Lead Article

Clinical evidence on dietary supplementation with chia seed (*Salvia hispanica* L.): a systematic review and meta-analysis

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Context: *Chia seed is a popular dietary supplement, taken mainly for its high content of alpha-linolenic acid, vegetable protein, and dietary fiber, yet information about its clinical effects is lacking.* ***Objective:*** *This review aims to summarize the clinical evidence regarding the use of chia seed for a wide variety of health conditions.* ***Data Sources:*** *A number of databases, including PubMed and Embase, were searched systematically.* ***Study Selection:*** *Randomized controlled trials that assessed the clinical effects of chia seed consumption in human participants were included. The quality of trials was assessed using the Cochrane Risk of Bias Tool.* ***Data Extraction:*** *Data on study design, blinding status, characteristics of participants, chia seed intervention, comparator, clinical assessment, duration of intake, interval of assessment, and study funding status were extracted. Meta-analysis was performed.* ***Results:*** *Twelve trials were included. Participants included healthy persons, athletes, diabetic patients, and individuals with metabolic syndrome. Pooling of results showed no significant differences except for the following findings of subgroup analysis at higher doses of chia seed: (1) lower postprandial blood glucose level (mean difference [MD] of −33.95 incremental area under the curve [iAUC] [mmol/L × 2 h] [95%CI, −61.85, −6.05] and −51.60 iAUC [mmol/L × 2 h] [95%CI, −79.64, −23.56] at medium doses and high doses, respectively); (2) lower high-density lipoprotein in serum (MD of −0.10 mmol/L [95%CI, −0.20, −0.01]); and (3) lower diastolic blood pressure (MD of −7.14 mmHg [95%CI, −11.08, −3.19]). The quality of all evidence assessed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach was low or very low. All trials employed only surrogate markers as outcomes.* ***Conclusions:*** *Future trials with improved methodological quality, well-described clinical events, and validated surrogate markers as outcomes are needed to support the potential health benefits of chia seed consumption.* ***Systematic Review Registration:*** *PROSPERO registration no. CRD42015029990.*

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INTRODUCTION

Chia seed, or *Salvia hispanica* L., is the seed of a summer herbaceous plant belonging to the Lamiaceae (mint) family.[1,2] The use of chia seed can be traced back to the pre-Columbian era, when chia seed was not only consumed as a food but was also used as a medicine and as an offering to the Aztec gods.[1] Today, chia seed is popularly consumed as a functional food[3] in many different forms, including chia fresca (ie, chia seeds mixed with a beverage),[1] baked items, cereal bars, etc.[4] Salba chia, a white variety of chia seed,[5] has been used in several trials,[5–8] largely on the basis of its standardized nutritional composition.

Chia seed has become increasingly popular, mainly because of its high content of omega-3 (n-3) fatty acids, although it also contains higher amounts of protein, fiber, and antioxidants than other plants.[1] Levels of n-3 fatty acids, specifically alpha-linolenic acid, are commonly reported to be as high as 60%.[1,2] Despite popular health claims associated with chia seed, such as reduced risks of cardiovascular heart disease, cognitive decline, and cancer,[9,10] the mechanism of action of chia seed is unclear. It could be due to the activity of alpha-linolenic acid, which is physiologically converted to eicosapentaenoic acid and docosahexaenoic acid, both of which are known to optimize cell membrane structure, cell function, and cellular responses.[11,12] One clinical trial has shown that chia seed intake increased plasma eicosapentaenoic acid levels significantly,[5] which may represent a link between chia seed and its health benefits.

Two previous reviews[13,14] summarized the evidence on the effects of chia seed. One of these,[13] however, used very broad inclusion criteria (ie, all types of literature, including nonhuman studies and nonclinical trials, that reported any information on chia seed were included), while the other one[14] evaluated the effect of chia seed on cardiovascular risk factors only. In addition, neither review conducted a risk-of-bias assessment.[13] Notably, neither review had a meta-analysis component. Therefore, the objective of this systematic review was to gather and critically appraise all available evidence on the clinical effects of chia seed in all health conditions and to perform a meta-analysis to summarize the findings.

