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Uma revisão sistemática e meta-análise dos benefícios anti-inflamatórios da suplementação de curcumina em indivíduos com síndrome metabólica e doenças relacionadas

Governador Valadares
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Trabalho de Conclusão de Curso (TCC) apresentado ao curso de Farmácia da Universidade Federal de Juiz de Fora, *campus* Governador Valadares, como requisito parcial para a conclusão do curso de Bacharel em Farmácia.

Orientador: Maisa Silva

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A systematic review and meta-analysis of the anti-inflammatory benefits of curcumin supplementation in individuals with metabolic syndrome and related diseases

Uma revisão sistemática e meta-análise dos benefícios antiinflamatórios da suplementação de curcumina em indivíduos com síndrome metabólica e doenças relacionadas

Una revisión sistemática y metanálisis de los beneficios antiinflamatorios de la suplementación con curcumina en personas con síndrome metabólico y enfermedades relacionadas

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ABSTRACT
Several randomized controlled studies (RTCs) have investigated the potential beneficial effects of curcumin in inflammatory process in metabolic syndrome. These studies have presented results controversial and inconclusive. In the present study, we aimed to conduct a systematic review and meta-analysis of RCTs to assess the effect of curcumin supplementation on inflammatory markers such as tumor necrosis factor-alpha (TNF-α), C-reactive protein (CRP), and interleukin-6 (IL-6) among in patients with metabolic syndrome and related disorders. PubMed, Scopus, Web of Science, and SciELO were searched from inception up to September 2023. The review has been registered at PROSPERO (CRD42023447460). Weighted mean differences (WMDs) were reported. P-values < 0.05 were considered significant. By employing the Cochrane tool, RCTs were assessed for bias risk. Assessment of study quality was conducted using the GRADE approach. Publication bias was evaluated using funnel plots and Egger's tests. In total, 26 studies were included in the meta-analysis, including 27 arms. The meta-analysis indicated that curcumin supplementation significantly decreased CRP (-0.75mg/dL, 95 % CI: -1.10, -0.39; p= <.0001), IL-6 (-1.41pg/mL, 95 % CI: -2.04, -0.77; p = <.0001), and TNF-α (-3,15pg/mL, 95 % CI: -4.52, -1.48; p = 0.0001) levels. Thus, this meta-analysis suggests that curcumin supplementation may exert anti-inflammatory effects, however, additional trials are needed to validate these results and reduce heterogeneity between studies.

Keywords: randomized clinical trials, curcumin, metabolic syndrome, inflammation, meta-analysis.

RESUMO
Vários estudos randomizados controlados (RTCs) investigaram os potenciais efeitos benéficos da curcumina no processo inflamatório na síndrome metabólica. Esses estudos apresentaram resultados controversos e inconclusivos. No presente estudo, nosso objetivo foi realizar uma revisão sistemática e meta-análise de ECRs para avaliar o efeito da suplementação de curcumina em marcadores inflamatórios, como fator de necrose tumoral alfa (TNF-α), proteína C reativa (PCR) e interleucina-6 (IL-6) em pacientes com síndrome metabólica e distúrbios relacionados. PubMed, Scopus, Web of Science e SciELO foram pesquisados desde o início até setembro de 2023. A revisão foi registrada no PROSPERO (CRD42023447460). Foram relatadas diferenças médias ponderadas. Valores de p < 0,05 foram considerados significativos. Ao empregar a ferramenta Cochrane, os ECRs foram avaliados quanto ao risco de viés. A avaliação da qualidade do estudo foi realizada utilizando a abordagem GRADE. O viés de publicação foi avaliado por meio de gráficos de funil e testes de Egger. No total, 26 estudos foram incluídos na meta-análise,

incluindo 27 braços. A metanálise indicou que a suplementação de curcumina diminuiu significativamente a PCR (-0,75mg/dL, IC 95%: -1,10, -0,39; p= <0,0001), IL-6 (-1,41pg/mL, IC 95%: - 2,04, -0,77; p = <0,0001) e níveis de TNF-α (3,15pg/mL, IC 95%: -4,52, -1,48; p = 0,0001). Assim, esta meta-análise sugere que a suplementação de curcumina pode exercer efeitos anti-inflamatórios, no entanto, são necessários ensaios adicionais para validar estes resultados e reduzir a heterogeneidade entre os estudos.

Palavras chave: ensaios clínicos randomizados, curcumina, síndrome metabólica, inflamação, metanálise.

