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The effects of curcumin supplementation on liver function, metabolic profile and body composition in patients with non-alcoholic fatty liver disease: A systematic review and meta-analysis of randomized controlled trials

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ABSTRACT

Background: Non-alcoholic fatty liver disease (NAFLD) is the most common liver disease worldwide. Curcumin is the anti-inflammatory, antioxidant, anti-diabetic and also anti-hyperlipidemia agent and uses as herbal medicine for treating liver diseases.

Objective: The present systematic review and meta-analysis was conducted to investigate the effects of curcumin supplementation on metabolic markers and anthropometric parameters in patients with (NAFLD).

Methods: PubMed, Embase, Scopus, Web of Science and Cochrane Library were systematically searched to identify relevant randomized controlled trials (RCTs) investigating the effects of curcumin supplementation on the arms of this study in patients with NAFLD up to September 2019. Mean difference (MD) was pooled using a random effects model. Potential publication bias was assessed using Egger's weighted regression tests.

Results: After excluding irrelevant records, 9 RCTs included in this meta-analysis. Pooled results of included studies indicated a significant reduction in alanine transaminase (ALT), aspartate transaminase (AST), serum total cholesterol (TC), low density lipoprotein (LDL), fasting blood sugar (FBS), HOMA-IR, serum insulin and waist circumference (WC), but not in serum triglyceride (TG), high density lipoprotein (HDL), HbA1c, body weight and body mass index (BMI) following curcumin supplementation. Additionally, age- and baseline TC-based subgroup analysis indicated a significant reduction in TG and also duration- and dosage-based showed a significant change in BMI.

Conclusion: The current study revealed that curcumin supplementation has favorable effect on metabolic markers and anthropometric parameters in patients with NAFLD.

1. Introduction

Non-alcoholic-fatty liver disease (NAFLD) is the most common liver disease and the second cause of liver transplantation all over the world [1] and has increases mortality in Americans for decades. [2] The prevalence of NAFLD in developed and developing countries is 25–30 % and 6–35 % [3] Also, its prevalence is 30 % in Western [4] and 20–30 % in Eastern counties. [5] Obesity, type 2 diabetes mellitus and hyperlipidemia are the main clinical risk factors for NAFLD. [6] However, we have not found any safe and effective drugs for NAFLD improvement until now. [1] Nowadays, 65 % of Americans use herbal medicines for NAFLD because of having lower side effect and toxicities than chemical drugs. [5,7]

Curcumin is the principal active component of the spice turmeric [8] and because of its anti-inflammatory, antioxidant, anti-diabetic and

Abbreviations: NAFLD, non-alcoholic fatty liver disease; ALT, alanine transaminase; AST, aspartate transaminase; FBS, fasting blood sugar; BMI, body mass index; HDL, high density lipoprotein; LDL, low density lipoprotein; TG, triglyceride; TC, total cholesterol; MD, mean difference; SD, standard deviation; CI, confidence interval

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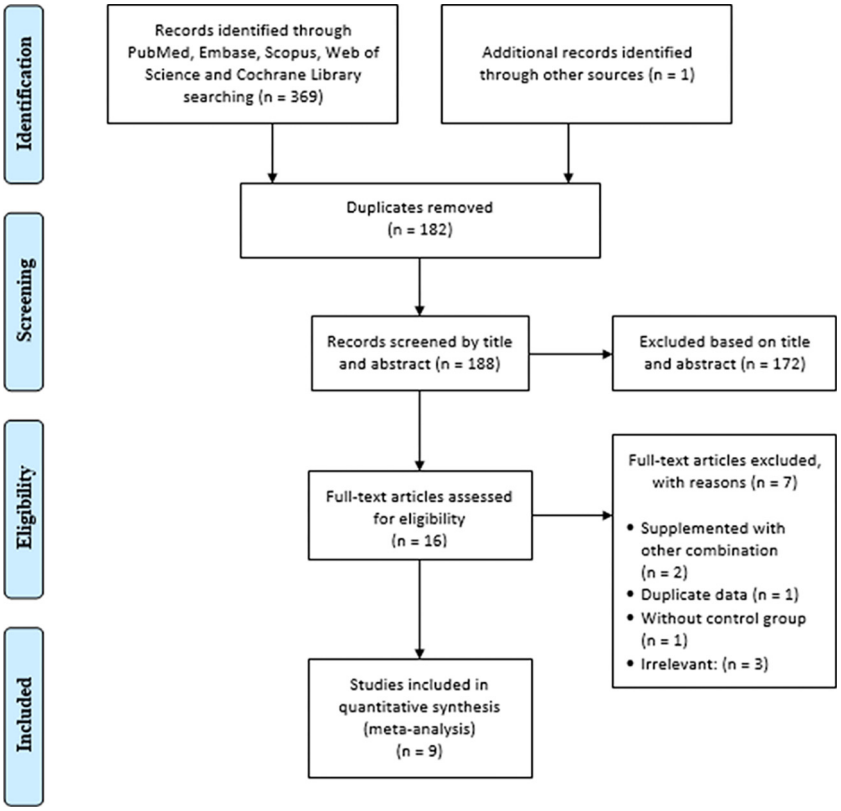

Fig. 1. Flow diagram of data selection process.

also anti-hyperlipidemia traits [8,9] uses as herbal medicine for treating jaundice, liver and biliary diseases. [10] It is discovered for the first time as an anti-bacterial compound at 1949 [11] and Asian use it as medical purposes [12,13] because of its effectiveness and safety. [14] Curcumin improves NAFLD through some mechanisms, first of all, it removes fat from liver and decreases synthesis of triglyceride (TG) [15] by inhibiting HMG-COA reductase, [8] and the second reason is that it decreases the absorption of cholesterol from intestine [15] and also increases the activation of cholesterol-7alpha-hydroxilase, thereby improves lipid profiles like: Low Density Lipoprotein (LDL) and decreases the risk of cardiovascular diseases. [7]

Some studies suggested the positive effect of curcumin supplementation on liver enzymes, lipid profiles, glycemic indices or anthropometric parameters,[16–22] but some others had no significant effects.[19,23–27] Given the inconsistent findings about the effect of curcumin supplementation on metabolic parameters, this study was conducted to collate and evaluate the overall effects of curcumin supplementation on liver enzymes, blood lipid profiles, glycemic indices and anthropometric parameters in patients with NAFLD.