METHODS

This systematic review was performed in accordance with the principles outlined in the *Cochrane Handbook for Systematic Reviews of Interventions*[15] and is reported in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement (Table S1).[16]

Protocol and registration

The review protocol is registered with PROSPERO (no. CRD42015029990).

Data sources and search strategy

Electronic databases were searched for relevant articles published from inception to December 31, 2016. The databases included PubMed, Embase, AMED (Allied and Complementary Medicine), CINAHL (Cumulative Index to Nursing and Allied Health Literature) Plus, Cochrane Central, International Pharmaceutical Abstracts, SciELO (Scientific Electronic Library Online), Scopus, LILACS (Latin-American and Caribbean System on Health Sciences Information), Redalyc Red de Revistas Científicas de América Latina y El Caribe, España y Portugal), ProQuest Dissertations & Theses, the WHO Registry Network, and ClinicalTrials.gov. Keywords used were (chia OR salvia hispanica OR salba) AND trial. There was no language restriction. In addition, bibliographies of relevant articles were examined to identify potential studies not indexed in the aforementioned databases. Authors of relevant articles were asked if they were aware of other relevant published or unpublished studies.

Study selection

Studies were included if they were randomized controlled trials that evaluated clinical effects of chia seed. The randomized controlled trials included were those that used chia seed in the intervention group compared with at least 1 comparator (either placebo or an active comparator). The PICOS (Participants, Intervention, Comparators, Outcomes, Study Design) criteria are shown in Table 1. Studies were screened by 2 authors (S.L.T. and P.V.) independently. Initially, titles and abstracts of articles were screened to identify potentially relevant studies. Thereafter, articles were retrieved for full-text review of relevant studies.

Data extraction

Two authors (S.L.T. and P.V.) working independently used a standardized data extraction sheet to extract the characteristics and results of the trials. Any disagreement was resolved by discussion. Information on study design, blinding status, characteristics of participants, dose of chia seed, type of chia seed, comparators, clinical assessment, duration of intake, interval of assessment, and funding status was extracted.

The aspects of clinical assessment extracted included any type of clinical event (eg, cardiovascular events, cerebrovascular events, diabetic complications) and any

Table 1 **PICOS criteria for inclusion of studies**

Parameter	Inclusion criteria
Participants	All populations
Intervention	Any intervention in which chia seed was a single ingredient or was incorporated with other ingredients
Comparator	Any comparator/control that incorporated a nonintervention group
Outcomes	Primary outcomes: all clinical effects in all identified indications, including clinical events (eg, cardiovascular events, cerebrovascular events, diabetic complications) and surrogate markers (eg, blood cholesterol level for cardiovascular disease, blood sugar level for diabetes)Secondary outcomes: any adverse effect reported by participants
Study design	Randomized controlled trials

surrogate marker (eg, blood cholesterol level for cardiovascular disease, blood sugar level for diabetes). The clinical effect in any health setting (investigated using either clinical events or surrogate markers) was the primary outcome of interest. In addition, any adverse effect (eg, gastrointestinal disturbance) reported in the trials was considered the secondary outcome of interest.

Study quality assessment

The methodological quality of each trial was assessed by 2 authors (S.L.T. and P.V.) independently using the Cochrane Risk of Bias Tool.[15] The domains for methodological evaluation using the Risk of Bias Tool include sequence generation, allocation concealment, blinding of participants, personnel and outcome assessors, incomplete outcome data, selective outcome reporting (assessed by comparing reported results with outcomes listed in the Methods section), and other sources of bias.[15] The funding of the trials was assessed within the domain of "other sources of bias." Each trial was classified as having low risk (low risk of bias for all domains), high risk (high risk of bias for 1 or more domains), or unclear risk (unclear risk of bias for 1 or more key domains, given no high risk of bias in any domain).

Data analysis

To determine the clinical effect of chia seed on continuous outcomes, the results were expressed as mean differences (MDs) with 95%CIs. For any clinical assessment, the change in outcome from baseline was compared between the chia seed group and the comparator group. Any missing data was requested from the author directly. Data from trials were pooled in a meta-analysis by 2 authors (S.L.T. and P.V.) independently, using the inverse-variance method with a random-effects model.[17] Heterogeneity of the included trials was assessed using the chi-squared test and the I^2 test. For the chi-squared test, $P \leq 0.10$ indicated statistically significant heterogeneity.[15] An I^2 value of more than 50% indicated substantial heterogeneity.[15] In cases of substantial heterogeneity, subgroup analysis was performed to explore possible sources of heterogeneity.

