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Systematic Review and Meta-analysis of the Effects of Elettaria Cardamomum Supplementation on Glycemic Indices and Anthropometric Measurements

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SYSTEMATIC REVIEW and META-ANALYSIS

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ABSTRACT

Background: Type 2 diabetes mellitus (T2DM) is considered a problem for public health worldwide and cardamom (Elettaria cardamomum) as a spice which contains polyphenolic components may have a beneficial effect on the status of diabetes patients. This systematic review and meta-analysis aims to update the efficacy of cardamom intake on weight reduction and glycemic control. **Methods:** Electronic databases were searched up to December 2023 to identify eligible articles. Mean differences were pooled using a fixed effects model, and standard methods were used for the assessment of heterogeneity, sensitivity analysis, and publication bias. **Results:** Totally, eight studies were included in the final analysis. Analysis showed that cardamom intake attenuated serum level of insulin [standard mean difference (SMD): -0.64, 95% CI: -0.86 to -0.43, P<0.001], whereas changes of fasting blood glucose (SMD: -0.13, 95% CI: -0.33 to 0.06), weight (SMD: -0.01, 95% CI: -0.23 to 0.20) and body mass index (SMD: -0.05, 95% CI: -0.02 to 0.11) were not significant. **Conclusion:** According to the findings of the present meta-analysis, cardamom intake significantly declined serum insulin level but did not have any significant effect on fasting blood glucose, weight, and body mass index.

Introduction

Type 2 diabetes mellitus (T2DM) is an endocrine disease identified by hyperglycemia and elevated insulin levels in the serum (DeFronzo *et al.*, 2015). T2DM is considered a public health problem worldwide due to its dramatic prevalence and public health consequences (Chen *et al.*, 2012). Various determinants are involved in the pathogenesis of T2DM such as genetic (Brunetti *et al.*, 2014), age (Zoungas *et al.*, 2014), diet and lifestyle (Hu *et al.*, 2001), inflammation (Cruz *et al.*, 2013), and obesity (Schnurr *et al.*, 2020). In fact, obesity is considered a major risk factor for various chronic diseases and threatens public health (World Health Organization, 2020). The main characteristic of obesity is the accumulation of excessive fat tissue in the body which causes

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chronic low inflammation in the body (Amin *et al.*, 2019) .Consequently, obesity increases the risk of insulin resistance and T2DM (Piché *et al.*, 2020). Nearly one-third of the population of the world is in the obese and overweight range (Chooi *et al.*, 2019). Previous studies indicated that the management of body weight and fat mass tissue had beneficial effects on glycemic control (Babio *et al.*, 2010). In fact, weight reduction decreases inflammatory markers in the body and improve the function of insulin receptors (Barazzoni *et al.*, 2018, Tutunchi *et al.*, 2020). Based on this, most of the interventions for the amelioration of hypoglycemia should be considered body weight (Koh-Banerjee *et al.*, 2004).

Cardamom (Elettaria cardamomum) is an herbal medicine that belongs to the ginger family (Zingiberaceae) and in some sources it is known as the queen of spices (Amma *et al.*, 2010). Cardamom natively grows in evergreen forests of the Western Ghats (Sinu and Shivanna, 2007). This spice is a rich source of polyphenolic components such as quercetin, kaempferol, luteolin, gallic acid, and pelargonidin (Deepa *et al.*, 2013). Previous studies expressed the desirable effect of cardamom on inflammation, oxidative stress (Kazemi *et al.*, 2017, Rahman *et al.*, 2017), and gastric lesions (Jamal *et al.*, 2006).

The effect of cardamom supplementation on anthropometric and glycemic variables is inconsistency in different clinical trials, such as Kazemi *et al*. who indicated that cardamom did not have any effects on weight and body mass index (BMI) in prediabetes patients (Kazemi *et al.*, 2017).Another study expressed that 12 weeks of cardamom supplementation significantly reduced weight and BMI (Daneshi-Maskooni *et al.*, 2019). The desirable effects of cardamom on fasting blood glucose (FBG) and insulin level were demonstrated in a clinical trial (Li *et al.*, 2017)The results were in line with the findings of the Aghasi *et al.'s* study regarding type 2 diabetes patients (Aghasi *et al.*, 2019). However, the findings of another study contradicted with others and did not have any significant effects on glycemic control (Fatemeh *et al.*, 2017).

Based on the previous studies, the beneficial effects of cardamom on glycemic control related to the stimulation expression of silent mating type information regulation 2 homolog-1 (SIRT-1). Many records indicated that SIRT-1 was involved in hemostasis of glucose by improving insulin secretion, protection pancreatic beta-cell as an antioxidant, declining inflammation via scrubbing free radicals, and positive effects on the adiponectin, adipogenesis, and hepatic glucose production (Kitada and Koya, 2013).

