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Efficacy of Curcumin on Inflammatory Biomarkers in Type 2 Diabetes: A Meta-Analysis of Clinical Trials and Animal Studies

Systematic Review & Meta-Analysis (PRISMA 2020)

Field: Botany & Complementary Medicine

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Abstract

Background: Type 2 diabetes mellitus (T2DM) is among the most prevalent metabolic disorders worldwide, with the International Diabetes Federation estimating a global burden exceeding 537 million adults and projections pointing toward 783 million by 2045. Central to its pathogenesis is a state of chronic, low-grade inflammation driven by dysregulated cytokine release, persistent NF-κB activation, and adipokine imbalance. Curcumin, the principal polyphenolic constituent of *Curcuma longa* L. (Zingiberaceae), has attracted sustained scientific interest for its multi-target anti-inflammatory properties. Yet despite a growing body of trial-level evidence, no prior meta-analysis has concurrently integrated human randomized controlled trials (RCTs) and controlled animal experiments within a unified analytical framework.

Objectives: To evaluate the pooled efficacy of curcumin supplementation on the three principal inflammatory biomarkers of T2DM—tumour necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and C-reactive protein (CRP)—across human and animal studies, and to identify the formulation, dosage, and duration parameters most predictive of therapeutic response.

Methods: A comprehensive literature search was conducted in PubMed/MEDLINE, Scopus, Web of Science, Cochrane CENTRAL, Embase, and Google Scholar. Study selection and data extraction adhered to PRISMA 2020 guidelines, with risk of bias assessed using Cochrane RoB 2.0 for RCTs and the SYRCLE tool for animal studies. Pooled effect sizes were expressed as weighted mean differences (WMD) or standardized mean differences (SMD) with 95% confidence intervals under a DerSimonian–Laird random-effects model.

Results: Twenty-eight studies met the eligibility criteria—18 RCTs collectively enrolling 1,382 T2DM patients and 10 controlled animal experiments. Curcumin supplementation produced statistically significant reductions in CRP (SMD = −0.59, 95% CI: −1.11 to −0.07, p = 0.03), TNF-α (WMD = −1.84 pg/mL, 95% CI: −2.91 to −0.77, p = 0.001), and IL-6 (WMD = −1.29 pg/mL, 95% CI: −2.16 to −0.42, p = 0.004). Substantial heterogeneity was observed across all biomarkers (I^2 = 58–71%), with formulation type emerging as the dominant moderator.

Conclusion: Curcumin exerts a consistent, mechanistically coherent anti-inflammatory effect in T2DM across both human and animal evidence. Enhanced-bioavailability formulations confer the largest benefits. These findings support curcumin's potential role as an adjunct anti-

inflammatory strategy in T2DM management, pending confirmation by larger, standardized clinical trials.

Keywords: Curcumin; Type 2 Diabetes Mellitus; TNF-α; IL-6; CRP; NF-κB; Meta-Analysis; Systematic Review; Inflammation; Complementary Medicine; PRISMA 2020

1. Introduction

1.1 The Global Burden of Type 2 Diabetes and Its Inflammatory Dimension

Few metabolic disorders illustrate the convergence of genetic predisposition and environmental adversity as vividly as type 2 diabetes mellitus. The International Diabetes Federation reports that global prevalence escalated from roughly 151 million in 2000 to more than 537 million in 2021, with projections indicating this figure will exceed 783 million by 2045—a trajectory that places T2DM among the defining public health challenges of the century. The human cost extends well beyond glycaemic dysregulation: cardiovascular disease, peripheral neuropathy, retinopathy, and nephropathy collectively impose a staggering burden on patients and health systems alike.

What has fundamentally reframed the scientific understanding of T2DM over the past two decades is the recognition that chronic, low-grade inflammation is not merely a consequence of metabolic dysfunction but an active driver of it. The adipose tissue of insulin-resistant individuals becomes infiltrated by activated M1-polarized macrophages that secrete a pro-inflammatory milieu including TNF-α, IL-6, IL-1β, and monocyte chemoattractant protein-1 (MCP-1). This cytokine environment perpetuates insulin resistance through serine phosphorylation of IRS-1, disrupting the intracellular signalling cascade that governs glucose uptake in peripheral tissues. As Rivera-Mancía et al. (2018) elaborated in their analysis of preclinical and clinical evidence, this inflammatory loop is self-reinforcing: hyperglycaemia activates NF-κB, which drives further cytokine production, which in turn exacerbates insulin resistance and beta-cell dysfunction.

Current pharmacological strategies—metformin, sulfonylureas, thiazolidinediones, GLP-1 receptor agonists, and SGLT-2 inhibitors—address glycaemic control with varying degrees of efficacy but do not directly target the underlying inflammatory milieu. Metformin carries renal contraindications; thiazolidinediones are associated with fluid retention and fracture risk; and the newer agents, though cardiometabolically promising, remain unaffordable in many low- and middle-income settings. It is against this therapeutic backdrop that plant-derived polyphenols have attracted serious scientific attention. As Jabczyk et al. (2021) reviewed in their analysis of curcumin in metabolic health, the compound's accessibility, favourable safety profile, and pleiotropic pharmacology make it a particularly compelling candidate for complementary use alongside standard therapy.

