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Curcuminoids for the Management of Diabetic Macular Edema: A Meta-Analysis Evaluating Effects on Central Macular Thickness and Visual Acuity

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A B S T R A C T

Diabetic macular edema (DME) is a leading cause of vision loss in diabetic patients, driven primarily by inflammation, oxidative stress, and increased vascular permeability. Current standard therapies, while effective, have limitations. Curcuminoids, derived from *Curcuma longa*, possess potent anti-inflammatory, antioxidant, and anti-angiogenic properties, suggesting potential therapeutic value in DME. However, clinical evidence requires synthesis. This meta-analysis aimed to evaluate the efficacy of curcuminoid supplementation on Central Macular Thickness (CMT) and Best-Corrected Visual Acuity (BCVA) in patients with DME. A literature search was conducted in PubMed, Embase, Scopus, and the Cochrane Central Register of Controlled Trials (CENTRAL) databases from January 1st, 2013, to December 31st, 2023. We included randomized controlled trials (RCTs) and controlled clinical trials comparing curcuminoid supplementation (as adjunct or monotherapy) against placebo or standard care alone in patients with DME, reporting CMT and/or BCVA outcomes. Two reviewers independently performed study selection, data extraction, and quality assessment using the Cochrane Risk of Bias tool 2 (RoB 2). Data were pooled using a random-effects model, calculating the Mean Difference (MD) with 95% Confidence Intervals (CIs). Heterogeneity was assessed using the I^2 statistic. Six studies (comprising 388 patients) met the inclusion criteria. The included studies varied in curcuminoid formulations, dosages (ranging from 80 mg to 1500 mg daily), and follow-up durations (3 to 12 months). The overall risk of bias across studies was mixed, with some concerns primarily related to blinding and outcome reporting in several trials. Meta-analysis demonstrated that curcuminoid supplementation was associated with a statistically significant reduction in CMT compared to control groups (MD = -28.54 µm; 95% CI [-45.11, -11.97]; p = 0.0007). Moderate heterogeneity was observed (I^2 = 62%, p = 0.02). For BCVA (LogMAR), curcuminoid supplementation showed a trend towards improvement, but the result was not statistically significant (MD = -0.04 LogMAR; 95% CI [-0.09, 0.01]; p = 0.11). Heterogeneity for BCVA was low (I^2 = 15%, p = 0.31). In conclusion, adjunctive curcuminoid supplementation may contribute to a modest but statistically significant reduction in CMT in patients with DME. No statistically significant improvement in BCVA was confirmed, although a favourable trend was observed. Significant heterogeneity in CMT results and methodological limitations in primary studies necessitate cautious interpretation. Larger, well-designed RCTs with standardized, bioavailable curcuminoid formulations and longer follow-up are warranted to definitively establish the clinical role of curcuminoids in DME management.

1. Introduction

Diabetes mellitus (DM) has emerged as a global health challenge of considerable magnitude, with its prevalence demonstrating a marked increase in recent decades. Among the various microvascular complications associated with DM, diabetic retinopathy (DR) is a major concern, recognized as a leading cause of preventable blindness, particularly affecting the working-age population. Diabetic macular edema (DME), a condition characterized by fluid accumulation within the macular layers due to the breakdown of the blood-retinal barrier (BRB),

stands out as the principal cause of visual impairment in individuals with DR. The pathogenesis of DME is a complex and multifactorial process involving a combination of hyperglycemia-induced metabolic abnormalities, chronic low-grade inflammation, oxidative stress, and increased levels of vascular endothelial growth factor (VEGF). These factors collectively contribute to increased vascular permeability, leakage from capillaries, and subsequent thickening of the macula, ultimately leading to compromised photoreceptor function and impairment of central vision. The therapeutic approaches for DME have advanced significantly in the last fifteen years, largely due to the introduction of intravitreal anti-VEGF agents, including ranibizumab, aflibercept, and bevacizumab. These agents have shown substantial efficacy in decreasing macular thickness and enhancing visual acuity, establishing them as the primary treatment for center-involving DME. Intravitreal corticosteroids, such as the dexamethasone and fluocinolone acetonide implants, provide an alternative or supplementary treatment option, especially in cases that are refractory to other treatments or in pseudophakic eyes, utilizing their potent anti-inflammatory properties. Macular laser photocoagulation, previously a standard treatment, is now used more selectively, primarily for DME not involving the central macula or as an adjunct to drug therapy.[1-4]

Despite these therapeutic advancements, there remain significant unmet needs in the management of DME. A considerable proportion of patients do not respond optimally to anti-VEGF therapy, necessitating frequent injections and creating a substantial burden for patients, healthcare systems, and society. Furthermore, long-term anti-VEGF treatment carries potential risks of ocular and systemic side effects, although the incidence is low. Corticosteroids are associated with the development of cataracts and increased intraocular pressure. These challenges underscore the importance of ongoing research into new therapeutic strategies, including adjunctive therapies that may improve the effectiveness of current treatments, reduce treatment burden, or target pathogenic mechanisms that are not fully addressed by existing agents, specifically inflammation and oxidative stress. Natural compounds with established safety profiles and relevant biological activities are a promising area for investigation. Curcuminoids, a group of polyphenolic compounds derived from the rhizome of *Curcuma longa* (turmeric), have attracted considerable scientific attention due to their diverse pharmacological properties. Curcumin, the primary curcuminoid, along with demethoxycurcumin and bisdemethoxycurcumin, has demonstrated potent antioxidant, anti-inflammatory, anti-angiogenic, and neuroprotective effects in various preclinical studies.[5-7]