RESUMEN

Varios estudios controlados aleatorios (RTC) han investigado los posibles efectos beneficiosos de la curcumina en el proceso inflamatorio del síndrome metabólico. Estos estudios han presentado resultados controvertidos y no concluyentes. En el presente estudio, el objetivo fue realizar una revisión sistemática y un metanálisis de ECA para evaluar el efecto de la suplementación con curcumina sobre marcadores inflamatorios como el factor de necrosis tumoral alfa (TNF-α), la proteína C reactiva (PCR) y interleucina-6 (IL-6) entre pacientes con síndrome metabólico y trastornos relacionados. Se realizaron búsquedas en PubMed, Scopus, Web of Science y SciELO desde su inicio hasta septiembre de 2023. La revisión se registró en PROSPERO (CRD42023447460). Se informaron las diferencias de medias ponderadas (DMP). Los valores de p <0,05 se consideraron significativos. Mediante el empleo de la herramienta Cochrane, se evaluó el riesgo de sesgo de los ECA. Evaluación de la calidad de los estudios se realizó mediante el enfoque GRADE. El sesgo de publicación se evaluó mediante gráficos en embudo y pruebas de Egger. En total, se incluyeron 26 estudios en el metanálisis, incluidos 27 brazos. El metanálisis indicó que la suplementación con curcumina disminuyó significativamente la PCR (-0,75 mg/dL, IC del 95 %: -1,10, -0,39; p= <0,0001), IL-6 (-1,41 pg/mL, IC del 95 %: -2,04, -0,77; p = <.0001) y niveles de TNF-α (-3,15pg/mL, IC 95 %: -4,52, -1,48; p = 0,0001). Por lo tanto, este metanálisis sugiere que la suplementación con curcumina puede ejercer efectos antiinflamatorios; sin embargo, se necesitan ensayos adicionales para validar estos resultados y reducir la heterogeneidad entre los estudios.

Palabras clave: ensayos clínicos aleatorios, curcumina, síndrome metabólico, inflamación, metanálisis.

1 INTRODUCTION

Metabolic syndrome (MetS) is a set of cardiometabolic dysregulations whose prevalence is increasing globally, some causes being abdominal obesity, atherogenic dyslipidemia, hypertension, insulin resistance and/or type 2 diabetes and pro-thrombotic and pro-inflammatory states (Expert Panel On Detection, 2001). Thus, MetS may be related by a combination of lifestyle factors, such as weight gain, unbalanced diet and inadequate physical activity. These

factors, coupled with chronic inflammation and hormonal activation, can lead to the progression of the syndrome, which in turn increases the risk of developing type 2 diabetes and other cardiovascular diseases (Fahed *et al.,* 2022).

Scientific evidence has demonstrated that the progress of obesity and metabolic syndrome is closely related to the chronic low-grade inflammation state (Dallmeier *et al.,* 2012). Inflammatory markers such as interleukin 6 (IL-6), tumor necrosis factor alpha (TNF-α) and C-reactive protein (CRP) are associated with an increase in adipose tissue, particularly in the abdominal region (Reijrink *et al.,* 2019; Ter Horst *et al.,* 2020; Torres *et al.,* 2019).

Various studies have been carried out to evaluate the efficacy of herbal medicines in the adjuvant treatment of MetS. Several researches have shown that curcuminoids have a variety of biological properties, exerting powerful anti-inflammatory (Sahebkar, 2013), antioxidant (Sahebkar *et al.,* 2013), antimicrobial (Naz *et al.,* 2016), hepatoprotective (Rahmani *et al.,* 2016), and neuroprotective effects (Shakeri *et al.,* 2016).

Clinical trials present controversial results on the effects of curcumin on inflammatory parameters related to MetS. Meta-analyses from 2023 in individuals with MetS and in the general population revealed that curcumin supplementation has beneficial and therapeutic, presenting a significant reduction in CRP, TNF-α and IL-6 (Dehzad *et al.,* 2023). However the results of meta-analysis developed by White *et al.,* in 2019 demonstrated that turmeric or curcumin did not significantly decrease levels in these inflammatory parameters in patients with chronic inflammatory diseases. Due to these conflicting findings and to our knowledge is not any recent meta-analysis on curcumin/turmeric and inflammatory mediators in patients with disorders related to metabolic syndrome, we developed this meta-analysis with the aim of investigate curcumin effect on CPR, IL-6 and TNF-α concentrations in these patients.

2 MATERIALS AND METHODS

The systematic review was conducted and reported according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines (LIBERATI *et al.,* 2009), and PRISMA 2020 check list (PAGE *et al.,* 2021). The review has been registered at PROSPERO international prospective register of systematic reviews (no. CRD42023447460).

2.1 SEARCH STRATEGY AND SELECTION CRITERIA

Medline, SCOPUS, Web of Science and Scielo databases were searched using the following search terms in titles and abstracts (also in combination with MESH terms): “curcumin” OR “turmeric” OR “curcuminoids” or “Curcuma longa” AND “Metabolic syndrome” “OR “diabetes” OR “obese” OR “hypertension” OR “coronary heart disease” OR “non-alcoholic fatty liver disease” OR “hypercholesterolemia” OR “polycystic ovary syndrome” AND “inflammation” AND “randomized controlled trial.” A manual review of the reference lists in each identified study was also conducted. Literature searches were conducted from database inception until September, 2023. When applicable, attempts were also made to contact investigators for clarification or additional unpublished data. No language restrictions were imposed.

The search was performed independently by four authors (AGC, BGC, LTSV e SSD). In case of disagreement, a fifth investigator was consulted (MS). Any discrepancies among the reviewers were resolved through consensus.