Given the controversy between the results of different studies, present systematic review and meta-analyses were aimed to assess all clinical trials published which investigated the effects of cardamom supplementation on weight, BMI, FBG and, insulin in the adult population.

Materials and Methods

Search strategy

This meta-analysis was conducted based on the guidelines of the preferred reporting items for systematic reviews and meta-analyses (PRISMA) (Page *et al.*, 2021). All studies were identified by an online search in the following databases: PubMed (http://www.pubmed.com), Scopus (http://www.scopus.com), ISI Web of Sciences (http://www.webofscience.com), and, Google Scholar up to December 2023. In this research, the authors used text word and medical subject's headings (mesh) by following keywords: "Elettaria cardamomum" OR "Cardamom" OR "Elettaria" AND "Clinical Trials" OR "Cross-Over Studies" OR "Double-Blind Method" OR "Single-Blind Method" OR "Random Allocation" OR "RCT" OR "Intervention Studies" OR "Intervention" OR "Controlled trial" OR "randomized" OR "randomized" OR "random" OR "randomly" OR "Placebos" OR "Assignment". Moreover, the reference list of eligible studies was screened to avoid missing relevant articles. Search strategy of different databases is presented in supplementary file.

Eligibility criteria

All clinical trials that evaluated the effects of cardamom intake on anthropometric variables and glycemic indexes were included in the present

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study. Inclusion criteria included the following; 1- the study design was a randomized controlled trial 2- there was supplementation of cardamom or combination with other agents 3- there was sufficient reported information about both placebo and treatment groups 4- the study was published in English. The exclusion criteria in the present study included; 1- non-RCT studies, 2- a trial without a control group, 3- duplicate studies and animal studies, 4- a trial that evaluated the effects of cardamom only at the end of the trial.

Data extraction and quality assessment

Two independent reviewers (Najaf M, Papi S) screened the title and abstract of all the obtained studies through an electronic systematic search. A disagreement between investigators regarding study selection was resolved by a third independent reviewer (Nikpayam O). Finally, the required information was extracted from the included studies. The extracted relevant information included the first author's name, year of publication, study design, number and characteristics of participants in each group, intervention type and dose, duration of intervention, disease type, the effects of cardamom on FBG, insulin, weight, and BMI. The quality of included trials was evaluated using GRADE tool based on the Cochrane Handbook of systematic reviews of interventions. This tool consists of five variables: bias risk, consistency of results, directness, precision, and publication bias. GRADE results were categorized as "high," "medium," "low," and "very low." If any of the above variables are not met, the quality of a level will decrease (Guyatt *et al.*, 2008).

Data analysis

Statistical analysis in this meta-analysis was conducted by STATA software version 15. The effect size of cardamom intake on FBG, insulin, weight, and BMI was explicated through standard mean difference (SMD) with a 95% confidence interval (CI) from the fixed-effects model (using inverse variance method, Cohen statistic). The heterogeneity was assessed by I square test, and significant heterogeneity was defined as $I^2 > 50\%$ with a P-value < 0.05. Sub-group analysis was performed for finding the probable source of heterogeneity among studies. For the influence of each study on pooled effect size, the authors used sensitivity analysis. Publication bias among the included studies was explored by funnel plots and also Egger's regression test and Begg's test.

Results

Included studies

Totally, 221 participants were identified after searching in Web of Sciences, Scopus, PubMed, and Google Scholar. After removing duplicate studies (114), 89 studies were excluded following screening the title and abstract, 18 studies remained for full-text evaluation, 10 studies were omitted due to not having the control group (n=1), duplicated data (n=1), being in Persian language (n=1), and not having enough data to analyze (n=7). Finally, 8 studies were included in this systematic review and meta-analysis (**Figure 1**).

Study characteristics

Characteristics of included studies in the present systematic review and meta-analysis are presented in **Table 1**. All included studies were performed in Iran (Aghasi *et al.*, 2019, Azimi *et al.*, 2014, Azimi *et al.*, 2016, Cheshmeh *et al.*, 2021, Daneshi-Maskooni *et al.*, 2018, Fatemeh *et al.*, 2017, Kazemi *et al.*, 2017) except one study which was conducted in China (Li *et al.*, 2017). These studies were published between 2015 and 2021. Totally, 765 participants enrolled in these studies with 387 and 378 patients respectively in the treatment and control groups. Six studies were conducted on both genders and two studies were done only on women. The duration of supplementation with cardamom was from 8 weeks up to 16 weeks. The cardamom dosage in all studies was a 3-gram exception for one study which administrated 30-gram cardamom (Li *et al.*, 2017). The studies included in this meta-analysis reported no side effects associated with cardamom. The quality of enrolled studies is presented in **Table 2.**