In addition, subgroup analysis was conducted for trials with homogenous characteristics specified a priori. Specifically, to examine the effect when different doses of chia seed were used, all trials that used similar doses of chia seed were grouped together and compared between each subgroup of low, medium, and high doses of chia seed. Similarly, to examine the effect of chia seed on participants with different health conditions, trials that recruited participants with similar health conditions were grouped together and compared against trials that recruited healthy adults. When a different comparator was used, trials that used similar comparators were grouped together and compared against trials that used active and nonactive comparators. When different types of chia seed were used, trials that used similar types of chia seed were grouped together and compared against trials that used non-Salba chia seed and Salba chia seed. When different forms of chia seed were used, trials that used similar forms of chia seed were grouped together and compared against trials that used whole chia seed and ground chia seed. For the dosage of chia seed, trials were categorized according to the 2 trials[6,8] included in this review that categorized doses as follows: (1) low dose when consumption was less than or equal to 7 g of chia seed daily; (2) medium dose when consumption was more than 7 g to equal to 15 g of chia seed daily; and (3) high dose when consumption was greater than 15 g of chia seed daily. To assess publication bias, Egger's test[18] (when more than 10 trials were included in the meta-analysis) was conducted to calculate the significance level of funnel plot asymmetry, where $P < 0.10$ indicates significant funnel plot asymmetry.[19] The software used for data analysis was Stata version 12 (StataCorp; College Station, Texas, USA).

Quality of evidence

The overall quality of evidence was assessed independently by 2 authors (S.L.T. and N.M.L.) using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach,[20] which considers study design, risk of bias of individual trials, heterogeneity, directness of evidence, precision of effect estimates, and possibility of publication bias.[20] GRADEpro software version 3.6.1 (McMaster University; Hamilton, Ontario, Canada) was used to generate the summary of findings table. The overall quality of evidence ranged from high, to moderate, to low, to very low, where high quality indicates a high degree of certainty that the estimated effect lies close to the

