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Antioxidant and anti-inflammatory effects of curcumin/turmeric supplementation in adults: A GRADE-assessed systematic review and dose–response meta-analysis of randomized controlled trials

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ABSTRACT

Turmeric and its prominent bioactive compound, curcumin, have been the subject of many investigations with regard to their impact on inflammatory and oxidative balance in the body. In this systematic review and *meta*-analysis, we summarized the existing literature on randomized controlled trials (RCTs) which examined this hypothesis. Major databases (PubMed, Scopus, Web of Science, Cochrane Library and Google Scholar) were searched from inception up to October 2022. Relevant studies meeting our eligibility criteria were obtained. Main outcomes included inflammatory markers (i.e. C-reactive protein (CRP), tumour necrosis factor α (TNF-α), interleukin-6 (IL-6), and interleukin 1 beta (IL-1β)) and markers of oxidative stress (i.e. total antioxidant capacity (TAC), malondialdehyde (MDA), and superoxide dismutase (SOD) activity). Weighted mean differences (WMDs) were reported. P-values < 0.05 were considered significant. Sixty-six RCTs were included in the final analysis. We observed that turmeric/curcumin supplementation significantly reduces levels of inflammatory markers, including CRP (WMD: −0.58 mg/l, 95 % CI: −0.74, −0.41), TNF-α (WMD: −3.48 pg/ml, 95 % CI: −4.38, −2.58), and IL-6 (WMD: −1.31 pg/ml, 95 % CI: −1.58, −0.67); except for IL-1β (WMD: −0.46 pg/ml, 95 % CI: −1.18, 0.27) for which no significant change was found. Also, turmeric/curcumin supplementation significantly improved anti-oxidant activity through enhancing TAC (WMD = 0.21 mmol/l; 95 % CI: 0.08, 0.33), reducing MDA levels (WMD = -0.33 μmol /l; 95 % CI: −0.53, −0.12), and SOD activity (WMD = 20.51 u/l; 95 % CI: 7.35, 33.67). It seems that turmeric/curcumin supplementation might be used as a viable intervention for improving inflammatory/oxidative status of individuals.

1. Introduction

Inflammation and oxidative stress are mediators of a plethora of chronic and/or metabolic diseases [1]. It is now evident that a low-state pro-inflammatory state, especially caused by accumulation of adipose tissue in obesity, might explain a lot of downstream consequences associated with obesity [2]; such as cardiovascular diseases (CVDs), type 2 diabetes mellitus, liver disorders, and cancer. The worldwide prevalence of these anomalies suggest that they compel huge expenses, in terms of both economic and social burdens caused by infliction with non-communicable disorders (NCDs), both in developed and developing countries [3]. Nonetheless, there is a bright side indicating that these disorders are mainly preventable and/or curable using different easy-to-apply, non-expensive methods [4].

Various approaches have been appointed to reduce long-term, low-state inflammation; such as major lifestyle modifications [5], weight-loss dietary regimens [6], and the use of single nutrients and/or individual foodstuff and herbs [7,8]. The latter, especially have gained some popularity, due to their widespread use and easy accessibility. Turmeric is one of these herbs that have great culinary and presumed medical usages in the Iranian culture [9]. Turmeric contains various bioactive compounds which have been associated with its claimed beneficial effects [10]. The most significant of these compounds is curcumin [11]. Curcumin is a polyphenol with potent anti-inflammatory properties [12]. The impact of regular consumption of curcumin have already been claimed in relation to long-term, metabolic-rooted disorders, such as

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overweight/obesity [13], type 2 diabetes mellitus [14], and even cognitive and psychological abnormalities, such as Alzheimer's disease and dementia [15,16]. In this systematic review and *meta*-analysis of randomized controlled trials (RCTs), we aim at investigating the impact of turmeric/curcumin supplementation on markers of inflammation and oxidative stress, such as C-reactive protein (CRP), interleukin-6 (IL-6), interleukin 1 beta (IL-1β), tumor necrosis factor-α (TNF-α), total antioxidant capacity (TAC), malondialdehyde (MDA), and superoxide dismutase (SOD). This will allow us to hypothesize that the health benefits attributed to turmeric/curcumin might be majorly mediated through its anti-inflammatory and/or antioxidant effects.

2. Methods

The current systematic review and *meta*-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and meta-Analyses (PRISMA) statement [17]. The protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) under the following code: CRD42022353946.

2.1. Search strategy

We used the PICOS model to determine the inclusion criteria standing for population (aged > 18 years old), intervention (curcumin/turmeric supplementation), comparison (matched control group), outcome (C-reactive protein (CRP), tumour necrosis factor α (TNF-α), interleukin-6 (IL-6), interleukin 1 beta (IL-1β), total antioxidant capacity (TAC), malondialdehyde (MDA), superoxide dismutase (SOD)) and study (randomized controlled trials). A comprehensive and systematic literature search, without language or time restrictions, was performed on the online databases of PubMed, Scopus, Web of Science, Cochrane Library, and Google Scholar from inception up to October 2022. The following medical subject headings (MeSH) and non-MeSH terms were used to find the relevant studies: ("Curcumin" OR "Curcuminoid" OR "Curcuma" OR "Turmeric" OR "Tumeric" OR "Curcuma longa" OR "C. longa") AND ("Intervention" OR "Intervention Studies" OR "controlled trial" OR "randomized" OR "randomised" OR "randomly" OR "random" OR "trial" OR "clinical trial" OR "randomized controlled trial" OR "randomized clinical trial" OR "RCT"). Moreover, to ensure that all of the relevant articles were retrieved, all reference lists of eligible studies and previous review articles were hand-searched. We did not include unpublished studies and gray literature in the present systematic review and *meta*-analysis.

2.2. Study selection and eligibility criteria

All clinical trials were then entered for final *meta*-analysis if they had the following criteria: (1) were randomized controlled trials; (2) were conducted on adult population aged>18 years; (3) reported the impact of curcumin/turmeric supplementation on CRP, TNF-α, IL-6, IL-1β, TAC, MDA, SOD before and after the trial in the intervention and placebo groups; (4) had an intervention period of>2 weeks; (5) we also included all studies which supplemented another compound along with curcumin/turmeric in both intervention and placebo groups. The studies which had the following criteria were not included: (1) studies which investigated the impact of another compound or lifestyle intervention along with curcumin/turmeric only in intervention group; (2) non-randomized trials; (3) studies not having a placebo group; (4) reviews, case reports, letters to editor, or editorial articles; and (5) studies that were carried out on animals, children, pregnant or breastfeeding women.

2.3. Data extraction

All recorded articles were entered into Endnote software for screening (EndNote X8, Thomson Reuters, New York). Two independent reviewers (MJD and HG) contributed to study selection and data extraction, while the other two reviewers registered the obtained data using a standardized electronic form (Excel, Microsoft Office). The chief investigator (MA) was responsible for solving the issues with regard to study selection. We obtained the following data from included studies: 1) the first author's last name, year of publication, and study location; 2) study design, participants' gender and number of participants in each group; 3) participants' age, study duration, and dose of curcumin/turmeric supplements used. Mean and standard deviation of CRP, TNF-α, IL-6, IL-1β, TAC, MDA, and SOD, before and after the intervention, were also registered.

2.4. Risk of bias assessment

Cochrane quality assessment tool was used to assess the risk of bias [18]. General sources of bias, including random sequence generation, allocation concealment, reporting bias, performance bias, detection bias, attrition bias, and other sources of bias were verified using this tool. The included studies were ranked as low (L), or high risk of bias (H) or unclear (U), regarding each domain of bias (Table 2). Two authors (MJD and HG) independently conducted the risk of bias assessment.

2.5. Statistical analysis

The effect sizes were calculated using mean change and standard deviations (SDs) for CRP, TNF-α, IL-6, IL-1β, TAC, MDA, and SOD in the intervention and placebo groups. In case mean changes were not reported, we estimated mean changes by calculating changes in the outcomes during the intervention period. Additionally, using the method of Hozo et al. [19], standard errors (SEs), 95 % confidence intervals (CIs), and interquartile ranges (IQRs) were converted to SDs. The following formula was used when the SD of the mean change was not reported: SD_{change} = square root [$(SD^2_{baseline} + SD^2_{final})$ - $(2 \times 0.9 \times SD_{baseline} \times SD_{final})$] [20]. A random effect model was considered which takes between-study variations into account (DerSimonian-Laird method). The effect sizes were estimated as weighted mean difference (WMD) and 95 % confidence interval (CI). Between-study heterogeneity was verified by the I^2 statistic and Cochrane's Q test. Between-study heterogeneity was assumed as significant when Q-test released I^2 value > 50 % or p-value < 0.05 [21,22]. We performed pre-planned subgroup analysis based on mean age of participants (years), baseline participant's health condition, type of supplementation, baseline body mass index (BMI) (kg/m^2), curcumin/turmeric dosage (g/d), duration of the follow-up period (weeks), sample size, and study's location, in order to find potential sources of heterogeneity. To evaluate the impact of each study on the overall effect size, we also carried out a sensitivity analysis via the one-study remove (leave-one-out) approach [23]. Furthermore, to determine the potential non-linear effects of curcumin/turmeric dosage (mg/d) and duration of treatment (weeks) on the outcomes of interest, fractional polynomial modelling was fitted [24]. Publication bias was assessed using the visual inspection of the funnel plots and Egger's regression tests. When publication bias was assumed, the trim and fill approach was used to estimate the adjusted effect size [25]. The Stata Software, version 14 (StataCorp) was used to conduct the *meta*-analysis. P-values < 0.05 were considered as statistically significant.

2.6. Certainty assessment

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group guidelines were used to rank the overall certainty of evidence across RCTs. Finally, four levels of quality, including high, moderate, low, and very low [26] were assigned using the specified criteria.