Effects of cardamom on FBG

The effects of cardamom intake on FBG are expressed in the **Figure 2**. According to the figure,

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cardamom supplementation does not have significant effects on FBG; furthermore, there was no heterogeneity between included effects size. Also, subgroup analysis based on the duration of treatment, type of supplement, and mean age of patients did not show any considerable effect (**Table 3**). According to Begg's, *P* (0.806) and Egger's *P* (0.896), and there was no publication bias between included studies. The funnel plot of studies is presented in the **figure. 3**. Sensitivity analysis revealed that excluding any one study did not have significant effects on SMD.

Effects of cardamom on insulin

Pooled findings of included studies indicated that cardamom supplementation significantly decreased the level of serum insulin, but there was heterogeneity between studies, as shown in Figure 4. So, subgroup analysis was conducted according to the duration of treatment, type of supplement, and mean age of participants. Analysis based on the duration of treatment showed that more than 8 weeks in comparison with less than 8 weeks, supplementation with cardamom plus other agents vs. cardamom and people under 50 in comparison to those above 50 had a significant effect on serum level of insulin (**Table 3**). Statistical analysis did not show publication bias among included studies (Begg's *P* (0.086) and Egger's *P* (0.051). Funnel plot of studies was shown in **Figure 5**. Sensitivity analysis indicated that omitting each study did not change significantly the overall result.

Effects of cardamom on weight

Data analysis showed that cardamom supplementation had no effect on weight, and there was no heterogeneity between studies, which is shown in **Figure 6.** In addition, subgroup analysis findings are reported in **Table 3**. There was no publication bias between clinical trials investigating the cardamom impacts on weight (Begg's *P*=0.718 and Egger's *P*=0.459). The funnel plot of weight is reported in **Figure 7**. Also, sensitivity analysis indicated that excluding any of the clinical trials did not have any significant effects.

