Hepatology International (2019) 13:302–313
https://doi.org/10.1007/s12072-018-9910-x

ORIGINAL ARTICLE

The effects of curcumin on the metabolic parameters of non-alcoholic fatty liver disease: a meta-analysis of randomized controlled trials

Zhongcao Wei[1] · Na Liu[1] · Xinxing Tantai[1] · Xin Xing[1] · Cailan Xiao[1] · Lirong Chen[1] · Jinhai Wang[1]

Received: 15 May 2018 / Accepted: 2 November 2018 / Published online: 16 November 2018

Abstract

Aims Evidence indicates that curcumin seems to improve outcomes in non-alcoholic fatty liver disease (NAFLD). A meta-analysis was performed to evaluate the effects of curcumin inNAFLD.

Methods We searched PubMed, EMBASE, and the Cochrane Library from inception through March 2018 to identify randomized controlled trials (RCTs) evaluating the role of curcumin inNAFLD. The mean difference (MD) and 95% confidence interval (CI) were calculated.

Results Four RCTs with a total of 229 NAFLD patients were included. Curcumin was more likely to lower LDL-C, triglycerides, FBS, HOMA-IR, weight and AST levels compared with placebo, and the difference was statistically significant [MD = − 27.02, 95% CI (− 52.30, − 1.74); MD = − 33.20, 95% CI (− 42.30, − 24.09); MD = − 5.63, 95% CI (− 10.36, − 0.90); MD = − 0.53, 95% CI (− 1.00, − 0.05); MD = − 2.27, 95% CI (− 3.11, − 1.44); MD = − 7.43, 95% CI (− 11.31, − 3.54), respectively]. However, the beneficial effect of curcumin did not achieve statistical significance in lowering total cholesterol, HDL-C, HbA1c, ALT or insulin levels [MD = − 30.47,95% CI (− 60.89. − 0.06); MD = − 0.98, 95% CI (− 2.88, 0.92); MD = − 0.41, 95% CI (− 1.41, 0.59); MD = − 6.02, 95% CI (− 15.61, 3.57); MD = − 0.92, 95% CI (− 2.33, 0.49)].

Conclusions Curcumin is effective in lowering LDL-C, triglycerides, FBS, HOMA-IR, weight, and AST levels in NAFLD patients, and it is well tolerated. Further RCTs are required to confirm our findings.

Keywords Curcumin · Non-alcoholic fatty liver disease · Meta-analysis

Abbreviations

NAFLD	Non-alcoholic fatty liver disease
MD	Mean difference
CI	Confidence interval
SDs	Standard deviations
RCTs	Randomized controlled trials
BMI	Body mass index
M	Male
F	Female
WC	Waist circumference
NA	Not available
HbA1c	Hemoglobin A1c
HOMA-IR	Homeostasis model assessment-insulin resistance index
FBS	Fasting blood sugar
LDL-C	Low density lipoprotein cholesterin
HDL-C	High density lipoprotein cholesterol
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
GRADE	Grading of recommendations assessment, development and evaluation

Zhongcao Wei and Xinxing Tantai contributed equally to this work.

✉ Na Liu
liunafmmu@163.com

✉ Jinhai Wang
jinhaiwang@hotmail.com

[1] Department of Gastroenterology, The Second Affiliated Hospital, Xi'an Jiaotong University, No. 157, Xi Wu Road, Xi'an, Shanxi, People's Republic of China

Introduction

Non-alcoholic fatty liver disease (NAFLD) is due to the accumulation of fat in the liver cells [1] and it is associated with diabetes, dyslipidemia, obesity, cardiovascular disease

and metabolic syndrome [2]. NAFLD is the most common chronic liver disease in affluent nations [3]. In Western countries, approximately 30% of adults develop NAFLD and the prevalence is steadily increasing owing to the rising epidemiology of obesity and diabetes [4]. Poor control can result in serious consequences, such as cirrhosis, liver failure, and hepatocellular carcinoma [5, 6].

The first-line therapy for NAFLD is lifestyle intervention which consists of diet, exercise, and weight loss. Of these, overall weight loss is the key [7], but only a few patients are able to reach the threshold required for NAFLD resolution [8]. A prospective study showed that only 10% of patients with NAFLD who committed to lifestyle intervention could reach the goal to induce regression of fibrosis [9, 10]. Health agencies have approved the development of new drugs and treatments for NAFLD, which are urgently needed [8, 11].

Curcumin is a naturally occurring polyphenol that is obtained from turmeric [12]. Previous animal studies have shown that curcumin has antioxidant, anti-inflammatory, antimicrobial and anticarcinogenic effects [13–17]. Several clinical trials have shown that curcumin can affect NAFLD; however, the sample sizes were relatively small and the outcomes were controversial. Various phase 2 trials have shown that curcumin had no side effects even at high doses of 8–12 g/day [18]. However, the precise effects of curcumin supplementation on NAFLD have not been established.

In this study, we systematically reviewed all the published randomized controlled trials on curcumin supplementation and assessed its overall efficacy and safety in patients with NAFLD. To our knowledge, this is the first meta-analysis about the effects of curcumin supplementation on NAFLD.

Methods

Search strategy

We conducted a literature search that assessed the association between curcumin and NAFLD in humans. We searched PubMed, EMBASE, and the Cochrane Library up to March 2018. The search strategy included free-text words and MeSH terms. The following search terms were used: (curcumin OR curcuminoid OR curcuminoids OR Curcuma OR Curcuma OR turmeric) AND (Non-alcoholic Fatty Liver Disease OR Non-alcoholic Fatty Liver Disease OR NAFLD OR Non-alcoholic Fatty Liver Disease OR Non-alcoholic Fatty Liver OR Non-alcoholic Fatty Livers OR Non-alcoholic Steatohepatitis OR Non-alcoholic Steatohepatitides). In addition, we conducted a manual literature search of the reference lists of manuscripts and reviews. The literature search was independently conducted by two systematic reviewers and any disagreement was resolved through discussion with a third reviewer.

Inclusion and exclusion criteria

Inclusion criteria

The included literature met the following criteria:

1. Randomized, placebo-controlled, parallel trial;
2. Patient age $\geq$ 18 years;
3. NAFLD (grades 1–3) was diagnosed according to liver ultrasound.
4. The intervention group received curcumin, and the comparison group received placebo;

Exclusion criteria

1. Pregnancy or breastfeeding.
2. NAFLD secondary to alcohol consumption, smoking, consumption of hypoglycemic, hypolipidemic, or anti-inflammatory medications.
3. NAFLD secondary to any drug known to affect hepatic function,.
4. Presence of hepatitis, coronary, renal, pulmonary, or thyroid diseases.