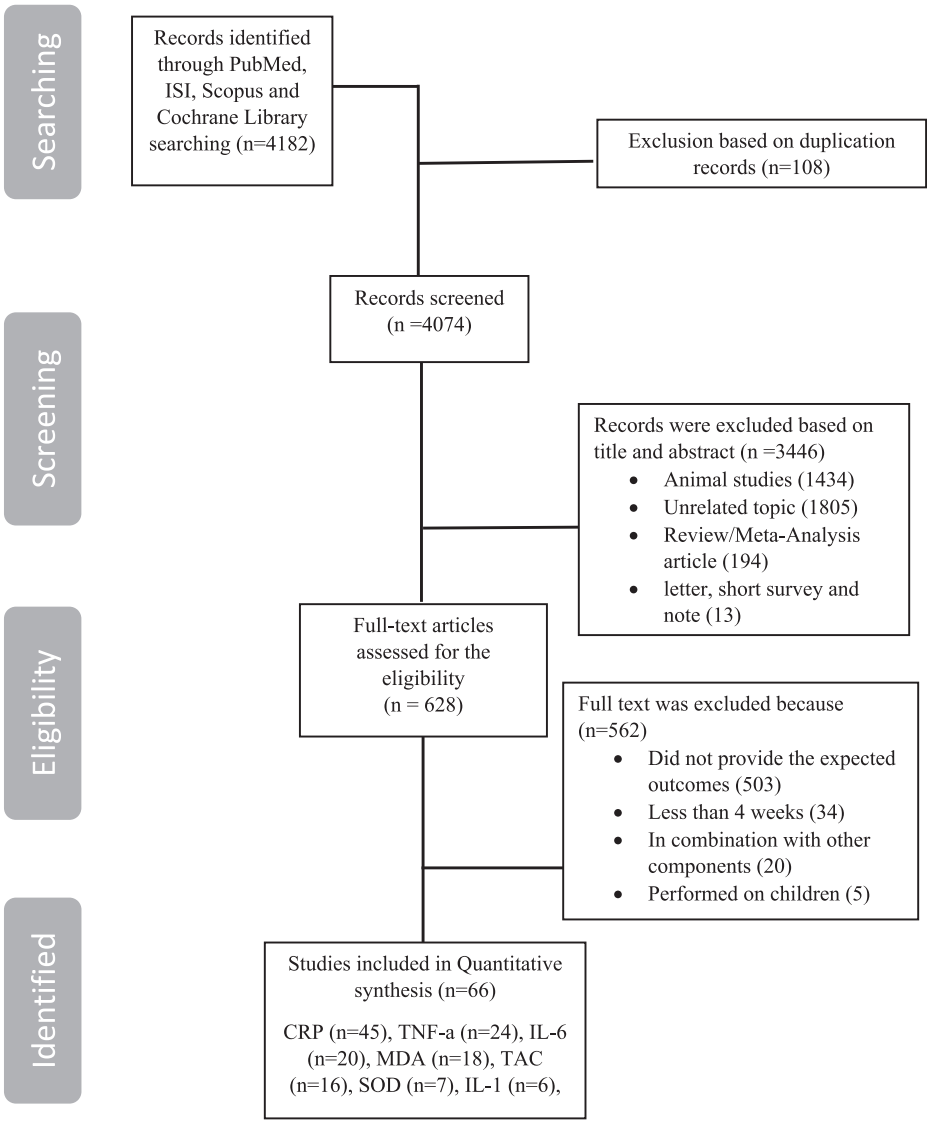

Fig. 1. Flow diagram of study selection.

3. Results

3.1. Study selection

Our initial search yielded 4182 articles. Then, duplicate articles were removed (n = 108). After screening the remaining 4074 records, 3446 irrelevant articles were eliminated based on title and abstract evaluation. Eventually, 628 papers were retained for more comprehensive full-text evaluation. Among those, 504 RCTs were excluded due to reporting irrelevant outcomes. Also, we had to exclude an additional 34 articles due to insufficient duration of intervention (i.e. less than two weeks) [27–60]. Moreover, we eliminated 20 RCTs from the analysis that used curcumin in combination with other compounds only in the intervention group; such as anthocyanin, resveratrol, ginger, pepper, and omega-3 fatty acids [61–80]. Five RCTs were also excluded because they were conducted on children [81–85]. Finally, 66 eligible RCTs were used in the current systematic review and *meta*-analysis [86–151], among which 45 articles assessed the impact of curcumin/turmeric on C-reactive protein [87–89,91–97,99,105,107,109–116,118,121–127,129–131,134–141,144,146–149,151], 24 articles on TNF-α [86,90,92–94,100,102,103,106,107,109–111,113,119,122,123,126,132,136,141,148,150], 20 articles on IL-6 [88,90,92–94,99,100,103,108,109,111,119,122,126,128,135,143,145,148,150], 18 articles on MDA [91,95,101,104,110,111,113,120,132,135,137,138,140–142,144,146,147], 16 articles on TAC [95,98,102,104,110,111,115,117,120,135,137,138,140,141,144,147], seven articles on SOD [92,93,98,113,133,141,143], and six studies reported IL-1β levels [90,101,102,119,126,141]. Fig. 1 depicts the flow diagram of the study selection process.

3.2. Characteristics of the included studies

Table 1 presents the characteristics of the 66 RCTs included in the current systematic review and *meta*-analysis. These RCTs were conducted in Iran [86,89–94,96,98,100,104,109–111,113–116,120,122–124,127,128,131,133,135–142,144,145,147,150], the United States [87,88,103,105,117], India [95,101,119,121,148,151], Japan [97,118,126,149], Germany [99], Iraq [102,143], China [107], Indonesia [106,108], Armenia [112], Australia [125,134], Brazil [129,132,146], and Turkey [130], and were published between years 2011 and 2021. Eight studies were exclusively performed on female subjects [88,124,130,133,135,140,145,147], six studies on male subjects [92,98,103,110,117,128], and others on both genders. The number of participants in the included RCT samples ranged from 14 to 246,

Table 1
Characteristics of included studies.

Author, Year (Location)	*Study design*	*Population*	*Gender*	*Number (Case/ control)*	*Intervention Mean (range) age (years)*	*Intervention Mean BMI (Kg/ m2)*	*Duration (Weeks)*	*Intervention Intervention group Control group*	*Outcome*
Khajehdehi et al., 2011 (Iran)	RCT, DB, Parallel	Overt type 2 diabetic nephropathy	M/F	20/20	52.9	NR	8	Turmeric (1500 mg/ day) Placebo (Starch)	TNF-a
Disilvestro et al., 2012 (USA)	RCT, Parallel	Healthy adult males and postmenopausal females	M/F	19/19	48	NR	4	Lipidated curcumin (80 mg/day) Placebo (Starch)	CRP
Nieman et al., 2012 (USA)	RCT, DB, Parallel	Obese	F	30/30	55.7	NR	4	Turmeric (2800 mg/ day) Placebo (White rice flour)	CRP IL-6 TNF-a
Mohammadi et al., 2013 (Iran)	RCT, DB, Crossover	Obese	M/F	30/30	38.42	32.6	4	Curcuminoid (1000 mg/day) Placebo	CRP
Ganjali et al., 2014 (Iran)	RCT, DB, Crossover	Obese	M/F	30/30	38.42	32.6	4	Curcuminoid (1000 mg/day) Placebo	TNF-a IL-1 IL-6
Pakfetrat et al., 2014 (Iran)	RCT, DB, Parallel	HD	M/F	39/39	46.8	NR	8	Turmeric (1500 mg/ day) Placebo (Starch)	CRP MDA
Panahi et al., 2014 (Iran)	RCT, DB, Parallel	Chronic Pulmonary Complications	M	25/25	50.97	28.08	4	Curcuminoid (1500 mg/day) Placebo	TNF-a CRP IL-6 SOD
Panahi et al., 2014 (Iran)	RCT, DB, Parallel	Solid Tumor	M/F	40/40	59.58	NR	8	Curcuminoid (180 mg/ day) Placebo	TNF-a CRP IL-6 SOD
Rahiminia et al., 2014 (Iran)	RCT, DB, Parallel	OA	M/F	19/21	57.32	28.75	6	Curcumin (1500 mg/ day + 15 mg Piperine) Placebo + 15 mg Piperine	TNF-a CRP IL-6
Maithili Karpaga Selvi et al., 2015 (India)	RCT, Parallel	T2DM	M/F	30/30	47	23.4	4	Turmeric (2000 mg/ day) + Metformin Placebo (Metformin)	CRP TAC MDA
Mirzabeigi et al., 2015 (Iran)	RCT, DB, Parallel	CAD	M/F	17/16	61.5	27.94	8	Curcumin (2000 mg/ day) Placebo	CRP
Funamoto et al., 2016 (Japan)	RCT, DB, Parallel	COPD	M/F	22/17	69.6	27.1	24	Curcumin (180 mg/ day) Placebo	CRP
Hejazi et al., 2016 (Iran)	RCT, DB, Parallel	Prostate Cancer	M	20/20	69.58	27.17	12	Curcumin (3000 mg/ day) Placebo (Roasted rice flour)	TAC SOD
Kocher et al., 2016 (Germany)	RCT, DB, Crossover	Hyperlipidemic	M/F	42/42	51	26.7	6	Micellar curcuminoid (294 mg/day) Placebo	CRP IL-6
Srivastava et al., 2016 (India)	RCT, DB, Parallel	Knee OA	M/F	66/67	50.23	28.32	16	Curcumin (500 mg/ day) Placebo	IL-1 MDA
Panahi et al., 2016 (Iran)	RCT, DB, Parallel	MetS	M/F	50/50	44.8	25.46	8	Curcumin + 5 mg piperine (1000 mg/day) Placebo (Lactose + 5 mg piperine)	TNF-a IL-6
Abbas et al., 2017 (Iraq)	RCT, Parallel	PUD	M/F	21/19	44.09	26.66	6	Curcumin (1500 mg/ day) Placebo	TNF-a IL-1 TAC
Campbell et al., 2017 (USA)	RCT, DB, Parallel	Obese	M	11/11	25.9	33.29	12	Curcumin (500 mg/ day) Placebo	TNF-a IL-6
Nasseri et al., 2017 (Iran)	RCT, DB, Parallel	Beta-thalassemia	M/F	31/30	25.97	20.6	12	Curcumin (1500 mg/ day) Placebo (Corn Starch)	TAC MDA
Santos-Parker et al., 2017 (USA)	RCT, DB, Parallel	Healthy adult males and postmenopausal females	M/F	20/19	63	25	12	Curcumin (400 mg/ day) Placebo (Maltodextrin)	CRP
Shao et al., 2017 (China)	RCT, DB, Parallel	Takayasu Arteritis	M/F	120/126	36.2	21.6	4	Curcumin (300 mg/ day) Placebo	TNF-a CRP
	RCT, DB, Parallel		M/F	19/20	27.9	20.8	12	Curcumin (60 mg/day) + 400 IU Vitamin D	IL-6