2. Methods

The present meta-analysis is based on the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA).[28]

2.1. Search strategy and data sources

A systematic literature search was conducted using PubMed, Embase, Scopus, Web of Science and Cochrane Library to find relevant RCTs that investigated the effects of curcumin supplementation on NAFLD patients up to 1 September 2019 using following keywords without any restrictions: ["NAFLD" OR "Fatty liver" OR "nonalcoholic fatty liver" OR "non-alcoholic fatty liver"] AND ["Curcumin*" OR "Curcuminoid*" OR "Curcuma*"] AND ["Clinical trial" OR "Clinical" OR "Random*" OR "Blind" OR "Placebo" OR "Trial" OR "Intervention" OR "Supplement*"]. EndNote X9 was used to simplify the process of records assessment. Additional search was performed in Google Scholar and reference lists of relevant articles.

2.2. Inclusion and exclusion criteria

Studies were included if they fulfilled the following criteria: (1) being randomized controlled trial (RCT), (2) evaluating the effects of curcumin on at least one of the following outcomes: liver enzymes (ALT and/or AST), blood lipid profiles (TG and/or TC and/or HDL and/or LDL), glycemic indices (FBS and/or HOMA-IR and/or serum insulin and/or HbA1c) and anthropometric parameters (WC and/or body weight and/or BMI) in subjects with diagnosed NAFLD, (3) English language.

We defined the followings as exclusion criteria: (1) combination of curcumin with any other medication; (2) studies without control group (3) studies which investigated the effects of turmeric. Also, Articles without sufficient data like reviews, book chapters, conference abstracts, editorials, and letters were excluded.

2.3. Data extraction

Two reviewers (MJ and RJ) independently assessed the titles and abstracts of the included studies, and the following information were extracted using a predesigned data collection form: last name of the first author, publication year, country, study design, type of supplement and control process, participants' characteristics, sample size of both intervention and control groups, mean ± standard deviation (SD) of participants' age, intervention duration, dosage and quality of study.

2.4. Quality assessment

The quality of the papers was determined by Jadad scale [29] that

Table 1
Characteristics of included RCTs.

First author (year)	Country	Study design	Type of supplement / Control	Population	Sample size (%male) (Intervention/Control)	Age, mean (SD) (Intervention/Control)	Duration	Dosage (mg/day)	Jadad score
Panahi (2016)	Iran	Randomized, parallel	Capsule / Placebo	NAFLD	44 (55.5) /43 (62.8)	44.98 (12.59) / 47.21 (10.29)	2 months	333.3	2
Rahmani (2016)	Iran	Randomized, parallel	Capsule / Placebo	NAFLD	40 (47.5) /40 (47.5)	46.37 (11.57) / 48.95 (9.78)	2 months	70	4
Panahi (2017)	Iran	Randomized, parallel	Capsule /Placebo	NAFLD	44 (55.5) /43 (62.8)	44.98 (12.59) / 47.21 (10.29)	2 months	333.3	3
Saadati (2018)	Iran	Randomized, parallel	Capsule /Placebo	NAFLD	25 (44) /21 (57.1)	46.64 (11.7) / 45.33 (11.47)	3 months	1500	4
Chashmniam (2019)	Iran	Randomized, parallel	Capsule /Placebo	NAFLD	25 (52) /20 (70)	46.56 (2.25) / 37.75 (3.22)	2 months	50	5
Jazayeri-Tehrani (2019)	Iran	Randomized, parallel	Capsule /Placebo	NAFLD	42 (54.8) /42 (54.8)	41.8 (5.6) / 42.5 (6.2)	3 months	80	5
Mirhafez (2019)	Iran	Randomized, parallel	Capsule /Placebo	NAFLD	32 (48.6) /29 (51.4)	44.8 (11.14) / 40.7 (11.83)	2 months	50	5
Saadati 1 (2019)	Iran	Randomized, parallel	Capsule /Placebo	NAFLD	27 (48.1) /23 (51.9)	46.19 (11.5) / 45.13 (10.9)	3 months	1425	5
Saadati 2 (2019)	Iran	Randomized, parallel	Capsule /Placebo	NAFLD	25 (48.1) /23 (51.9)	46.19 (11.5) / 45.13 (10.9)	3 months	1425	5

assess the quality of RCTs in 5 points based on randomization (2 points), blinding (2 points), and dropouts description (1 point). Studies with score 3–5 were considered as high-quality studies, and < 3 ones were regarded as low quality.

