2 = 68%) (Figure 3B).

Subgroup analysis stratified by curcumin dosage showed that in the low-dose subgroup (≤100 mg/kg body weight), 9 comparisons involving 82 animals per group were included. The pooled effect was statistically significant (SMD = 1.41, 95% CI: 0.81 to 2.00, $p < 0.00001$, I^2 = 63%). In contrast, the high-dose subgroup (>100 mg/kg body weight), comprising 3 comparisons with 22 animals per group, did not show a statistically significant pooled effect (SMD = 1.11, 95% CI: −0.56 to 2.78, p = 0.19, I^2 = 81%). No statistically significant difference was observed between dose-based subgroups (Chi^2 = 0.10, p = 0.75, I^2 = 0%) (Supplementary Figure 2). Subgroup analysis stratified by treatment duration showed that in the short-duration subgroup (≤30 days), 5 comparisons involving 40 animals per group were included, with a significant pooled effect (SMD = 1.47, 95% CI: 0.30 to 2.65, p = 0.01, I^2 = 79%). In the long-duration subgroup (>30 days), comprising 7 comparisons with 64 animals per group, the pooled effect remained significant (SMD = 1.26, 95% CI: 0.60 to 1.92, p = 0.0002, I^2 = 63%). No statistically significant difference was observed between duration-based subgroups (Chi^2 = 0.09, p = 0.76, I^2 = 0%) (Supplementary Figure 5).

NO levels were evaluated across nine comparisons involving 152 animals, with 76 animals in each group. Meta-analysis revealed a significant effect of curcumin (SMD = 1.15, 95% CI: 0.79 to 1.50, $p < 0.00001$, I^2 = 0%) (Figure 3C).

Subgroup analysis based on treatment duration indicated that in the short-duration subgroup (≤30 days), 2 comparisons involving 18 animals per group were included, showing a significant pooled effect (SMD = 1.46, 95% CI: 0.70 to 2.22, p = 0.0002, I^2 = 0%). In the long-duration subgroup (>30 days), comprising 7 comparisons with 58 animals per group, the pooled effect was also significant (SMD = 1.06, 95% CI: 0.65 to 1.47, p = 0.00001, I^2 = 3%). No statistically significant difference was observed between the duration-based subgroups (Chi^2 = 0.83, p = 0.36, I^2 = 0%) (Supplementary Figure 6). Due to the limited number of comparisons in the high-dose category, subgroup analysis based on dosage was not performed for NO levels, as most studies used low-dose regimens and only one study applied a high-dose intervention.

Effect of Curcumin on Oxidative Stress

The effect of curcumin on oxidative stress was examined by pooling data on key lipid and reactive oxygen species markers from the included preclinical studies. Thirteen comparisons were included in the meta-analysis of superoxide (O_2^-) levels, comprising 117 animals in the curcumin-treated group and 117 animals in the negative control group. The pooled results showed a marked reduction in superoxide levels following curcumin administration (SMD = −2.14, 95% CI: −2.88 to −1.41, $p < 0.00001$, I^2 = 76%) (Figure 4A).

When stratified by treatment duration, subgroup analysis indicated that in the short-duration subgroup (≤30 days), 5 comparisons involving 43 animals per group were included, demonstrating a significant pooled effect (SMD = −1.71, 95% CI: −2.65 to −0.76, p = 0.0004, I^2 = 68%). In the long-duration subgroup (>30 days), comprising 8 comparisons with 74 animals per group, a greater magnitude of reduction was observed (SMD = −2.62, 95% CI: −3.74 to −1.50, $p < 0.00001$, I^2 = 81%). However, no statistically significant difference was detected between duration-based subgroups (Chi^2 = 1.48, p = 0.22, I^2 = 32.6%) (Supplementary Figure 7). Subgroup analysis based on dosage was not conducted for superoxide levels due to the limited number of high-dose studies.