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Table 1 (*continued*)

Author, Year (Location)	*Study design*	*Population*	*Gender*	*Number (Case/ control)*	*Intervention Mean (range) age (years)*	*Intervention Mean BMI (Kg/ m2)*	*Duration (Weeks)*	*Intervention Intervention group Control group*	*Outcome*
Singgih et al., 2017 (Indonesia)		Lupus Erythematosus Patients with Hypovitamin D						Placebo (400 IU Vitamin D)	
Setiawati et al., 2017 (Indonesia)	RCT, DB, Parallel	Lupus Erythematosus	M/F	10/4	29.7	NR	4	Curcuminoid (150 mg/ day) Placebo	TNF-a
Abdolahi et al., 2018 (Iran) (a)	RCT, DB, Parallel	Migraine	M/F	19/19	37.36	27.59	8	Nano-Curcumin (80 mg/day) Placebo	TNF-a CRP IL-6
Abdolahi et al., 2018 (Iran) (b)	RCT, DB, Parallel	Migraine	M/F	17/19	35.82	26.02	8	Nano-Curcumin (80 mg/day) + ω3 Placebo + ω3	TNF-a CRP IL-6
Alizadeh et al., 2018 (Iran)	RCT, DB, Parallel	Infertile Men	M	26/26	30.54	26.06	10	Nano-Curcumin (80 mg/day) Placebo	TNF-a CRP TAC MDA
Ghaffari et al., 2018 (Iran)	RCT, DB, Parallel	NAFLD	M/F	21/21	42.57	31.51	12	Turmeric (3000 mg/ day) Placebo (Corn Starch)	TNF-a CRP IL-6 TAC MDA
Haroyan et al., 2018 (Armenia)	RCT, DB, Parallel	OA	M/F	56/58	54.65	28.94	12	Curcuminoid (1000 mg/day) Placebo	CRP
Panahi et al., 2018 (Iran)	RCT, DB, Parallel	T2DM	M/F	50/50	43	26.59	12	Curcumin (1000 mg/ day + 10 mg piperine) Placebo (Lactose + 10 mg piperine)	TNF-a CRP MDA SOD
Saberi-Karimian et al., 2018 (Iran) (a)	RCT, Parallel	MetS	M/F	37/36	40.05	30.66	6	Curcumin-phospholipid complex (1000 mg/ day) Placebo (lactose + starch)	CRP
Saberi-Karimian et al., 2018 (Iran) (b)	RCT, Parallel	MetS	M/F	36/36	37.52	30.67	6	Curcumin (Unformulated) (1000 mg/day) Placebo (lactose + starch)	CRP
Adab et al., 2019 (Iran)	RCT, DB, Parallel	Hyperlipidemic T2DM	M/F	39/36	54.76	28.98	8	Turmeric (2100 mg/ day) Placebo (Corn Starch)	CRP TAC
Adibian et al., 2019 (Iran)	RCT, DB, Parallel	T2DM	M/F	21/23	58	NR	10	Curcumin (1500 mg/ day) Placebo (Rice Flour)	CRP
Campbell et al., 2019 (USA)	RCT, DB, Parallel	Obese	M	10/10	18–35	NR	12	Curcumin (500 mg/ day) Placebo	TAC
Funamoto et al., 2019 (Japan)	RCT, DB, Parallel	IGTT	M/F	15/18	70	24.9	24	Curcumin (180 mg/ day) Placebo	CRP
Gupte et al., 2019 (India)	RCT, Parallel	Knee OA	M/F	17/25	57	28.22	12	Curcumin (160 mg/ day) Placebo	TNF-a IL-1 IL-6
Hodaei et al., 2019 (Iran)	RCT, DB, Parallel	T2DM	M/F	21/23	58	29.2	10	Curcumin (1500 mg/ day) Placebo (Cooked rice flour)	TAC MDA
Jacob et al., 2019 (India) (a)	RCT, DB, Parallel	RA	M/F	8/8	18–65	NR	12	Curcumin (500 mg/ day) Placebo	CRP
Jacob et al., 2019 (India) (b)	RCT, DB, Parallel	RA	M/F	8/8	18–65	NR	12	Curcumin (250 mg/ day) Placebo	CRP
Jazayeri-Tehrani et al., 2019 (Iran)	RCT, DB, Parallel	NAFLD	M/F	42/42	41.8	30.6	12	Nano-Curcumin (80 mg/day) Placebo	TNF-a CRP IL-6
Saadati et al., 2019 (Iran)	RCT, Parallel	NAFLD	M/F	27/23	46.19	32.3	12	Curcumin (1500 mg/ day) Placebo (Maltodextrin)	TNF-a CRP
Sohaei et al., 2019 (Iran)	RCT, DB, Parallel	Obese PCOS Women	F	27/24	29.4	29.67	6	Curcumin (1000 mg/ day) Placebo	CRP
Thota et al., 2019 (Australia)	RCT, DB, Parallel	High Risk T2DM	M/F	15/16	55	30.9	12		CRP

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Table 1 (*continued*)

Author, Year (Location)	*Study design*	*Population*	*Gender*	*Number (Case/ control)*	*Intervention Mean (range) age (years)*	*Intervention Mean BMI (Kg/ m2)*	*Duration (Weeks)*	*Intervention Intervention group Control group*	*Outcome*
								Curcumin (1000 mg/ day) Placebo	
Thota et al., 2019 (Australia)	RCT, DB, Parallel	High Risk T2DM	M/F	16/17	57	31.7	12	Curcumin (1000 mg/ day) + Fish oil Placebo + Fish oil	CRP
Uchio et al., 2019 (Japan)	RCT, DB, Parallel	Overweight or pre-HTN	M/F	43/44	58.8	25	12	Hot water extract of C. longa L (900 mg/day) Placebo	TNF-a CRP IL-1 IL-6
Afshar et al., 2020 (Iran)	RCT, DB, Parallel	HD	M/F	27/27	55.33	26.1	12	Nano-Curcumin (120 mg/day) Placebo	CRP
Ahmadi et al., 2020 (Iran)	RCT, DB, Parallel	Ankylosing Spondylitis	M	12/12	34.6	32.58	16	Nano-Curcumin (80 mg/day) Placebo	IL-6
Alvarenga et al., 2020 (Brazil)	RCT, DB, Parallel	HD	M/F	14/14	54	27.1	12	Turmeric (2500 mg/ day) Placebo	CRP
Asan et al., 2020 (Turkey)	RCT, Parallel	PCOS	F	15/15	27.6	29.8	8	Gel optimised curcumin (93.38 mg/day) Placebo	CRP
Atabaki et al., 2020 (Iran)	RCT, DB, Parallel	OA	M/F	15/15	49.13	22	12	Nano-Curcumin (80 mg/day) Placebo	CRP
Da Sliva et al., 2020 (Brazil)	RCT, DB, Crossover	HIV	M/F	20/20	45.5	23.7	4	Curcumin (1000 mg/ day) Placebo (Microcrystalline Cellulose)	TNF-a MDA
Heshmati et al., 2020 (Iran)	RCT, Parallel	PCOS	F	34/33	31	28.3	12	Curcumin (1500 mg/ day) Placebo (Maltodextrin)	SOD
Kuszewski et al., 2020 (Australia)	RCT, DB, Parallel	Older sedentary overweight/obese adults	M/F	38/36	65.4	30.5	16	Curcumin (160 mg/ day) Placebo	CRP
Osali et al., 2020 (Iran) (a)	RCT, DB, Parallel	MetS	F	11/11	60–65	31.24	6	Nano-curcumin (80 mg/day) + exercise Placebo (Maltodextrin) + exercise	CRP IL-6 TAC MDA
Osali et al., 2020 (Iran) (b)	RCT, DB, Parallel	MetS	F	11/11	60–65	29.54	6	Nano-curcumin (80 mg/day) Placebo (Maltodextrin)	CRP IL-6 TAC MDA
Sadeghi et al., 2020 (Iran)	RCT, DB, Parallel	UC	M/F	31/32	40.1	25.9	8	Curcumin (1500 mg/ day) Placebo	TNF-a CRP
Shafabakhsh et al., 2020 (Iran)	RCT, DB, Parallel	Patients with diabetes on HD	M/F	26/27	58.3	27.9	12	Nano-curcumin (80 mg/day) Placebo	CRP TAC MDA
Shafabakhsh et al., 2020 (Iran)	RCT, DB, Parallel	T2DM + 2 and 3 vessel coronary heart disease	M/F	25/24	64.9	30.3	12	Curcumin (1000 mg/ day) Placebo (Starch)	TAC MDA
Tamaddoni et al., 2020 (Iran)	RCT, DB, Parallel	Beta-thalassemia	M/F	31/30	25.97	20.6	12	Curcumin (1000 mg/ day) Placebo (Corn Starch)	CRP
Darmian et al., 2021(Iran) (a)	RCT, Parallel	Hyperlipidemia and T2DM	F	11/10	43.02	28.15	8	Turmeric (2100 mg/ day) + Aerobic training Placebo (Corn starch) + Aerobic training	CRP TAC MDA
Darmian et al., 2021(Iran) (b)	RCT, Parallel	Hyperlipidemia and T2DM	F	11/10	44.33	29.3	8	Turmeric (2100 mg/ day) Placebo (Corn starch)	CRP TAC MDA
Helli et al., 2021 (Iran) (a)	RCT, DB, Parallel	Coronary elective angioplasty	M/F	30/30	55.27	28.1	8	Curcumin (500 mg/ day) Placebo	TNF-a CRP IL-1 TAC MDA SOD
Helli et al., 2021 (Iran) (b)	RCT, DB, Parallel	Coronary elective angioplasty	M/F	30/30	56.19	27.81	8	Nano-curcumin (80 mg/day) Placebo	TNF-a CRP IL-1 TAC

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Table 1 (*continued*)