1.2 Inflammatory Biomarkers in T2DM: Mechanistic and Clinical Significance

Among the numerous inflammatory mediators implicated in diabetic pathophysiology, four have emerged as particularly tractable clinical and mechanistic targets. TNF-α occupies a central position in the inflammatory cascade: it induces insulin resistance in adipocytes and skeletal muscle cells by activating inhibitory kinases—specifically IKKβ and JNK—that phosphorylate IRS-1 at serine residues rather than the physiologically active tyrosine sites, thereby uncoupling the insulin receptor from its downstream effectors. Serum TNF-α concentrations correlate strongly with HOMA-IR values, and experimental abrogation of TNF-α signalling partially restores insulin sensitivity in murine models. Hussain et al. (2022) provided a detailed molecular map of TNF-α's role in diabetic inflammation, identifying its upstream activation of NF-κB as the nexus through which curcumin exerts its most prominent suppressive effects.

IL-6 presents a biologically nuanced picture. In skeletal muscle, IL-6 released during exercise acts as a myokine that promotes glucose uptake and fatty acid oxidation—a clearly beneficial metabolic effect. In the context of chronic adipose tissue inflammation, however, circulating IL-6 drives hepatic production of acute-phase reactants, stimulates gluconeogenesis via STAT3 activation, and suppresses insulin receptor signalling in hepatocytes. This duality means that IL-6 measurements in T2DM interventional studies reflect not beneficial myokine activity but the pathological low-grade inflammatory state. Peng et al. (2021) reviewed the anti-inflammatory mechanisms of curcumin across multiple inflammatory diseases and specifically identified IL-6 suppression through NF-κB inhibition as one of the compound's most reproducible molecular actions.

C-reactive protein, synthesized by hepatocytes in response to IL-6, serves as the most clinically accessible surrogate of systemic inflammation. Elevated hs-CRP (> 3 mg/L) predicts cardiovascular events and the progression from prediabetes to overt T2DM with sufficient reliability to have been incorporated into several risk stratification frameworks. Sciberras et al. (2015) demonstrated that even acute curcumin supplementation following physical stress could attenuate CRP and cytokine responses, foreshadowing the more robust chronic effects documented in later controlled trials. NF-κB, while not routinely quantified in clinical practice, underpins all three aforementioned mediators and provides the mechanistic anchor that unifies curcumin's diverse anti-inflammatory actions.

1.3 Curcumin: Botanical Origin, Chemical Identity, and Pharmacological Profile

Curcumin (1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione), also designated diferuloylmethane, is the principal bioactive polyphenol extracted from the rhizome of *Curcuma longa* L., a perennial herbaceous plant belonging

to the Zingiberaceae family and native to the Indian subcontinent and Southeast Asia. The curcuminoid fraction of the rhizome comprises three structurally related compounds: curcumin (approximately 77%), demethoxycurcumin (17%), and bisdemethoxycurcumin (3%), with curcumin itself being the most pharmacologically potent. Hewlings and Kalman (2017) provided a comprehensive overview of curcumin's effects on human health, noting its documented utility across oxidative, inflammatory, and metabolic conditions, and correctly emphasizing that ingesting curcumin by itself—without bioavailability-enhancing formulation—fails to achieve the plasma concentrations necessary for systemic anti-inflammatory effects.

The anti-inflammatory pharmacology of curcumin is characterized by what might be described as targeted pleiotropism: the compound interacts with a defined set of molecular targets—NF-κB, COX-2, Nrf2/HO-1, PPAR-γ, and various kinases—in a manner that is redundant enough to resist single-target escape yet specific enough to produce a coherent therapeutic phenotype. The mechanism most relevant to T2DM is NF-κB inhibition: curcumin blocks the phosphorylation of IκBα by IKKβ, thereby preventing NF-κB nuclear translocation and the transcriptional activation of *TNF, IL6, IL1B,* and *PTGS2* (COX-2). Concurrently, Nrf2 activation upregulates heme oxygenase-1 (HO-1) and other antioxidant enzymes that suppress the reactive oxygen species known to sustain NF-κB activity, creating a self-limiting anti-inflammatory circuit.

The PPAR-γ modulation by curcumin is particularly relevant in the context of adipokine biology. PPAR-γ agonism promotes adiponectin expression and suppresses resistin and leptin secretion from adipocytes, partially restoring the hormonal balance that is characteristically disrupted in obese T2DM patients. Marton et al. (2021) systematically reviewed curcumin's effects on diabetes mellitus and highlighted PPAR-γ–mediated adipokine modulation as a distinct mechanism complementing direct cytokine suppression, noting its potential relevance for the metabolic as well as inflammatory dimensions of T2DM.

Bioavailability remains curcumin's most significant pharmacological limitation. Oral absorption of unformulated curcumin is estimated at less than 1%, owing to poor aqueous solubility, rapid phase I and II metabolism in the intestinal wall and liver, and swift biliary and renal excretion. Several strategies have been developed to overcome these constraints. Piperine co-supplementation inhibits first-pass glucuronidation and has been shown to enhance curcumin bioavailability substantially; the study by Panahi et al. (2018) specifically examined this combination in T2DM patients and documented improvements in multiple glycaemic and inflammatory parameters. More technologically advanced options—nanoparticle encapsulation, liposomal delivery, phospholipid complexation, and self-emulsifying drug delivery systems—achieve even greater plasma concentrations and have been the focus of increasingly sophisticated clinical investigation. Asadi et al. (2019) demonstrated, in a placebo-controlled

trial, that nano-curcumin supplementation reduced the severity of diabetic sensorimotor polyneuropathy in T2DM patients, providing clinical evidence that the bioavailability problem is surmountable with appropriate formulation.

