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Title: A Meta-analysis of Cumin (Cuminum cyminim L.) Consumption on Matabolic and Anthropometric Indices in Overweight and Type 2 Diabetics

Article Type: Review Article

Keywords: Cumin; Anthropometrics; Glycaemic Status; Lipid Profile; Type 2 Diabetes; Overweight

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Abstract: Objective: To conduct a systematic review, including meta-analysis, of published RCTs of cumin to determine the effect on anthropometric and metabolic indices in overweight and/or type 2 diabetics, relative to controls.
Methods: Studies were identified by a search of electronic databases before December 2017. Seven RCTs were included, and combined and stratified analyses were used.
Results: Seven trials were identified, and data from 412 subjects were included. Pooled analysis showed improvements in bodyweight, BMI and FBG by -1.74 kg, -0.67 kg/m2 and -17.82 mg/dL respectively. Significant findings were also observed in TG [WMD: -21.23 (95% CI: -37.64 to -4.82; P< 0.001, I^2 = 92%)] and HDL-c [WMD: 4.16 (95%CI: 3.30, 5.01; P< 0.001, I2=82%)] following cumin intake. No changes were found in controls.
Conclusions: Cumin improves anthropometric and metabolic indices in overweight and/or type 2 diabetic subjects. The changes were related to the clinical condition and quality assessment.

COVER LETTER FOR SUBMISSION OF MANUSCRIPT

Subject: **SUBMISSION OF A MANUSCRIPT FOR EVALUATION**

Dear Editor

I am enclosing herewith a manuscript entitled "Effects of Cumin Consumption on Glycaemic Status, Lipid Profile and Anthropometric indices in Overweight and/or Type 2 Diabetic Subjects: A meta-analysis of randomized controlled trials" for publication in "Journal of Functional Foods" for possible evaluation.

With the submission of this manuscript I would like to undertake that the above mentioned manuscript has not been published elsewhere, accepted for publication elsewhere or under editorial review for publication elsewhere; and that my Institute's (Research Center for Biochemistry and Nutrition in Metabolic Diseases, Kashan University of Medical Sciences, Kashan, I.R. Iran) representative is fully aware of this submission.

Submitted manuscript is a (Select one option)

- Review Article

For the Editors, I would like to disclose the following information about the project:

The research project was conducted under the supervision of:

Dr. Sadegh Jafarnejad
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***Highlights**

1- Cumin has beneficial effects on both anthropometric and metabolic indices.

2- The changes are related to the clinical condition and quality assessment.

3- Common factors that are significantly affected in all clinical conditions are FBG and HDL-c.

4- The favorable effects of cumin consumption are mainly by phytoestrogen content and presence of insulin-like growth factors.

A Meta-analysis of Cumin (Cuminum cyminim L.) Consumption on Matabolic and Anthropometric Indices in Overweight and Type 2 Diabetics

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A shortened version of the title: Cumin Supplementation on Anthropometric and Metabolic indicators.

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Abstract

Objective: To conduct a systematic review, including meta-analysis, of published RCTs of cumin to determine the effect on anthropometric and metabolic indices in overweight and/or type 2 diabetics, relative to controls.

Methods: Studies were identified by a search of electronic databases before December 2017. Seven RCTs were included, and combined and stratified analyses were used.

Results: Seven trials were identified, and data from 412 subjects were included. Pooled analysis showed improvements in bodyweight, BMI and FBG by -1.74 kg, -0.67 kg/m^2 and -17.82 mg/dL respectively. Significant findings were also observed in TG [WMD: -21.23 (95% CI: -37.64 to -4.82; P< 0.001, I^2 = 92%)] and HDL-c [WMD: 4.16 (95%CI: 3.30, 5.01; P< 0.001, I^2=82%)] following cumin intake. No changes were found in controls.

Conclusions: Cumin improves anthropometric and metabolic indices in overweight and/or type 2 diabetic subjects. The changes were related to the clinical condition and quality assessment.

Keywords: Cumin, Anthropometrics, Glycaemic Status, Lipid Profile, Type 2 Diabetes, Overweight

Introduction

Overweight and obesity, and their associated comorbidities including type 2 diabetes mellitus (T2DM), cardiovascular disease (CVD) and hypertension, are increasingly prevalent and considered major public health issues globally (Grundy 2004). T2DM is a serious metabolic disorder associated with the accelerated development of end-stage renal disease, diabetic retinopathy and peripheral nerve damage (WHO 2016). Preventative measures include dietary approaches in the control of blood glucose and body weight regulation, and dietary constituents with anti-obesity and anti-diabetic potential may be important in the management of hyperlipidemia and hyperglycemia (Tuomilehto et al. 2001).

Cumin (Cuminum cyminum L.) is a flowering annual herbaceous plant of the Apiaceae family, native to the Mediterranean, India, Egypt and Iran and is widely used for its culinary and medicinal properties (Sowbhagya et al. 2007). The putative health properties of cumin has been ascribed to aldehydes, terpenes, alkaloids, tannins, sterols, dietary fibre and polyphenols (Jalali-Heravi et al. 2007, Thippeswamy and Naidu 2005). The total phenolic content of cumin ranges from 4.1 to 53.6 mg/g dry weight, and over 19 compounds including phenolic acids and flavonoids, have been identified (Rebey et al. 2012). Evidence from experimental and clinical studies indicate some improvements on metabolic indices, with polyphenols exhibiting an inhibitory effect on

pancreatic lipase and cuminaldehyde inhibiting α-glycosidase and aldose reductase indicating their potential antidiabetic properties (Jafari et al. 2017, Keyhan et al. 2016, Zare et al. 2014). However, evidence from RCTs are limited and remain inconclusive. Therefore, the aim of the present study was to conduct a systematic review and meta-analysis to assess the efficacy of cumin supplementation on anthropometric and metabolic indicators in overweight and/or T2DM populations.

Materials and Methods

The present meta-analysis was conducted in accordance with PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analysis) requirements for interventional research(Moher et al. 2009).