Author, Year (Location)	*Study design*	*Population*	*Gender*	*Number (Case/ control)*	*Intervention Mean (range) age (years)*	*Intervention Mean BMI (Kg/ m2)*	*Duration (Weeks)*	*Intervention Intervention group Control group*	*Outcome*
									MDA SOD
Jarhahzadeh et al., 2021 (Iran)	RCT, DB, Parallel	NAFLD	M/F	32/32	44.12	29.51	8	Turmeric (2000 mg/ day) Placebo (Wheat Flour)	MDA
Khdair et al., 2021 (Iraq)	RCT, Parallel	Chronic bronchial asthma	M/F	23/17	44.83	NR	8	Curcumin (1500 mg/ day) Placebo	IL-6 SOD
Mokhtari et al., 2021 (Iran)	RCT, DB, Parallel	Diabetic foot ulcer	M/F	25/25	57.4	27.5	12	Nano-curcumin (80 mg/day) Placebo	CRP TAC MDA
Rezaie et al., 2021 (Iran)	RCT, DB, Parallel	Migraine	F	22/22	37	27.5	8	Curcumin (1000 mg/ day) Placebo	IL-6
Rodrigues et al., 2021 (Brazil)	RCT, DB, Parallel	HD	M/F	20/23	48.5	26.6	12	Curcumin (1000 mg/ day) Placebo (Corn Starch)	CRP MDA
Salehi et al., 2021 (Iran)	RCT, DB, Parallel	Healthy women moderate exercise	F	32/33	21	21.75	8	Curcumin (500 mg/ day) Placebo (Corn starch)	CRP TAC MDA
Thanawala et al., 2021 (India)	RCT, DB, Parallel	Healthy Adults with Chronic Knee Pain	M/F	49/47	36.6	23.7	12	Curcuminoid (150 mg/ day) Placebo	TNF-a CRP IL-6
Uchio et al., 2021 (Japan)	RCT, DB, Parallel	Overweight	M/F	39/40	56.7	26.6	12	Turmeric extract (900 mg/day) Placebo	CRP
Vafadar et al., 2021 (Iran)	RCT, DB, Parallel	HD	M/F	27/27	55.33	26.1	12	Nano-curcumin (120 mg/day) Placebo (Paraffin Oil)	TNF-a IL-6
Varma et al., 2021 (India)	RCT, DB, Parallel	Healthy Elderly	M/F	15/15	69.8	NR	12	Curcuminoid (500 mg/ day) Placebo	CRP

DB: double-blind / T2DM: type 2 diabetes mellitus / MetS: metabolic syndrome / RA: rheumatoid arthritis / OA: osteoarthritis /NAFLD: non-alcoholic fatty liver disease / IGTT: impaired glucose tolerance test / HD: hemodialysis / UC: ulcerative colitis / PUD: peptic ulcer disease / HTN: hypertension /PCOS: polycystic ovary syndrome / M: male / F: female / TNF: tumor necrosis factor / CRP: C-reactive protein / IL: interleukin / MDA: malondialdehyde / TAC: total antioxidant capacity / SOD: superoxide dismutase.

yielding a total sample size of 3953 individuals. The mean age of participants was between 18 and 70 years. The dosage of curcumin supplementation varied between 80 mg/day (nano-curcumin) and 3000 mg/day (turmeric powder), and the duration of intervention ranged from 4 to 24 weeks across selected RCTs. Except for five studies that had cross-over designs [88–90,99,132], the majority of studies took advantage of a parallel design. Regarding the types of curcumin supplements used in the intervention, 41 studies used curcumin/curcuminoids [89,90,92–94,96–98,100–108,112,113,116–121,123–125,132-–134,136,138,139,141,143,145–148,151], 11 studies administered turmeric [86,88,91,95,111,115,126,129,140,142,149], and 14 studies used highly absorbable / nano-curcumin [87,99,109,110,114,122,127,128,130,131,135,137,144,150]. Also, four articles examined the effect of turmeric in combination with piperine [92,94,100,113], two RCTs examined the use of turmeric/curcumin with exercise [135,140], and one RCT assessed the effect of curcumin with Metformin [95]. It should be noted that we made sure that in case of combined intervention, the control group received the same accompanied treatment. The included studies were conducted on healthy individuals [87,105,147,148,151], patients with type 2 diabetes and hyperlipidemia [86,95,99,113,115,116,118,120,125,138,140,144], metabolic syndrome [100,114,135], non-alcoholic fatty liver disease [111,122,123,142], overweight and obese individuals [88–90,103,117,126,134,149], patients with rheumatoid arthritis and osteoarthritis [94,101,112,119,121,131], patients with polycystic ovary syndrome and infertile men [110,124,133], patients undergoing hemodialysis [91,127,129,137,146,150], patients with beta-thalassemia [104,139], HIV/AIDS [132], pulmonary complications [92,97,143], solid tumor and cancer [93,98], migraine [109,145], cardiovascular diseases [96,138,141], lupus erythematosus [106,108], peptic ulcer and ulcerative colitis [102,136], and Takayasu arteritis [107].

3.3. Results from quality assessment

Random sequence generation of participants was mentioned in all included trials, and 5 studies had high risk of sequence generation bias [87,102,119,135,143]. Three trials had high risk bias with respect to allocation to interventions [102,119,130], and 4 trials did not report allocation concealment [87,100,116,135]. Moreover, three trials had high risk of bias concerning blinding of participants and personnel [102,130,143], and five studies had high risk of bias with respect to blinding outcome assessors [119,130,140,143,144]. Most studies showed low risk of bias based on incomplete outcome data, and 27 studies had unclear risk of attrition bias. Thirty-seven studies had low risk of bias regarding selective outcome reporting. Three studies had low risk of other potential biases [123,134,150], while 63 studies had unclear risk of bias with regard to other potential threats to validity. None of the RCTs had a low risk of bias in all domains of the Cochrane Risk of Bias Assessment tool (Table 2).

3.4. Effect of curcumin/turmeric supplementation on C - reactive protein (CRP)

The effect of the curcumin/turmeric supplementation on CRP was examined in 52 arms of clinical trials. Curcumin/turmeric supplementation significantly reduced CRP levels (WMD: −0.58 mg/l, 95 % CI: −0.74, −0.41; $P < 0.001$), with significant between-study heterogeneity ($I^2 = 98.9$ %, $P < 0.001$) (Fig. 2). Since we observed a significant heterogeneity, subgroup analysis was performed, based on participants' mean age and baseline BMI, supplementation dosage, health status of

Table 2
Results of risk of bias assessment for randomized clinical trials included in the current *meta*-analysis.

Study	Sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reporting	Other potential threats to validity
Khajehdehi et al. 2011	L	L	L	U	L	L	U
Disilvestro et al. 2012	H	U	L	U	U	L	U
Nieman et al. 2012	L	L	L	U	L	L	U
Mohammadi et al. 2013	L	L	L	L	L	L	U
Ganjali et al. 2014	L	L	L	L	L	L	U
Pakfetrat et al. 2014	L	L	L	L	L	U	U
Panahi et al. 2014	L	L	L	L	U	L	U
Panahi et al. 2014	L	L	L	L	U	L	U
Rahiminia et al. 2014	L	L	L	U	U	L	U
Maithili Karpaga Selvi et al. 2015	L	L	L	U	L	L	U
Mirzabeigi et al. 2015	L	L	L	U	U	L	U
Funamoto et al. 2016	L	L	L	L	U	U	U
Hejazi et al. 2017	L	L	L	L	L	U	U
Kocher et al. 2016	L	L	L	L	L	L	U
Srivastava et al. 2016	L	L	L	U	U	L	U
Panahi et al. 2016	L	U	L	U	U	L	U
Abbas et al. 2017	H	H	H	U	U	L	U
Campbell et al. 2017	L	L	L	L	L	L	U
Nasseri et al. 2017	L	L	L	L	U	U	U
Santos-Parker et al. 2017	L	L	L	L	U	U	U
Shao et al. 2017	L	L	L	U	U	L	U
Setiawati et al. 2017	L	L	L	U	L	U	U
Singgih et al. 2017	L	L	L	U	L	L	U
Abdolahi et al. 2018	L	L	L	L	L	U	U
Alizadeh et al. 2018	L	L	L	L	L	U	U
Ghaffari et al. 2018	L	L	L	L	L	L	U
Haroyan et al. 2018	L	L	L	L	U	L	U
Panahi et al. 2018	L	L	L	U	U	U	U
Saberi-Karimian et al. 2018	L	L	L	L	L	U	U
Adab et al. 2019	L	L	L	U	L	L	U
Adibian et al. 2019	L	U	L	U	U	L	U
Campbell et al. 2019	L	L	L	L	L	U	U
Funamoto et al. 2019	L	L	L	U	L	U	U
Gupte et al. 2019	H	H	L	H	U	U	U
Hodaei et al. 2019	L	L	L	U	L	L	U
Jacob et al. 2019	L	L	L	L	L	U	U
Jazayeri-Tehrani et al. 2019	L	L	L	U	L	L	U
Saadati et al. 2019	L	L	L	U	L	U	L
Sohaei et al. 2019	L	L	L	U	L	L	U
Thota et al. 2019	L	L	L	L	U	U	U
Uchio et al. 2019	L	L	L	U	L	L	U
Afshar et al. 2020	L	L	L	U	L	U	U
Ahmadi et al. 2020	L	L	L	U	L	L	U
Alvarenga et al. 2020	L	L	L	U	L	L	U
Asan et al. 2020	L	H	H	H	U	U	U
Atabaki et al. 2020	L	L	L	U	L	L	U
Da Silva et al. 2020	L	L	L	L	L	L	U
Heshmati et al. 2020	L	L	L	U	L	L	U
Kuszewski et al. 2020	L	L	L	U	L	U	L
Osali et al. 2020	H	U	L	U	U	L	U
Sadeghi et al. 2020	L	L	L	L	L	U	U
Shafabakhsh et al. 2020	L	L	L	L	U	U	U
Shafabakhsh et al. 2020	L	L	L	L	U	U	U
Tamaddoni et al. 2020	L	L	L	L	L	L	U
Darmian et al. 2021	L	L	L	H	U	U	U
Helli et al. 2021	L	L	L	U	H	U	U
Jarhahzadeh et al. 2021	L	L	L	U	L	L	U
Khdair et al. 2021	H	L	H	H	L	L	U
Mokhtari et al. 2021	L	L	L	H	U	U	U
Rezaie et al. 2021	L	L	L	L	U	U	U
Rodrigues et al. 2021	L	L	L	L	L	L	U
Salehi et al. 2021	L	L	L	L	U	U	U

(*continued on next page*)

Table 2 (*continued*)

Study	Sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reporting	Other potential threats to validity
Thanawala et al. 2021	L	L	L	L	H	U	U
Uchio et al. 2021	L	L	L	L	U	L	U
Vafadar et al. 2021	L	L	L	U	L	U	L
Varma et al. 2021	L	L	L	L	U	U	U

H: high risk of bias, L: low risk of bias, U: unknown risk of bias.

participants, number of participants, type of supplementation, duration of intervention, and study's location (Table 3). The decreasing effect of curcumin/turmeric supplementation on CRP was significant in all subgroups, except for studies which used high absorption curcumin as their intervention and those conducted on hemodialysis patients.