2.5. Statistical analysis

Stata version 13 (Stata Corp LP) was used to analyze data. Fixed- and random-effect models were used to calculate pooled mean difference (MD) and 95 % confidence interval (CI). I^2 (> 50 %) and *P*-value (< 0.05) were used to identify the source of heterogeneity among the included studies. In addition, random effect meta-regressions were conducted to determine the effects of potential moderators like curcumin dosage and duration of supplementation on calculated net changes. To assess the impact of each study on the overall effect, sensitivity analysis was performed. Potential publication bias was checked using Egger's regression test. Subgroup analysis was performed based on the mean age of subjects (≥ 45 years and < 45 years), intervention duration (2 and 3 months), dosage of pure curcumin (≥ 500 mg/day and < 500 mg/day), baseline TC (≥ 200 mg/dl and < 200 mg/dl) and baseline FBS (≥ 100 mg/dl and < 100 mg/dl) to detect the potential source of heterogeneity between trials. A *P*-value < 0.05 was considered as statistically significant.

3. Results

3.1. Study selection and data extraction

The flow chart of data selection is presented in Fig. 1. At first, 369 relevant records were identified through a systematic search in electronic databases (PubMed, Embase, Scopus, Web of Science and Cochrane Library) and one paper was added by hand searching. After duplicates omitting, 188 references were retrieved for title and abstract screening. Then, 172 records of them that did not meet inclusion criteria were excluded. At the next step, 16 full-text articles were assessed for eligibility. After full-text evaluation, 7 articles were removed and finally, 9 full-text articles that met the inclusion criteria were included to the present meta-analysis.[1,16,20–22,30–33]

3.2. Study characteristics

Characteristics of 9 RCTs that were included in this study are shown in Table 1. These included trials were published between 2016 [16,30] and 2019.[1,20,21,32,33] All studies had a parallel design and conducted in Iran. Subjects with NAFLD were the target population of all included trials. The range of sample size was between 25–44 and 20–43 in intervention group and control group, respectively. Mean range of age was between 41.8–46.64 years and 37.75–48.95 years in intervention and control groups, respectively. All trials, were conducted among both men and women. The intervention periods of the trial ranged from 2 months [1,16,20,22,30] to 3 months.[21,31–33] Minimum and maximum dosage of pure curcumin that supplemented in included RCTs were 50 mg/day [1,20] and 1500 mg/day.[31] Five of studies had point 5 [1,20,21,32,33] in quality, 2 had point 4,[30,31] one had point 3 [22] and one other had point 2.[16]

3.3. Meta-analysis

3.3.1. Effect of curcumin supplementation on liver enzymes

A forest plot of 7 datasets indicated a significant reduction in ALT (MD: -0.458, 95 % CI: [-0.914, -0.002], $P = 0.049$) and AST (MD: -0.784, 95 % CI: [-1.501, -0.068], $P = 0.032$) (Fig. 2) after curcumin supplementation compared to the placebo with a maximum heterogeneity (ALT: I^2: 82.3 %, $P < 0.0001$ and AST: I^2: 92.2 %, $P < 0.0001$). Potential sources of heterogeneity were evaluated by subgroup analysis; heterogeneity disappeared in baseline TC (< 200 mg/dl) and baseline FBS (≥ 100 mg/dl) for both ALT and AST (Table 2). There was no

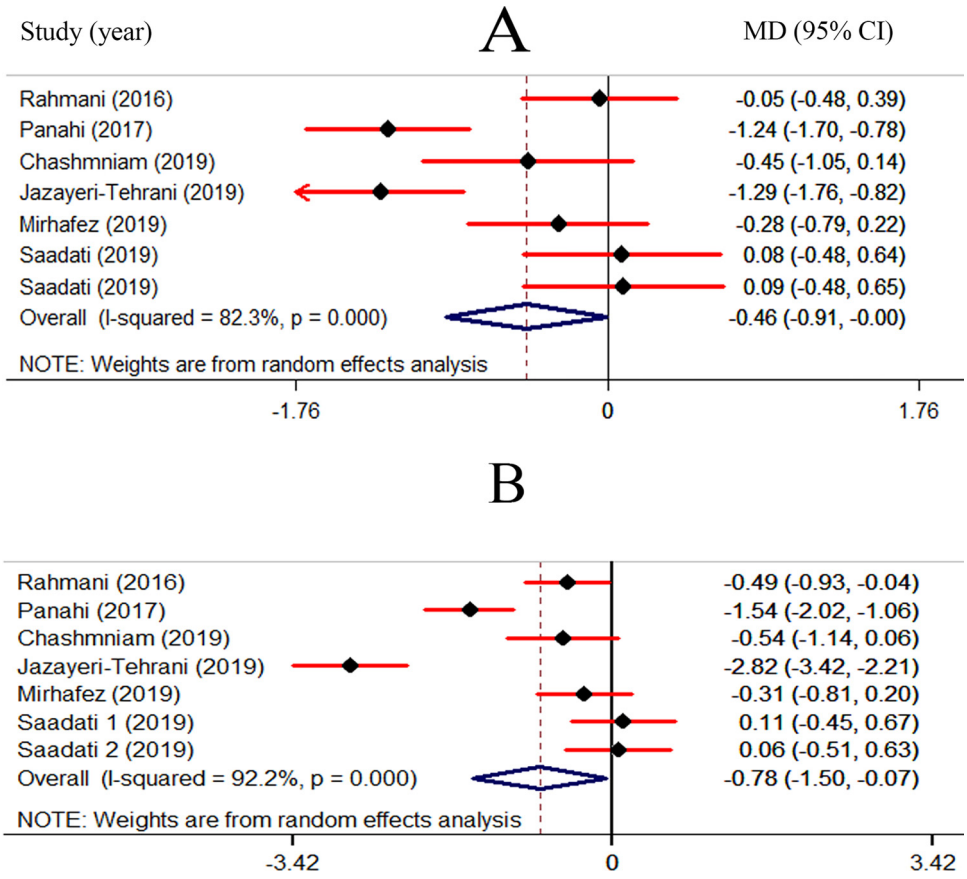

Fig. 2. Effect of curcumin supplementation on ALT (A) and AST (B).

significant publication bias in this meta-analysis (ALT: $P = 0.367$, AST: $P = 0.729$). The sensitivity analysis showed that overall pooled effect affected by none of the studies.