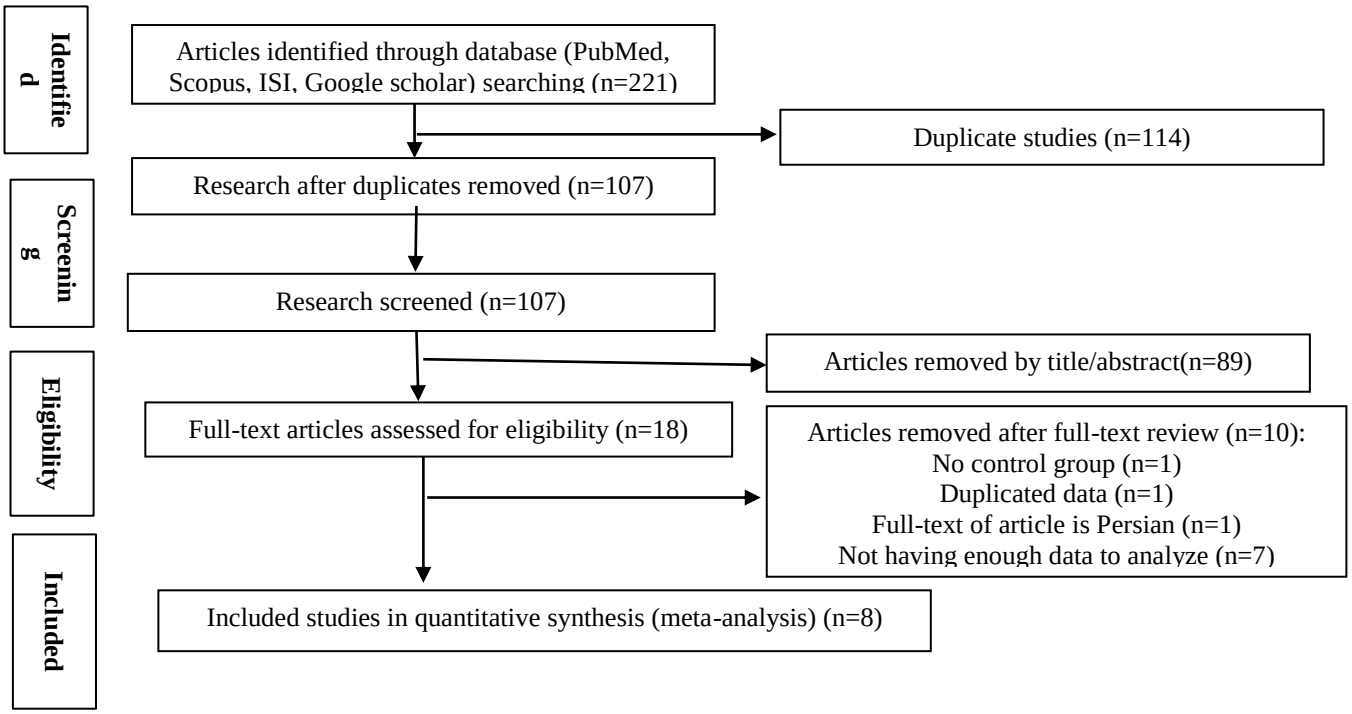

Figure 1. Flow chart of included studies.

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Table 1. Characteristics of included studies.

First author (year)	Country	Type of disease	Participants (n)		Age (year)		Dose (g)	Duration of treatment	Cardamom formulation
			Treatment	Control	Treatment	Control			
Cheshmeh (2021)	Iran	PCOS	99[a]	95[a]	32.99	32.13	3	16 weeks	Green cardamom powder capsule
Aghasi (2019)	Iran	T2DM	41	42	53.90	53.30	3	10 weeks	Green cardamom powder capsule
Daneshi-Maskooni (2018)	Iran	NAFLD	43	44	45.50	45.50	3	12 weeks	Green cardamom powder capsule
Yaghooblou (2017)	Iran	Overweight or obese pre-diabetic	40*	40*	48.3	47.5	3	8 weeks	Green cardamom powder capsule
Li (2017)	China	T2DM	40	40	55.16	43.35	30	12 weeks	Traditional Chinese medicine including cardamom
Kazemi (2017)	Iran	Overweight, and obese pre-diabetic	40	40	48.30	47.50	3	8 weeks	Green cardamom powder capsule
Azimi (2016)	Iran	T2DM	42	39	54.33	53.64	3	8 weeks	Green cardamom powder + black tea
Azimi (2015)	Iran	T2DM	42	39	51.59	53.64	3	8 weeks	Green cardamom powder + black tea

[a]*: Conducted exclusively on women;* ***NAFLD****: Non-alcohol fatty liver disease;* ***T2DM****: Type 2 diabetes mellitus* ***; PCOS****: Polycystic ovary syndrome.*

Table 2. Summary of findings and quality of evidence assessment using GRADE approach.

Outcome measures	Summary of findings		Quality of evidence assessment (GRADE)					
	None of patients (trials)	Effect size (95% CI)	Risk of bias[a]	Inconsistency[b]	Indirectness[c]	Imprecision[d]	Publication bias[e]	Quality of evidence[f]
Insulin	411 (5)	-0.64 (-0.86,- 0.43)	Not Serious	Serious	Serious	Not serious	Not serious	Low
Fasting blood glucose	411 (5)	-0.13 (-0.33, 0.06)	Not Serious	Not Serious	Serious	Not serious	Not serious	Moderate
Weight	523 (5)	-0.02 (-0.19, 0.15)	Not Serious	Not Serious	Serious	Not serious	Not serious	Moderate
Body mass index	606 (6)	-0.05 (-0.21, 0.11)	Not Serious	Not Serious	Serious	Not serious	Not serious	Moderate

[a]*: Risk of bias based on the Cochrane risk of bias tool. This tool assesses selection bias, performance bias, detection bias, attrition bias, and reporting bias;* [b]*: Downgraded if there was a substantial unexplained heterogeneity (I^2 > 50%, P < 0.10) that was unexplained by subgroup analyses;* [c]*: Downgraded if there were factors present relating to the participants, interventions, or outcomes that limited the generalizability of the results. Participants of the included studies were from different health conditions;* [d]*: Downgraded if 95% confidence interval (95% CI) crossed the minimally important difference (MID) for benefit or harm;* [e]*: Downgraded if there was an evidence of publication bias using funnel plot;* [f]*: Since all the included studies were randomized controlled trials, the certainty of the evidence was graded as high for all outcomes by default and then downgraded based on prespecified criteria. Quality was graded as high, moderate, low, very low.*