2.2 INCLUSION/EXCLUSION CRITERIA

All clinical trials were then entered for final meta-analysis if they had the following criteria: (I) human trials with either crossover design or parallel,; (II) the subjects in the trial were exposed to the intervention for a minimum of 1 weeks; (III) reported the impact of curcumin/turmeric/nano-curcumin supplementation on CRP, TNF-α, IL-6 before and after the trial in the intervention and placebo groups; (IV) performed in adult subjects: (V) patients with metabolic syndrome or related disorders. Studies in which substances such piperine were added to turmeric or curcumin to enhance their bioavailability or to reduce their gastrointestinal metabolism were also included. In this meta-analysis, letters, short communications, reviews, animal studies and in vitro were excluded from the analysis. Duplicate studies, trials without sufficient data and the intervention used a mixture of curcumin and other substances were also excluded. Studies with curcumin supplementation and physical exercise or lifestyle intervention were not included in this review. Trials evaluating multiple treatment arms (low- or high-dose curcumin) were included in the meta-analysis as a separate trial.

2.3 DATA EXTRACTION AND QUALITY ASSESSMENT

Eligible studies were reviewed and the following data were abstracted: study characteristics (authors and publication year), study design, population information (number and gender of participants), the dose and type of curcumin supplementation, the duration of the study, health condition, and inflammatory markers (main outcomes).

Five investigators independently used the Cochrane Collaboration tool to assess risk of bias for each included trial RCTs (Sterne *et al.,* 2019). Disagreements between investigators were resolved by consultation with the senior investigator. Quality was assessed according to the following criteria: randomization process, deviations from intended interventions, missing outcomes data, measurement of outcomes, and selection of the reported results. Each domain was graded (low, high, or some concerns) based on the available information in the study. All disagreements were resolved by discussion.

We assessed the quality of evidence for each category using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (Ryan; Hill, 2016). We rated the quality of evidence of the outcomes across trials using GRADE-provided criteria, including study risk-of-bias, inconsistency, indirectness, imprecision, and publication bias. GRADE categorized the quality of evidence into four levels: High, Moderate, Low and Very Low quality.

2.4 STATISTICAL ANALYSIS

For each factor, we extracted the mean at baseline and post-intervention, from both the intervention and control groups. The meta-analysis was performed using R software (R Foundation for Statistical Computing, Vienna, Austria, URL http://www.R-project.org, 2020). Statistic heterogeneity of treatment effects between studies was formally tested with Cochrane's test (Borenstein *et al.,* 2010). The I2 statistic was also examined, and we considered an I2 value >50% and >75% to indicate substantial and considerable heterogeneity, respectively, between the trials. Based on the heterogeneity between included studies, a random effect or a fixed model was applied in the meta-analysis. The pooled effect size estimated using the DerSimonian-Laird Based random-effects model (Dersimonian; Laird, 2015). Effect sizes were presented as mean

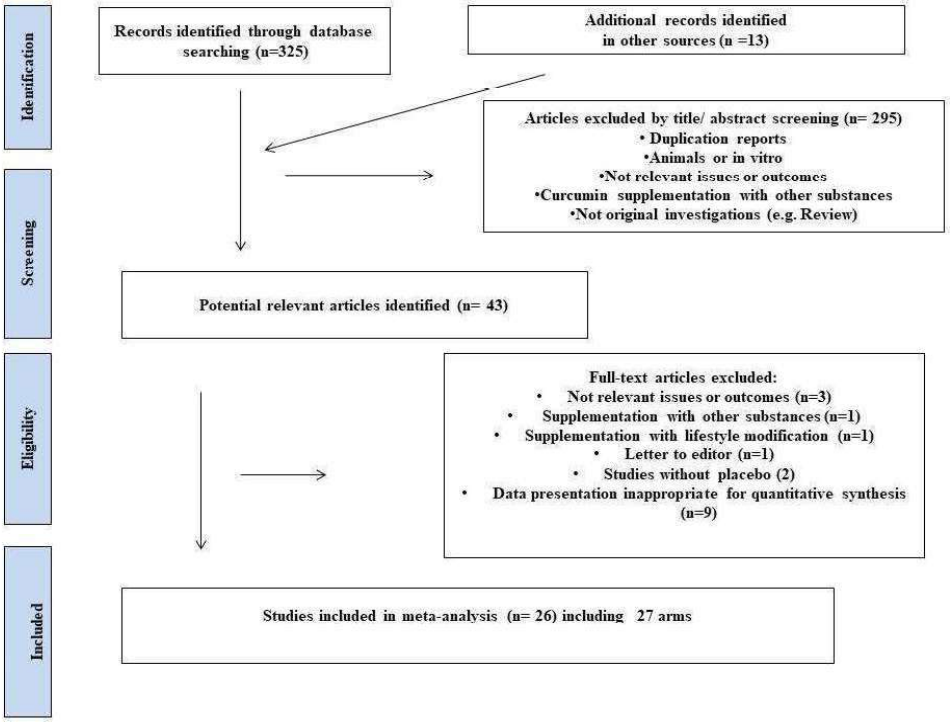
differences with 95% confidence intervals, and p-values < 0.05 were considered as statistically significant.

3 RESULTS

3.1 SEARCH RESULTS

An overall of 325 studies were retrieved through initial online database search and 13 additional records identified in other sources. After removing that did not meet the inclusion criteria, 43 references remained. These potentially relevant articles were examined for full text evaluation. The other 17 articles were excluded for the following reasons: outcomes was not measured in three trials, one article with curcumin supplementation and other substances was discarded and one were supplementation and lifestyle modification. Two studies did not have a placebo group and one study was a letter to the editor. In addition, in nine articles the data presentation was inappropriate for quantitative synthesis. Thus, 26 studies were included in the meta-analysis, including 27 arms (Figure 1).