3.3.2. *Effect of curcumin supplementation on blood lipid profiles*

As displayed in Fig. 3A, pooling 6 effect sizes did not reduce serum TG levels significantly following curcumin supplementation (MD: -0.608, 95 % CI: [-1.253, 0.038], $P = 0.065$). A significant heterogeneity was observed among the included studies (I^2: 89.7 %, $P < 0.0001$). Subgroup analysis revealed no change in significance of heterogeneity. No publication bias was found ($P = 0.741$). In subgroup analysis that shown in Table 2, TG reduced significantly in subjects with equal or more than 45 years old (3 studies, 95 % CI: [-1.217, -0.085], $P = 0.024$) and also in patients with less than 200 mg/dl serum TC at baseline (3 studies, 95 % CI: [-1.217, -0.085], $P = 0.024$).

As exhibited in Fig. 3B, this meta-analysis reported a significant reduction in serum TC in the curcumin group compared to the placebo group (MD: -0.645, 95 % CI: [-1.047, -0.243], $P = 0.002$). High amount of heterogeneity was found among studies (I^2: 74.1 %, $P = 0.002$). Evidence of publication bias was not identified ($P = 0.469$). When subgroup analysis was performed, heterogeneity was decreased in duration-(3 months) and baseline TC-based (≥ 200 mg/dl) subgroup analysis. Findings from the sensitivity analysis revealed that the exclusion of any single study from the analysis did not alter the overall effect.

Pooled estimate of 6 trials (Fig. 3) manifested that curcumin supplementation in subjects with NAFLD was effective in diminishing LDL concentration (MD: -1.028, 95 % CI: [-1.942, -0.113], $P = 0.028$) but not in increasing HDL serum levels (MD: 0.880, 95 % CI: [-0.285, 2.044], $P = 0.139$). High heterogeneity was observed in both HDL (I^2: 96.4 %, $P < 0.0001$) and LDL level (I^2: 94.2 %, $P < 0.0001$). When subgroup analysis was performed for HDL, heterogeneity disappeared only in age (≥ 45 years), duration (2 months) and baseline TC (< 200 mg/dl). No publication bias was found in LDL analysis ($P = 0.623$). Based on Table 2, HDL did not significantly reduce in none of the subgroup analysis following the intervention. Sensitivity analysis showed that no particular study prominently affected the overall effects.

3.3.3. *Effect of curcumin supplementation on glycemic indices*

As illustrated in Fig. 4A, this meta-analysis on 210 subjects in intervention group and 197 subjects in control group showed a significant change in FBS following curcumin supplementation in the overall effect (MD: -0.221, 95 % CI: [-0.417, -0.025], $P = 0.027$). The evidence of high heterogeneity was not found among studies (I^2: 0.0 %, $P = 0.313$). No publication bias was found ($P = 0.781$). Based on the sensitivity analysis, no impact of each study on this result was found.

This meta-analysis (Fig. 4B, C) showed that curcumin significantly decreased HOMA-IR compared to placebo (MD: -0.365, 95 % CI: [-0.696, -0.034], $P = 0.031$) with a significant heterogeneity (I^2: 98.7 %, $P < 0.0001$) and also serum insulin (MD: -0.487, 95 % CI: [-0.814, -0.160], $P = 0.003$) with high heterogeneity among studies (I^2: 98.6 %, $P < 0.0001$). No significant publication bias was observed in HOMA-IR ($P = 0.234$) and serum insulin analysis ($P = 0.121$). Sensitivity analysis has revealed that a significant change of HOMA-IR is affected by Jazayeri-Tehrani et al. [21] study and after exclusion of this study the pooled effect size of association between curcumin and HOMA-IR changed to non-significant.

Serum HbA1c (Fig. 4D) did not significantly change following curcumin supplementation compared to placebo (MD: -0.159, 95 % CI: [-0.408, 0.091], $P = 0.213$). A significant heterogeneity was found among studies (I^2: 71.5 %, $P = 0.030$).

Table 2
Subgroup analysis for effectiveness of curcumin supplementation on NAFLD patients.