Data extraction

Two reviewers independently extracted data from the literature in this review, and disagreements were resolved by consensus and discussion with a third reviewer. The extracted data included the following: author, year, geographic location, interventions, dose, duration, inclusion criteria, exclusion criteria, blinding, sample size, gender (M/F), age, weight, body mass index (BMI), waist circumference (WC), diabetes, dyslipidemia, total cholesterol, low density lipoprotein cholesterin (LDL-C), high density lipoprotein cholesterol (HDL-C), triglycerides, fasting blood sugar (FBS), aspartate aminotransferase (AST), alanine aminotransferase (ALT), hemoglobin A1c (HbA1c), insulin, and homeostasis model assessment-insulin resistance index (HOMA-IR).

Quality assessment

The Cochrane Risk Bias Tool was used to evaluate the study quality [19, 20]. The key points of the Cochrane Handbook include the following: selection bias, performance bias, detection bias, attrition bias, reporting bias,

and other biases. The quality assessment was carried out independently by two researchers, and disagreements were resolved through discussion with a third reviewer.

Quality of evidence

To evaluate the quality of evidence, we adopted the Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria [21]. The quality of evidence involves consideration of the following factors: inconsistency of findings, indirectness, imprecision, magnitude of effect, dose–response relationship, publication bias and other biases.

Statistical analyses

Analyses were performed using Review Manager5.3 (Copenhagen, Denmark: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). The mean differences (MDs), standard deviations (SDs), and 95% confidence intervals (CIs) were calculated. In the studies that only provided medians and interquartile ranges, the SDs of the mean differences were calculated using the following formula, which was recommended by Hozo et al. [22]: $SD^2 = (SD_{pretreatment})^2 + (SD_{posttreatment})^2 - (2R \times SD_{pretreatment} \times SD_{posttreatment})$, assuming $R = 0.5$. The heterogeneity analysis was performed using the Cochran Q test (significant when $p < 0.10$) and the I^2 value (significant when $I^2 > 50\%$) [23]. A random effects model was applied to combine the outcome effects of the difference between the experimental group and the control group. Sensitivity analysis was‘ conducted using the 1-study-removed method on all outcomes with ≥ 3 studies to assess the influence of each study on the total effect. Publication bias was achieved by Begg test and Egger test using stata12.0 (Stata Corp., College Station, TX, USA). A p value less than 0.05 was considered to indicate statistical significance.

Results

Literature search

The literature search identified 99 studies, of which 53 studies were from PubMed, 11 were from the Cochrane Library and 35 were from Embase. After excluding 79 repeated titles, 20 titles and abstracts were reviewed, and 14 records were excluded after the titles and abstracts were reviewed. Furthermore, we screened the remaining six studies, and two studies were excluded based on the inclusion criteria. One study with no relevant data [24] and a protocol article [25] were excluded. Thus, a total of four RCTs were included in this meta-analysis (Fig. 1 details the study selection flowchart).

Study characteristics and quality assessment

Study characteristics are listed in Table 1. The included trials were conducted between 2012 and 2017. There were four RCTs [12, 26–28] with a total of 229 NAFLD patients (115 curcumin users and 114 placebo). The number of participants in these four RCTs ranged from 20 to 87. A wide range of curcumin dosing (turmeric powder3000 mg/day, curcumin 500–1000 mg/day) was used in the included trials. Duration of supplementation with curcumin ranged from 8 weeks to 6 months. In all trials, three adverse effects were reported in the curcumin group. All the trials were parallel-group studies and had high quality according to the Cochrane risk bias tool. The quality assessment of the included studies is summarized in Fig. 2.

Meta-analyses

The effect of curcumin on serum lipids

Lowering total cholesterol levels

A total of three RCTs [12, 27, 28] with 187 patients (94 curcumin users and 93 nonusers) reported a change in total cholesterol. Compared with placebo, curcumin is more likely to lower total cholesterol levels than placebo; however, the statistical difference was not critically significant [mean difference = − 30.47, 95% CI (− 60.89, − 0.06), $p = 0.05$], and there was significant heterogeneity between studies ($p < 0.001$, $I^2 = 92\%$) (Fig. 3).

Lowering LDL-C levels

A total of three RCTs [12, 27, 28] reported a change in LDL-C in 187 patients (94 curcumin users and 93 nonusers). The results of the meta-analysis showed that there was a significant effect of the curcumin supplementation on lowering LDL-C levels compared to the placebo [mean difference = − 27.02, 95% CI (− 52.30, − 1.74), $p = 0.04$]. Significant heterogeneity among studies was observed ($p < 0.001$, $I^2 = 91\%$) (Fig. 3).

Lowering HDL-C levels

Two RCTs [12, 27] reported the results of HDL-C levels in 84 curcumin users and 83 nonusers. Compared with placebo, curcumin was more likely to lower HDL-C levels, but the difference was not statistically significant [mean difference = − 0.98, 95% CI (− 2.88, 0.92), $p = 0.31$].

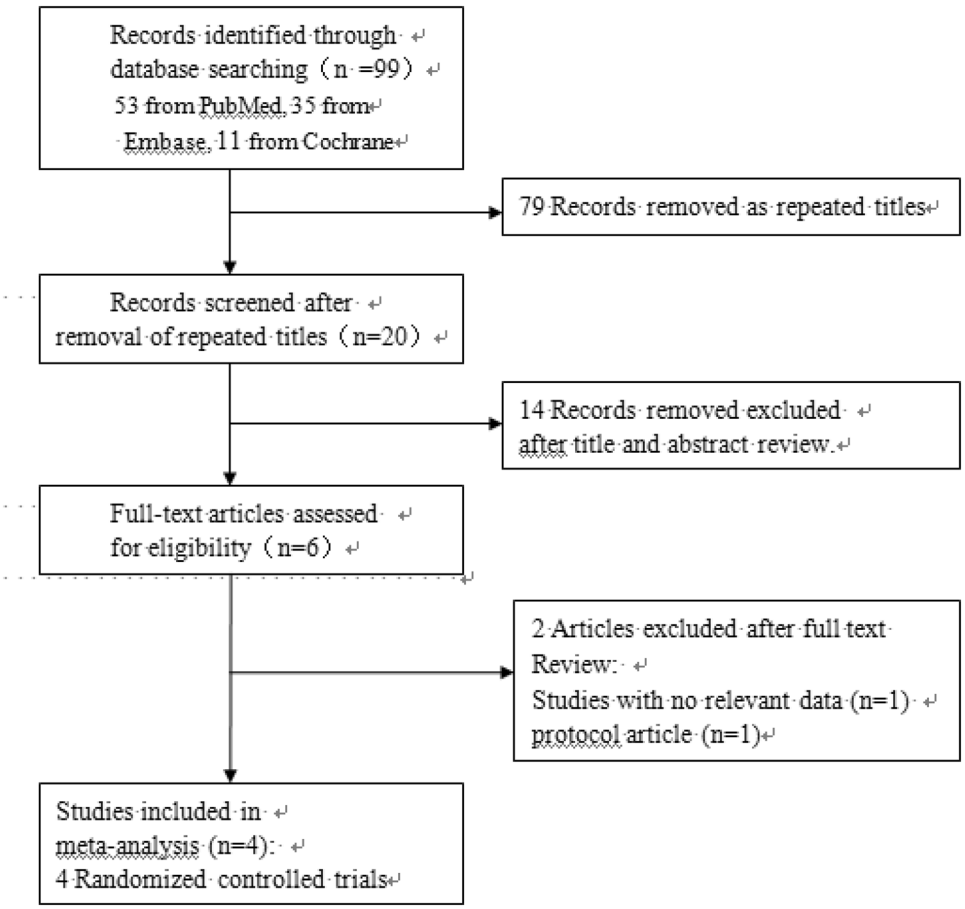

Fig. 1 Study selection flowchart

There was no evidence of heterogeneity between the included studies ($p = 0.75$, $I^2 = 0\%$) (Fig. 3).