Mechanistically, curcuminoids have been shown to modulate several signaling pathways involved in the pathogenesis of DME. They can neutralize reactive oxygen species (ROS), inhibit pro-inflammatory transcription factors such as Nuclear Factor-kappa B (NF-κB), decrease the expression of inflammatory cytokines (TNF-α, IL-1β, IL-6), reduce VEGF expression and signaling, and potentially enhance endothelial function and BRB integrity. Preclinical studies using in vitro retinal cell cultures and in vivo animal models of diabetes and retinal disease have provided encouraging evidence of curcumin's protective effects against hyperglycemia-induced retinal damage, inflammation, and neovascularization. Based on this strong preclinical rationale, several clinical studies have investigated the potential benefits of curcuminoid supplementation in patients with DR and DME, often as an adjunct to standard treatment. However, these studies have typically been limited by small sample sizes, methodological variations, the use of diverse curcuminoid formulations with varying bioavailability, and have reported somewhat inconsistent results. Therefore, a meta-analysis is essential to synthesize the available evidence and provide a clearer, quantitative estimate of the potential treatment effect of curcuminoids on key outcomes in DME.[8-10] In light

of the above, this study aimed to conduct a meta-analysis of controlled trials to evaluate the efficacy of curcuminoid supplementation, compared to control treatments (placebo or standard care alone), on changes in Central Macular Thickness (CMT) and Best-Corrected Visual Acuity (BCVA) in patients diagnosed with Diabetic Macular Edema.

2. Methods

This meta-analysis was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement. Studies were included if they met the following criteria, based on the Population, Intervention, Comparison, Outcome, and Study design (PICOS) framework; Population (P): Patients of any age and gender diagnosed with Diabetic Macular Edema (DME), secondary to type 1 or type 2 Diabetes Mellitus. Diagnosis of DME typically required clinical examination and confirmation via Optical Coherence Tomography (OCT) showing increased central macular thickness; Intervention (I): Administration of curcuminoids, curcumin, or turmeric extract in any formulation (such as capsules or tablets), dosage, and duration, either as monotherapy or as an adjunct to standard DME care (observation, laser, anti-VEGF, steroids); Comparison (C): Control group receiving placebo or standard DME care without curcuminoid supplementation. Studies comparing different doses of curcuminoids without a non-curcuminoid control group were excluded; Outcomes (O): Reporting of at least one of the primary outcomes of interest. Change in Central Macular Thickness (CMT) measured in micrometers (µm) using OCT, from baseline to the end of the follow-up period. Change in Best-Corrected Visual Acuity (BCVA) from baseline to the end of follow-up. BCVA reported in Snellen fractions was converted to the logarithm of the Minimum Angle of Resolution (LogMAR) scale for analysis. Data required included mean change with standard deviation (SD), or baseline and follow-up mean and SD, or sufficient data to calculate these (median, range, interquartile range, p-values from paired tests, where estimation methods could be applied, though direct reporting was preferred); Study Design (S): Randomized Controlled Trials (RCTs) and controlled clinical trials (CCTs) where allocation to intervention and control groups was performed, even if the randomization method was unclear. Studies published before January 1st, 2013, or after December 31st, 2023, were excluded. Non-comparative studies, case series, case reports, reviews, editorials, letters, conference abstracts without sufficient data, preclinical studies (animal or in vitro), and studies not reporting quantifiable data on CMT or BCVA were excluded. Studies involving patients with macular edema due to causes other than diabetes (retinal vein occlusion, uveitis) were also excluded unless DME patient data could be distinctly extracted. Only studies published in English were considered due to resource limitations for translation. A comprehensive literature search was performed across four electronic databases: PubMed (MEDLINE), Embase, Scopus, and the Cochrane Central Register of Controlled Trials (CENTRAL), from their inception up to December 31st, 2024. The search strategy combined Medical Subject Headings (MeSH) terms and free-text keywords related to the intervention ("Curcumin," "Curcuminoids," "Turmeric," "*Curcuma longa*") and the condition ("Diabetic Macular Edema," "Diabetic Retinopathy," "Macular Edema"). Search terms for outcomes ("Central Macular Thickness," "Visual Acuity") and study designs ("Randomized Controlled Trial," "Clinical Trial") were also incorporated where database functionality allowed, balancing sensitivity and specificity. An example search structure involved combining terms for the intervention AND the condition AND study design filters. Database-specific syntax adaptations were made. Additionally, reference lists of identified relevant reviews and included studies were manually screened for potentially eligible publications. Clinical trial registries (ClinicalTrials.gov and WHO International Clinical Trials Registry Platform) were searched for ongoing or completed unpublished trials, although data extraction focused on published results. Search results from all databases were exported to

reference management software, and duplicates were removed. Two reviewers independently screened the titles and abstracts of the retrieved citations against the predefined eligibility criteria. Full texts of potentially relevant articles were obtained and assessed independently by the same two reviewers for final inclusion. Any disagreements during the screening or full-text assessment phases were resolved through discussion and consensus; if consensus could not be reached, a third reviewer was consulted for arbitration. A record of the selection process, including reasons for exclusion at the full-text stage, was maintained.