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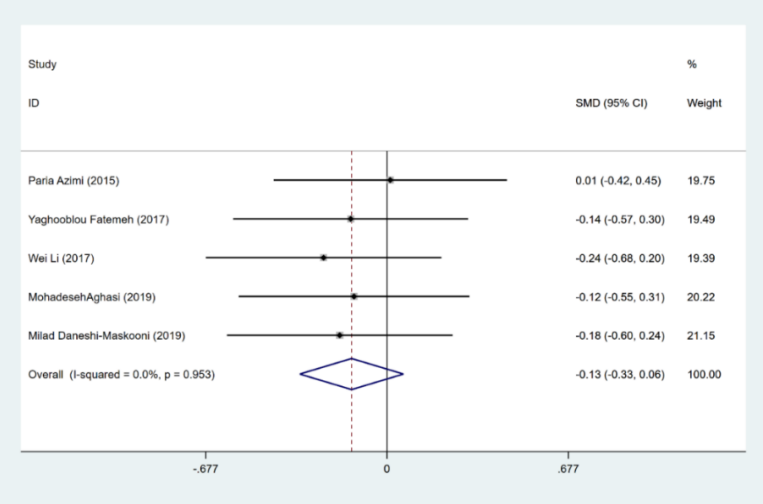

Figure 2. Forest plot of the cardamom supplementation on fasting blood glucose.

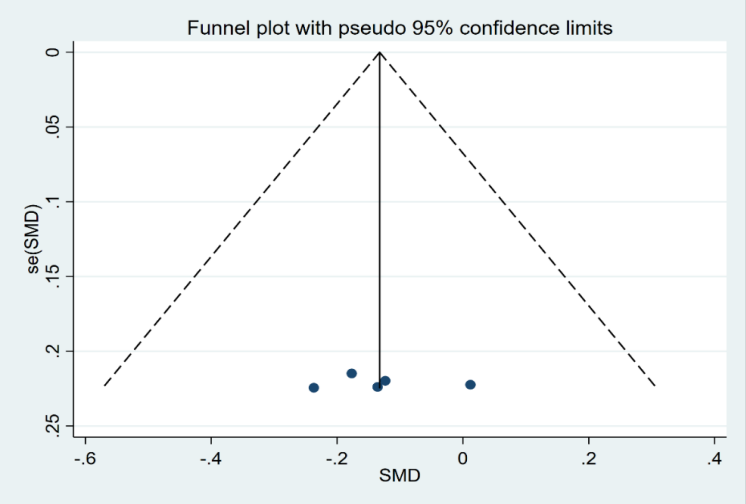

Figure 3. Funnel plot of the cardamom supplementation on fasting blood glucose.

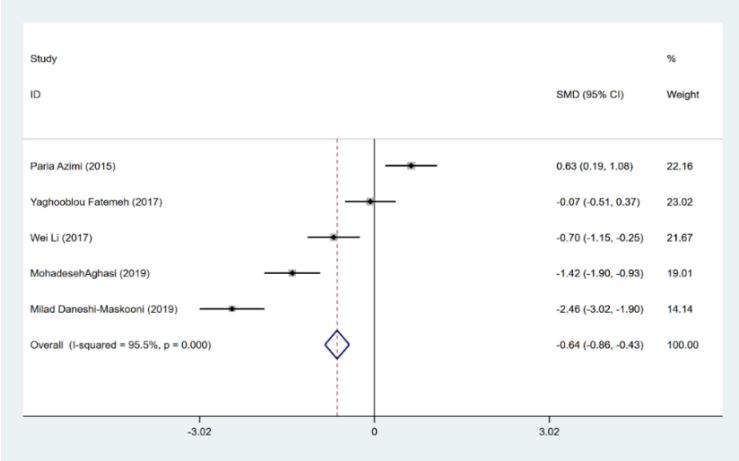

Figure 4. Forest plot of the cardamom supplementation on insulin.

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Table 3. Results of subgroup analysis of the included studies in meta-analysis.