Figure 1 - Literature search and review flow chart for selection of studies.



Source: prepared by the authors.

The main characteristics of trials included in this meta-analysis are summarized in Table 1. Treatment duration ranged from 1 week to 24 weeks and sample size ranged from 21 to 234 participants. These studies reported the average age of participants, which ranged between 18 and 76 years. Four studies recruited only women, two recruited only men, while two studies did not identify the gender of subjects. The method of intervention was using curcumin in nine studies, curcumin plus piperine in five studies, nano-curcumin in seven studies, turmeric in six studies, and theracurmin in one study. Dosages of curcumin used were different from 180 mg/day to 2.8 g/day.

Table 1- Characteristics of included studies.

First author (publication year)	Design	Number of participants/Gender	Mean age (years) mean ± SD	Type and amount of Curcumin	Duration	Notes about participants	Main outcomes
Alhashemi et al. 2022	Double-blind, parallel.	Placebo: 121 (78 male) Curcumin: 113 (80 male)	Placebo: 62.35±9.2 Curcumin: 61.56± 8.35	240 mg/day nano-curcumin	1 week	Coronary artery bypass graft surgery	CRP
Bateni et al. 2022	Double-blind, parallel.	Placebo: 21 (5 male) Curcumin: 22 (5 male)	Placebo: 54 ± 7 Curcumin: 50 ± 9	80 mg/day nano-curcumin	12 weeks	Metabolic syndrome	CRP
Darmian et al. 2022	Single-blind, parallel	Placebo: 10 Curcumin: 11	Placebo: 44.22± 3.07 Curcumin: 44.33± 1.23	2100 mg/day turmeric poder	8 weeks	Women Hyperlipidemic Type 2 Diabetes Mellitus	CRP
Helli et al. 2021 a	Double-blind, parallel.	Placebo: 30 Curcumin: 30	Placebo: 54.06 ± 5.23 Curcumin: 55.27 ± 7.11	500 mg/day curcumin	8 weeks	coronary elective angioplasty	CRP, TNF-α
Helli et al. 2021 b	Double-blind, parallel.	Placebo: 30 Curcumin: 30	Placebo: 54.06 ± 5.23 Curcumin: 56.19 ± 6.9	80 mg/day nano-curcumin	8 weeks	coronary elective angioplasty	CRP, TNF-α
Mokhtari et al. 2021	Double-blind, parallel.	Placebo: 25 (20 male) Curcumin: 25 (19 male)	Placebo: 55.8 ± 9.4 Curcumin: 57.4 ± 11.7	80 mg/day nano-curcumin	12 weeks	diabetic foot ulcer	CRP
Shafabakhsh et al. 2020	Double-blind, parallel.	Placebo: 27 (15 male) Curcumin: 26 (17 male)	Placebo: 56.2 ± 9.8 Curcumin: 58.3 ± 9.4	80 mg/day nano-curcumin	12 weeks	Diabetes on Hemodialysis	CRP

Osali et al. 2020	Double-blind, parallel.	Placebo: 11 Curcumin: 11	62.3±1.23	80 mg/day nano-curcumin	6 weeks	Women with metabolic syndrome.	CRP, IL-6
Kuszewski et al. 2020	Double-blind, parallel.	Placebo: 36 (18 male) Curcumin: 38 (17 male)	Placebo: 65.4 ± 1.3 Curcumin: 65.4 ± 1.2	160 mg/day curcumin	16 weeks	Overweight/obese.	CRP
Adab et al. 2019	Double-blind, parallel.	Placebo: 36 (17 male) Curcumin: 39 (19 male)	Placebo: 55.66 ± 8.64 Curcumin: 54.76 ± 6.00	2,100 mg/day powder turmeric	8 weeks	hyperlipidemic type 2 diabetes mellitus	CRP
Adibian et al. 2019	Double-blind, parallel.	Placebo: 23 (9 male) Curcumin: 21 (13 male)	Placebo: 58 Curcumin: 60 ± 7	1,500 mg/day curcumin	10 weeks	Type 2 diabetes	CRP
Jazayeri-Tehrani et al. 2019	Double-blind, parallel.	Placebo: 42 (23 male) Curcumin: 42 (23 male)	Placebo: 42.5±6.2 Curcumin: 41.8±5.6	80 mg/day nano-curcumin	3 months	NAFLD	CRP, IL-6, TNF-α
Sohaei et al. 2019	Double-blind, parallel.	Placebo: 24 Curcumin: 27	Placebo: 29.58 ± 5 Curcumin: 29.40 ± 5.33	500 mg/day Curcumin	6 weeks	Women with polycystic ovary syndrome.	CRP
Uchio et al. 2019	Double-blind, parallel.	Placebo: 44 (22 male) Curcumin: 43 (23 male)	Placebo: 58.5± 5.5 Curcumin: 58.8 ± 5.3	Turmeric Extract	12 weeks	Overweight or Prehypertension/Mild Hypertension.	CRP, IL-6, TNF-α
Panahi et al., 2018	Double-blind, parallel.	Placebo: 50 (26 male) Curcumin: 50 (25 male)	Placebo: 41 ± 7 Curcumin: 43 ± 8	500 mg/day curcumin plus 5 mg bioperine	3 months	Type 2 Diabetes	CRP
Campbell et al. 2017	Double-blind, parallel.	Placebo: 11 Curcumin: 11	Placebo: 26.64 ± 4.06 Curcumin: 25.91 ± 4.46	500 mg/day curcumin	12 weeks	Obese men with higher initial stiffness	IL-6, TNF-a
Funamoto et al. 2016	Double-blind, parallel.	Placebo: 16 (15 male) Curcumin: 22 (19 male)	Placebo: 69.9±6.3 Curcumin: 69.6±6.6	180 mg/day Theracurmin	24 weeks	Mild Chronic obstructive pulmonary disease at stage 0, I, or II.	CRP
Panahi et al. 2016	Double-blind, parallel.	Placebo: 50 (23 male) Curcumin: 50 (27 male)	Placebo: 43.46 ± 9.70 Curcumin: 44.80 ± 8.67	1 g/day curcumin plus 5 mg bioperine	8 weeks	Metabolic syndrome .	IL-6, TNF-a
Kocher et al. 2016	Double-blind, crossover	42 (17 male)	52 ± 16 (female) 50 ± 20 (male)	294 mg/day curcuminoids (as micelles)	6 weeks	Moderately hyperlipidemic	CRP, IL-6