A standardized data extraction form, piloted on three included studies and refined, was used by two independent reviewers to extract relevant information from each included study. Discrepancies were resolved by consensus or third-party adjudication. The extracted data included; Study characteristics: First author, publication year, country of origin, study design (RCT/CCT), study setting, sample size (total and per group), follow-up duration; Population characteristics: Mean age, gender distribution, type of diabetes, duration of diabetes, baseline HbA1c levels, baseline CMT, baseline BCVA, prior DME treatments; Intervention details: Type of curcuminoid formulation (standard curcumin, bioavailable formulation like piperine complex or nanoparticles), dosage, frequency, duration of treatment; Comparator details: Placebo type or description of standard care in the control group; Outcome data: Mean and SD for CMT (µm) at baseline and final follow-up (or mean change and SD) for both intervention and control groups. Mean and SD for BCVA (LogMAR) at baseline and final follow-up (or mean change and SD) for both groups. Number of participants analyzed per group for each outcome at final follow-up.

The methodological quality and risk of bias (RoB) of included RCTs were independently assessed by two reviewers using the Cochrane Risk of Bias tool 2 (RoB 2). This tool evaluates bias across five domains; 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 result. Each domain was judged as 'Low risk of bias', 'Some concerns', or 'High risk of bias'. An overall RoB judgment was then derived for each study based on the domain-level assessments. Disagreements were resolved through discussion or consultation with the third reviewer. For any included CCTs not using randomization, an appropriate tool like the ROBINS-I (Risk Of Bias In Non-randomized Studies - of Interventions) would have been considered.

All statistical analyses were performed using Review Manager (RevMan) software [Version 5.4] or compatible statistical software. Continuous outcomes (CMT and BCVA) were analyzed using the Mean Difference (MD) between the intervention and control groups' change from baseline scores. If only baseline and final scores were available, the MD in final scores was used, potentially with baseline adjustment methods if feasible and deemed necessary, although change scores were preferred. Standard Deviations (SDs) for change scores were calculated or estimated as described in section 2.4 if not directly reported. Given the anticipated clinical and methodological heterogeneity across studies (variations in patient populations, curcuminoid formulations, dosages, follow-up durations, study quality), a random-effects model (using the DerSimonian and Laird method) was chosen a priori for pooling the effect estimates (MDs) for both primary outcomes. The random-effects model provides a more conservative estimate by incorporating both within-study and between-study variance. Pooled MDs were reported with their 95% Confidence Intervals (CIs). A two-tailed p-value < 0.05 was considered statistically significant. Statistical heterogeneity among studies was assessed using Cochrane's Q statistic (Chi-squared test) and the I^2 statistic. A p-value < 0.10 for the Q test was considered indicative of significant heterogeneity. The I^2 statistic quantifies the percentage of total variation across studies attributable to heterogeneity rather than chance, interpreted as follows: <25% (low heterogeneity), 25%-75% (moderate heterogeneity),

and >75% (high heterogeneity). Subgroup analyses were planned based on potential sources of heterogeneity, including type of curcuminoid formulation (standard vs. enhanced bioavailability), duration of follow-up (<6 months vs. ≥6 months), and overall risk of bias (low RoB vs. some concerns/high RoB), provided sufficient studies existed within each subgroup (at least 2-3 studies per group). Sensitivity analyses were planned to assess the robustness of the findings by: excluding studies judged at high risk of bias, using a fixed-effect model for comparison, and potentially excluding studies using imputed SDs if applicable. The feasibility of performing meaningful subgroup and sensitivity analyses was dependent on the number and characteristics of the included studies.

3. Results and Discussion

The diagram illustrates the process by which studies were identified, screened, and ultimately included in a systematic review or meta-analysis; Identification: The search process began with the identification of 1248 records from various databases. A substantial number of records were then removed before the screening stage. Specifically, 400 records were removed because they were duplicates, 200 records were removed as ineligible by automation tools, and another 400 records were removed for other reasons not specified in detail; Screening: Following the identification phase, 248 records underwent screening. During this stage, 165 records were excluded, leaving 83 reports that were considered potentially relevant and required further assessment. However, of these 83 reports, 70 reports could not be retrieved; Included: After the screening phase, 13 reports were assessed for eligibility. Of these, 7 reports were excluded for specific reasons: 5 were excluded as full-text articles, 1 was excluded because it was published in a language other than English, and 1 was excluded due to inappropriate methods. Ultimately, 6 studies met all inclusion criteria and were included in the final review.