ALT	Subgroups		No. of effect sizes	95 % CI	*P* value	I^2	*P* value for heterogeneity
	Age	≥ 45 years	4	−0.950, 0.370	0.389	85.6 %	< 0.0001
		< 45 years	3	−1.331, -0.037	0.038	78.4 %	0.010
	Duration	3 months	3	−1.327, 0.559	0.425	89.5 %	< 0.0001
		2 months	4	−1.057, 0.045	0.072	79.8 %	0.002
	Dosage	≥ 500 mg/day	2	−0.314, 0.480	0.682	0.0 %	0.983
		< 500 mg/day	5	−1.190, -0.139	0.013	82.7 %	< 0.0001
	Baseline TC	≥ 200 mg/dl	3	−1.331, -0.037	0.038	78.4 %	< 0.0001
		< 200 mg/dl	2	−342, 0.346	0.990	0.0 %	0.731
	Baseline FBS	≥ 100 mg/dl	3	−0.508, 0.071	0.139	0.0 %	0.537
		< 100 mg/dl	2	−1.949, 0.725	0.370	92.6 %	< 0.0001
AST	Age	≥ 45 years	4	−1.226, 0.278	0.216	88.6 %	< 0.0001
		< 45 years	3	−2.748, 0.318	0.120	95.4 %	< 0.0001
	Duration	3 months	3	−2.724, 0.966	0.350	96.7 %	< 0.0001
		2 months	4	−1.288, -0.157	0.012	80.2 %	< 0.0001
	Dosage	≥ 500 mg/day	2	−0.312, 0.482	0.674	0.0 %	0.902
		< 500 mg/day	5	−1.982, -0.276	0.009	92.6 %	< 0.0001
	Baseline TC	≥ 200 mg/dl	3	−2.748, 0.318	0.120	95.4 %	< 0.0001
		< 200 mg/dl	2	−0.795, 0.369	0.474	64.8 %	0.101
	Baseline FBS	≥ 100 mg/dl	3	−0.730, -0.147	0.003	0.0 %	0.814
		< 100 mg/dl	2	−4.219, 1.517	0.356	97.9 %	< 0.0001
TG	Age	≥ 45 years	3	−1.217, -0.085	0.024	75.6 %	0.017
		< 45 years	3	−1.954, 0.831	0.430	95.0 %	< 0.0001
	Duration	3 months	2	−2.656, 0.158	0.082	92.5 %	< 0.0001
		2 months	4	−0.915, 0.320	0.345	84.1 %	< 0.0001
	Dosage	≥ 500 mg/day	1	−1.093, 0.039	0.068	–	–
		< 500 mg/day	5	−1.396, 0.151	0.115	91.7 %	< 0.0001
	Baseline TC	≥ 200 mg/dl	3	−1.954, 0.831	0.430	95.0 %	< 0.0001
		< 200 mg/dl	3	−1.217, -0.085	0.024	75.6 %	0.017
TC	Age	≥ 45 years	3	−1.540, -0.276	0.005	79.4 %	0.008
		< 45 years	3	−0.763, -0.037	0.031	35.0 %	0.215
	Duration	3 months	2	−0.889, -0.197	0.002	0.0 %	0.332
		2 months	4	−1.311, -0.099	0.023	82.7 %	0.001
	Dosage	≥ 500 mg/day	1	−0.885, 0.235	0.255	–	–
		< 500 mg/day	5	−1.161, -0.246	0.003	77.1 %	0.002
	Baseline TC	≥ 200 mg/dl	3	−0.763, -0.037	0.031	35.0 %	0.215
		< 200 mg/dl	3	−1.540, -0.276	0.005	75.6 %	0.008
HDL	Age	≥ 45 years	3	−0.465, 0.069	0.147	0.0	0.838
		< 45 years	3	−0.884, 5.118	0.167	98.3 %	< 0.0001
	Duration	3 months	2	−0.307, 0.169	0.372	99.2 %	< 0.0001
		2 months	4	−3.604, 9.641	0.572	0.0 %	0.573
	Dosage	≥ 500 mg/day	1	−0.905, 0.216	0.229	–	–
		< 500 mg/day	5	−0.258, 2.548	0.110	97.1 %	< 0.0001
	Baseline TC	≥ 200 mg/dl	3	−0.884, 5.118	0.167	98.3 %	< 0.0001
		< 200 mg/dl	3	−0.465, 0.069	0.147	0.0 %	0.838
LDL	Age	≥ 45 years	3	−2.029, 0.204	0.109	93.1 %	< 0.0001
		< 45 years	3	−2.938, 0.637	0.207	96.5 %	< 0.0001
	Duration	3 months	2	−4.550, 1.552	0.335	98.1 %	< 0.0001
		2 months	4	−1.635, 0.027	0.058	90.4 %	< 0.0001
	Dosage	≥ 500 mg/day	1	−0.503, 0.610	0.850	–	–
		< 500 mg/day	5	−2.254, -0.233	0.016	94.45	< 0.0001
	Baseline TC	≥ 200 mg/dl	3	−2.938, 0.637	0.207	96.5 %	< 0.0001
		< 200 mg/dl	3	−2.029, 0.204	0.109	93.1 %	< 0.0001
FBS	Age	≥ 45 years	3	−0.306, 0.227	0.770	0.0 %	0.866
		< 45 years	3	−0.723, -0.145	0.003	0.0 %	0.410
	Duration	3 months	2	−0.733, -0.043	0.027	73.4 %	0.052
		2 months	4	−0.379, 0.097	0.246	0.0 %	0.842
	Dosage	≥ 500 mg/day	1	−0.512, 0.600	0.877	–	–
		< 500 mg/day	5	−0.468, -0.049	0.016	19.0 %	0.294
	Baseline TC	≥ 200 mg/dl	3	−0.723, -0.145	0.003	0.0 %	0.410
		< 200 mg/dl	3	−0.306, 0.227	0.770	0.0 %	0.866
	Baseline FBS	≥ 100 mg/dl	4	−0.379, 0.097	0.246	0.0 %	0.842
		< 100 mg/dl	2	−0.733, -0.025	0.027	73.4 %	0.052
Body weight	Age	≥ 45 years	2	−0.303, 0.389	0.808	60.5 %	0.111
		< 45 years	3	−0.271, 0.170	0.433	0.0 %	0.863
	Duration	3 months	2	−0.295, 0.170	0.793	59.2 %	0.117
		2 months	3	−0.408, 0.169	0.417	0.0 %	0.850
	Dosage	≥ 500 mg/day	1	−0.159, 0.964	0.160	–	–
		< 500 mg/day	5	−0.372, 0.107	0.277	0.0 %	0.509
	Baseline TC	≥ 200 mg/dl	3	−0.399, 0.171	0.433	0.0 %	0.863
		< 200 mg/dl	2	−0.303, 0.389	0.808	60.5 %	0.111