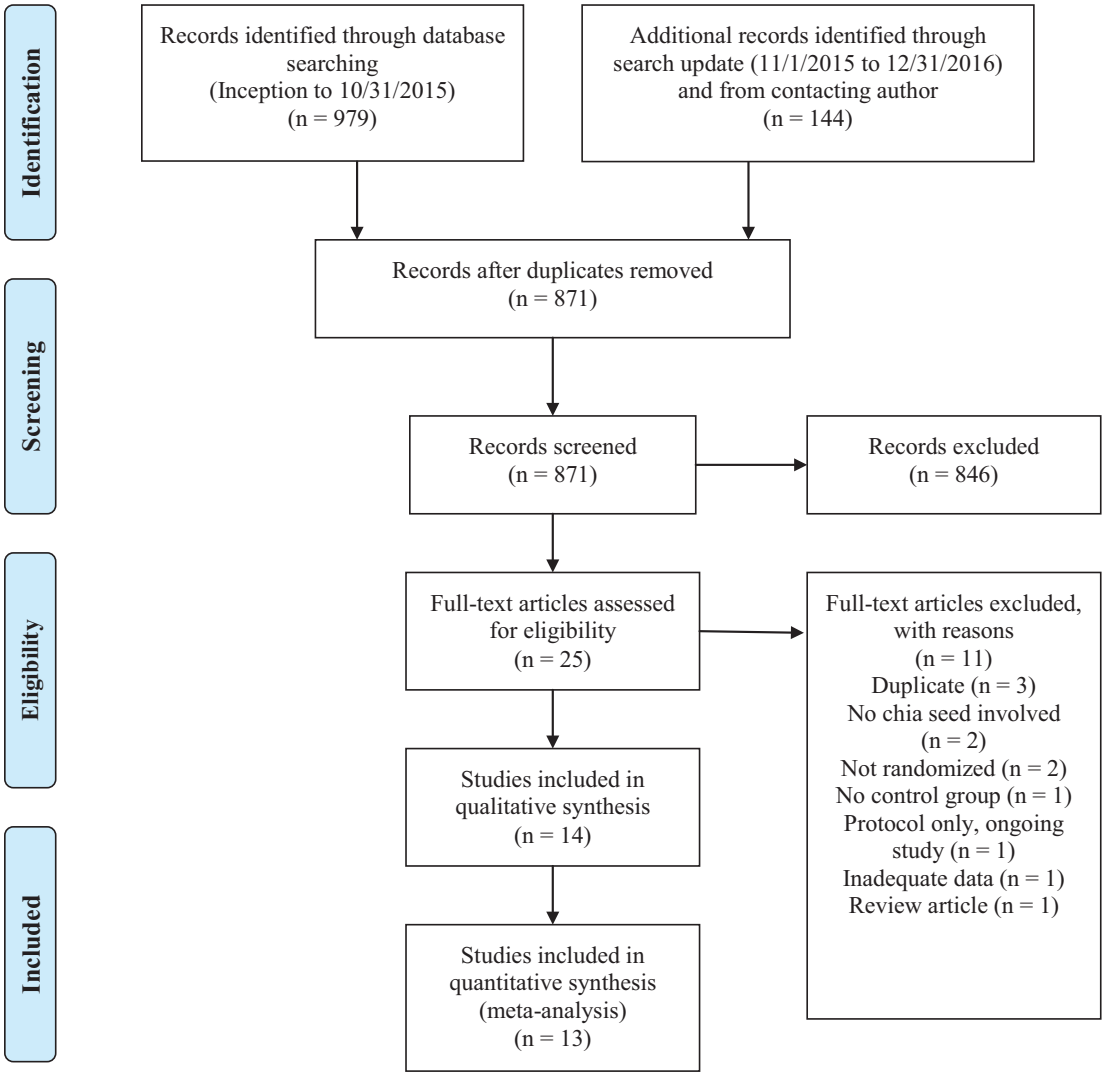

Figure 1 **Flow diagram of the literature search process.**

true effect, while very low quality indicates substantial uncertainty about the estimated effect.[21]

Sensitivity analysis

To ensure robustness of results, sensitivity analysis was performed by meta-analysis using a fixed-effects model when there was no heterogeneity[22] and by excluding the data of trials shown to be of low quality in the meta-analysis.

RESULTS

Study selection

The search yielded a total of 1123 articles: 1121 identified from electronic databases and 2 obtained by contacting the authors. A total of 252 duplicates were removed. Of the remaining 871 studies screened, only 25 were relevant and were retrieved for full-text review. Full-text review revealed only 14 studies that met the inclusion criteria. The 11 excluded studies were duplicates (n = 3) or a review article (n = 1), did not involve chia seed (n = 2), were not randomized (n = 2), did not have a comparator group (n = 1), described a protocol only (n = 1), or had inadequate information for data extraction (n = 1). Thus, 14 trials involving 526 participants were included in this review. One trial[23] that assessed the effects of chia seed only on the chia seed group was not included in the meta-analysis. The flow diagram of study selection is shown in Figure 1. The list of excluded studies is available in Table S2 in the Supporting Information online.

Study characteristics

The characteristics of the 14 included studies are summarized in Table 2.[5–8,23–32] The trials were conducted