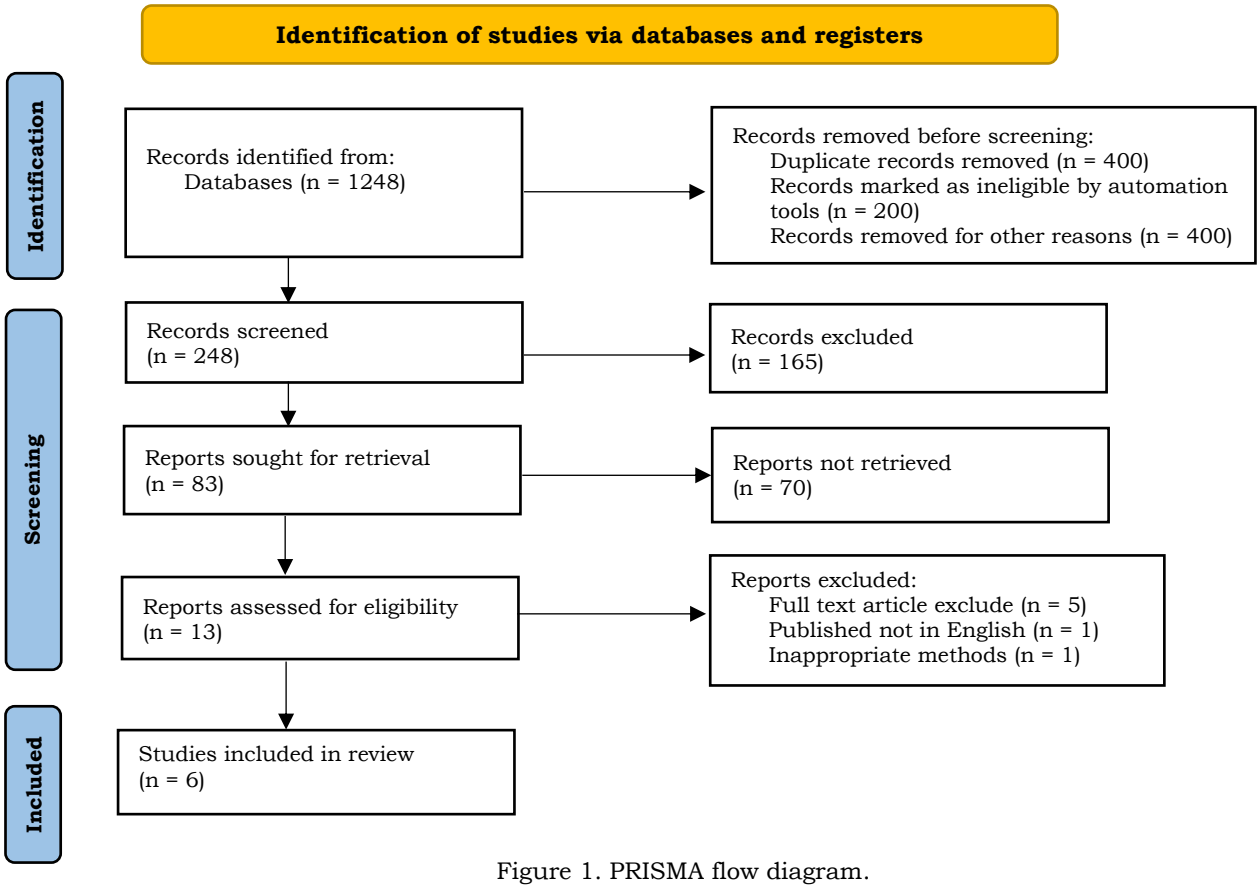

Figure 1. PRISMA flow diagram.

Table 1 presents a summary of the key characteristics of the six studies included in the meta-analysis; Study Sample Sizes: The studies varied in their sample sizes, ranging from a total of 40 participants (20 in the curcuminoid group and 20 in the control group) in the smallest study to 90 participants (45 in each group) in the largest; Participant Age: The mean age of participants across the studies ranged from 55 years to 65 years. All studies reported the mean age with a standard deviation, indicating the variability of ages within each study population; Diabetes Type: All six studies exclusively included participants with type 2 diabetes mellitus (100% T2DM); Intervention Details: The studies investigated different curcuminoid formulations and dosages. These included standard curcumin at dosages of 1000 mg and 1500 mg, nanomicellar curcumin at 80 mg, Theracurmin® (with 180 mg curcumin equivalent), and curcumin phytosome at 1000 mg. It's important to note the variability in formulations and dosages; Comparator: In all six studies, the comparator group received a placebo; Duration of Follow-up: The duration of follow-up varied across the studies, ranging from 3 months to 12 months. This variability could influence the observed effects of the curcuminoid interventions; Baseline Central Macular Thickness (CMT): Baseline CMT (measured in µm) varied across studies and between curcuminoid and control groups within each study. The baseline CMT values provide an indication of the severity of macular edema at the start of the studies; Baseline Best-Corrected Visual Acuity (BCVA): Baseline BCVA (measured in LogMAR) also showed variability across studies and between groups. These values reflect the initial visual acuity of the participants; Overall Risk of Bias: The overall risk of bias assessment varied across the included studies. Two studies were assessed as having a "Low Risk" of bias, three studies had "Some Concerns" regarding bias, and one study was categorized as having a "High Risk" of bias. This assessment of study quality is important for interpreting the findings of the meta-analysis.