Mirzabeigi et al. 2015	Double-blind, parallel.	Placebo: 16 (14 male) Curcumin: 17 (10 male)	Placebo: 64.3±8.42 Curcumin: 61.5±8.7	2 g/day curcumin	8 weeks	Coronary artery disease	CRP
Panahi et al., 2015	Double-blind, parallel.	Placebo: 50 (23 male) Curcumin: 50 (27 male)	Placebo: 43.46 ± 9.70 Curcumin: 44.80 ± 8.67	1 g/day curcumin plus 5 mg bioperine	8 weeks	Metabolic syndrome	CRP
Amin et al. 2015	Double-blind, parallel.	Placebo: 63 Curcumin: 63	Placebo: 41.57 ± 12.8 Curcumin: 42.4 ± 13.7	Turmeric (2.4 g/day)	8 weeks	Metabolic syndrome men	CRP
Ganjali et al. 2014	Double-blind, parallel.	Placebo: 15 Curcumin: 15	18–65 years	1 g/day curcumin plus 5 mg bioperine	4 weeks	Obese	IL-6, TNF-α
Nieman et al. 2012	Double-blind, crossover	31	55.7±1.4	2.8 g/day tumeric	4 weeks	Overweight women	CRP, IL-6, TNF-α
Mohammadi et a. 2013	Double-blind, crossover	Placebo: 15 Curcumin: 15	Placebo: 39.0±9.0 Curcumin: 37.9 ±12.7	1 g/day curcuminoids with 10mg piperine	4 weeks	Obese	CRP
Khajehdehi et al. 2011	Double-blind, parallel.	Placebo: 20 (13 male) Curcumin: 20 (9 male)	Placebo: 52.6 ± 9.7 Curcumin: 52.9 ± 9.2	1,500 mg/day turmeric	2 months	Otype 2 diabetic nephropathy	TNF- α
Usharani et al. 2008	Parallel	Placebo: 21 (11 male) Curcumin: 23 (12 male)	Placebo: 49.75 ± 8.18 Curcumin: 50.47 ± 10.35	300 mg/day curcumin	8 weeks	Type 2 Diabetes	IL-6, TNF-α

Source: prepared by the authors.

3.2 RISK OF BIAS ASSESSMENT

The Cochrane bias evaluation was performed to evaluate study and reporting quality are shown in Figure 2. Seven studies provided comprehensive explanations of random sequence generation. Four trials were considered high risk of bias in measurement of the outcome .A low risk of selective outcome reporting was identified in almost all the studies.

Figure 2 - The summary of review authors' judgments about each risk of bias item for included studies.