3.5. Effect of curcumin/turmeric supplementation on tumour necrosis factor-α (TNF-α)

Combining 26 effect sizes via the random-effects model showed that curcumin/turmeric consumption could significantly reduce TNF-α (WMD: −3.48 pg/ml, 95 % CI: −4.38, −2.58, P < 0.001). However, there was a high between-study heterogeneity (I^2 = 99.4 %, P < 0.001) (Fig. 2). The pre-defined subgroup analysis demonstrated a significant reduction in TNF-α, except for those studies which used turmeric or high absorption curcumin (Table 3).

3.6. Effect of curcumin/turmeric supplementation on interleukin-6 (IL-6)

Curcumin/turmeric supplementation significantly reduced IL-6 levels, when effect sizes were pooled using 22 arms of trial (WMD: −1.31 pg/ml, 95 % CI: −1.58, −0.67, P < 0.001), with significant between-study heterogeneity (I^2 = 88.2 %, P < 0.001) (Fig. 2). Results from subgroup analysis confirmed the reducing effect of curcumin/turmeric supplementation on IL-6 in all subgroups (Table 3).

3.7. Effect of curcumin/turmeric supplementation on interleukin 1 beta (IL-1β)

The pooled effect size from 7 studies which investigated the effect of curcumin/turmeric supplementation on IL-1β, showed no significant reduction in IL-1β (WMD: −0.46 pg/ml, 95 % CI: −1.18, 0.27, P = 0.218), with significant between-study heterogeneity (I^2 = 75.8, P < 0.001) (Fig. 2). Moreover, subgroup analysis did not detect any significant effects on IL-1β in all of subgroups. Due to lack of sufficient studies, subgroup analysis based on health status of the participants was not applicable, and thus, not conducted (Table 3).

3.8. Effect of curcumin/turmeric supplementation on total antioxidant capacity (TAC)

Meta-analysis of 19 arms of clinical trials showed that curcumin/turmeric supplementation significantly increased TAC (WMD = 0.21 mmol/l; 95 % CI: 0.08, 0.33, P = 0.001), with significant heterogeneity between studies (I^2 = 99.6 %, P < 0.001) (Fig. 3). Subgroup analysis showed that curcumin/turmeric intake resulted in a significant increase in TAC in all subgroups, except for the studies conducted on individuals aged ≥ 45 years old, studies conducted Iranian population, and when turmeric or high absorption curcumin was used as the intervention (Table 3).

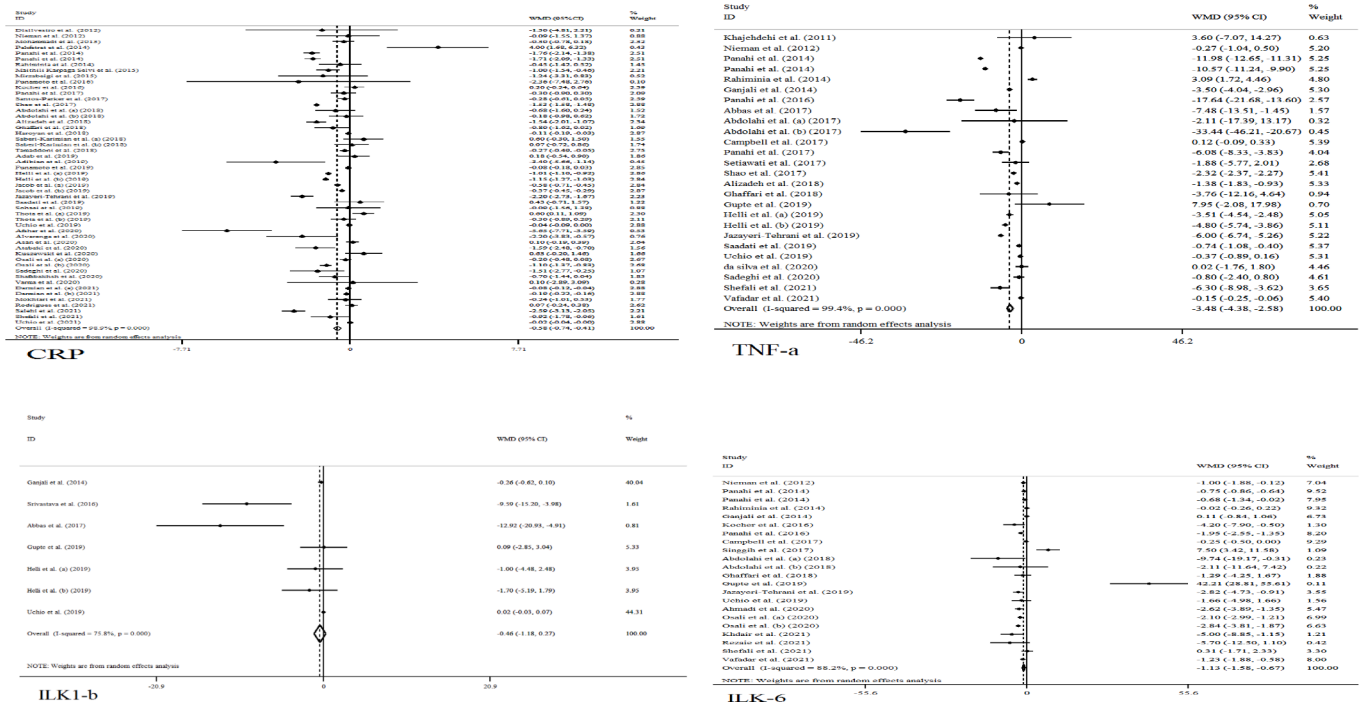

Fig. 2. Forest plots for the effect of curcumin/turmeric supplementation on inflammatory markers. Horizontal lines represent 95% CIs. Diamonds represent pooled estimates from random-effects analysis. WMD: weighted mean difference, CI: confidence interval.

Table 3
Subgroup analysis to assess the effect of curcumin/turmeric supplementation on inflammatory markers and antioxidant status.

Variable	No. of trials	WMD (95 % CI)	P-Value[1]	I^2 (%)[2]	P for heterogeneity[3]	P for between Subgroup heterogeneity[4]
CRP						
Overall	52	−0.58 (-0.74, −0.41)	<0.001	98.9	<0.001	–
Age (years)						<0.001
<45	20	−0.43 (-0.45, −0.41)	<0.001	99.3	<0.001	
≥45	32	−0.09 (-0.10, −0.07)	<0.001	97.1	<0.001	
BMI (kg/m^2)						0.644
<30	41	−0.22 (-0.24, −0.21)	<0.001	99.1	<0.001	
≥30	11	−0.26 (-0.43, −0.09)	0.002	86.8	<0.001	
Dosage (g/d)						<0.001
<1	28	−0.25 (-0.27, −0.24)	<0.001	99.4	<0.001	
≥1	24	−0.16 (-0.18, −0.13)	<0.001	84.7	<0.001	
Duration (Weeks)						<0.001
≤8	26	−0.48 (-0.50, −0.46)	<0.001	99.2	<0.001	
>8	26	−0.05 (-0.07, −0.04)	<0.001	92.3	<0.001	
Health status						<0.001
Healthy	10	−0.29 (-0.46, −0.01)	0.001	90.9	<0.001	
Diabetes and Dyslipidemia	9	−0.15 (-0.18, −0.13)	<0.001	80.5	<0.001	
NAFLD	3	−1.49 (-1.91, −1.08)	<0.001	90.3	<0.001	
MetS and prediabetes	7	−0.17 (-0.26, −0.08)	<0.001	90.4	<0.001	
Hemodialysis	4	−0.05 (-0.35, 0.23)	0.696	93.7	<0.001	
Miscellaneous	19	−0.98 (-1.06, −0.95)	<0.001	98.7	<0.001	
Type of intervention						<0.001
Turmeric	10	−0.07 (-0.08, −0.05)	<0.001	93.3	<0.001	
Unformulated curcumin	27	−0.80 (-0.91, −0.85)	<0.001	98.5	<0.001	
High absorption curcumin	4	0.15 (-0.80, 0.39)	0.194	0.0	0.626	
Nano-curcumin	11	−1.06 (-1.15, −0.96)	<0.001	89.2	<0.001	
Location of study						<0.001
Iran	31	−0.27 (-0.29, −0.24)	<0.001	96.9	<0.001	
Non-Iran	21	−0.20 (-0.22, −0.19)	<0.001	99.5	<0.001	
Number of participants						<0.001
<45	25	−0.18 (-0.20, −0.16)	<0.001	86.6	<0.001	
≥45	27	−0.22 (-0.26, −0.23)	<0.001	99.4	<0.001	
TNF-α						
Overall	26	−3.48 (-4.38, −2.58)	<0.001	99.4	<0.001	–
Age (years)						<0.001
<45	14	−2.25 (-2.27, −2.17)	<0.001	98.2	<0.001	
≥45	12	−0.64 (-0.72, −0.55)	<0.001	99.5	<0.001	
BMI (kg/m^2)						<0.001
<30	20	−1.96 (-2.00, −1.92)	<0.001	99.4	<0.001	
≥30	6	−0.73 (-0.89, −0.56)	<0.001	98.6	<0.001	
Dosage (g/d)						<0.001
<1	12	−1.86 (-1.90, −1.82)	<0.001	99.0	<0.001	
≥1	14	−2.69 (-2.92, −2.45)	<0.001	99.5	<0.001	
Duration (Weeks)						<0.001
≤8	16	−2.41 (-2.45, −2.36)	<0.001	99.1	<0.001	
>8	10	−0.28 (-0.36, −0.19)	<0.001	97.3	<0.001	
Health status						<0.001
Healthy	5	−0.39 (-0.57, −0.21)	<0.001	97.6	<0.001	
Diabetes and Dyslipidemia	2	−5.66 (-7.86, −3.47)	<0.001	67.0	<0.001	
NAFLD	3	−1.67 (-1.98, −1.36)	<0.001	98.8	<0.001	
MetS and prediabetes	1	−17.64 (-21.68, −13.59)	<0.001	–	–	
Hemodialysis	1	−0.15 (-0.25, −0.05)	0.002	–	–	
Miscellaneous	14	−0.238 (-2.44, −2.35)	<0.001	99.1	<0.001	
Type of intervention						<0.001
Turmeric	5	−0.37 (-0.80, 0.05)	0.087	39.1	0.161	
Unformulated curcumin	14	−2.38 (-2.43, −2.33)	<0.001	99.2	<0.001	
High absorption curcumin	1	0.12 (-0.09, 0.33)	0.271	–	–	
Nano-curcumin	6	−0.34 (-0.44, −0.25)	<0.001	98.7	<0.001	
Location of study						<0.001
Iran	17	−0.84 (-0.93, −0.76)	<0.001	98.6	<0.001	
Non-Iran	9	−2.18 (-2.23, −2.13)	<0.001	99.4	<0.001	
Number of participants						<0.001
<45	11	−0.31 (-0.51, −0.12)	0.002	95.2	<0.001	
≥45	15	−1.96 (-2.00, −1.91)	<0.001	99.6	<0.001	
IL-6						
Overall	22	−1.13 (-1.58, −0.67)	<0.001	88.2	<0.001	–
Age (years)						0.319
<45	12	−0.56 (-0.78, −0.34)	<0.001	84.5	<0.001	
≥45	10	−0.68 (-0.78, −0.59)	<0.001	91.5	<0.001	
BMI (kg/m^2)						0.123
<30	15	−0.69 (-0.79, −0.60)	<0.001	89.9	<0.001	
≥30	7	−0.50 (-0.72, −0.28)	<0.001	83.2	<0.001	
Dosage (g/d)						0.916
<1	14	−0.67 (-0.88, −0.47)	<0.001	89.1	<0.001	