Search strategy

Four databases; including Pubmed™, Google Scholar™, Web of Science™, and Scopus™ were used to identify related publications. Published RCTs were searched from inception to November 2017. Reference lists from retrieved studies were also manually searched for additional relevant publications. Three groups of medical subject headings; (MeSH) and non-MeSH keywords were considered for searching the studies: Group 1: “Cumin”, “Cumin oil”, “Cumin supplementation”, “cumin seed”, “Cuminum cyminum”; group 2: “weight”, “bodyweight”, “BMI”, “body mass index” and group 3: "glycemic control” and lipid indices (cholesterol OR ‘‘plasma lipids’’ OR triglycerides OR LDL-c OR

HDL-c OR ‘‘serum lipids’’ OR FBS OR FBG OR ‘’fasting blood glucose’’ OR diabetes OR T2DM).

Studies were included if they followed a RCT study design with cumin or cumin-containing products as the intervention. Those published in English and/or Persian were included, in addition to studies reporting mean changes with their standard deviations of metabolic indices (including glycaemic and lipidemic indicators) and anthropometric parameters (including weight change and BMI), or data for calculating these indicators.

Data extraction

Data were extracted from published studies independently by three reviewers and any disagreements were resolved by consensus among the researchers using the standardised extraction forms to guarantee accuracy and consistency. The following key data were extracted: year of publication, country where the intervention was conducted, sample size of both intervention and control groups, clinical condition of subjects, intervention/placebo details and composition including the dosage of cumin supplementation (gram or mg per day), treatment duration and significant outcomes. In addition, anthropometric measures (BMI and weight change) were reported as kg/m^2 and kg respectively, and serum levels of both glycaemic indices (FBG and HbA1C), and lipid indices (TC, LDL-c, HDL-c and TG) were reported as mg/dL. For papers containing data in mmol/l, a numerical conversion to mg/dL was carried out

based on molecular weight. Serum HbA1c was represented as a percentage value. Corresponding authors of trials with no reported mean and SD values for any outcomes of interest were contacted to request their data. Only the studies providing these data were included in the present meta-analysis.

Quality assessment

The Jadad scale was used to assess the methodological quality of included trials. The score ranges from 0 (very low) to 5 (very high). The Jadad scale assesses the quality of published clinical trials based on three parameters; randomisation, blinding and follow-up. The description of the Jadad scale system is as follows; for randomisation or blinding: 1 point if randomisation/blinding is mentioned, 1 additional point if the method of randomisation/blinding is appropriate and deduction of 1 point if the method of randomisation/blinding is inappropriate; and for follow up: 1 point if the fate of all subjects is known (Jadad et al. 1996).

Statistical analysis

The statistical analyses were performed using Review Manager Software (RevMan 5.3; Cochrane Collaboration, Oxford, England). Pooled weighted mean difference (WMD) and its 95% confidence interval (CI) were calculated to assess the effects of cumin on anthropometric and metabolic indices, including glycemic and lipid parameters. A threshold of $P<0.1$ was set for identifying presence of heterogeneity. The degree of inconsistency between the studies was considered significant when $I^2>50\%$. A random effects model was

used if I^2>50% and P<0.1. A fixed effects model was used if I^2<50% and P>0.1. Moreover, Subgroup analyses were conducted according to the Cochrane guidelines(Gopalakrishnan and Ganeshkumar 2013). The funnel plot test was used in order to examine the existence of publication bias. If publication bias exists, the funnel plot shows an asymmetric appearance. A P-value <0.05 was considered statistically significant.

Results

Search results and study selection

A flow chart depicting the process of selection and literature search is presented in Figure 1. The literature search of electronic databases, identified 93 relevant articles, of which 62 total abstracts were excluded due to review articles (n=3), non-English (n=8), duplicate (n=18) studies, and 33 irrelevant articles such as editorials, letters and case reports. All remaining abstracts were considered for full-text review. Out of the 31 studies, 24 were excluded because they were preclinical studies or containing insufficient reporting of clinical data, inadequate characterization of the patients or primary or secondary outcomes other than metabolic or anthropometric indices. Finally, a total of 7 RCTs were included in this meta-analysis (Andallu and Ramya 2007, Jafari et al. 2017, Shavakhi et al. 2015, Taghizadeh et al. 2016, Taghizadeh et al. 2015, Zare et al. 2014, Keyhan et al. 2016).

Description of the studies and quality assessment

Characteristics of the included trials are shown in Table 1. All trials were published between 2007 and 2017, of which six studies were conducted in Iran and one study was3 performed in India. A total of 412 adults with T2DM (+overweight) or overweight subjects (Intervention group, n=203; Control group, n=209) were re-analysed in the study. The estimated average age of subjects was 41 years. Duration of follow-up ranged from 60 days to 6 months. Cumin dosing ranged from 25 mg/day to 5 g/day. Cumin seed powder (Andallu and Ramya 2007, Zare et al. 2014) Cuminum cyminum essential oil (Jafari et al. 2017, Keyhan et al. 2016, Shavakhi et al. 2015, Taghizadeh et al. 2015) and capsule (Taghizadeh et al. 2016) were the forms used in the trials. After evaluation of the study quality, three studies were classified as low quality with Jadad score of ≤3 (Andallu and Ramya 2007, Jafari et al. 2017, Shavakhi et al. 2015) and the remaining four as high quality studies with Jadad score of >3 (Keyhan et al. 2016, Taghizadeh et al. 2016, Taghizadeh et al. 2015, Zare et al. 2014)

The effects of cumin on anthropometric indices

The pooled analysis was generated from the data of 317 subjects in 5 trials reporting changes in BMI or weight change (Intervention group, n=158 and control group, n=159)(Shavakhi et al. 2015, Taghizadeh et al. 2016, Taghizadeh

et al. 2015, Zare et al. 2014). Among them, four trials reported a reduction of BMI and bodyweight after consuming cumin. The meta-analysis of the trials showed a significant reduction of bodyweight by -1.74 kg [95% confidence interval (CI), -2.2 to -1.28; p<0.00001] compared with control groups. The pooled mean net change in BMI for the treatment group compared to controls was -0.67 kg/m^2 (95% CI: -0.83 to -0.5; p<0.00001). The forest plots of the effects were presented in Figure 2 (a, b). There was no statistical heterogeneity among studies in the bodyweight and BMI meta-analysis (I^2=30%; p=0.23 and I^2=0%; p=0.42 for bodyweight and BMI, respectively). The funnel plot of data taken from different variables including BMI, bodyweight and LDL-c showed no asymmetry, indicating a low risk of publication bias (Figure 4a, b, c).