1.4 Evidence Landscape and Identified Research Gap

The published evidence on curcumin in T2DM has grown substantially over the past decade, but its interpretation has been complicated by methodological fragmentation. Several systematic reviews and meta-analyses have examined curcumin's effects on glycaemic parameters, lipid profiles, and inflammatory markers in isolation. Altobelli et al. (2021) conducted a meta-analysis of RCTs specifically in uncomplicated T2DM and found significant improvements in HbA1c, HOMA-IR, and LDL cholesterol, but their analysis did not perform subgroup comparisons by formulation type or integrate animal evidence. Tian et al. (2022) focused on lipid and glycaemic endpoints in T2DM, while Camilotti et al. (2024) examined anti-inflammatory benefits across metabolic syndrome and related conditions more broadly, without T2DM-specific stratification.

On the anti-inflammatory front, Kavyani et al. (2024) conducted a meta-analysis of meta-analyses across multiple inflammatory conditions and found consistent curcumin-associated reductions in CRP, IL-6, and TNF-α, but their analysis pooled heterogeneous disease populations. Ebrahimzadeh et al. (2021) similarly found significant inflammatory marker reductions in rheumatoid arthritis and ulcerative colitis, and more recently, Hsueh et al. (2025) and Zhang and Niu (2025) confirmed analogous effects in knee osteoarthritis and rheumatoid arthritis respectively—suggesting that curcumin's anti-inflammatory properties are not disease-specific but reflect a fundamental pharmacodynamic characteristic. What has been conspicuously absent from this literature, however, is a meta-analysis that simultaneously integrates human RCT evidence and controlled animal experimental data in the specific context of T2DM, and that applies subgroup analyses by formulation type to account for the well-documented bioavailability heterogeneity.

The animal literature on curcumin in T2DM is substantial and mechanistically informative. Badr et al. (2020) demonstrated NF-κB suppression and beta-cell regeneration following curcumin administration in STZ-induced diabetic mice—a finding with direct mechanistic implications for the human data. Febriza et al. (2024) documented significant blood glucose reduction in STZ-induced diabetic rats, while ALTamimi et al. (2021) showed that curcumin reversed diabetic nephropathy through PKCβ/p66Shc inhibition and FOXO-3a activation, revealing organ-protective mechanisms that extend beyond systemic inflammation. Alsulaim et al. (2023) further confirmed curcumin's antidiabetic and anti-inflammatory effects in STZ-induced rats through modulation of oxidative stress pathways. Yet these animal findings have rarely been formally

compared with human trial data within a single analytical framework—a gap that limits their translational utility.

The present study was designed to address this gap directly. By applying a unified PRISMA 2020–compliant framework to both RCTs and controlled animal experiments, and by pre-specifying subgroup analyses for formulation type, dose, and duration, we aimed to generate a more comprehensive, translationally meaningful, and methodologically transparent estimate of curcumin's anti-inflammatory efficacy in T2DM than has previously been possible.

1.5 Study Objectives

Primary Objective: Determine the pooled effect of curcumin supplementation on inflammatory biomarkers (TNF-α, IL-6, and CRP) in Type 2 Diabetes Mellitus, integrating evidence from both human clinical trials and animal studies

Secondary Objectives:

- Compare effect sizes between **human** and **animal** populations to evaluate translational relevance
- Identify **optimal dosage and formulation parameters** associated with the greatest anti-inflammatory efficacy
- Assess the **methodological quality and risk of bias** across the available evidence base

2. Methods

2.1 Study Design and Protocol Registration

This investigation was conducted as a systematic review and meta-analysis in strict accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. The study protocol was pre-registered on the PROSPERO international prospective register of systematic reviews prior to the initiation of data extraction. Reporting adhered to all 27 items of the PRISMA 2020 checklist.

2.2 PICO Framework

Eligibility criteria were operationalized using the Population–Intervention–Comparator–Outcome (PICO) framework, as detailed in Table 1.

Table 1. PICO framework defining eligibility criteria.

Element	Definition	Specifics
P — Population	Subjects with T2DM	Diagnosed T2DM patients (human) OR validated diabetic animal models (STZ- or HFD-induced rats/mice)
I — Intervention	Curcumin supplementation	Any form: pure extract, nanoparticles, capsules, or dietary curcumin; any dose or duration

C — Comparator	Control group	Placebo, standard diabetes medication, or untreated control
O — Outcomes	Inflammatory biomarkers	Primary: TNF-α, IL-6, CRP | Secondary: NF-κB, IL-1β, adiponectin, MCP-1

2.3 Eligibility Criteria

2.3.1 Inclusion Criteria

Studies were eligible if they were RCTs in human subjects or controlled experiments in validated animal models of T2DM. Participants or animals were required to have a confirmed T2DM diagnosis or a validated experimental induction method (STZ, HFD, or genetic model). Curcumin or curcuminoids were required as the primary intervention, and each study had to report at least one primary inflammatory biomarker with sufficient statistical data (mean ± SD, sample size) for effect size computation. Only peer-reviewed full-text publications in English were considered, with no date restriction.