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Table 3 (*continued*)

Variable	No. of trials	WMD (95 % CI)	P-Value[1]	I^2 (%)[2]	P for heterogeneity[3]	P for between Subgroup heterogeneity[4]
≥1	8	−0.66 (-0.76, −0.57)	<0.001	87.9	<0.001	
Duration (Weeks)						0.044
≤8	13	−0.70 (-0.79, −0.61)	<0.001	87.1	<0.001	
>8	9	−0.45 (-0.67, −0.22)	<0.001	90.0	<0.001	
Health status						<0.001
Healthy	5	−0.28 (-0.51, −0.04)	0.018	6.5	0.370	
Diabetes and Dyslipidemia	1	−4.20 (-7.89, −0.50)	0.026	–	–	
NAFLD	2	−2.37 (-3.97, −0.76)	0.004	0.0	0.394	
MetS and prediabetes	3	−2.17 (-2.61, −1.72)	<0.001	15.2	0.308	
Hemodialysis	1	−1.23 (-1.87, −0.58)	<0.001	–	–	
Miscellaneous	10	−0.64 (-0.73, −0.54)	<0.001	91.4	<0.001	
Type of intervention						<0.001
Turmeric	3	−1.06 (-1.87, −0.24)	0.011	0.920	0.0	
Unformulated curcumin	10	−0.65 (-0.74, −0.55)	<0.001	<0.001	92.0	
High absorption curcumin	2	−0.26 (-0.52, −0.01)	0.037	0.037	77.1	
Nano-curcumin	7	−1.97 (-2.40, −1.55)	<0.001	0.051	52.1	
Location of study						0.001
Iran	14	−0.72 (-0.81, −0.63)	<0.001	87.1	<0.001	
Non-Iran	8	−0.30 (-0.53, −0.06)	0.014	89.4	<0.001	
Number of participants						<0.001
<45	14	−0.31 (-0.48, −0.15)	<0.001	90.0	<0.001	
≥45	8	−0.80 (-0.90, −0.70)	<0.001	69.3	0.002	
IL-1β						
Overall	7	−0.46 (-1.18, 0.27)	0.218	75.8	<0.001	–
Age (years)						0.099
<45	2	−0.28 (-0.64, 0.073)	0.119	89.6	0.002	
≥45	5	0.01 (-0.03, 0.06)	0.441	68.1	0.014	
BMI (kg/m^2)						0.132
<30	6	0.01 (-0.02, 0.06)	77.8	<0.001	0.452	
≥30	1	−0.26 (-0.61, 0.09)	–	–	0.156	
Dosage (g/d)						0.099
<1	2	−0.28 (-0.64, 0.07)	0.441	0.014	89.6	
≥1	5	0.01 (-0.02, 0.06)	0.119	0.002	68.1	
Duration (Weeks)						0.074
≤8	4	−0.30 (-0.66, 0.04)	0.090	71.0	0.016	
>8	3	0.01 (-0.02, 0.06)	0.429	82.3	0.004	
Type of intervention						0.105
Turmeric	1	0.020 (-0.02, 0.06)	0.413	–	–	
Unformulated curcumin	5	−0.32 (-0.67, 0.02)	0.07	80.3	<0.001	
Nano-curcumin	1	−1.70 (-5.18, 1.78)	0.339	–	–	
Location of study						0.099
Iran	3	−0.28 (-0.63, 0.07)	0.119	0.0	0.666	
Non-Iran	4	0.01 (-0.02, 0.06)	0.440	85.9	<0.001	
Number of participants						0.103
<45	3	−0.28 (-0.63, 0.07)	0.123	79.3	0.008	
≥45	4	0.01 (-0.02, 0.06)	0.442	76.1	0.006	
TAC						
Overall	19	0.21 (0.08, 0.33)	0.001	99.6	<0.001	–
Age (years)						<0.001
<45	8	0.11 (0.10, 0.12)	<0.001	99.8	<0.001	
≥45	11	0.01 (-0.05, 0.03)	0.146	96.9	<0.001	
BMI (kg/m^2)						0.995
<30	16	0.10 (0.09, 0.10)	<0.001	99.7	<0.001	
≥30	3	0.10 (0.06, 0.14)	<0.001	87.7	<0.001	
Dosage (g/d)						<0.001
<1	9	0.01 (0.009, 0.02)	<0.001	94.2	<0.001	
≥1	10	0.55 (0.53, 0.56)	<0.001	99.4	<0.001	
Duration (Weeks)						<0.001
≤8	10	0.02 (0.02, 0.03)	<0.001	96.1	<0.001	
>8	9	0.24 (0.23, 0.25)	<0.001	99.8	<0.001	
Health status						<0.001
Healthy	2	0.10 (0.04, 0.15)	<0.001	0.0	0.365	
Diabetes and Dyslipidemia	8	0.02 (0.01, 0.03)	<0.001	95.0	<0.001	
NAFLD	1	0.29 (0.18, 0.39)	<0.001	–	–	
MetS and prediabetes	2	0.124 (-0.11, 0.36)	<0.001	91.0	<0.001	
Miscellaneous	6	0.16 (0.15, 0.17)	<0.001	99.9	<0.001	
Type of intervention						<0.001
Turmeric	5	0.04 (0.03, 0.05)	<0.001	90.2	<0.001	
Unformulated curcumin	7	0.004 (-0.004,0.01)	0.332	96.6	<0.001	
High absorption curcumin	1	0.32 (-0.15, 0.79)	0.185	–	–	
Nano-curcumin	6	0.59 (0.57, 0.61)	<0.001	99.5	<0.001	
Location of study						<0.001
Iran	16	0.14 (0.14, 0.15)	<0.001	99.7	<0.001	
Non-Iran	3	0.008 (-0.003, 0.01)	0.159	46.7	0.153	
Number of participants						<0.001
<45	9	0.01 (0.004, 0.02)	0.003	94.5	<0.001	

(*continued on next page*)

Table 3 (*continued*)

Variable	No. of trials	WMD (95 % CI)	P-Value[1]	I^2 (%)[2]	P for heterogeneity[3]	P for between Subgroup heterogeneity[4]
≥45	10	0.28 (0.27, 0.30)	<0.001	99.7	<0.001	
MDA						
Overall	21	−0.33 (-0.53, −0.12)	0.001	99.6	<0.001	–
Age (years)						<0.001
<45	8	−0.17 (-0.19, −0.16)	<0.001	97.6	<0.001	
≥45	13	−0.67 (-0.68, −0.65)	<0.001	99.6	<0.001	
BMI (kg/m^2)						<0.001
<30	15	−0.41 (-0.42, −0.40)	<0.001	99.7	<0.001	
≥30	6	−0.14 (-0.18, −0.09)	<0.001	93.4	<0.001	
Dosage (g/d)						<0.001
<1	9	−0.58 (-0.59, −0.56)	<0.001	99.7	<0.001	
≥1	12	−0.07 (-0.09, −0.06)	<0.001	95.0	<0.001	
Duration (Weeks)						<0.001
≤8	11	−0.13 (-0.14, −0.11)	<0.001	96.5	<0.001	
>8	10	−0.56 (-0.58, −0.55)	<0.001	99.7	<0.001	
Health status						<0.001
Healthy	1	−0.19 (-0.25, −0.12)	<0.001	–	–	
Diabetes and Dyslipidemia	8	−0.15 (-0.18, −0.13)	<0.001	94.3	<0.001	
NAFLD	2	0.01 (-0.01, 0.04)	0.265	61.9	0.105	
MetS and prediabetes	2	−0.51 (-0.71, −0.31)	<0.001	97.8	<0.001	
Hemodialysis	2	0.01 (-0.06, 0.09)	0.633	64.3	0.094	
Miscellaneous	6	−0.62 (-0.63, −0.60)	<0.001	99.8	<0.001	
Type of intervention						<0.001
Turmeric	6	−0.07 (-0.10, −0.05)	<0.001	95.6	<0.001	
Unformulated curcumin	9	−0.73 (-0.75, −0.71)	<0.001	99.7	<0.001	
Nano-curcumin	6	−0.26 (-0.28, −0.23)	<0.001	94.5	<0.001	
Location of study						<0.001
Iran	17	−0.18 (-0.19, −0.16)	<0.001	96.4	<0.001	
Non-Iran	4	−0.89 (-0.91, −0.87)	<0.001	99.8	<0.001	
Number of participants						<0.001
<45	9	−0.14 (-0.17, −0.11)	<0.001	93.5	<0.001	
≥45	12	−0.44 (-0.46, −0.43)	<0.001	99.8	<0.001	
SOD						
Overall	8	20.51 (7.35, 33.67)	0.002	95.4	<0.001	–
Age (years)						0.028
<45	3	22.74 (14.37, 31.12)	<0.001	97.2	<0.001	
≥45	5	13.10 (11.07, 15.13)	<0.001	94.7	<0.001	
Dosage (g/d)						0.231
<1	4	13.33 (11.66, 15.61)	<0.001	95.0	<0.001	
≥1	4	18.47 (10.23, 26.62)	<0.001	96.7	<0.001	
Duration (Weeks)						<0.001
≤8	5	48.36 (36.13, 60.59)	<0.001	94.3	<0.001	
>8	3	12.71 (10.70, 14.71)	<0.001	96.0	<0.001	
Number of participants						<0.001
<45	2	−9.89 (-20.33, 0.53)	0.063	86.6	0.006	
≥45	6	14.51 (12.05, 15.61)	<0.001	96.0	<0.001	

Abbreviation: WMD: weighted mean difference, CI: confidence interval, BMI: body mass index, CRP: c- reactive protein, TNF-α: tumour necrosis factor α, IL-6: interleukin-6, IL-1β: interleukin 1 beta, TAC: total antioxidant capacity, MDA: Malondialdehyde, SOD: superoxide dismutase, NAFLD: Non-alcoholic fatty liver disease.