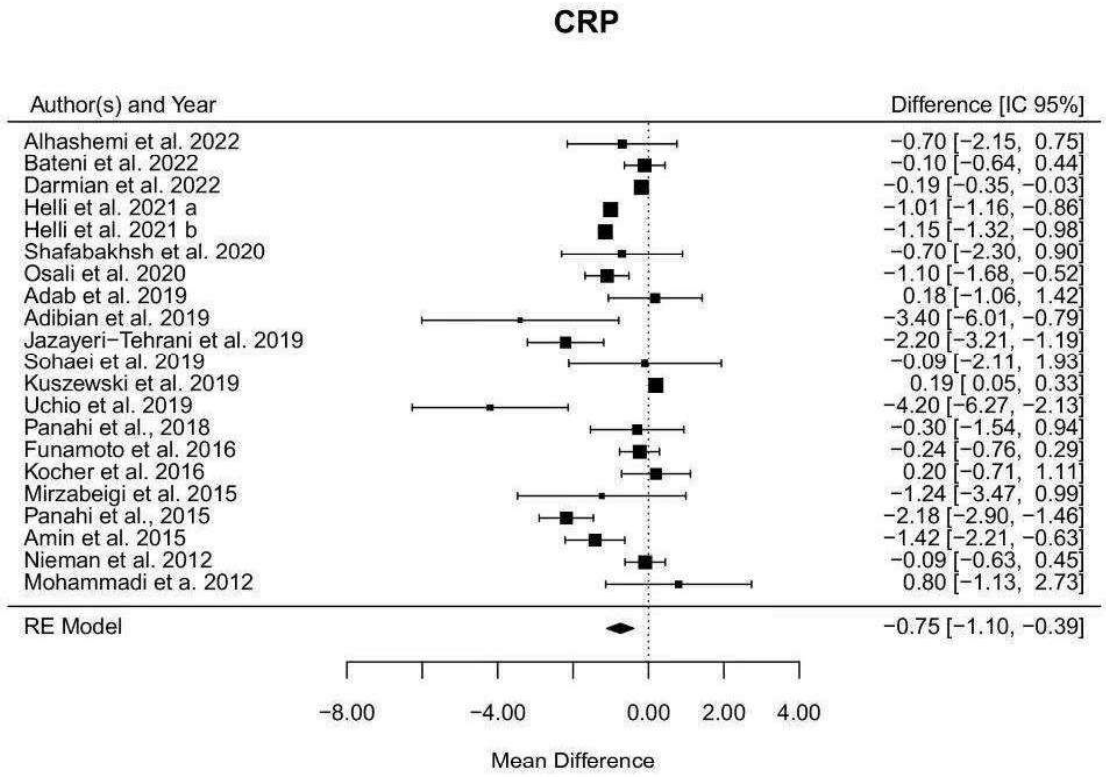
Source: prepared by the authors.

3.3 QUANTITATIVE ANALYSIS

3.3.1 Effect of curcumin on C-reactive protein (CRP)

Sensitivity analysis revealed a large standard deviation of the data from the study carried out by Mokhtari et al. 2021, thus this study was removed from the analysis. The effects of curcumin supplementation in twenty-one studies were analyzed, meta-analysis did verify a significant effect on CRP levels (-0.75 mg/dL, 95 % CI: -1.10, -0.39; p= <.0001), with between-study heterogeneity (p = < .0001, I2 = 92.81%) (Figure 3).

Figure 3 - Forest plot of the effect of curcumin supplementation on CRP.



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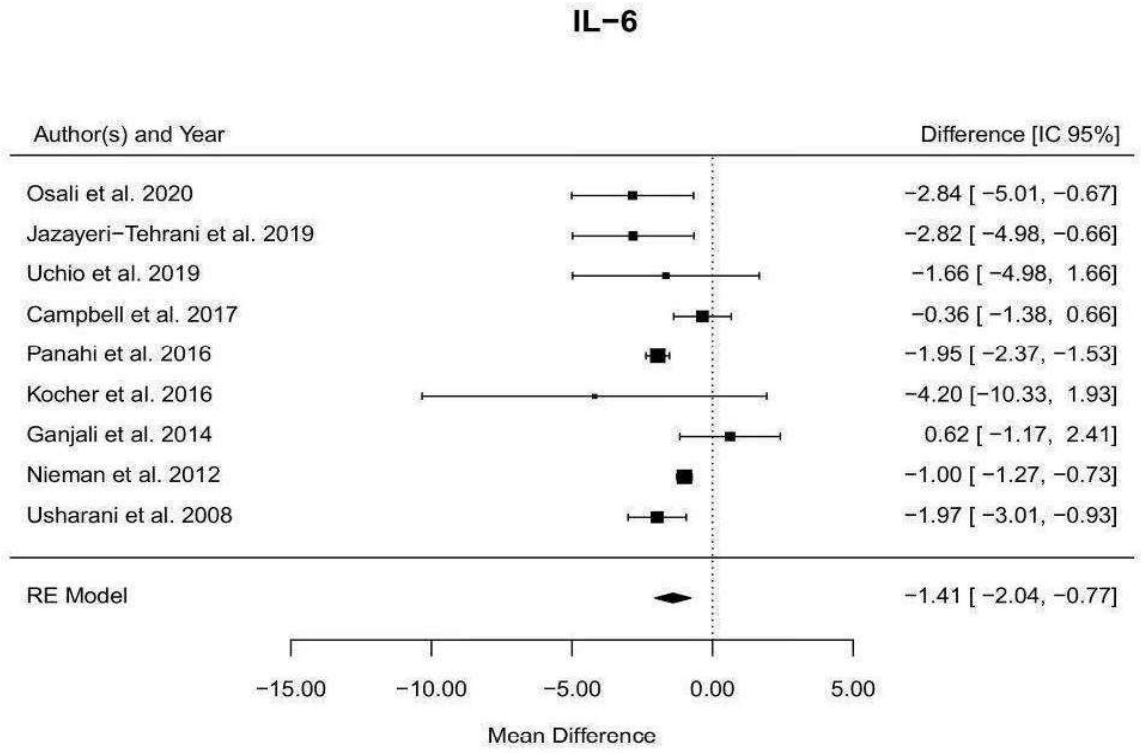
3.3.2 Effect of curcumin on interleukin-6 (IL-6)

The meta-analysis of nine studies revealed significant change in serum IL-6 levels in which curcumin was administered (-1.41pg/mL, 95 % CI: -2.04, -0.77; p = <.0001), with between-study heterogeneity (p = < .0001, I2 = 71.46%) (Figure 4).