The effects of cumin on metabolic indices including blood glucose and lipid concentration

Since the varying units for indices (including for FBG, TG, TC, LDL-c and HDL-c) had been used in the included studies, all the values were converted to the same unit (mg/dL).

A high level of statistical heterogeneities were observed for the meta-analysis of all metabolic indices except for LDL-c. Therefore, the random effects model was selected for synthesis of the data. Subgroup analyses were performed to explore the potential factors contributing to heterogeneity. Compared to the overall results, the heterogeneity showed a decrease in indicators including TG and HDL-c in subgroup analyses by clinical condition.

The serum level of FBG was analyzed in seven included studies (Andallu and Ramya 2007, Jafari et al. 2017, Keyhan et al. 2016, Shavakhi et al. 2015, Taghizadeh et al. 2016, Taghizadeh et al. 2015, Zare et al. 2014). The pooled estimate indicated significant differences between the mean changes in FBG in the treatment group compared with the control group [WMD: -17.82 mg/dL (95% CI: -32.12 to -3.53; P for heterogeneity < 0.00001, I^2 = 99%)] (Figure 3-A), while HbA1c mean changes did not show any significant differences between treatment and control group[WMD: -0.95 mg/dL (95% CI: -2.07 to 0.16; P for heterogeneity < 0.0004, I^2 = 87%)](Figure 3-B).

As regards to the investigated serum lipid indices, the effects of cumin intake were evaluated in six studies (Andallu and Ramya 2007, Keyhan et al. 2016, Shavakhi et al. 2015, Taghizadeh et al. 2016, Taghizadeh et al. 2015, Zare et al. 2014). The pooled mean net change in TG for the treatment group compared to controls was -21.23 mg/dL that was statistically significant (95% CI: -37.64 to -4.82; P for heterogeneity < 0.0001, I^2 = 92%) (Figure 3-C). The difference between pooled mean net change in total cholesterol and LDL-c for the treatment group compared to control group were not significant (WMD for total cholesterol: -7.84 mg/dL, 95% CI: -17.93 to 2.25, P for heterogeneity < 0.00001, I^2 = 88%; WMD for LDL-c: -2.23 mg/dL, 95% CI: -4.77 to 0.30, P for heterogeneity < 0.17, I^2 = 34%) (Figure 3-D, 3-E). For serum HDL-c level, the pooled mean net change was 4.16 in the treatment group [95%CI: 3.30, 5.01; p

for heterogeneity < 0.00001, I^2=82%], which was significantly different from controls (Figure 3-F).

Effect of clinical condition

A subgroup analysis based on the clinical condition was performed to clarify the sources of heterogeneity (Table 2). Compared to the overall results, the heterogeneity of two investigated indicators, FBG and TG, decreased significantly in subgroup analysis by clinical condition of T2DM (+overweight). Significant differences in the mean change of FBG, TG and LDL-c levels were found in the subgroup analysis by diabetic (+overweight) intervention (FBG WMD = -30.86, 95% CI -53.80 to -7.91; TG WMD = -64.17, 95% CI -82.3 to -46.03; LDL-c WMD= 5.48, 95% CI 4.41 to 6.54) which was consistent with the overall analysis (Table 2). In addition, the analysis confirmed a significant difference in the mean change of LDL-c, which is inconsistent with the overall results [WMD: -2.28 mg/dL (95% CI: -4.51 to -0.05; P for heterogeneity < 0.6, I^2 = 0%)] (Table 2). As regards to the second clinical condition, overweight status, subgroup analysis demonstrated a significant difference in the mean change of the investigated indicators same as those indicators of overall analysis except for TG levels, as shown in Table 2 (FBG WMD = -7.71, 95% CI -15.02 to -0.39; LDL-c WMD= 1.81, 95% CI 0.39 to 3.24). In contrast with the overall results, the pooled estimate indicated a non-significant difference between treatment and control groups in the mean change of TG level [WMD: -7.63

mg/dL (95% CI: -21.76 to 6.51; P for heterogeneity < 0.00001, I^2 = 88%) (Table 2).

Effect of study quality

In another subgroup analysis by quality assessment, high quality studies showed significant differences in the mean change of FBG, TG and HDL-c which are in line with the overall results (FBG WMD = 0.52, 95% CI 0.11 to 0.93; TG WMD = -23.73, 95% CI -44.29 to -3.16; LDL-c WMD= 3.78, 95% CI 2.83 to 4.72). However, after the analysis of the low quality subgroup, the only factor which showed a significant difference in the mean change was HDL-c [WMD: 5.86 mg/dL (95% CI: 3.86 to 7.86; P for heterogeneity < 0.44, I^2 = 0%). The heterogeneity of HDL-c decreased significantly after subgroup analysis by low quality studies, though the heterogeneities in other indices still persist.

Publication bias

The publication bias of this meta-analysis was assessed by examining funnel plot of the effects on LDL-c as a representative index for metabolic profile and both bodyweight and BMI as the representative indicators of anthropometric indices. The symmetrical funnel plots suggested that the selection of publication was not a possible source of bias (Figure 4).

Discussion

The present meta-analysis included a total of 412 adults with T2DM (+overweight) or overweight from 7 RCTs. Despite considerable heterogeneity amongst the trials, our findings indicate several benefits following cumin supplementation; reduced bodyweight, and improved glycaemic control and lipid parameters. To our knowledge, this is the first systematic review that has assessed the effects of cumin supplementation on anthropometric and metabolic indices.

Significant reductions in bodyweight and BMI were observed following cumin supplementation with no detectable changes in the control group. These findings were consistent across four of the seven individual RCTs assessed in this study. There were also improvements in some indices of glycaemic control (i.e. FBG). Certain bioactives in cumin may contribute to improving insulin function via preservation of β-cells, thus enhancing insulin secretion and sensitivity of hepatocytes to insulin (El-Dakhakhny et al. 2002). There is some evidence to suggest that overweight participants may respond more effectively to the hypoglycaemic properties of certain compounds (i.e. phenolic compounds) (Almoosawi et al. 2012). Several mechanisms may explain their putative antidiabetic effects including activation of the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway, leading to the upregulation of the antioxidant

response element (ARE) gene expression, thus reducing oxidative stress, cell death and inflammation (Zheng et al. 2013).