Sixteen comparisons were included in the meta-analysis of MDA levels, comprising 134 animals in each group. Meta-analysis demonstrated a significant decrease in MDA levels associated with curcumin treatment (SMD = −1.65, 95% CI: −2.10 to −1.19, $p < 0.00001$, I^2 = 55%) (Figure 4B).

Dose-based subgroup analysis revealed differential effect sizes across curcumin dosages.

In the low-dose subgroup (≤100 mg/kg body weight), 12 comparisons involving 106 animals per group were included, showing a significant pooled effect (SMD = −1.40, 95% CI: −1.72 to −1.09, p < 0.00001, I^2 = 0%). In the high-dose subgroup (>100 mg/kg body weight), comprising 4 comparisons with 28 animals per group, a substantially larger effect size was observed (SMD = −4.26, 95% CI: −6.92 to −1.60, p = 0.002, I^2 = 84%). A statistically significant difference was found between dose-based subgroups (Chi^2 = 4.38, p = 0.04, I^2 = 77.1%) (Supplementary Figure 3). Further stratification by intervention duration indicated consistent effects across treatment periods. In the short-duration subgroup (≤30 days), 8 comparisons involving 65 animals per group were included, demonstrating a significant pooled effect (SMD = −1.73, 95% CI: −2.59 to −0.88, p < 0.0001, I^2 = 70%). In the long-duration subgroup (>30 days), comprising 8 comparisons with 69 animals per group, the pooled effect remained significant (SMD = −1.66, 95% CI: −2.12 to −1.20, p < 0.00001, I^2 = 20%). No statistically significant difference was observed between duration-based subgroups (Chi^2 = 0.02, p = 0.88, I^2 = 0%) (Supplementary Figure 8).