Figure 4 - Forest plot of the effect of curcumin supplementation on IL-6.

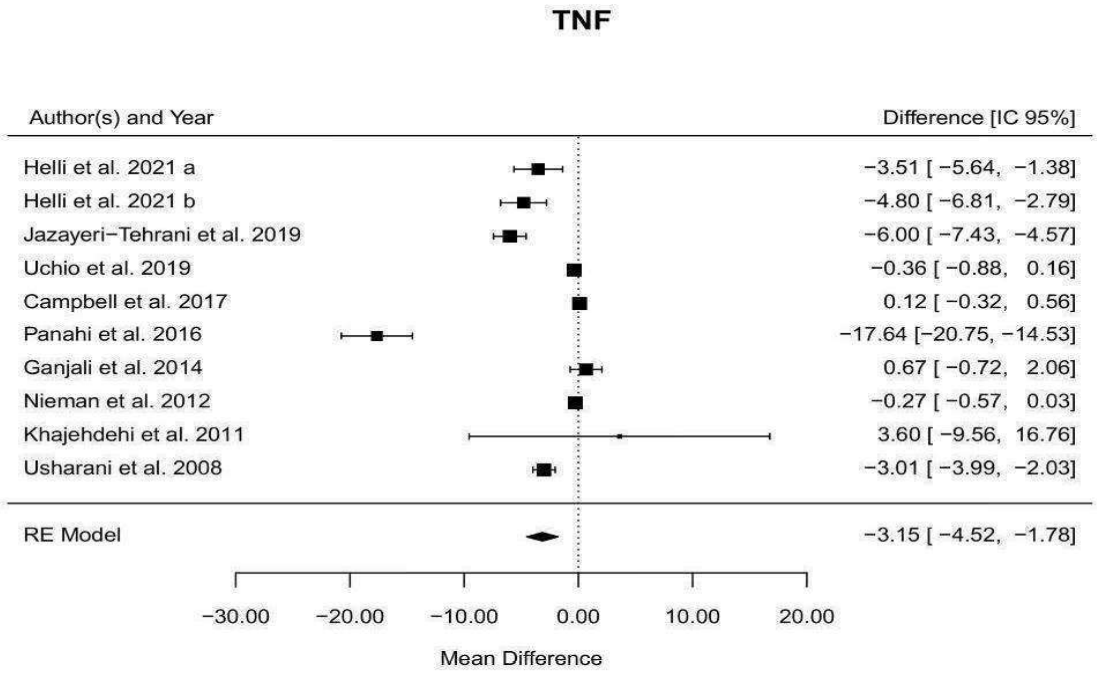


Source: prepared by the authors.

3.3.3 Effect of curcumin on tumor necrosis factor-alpha (TNF-α)

Ten RCTs were used to investigate TNF-α and significant effect in the reduction this parameter with curcumin supplementation was found by meta-analysis (-3,15pg/mL, 95 % CI: -4.52, -1.48; p = 0.0001), with between-study heterogeneity (p = 0.0001, I2 = 96.20%) (Figure 5).

Figure 5 - Forest plot of the effect of curcumin supplementation on TNF-α



Source: prepared by the authors.

3.4 PUBLICATION BIAS

Publication bias assessment through funnel plot and Egger's linear regression test. Egger's linear regression test confirmed the absence of publication of bias in CRP: p = 0.2928 and IL-6: p = 0.5480, however this test verified publication of bias in TNFα: p = 0.0344). On a visual inspection of funnel plot depicted no publication bias in included studies in CRP and IL-6 (data not shown).

3.5 QUALITY OF THE EVIDENCE FOR THE OUTCOME USING GRADE

All outcomes were rated as high, moderate, or low quality of evidence using the GRADE approach. Due risk of bias (inconsistencies that may affect the quality of evidence) and publication bias since small studies with negative results were missing, some studies had reduced scores (Table 2).

Table 2 - Summary of main results

Outcome	Studies	Participants	Effect Estimate	P value	GRADE
CRP	21	1408	-0,75 [-1.10, -0.39]	<.0001	⊕⊕⊕⊖ Moderate[1]
IL-6	9	462	-1.41 [-2.04, -0.77]	<.0001	⊕⊕⊕⊖ Moderate[1]
TNF-α	10	558	-3.15 [-4.52, -1.78]	0.0001	⊕⊕⊖⊖ Low[1,2]

Source: prepared by the authors.
[1] Downgraded due to risk of bias (inconsistencies that may affect the quality of evidence).
[2]Publication bias: Literature was searched exhaustively. Funnel plots were conducted and showed asymmetry.