Variable	Duration of treatment		Type of supplement		Mean age	
	< 8 week	> 8 week	Cardamom	Cardamom + other agents	< 50	> 50
Insulin						
No. of comparisons	2	3	2	3	2	2
SMD	0.27	-1.40	-0.04	-1.86	-0.48	-0.31
95%CI						
Lower	-0.04	-1.69	-0.3	-2.23	-1.32	-0.64
Higher	0.59	-1.12	0.21	-1.49	-0.63	0.01
P-value	0.086	0.0	0.0	0.006	0.001	0.061
I^2 (%)	79.4	91.3	88.2	86.9	97.3	96.6
P-heterogeneity	0.028	0.001	0.001	0.006	0.001	0.001
Fasting blood glucose						
No. of comparisons	2	3	3	2	3	2
SMD	-0.06	-0.18	-0.15	0.11	-0.18	-0.06
95%CI						
Lower	-0.37	-0.43	-0.39	-0.42	-0.43	-0.36
Higher	0.25	0.07	0.10	0.20	0.07	0.25
P-value	0.697	0.160	0.481	0.250	0.152	0.718
I^2 (%)	0.0	0.0	0.0	0.0	0.0	0.0
P-heterogeneity	0.640	0.953	0.984	0.431	0.950	0.665
Weight						
No. of comparisons	3	2	3	2	3	2
SMD	0	-0.03	-0.04	0.02	-0.04	0.02
95%CI						
Lower	-0.25	-0.27	-0.24	-0.29	-0.24	-0.29
Higher	0.25	0.20	0.17	0.33	0.17	0.33
P-value	0.999	0.775	0.735	0.899	0.735	0.899
I^2 (%)	0.0	0.0	0.0	0.0	0.0	0.0
P-heterogeneity	0.975	0.938	0.997	0.999	0.997	0.999
Body mass index						
No. of comparisons	3	3	4	2	3	3
SMD	0.01	-0.09	-0.09	0.06	-0.08	0.00
95%CI						
Lower	-0.24	-0.29	-0.27	-0.25	-0.29	-0.25
Higher	0.27	0.12	0.10	0.37	0.13	0.25
P-value	0.920	0.403	0.366	0.733	0.446	0.995
I^2 (%)	0.0	0.0	0.0	0.0	0.0	0.0
P-heterogeneity	0.884	0.980	0.998	0.999	0.987	0.823

***SMD**: standard mean difference*

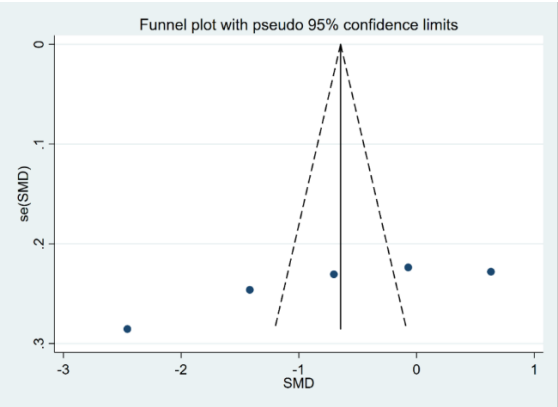

Figure 5. Funnel plot of the cardamom supplementation on insulin.

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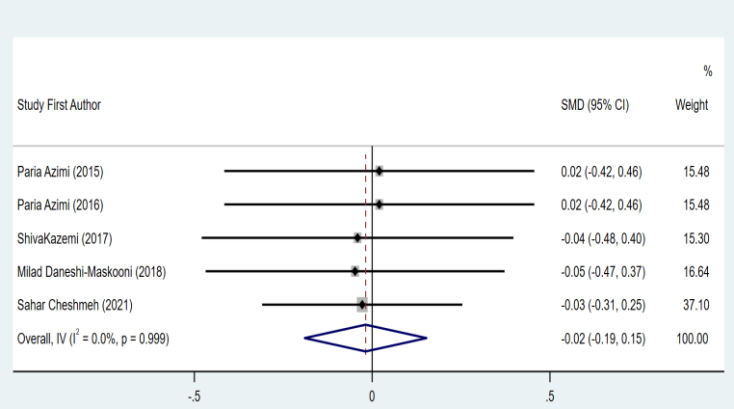

Figure 6. Forest plot of the cardamom supplementation on weight.

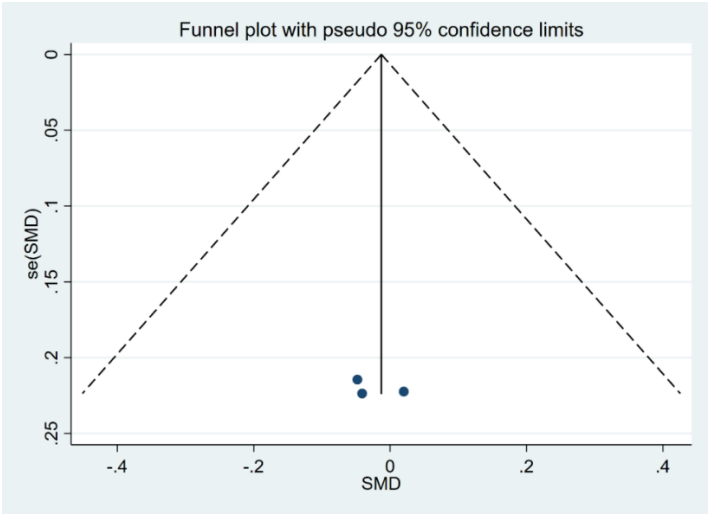

Figure 7. Funnel plot of the cardamom supplementation on weight.