Cumin supplementation was also associated with significantly increased serum levels of HDL-c. Although reductions were observed in HbA1C, TC, LDL-c, they were not statistically significant. Evidence from experimental studies have demonstrated hypolipidemic effects of phenolic compounds and sterols by inhibiting the absorption of lipids from the intestines, and de novo cholesterol synthesis and/or stimulation of bile acid excretion (Bamosa et al. 2002, Kanter et al. 2005).

After stratifying the trials according to clinical condition (T2DM with overweight and overweight subjects), we observed reduced serum levels of TG, LDL-c and FBG and increased level of HDL-c in T2DM with overweight group, which is consistent with the overall analysis except for LDL-c. HDL-c and FBG are the only factors that significantly changed after subgroup analyses by overweight group. Therefore, concerning subgroup analysis based on intervention, common factors that are significantly affected are FBG and HDL-c. One of the interesting findings of the present meta-analysis is the effectiveness of cumin on LDL-c in diabetic subjects, contrary to overweight subjects. According to these finding, it seems that the improving effect of cumin on LDL-c is more reliable in diabetic patients. Therefore, cumin supplementation may reduce the cardiovascular events and deaths by the

significant reduction in TG and LDL-c and elevation in HDL-c in diabetic patients.

Analysis of RCTs by subgroup (i.e. low and high quality studies) based on Jadad scores indicated some differences between metabolic indices. Significant improvements in serum TG, HDL-c and FBG were observed in high quality studies (i.e. Jadad score ≥3) and were similar to our overall findings in this meta-analysis. From the one low quality study we analysed (i.e. Jadad score <3), only HDL-c concentrations had improved. The rationale behind including the study of Andallu et al. (2007), as a low quality study, was due to its characteristics. This was the only study with a much higher dose (i.e. 5 g) and a shorter duration (60 days). Moreover, they included overweight and T2DM participants, which is one of the primary inclusion criteria of the study.

Heterogeneity and inconsistencies between studies may have influenced some of the metabolic indices observed. Possible factors include; between-study differences, selected cut-points used for positivity, differences in methodologies, participant selection procedures, study duration, method of delivery and dosage. For example, the dose of cumin supplemented in the 7 RCTs analysed was highly variable (i.e. range: 25 mg/day to 5 g/day). Differences in geographical region, distribution and time of harvest of the plant would also significantly influence the concentrations of bioactive ingredients in cumin, and the formulation supplemented (i.e. powder or oil) (Kamal et al.

2010, Taghizadeh et al. 2016). In the present study, 6 out of the 7 RCTs analysed in the meta-analysis were from Iran. One of the reasons for this was due to the restricted availability of RCTs, which is maybe because cumin is one of the traditional plant species cultivated in the Middle East, India and Iran. Similarly, this also explains why we did not include non-English RCTs in the present study due to limited number of high quality RCTs available. Despite this, studies from the same geographical region (i.e. Iran) could have minimised some of the variations discussed earlier (i.e. concentrations of bioactive compounds in cumin, similarities in clinical setting, methodologies, participant selection).

We did not observe any adverse effects following cumin supplementation from the RCTs analysed in the present study (i.e. from 60 days to 6 months). A recent animal study assessed the toxicity of essential oil derived from cumin after 23 and 45 days of oral administration. No obvious clinical signs or adverse effects were observed at doses of ≥500 mg/kg/d (Taghizadeh et al. 2017).

Some limitations of this meta-analysis include not controlling for confounding factors (i.e. dietary intake and physical activity) which may have influenced the results. Most of the RCTs included were of a relatively small sample size, and three studies did not use a double blind trial design (Andallu and Ramya 2007, Jafari et al. 2017, Shavakhi et al. 2015).

Despite these limitations, there were several strengths to this study. Firstly, it is to our knowledge, the first time a systematic review and meta-analysis has been performed in the evaluation of cumin supplementation on anthropometric and metabolic indices. A random effects model was utilised for assessing heterogeneity between studies, and RCTs were assessed using subgroup analysis based on clinical condition and quality assessment.

Conclusion

In conclusion, the findings from this present meta-analysis suggest some improvement in anthropometric and metabolic indices following cumin supplementation. However, due to the limited availability of studies and relatively small sample sizes of included RCTs, further investigation is warranted.

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Table 1: Characteristics of included trials

Auther	Year	Country	No. of Subjects in case group	No. of controls	Gender	Age(mean)	Follow-up Duration	Clinical Condition	Dosage	Significant Outcome	Jadad score
Andallu	2007	India	10	10	F/M	40-60	60 days	Overweight with T2DM	Cumin seed powder;5 g/day	Reduction in FBG, TG, TC and HDL	1
Jafari	2017	Iran	30	30	F/M	47.33 ±6.35	8 weeks	Overweight with T2DM	essential oil of C. cyminum;100/50 mg/day	Reduction in FBS and HbA1C	3
Keyhan	2016	Iran	29	34	F/M	30-75	3 months	Overweight with T2DM	essential oil of C. cyminum;25 mg/day	FBG, HbA1c% and TG were significantly reduced	4
Shavakhi	2015	Iran	40	41	F/M	38.6 ±9.9	6 months	Overweight and Obese	essential oil of C. cyminum;25 mg/day	Elevation of AST and HDL-C	3
Taghizadeh	2015	Iran	26	26	F/M	18-60	8 weeks	Overweight	essential oil of C. cyminum;100 mg/day	Reduction in serum insulin levels and HOMA-B and rise in QUICKI	4
Taghizadeh	2016	Iran	24	24	F/M	18-50	8 weeks	Overweight	C. cyminum capsule;75/25 mg/day	Significant weight loss, reduction in fasting plasma glucose and a significant rise in quantitative insulin sensitivity check index	4
Zare	2014	Iran	44	44	F	37.2±8.4	3 months	Overweight and Obese	C. cyminum powder;1.5 g/day	Reduction of serum levels of fasting cholesterol, triglyceride, LDL, weight, BMI, waist circumference, fat mass and increasing of serum HDL.Weight, BMI, waist circumference, fat mass	5