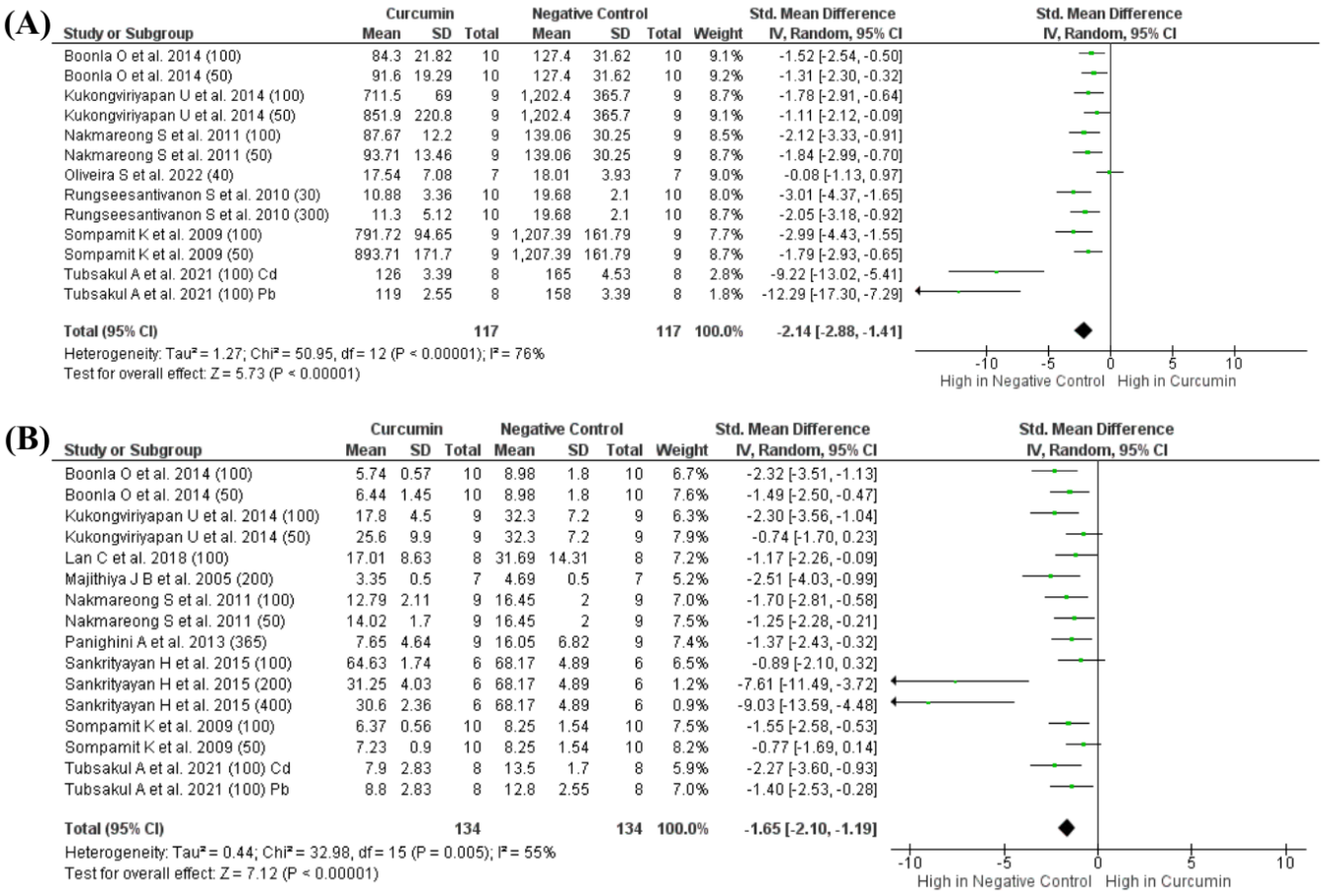


Figure 4. Meta-analysis results of oxidative stress markers: (A) Superoxide and (B) MDA

Leave-one-out sensitivity analysis demonstrated that the pooled effect estimates across all outcomes remained consistent after sequential exclusion of individual studies, indicating that no single study disproportionately influenced the overall results. These findings suggest that the observed effects of curcumin on endothelial function and oxidative stress markers were robust.

Meta-regression Analysis

Meta-regression demonstrated a statistically significant linear dose–response association between curcumin dosage and EDV (k = 24, β =

0.00332, QM = 4.218; p = 0.040). Increasing curcumin dose was associated with progressively greater improvements in endothelial function, accounting for a substantial proportion of between-study heterogeneity (R^2 = 26.38%). Moderate residual heterogeneity persisted (τ^2 = 0.2031, I^2 = 38.61%), suggesting that additional unmeasured factors may contribute to variability in effect size. In contrast, no significant dose–response relationships were observed for eNOS expression (k = 12, β = −0.00074, p = 0.837), superoxide levels (k = 13, β = −0.0038, p = 0.65), or MDA levels (k = 16, β = −0.00011, p = 0.944). For these outcomes, dose did not explain between-study heterogeneity (R^2 = 0%), and substantial residual variability remained (Supplementary Figure 10). Collectively, these findings indicate that dose-dependent effects of curcumin are more evident at the functional vascular level (EDV) than at the level of molecular or oxidative stress biomarkers within the evaluated dose range.

Meta-regression demonstrated a statistically significant inverse association between treatment duration and EDV (k = 24, β = −0.00823, QM = 6.7249, p = 0.0095), indicating that longer intervention periods were associated with smaller effect sizes. Duration accounted for 46.93% of the between-study heterogeneity (R^2 = 46.93%), while moderate residual heterogeneity persisted (τ^2 = 0.1464, I^2 = 30.51%), suggesting that additional factors beyond duration contributed to variability in treatment response. A significant inverse association was likewise observed for superoxide levels (k = 13, β = −0.0541, QM = 9.777, p = 0.0018), indicating greater reductions in oxidative stress with prolonged treatment. However, duration did not account for the observed heterogeneity in this outcome (R^2 = 0%), and substantial residual variability remained (τ^2 = 2.166, I^2 = 84.69%). In contrast, no significant duration–response relationships were detected for eNOS expression (k = 12, β = −0.01279, p = 0.1518) or MDA levels (k = 16, β = −0.00580, p = 0.1196). Residual heterogeneity was moderate to high for eNOS (I^2 = 65.58%) and negligible for MDA (I^2 = 0.00%) (Supplementary Figure 11). Meta-regression was not conducted for NO levels because fewer than ten comparisons were available, which did not meet the predefined methodological threshold for reliable moderator analysis.