Table 2 **Characteristics of the studies included in the systematic review**

Reference	Country of study	RCT design; blinding status (stated by author)	Characteristics of participants	Total no. of participants (ITT; completed trial)	Mean age (range) of participants	Form of CS and comparator used	Comparator; test conducted to check similarity between CS and comparator	Daily quantity of CS; diet control?	Duration of intake	Interval assessed	Washout period for crossover RCT
Vuksan et al (2007)[5]	Canada	Crossover; single-blinded	Stable type 2 diabetes (HbA1C, 6.0%–8.5%; fasting plasma glucose, 6.4–8.5 mmol/L	27; 20	64 y (18–75 y)	Ground form added to bread for both groups[a]	Wheat bran; no	37 g; yes	84 d	0, 14, 28, 42, 56, 70, and 84 d	28–42 d
Nieman et al (2009)[25]	USA	Parallel; single-blinded	No known disease; overweight or obese	90; 76	NR (20–70 y)	Whole form (with flavoring and sweetener) for CS group	Ground powder of concentrated soy, sunflower oil, carrot fiber, and tapioca starch; yes	50 g; yes	84 d	0, 14, 28, 42, 56, 70, and 84 d	NA
Vuksan et al (2010)[8]	Canada	Crossover; double-blinded	No known disease; normal BMI	11; 11	30 y (NR)	Whole form added onto white bread for CS group[a]	White bread only (no CS); no	7 g (low dose), 15 g (medium dose), 24 g (high dose); NR	1 d	0, 15, 30, 45, 60, 90, and 120 min	At least 2 d
Guevara-Cruz et al (2012)[30]	Mexico	Parallel; double-blinded	With metabolic syndrome; overweight or obese	97; 67	NR (20–60 y)	Dehydrated mixture for both groups	Calcium caseinate, maltodextrin, sweetener, and flavoring; yes	4 g of a 33-g mixture; yes	60 d	0 and 60 d	NA
Nieman (2012)[31]	USA	Parallel; double-blinded	No known disease; overweight or obese	62; 56	Whole CS group: 60.4 y (NR); ground CS group: 52.7 y; comparator group: 58.5 y (49–75 y)	Whole or ground form added to food or beverages for both groups	Poppy seed; no	25 g; yes	70 d	0 and 70 d	NA

(continued)

Table 2 **Continued**

Reference	Country of study	RCT design; blinding status (stated by author)	Characteristics of participants	Total no. of participants (ITT; completed trial)	Mean age (range) of participants	Form of CS and comparator used	Comparator; test conducted to check similarity between CS and comparator	Daily quantity of CS; diet control?	Duration of intake	Interval assessed	Washout period for crossover RCT
Brissette (2013)[24] and Vuksan et al (2017) (a)[32]	Canada	Parallel; double-blinded	Stable type 2 diabetes (HbA1C, 6.5%–8.0%); obese	78; 58	Intervention group: 60.0 y (NR); comparator group: 60.1 y (35–75 y)	Ground form sprinkled on bread (up to 2 slices daily) for both groups[a]	Oat bran, inulin, maltodextrin; no	7.5 g; yes	168 d	−28, 0, 14, 42, 84, 126, and 168 d	NA
Ho et al (2013)[6]	Canada	Crossover; NR	No known disease; overweight	13; 13	NR	Whole or ground form baked into bread for CS group[a]	White bread only (no CS); no	7 g (low dose), 15 g (intermediate dose), 24 g (high dose); NR	1 d	0, 15, 30, 45, 60, 90, and 120 min	At least 2 d
Toscano et al (2014)[28] and (2015)[29]¤	Brazil	Parallel; double-blinded	Risk factors for metabolic syndrome; overweight or obese	29; 26	Intervention group: 48.8 y; comparator group: 51.4 y (35–65 y)	Ground form added to food or drinks for both groups	Toasted wheat bran; no	25 g; yes	84 d	0, 28, 56, and 84 d	NA
Wu (2015)[23]	USA	Crossover; NR	No known disease; normal BMI	55; 23	21.43 y (18–45 y)	Whole form for CS group	No CS; no	15 g; yes	35 d	−7, 0, 7, 14, 21, 28, and 35 d	35 d
Nieman et al (2015)[26]	USA	Crossover; NR	Athletes; BMI NR	24; 24	38 y (24–55 y)	CS oil added to flavored water for CS group	Flavored water only (no CS oil); no	7 kcal/kg (or 103 g); NR	1 d	1 d	At least 14 d
Nieman & Meaney (2016)[27]	USA	Crossover; NR	Athletes; BMI NR	18; NR	34.9 y (NR)	Milled CS to be added into normal diet	No CS (normal diet); no	25 g; yes	14 d	14 d	NR
Vuksan et al (2017) (b)[7]	Canada	Crossover; NR	No known disease; normal BMI	22; 15	23.9 y (NR)	Ground CS dissolved in glucose water[a]	Glucose water or ground flax in glucose water; no	25 g; yes	1 d	0, 15, 30, 45, 60, 90, and 120 min	At least 4 d