Lowering triglyceride levels

A total of three RCTs [12, 27, 28] reported the impact of curcumin on triglycerides. There were 94 curcumin users and 93 nonusers included in the study. Compared with placebo, curcumin was significantly associated with lower triglyceride levels [mean difference = − 33.20, 95% CI (− 42.30, − 24.09), $p < 0.001$]. Heterogeneity was not observed among the studies ($p = 0.41$, $I^2 = 0\%$) (Fig. 3).

Based on the RCTs, there was considerable evidence in the estimates supporting the use of curcumin for lowering triglyceride levels in NAFLD patients. Because of the heterogeneity, there was moderate evidence in the estimates supporting the use of curcumin for lowering total cholesterol and LDL-C levels in NAFLD patients. In addition, there was moderate evidence in the estimates supporting the use of curcumin for not lowering HDL-C levels in NAFLD patients, primarily because of the inconsistency.

The effect of curcumin on glycemic indices

Lowering FBS levels

A total of four RCTs [12, 26–28] evaluated the change in FBS in 115 curcumin users and 114 nonusers. The meta-analysis showed that there was a significant effect of the curcumin supplementation on lowering FBS levels compared to placebo [mean difference = − 5.63, 95% CI (− 10.36, − 0.90), $p = 0.02$]. There was no evidence of heterogeneity between the included studies ($p = 0.43$, $I^2 = 0\%$) (Fig. 4).

Lowering HbA1c levels

Two RCTs [12, 27] reported the results of HbA1c levels in 84 curcumin users and 83 nonusers. Compared with placebo, curcumin was more likely to lower HbA1c levels, but the difference was not statistically significant [mean difference = − 0.41, 95% CI (− 1.41, 0.59), $p = 0.42$]. Significant heterogeneity between the studies was observed ($p = 0.0003$, $I^2 = 92\%$) (Fig. 4).

Table 1 Characteristics of included studies

Study	Ghaffari 2017 [25]		Rahmani 2016 [12]		Panahi 2016 [26]		Chirapongsathorn 2012 [27]	
Location	Iran		Iran		Iran		Thailand	
Design	RCT		RCT		RCT		RCT	
Interventions	Turmeric powder	Placebo	Curcumin	Placebo	Curcumin	Placebo	Curcumin	Placebo
Dosage	3000 mg/day	3000 mg/day	500 mg/day	500 mg/day	1000 mg/day	1000 mgday	NA	NA
Duration	12 weeks	12 weeks	8 weeks	8 weeks	8 weeks	8 weeks	6 month	6 month
Sample size (*n*)	21	21	40	40	44	43	10	10
Gender (M/F)	11/10	8/13	19/21	19/21	24/20	27/16	7/3	4/6
Age (year)	42.09 ± 7.23	40.38 ± 9.26	46.37 ± 11.57	48.95 ± 9.78	44.98 ± 12.59	47.21 ± 10.29	52.7 ± 7.57	56.67 ± 14.62
Weight (kg)	85.26 ± 16.47	87.40 ± 15.08	81.14 ± 12.13	80.20 ± 13.82	NA	NA	NA	NA
BMI (kg/m2)	31.81 ± 4.58	32.92 ± 4.81	30.84 ± 4.45	31.35 ± 5.67	28.97 ± 3.42	29.07 ± 3.48	29.71 ± 4.14	28.92 ± 3.25
WC (cm)	NA	NA	NA	NA	97.07 ± 11.04	101.90 ± 11.43	97.9 ± 9.15	95.89 ± 9.17
Diabetes (%)	NA	NA	NA	NA	25	23	40	30
Dyslipidemia (%)	NA	NA	NA	NA	48	67	50	30
Total cholesterol (mg/dL)	NA	NA	198.59 ± 41.76	187.78 ± 32.95	199.57 ± 40.80	184.06 ± 46.85	NA	NA
LDL-C (mg/dL)	NA	NA	107.06 ± 31.36	115.57 ± 22.30	130.60 ± 33.45	108.94 ± 46.22	NA	NA
HDL-C (mg/dL)	NA	NA	44.26 ± 11.83	42.62 ± 6.67	46.82 ± 9.84	47.44 ± 10.60	NA	NA
Triglycerides (mg/dL)	NA	NA	199.68 ± 91.46	160.20 ± 61.94	151.41 ± 75.61	150.07 ± 68.46	NA	NA
AST (mg/dL)	24.00 ± 11.59	24.33 ± 13.69	28.88 ± 10.60	32.05 ± 17.64	NA	NA	56.5 ± 24.03	40.22 ± 14.05
ALT (mg/dL)	21.00 (15.50, 34.00)	23.00 (15.00, 31.50)	39.07 ± 19.79	30.35 ± 13.97	NA	NA	77.6 ± 28.39	54.44 ± 17.56
HbA1c (%)	NA	NA	6.31 ± 1.62	7.37 ± 1.33	6.17 ± 1.37	6.06 ± 1.03	NA	NA
Adverse events (*n*)	No	No	3	No	No	No	NA	NA

Values are expressed as the mean ± SD or medians (25th percentile 75th percentile)