Effects of cardamom on BMI

Pooled 5 clinical trials together showed cardamom intake had no significant effect on BMI, with no heterogeneity as shown in **Figure 8**. Moreover, the results of the subgroup analysis are presented in **Table 3**. No publication bias was discovered among the studies on BMI (Begg's *P*=0.327 and Egger's *P*=0.309). The funnel plot of included studies is expressed in **Figure 9**. Sensitivity analysis for studies that considered the effect of cardamom on BMI did not show any significant effect on SMD by excluding any studies.

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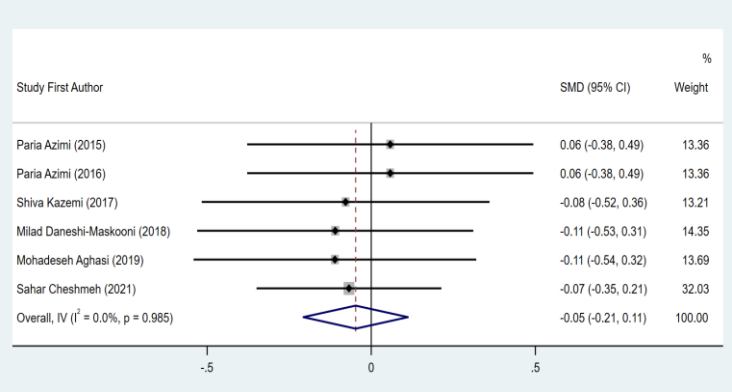

Figure 8. Forest plot of the cardamom supplementation on body mass index.

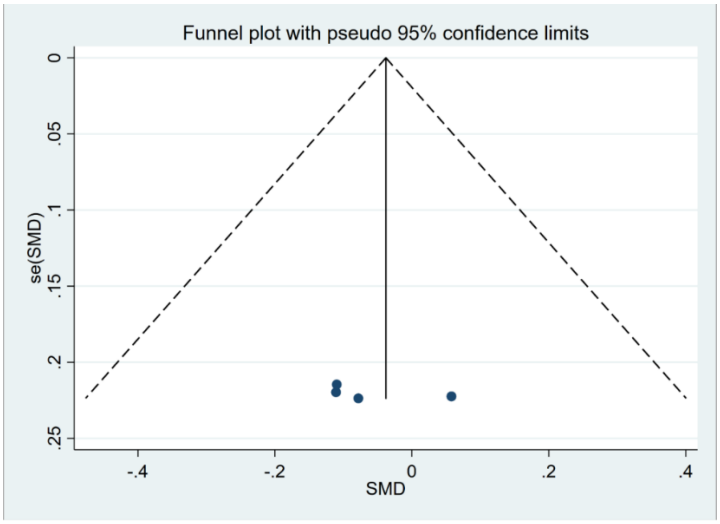

Figure 9. Funnel plot of the cardamom supplementation on body mass index.

Discussion

Previous systematic reviews and meta-analyses did not consider all published studies on the effects of cardamom supplementation in human subjects, which may have introduced bias in the reported results. The study did not evaluate the effect of cardamom supplementation on insulin levels. Instead, it focused on updated systematic reviews and meta-analyses that examined the impact of cardamom intake on anthropometric variables and glycemic control. The findings indicated that cardamom intake improved serum insulin levels, but had no effect on weight, BMI, or FBG.

However, most of the included studies showed beneficial effects on FBG, but analysis in the present meta-analysis did not show any significant effect. Subgroup analysis based on the duration of treatment, type of supplement, and mean age of subjects illustrated that although cardamom supplementation had a greater effect when subjects were younger than 50, via supplementation just with cardamom and more than 8 weeks, these effects were insignificant. Overall cardamom administration had a considerable effect on the serum insulin level. The finding of subgroup analysis according to the duration of supplementation, type of supplement, and mean age of participants showed that cardamom intake could decrease the level of serum insulin when the duration of treatment was more than 8 weeks in comparison to less than 8 weeks. In addition, cardamom exclusively had a significant effect on

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insulin compared with cardamom with other ingredients; in addition, cardamom was more effective when the mean age of patients was under 50. However, it did not have any remarkable effect on weight. But, analysis based on the duration of treatment, type of supplement, and mean age of participants indicated that supplementation exclusively with cardamom for more than 8 weeks' in patients above 50 was more helpful in weight management. Based on the findings of the included studies, cardamom consumption did not have any substantial effect on BMI. Subgroup analysis revealed that cardamom had a more significant impact on BMI when supplementation was conducted for more than 8 weeks compared to less than 8 weeks. Additionally, cardamom was more effective than the combination of cardamom with other ingredients in patients younger than 50 years old compared to those aged 50 and older.