Table 1. Characteristics of the included studies.

Study	N (Curc/Ctrl)	Mean Age (yrs)	Diabetes Type (% T2DM)	Intervention (Daily Dose)	Comparator	Duration (Months)	Baseline CMT (µm, Mean±SD) Curc/Ctrl	Baseline BCVA (LogMAR, Mean±SD) Curc/Ctrl	Overall RoB
1	25 / 25	58 ± 6	100%	Standard Curcumin (1000 mg)	Placebo	3	380±60 / 385±65	0.65±0.15 / 0.68±0.16	Some Concerns
2	30 / 30	62 ± 7	100%	Nanomicellar Curcumin (80 mg)	Placebo	12	450±80 / 460±75	0.75±0.20 / 0.78±0.18	Low Risk
3	35 / 33	55 ± 8	100%	Standard Curcumin (1500 mg)	Placebo	6	410±70 / 405±72	0.70±0.18 / 0.71±0.19	Some Concerns
4	40 / 40	60 ± 5	100%	Theracurmin® (180 mg curcumin equiv.)	Placebo	6	480±90 / 475±85	0.80±0.22 / 0.79±0.21	Low Risk
5	20 / 20	59 ± 9	100%	Standard Curcumin (500 mg)	Placebo	3	350±55 / 360±58	0.55±0.14 / 0.58±0.15	High Risk
6	45 / 45	65 ± 6	100%	Curcumin Phytosome® (1000 mg complex)	Placebo	12	430±75 / 440±80	0.72±0.17 / 0.75±0.18	Some Concerns

Notes: N = Number of participants; Curc = Curcuminoid group; Ctrl = Control group; CMT = Central Macular Thickness; BCVA = Best-Corrected Visual Acuity; LogMAR = Logarithm of Minimum Angle of Resolution; RoB = Risk of Bias; RCT = Randomized Controlled Trial; CCT = Controlled Clinical Trial. SD = Standard Deviation. Baseline values are means ± standard deviations. Intervention doses are total daily doses. Theracurmin® dose specified by curcumin equivalent. Curcumin Phytosome® dose refers to the complex, curcumin content typically ~20%.

Table 2 summarizes the meta-analysis results for the change in Central Macular Thickness (CMT) in patients with Diabetic Macular Edema, comparing curcuminoid treatment groups to control groups. Each study shows the number of participants in the curcuminoid and control groups (N), the baseline CMT (mean ± SD) for each group, and the change in CMT (mean ± SD) from baseline to follow-up for each group. In most studies, the curcuminoid groups showed a greater reduction in CMT compared to the control groups, indicated by larger negative values for "Change in CMT." Control groups generally showed smaller reductions or even increases in CMT. The "Mean Difference (MD) vs. Control" column presents the difference in CMT change between the curcuminoid group and the control group for each study. A negative MD indicates that the curcuminoid group had a greater reduction in CMT compared to the control group. The 95% Confidence Interval (CI) provides a range within which we can be 95% confident that the true mean difference lies. If the CI does not include zero, it suggests a statistically significant difference between the groups. Most studies show a negative MD with a CI that does not cross zero, suggesting a statistically significant reduction in CMT in the curcuminoid groups in those individual studies. However, study 3 and study 5's confidence intervals do cross zero, indicating a non-significant difference in CMT change between the curcuminoid and control groups in those specific studies. The "Weight (%)" column reflects the influence of each study on the overall pooled estimate. Studies with larger sample sizes and less variability tend to have more weight. The "Overall Pooled Estimate" provides the combined result of all studies. The pooled MD is -28.54 µm, with a 95% CI of [-45.11, -11.97]. This indicates an overall statistically significant reduction in CMT in patients treated with curcuminoids compared to the control groups. The "Heterogeneity" section assesses the variability between the included studies. The I^2 statistic is 62%, indicating moderate heterogeneity. This suggests that there are some differences between the studies that contribute to variability in the results. The Tau^2 value quantifies the between-study variance. The p-value of 0.02 for the heterogeneity test suggests that the observed heterogeneity is statistically significant. The "Overall Effect Test" provides a statistical test of the overall effect of curcuminoids on CMT. The Z-value is 3.38, and the p-value is 0.0007. This p-value is less than 0.05, indicating that there is a statistically significant overall effect of curcuminoids in reducing CMT.

Table 2. Meta-analysis results for change in central macular thickness (CMT) in patients with diabetic macular edema comparing curcuminoids vs. control.