M male, *F* female, *WC* waist circumference, *NA* not available

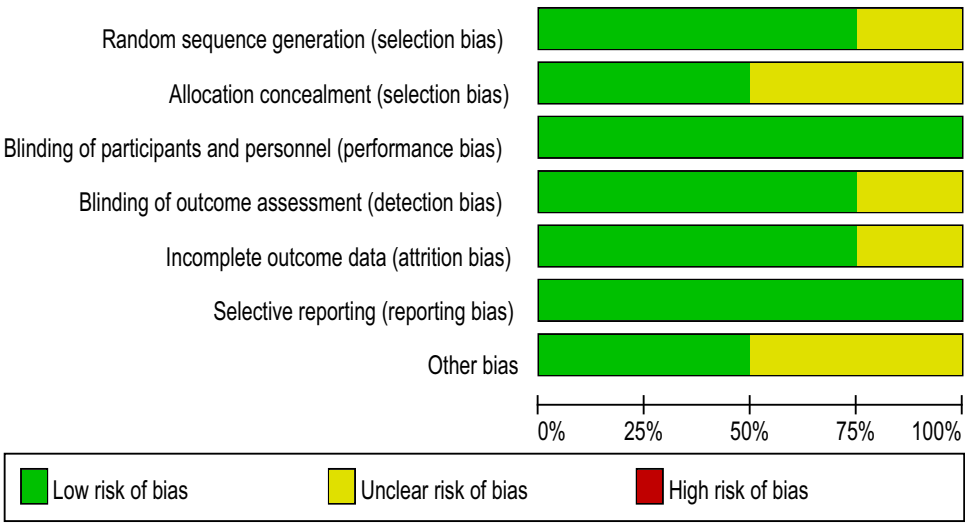

Fig. 2 Quality assessment of included studies

Lowering insulin levels

Two RCTs [26, 27] evaluated the change in insulin in 65 curcumin users and 64 nonusers. Compared with placebo, curcumin was more likely to lower insulin levels, but the difference was not statistically significant [mean difference = − 0.92, 95% CI (− 2.33, 0.49), $p = 0.20$]. The heterogeneity test showed that there was low heterogeneity between the studies ($p = 0.24$, $I^2 = 28\%$) (Fig. 4).

Lowering HOMA-IR levels

Two RCTs [26, 27] reported the results of HOMA-IR levels in two groups consisting of 65 curcumin users and 64 nonusers. Compared with placebo, curcumin significantly decreased HOMA-IR levels [mean difference = − 0.53, 95% CI (− 1.00, − 0.05), $p = 0.03$]. Heterogeneity between the studies was not observed ($p = 0.37$, $I^2 = 0\%$) (Fig. 4).

The data were derived from high-quality RCTs with no inconsistencies, which qualify as high-quality evidence regarding the effect of curcumin in lowering FBS, insulin, and HOMA-IR levels. Because of the heterogeneity, this constitutes moderate-quality evidence to support the association between curcumin use and HbA1c levels in NAFLD patients.

The effect of curcumin on transaminase

Lowering ALT levels

Two RCTs [12, 28] evaluated the change in ALT levels in 50 curcumin users and 50 nonusers. Compared with placebo, curcumin was more likely to lower ALT levels, but the difference was not statistically significant[mean difference = − 6.02, 95% CI (− 15.61, 3.57), $p = 0.22$]. Heterogeneity was not observed between the studies ($p = 0.44$, $I^2 = 0\%$) (Fig. 5).

Lowering AST levels

Two RCTs [12, 28] reported the results of AST levels in 50 curcumin users and 50 nonusers. The meta-analysis showed that there was a significant effect of curcumin supplementation on lowering AST levels compared to the placebo [mean difference = − 7.43, 95% CI (− 11.31, − 3.54), $p = 0.0002$]. Heterogeneity was not observed between the studies ($p = 0.64$, $I^2 = 0\%$) (Fig. 5).

Based on the RCTs, there was high evidence in the estimates supporting the use of curcumin for lowering ALT and AST levels in NAFLD patients.

The effect of curcumin on weight

Two RCTs [12, 28] evaluated the impact of curcumin on weight in 50 curcumin users and 50 nonusers. Compared with placebo, curcumin could significantly lower weight [mean difference = − 2.27, 95% CI (− 3.11, − 1.44), $p < 0.0001$]. Heterogeneity was not observed between the studies ($p = 0.62$, $I^2 = 0\%$) (Fig. 6).

The overall confidence in this estimate was high as the data were derived from high-quality RCTs with no inconsistencies.

Adverse events

Three RCTs [12, 26, 27] reported the results of adverse events, of which two RCTs reported no adverse events in the curcumin and placebo groups. One RCT [12] reported three cases of adverse events in the curcumin group (one

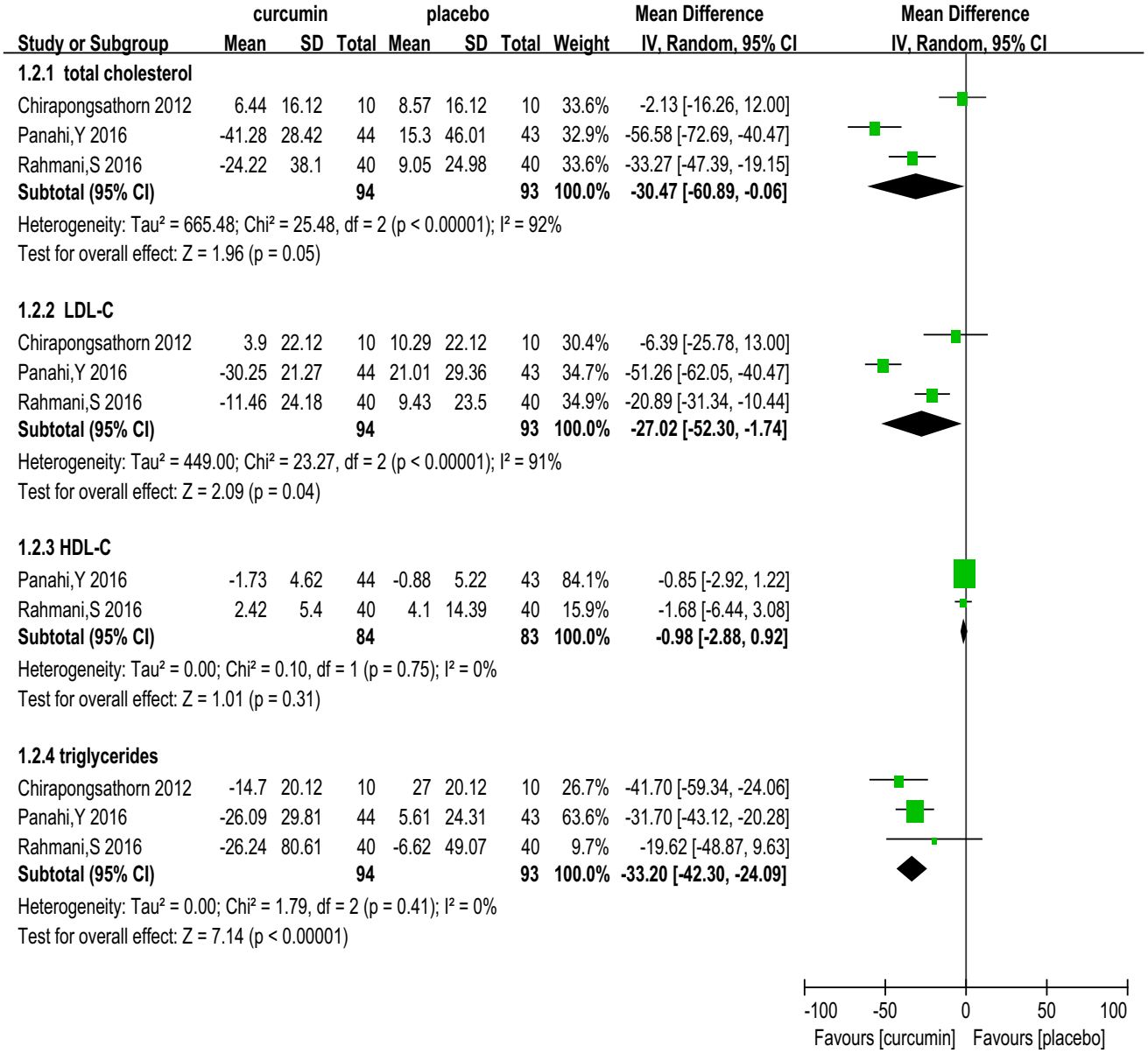

Fig. 3 Meta-analysis of the effect of curcumin supplementation on serum lipids compared with the control group

case of abdominal pain and two cases of combined abdominal pain and nausea).