Table 2: Subgroup analysis*

subgroup		TG			TC			LDL		
		WMD (95% CI)	*Test for heterogeneity(I2, P)*	*Test for overall effect*	*WMD (95% CI)*	*Test for heterogeneity(I2, P)*	*Test for overall effect*	*WMD (95% CI)*	*Test for heterogeneity(I2, P)*	*Test for overall effect*
Clinical Condition										
	Overweight with T2DM	-64.17 [-82.3, -46.03]	23%, P =0.26	P<0.0001	-21.93 [-57.98, 14.12]	97%, P < 0.00001	P=0.23	-2.28 [-4.51, -0.05]	0%, P=0.63	P=0.04
	Overweight	-7.63 [-21.76, 6.51]	88%, P < 0.00001	p=0.29	-6.56 [-23.78, 10.67]	96%, P < 0.00001	p=0.46	-2.30 [-7.97, 3.36]	55%, P=0.06	p=0.43
Quality of study										
	Low Quality	-18.46 [-73.16, 36.25]	90%, P = 0.001	p=0.51	-18.36 [-61.77, 25.05]	97%, P < 0.00001	P=0.41	-1.43 [-3.84, 0.97]	0%, P=0.81	P=0.24
	High Quality	-23.73 [-44.29, -3.16]	91%, P < 0.00001	p=0.02	-8.33 [-22.30, 5.64]	97%, P < 0.00001	p=0.24	-2.92 [-8.26, 2.43]	52%, P=0.08	p=0.29

*: Abbreviations: TG, triglycerides; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol;; FBG, fasting blood glucose; WMD, weighted mean difference; CI, confidence interval.

Table 2: Subgroup analysis* (Continued)

subgroup		HDL			FBG			HbA1c		
		WMD (95% CI)	*Test for heterogeneity(I2, P)*	*Test for overall effect*	*WMD (95% CI)*	*Test for heterogeneity(I2, P)*	*Test for overall effect*	*WMD (95% CI)*	*Test for heterogeneity(I2, P)*	*Test for overall effect*
Clinical Condition										
	Overweight with T2DM	5.48 [4.41,6.54]	0%, P=0.38	p<0.00001	-30.86 [-53.80, -7.91]	95%, P < 0.00001	p=0.008	-0.95 [-2.07, 0.16]	87%, P=0.0004	p=0.09
	Overweight	1.81 [0.39, 3.24]	75%, P=0.003	P=0.01	-7.71 [-15.02, -0.39]	91%, P < 0.00001	p=0.04	Not Applicable	Not Applicable	Not Applicable
Quality of study										
	Low Quality	5.86 [3.86, 7.86]	0%, P=0.44	P<0.0001	-17.27 [-37.79, 3.24]	99%, P < 0.00001	P=0.1	Not Applicable	Not Applicable	Not Applicable
	High Quality	3.78 [2.83, 4.72]	86%, P < 0.00001	p=0.02	0.52 [0.11, 0.93]	57%, P = 0.04	p=0.01	0.05 [-0.12, 0.21]	71%, P = 0.02	p=0.59

*: Abbreviations: TG, triglycerides; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol;; FBG, fasting blood glucose; WMD, weighted mean difference; CI, confidence interval.

Figure

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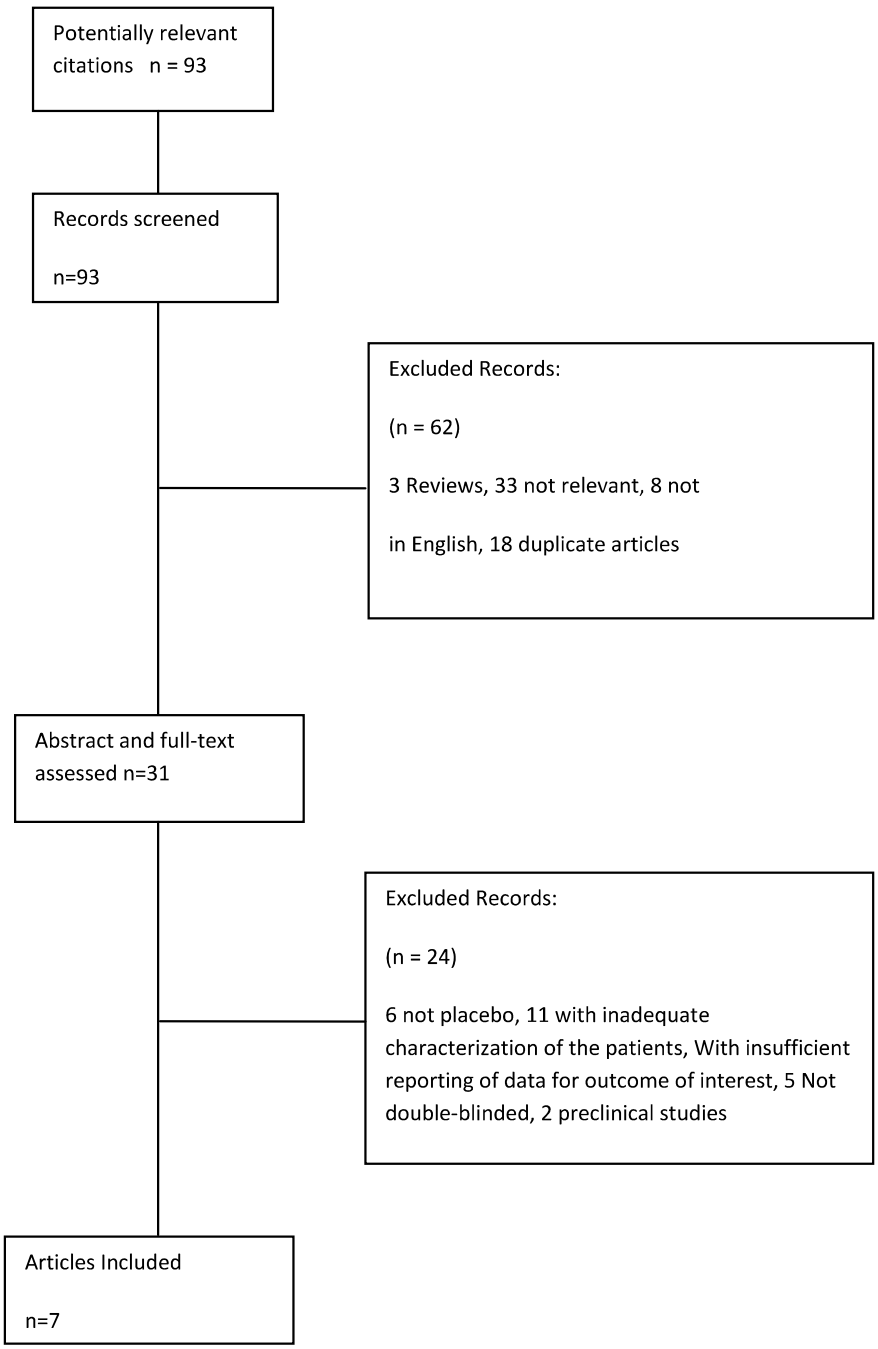
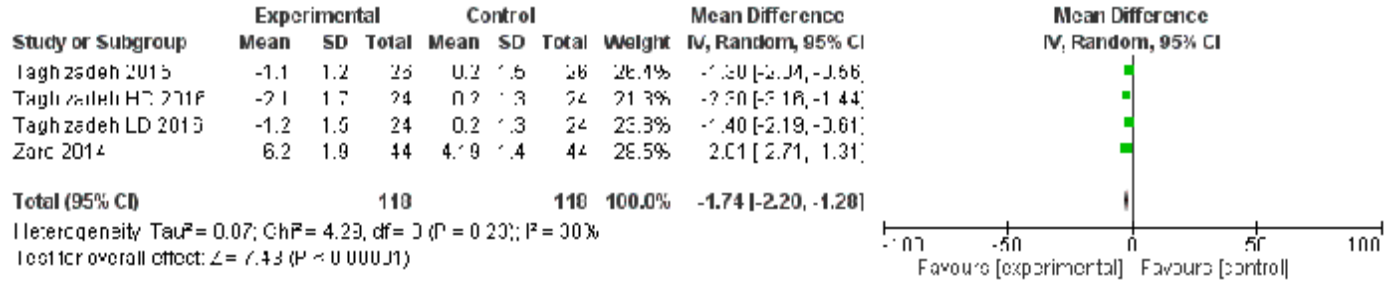