(*continued on next page*)

Table 2 (*continued*)

ALT	Subgroups		No. of effect sizes	95 % CI	*P* value	I^2	*P* value for heterogeneity
BMI	Age	≥ 45 years	4	−0.428, 0.061	0.142	65.5 %	0.034
		< 45 years	3	−0.460, 0.111	0.231	0.0 %	0.831
	Duration	3 months	3	−0.282, 0.006	0.940	16.4 %	0.302
		2 months	4	−0.547, -0.067	0.012	24.6 %	0.264
	Dosage	≥ 500 mg/day	2	−0.202, 0.605	0.327	0.0 %	0.451
		< 500 mg/day	5	−0.492, -0.073	0.008	3.6 %	0.386
	Baseline TC	≥ 200 mg/dl	3	−0.460, 0.111	0.231	47.6 %	0.831
		< 200 mg/dl	2	−0.305, 0.386	0.819	0.0 %	0.167

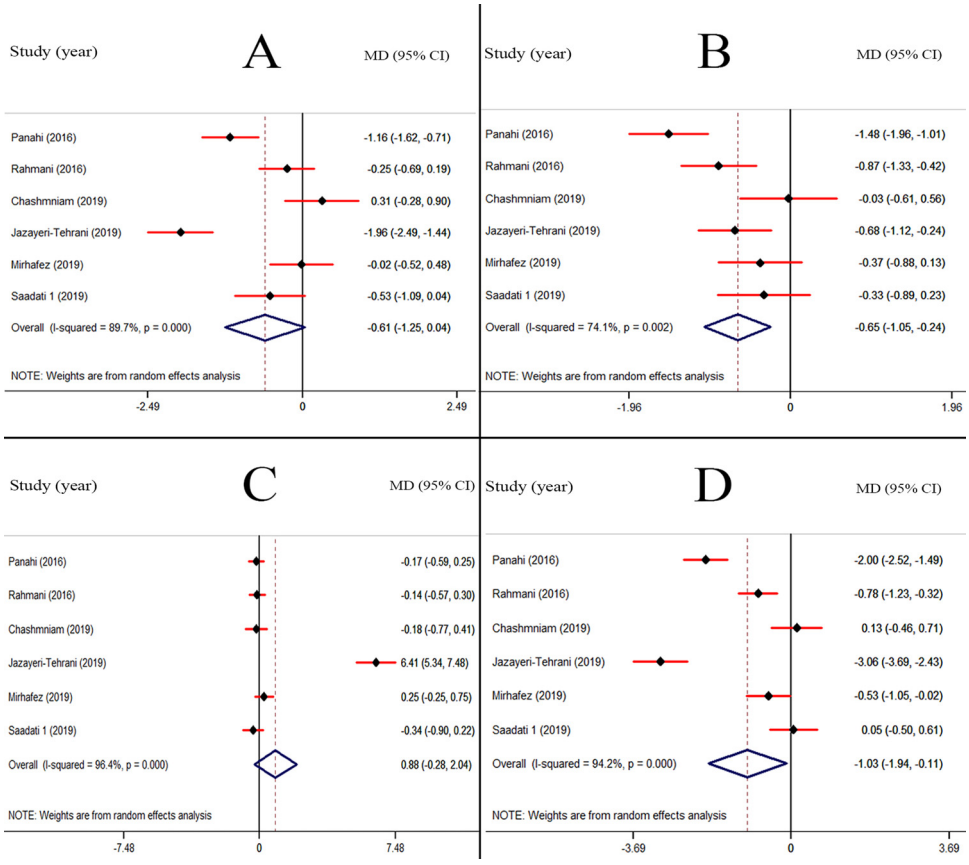

Fig. 3. Effect of curcumin supplementation on TG (A), total serum cholesterol (B), HDL (C) and LDL (D).

3.3.4. Effect of curcumin supplementation on anthropometric parameters

The WC (Fig. 5A) decreased significantly following curcumin intervention (MD: -1.005, 95 % CI: [-1.304, -0.706, $P < 0.0001$). A significant heterogeneity (I^2: 96.1 %, $P < 0.0001$) and no publication bias ($P = 0.503$) were observed. None of the included RCTs effected on the pooled estimate of this meta-analysis.

Pooled estimate of 5 trials (Fig. 5B) reported non-significant effect of curcumin supplementation on the body weight change in comparison with placebo (MD: -0.051, 95 % CI: [-0.271, 0.170, $P = 0.653$), with no heterogeneity (I^2: 0.0 %, $P = 0.509$).

Following curcumin consumption, BMI (Fig. 5C) did not significantly decreased (MD: -0.179, 95 % CI: [-0.365, 0.006, $P = 0.058$). Also, heterogeneity among included studies was not significant (I^2: 33.9 %, $P = 0.169$). However, based on subgroups analysis, BMI decreased significantly in 2 months of study duration and doses less than 500 mg/day of the pure curcumin.

3.4. Meta-regression

The meta-regression analysis was performed to assess whether the changes in outcomes in response to curcumin supplementation might be associated with dosage and duration of intervention. The meta-regression showed that the effect of curcumin on outcomes was independent of dosage and duration of intervention (Table 3).

4. Discussion

Based on our knowledge, no prior meta-analysis has been conducted in this relate. Therefore, in the present study, we systematically reviewed the RCTs that investigated the effects of curcumin supplementation on liver function, metabolic profile and anthropometric factors in patients with NAFLD.

Our findings revealed that consumption of curcumin significantly reduced liver enzymes level. However, subgroup analyses revealed that liver enzymes level were significantly reduced after curcumin supplementation only in specific subgroups.