Sensitivity analysis

By exclusion of each individual study one at a time, we found a significant change in the heterogeneity of lowering LDL-C levels (heterogeneity $p < 0.001$, $I^2 = 91\%$). If Panahi's study was removed, there was a low heterogeneity of lowering LDL-C levels (heterogeneity $p = 0.20$, $I^2 = 40\%$). Sensitivity analysis was performed on other outcomes with three studies and there were no significant changes in the heterogeneity of other outcomes.

Publication bias

Due to the small number of included studies, we took the effect of the curcumin supplementation on lowering FBS levels as an example, and the visual inspection of the funnel plot revealed a roughly symmetrical distribution of included studies (Fig. 7). The Begg test ($p = 0.089$) and Egger test ($p = 0.155$) were not significant for publication bias. However, the reliability was limited by the small number of studies.

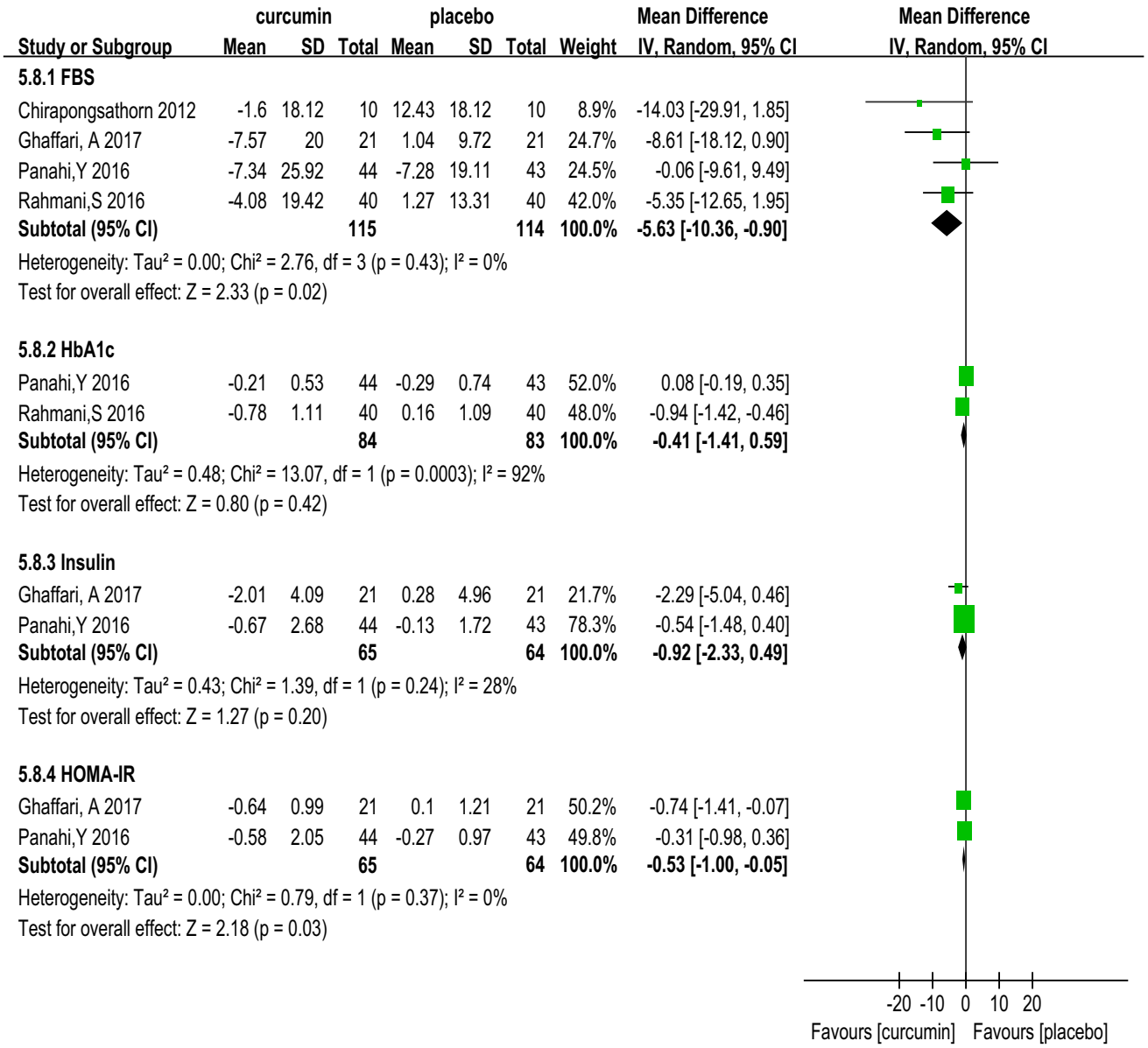

Fig. 4 Meta-analysis of the effect of curcumin supplementation on glycemic indices compared with the control group

Discussion

To our knowledge, this is the first meta-analysis to comprehensively assess the effects of curcumin on NAFLD. In the present meta-analysis, we observed a significantly beneficial effect of curcumin supplementation on reduction in LDL-C, triglycerides, FBS, HOMA-IR, weight, and AST. However, the beneficial effect of curcumin did not achieve statistical significance in total cholesterol, HDL-C, HbA1c, ALT and insulin levels.