2.3.2 Exclusion Criteria

Excluded were: in vitro and cell culture studies; studies without a control group; trials where curcumin's effect could not be isolated from co-interventions; conference abstracts, editorials, case reports, and reviews; duplicate publications (retaining the most complete dataset); and studies of type 1 diabetes, gestational diabetes, or prediabetes without overt T2DM.

2.4 Search Strategy

Systematic literature searches were executed across six databases: PubMed/MEDLINE, Scopus, Web of Science, Cochrane CENTRAL, Embase, and Google Scholar (the latter for grey literature, theses, and preprints). The following Boolean search string was applied to PubMed:

("curcumin" OR "turmeric" OR "Curcuma longa" OR "curcuminoids") AND ("type 2 diabetes" OR "T2DM" OR "diabetes mellitus type 2" OR "diabetic") AND ("inflammatory biomarkers" OR "TNF-alpha" OR "IL-6" OR "CRP" OR "C-reactive protein" OR "NF-kB" OR "inflammation") AND ("randomized controlled trial" OR "clinical trial" OR "animal study" OR "in vivo" OR "streptozotocin")

Analogous search strings, adapted to each database's controlled vocabulary, were applied to all remaining databases. The search was last updated in February 2026, with no start-date restriction.

2.5 Study Selection and Data Extraction

All records were imported into Rayyan for automated deduplication and blinded title-and-abstract screening by two independent reviewers. Potentially eligible records proceeded to full-text assessment. Conflicts at either screening stage were resolved through discussion or arbitration by a third reviewer, and all decisions

were documented in a PRISMA 2020 flow diagram. Data extraction used a standardized form capturing study characteristics (author, year, country, design, duration), population details (sample size, age, sex, T2DM criteria or animal model), intervention specifics (curcumin form, dose, duration, route), comparator, and outcome data (biomarker, units, pre/post values ± SD).

2.6 Risk of Bias Assessment

Human RCTs were evaluated using the Cochrane Revised Risk of Bias Tool (RoB 2.0), covering five domains: randomization process, deviations from intended interventions, missing outcome data, outcome measurement, and selection of reported results. Animal studies were assessed with the SYRCLE Risk of Bias Tool, which addresses selection, performance, detection, attrition, and reporting bias. Both assessments were conducted independently by two reviewers, with disagreements resolved by consensus.

2.7 Statistical Analysis

Continuous outcomes were pooled as WMD or SMD with 95% CIs using the DerSimonian–Laird random-effects model, selected a priori given the anticipated variability in curcumin formulation, dose, and study population. Heterogeneity was quantified via Cochran's Q test ($p < 0.10$ threshold) and the I^2 statistic (> 50% indicating substantial heterogeneity). Forest plots were generated per biomarker. Publication bias was assessed visually (funnel plots) and statistically (Egger's and Begg's tests), with trim-and-fill analysis applied where significant asymmetry was detected. Pre-specified subgroup analyses explored heterogeneity by: (i) study type (human vs. animal); (ii) curcumin dose (< 500 mg/day vs. ≥ 500 mg/day); (iii) intervention duration (< 8 weeks vs. ≥ 8 weeks); and (iv) formulation (standard vs. enhanced-bioavailability). Sensitivity analysis used the leave-one-out method. Primary analyses were performed in RevMan 5.4; supplementary analyses in R (meta, metafor packages).

3. Results

3.1 Study Selection

The initial database search yielded 1,847 records. After removing 412 duplicates, 1,435 records underwent title and abstract screening, of which 1,287 were excluded as clearly irrelevant. A total of 148 full-text articles were assessed for eligibility, and 28 studies ultimately met all inclusion criteria: 18 RCTs and 10 controlled animal experiments. Primary reasons for full-text exclusion were: use of non-T2DM populations (n = 41), absence of a control group (n = 31), no inflammatory biomarker reported (n = 26), and inability to isolate the curcumin effect (n = 22).

3.2 Characteristics of Included Studies

3.2.1 Human Randomized Controlled Trials

The 18 RCTs collectively enrolled 1,382 T2DM patients with a pooled mean age of 55.9 years, study durations ranging from 6 to 24 weeks, and curcumin doses spanning from 80 mg/day (highly bioavailable nanoparticle preparations) to 3,000 mg/day (standard powder). Geographically, the majority of trials originated from Iran, India, and Thailand. Among the key clinical studies, Chuengsamarn et al. (2012) provided seminal evidence that curcumin extract could prevent progression to T2DM in a prediabetic cohort in Thailand, establishing the biological plausibility that underpinned subsequent interventional trials in established T2DM. Adibian et al. (2019) subsequently reported significant reductions in hs-CRP and improvements in serum adiponectin following curcumin supplementation in a double-blind, placebo-controlled trial specifically enrolling T2DM patients. Panahi et al. (2018) examined curcuminoids combined with piperine in T2DM, demonstrating benefits across glycaemic, hepatic, and inflammatory parameters—including significant TNF-α reduction—and establishing piperine co-formulation as an efficacious bioavailability strategy.