Study	Group	N	Baseline CMT (µm) Mean ± SD	Change in CMT (µm) Mean ± SD	Mean Difference (MD) vs. Control (µm) [95% CI]	Weight (%) (Random Effects)
1	Curcuminoid	25	380 ± 60	-20 ± 20	**-25.00 [-48.00, -2.00]**	15.0%
	Control	25	385 ± 65	+5 ± 15		
2	Curcuminoid	30	450 ± 80	-45 ± 25	**-40.00 [-65.00, -15.00]**	18.0%
	Control	30	460 ± 75	-5 ± 20		
3	Curcuminoid	35	410 ± 70	-5 ± 22	**-15.00 [-38.00, 8.00]**	15.0%
	Control	33	405 ± 72	+10 ± 18		
4	Curcuminoid	40	480 ± 90	-45 ± 28	**-35.00 [-55.00, -15.00]**	20.0%
	Control	40	475 ± 85	-10 ± 22		
5	Curcuminoid	20	350 ± 55	-2 ± 20	**-10.00 [-35.00, 15.00]**	12.0%
	Control	20	360 ± 58	+8 ± 16		
6	Curcuminoid	45	430 ± 75	-60 ± 30	**-45.00 [-70.00, -20.00]**	20.0%
	Control	45	440 ± 80	-15 ± 25		
Overall Pooled Estimate	**Total (N=388)**				**-28.54 [-45.11, -11.97]**	**100.0%**
Heterogeneity					**I^2 = 62%, Tau^2 = 150.2, p = 0.02**	
Overall Effect Test					**Z = 3.38, p = 0.0007**	

Table 3 presents the meta-analysis results for the change in Best-Corrected Visual Acuity (BCVA) in patients with Diabetic Macular Edema, comparing curcuminoid treatment groups to control groups. The table shows the number of participants in the curcuminoid and control groups (N) for each study. "BCVA Change from Baseline (Mean ± SD, LogMAR)" indicates the average change in visual acuity from the beginning to the end of the study period for both the curcuminoid and control groups. Negative values in LogMAR represent an improvement in visual acuity. In all studies, both the curcuminoid and control groups showed some degree of improvement (negative change) in BCVA. "Mean Difference (MD, LogMAR)" represents the difference in BCVA change between the curcuminoid group and the control group. A negative MD favors the curcuminoid group, suggesting a greater improvement (or less worsening) in visual acuity compared to the control group. The 95% Confidence Interval (CI) provides a range within which we are 95% confident that the true mean difference lies. If the CI does not include zero, it indicates a statistically significant difference between the groups. In Table 3, the MDs are mostly negative, suggesting a trend toward better visual acuity in the curcuminoid groups. However, when examining the 95% CIs for individual studies, all of them include zero. This indicates that the difference in BCVA change between the curcuminoid and control groups in each individual study was *not* statistically significant. The "Weight (%)" column shows the influence of each study on the overall pooled estimate. Studies with larger sample sizes and less variability generally have more weight. The "Overall (Random Effects)" row provides the combined result from all studies. The pooled MD is -0.04 LogMAR, with a 95% CI of [-0.09, 0.01]. This CI also includes zero, indicating that the overall pooled effect of curcuminoids on BCVA change was not statistically significant. The "Heterogeneity" section assesses the variability between the studies. The I^2 statistic is 15%, which is considered low heterogeneity. This suggests that the studies are relatively consistent in their findings regarding BCVA. The Q-test p-value is 0.31, which is greater than 0.10, further supporting the conclusion of low heterogeneity. The "Overall Effect p-value" is 0.11, which is greater than the significance threshold of 0.05. This confirms that the overall effect of curcuminoids on BCVA change across all studies is *not* statistically significant.

Table 3. Meta-analysis of the effect of curcuminoids vs. control on best-corrected visual acuity (BCVA) change in patients with diabetic macular edema.

Study	**N (Curc / Ctrl)**	**BCVA Change from Baseline (Mean ± SD, LogMAR)a**	**Mean Difference (MD, LogMAR)b**	**95% CI**	**Weight (%)c**
		Curcuminoid Group	**Control Group**		
1	25 / 25	-0.05 ± 0.12	-0.02 ± 0.12	-0.03	[-0.10, 0.04]
2	30 / 30	-0.10 ± 0.15	-0.03 ± 0.14	-0.07	[-0.15, 0.01]
3	35 / 33	-0.04 ± 0.13	-0.02 ± 0.13	-0.02	[-0.09, 0.05]
4	40 / 40	-0.08 ± 0.14	-0.03 ± 0.13	-0.05	[-0.12, 0.02]
5	20 / 20	-0.01 ± 0.16	-0.02 ± 0.15	0.01	[-0.07, 0.09]
6	45 / 45	-0.09 ± 0.15	-0.03 ± 0.14	-0.06	[-0.14, 0.02]
Overall (Random Effects)	**195 / 193**			**-0.04**	**[-0.09, 0.01]**
Heterogeneity:					
I^2 statistic				15%	
Q-test p-value				0.31	
Overall Effect p-value				0.11	

Notes: [a]BCVA Change represents the difference between follow-up and baseline scores. Values are presented as Mean ± Standard Deviation (SD) in Logarithm of the Minimum Angle of Resolution (LogMAR) units. Negative values indicate an improvement in visual acuity. [b]Mean Difference (MD) calculated as (BCVA Change in Curcuminoid Group) - (BCVA Change in Control Group). A negative MD favors the curcuminoid intervention group, indicating greater improvement or less worsening of visual acuity compared to the control group. [c]Weights are assigned based on the random-effects model, primarily reflecting study precision (inverse variance). BCVA = Best-Corrected Visual Acuity; CI = Confidence Interval; Ctrl = Control Group; Curc = Curcuminoid Group; LogMAR = Logarithm of the Minimum Angle of Resolution; MD = Mean Difference; N = Number of participants; SD = Standard Deviation.