NAFLD is the result of hepatic fat accumulation not due to excessive alcohol consumption [29]. NAFLD is always accompanied by metabolic and nonmetabolic changes, such as dyslipidemia, insulin resistance, inflammation and oxidative stress. Therefore, the treatment of NAFLD should be concerned with correcting all of these disorders. Curcumin is the active ingredient of turmeric and is the reason for its unique pharmacological action. Curcumin has been shown to be active against various chronic diseases including diabetes, obesity, cancers, and cardiovascular and pulmonary diseases [30]. Curcumin is a highly potent antimicrobial agent and exhibits effects against different liver diseases such as hepatitis B, hepatitis C, NAFLD, and alcoholic liver disease [31, 32]. Additionally, curcumin has been shown to reduce liver damage in animal models of liver injury [33]. Previous studies have shown that curcumin has antioxidant, anti-inflammatory, antimicrobial and anticarcinogenic effects [13–17], and using curcumin

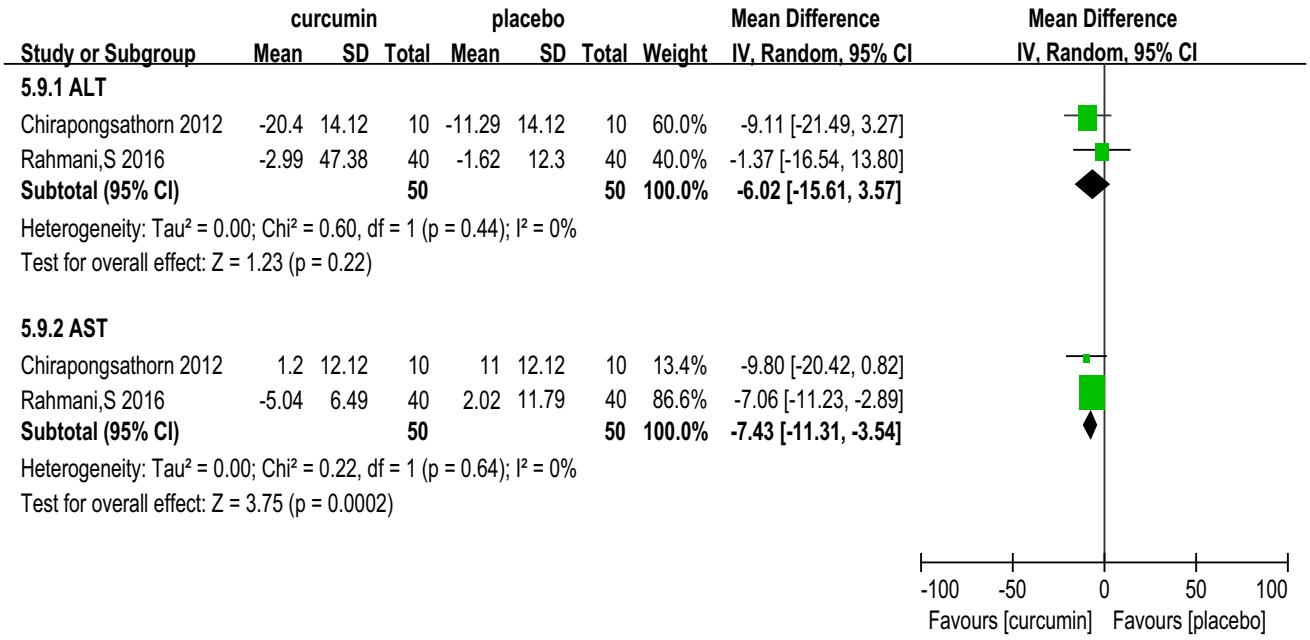

Fig. 5 Meta-analysis of the effect of curcumin supplementation on transaminase levels compared with the control group

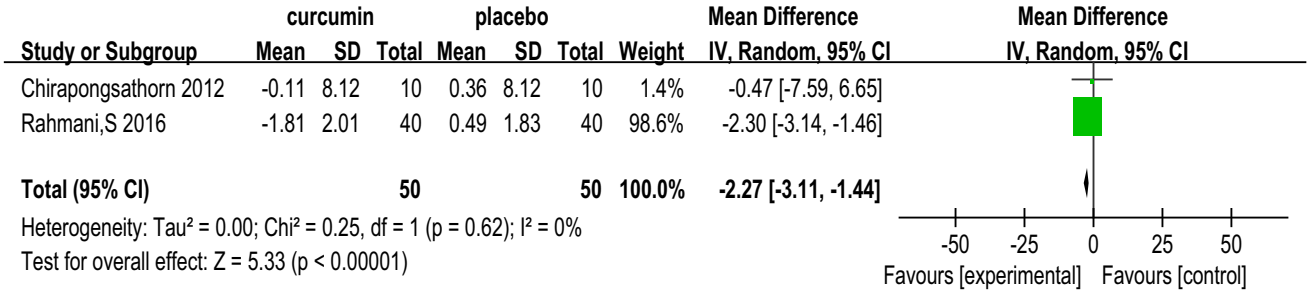

Fig. 6 Meta-analysis of the effect of curcumin supplementation on weight compared with the control group

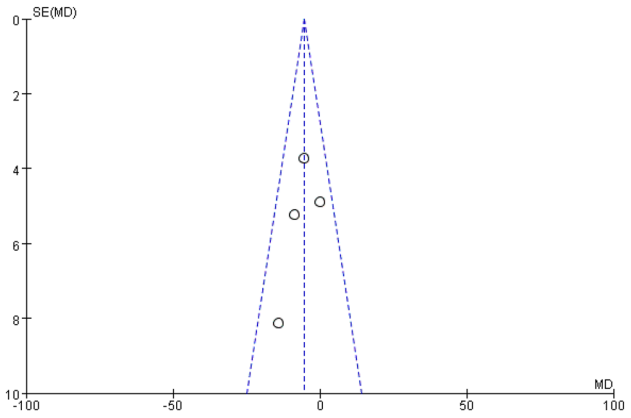

Fig. 7 The funnel plot of the effect of curcumin supplementation on lowering FBS levels

in patients is safe [18]. Through multiple pharmacological mechanisms, curcumin might play an important role in preventing fatty liver disease and its fibrotic evolution. Several meta-analyses have been conducted on the effects of curcumin on metabolic parameters [34–37]. A review presents pathophysiological mechanisms of curcumin supplementation on NAFLD [38]. However, the effect of curcumin on NAFLD is still unknown in clinical studies, which warrants further investigation and consideration.

Numerous studies revealed that curcumin could lower serum lipid levels and prevent hepatic lipid accumulation through a variety of mechanisms. Yiu et al. [39] found that curcumin supplementation significantly decreased plasma total cholesterol levels in hypercholesterolemic rats. Kim et al. [40]. demonstrated that curcumin supplementation significantly decreased TG, TC, and LDL-cholesterol. The possible mechanisms included a curcumin-induced increase in the expression of cholesterol 7α-hydroxylase, hemeoxygenase-1, and low density lipoprotein receptors and a similar decrease in the expression of HMG-CoA reductase [39]. Obesity is an important factor leading to non-alcoholic fatty liver disease and could accelerate the

progression of NAFLD. Many studies have documented improvement in fatty liver following steady weight loss [41]. The results of Agrawal et al. [42] showed that curcumin supplementation could decrease body weight and significantly decreased liver weight. A possible mechanism could be that curcumin decreases the expression of the key transcription factors in adipogenesis and lipogenesis (PPARγ andC/EBPα).