Negligible effect of cardamom on weight, BMI, and FBG in present study may be associated with different reasons including high heterogeneity among included studies to the quantity analysis, small number of studies in subgroup analysis which were conducted to eliminate heterogeneity among studies, mean of weight or BMI of participants in studies which were not very high (Aghasi *et al.*, 2019, Azimi *et al.*, 2014, Kazemi *et al.*, 2017), administration cardamom in combination with other substances in some studies (Azimi *et al.*, 2014, Azimi *et al.*, 2016, Li *et al.*, 2017), and studies that have been performed on samples with different disease (Azimi *et al.*, 2016, Daneshi-Maskooni *et al.*, 2018, Kazemi *et al.*, 2017). The contradictions among all the mentioned causes hinder the ability to make a definitive decision.

Obesity is a condition in the body in which adipose tissues are incremented and is considered an increase in body weight and accumulation of excessive fat (Fernández-Sánchez *et al.*, 2011). Given that metabolism energy expenditure reduces along with aging, aging is considered a risk factor for obesity (Ebrahimzadeh Attari *et al.*, 2018, Geisler and Müller, 2017), which may due to the cardamom supplementation being more effective in older patients. Most studies lasting more than 8 weeks that administered only cardamom for supplementation highlight its beneficial effects related to the type of intervention.

Polyphenols improved weight and glycemic control throughout the activation of SIRT-1; in fact, polyphenolic compounds elevated SIRT-1 expression (Chaudhary and Pfluger, 2009, Chung *et al.*, 2010). SIRT-1 belongs to a family of highly conserved nicotinamide adenine dinucleotide (NAD^+)-dependent enzymes with deacetylate residues of acetylated lysine (Coppari, 2012). The findings of this study showed that cardamom intake did not have any significant effects on body weight but 3 out of 5 studies reported a decreasing trend in body weight (Aghasi *et al.*, 2019, Azimi *et al.*, 2016, Daneshi-Maskooni *et al.*, 2019). SIRT-1 contributes to weight control by regulating peroxisome proliferator-activated receptor gamma (PPAR-γ) and adipogenesis (Kitada and Koya, 2013). Furthermore, a critical stage in the activation of mitochondrial fatty acid oxidation is PGC-1-a deacetylation by Sirt-1 (Chaudhary and Pfluger, 2009). SIRT-1 also contributes to glucose homeostasis by a different mechanism such as SIRT-1 downregulates mitochondrial uncoupling proteins-2 (UCP-2) and deacetylates the FOXO transcription factors stimulate insulin secretion, protects from pancreatic β-cells against oxidative stress, release adiponectin and regulation of hepatic gluconeogenesis (Chaudhary and Pfluger, 2009, Kitada and Koya, 2013).

There are some limitations in the present systematic meta-analysis. First, the protocol of the present study did not register in PROSPERO due to we didn't report it in the text. Second, included studies in the current systematic meta-analysis were different in terms of target populations, type of supplement (exclusive cardamom *vs.* combination of cardamom with other substance) and duration of treatment; however, the authors tried to minimize heterogeneity via subgroup analysis. Third, they could not perform an analysis on the effects of cardamom intake on hemoglobin A1c because the included studies have not reported this variable; so, it is proposed that future studies evaluate the effects of cardamom intake on hemoglobin A1c. Fourth, all

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the included clinical trials were carried out in Iran; therefore, the authors could not generalize the results of this meta-analysis worldwide, although statistical analysis did not show publication bias for included studies. Finally, despite that subgroup analysis, the authors could not find a source of heterogeneity in the analysis of results of the insulin. The present systematic meta-analysis had several strengths and was an updated systematic meta-analysis that included new trials to the analysis and considered all sources of heterogeneity for a better decision. Furthermore, based on the Cochrane collaboration's tool, overall quality of all the included studies were good.

Conclusion

According to the findings of the present meta-analysis, cardamom intake might improve insulin levels but did not have any effects on weight, BMI, and FBG. It seems that further investigations with various dosages of cardamom, intervention period, nationality, and indicators need to decide about the potential effects of cardamom intake on weight reduction and glucose hemostasis; therefore' according to the results of this systematic meta-analysis cardamom intake is not recommended for glycemic control and weight management.

Authors' contributions

O Nikpayam, G Sohrab, and M Najafi were involved in data curation. O Nikpayam and Najafi M conducted formal analysis. O Nikpayam, A Ostadrahimi designed the methodology and supervised the work. Nikpayam O, G Sohrab, and M Najafi wrote the original draft. All authors finally read the manuscript and approved it for publishing.

Conflict of interests

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