Figure 1: Meta-analysis Flow Diagram

A) Bodyweight



B) BMI

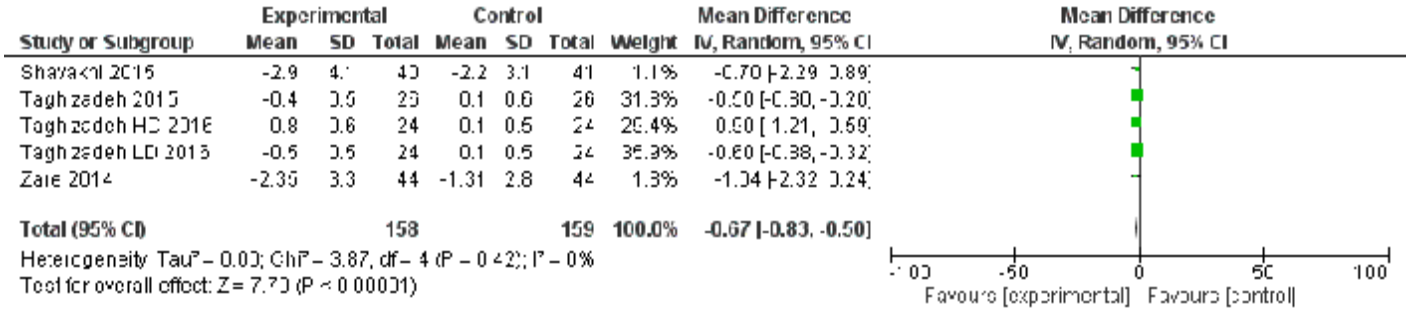
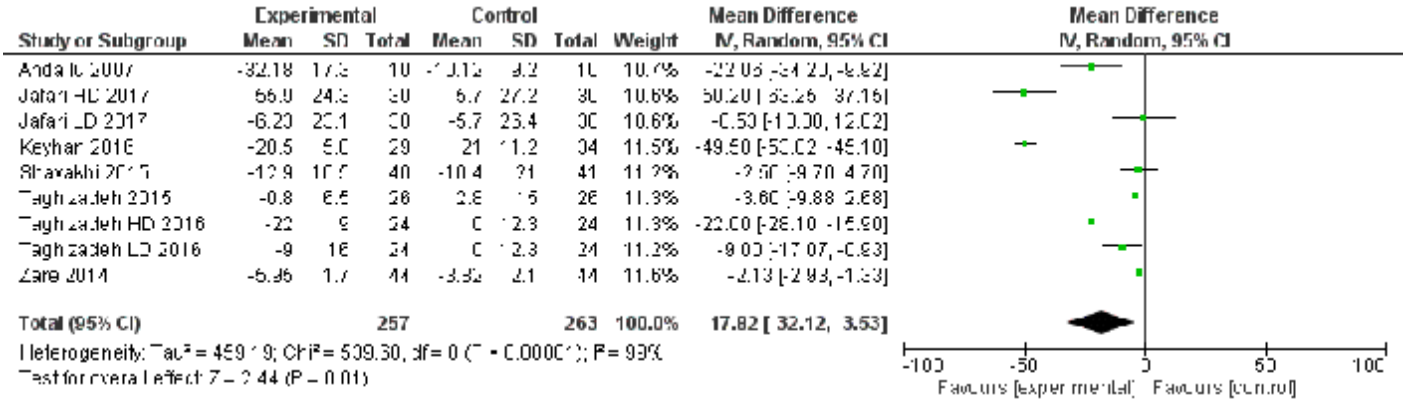
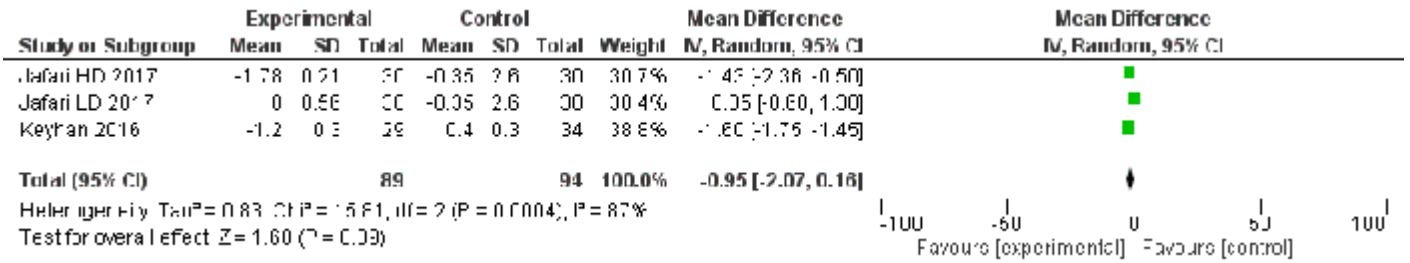