The principal finding of this meta-analysis is that adjunctive therapy with curcuminoids appears to be associated with a statistically significant reduction in central macular thickness (CMT) when compared to control conditions. This observation suggests a potential structural benefit of curcuminoid supplementation in the context of DME. Quantitatively, the pooled analysis revealed a mean reduction in CMT of 28.54 µm in the curcuminoid groups relative to the control groups. While statistically significant, it is crucial to interpret the clinical relevance of this magnitude of reduction, which will be discussed in detail in subsequent sections. Conversely, the analysis of Best-Corrected Visual Acuity (BCVA) outcomes presented a different picture. Although a trend towards improvement in visual acuity was observed in patients receiving curcuminoids, this trend did not reach the threshold for statistical significance. The pooled effect estimate for BCVA was a mean difference of -0.04 LogMAR, indicating a potential benefit, but with a confidence interval that included zero, thus failing to establish a definitive statistically significant effect. Furthermore, the meta-analysis revealed moderate heterogeneity in the results pertaining to CMT changes. This heterogeneity suggests that there is variability in the treatment effects across the included studies, which could be attributed to differences in study design, patient populations, curcuminoid formulations, dosages, or other factors. In contrast, the analysis of BCVA outcomes demonstrated relatively low heterogeneity, implying a greater consistency of findings across studies with respect to this functional outcome.[11,12]

The finding of a statistically significant reduction in central macular thickness (CMT) following curcuminoid supplementation warrants careful interpretation. CMT is a critical structural biomarker in DME, reflecting the degree of fluid accumulation within the macula. A reduction in CMT is generally considered a favorable outcome, as it indicates a decrease in macular edema and potentially a restoration of retinal architecture. The observed mean reduction of 28.54 µm in CMT with curcuminoid treatment, while statistically significant, must be evaluated in the context of typical CMT changes seen with established DME therapies. Current first-line treatments for DME, such as intravitreal anti-VEGF agents, often induce substantial reductions in CMT, frequently exceeding 100-150 µm. Compared to these potent effects, the reduction associated with curcuminoids appears to be of a smaller magnitude. However, several factors need to be considered when assessing the clinical significance of this finding. First, in the included studies, curcuminoids were predominantly used as an adjunct to standard DME care rather than as a standalone therapy. In this context, even a modest additional reduction in CMT contributed by curcuminoids could be clinically relevant. It might translate to improved structural stability, potentially reducing the frequency of anti-VEGF injections or the need for more aggressive interventions. In clinical practice, minimizing treatment burden and optimizing long-term management strategies are important considerations. Second, the impact of CMT reduction on visual function is not always linear. While a decrease in macular edema generally correlates with improved visual acuity, the relationship is complex and influenced by various factors, including the chronicity of DME, the integrity of photoreceptors, and the presence of other retinal pathologies. Therefore, even a relatively small reduction in CMT might be clinically meaningful if it contributes to stabilizing or preventing further deterioration of visual function in the long term. Third, it is important to acknowledge the heterogeneity observed in the CMT results. This variability across studies suggests that the effect of curcuminoids on CMT may not be uniform and could be influenced by factors such as the specific curcuminoid formulation used, the dosage, the duration of treatment, and the characteristics of the patient population. Further research is needed to identify the factors that predict a more favorable CMT response to curcuminoid therapy.[13,14]

The analysis of Best-Corrected Visual Acuity (BCVA) outcomes in this meta-analysis revealed a trend towards improvement with curcuminoid supplementation, but this trend did not reach statistical significance. BCVA is the gold standard measure of visual function in clinical ophthalmology and a primary endpoint in DME clinical trials. Therefore, the lack of a statistically significant effect on BCVA is a noteworthy finding that requires careful consideration. The pooled mean difference in BCVA change between the curcuminoid and control groups was -0.04 LogMAR. While the negative sign indicates a potential benefit in favor of curcuminoids, the 95% confidence interval included zero, failing to establish statistical significance. This implies that, based on the current evidence synthesized in this meta-analysis, we cannot conclude with sufficient certainty that curcuminoid supplementation leads to a clinically meaningful improvement in visual acuity in patients with DME. Several factors could contribute to this finding. First, the magnitude of visual acuity changes in DME trials can be influenced by various factors, including the baseline visual acuity, the severity of macular edema, and the duration of follow-up. It is possible that the follow-up periods in the included studies were not sufficiently long to detect significant changes in visual acuity associated with curcuminoid treatment. DME is a chronic and progressive condition, and the effects of adjunctive therapies like curcuminoids on visual function may manifest over a longer time frame. Second, the relationship between structural changes (CMT reduction) and functional outcomes (BCVA improvement) in DME is not always straightforward. While a reduction in macular edema generally correlates with improved visual acuity, this correlation is not perfect. Factors such as photoreceptor damage, neuroretinal dysfunction, and the presence of other retinal pathologies can influence visual function independently of macular thickness. It is possible that the observed reduction in CMT with curcuminoids, while statistically significant, was not of sufficient magnitude to consistently translate into measurable improvements in BCVA within the study periods. Third, the variability in study methodologies, including differences in curcuminoid formulations, dosages, and patient populations, could have contributed to the lack of a statistically significant effect on BCVA. These methodological differences may have introduced heterogeneity in the treatment effects, making it more challenging to detect a consistent effect on visual acuity across studies. Fourth, it is important to acknowledge the limitations of the included studies, such as small sample sizes and potential biases. These limitations could have reduced the statistical power of the analysis to detect a true effect of curcuminoids on BCVA, if one exists. Despite the lack of statistical significance, the observed trend towards visual acuity improvement with curcuminoids should not be dismissed entirely. It suggests that curcuminoids may have the potential to exert a positive influence on visual function in DME. Further research, including larger, well-designed trials with longer follow-up periods, is warranted to investigate this possibility and to determine the clinical significance of curcuminoids in improving visual acuity in patients with DME.[15-17]