Abbreviations: BMI, body mass index; CS, chia seed; ITT, intention-to-treat; NA, not applicable; NR, not reported; RCT, randomized controlled trial.
[a]Salba chia seed.

in Canada (n = 6),[5–8,24,32] the United States (n = 5),[23,25–27,31] Brazil (n = 2),[28,29] and Mexico (n = 1).[30] Half of the 14 trials[7,24,26,27,30–32] employed a parallel design, and the other half[5,6,8,23,25,28,29] employed a crossover design. Almost all crossover trials included a washout period, which ranged from 2 days[6,8] to 42 days,[5] though 1 trial[27] did not report on this.

Notably, 2 trials[23,24] were Master's theses. One trial[24] was later published[7] with some data that was available only in the thesis; therefore, both trials[7,24] were included. On a separate note, upon confirmation by the authors, 2 trials[28,29] included were essentially the same study with same group of participants, but they investigated different clinical assessments. One trial[28] reported the clinical effects in separate intervention groups (ie, intervention groups who took and who did not take antihypertensive medication), while the other trial[29] reported the effects only in 1 group that included a combination of those who took and those who did not take antihypertensive medication. The participants in the comparator group reported in both trials[28,29] all took antihypertensive medication. Therefore, to ensure comparability between groups, the comparison of clinical effects between intervention and comparator groups who took antihypertensive medication[28] was used as the main analysis if results of both trials[28,29] were available.

The total number of participants included in each trial was relatively small, ranging from 11 participants[8] to 97 participants.[32] Participants in the included trials ranged between 18 and 75 years of age, with the mean age being above 48 years (n = 6),[5,24,28,29,31,32] below 40 years (n = 5),[7,8,23,26,27] or not reported (n = 3).[6,25,30] None of the trials assessed the effects of chia seed in children. The participants recruited were generally healthy, having no known disease in 6 trials,[6–8,23,25,31] type 2 diabetes with a stable glycemic condition in 3 trials,[5,24,32] and risk factors for metabolic syndrome in 3 trials.[28–30] In 2 trials,[26,27] the participants were athletes.

The most common form of chia seed used in the intervention group was chia seed incorporated into food or drink, used in 10 trials,[5–8,24,27–29,31,32] followed by chia seed taken on its own in 2 trials,[23,25] a dehydrated mixture of chia seed and nopal, oat, and soybean protein in 1 trial,[30] and chia seed oil added to water in 1 trial.[26] Notably, 6 trials[5–8,24,32] used Salba chia seed. The daily quantity of chia seed consumed ranged from 4 g to 50 g in 13 trials,[5–8,24–32] though 1 trial[26] used calories as the unit of measurement, ie, 7 kcal/kg.[26] To enable comparability, the measurement was converted to grams using the US Department of Agriculture's estimation of 486 kcal per 100 g of chia seed[33] and the mean weight reported in the trial,[26] resulting in a daily quantity of 103 g of chia seed.[26] Complete details of chia seed and the comparators used are summarized in Table 2.

All of the included trials assessed outcomes on surrogate markers only and not on any type of clinical event. The most commonly assessed outcomes were glycemic measures (n = 10),[5–8,24,25,28,29,30,32] anthropometric measures (n = 9),[5,23,24,26,28–32] markers of inflammation (n = 7),[5,24–26,28,30,31] lipids (n = 6),[5,24,25,28,30,31] and blood pressure (n = 6),[5,24,25,28,30,31] followed by markers of liver and renal function,[5,24,32] measures of athletic performance,[26,27] and others, including markers related to hemostasis,[24,32] appetite,[7,8] satiety or glucose-regulating hormone,[7,24,30] cortisol,[26] oxidative stress,[28] and nitric oxide.[28] Trials that assessed outcomes related to athletic performance used shorter durations of chia seed intake of 2 days[26] and 14 days.[27] The other 3 trials[6–8] used a 1-day duration of chia seed intake and assessed postprandial blood glucose every 15 minutes up to 60 minutes, followed by assessment every 30 minutes up to 120 minutes. The remaining trials used a longer duration of intake that ranged from 35 days[23] to 168 days[24,32] for other outcome assessments. In the majority of trials (n = 11),[5,7,23–25,27–32] participants were instructed to control their diet during the trial, while 3 trials[6,8,26] did not report whether participants were instructed to control their diet.