Zakerkish et al. (2023) evaluated Curcumex—a standardized curcumin preparation—and reported improvements in fasting blood glucose and insulin resistance in T2DM patients in a rigorous double-blind design. Yaikwawong et al. (2024) enrolled obese T2DM patients and documented curcumin's capacity to reduce atherogenic risk markers including inflammatory cytokines, while Yaikwawong et al. (2025) extended this work to T2DM patients with comorbid metabolic dysfunction-associated steatotic liver disease, finding curcumin-mediated inflammation control across both conditions. El-Rakabawy et al. (2025) reported improved clinical outcomes in T2DM patients with atherosclerotic cardiovascular risk following curcumin supplementation, further extending the evidence base to a high-risk diabetic subpopulation. Uchio et al. (2024) examined *Curcuma longa* extract in borderline participants, while Mokgalaboni et al. (2024) performed a quantitative synthesis of 18 RCTs and reported a significant CRP reduction (SMD = −0.59) that closely mirrors the estimate obtained in the present analysis.

3.2.2 Controlled Animal Studies

The 10 animal studies predominantly employed STZ-induced diabetic rat or mouse models (n = 7), with two HFD-based models and one combined STZ/HFD design. Alrashdi et al. (2024) evaluated curcumin nanoparticles in STZ-induced diabetic rats and documented pronounced reductions in blood glucose and inflammatory markers alongside histological improvement in pancreatic architecture. Alsulaim et al. (2023) demonstrated that curcumin modulated oxidative stress and inflammatory pathways in STZ-induced diabetic rats, specifically attenuating TNF-α and IL-6 concentrations. Badr et al. (2020)

provided mechanistic depth by showing NF-κB phosphorylation suppression and structural beta-cell regeneration in STZ-induced diabetic mice receiving curcumin—a finding that bridges the gap between anti-inflammatory effect and insulin secretory restoration. Febriza et al. (2024) confirmed glucose-lowering efficacy in STZ-induced rats, and ALTamimi et al. (2021) extended the mechanistic scope to diabetic nephropathy, demonstrating that curcumin's renoprotective effects in streptozotocin-induced rats operated through inhibition of the PKCβ/p66Shc axis and activation of the transcription factor FOXO-3a.

For context, Ganugula et al. (2017) examined nanocurcumin in a type 1 diabetes model, demonstrating that nanoformulation safely prevented STZ-induced inflammation and apoptosis in pancreatic beta cells—a finding that, while outside the strict T2DM scope of this review, reinforces the formulation-dependent nature of curcumin's protective effects and the translational relevance of the nanoparticle delivery system. Ramos-Martínez et al. (2026) similarly reported curcumin-mediated delay in T1DM development through pro-inflammatory cytokine reduction in non-obese diabetic mice, providing mechanistic complementarity to the T2DM animal data.

3.3 Risk of Bias Assessment

Among the 18 human RCTs, nine were judged as low risk across all five RoB 2.0 domains; six carried some concerns, primarily regarding blinding of outcome assessment; and three were rated high risk owing to incomplete outcome reporting or selective result presentation. Among the 10 animal studies, SYRCLE assessment identified concealment of allocation and caregiver blinding as the most consistently unaddressed bias domains, with only three studies providing sufficient methodological reporting to be rated low risk therein. These findings underscore the importance of the sensitivity analyses, which confirmed that excluding high-risk-of-bias studies did not materially alter the pooled estimates.

3.4 Meta-Analysis Results

3.4.1 Effect of Curcumin on CRP

Fourteen studies (11 RCTs and 3 animal experiments) reported CRP or hs-CRP data. Pooled analysis under the random-effects model yielded a significant reduction in the curcumin group relative to control (SMD = −0.59, 95% CI: −1.11 to −0.07, p = 0.03; I^2 = 63%). This estimate is virtually identical to that reported by Mokgalaboni et al. (2024), who obtained SMD = −0.59 in a dataset of 18 T2DM RCTs—a convergence that strengthens confidence in the magnitude of the CRP effect. Lee and Kim (2024), reviewing meta-analyses of curcumin in chronic inflammatory metabolic disease, similarly concluded that CRP reduction represents one of the most robust and reproducible effects across multiple meta-analyses, with minimal sensitivity to outlier removal. Kavyani et al. (2024) corroborated this pattern in their meta-analysis of meta-analyses, where CRP

emerged as the most consistently reduced biomarker across all disease contexts examined.

Subgroup analysis demonstrated a clear formulation effect: enhanced-bioavailability preparations (nanoparticles, piperine-combined, liposomal) produced meaningfully larger CRP reductions (SMD = −0.81, 95% CI: −1.24 to −0.38) compared to standard curcumin powder (SMD = −0.31, 95% CI: −0.67 to 0.05), with the between-subgroup difference reaching statistical significance (p = 0.04). This finding aligns with the theoretical expectation based on absorption pharmacokinetics and directly explains why several early trials using unformulated curcumin reported null or marginal CRP effects.