[1] Refers to the mean (95% CI).

[2] Inconsistency, percentage of variation across studies due to heterogeneity.

[3] Obtained from the Q-test.

[4] Obtained from the fixed-effects model.

3.9. Effect of curcumin/turmeric supplementation on malondialdehyde (MDA)

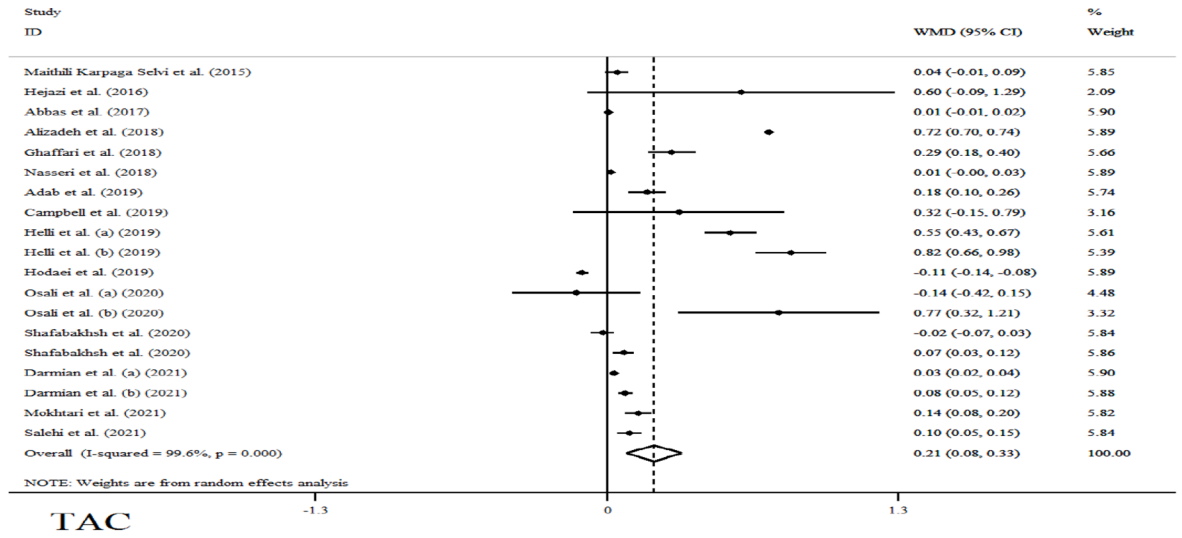
21 arms of trial were included to assess the impact of supplementation with curcumin/turmeric on MDA. We observed that curcumin/turmeric supplementation significantly reduced MDA (WMD = -0.33 μmol /l; 95 % CI: −0.53, −0.12, P = 0.001). Likewise, we found significant between-study heterogeneity (I^2 = 99.6 %, P < 0.001) (Fig. 3). Subgroup analysis showed that curcumin/turmeric supplementation could decrease MDA for all subgroups, except for patients who suffered from non-alcoholic fatty liver disease and hemodialysis (Table 3).

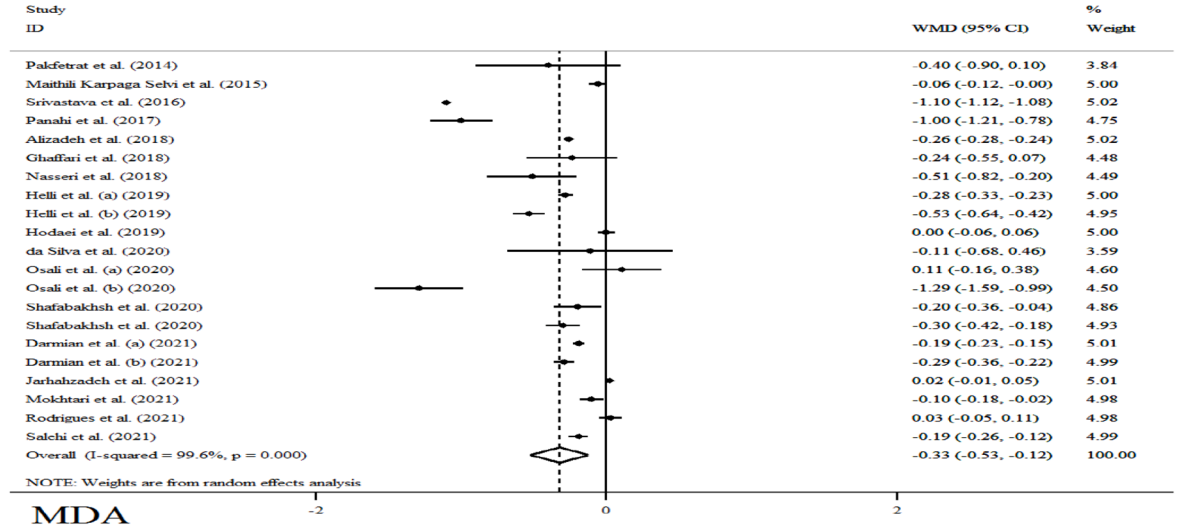
3.10. Effect of curcumin/turmeric supplementation on superoxide dismutase (SOD)

The pooled effect of 8 arms of trials revealed that curcumin/turmeric supplementation could significantly reduce SOD activity (WMD = 20.51 u/l; 95 % CI: 7.35, 33.67, P = 0.002), with significant between-study heterogeneity (I^2 = 95.4 %, P < 0.001) (Fig. 3). Subgroup analysis showed that the results remained significant, except when sample size was<45 (Table 3). Due to insufficient number of studies in each subgroup, we could not perform subgroup analysis based on baseline BMI, health status, supplementation type, or type of country.

3.11. Sensitivity analysis

To find each study's impact on the overall effect size, studies was omitted from the analysis one by one. The results indicated that the elimination of none of the studies could alter the pooled effect sizes of the outcomes of interest (CRP (95 % CI: −0.79, −0.37), TNF-α (95 % CI: −4.98, −2.11), IL-6 (95 % CI: −1.81, −0.55), IL-1β (95 % CI: −5.20, 0.34), TAC (95 % CI: 0.05, 0.37), MDA (95 % CI: −0.57, −0.07), and SOD (95 % CI: 1.87, 39.45)).





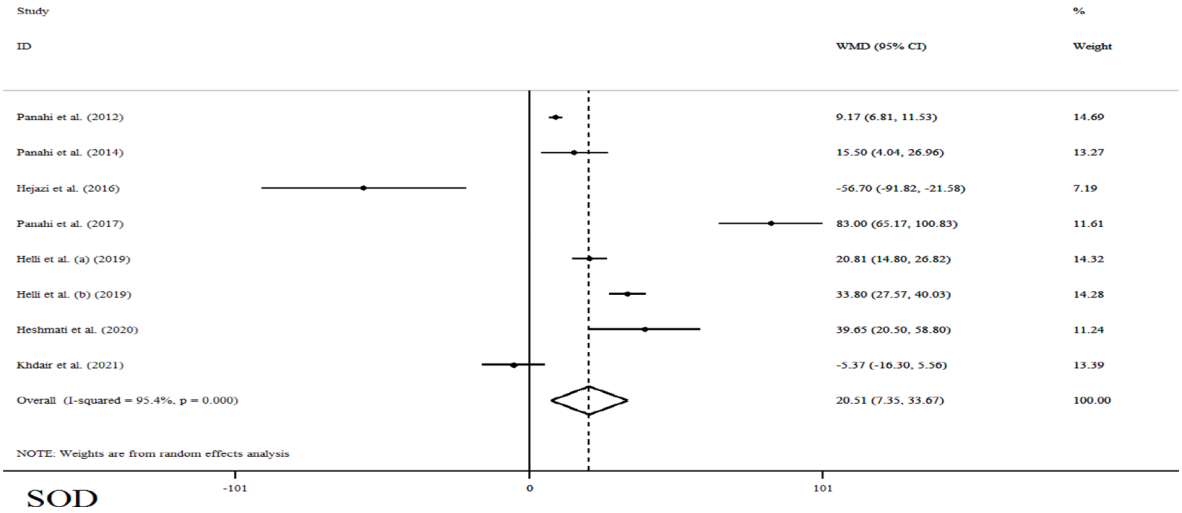


Fig. 3. Forest plots for the effect of curcumin/turmeric supplementation on antioxidant status. Horizontal lines represent 95% CIs. Diamonds represent pooled estimates from random-effects analysis. WMD: weighted mean difference, CI: confidence interval.