The accumulating evidence showed the relationship between oxidative stress and lipid peroxidation and the involvement of these in liver injury of experimental animals. Thus, it has attracted much consideration to the beneficial effects of antioxidants.[34]

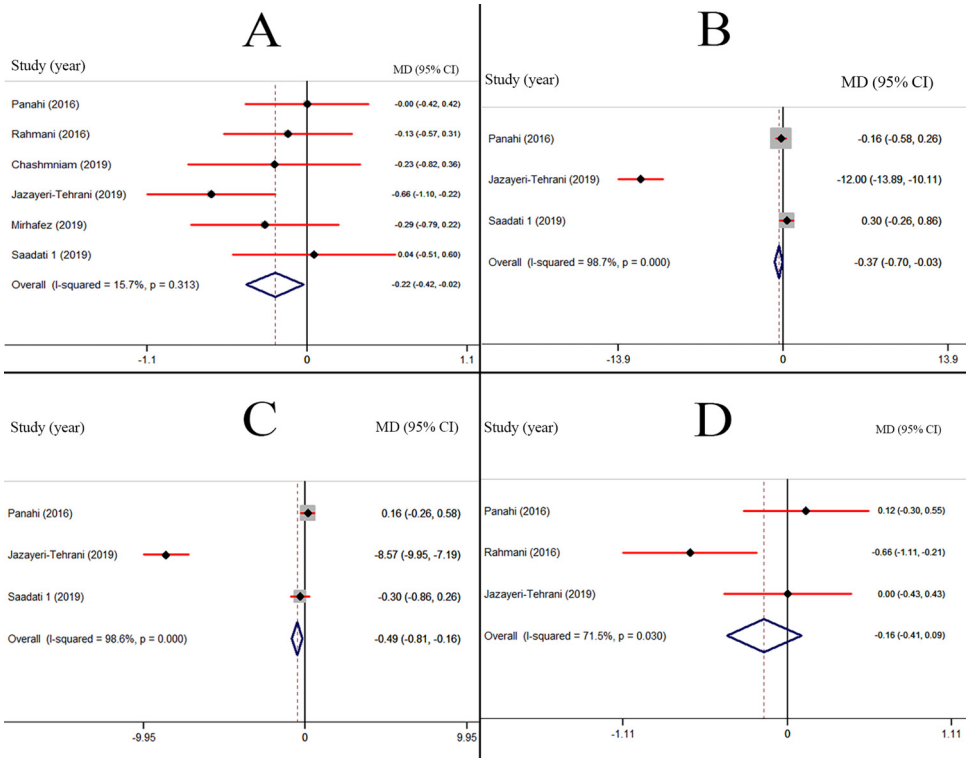

Fig. 4. Effect of curcumin on FBS (A), HOMA-IR (B), serum insulin (C) and serum HbA1c (D).

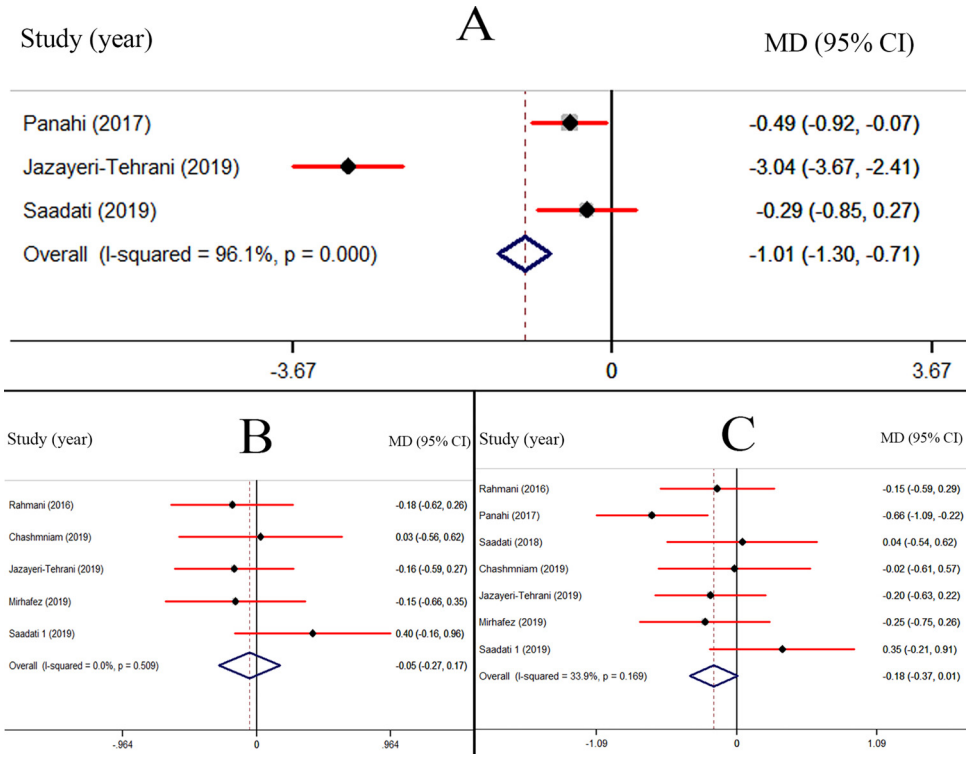

Fig. 5. Effect of curcumin on WC (A), weigh (B) and BMI (C).