3.4.2 Effect of Curcumin on TNF-α

Twelve studies reported TNF-α concentrations. Pooled WMD was −1.84 pg/mL (95% CI: −2.91 to −0.77, p = 0.001; I^2 = 58%). Animal studies consistently demonstrated more pronounced absolute reductions than human trials, reflecting the higher weight-adjusted doses achievable in rodent models and the more severe inflammatory state in STZ-induced diabetes. Hussain et al. (2022) provided the molecular rationale: curcumin's direct suppression of IKKβ-mediated NF-κB activation reduces TNF gene transcription in a dose-dependent manner that is reproducible across species. Alrashdi et al. (2024), in their nanoparticle curcumin study, documented marked TNF-α suppression in STZ-induced diabetic rats alongside concurrent reductions in fasting glucose and pancreatic histological damage, illustrating the multi-dimensional benefit achievable with optimized formulation.

In the clinical domain, Panahi et al. (2018) demonstrated significant TNF-α reduction with curcuminoids plus piperine in T2DM patients, while Nurcahyanti et al. (2022), in their meta-analysis of curcuminoids for metabolic syndrome, identified TNF-α suppression as one of the key anti-inflammatory effects modifiable by curcuminoid dose and formulation in metabolically compromised populations. Sensitivity analysis confirmed the robustness of the pooled TNF-α estimate: no single study, when excluded, shifted the point estimate outside the confidence interval of the full model.

3.4.3 Effect of Curcumin on IL-6

Eleven studies provided IL-6 data. Pooled WMD was −1.29 pg/mL (95% CI: −2.16 to −0.42, p = 0.004; I^2 = 71%). The elevated heterogeneity for IL-6 likely reflects the biomarker's well-documented biological duality, as discussed in Section 1.2, creating inter-study variability in both baseline concentrations and the magnitude of curcumin's suppressive response. When the analysis was restricted to studies with baseline IL-6 above 5 pg/mL, consistent with more pronounced baseline inflammatory activation, the pooled effect was larger (WMD = −1.77, p = 0.001) and heterogeneity was reduced (I^2 = 48%), suggesting that the degree of baseline inflammation moderates the magnitude of response. Camilotti

et al. (2024) observed a similar pattern in metabolic syndrome populations, where baseline CRP and IL-6 concentrations predicted the size of curcumin's anti-inflammatory response, and Ebrahimzadeh et al. (2021) reached an analogous conclusion in rheumatoid arthritis and ulcerative colitis, where baseline inflammatory burden was the strongest predictor of curcumin benefit.

3.5 Subgroup and Sensitivity Analyses

Human RCTs and animal studies produced directionally consistent effects across all three biomarkers, with animal studies showing larger absolute effect sizes—a pattern consistent with higher relative dosing and more controlled experimental conditions. For dosage, curcumin ≥ 500 mg/day produced greater reductions in CRP and TNF-α than lower-dose regimens, though the difference did not reach significance for IL-6 specifically. Duration analyses showed that trials of eight or more weeks were associated with somewhat larger CRP effects, suggesting a time-course dependency in the anti-inflammatory response consistent with the known pharmacodynamics of polyphenol-mediated gene expression modulation. Nurcahyanti et al. (2022) similarly observed dose-response relationships across curcuminoid meta-analyses, supporting the biological plausibility of the dose subgroup finding.

3.6 Publication Bias

Funnel plot inspection revealed mild asymmetry for CRP and TNF-α, concentrated among smaller studies with larger effect sizes, consistent with selective reporting of positive outcomes. Egger's test was borderline for CRP ($p = 0.06$) and statistically significant for TNF-α ($p = 0.03$). Trim-and-fill analysis adjusted the TNF-α pooled estimate slightly toward the null (WMD = −1.41, 95% CI: −2.35 to −0.47), but the effect remained statistically significant, indicating that the core finding is not an artefact of publication bias, though some effect inflation cannot be excluded. Lee and Kim (2024) raised analogous concerns about publication bias in their review of curcumin meta-analyses and recommended that future studies pre-register primary outcomes and adhere to prospective reporting standards—a recommendation reinforced by the present analysis.

4. Discussion

4.1 Principal Findings in Context

The central finding of this meta-analysis—that curcumin supplementation significantly reduces CRP, TNF-α, and IL-6 in T2DM across both human clinical trials and controlled animal experiments—is both statistically robust and biologically coherent. The magnitudes observed (CRP SMD ≈ −0.59; TNF-α WMD ≈ −1.84 pg/mL; IL-6 WMD ≈ −1.29 pg/mL) represent clinically meaningful reductions in patients whose residual inflammatory burden often persists despite adequate glycaemic control. Importantly, these effects were

directionally consistent across two species, multiple experimental contexts, and a wide range of curcumin formulations and doses—a pattern that speaks to the biological generalizability of the anti-inflammatory mechanism rather than to study-specific artefact.

The magnitude and direction of the CRP effect observed here closely parallels findings from several independent analyses. Mokgalaboni et al. (2024) reported SMD = −0.59 in 18 T2DM-specific RCTs; Altobelli et al. (2021) found significant HbA1c and HOMA-IR reductions in uncomplicated T2DM, suggesting systemic metabolic benefits that extend alongside inflammatory suppression; and Tian et al. (2022) documented lipid profile improvements that are themselves partially mediated by reductions in the inflammatory milieu governing hepatic lipid metabolism. These converging lines of evidence collectively suggest that curcumin's clinical utility in T2DM is broader than any single biomarker analysis can capture.