4 DISCUSSION

The current meta-analysis of 26 RCTs, including 27 arms, demonstrated that curcumin was associated with a significant reduction in serum CRP, IL-6, and TNF-α levels. The CRP is inflammatory parameter related to factors for metabolic syndrome, CVD, hypertension, diabetes and visceral obesity (Koziarska-Rościszewska *et al.* 2021). Furthermore, its abundance can be used to predict cardiovascular events and mortality in patients with type 2 diabetes (Tian *et al.,* 2019). Our study found that curcumin decreased serum levels of CRP in MetS patients and related disorders. Two meta-analyses developed in 2023, with individuals with MetS, also corroborate our result (Qiu *et al.,* 2023; SUN *et al.,* 2023). Curcumin supplementation also decreased CRP levels in patients with systemic inflammation (Gorabi *et al.,* 2022), in hemodialysis patients (Arabi *et al.,* 2022) and chronic kidney disease (Supriyadi *et al.,* 2023) and cardiovascular disease (Ashtary-Larky *et al.,* 2021). However, Ebrahimzadeh *et. al* in 2024, carried out a meta-analysis containing 21 RCTs in individuals with NAFLD, no finding decreased CRP. In addition, Abdelazeem et. al in 2022 no observed reduction on CRP levels in women with PCOS and White CM. et. al in 2019 with individuals with chronic inflammatory diseases. The discrepancies found in these studies may be due to the low bioavailability of curcumin and the ability of some diseases to develop a greater baseline inflammatory state than others, causing a more significant apparent drop when curcumin is introduced.

O TNF-α is a pro-inflammatory cytokine secreted mainly by macrophages e although it is fundamental for cell defense, excessive expression of this cytokine, in addition to exacerbating and chronicizing underlying diseases and infections, is associated with a greater risk of developing obesity and type 2 diabetes (Autran, 2017). A meta-analysis, involving more than two thousand individuals, the majority with some inflammatory condition, showed that curcumin supplementation significantly reduced the level of TNF-α (Ferguson *et al.,* 2021). Furthermore, the meta-analysis developed by Sahebkar et al. in 2016, including participants with some

comorbidity such as depression, neoplasia, lung disease, osteoarthritis, end-stage renal disease or metabolic syndrome, found that although curcumin reduced TNF-α values, there was no variation in the result depending on the dose and duration of treatment (Sahebkar *et al.,* 2016). On the other hand, Tabrizi et al. in 2019, when analyzing patients with metabolic syndrome, they pointed out that curcumin intake was efficient in reducing other inflammatory parameters, such as CRP and IL-6, but did not have a significant effect on TNF-α. However, the authors considered that the study has limitations, especially due to the limited number of studies included, the vast majority of which had an insufficient sample size. In addition, a meta-analysis including only patients with chronic inflammatory conditions found that curcumin did not change any of the main inflammatory markers, including TNF-alpha. However, this is a review with high heterogeneity and which brought together a substantial number of studies with a high risk of bias (White *et al.,* 2019).

IL-6 is a pleiotropic pro-inflammatory cytokine that is associated with parameters of metabolic syndrome, such as hypertension, high BMI, insulin and DM2 (Said *et al.,* 2021). Dehzad et. al. developed a meta-analysis with 60 RCTs, analyzing healthy individuals and individuals with metabolic syndrome disorders, such as diabetes, dyslipidemia and NAFLD, and found that curcumin supplementation significantly reduced IL-6 levels (Dehzad *et al.,* 2023). A meta-analysis carried out by Larky et. al., in 2021, determined the impact of nanocurcumin supplementation on risk factors for cardiovascular diseases and this supplementation was associated with improvements in the glycemic profile and inflammation, corresponding with a decrease in the effects of IL-6. However, Supriyadi et. al, in 2023, developed a meta-analysis with 32 published studies on the effects of curcumin in patients with Chronic Kidney Disease and found no changes in serum IL-6 levels. Furthermore, Gorabi et. al., in 2021, analyzed that curcumin supplementation also reduced the concentration of pro-inflammatory cytokines in patients with an inflammatory background.

This meta-analysis possessed numerous significant strengths. Initially, we executed a systematic review and meta-analysis following the PRISMA guidelines, ensuring minimal risk of bias. Secondly, the Egger regression test results revealed no notable asymmetry in the funnel plot concerning the overall effect estimate. Thirdly, we conducted subgroup analyses to pinpoint sources of heterogeneity within the findings. Fourthly, a meta-regression analysis was undertaken to examine the correlation between the effects on anti-inflammatory parameters and the dosage

and duration of treatment. Furthermore, our review encompassed PROSPERO registration and underwent GRADE analysis.

This meta-analysis is subject to several limitations. The most important is the considerable variability in study design, curcumin dosage and type, age, and study quality. Within the trials incorporated in this review, certain individuals might not exhibit sufficiently elevated levels of inflammation, making it difficult to see the effects of curcumin. These factors may have contributed to the difficulty in identifying the possible sources of heterogeneity found in this meta-analysis.

5 CONCLUSION

In conclusion, the present meta-analysis of RCTs indicates the beneficial effect of curcumin on levels of CRP, TNF-α and IL-6 in individuals with metabolic syndrome and related disorders. Further investigation involving larger, meticulously designed studies is needed to mitigate confounding variables such as dosage and duration of supplementation, as well as gender differences, in order to provide a clearer understanding of the impact of curcumin on inflammatory markers.

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