One of the curcumin's most recognized effects is the ability to increase insulin sensitivity. Panzhinskiy et al. [43] found that curcumin restored glucose uptake and reversed insulin resistance and protein kinase B phosphorylation. Consequently, curcumin could improve insulin signaling and glucose intolerance. Curcumin showed liver protection in acute and chronic liver injury [31]. Gu et al. [44] demonstrated that curcumin supplementation decreased the production of ALT, proinflammatory cytokines such as TNF-α and IFN-γ, and CRP, IL-6 levels [45, 46] and, as a result, reduced hepatocyte apoptosis.

Another mechanism that could contribute to the efficacy of curcumin in the treatment of NAFLD is related to gut microbiota composition [47]. It is increasingly recognized that changes of gut microbiota are closely related to the development of NAFLD [48]. The oral bioavailability of curcumin is very low and curcumin reaches the gut almost unaltered [49]. Curcumin supplementation has been shown to improve gut barrier function, which may be related to the effects of curcumin on microbiota; as a result, curcumin could exert potentially beneficial effects on the gut microbiota and finally improve metabolic parameters of NAFLD [50].

This meta-analysis has several limitations. First, similar to other medicines obtained from herbs such as silymarin [51], curcumin is endemic to the Eastern hemisphere; thus, it may not have the same effect on all populations worldwide. Therefore, there may be an intrinsic geographic bias of the human population. Additional studies of curcumin applied to a wider area are needed to confirm our findings. Second, there were few eligible RCTs, and most of them had small number of patients, which might be the reason why some results were not significant. Moreover, several outcomes only included two studies, and the heterogeneity was significant. We performed the sensitivity analysis, but did not find the cause of heterogeneity. This might be related to population characteristics, curcumin dose and duration of supplementation. However, heterogeneity was minimized using a random effects mode of analysis. Furthermore, only one study [12] evaluated the influence of curcumin on severity of hepatic steatosis and found that curcumin could significantly reduce the severity of hepatic steatosis, which might be an important outcome; however, we could not perform further analysis due to the limited number of studies. Finally, studies with dyslipidemia or hyperglycemia were not available for all subjects with NAFLD, which might affect the degree of changes in glycemic indices and serum lipids caused by curcumin.

In conclusion, for non-alcoholic fatty liver disease, curcumin supplementation is likely to lower LDL-C, triglycerides, FBS, HOMA-IR levels, weight and AST levels compared to placebo and is not better than placebo in lowering total cholesterol, HDL-C, HbA1c, ALT and insulin levels. More RCTs with large sample sizes are needed to confirm our findings.

Funding No funding was received.

Compliance with ethical standards

Conflict of interest Zhongcao Wei, Na Liu, Xinxing Tantai, Xin Xing, Cailan Xiao, Lirong Chen, and Jinhai Wang declare that there are no conflicts of interest.

Ethical approval All procedures were in accordance with the ethical standards of the responsible committee on human experimentation and the Helsinki Declaration. There was no interaction with patients directly, as we acquired data from already published articles.

References

1. Akhavan Rezayat A, Dadgar Moghadam M, Ghasemi Nour M, et al. Association between smoking and non-alcoholic fatty liver disease: a systematic review and meta-analysis. SAGE Open Med 2018;6:2050312117745223
2. Angulo P. Treatment of nonalcoholic fatty liver disease. Ann Hepatol 2002;1(1):12–19
3. Wang J, Guo XF, Yu SJ, et al. Adiponectin polymorphisms and non-alcoholic fatty liver disease risk: a meta-analysis. J Gastroenterol Hepatol 2014;29(7):1396–1405
4. Bhala N, Younes R, Bugianesi E. Epidemiology and natural history of patients with NAFLD. Curr Pharm Des 2013;19(29):5169–5176
5. Keating SE, Hackett DA, George J, Johnson NA. Exercise and non-alcoholic fatty liver disease: a systematic review and meta-analysis. J Hepatol 2012;57(1):157–166
6. Ratziu V, Bellentani S, Cortez-Pinto H, Day C, Marchesini G. A position statement on NAFLD/NASH based on the EASL 2009 special conference. J Hepatol 2010;53(2):372–384
7. Chalasani N, Younossi Z. The diagnosis and management of nonalcoholic fatty liver disease: practice guidance from the American Association for the Study of Liver Diseases. Hepatology 2018;67(1):328–357
8. Lassailly G, Caiazzo R, Pattou F, Mathurin P. Perspectives on treatment for nonalcoholic steatohepatitis. Gastroenterology 2016;150(8):1835–1848
9. Vilar-Gomez E, Martinez-Perez Y, Calzadilla-Bertot L, et al. Weight loss through lifestyle modification significantly reduces features of nonalcoholic steatohepatitis. Gastroenterology 2015;149(2):367–378 **(quiz e314-365)**
10. Wadden TA, Volger S, Sarwer DB, et al. A two-year randomized trial of obesity treatment in primary care practice. N Engl J Med 2011;365(21):1969–1979