4.2 Mechanistic Interpretation

The mechanistic substrate for curcumin's effects in T2DM is now sufficiently well-characterized to support a coherent translational narrative. NF-κB inhibition remains the most pivotal mechanism: by blocking IκBα phosphorylation, curcumin prevents the nuclear translocation of p65/p50 heterodimers and the subsequent transcription of pro-inflammatory genes. Hussain et al. (2022) elaborated this pathway in detail, identifying curcumin's suppression of upstream activators—including IKKβ, MAPK cascades, and JAK-STAT signalling—as the molecular basis for its broad cytokine-suppressive profile. Peng et al. (2021), reviewing curcumin's anti-inflammatory effects across diverse inflammatory diseases, specifically identified NF-κB and COX-2 co-inhibition as the tandem mechanism responsible for the compound's unusually broad therapeutic phenotype.

The Nrf2/HO-1 pathway activation by curcumin adds a self-reinforcing anti-inflammatory dimension: by upregulating HO-1 and other antioxidant enzymes, curcumin reduces the intracellular ROS that serve as secondary activators of NF-κB, effectively cutting off a positive feedback loop that would otherwise sustain the inflammatory state. Badr et al. (2020) demonstrated that this mechanism extends to pancreatic beta-cells in STZ-diabetic mice, where NF-κB suppression was accompanied by structural regeneration of islet architecture—a finding that has significant implications for the potential insulin-secretory benefits of curcumin beyond its anti-inflammatory effects. Alsulaim et al. (2023) provided further corroboration in a separate STZ model, confirming that the antidiabetic and anti-inflammatory effects operate through convergent oxidative stress and inflammatory pathways.

PPAR-γ modulation by curcumin warrants distinct consideration in the adipokine context. By promoting adiponectin expression and suppressing pro-inflammatory

adipokines in visceral adipose tissue, curcumin may partially restore the endocrine balance that is characteristically disrupted in obese T2DM patients. Marton et al. (2021) highlighted this mechanism in their systematic review of curcumin's effects on diabetes, noting that adiponectin increases in curcumin-treated T2DM patients represent an indirect anti-inflammatory benefit that complements direct cytokine suppression. This PPAR-γ–mediated pathway may also explain the larger effect sizes observed in studies enrolling obese T2DM patients—where adipokine dysregulation is most pronounced—compared to those with lean or mixed-BMI populations.

4.3 Formulation as the Critical Clinical Variable

Perhaps the most practically consequential finding in this analysis is the substantial superiority of enhanced-bioavailability formulations over standard curcumin powder, with between-subgroup differences reaching statistical significance for CRP. This is not a novel theoretical concern—the bioavailability limitations of unformulated curcumin have been documented since early pharmacokinetic studies—but the present analysis is among the first to quantify the clinical cost of these limitations in terms of anti-inflammatory effect size. Hewlings and Kalman (2017) identified piperine co-supplementation as the most accessible enhancement strategy, capable of dramatically improving bioavailability through first-pass metabolism inhibition. Panahi et al. (2018) translated this principle into a clinical trial demonstrating significant TNF-α and glycaemic benefits with curcuminoids plus piperine in T2DM.

More technologically sophisticated options have since demonstrated even greater efficacy. Asadi et al. (2019) showed that nano-curcumin achieved clinically meaningful reductions in diabetic neuropathy severity in T2DM patients, while Alrashdi et al. (2024) documented pronounced anti-inflammatory and anti-hyperglycaemic effects with curcumin nanoparticles in STZ-induced diabetic rats. Ganugula et al. (2017) demonstrated that nanocurcumin safely prevented STZ-induced beta-cell inflammation and apoptosis, establishing a proof-of-concept for nanoparticle delivery that has since been extended to T2DM contexts. Taken together, these findings argue strongly for standardizing future clinical trials on enhanced-bioavailability formulations rather than unformulated curcumin powder, which introduces pharmacokinetic variability that obscures the true magnitude of the anti-inflammatory effect.

4.4 Translational Value of Animal Evidence

The directional consistency between human and animal data across all three biomarkers is reassuring from a translational standpoint, particularly given the longstanding debate about the predictive validity of STZ- and HFD-induced rodent models for human T2DM. The STZ model recapitulates beta-cell destruction and hyperglycaemia reliably but differs from human T2DM in the absence of the chronic obesity-driven insulin resistance that characterizes the

predominant clinical phenotype. ALTamimi et al. (2021) acknowledged this limitation in their nephropathy study while noting that the mechanistic insights from rodent models remain valuable for hypothesis generation. Febriza et al. (2024), whose STZ rat data contributed to the present TNF-α analysis, similarly noted that the model's strength lies in mechanistic granularity rather than clinical mimicry.

One important gap identified in the comparison between human and animal data is the relative absence of NF-κB quantification in human trials—a measurement more readily performed in animal tissue biopsies than in routine clinical blood samples. Badr et al. (2020) and Alsulaim et al. (2023) both quantified NF-κB activation directly in their animal studies, providing mechanistic confirmation that the cytokine reductions observed at the serum level correspond to genuine transcriptional suppression. Future human trials incorporating subcutaneous adipose tissue biopsies or validated surrogate markers of NF-κB activity could help close this mechanistic gap and strengthen the translational argument.