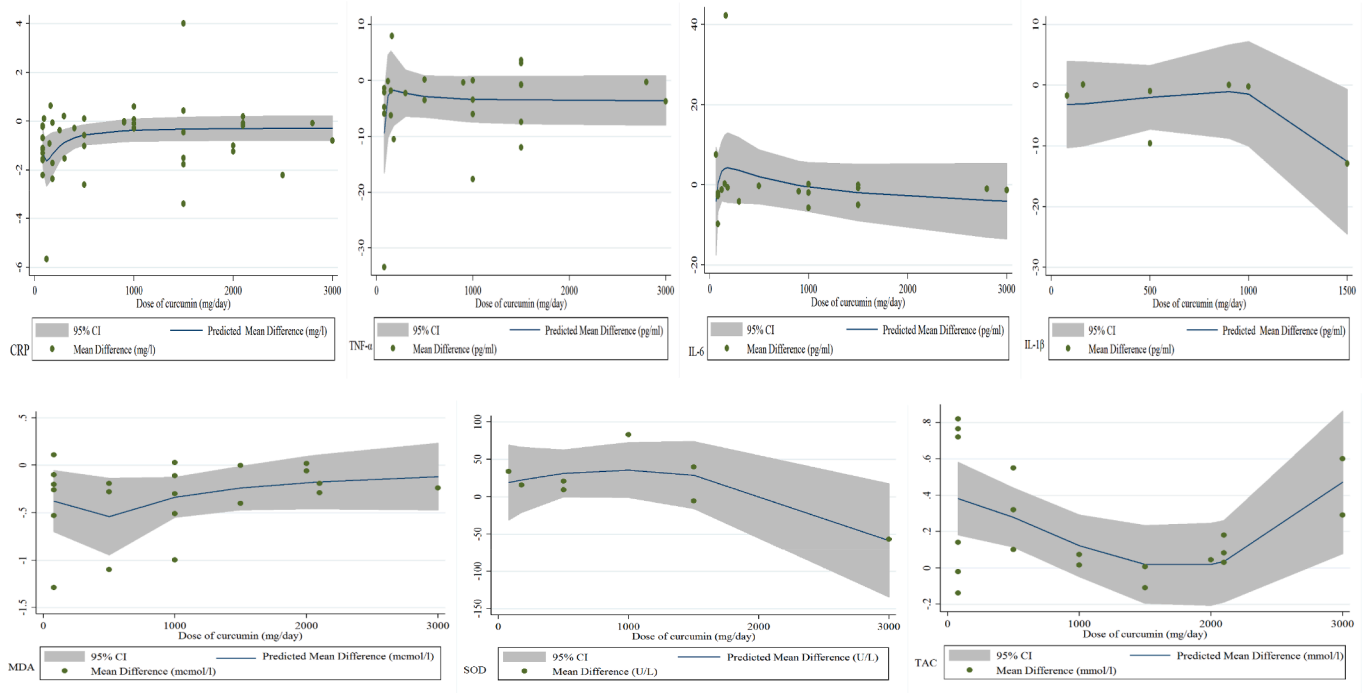


Fig. 4. Dose-response relations between curcumin/turmeric dosage (mg/day) and absolute (unstandardized) mean differences of the outcomes in nonlinear fashion.

3.12. Publication bias and trim and fill analysis

All of the included studies were assessed for publication bias by Egger's weighted regression tests and visual inspection. Based on visual evaluation, the funnel plots indicated moderate asymmetry for all the outcomes (**Supplementary** Fig. 1). However, the results of Egger's test indicated no publication bias for CRP (P = 0.09), TNF-α (P = 0.551), IL-6 (P = 0.474), TAC (P = 0.579), MDA P = 0.417), and SOD (P = 0.389). Even though we observed publication bias with respect to IL-1β (P = 0.038), the trim and fill method showed no change in the overall effect size (WMD: −0.46 pg/ml, 95 % CI: −1.18, 0.27, P = 0.218).

3.13. Non-linear dose-responses effect of duration of intervention and dose of curcumin/turmeric supplement on inflammatory and antioxidants markers

Non-linear dose–response analysis showed that the dosage of supplementation had no association with levels of CRP (P-nonlinearity = 0.089), TNF-α (P-nonlinearity = 0.254), IL-6 (P-nonlinearity = 0.507), IL-1β (P-nonlinearity = 0.185), MDA (P-nonlinearity = 0.365), or SOD activity (P-nonlinearity = 0.097) (Fig. 4). However, we found a significant association between dose of supplementation and TAC (P-nonlinearity = 0.049). Moreover, we found no association between duration of intervention and levels of CRP (P-nonlinearity = 0.549), TNF-α (P-nonlinearity = 0.261), IL-6 (P-nonlinearity = 0.388), IL-1β (P-nonlinearity = 0.422), TAC (P-nonlinearity = 0.691), MDA (P-nonlinearity = 0.115), and SOD activity (P-nonlinearity = 0.826) (**Supplementary** Fig. 2).

3.14. Grading of evidence

The quality of evidence of the outcomes of interest was assessed using the GRADE framework. The results showed that the quality of evidence regarding all of the outcomes of interest should be considered as low, except IL-1β to which a very-low quality was assigned (**Supplementary** Table 1).

4. Discussion

In this systematic review and *meta*-analysis of the literature, we observed that collectively curcumin supplementation positively impacts markers of systematic inflammation and oxidative stress, such as CRP, TNF-α, IL-6, TAC, MDA, and SOD. However, we found that curcumin could not significantly improve IL-1β levels, neither in crude nor in subgroup analyses. Moreover, non-linear dose–response analyses were conducted to reveal possible effects of dosage and/or duration of the intervention on the parameters of interest. We observed that except for TAC which showed marginal significant association with the dosage of the intervention, neither dosage nor duration of the intervention exerted no impacts on inflammatory/oxidative status of the patients.

Among inflammatory markers, CRP is the most common with both clinical and research implications. CRP is an acute inflammatory protein that quickly and abundantly responds to inflammation and/or infection in the body [152]. A recent systematic review and *meta*-analysis has shown that curcumin supplementation significantly decreases CRP and high-sensitivity CRP (hs-CRP). Some mechanisms have been postulated to describe the CRP-lowering effect of curcumin. It has been suggested that curcumin supplementation suppresses the nuclear factor-kappa B (NF-κB) pathway [153], which in turn might have the downstream effect of suppressing the expression of IL-6, and finally CRP [154].

We also found a significant impact of curcumin/turmeric supplementation on TNF-α levels. Likewise, a systematic review and *meta*-analysis of the eight studies revealed that curcumin significantly reduces TNF-α; they also could not find any impact of dose and duration on TNF-α levels [155]. Similarly, it is believed that curcumin exerts its anti-inflammatory effects through inactivation of several kinases (such as AKT, phosphoinositide-3 kinase (PI3K), and IκB kinase (IKK)) which will consequently suppress the production of NF-κB [156]. In fact, curcumin has been shown to exert such potent TNF-α-reducing effect that makes it as an alternate medication in the treatment of Crohn's disease (CD), along with an impact on reducing the risk of possible colorectal malignancies associated with CD [157].

The effect of turmeric/curcumin on other direct pro-inflammatory markers, such as IL-6 and IL-1β have been previously speculated

[158]. A systematic review and *meta*-analysis has shown that curcumin supplementation reduces IL-6 levels by as much as 0.6 pg/mL, making its effectiveness comparable to solid medications, such as aspirin, metformin, and statins [159]. It seems that an identical pathway mediates its IL-6 and IL-1β-reducing impacts; i.e. inhibition of several inflammatory cascades, including NF-κB, toll-like receptor-4 (TLR4), and mitogen-activated protein kinases (MAPKs) [160]. However, we were not able to show any impact of curcumin on IL-1β levels; this observation was echoed in a study by White et al [161]. They investigated the effect of turmeric / curcumin of factors of inflammation. Arguably, they did not find any significant impact of such intervention on none of the direct pro-inflammatory markers; including IL-6, IL-1β, CRP, and TNF-α. Nonetheless, the objective of their study was to examine the claimed healing effects of curcumin on inflammatory markers only in diseases in which inflammation is believed to be the main contributor of their pathophysiology, such as rheumatic disorders, metabolic syndrome (MetS), and CVDs. Therefore, the exclusion of healthy subjects may justify the dissonance between their findings and ours. Nonetheless, their results agree with ours with respect to IL-1β which warrants further research to clarify the existence or lack of such an effect. It is worthy of note that we also found that the quality of evidence with respect to IL-1β is very low, highlighting the need of higher-quality interventions specifically for this outcome.

In the present study, we also examined the possible impact of turmeric/curcumin on indices/measurements of overall antioxidant capacity of body, including TAC, MDA, and SOD levels. In an experimental study, Al-Rubaei et al [162] showed that curcumin supplementation could hamper the oxidative damage artificially induced by H2O2 in rats. Likewise, Ranjbar et al [163] conducted an experimental model in which oxidative stress was induced in rats using aluminum phosphide. They reported that nano-curcumin significantly improved TAC, total thiol groups (TTG), and SOD activity. In a systematic review and *meta*-analysis of four studies, Jakubczyk et al [164] reported that curcumin supplementation could improve TAC of patients, and not the MDA levels. However, our results might be assumed as a more accurate picture, due to much larger population included in the present study. The antioxidant impact of curcumin has been mainly attributed to the β-diketone group in its structure through which it functions by scavenging superoxide radicals, hydrogen peroxide, and nitric oxide radicals [165]. Previous studies have also indicated the impact of curcumin on improved activity of SOD, as well as glutathione peroxidase (GPx) and catalase (CAT) [166]. We were also able to find a dose–response relationship between increased dosages of administered curcumin and TAC which boosts the existing evidence with regard to its potential role in oxidative balance of the body.

To the best of our knowledge, this systematic review and *meta*-analysis is the first to comprehensively sum up the existing literature with respect to the impact turmeric/curcumin supplementation on both anti-inflammatory and anti-oxidant status of participants with different health status. Sixty-six studies were included in the present study, making the findings more generalizable compared to the previous studies in the field. We also verified the quality of evidence via grading the evidence analyses. Moreover, to determine the impact of dosage and duration of intervention on the variables of interest, we conducted non-linear dose–response analyses. However, as a common restriction in such studies, we observed significant heterogeneity among studies with respect to most of the outcomes; to detect the sources of these heterogeneities, various subgroup analyses were carried out. Also, we assessed the quality of evidence with respect to the outcomes of interest to be low and very low. This latter observation signifies the necessity to conduct further higher quality trials.

5. Conclusion

In this systematic review and *meta*-analysis, we summed up the existing literature regarding the impact of turmeric/curcumin supplementation on inflammatory and oxidative status. Overall, it could be assumed that turmeric/curcumin improves indices/measurements of inflammation and oxidative stress in individuals with various health status.

Declaration of Competing Interest

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

Data availability

Data will be made available on request.

Acknowledgements

Not applicable.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cyto.2023.156144.

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