Figure 2: Forest plots showing the association between cumin intake and anthropometric indices: Weight Change (A), BMI (B). Abbreviation(s): BMI, body mass index; d. Random effects model was used to pool the mean change of indicators.

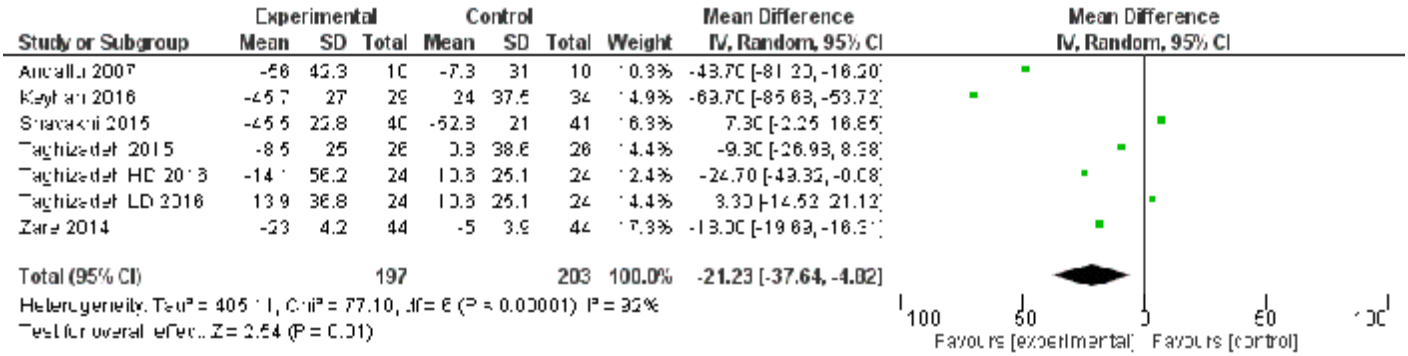
A) FBG



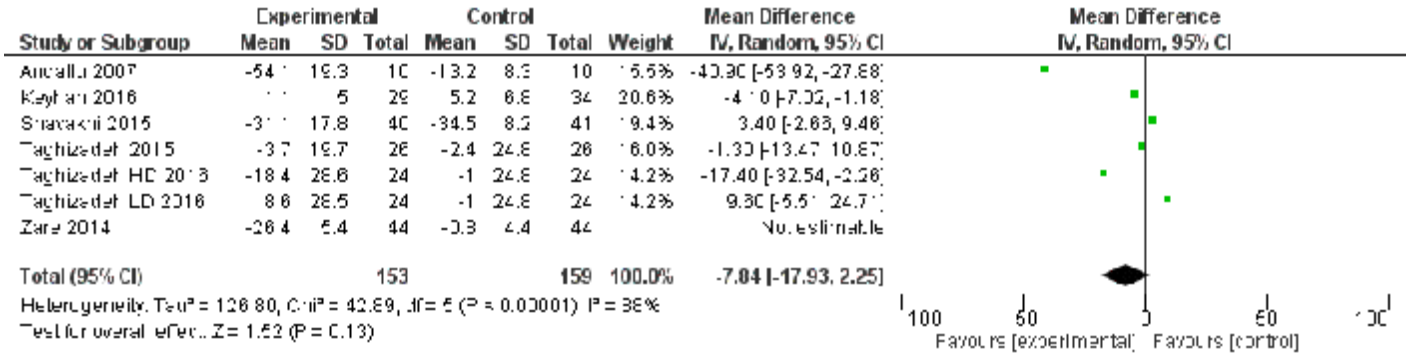
B) HbA1c



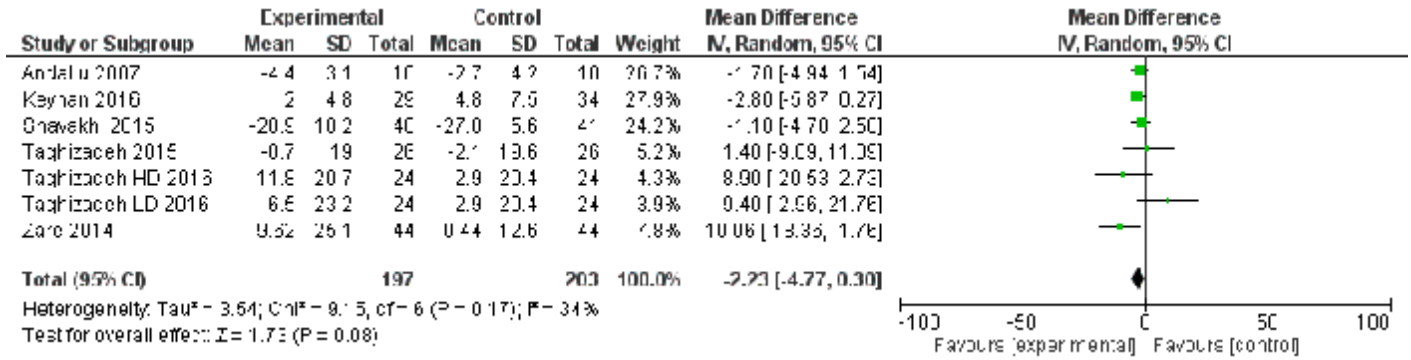
C) TG



D) TC



E) LDL-c



F) HDL-c

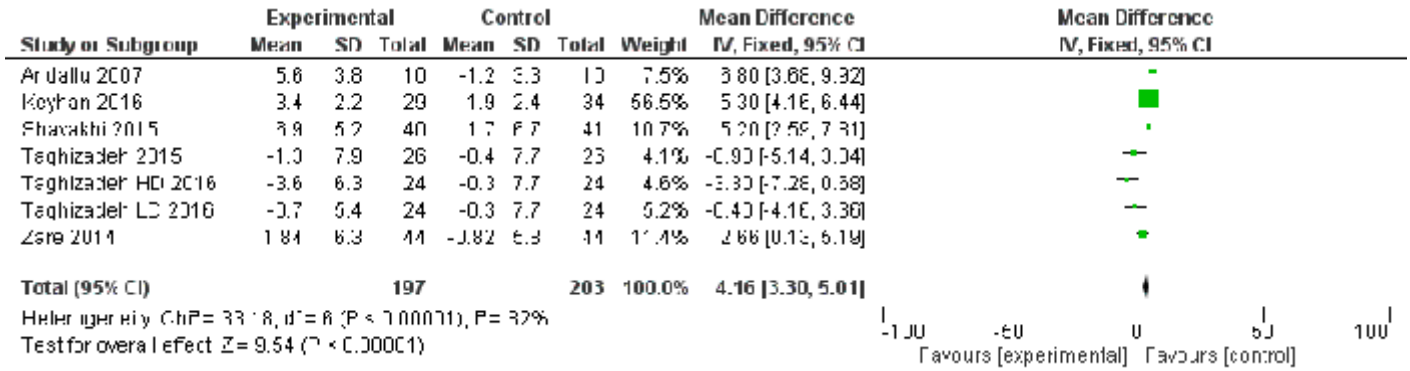
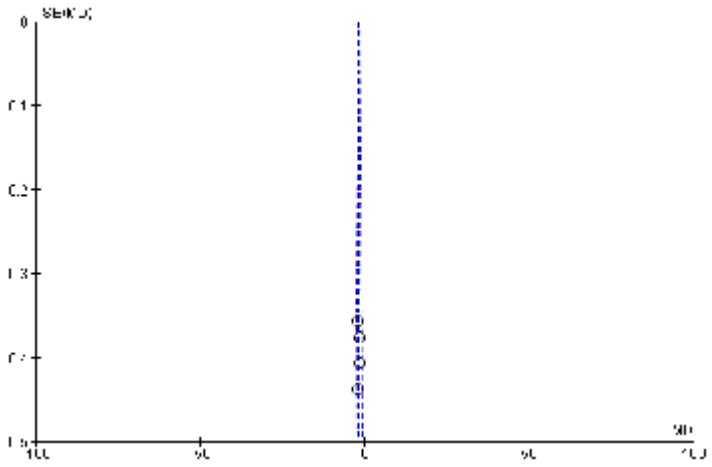
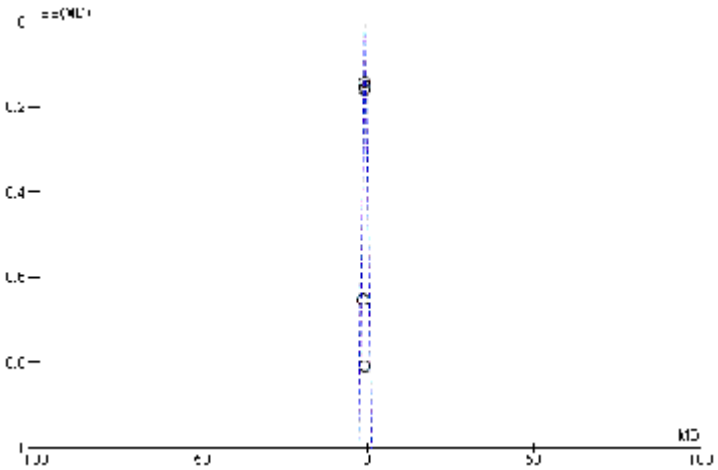