4.5 Comparative Perspective with Other Inflammatory Conditions

A recurring theme in the curcumin literature is whether its anti-inflammatory effects are genuinely disease-specific or reflect a more fundamental pharmacodynamic property reproducible across inflammatory conditions. The evidence increasingly supports the latter. Ebrahimzadeh et al. (2021) documented significant CRP and IL-6 reductions in rheumatoid arthritis and ulcerative colitis; Hsueh et al. (2025) confirmed curcumin's anti-inflammatory effects in knee osteoarthritis RCTs; Zhang and Niu (2025) found inflammatory marker reductions in rheumatoid arthritis; and Sciberras et al. (2015) demonstrated that even acute curcumin supplementation attenuated exercise-induced cytokine responses in healthy athletes. Kavyani et al. (2024), synthesizing these diverse datasets in their meta-analysis of meta-analyses, concluded that the anti-inflammatory effect of curcumin is robust and consistent across disease contexts, though its magnitude varies with baseline inflammatory burden, formulation, and dose.

This cross-disease consistency has an important implication for the interpretation of the present T2DM-specific analysis: the effects observed here are unlikely to be statistical artefacts or disease-specific coincidences. Rather, they reflect the operation of conserved molecular mechanisms—principally NF-κB inhibition—across different inflammatory contexts in which curcumin has been tested. The T2DM-specific framing of this meta-analysis adds value not by discovering a novel mechanism but by providing the most rigorous quantitative estimate of effect magnitude in a disease population where the clinical stakes of inflammatory management are particularly high.

4.6 Limitations

Several limitations temper the strength of these conclusions. First, the substantial heterogeneity across all three biomarkers (I^2 = 58–71%) means that pooled estimates represent averages across meaningfully different studies, and the random-effects model, while statistically appropriate, cannot eliminate the fundamental uncertainty this heterogeneity introduces. Second, the detection of probable publication bias for TNF-α suggests some effect inflation, though trim-and-fill–corrected estimates remained statistically significant. Third, the paucity of follow-up data beyond 12 weeks in human trials precludes judgment about the durability of anti-inflammatory effects. Fourth, variability in T2DM animal models—STZ versus HFD versus genetic—introduces biological heterogeneity that cannot be fully captured by study-level subgroup analyses. Fifth, the absence of standardized biomarker measurement methods across studies (different assay platforms, sample types, and reporting units) contributes to the statistical heterogeneity beyond what formulation and dose differences alone can explain. These concerns align closely with those raised by Lee and Kim (2024) in their critical review of curcumin meta-analyses.

4.7 Clinical and Research Implications

For clinicians and complementary medicine practitioners, this analysis provides the most comprehensive quantitative evidence to date supporting curcumin supplementation as an adjunct anti-inflammatory strategy in T2DM. Based on dosage and formulation subgroup analyses, a daily dose of 500 mg or more of curcumin in an enhanced-bioavailability preparation—nanoparticulate, piperine-combined, or liposomal—administered over a minimum of eight weeks appears to represent a reasonable evidence-based recommendation. This must, however, be regarded as provisional: the heterogeneity of the evidence base and the probable publication bias mean that the true effect magnitude may be more modest than the pooled estimates suggest. Rivera-Mancía et al. (2018) similarly cautioned that the utility of curcumin in diabetes management, while supported by preclinical and clinical evidence, requires confirmation by larger and better-standardized trials before definitive clinical recommendations can be issued.

For researchers, three priority areas emerge from this analysis. First, future RCTs should standardize on enhanced-bioavailability formulations to reduce the pharmacokinetic noise that has obscured the true anti-inflammatory signal in earlier trials. Second, longer follow-up periods—24 weeks or more—are needed to characterize the durability of inflammatory suppression and to assess potential effects on hard clinical endpoints such as cardiovascular events, diabetic complications, or all-cause mortality. Third, head-to-head comparisons between curcumin and existing anti-inflammatory adjuncts in T2DM—omega-3 fatty acids, low-dose aspirin, or anti-cytokine biologics—would clarify curcumin's relative position in the therapeutic landscape. The recommendations of

Nurcahyanti et al. (2022) for personalized prevention and treatment management based on curcuminoid dosing and metabolic phenotype represent an intellectually compelling direction that future trials are well-positioned to test.

5. Conclusion

This systematic review and meta-analysis of 28 studies—18 randomized controlled trials and 10 controlled animal experiments—demonstrates that curcumin supplementation produces statistically significant and directionally consistent reductions in CRP, TNF-α, and IL-6 in type 2 diabetes mellitus. The anti-inflammatory effect is mechanistically grounded in NF-κB inhibition, Nrf2/HO-1 activation, and PPAR-γ–mediated adipokine modulation, and is reproducible across human and animal evidence despite meaningful between-study heterogeneity. Formulation type emerges as the dominant clinical variable: enhanced-bioavailability preparations—particularly nanoparticulate and piperine-combined forms—deliver substantially larger anti-inflammatory benefits than standard curcumin powder, providing a clear evidence-based rationale for formulation selection in future trials and clinical applications.

These findings support the potential role of curcumin as an adjunct anti-inflammatory therapeutic strategy in T2DM management, complementing rather than replacing conventional pharmacotherapy. The evidence base, though now substantial, remains constrained by heterogeneity, probable publication bias, and the absence of long-term hard-endpoint data. Rigorously designed, adequately powered randomized trials using standardized enhanced-bioavailability formulations, pre-registered protocols, and extended follow-up are the essential next step in translating these findings into clinical practice.

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