Study quality assessment

Most of the trials (n = 11)[5–8,23,24,28–32] were found to have an overall unclear risk of bias, and 2 trials had a high risk of bias.[25,26] One trial[27] was available only as a conference abstract and therefore did not have sufficient information for quality assessment. Consequently, it was assessed to have an unclear risk of bias in this review.

For the sequence generation domain, more than half of the trials (n = 8)[5–7,24,26,28,29,32] were found to have a low risk of bias with an appropriate randomization method. Five trials[8,23,25,30,31] had an unclear risk of bias and lacked a description of the randomization method, even though "randomized" was described. For allocation concealment, half of the trials (n = 7)[6–8,23,25,26,30] had an unclear risk of bias because they did not provide adequate information. Six trials[5,24,28,29,31,32] concealed the allocation sequence using an appropriate method and had a low risk of bias. For the blinding domain, all trials were found to have either an unclear or a high risk of bias. Of the 11 trials with an unclear risk of bias,[5–8,23,24,28–32] 6 trials[6,8,23,28,29,31] mentioned "double-blind" but provided no description of the method. Although the other 5 trials[5,7,24,30,32] endeavored to ensure both the appearance and the taste of

Table 3 **Risk-of-bias assessment of trials included in the systematic review**

Reference	Sequence generation	Allocation concealment	Blinding	Incomplete outcome data	Selective reporting	Other sources of bias	Overall
Vuksan et al (2007)[5]	Low	Low	Unclear	Low	Low	Unclear	Unclear
Nieman et al (2009)[25]	Unclear	Unclear	High	Low	Low	Unclear	High
Vuksan et al (2010)[8]	Unclear	Unclear	Unclear	Low	Low	Low	Unclear
Guevara-Cruz et al (2012)[30]	Unclear	Unclear	Unclear	Low	Low	Low	Unclear
Nieman et al (2012)[31]	Unclear	Low	Unclear	Low	Low	Low	Unclear
Brissette (2013)[24] and Vuksan et al (2017) (a)[32]	Low	Low	Unclear	Low	Low	Low	Unclear
Ho et al (2013)[6]	Low	Unclear	Unclear	Low	Low	Unclear	Unclear
Toscano et al (2014)[28] and (2015)[29,a]	Low	Low	Unclear	Low	Low	Low	Unclear
Wu (2015)[23]	Unclear	Unclear	Unclear	Low	Low	Unclear	Unclear
Nieman et al (2015)[26]	Low	Unclear	High	Unclear	Low	Unclear	High
Nieman & Meaney (2016)[27]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Vuksan et al (2017) (b)[7]	Low	Unclear	Unclear	Low	Low	Unclear	Unclear

[a]Based on the latest studies.

chia seed and the comparator were the same, there was no test to clarify whether the blinding was successful. Two trials[25,26] had a high risk of bias: 1 of these[26] described "no blinding" and the other[25] described that the blinding was highly likely broken. For the incomplete outcome data domain, almost all of the trials assessed (n = 12)[5–8,23–25,28–32] had adequately reported the reason for withdrawals or dropouts from the trials. The other trial[26] had no description about the withdrawals or dropouts and thus had an unclear risk of bias. As for the selective reporting domain, all trials reported all the prespecified outcomes.

For the other sources of bias domain, half of the trials had a low risk of bias and the other half had an unclear risk of bias. Of the trials with a low risk of bias, 5 trials[8,28–31] were not funded and declared no conflict of interest, and another 2 trials[24,32] were funded by a Canadian Diabetes Association operating grant, which was not considered to have introduced bias. Of the trials with an unclear risk of bias, 2 trials[5,23] did not describe the funding, 1 trial[25] was funded by market research and a nonprofit research institute (ie, Nutritional Science Research Institute, Marlborough, Massachusetts, USA), 2 trials were funded by chia seed companies that included the Dole Food Company (Westlake Village, California, USA)[26] and Salba Smart Natural Products (Littleton, Colorado, USA),[6] and 1 trial used an employee of a chia seed company to assist in the manuscript preparation.[7] The risk-of-bias assessment of the included trials is summarized in Table 3,[5–8,23–32] with further details provided in Table S3 in the Supporting Information online.