Figure 3: Forest plots showing the association between cumin intake and serum metabolic indices; FBG(A), HbA1c(B), TG (C), TC(D), LDL-c (E), HDL-c (F), Abbreviations: FBG, fasting blood glucose; TG, triglyceride; TC, total cholesterol; LDL-c, low-density lipoprotein cholesterol; HDL-c, high-density lipoprotein cholesterol; d. Random effects model was used to pool the mean change of indicators.

A)



B)



C)

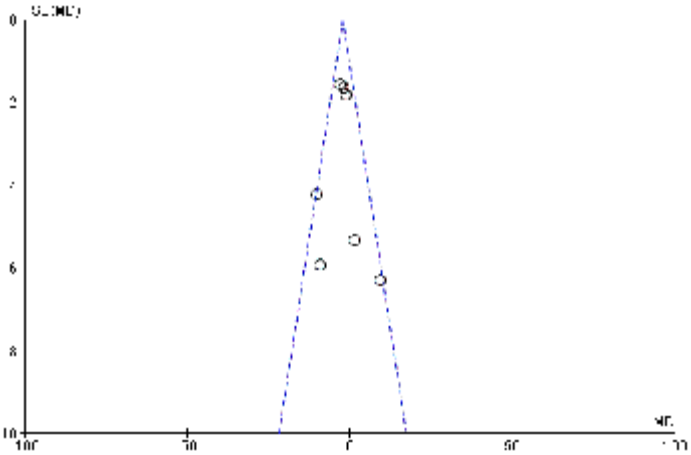


Figure 4: Funnel plot of studies included in the meta-analysis for the outcome of Bodyweight (A),BMI (B) and LDL-c(C) . MD = Mean Difference, SE = standard error.

Supplementary Interactive Plot Data (CSV)

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