Curcumin had anti-oxidant and anti-inflammatory properties through suppressing NF-Kβ and reducing oxidative stress and inflammation.[35] Moreover, it can potentiate the activities of antioxidant enzymes such as superoxide dismutase (SOD) and glutathione peroxidase (GSH) by scavenging free radicals.[36] This result brings to mind the idea that curcumin could be effective in protecting the liver by reducing oxidative stress. This hypothesis has been highlighted by other studies. In a study by Moghaddam et al. showed that the beneficial properties of curcumin were related to its ability to ameliorate the antioxidant defense system and decreased lipid peroxidation levels.[37]

In addition, other results demonstrated that participants who receiving curcumin had a significant reduction in FBS, HOMA-IR and

Table 3
Meta-regression analyses.

Outcomes	Subgroups	Coefficient	*P* value	95 % CI
AST	Duration	0.0405298	0.856	−0.50, 0.58
	Dosage	0.0253139	0.918	−0.57, 0.62
ALT	Duration	0.0188947	0.928	−0.49, 0.53
	Dosage	0.039823	0.870	−0.55, 0.63
TG	Duration	0.0294419	0.905	−0.61, 0.67
	Dosage	0.037958	0.908	−0.82, 0.89
TC	Duration	−0.0066353	0.977	−0.61, 0.59
	Dosage	0.0384972	0.906	−0.81, 0.88
HDL	Duration	0.1009185	0.738	−0.67, 0.88
	Dosage	0.0305479	0.926	−0.82, 0.88
HbA1c	Duration	−0.0034706	0.992	−3.41, 3.41
	Dosage	0.2205063	0.226	−0.32, 0.76
Serum insulin	Duration	0.1297372	0.768	−4.19, 4.45
	Dosage	0.0289827	0.948	−4.43, 4.49
HOMA-IR	Duration	0.1253478	0.780	−4.29, 4.54
	Dosage	0.0351331	0.937	−4.46, 4.53
WC	Duration	0.0838884	0.829	−3.79, 3.96
	Dosage	0.0347745	0.935	−4.25, 4.32

insulin level. It has been shown that curcumin had a role in lowering pro-inflammatory cytokines through regulating key mediators of cellular inflammation such as NF-κB, 5-lipoxygenase (5-LOX) and cyclooxygenase-2 (COX-2).[38] Therefore, curcumin, desirable effect in NAFLD are likely associated with its anti-diabetic properties by the inactivation of NF-κB in adipocytes.[36]

Our findings showed that Curcumin also significantly decreased serum LDL and total cholesterol. Although, serum TG did not significantly decrease in the overall effect, it had reduction following curcumin supplementation. It has been shown that curcumin reduced the NAFLD severity by decreasing the fat content in the liver.[6] There are several mechanisms to explain these results. The lipid lowering property of curcumin is related to interact with the expression of multiple gene such as peroxisome proliferator-activated receptor alpha (PPAR-α), PPAR-γ, cholesteryl ester transfers protein (CETP), and lipoprotein lipase and could thereby decrease plasma triglyceride levels. Curcumin can also inhibit gene expression of LDL receptor by PPAR-γ activation. Additionally, it appears that curcumin affected both synthesis and catabolism of triglyceride-rich lipoproteins along with all pathways of cholesterol metabolism. Therefore, curcumin supplementation had a role in lowering both plasma triglycerides and cholesterol concentrations through mitigating the expressions of lipogenic genes.[39]

Moreover, we did observe the significant reduction in WC with curcumin supplementation, However, we failed to find a significant effect of curcumin supplementation on BMI and body weight in this study. Additionally, a study conducted by Panahi et al. showed that (1000 mg/day) curcumin supplementation for 8 weeks significantly reduced WC in patients with Non-alcoholic fatty liver disease (NAFLD).[40] However, other studies could not show a significant effect of curcumin supplementation on WC.[41–43] The exact mechanism through which curcumin might affect body composition is associated with reducing energy expenditure.[44] Moreover, curcumin beneficial effect on body composition is related to reduces body fat through suppressing angiogenesis in adipose tissue, downregulating pre-adipocyte differentiation, and upregulating adipocyte energy metabolism, apoptosis, increasing monophosphate-activated protein kinase and consequently lipolysis.[45]

In our subgroup analysis, the significant reduction property of curcumin supplementation on liver enzymes, serum total cholesterol, LDL, FBS and BMI was observed only in trials with doses ≤ 500 mg/day. It appears that lower doses are sufficient to affect the status of patients with NAFLD. In addition, meta-regression analysis suggested no influence of supplementation dosage, and study duration on the effects of curcumin supplementation on calculated net changes.

Several limitations of the present meta-analysis should be mentioned while interpreting outcomes. First, the main limitation of the study is that most of the included studies were conducted with unformulated curcumin, which has low bioavailability its owing because of poor absorption, rapid metabolism, and rapid removal from the body. Second, various dosages and sources of curcumin were administered for intervention in the included studies. Third, since most of the included studies did not report information about the severity of NAFLD, subgroup analysis based on severity of NAFLD was not possible. Fourth, all studies which met the inclusion criteria were conducted in IRAN. However, in our systematic search, no restriction was made for publication country. Fifth, most of the included studies had a small number of participants and the number of studies was limited.

5. Conclusion

Our findings show that curcumin supplementation might serve as valuable adjunct therapy for the prevention and treatment of NAFLD. However, more research is needed with larger sample sizes and adequate durations in order to confirm the efficacy of curcumin supplementation on liver function.

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Authorship

MJ contributed in conception and analysis. MJ, ZM, and RJ contributed in search and data extraction. MJ, ZM, MM, and SPM contributed to the drafting of manuscript. MJ, SPM and MHI read and approved the final manuscript.

Declaration of Competing Interest

The authors declare no conflict of interest.

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