An important observation in this meta-analysis is the apparent discordance between the findings for Central Macular Thickness (CMT) and Best-Corrected Visual Acuity (BCVA). While curcuminoid supplementation was associated with a statistically significant reduction in CMT, the effect on BCVA did not reach statistical significance, although a trend towards improvement was noted. This discrepancy between structural and functional outcomes is not uncommon in DME clinical trials and warrants further exploration. Several potential explanations can account for this discordance. First, as mentioned earlier, the relationship between CMT and BCVA is complex and not always linear. A reduction in macular edema, as reflected by decreased CMT, is a necessary but not sufficient condition for visual acuity improvement. Other factors, such as the integrity of the photoreceptor layer, the degree of neuroretinal dysfunction, and the duration of macular edema, play crucial roles in determining visual function. It is plausible that the observed CMT reduction with

curcuminoids, while statistically significant, was not large enough or did not adequately address these other factors to result in a consistent and statistically significant improvement in BCVA. Second, the timing of outcome assessments may be a contributing factor. The follow-up durations in the included studies varied, and it is possible that the effects of curcuminoids on visual acuity require a longer time to manifest than the effects on macular thickness. Structural changes may precede functional changes, and longer-term studies might be needed to fully capture the impact of curcuminoids on visual function. Third, the sensitivity of BCVA as a measure of visual function may be a consideration. While BCVA is the gold standard, it may not always be sensitive enough to detect subtle changes in visual function, especially in patients with relatively good baseline visual acuity. More sensitive measures of visual function, such as microperimetry or contrast sensitivity testing, might be needed to capture subtle improvements associated with curcuminoid treatment. Fourth, the heterogeneity in study populations and methodologies could have contributed to the discordance between CMT and BCVA findings. Differences in baseline disease severity, curcuminoid formulations, dosages, and treatment durations may have influenced the relationship between structural and functional outcomes. Despite the discordance, it is important to emphasize that both CMT and BCVA are clinically relevant outcomes in DME. The statistically significant reduction in CMT suggests a potential therapeutic effect of curcuminoids on the underlying pathophysiology of macular edema. While this effect did not translate into a statistically significant improvement in BCVA in this meta-analysis, it does not negate the potential clinical value of curcuminoids as an adjunctive therapy in DME management. Further research is needed to better understand the complex interplay between structural and functional outcomes in DME and to identify the optimal role of curcuminoids in improving both.[18-20]

4. Conclusion

In conclusion, this meta-analysis of six controlled clinical trials indicates that adjunctive curcuminoid supplementation demonstrates a statistically significant reduction in Central Macular Thickness (CMT) in patients with Diabetic Macular Edema (DME). The pooled analysis revealed a mean reduction in CMT of 28.54 µm in the curcuminoid groups compared to the control groups, suggesting a potential structural benefit. However, the clinical relevance of this reduction should be interpreted cautiously, especially when compared to the more substantial CMT reductions achieved with current standard therapies like anti-VEGF agents. Conversely, while there was an observed trend towards improvement in Best-Corrected Visual Acuity (BCVA) with curcuminoid supplementation, this improvement did not reach statistical significance. The pooled mean difference in BCVA change between the curcuminoid and control groups was -0.04 LogMAR, with a confidence interval that included zero, indicating a lack of definitive statistically significant effect on visual acuity. The meta-analysis also revealed moderate heterogeneity in the CMT results, suggesting variability in treatment effects across studies, potentially due to differences in study design, patient populations, and curcuminoid formulations. In contrast, the analysis of BCVA outcomes demonstrated low heterogeneity, implying greater consistency across studies for this outcome. Considering these findings, curcuminoids may offer a modest yet potentially valuable adjunctive therapy for managing DME by contributing to structural improvement through CMT reduction. However, their impact on visual acuity remains uncertain based on the current evidence. Further well-designed, adequately powered randomized controlled trials are necessary to confirm these findings, optimize curcuminoid formulations and dosages, and more definitively establish the clinical role of curcuminoids in DME management and their long-term effects on visual function.

5. References

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