11. Suzuki A, Diehl AM. Nonalcoholic steatohepatitis. Annu Rev Med 2017;68:85–98
12. Rahmani S, Asgary S, Askari G, et al. Treatment of non-alcoholic fatty liver disease with curcumin: a randomized placebo-controlled trial. Phytother Res PTR 2016;30(9):1540–1548
13. Ganjali S, Sahebkar A. Investigation of the effects of curcumin on serum cytokines in obese individuals: a randomized controlled trial. Sci World J 2014;2014:898361
14. Panahi Y, Sahebkar A, Parvin S, Saadat A. A randomized controlled trial on the anti-inflammatory effects of curcumin in patients with chronic sulphur mustard-induced cutaneous complications. Ann Clin Biochem 2012;49(Pt 6):580–588
15. Kanai M, Imaizumi A, Otsuka Y, et al. Dose-escalation and pharmacokinetic study of nanoparticle curcumin, a potential anticancer agent with improved bioavailability, in healthy human volunteers. Cancer Chemother Pharmacol 2012;69(1):65–70
16. Shehzad A, Ha T, Subhan F, Lee YS. New mechanisms and the anti-inflammatory role of curcumin in obesity and obesity-related metabolic diseases. Eur J Nutr 2011;50(3):151–161
17. Um MY, Hwang KH, Ahn J, Ha TY. Curcumin attenuates diet-induced hepatic steatosis by activating AMP-activated protein kinase. Basic Clin Pharmacol Toxicol 2013;113(3):152–157
18. Balachandran K, Stebbing J. Turmeric: a spice for life? Lancet Oncol 2016;17(12):1639
19. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 1996;17(1):1–12
20. Higgins JPT, Green S (eds). Cochrane handbook for systematic reviews of interventions version 5.1.0. The Cochrane Collaboration 2011. http://handbook.cochrane.org
21. Guyatt G, Oxman AD, Sultan S, et al. GRADE guidelines: 11. Making an overall rating of confidence in effect estimates for a single outcome and for all outcomes. J Clin Epidemiol 2013;66(2):151–157
22. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol 2005;5:13
23. Prakash SR, Verma S, McGowan J, et al. Improving the quality of colonoscopy bowel preparation using an educational video. Can J Gastroenterol J Canadien de gastroenterologie 2013;27(12):696–700
24. Basu P, Shah NJ, Siriki R, et al. Mo1007 curcumin, anti-oxidant, and pioglitazone therapy with inclusion of vitamin E in non alcoholic fatty liver disease-a randomized open label placebo controlled clinical prospective trial (CAPTIVE). Gastroenterology 2013;144(1):S26–S27
25. Jazayeri-Tehrani SA, Rezayat SM, Mansouri S, et al. Efficacy of nanocurcumin supplementation on insulin resistance, lipids, inflammatory factors and nesfatin among obese patients with non-alcoholic fatty liver disease (NAFLD): a trial protocol. Evid Based complement Altern Med eCAM 2017;7(7):e016914
26. Ghaffari A, Rafraf M, Navekar R, et al. Effects of turmeric on homocysteine and fetuin-A in patients with nonalcoholic fatty liver disease: a randomized double-blind placebo-controlled study. Iran Red Crescent Med J 2017;19(4):e43193
27. Panahi Y, Kianpour P, Mohtashami R, Jafari R, Simental-Mendia LE, Sahebkar A. Curcumin lowers serum lipids and uric acid in subjects with nonalcoholic fatty liver disease: a randomized controlled trial. J Cardiovasc Pharmacol 2016;68(3):223–229
28. Chirapongsathorn S. Curcumin trend to improve alanine transaminase (ALT) in non-alcoholic fatty liver disease (NAFLD) with abnormal ALT. Paper presented at: Asian Pacific Digestive Week 2012
29. Day CP, Saksena S. Non-alcoholic steatohepatitis: definitions and pathogenesis. J Gastroenterol Hepatol 2002;17(Suppl 3):S377–S384
30. Kunnumakkara AB, Bordoloi D, Padmavathi G, et al. Curcumin, the golden nutraceutical: multitargeting for multiple chronic diseases. Br J Pharmacol 2017;174(11):1325–1348
31. Rivera-Espinoza Y, Muriel P. Pharmacological actions of curcumin in liver diseases or damage. Liver Int 2009;29(10):1457–1466
32. Nanji AA, Jokelainen K, Tipoe GL, Rahemtulla A, Thomas P, Dannenberg AJ. Curcumin prevents alcohol-induced liver disease in rats by inhibiting the expression of NF-kappa B-dependent genes. Am J Physiol Gastrointest Liver Physiol 2003;284(2):G321–G327
33. Bruck R, Ashkenazi M, Weiss S, et al. Prevention of liver cirrhosis in rats by curcumin. Liver Int 2007;27(3):373–383
34. Simental-Mendia LE, Pirro M. Lipid-modifying activity of curcuminoids: A systematic review and meta-analysis of randomized controlled trials. Crit Rev Food Sci Nutr 2017. https://doi.org/10.1080/10408398.2017.1396201
35. Qin S, Huang L, Gong J, et al. Efficacy and safety of turmeric and curcumin in lowering blood lipid levels in patients with cardiovascular risk factors: a meta-analysis of randomized controlled trials. Nutr J 2017;16(1):68
36. Melo ISV, Santos AFD, Bueno NB. Curcumin or combined curcuminoids are effective in lowering the fasting blood glucose concentrations of individuals with dysglycemia: systematic review and meta-analysis of randomized controlled trials. Pharmacol Res 2018;128:137–144
37. Hariri M, Haghighatdoost F. Effect of curcumin on anthropometric measures: a systematic review on randomized clinical trials. J Am Coll Nutr 2018;37(3):215–222
38. Zabihi NA, Pirro M, Johnston TP, Sahebkar A. Is there a role for curcumin supplementation in the treatment of non-alcoholic fatty liver disease? The data suggest yes. Curr Pharm Des 2017;23(7):969–982
39. Yiu WF, Kwan PL, Wong CY, et al. Attenuation of fatty liver and prevention of hypercholesterolemia by extract of *Curcuma longa* through regulating the expression of CYP7A1, LDL-receptor, HO-1, and HMG-CoA reductase. J Food Sci 2011;76(3):H80–H89
40. Kim M, Kim Y. Hypocholesterolemic effects of curcumin via up-regulation of cholesterol 7a-hydroxylase in rats fed a high fat diet. Nutr Res Pract 2010;4(3):191–195
41. Tendler D, Lin S, Yancy WS Jr, et al. The effect of a low-carbohydrate, ketogenic diet on nonalcoholic fatty liver disease: a pilot study. Dig Dis Sci 2007;52(2):589–593
42. Agrawal R, Mishra B, Tyagi E, Nath C, Shukla R. Effect of curcumin on brain insulin receptors and memory functions in STZ (ICV) induced dementia model of rat. Pharmacol Res 2010;61(3):247–252
43. Panzhinskiy E, Hua Y, Lapchak PA, et al. Novel curcumin derivative CNB-001 mitigates obesity-associated insulin resistance. J Pharmacol Exp Ther 2014;349(2):248–257
44. Gu Q, Guan H, Shi Q, Zhang Y, Yang H. Curcumin attenuated acute propionibacterium acnes-induced liver injury through inhibition of HMGB1 expression in mice. Int Immunopharmacol 2015;24(2):159–165
45. Na LX, Yan BL, Jiang S, Cui HL, Li Y, Sun CH. Curcuminoids target decreasing serum adipocyte-fatty acid binding protein levels in their glucose-lowering effect in patients with type 2 diabetes. Biomed Environ Sci BES 2014;27(11):902–906
46. Panahi Y, Saadat A, Beiraghdar F, Sahebkar A. Adjuvant therapy with bioavailability-boosted curcuminoids suppresses systemic inflammation and improves quality of life in patients with solid tumors: a randomized double-blind placebo-controlled trial. Phytother Res PTR 2014;28(10):1461–1467

47. Ng QX, Soh AYS, Loke W, Venkatanarayanan N, Lim DY, Yeo WS. A meta-analysis of the clinical use of curcumin for irritable bowel syndrome (IBS). J Clin Med 2018;7(10):298
48. Bashiardes S, Shapiro H, Rozin S, Shibolet O, Elinav E. Non-alcoholic fatty liver and the gut microbiota. Mol Metab 2016;5(9):782–794
49. Sharma RA, McLelland HR, Hill KA, et al. Pharmacodynamic and pharmacokinetic study of oral curcuma extract in patients with colorectal cancer. Clin Cancer Res 2001;7(7):1894–1900
50. Feng W, Wang H, Zhang P, et al. Modulation of gut microbiota contributes to curcumin-mediated attenuation of hepatic steatosis in rats. Biochim Biophys Acta 2017;1861(7):1801–1812
51. Zhong S, Fan Y, Yan Q, et al. The therapeutic effect of silymarin in the treatment of nonalcoholic fatty disease: a meta-analysis (PRISMA) of randomized control trials. Medicine 2017;96(49):e9061