Discussion

These systematic review and meta-analysis suggest that curcumin may improve endothelial dysfunction in preclinical animal models, as reflected by consistent benefits across functional, molecular, and biochemical vascular outcomes. Administration of curcumin was associated with significant improvements in EDV, indicating a direct restoration of endothelial function (53). These functional benefits were accompanied by increases in eNOS expression and NO bioavailability, both of which play central roles in maintaining endothelial homeostasis and regulating vascular tone (54-56).

In parallel, curcumin administration was associated with marked reductions in key markers of oxidative stress, including superoxide production and MDA levels (57, 58). Given the well-established contribution of oxidative stress to endothelial injury, these findings suggest a potential protective effect of curcumin on the vascular endothelium by attenuating oxidative damage (20, 59, 60). The concurrent improvement in EDV, enhancement of nitric oxide signaling, and reduction in oxidative stress parameters suggests that the vascular effects of curcumin are integrated and biologically interconnected rather than independent or isolated phenomena (26, 61-63).

The increase in nitric oxide bioavailability occurring alongside attenuation of oxidative stress suggests restoration of vascular redox balance as a central mechanism underlying improved endothelial function (64). By reducing excessive reactive oxygen species, curcumin may limit nitric oxide inactivation, thereby preserving endothelial vasodilatory signaling pathways, a process that is critically dependent on the balance between nitric oxide production and oxidative degradation (65). This coordinated modulation of oxidative stress and nitric oxide signaling supports a mechanistically coherent protective role of curcumin in maintaining endothelial redox homeostasis, consistent with established concepts of eNOS coupling and redox-sensitive regulation of vascular function (9). Collectively, the concordant improvements across functional,

molecular, and biochemical outcomes reinforce the interpretation that oxidative stress regulation represents a key pathway through which curcumin mediates its endothelial benefits (9, 65).

At the molecular level, the findings reveal a consistent pattern linking recovery of endothelial function with attenuation of oxidative stress (66, 67). Improvements in EDV were accompanied by enhanced eNOS expression and nitric oxide bioavailability, indicating restoration of the primary vasodilatory signaling pathway within the endothelium (66, 68). Concurrent reductions in superoxide production and MDA levels further suggest decreased oxidative burden and lipid peroxidation (67, 69). Given that excessive superoxide rapidly inactivates nitric oxide and disrupts endothelial signaling, these findings provide a plausible mechanistic explanation for the observed improvement in nitric oxide–mediated vasodilation, supporting a coordinated protective effect of curcumin on endothelial redox homeostasis (66, 69, 70).

The robustness of these conclusions is supported by leave-one-out sensitivity analyses demonstrating stable pooled effect estimates following sequential exclusion of individual studies, indicating that no single experiment disproportionately influenced the results. Subgroup analyses further showed consistent improvements in endothelial functional outcomes across different curcumin doses and treatment durations, with no statistically significant differences between subgroups. Similar patterns were observed for molecular endpoints, including eNOS expression and nitric oxide levels, suggesting that the endothelial benefits of curcumin are broadly reproducible across experimental settings. However, the absence of statistically significant subgroup differences and the presence of moderate to substantial heterogeneity indicate that these effects should be interpreted with caution and may not be uniformly expressed across all experimental conditions.

In contrast, oxidative stress outcomes exhibited more pronounced exposure-related patterns. Greater reductions in MDA levels were observed at higher curcumin doses, with significant between-subgroup differences, suggesting a potential, but not definitive, dose–response relationship for lipid peroxidation. Meta-regression analyses further indicated that EDV was influenced by both dose and duration, whereas molecular and oxidative stress markers showed weaker or non-linear associations with these moderators. These findings imply that functional endothelial outcomes may be more sensitive to exposure-related factors, while molecular and oxidative endpoints exhibit greater variability across studies, potentially reflecting differences in experimental design, disease models, or outcome assessment.

Curcumin is widely recognized to exhibit limited oral bioavailability, largely due to poor absorption, rapid metabolism, and systemic elimination (71, 72). Although various strategies such as nano-formulations or co-administration with bioavailability enhancers have been proposed to improve systemic exposure, the studies included in this meta-analysis predominantly administered conventional curcumin as a single intervention without additional formulation enhancers. Therefore, variability in the observed effect sizes across studies is more likely attributable to differences in dosage, treatment duration, and experimental conditions rather than formulation-related differences. This interpretation is consistent with the subgroup findings indicating exposure-related patterns, particularly for oxidative stress markers.

This meta-analysis has several important limitations. The exclusive inclusion of preclinical animal studies limits direct translational relevance, and the overall certainty of evidence was rated as very low under GRADE due to indirectness, inconsistency, and imprecision. Methodological reporting was frequently inadequate, with SYRCLE assessment indicating unclear risk of bias in key domains, including sequence generation, allocation concealment, and blinding, potentially affecting internal validity. Moderate to high heterogeneity was observed across outcomes (eNOS I^2 = 68%, superoxide I^2 = 76%, MDA I^2 = 55%), reflecting variability in species, disease models, dosing regimens, and treatment duration. Evidence of small-study effects and funnel plot asymmetry suggests

potential publication bias, and the absence of grey literature and manual searches may have limited comprehensiveness.

In addition, animal models cannot fully replicate the complex physiological and pathological environment of human endothelial dysfunction. In humans, endothelial impairment develops through multifactorial interactions involving aging, metabolic disorders, chronic inflammation, lifestyle factors, and environmental exposures, which are difficult to reproduce simultaneously in experimental animal settings. Furthermore, interspecies differences in vascular physiology, pharmacokinetics, and curcumin metabolism may influence the biological response to treatment. Consequently, while the present findings provide valuable mechanistic insights, their direct extrapolation to human clinical outcomes should be interpreted with caution.

Although sensitivity analyses supported the robustness of pooled estimates, dose–response findings remain exploratory due to limited high-dose comparisons and residual heterogeneity. Therefore, these results should be interpreted as mechanistic evidence rather than definitive translational proof.

Conclusion

This meta-analysis suggests that curcumin may improve endothelial dysfunction in preclinical animal models, as indicated by improvements in EDV, increased eNOS expression and NO bioavailability, and reducing oxidative stress markers, reflecting restoration of endothelial redox balance. These findings imply a potential role of curcumin in restoring endothelial redox balance. However, the certainty of evidence was rated as very low, primarily due to heterogeneity and methodological limitations of the included animal studies. Therefore, these results should be interpreted with caution. Further well-designed experimental and clinical studies are needed to confirm the translational relevance and potential therapeutic implications of curcumin.

Author's Contributions

Marita Feliana : Writing – original draft, Methodology, Visualization, Investigation, Formal analysis, Data curation. **Aghnia Nurvianti Nafilah :** Writing – original draft, Methodology, Visualization, Investigation, Formal analysis, Data curation. **Hendra Mahakam Putra :** Writing – review and editing, Methodology, Validation. **Marita Kaniawati :** Methodology, Validation. **Agus Sulaeman :** Conceptualization, Methodology, Validation, Project administration.

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Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Avaibility

All data generated or analyzed during this study are included in this article and its Supporting Information.

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