Clinical effects of chia seed

Anthropometric outcomes. There were no significant differences in any of the anthropometric parameters between participants who received chia seed and the control group, except for gynoid fat. These included pooled MDs for the following: (1) body weight, 0.07 kg (95%CI, −0.18 to 0.31; 5 trials; GRADE low),[5,29–32] (2) body fat mass, −0.07% (95%CI, −1.91 to 1.78; 4 trials; GRADE low),[29–32] (3) body mass index, 0.04 kg/m^2 (95%CI, −1.58 to 1.66; 2 trials; GRADE low),[28,30] and (4) waist circumference, −1.21 cm (95%CI, −4.16 to 1.74; 3 trials; GRADE low),[28,30,32] all with no heterogeneity ($I^2 = 0.0\%$, $P > 0.10$). The effects on hip circumference and android fat were not significant, with an MD of −2.90 cm (95%CI, −7.36 to 1.56; 1 trial; GRADE low)[24] and −0.18% (95%CI, −4.82 to 1.22; 1 trial; GRADE low),[32] respectively, while the effect on gynoid fat was significant, with an MD of −5.20% (95%CI, −10.24 to −0.16; 1 trial; GRADE low),[32] with all effects assessed by single trials. The effect estimates are summarized in Table 4,[5–8,24–32] and forest plots are shown in Figure S1 in the Supporting Information online. Subgroup analysis showed that the lack of statistical significance in all anthropometric parameters remained unchanged (Table 5[5–8,24–26,28–32]). However, participants who were overweight/obese appeared to have a nonsignificantly higher body weight gain and a nonsignificantly higher body fat mass gain compared with those with health conditions who were also overweight/obese (Table 5). In addition, participants who took ground chia seed appeared to have nonsignificantly less body weight gain and more body fat reduction compared with those who took whole chia seed. However this finding was based only on the effect reported in 1 trial that recruited overweight/obese participants and used whole chia seed.[27] Details of the GRADE quality of evidence are shown in Table 6. Forest plots of subgroup analyses are provided in Figure S2 in the Supporting Information online.

Glycemic outcomes. There were no significant differences in any of the glycemic parameters between

Table 4 **Summary of effect estimates of chia seed for all indications**

Outcome category	Outcome (unit of measurement)	References	Mean difference (95%CI)[a]
Anthropometric	Body weight (kg)	Vuksan et al (2007)[5] Guevara-Cruz (2012)[30] Toscano et al (2015)[29,b] Nieman et al (2012)[31,c] Vuksan et al (2017) (a)[32]	**0.07 (−0.18, 0.31)** **I^2 = 0.0%, P = 0.991**
	Body fat mass (%)	Guevara-Cruz (2012)[30] Nieman et al (2012)[31,c] Toscano et al (2015)[29,b] Vuksan et al (2017) (a)[32]	**−0.07 (−1.91, 1.78)** **I^2 = 0.0%, P = 0.457**
	Body mass index (kg/m^2)	Guevara-Cruz (2012)[30] Toscano et al (2014)[28,d]	**0.04 (−1.58, 1.66)** **I^2 = 0.0%, P = 0.868**
	Waist circumference (cm)	Guevara-Cruz (2012)[30] Toscano et al (2014)[28,d] Vuksan et al (2017) (a)[32]	**−1.21 (−4.16, 1.74)** **I^2 = 0.0%, P = 0.472**
	Hip circumference (cm)	Brissette (2013)[24]	−2.90 (−7.36, 1.56)
	Android fat (%)	Vuksan et al (2017) (a)[32]	−1.80 (−4.82, 1.22)
	Gynoid fat (%)	Vuksan et al (2017) (a)[32]	−5.20 (−10.24, −0.16)[e]
Glycemic	HbA1c (%)	Vuksan et al (2007)[5] Vuksan et al (2017) (a)[32]	**0.02 (−0.37, 0.41)** **I^2 = 16.9%, P = 0.273**
	Fasting blood glucose (mmol/L)	Vuksan et al (2007)[5] Nieman et al (2009)[25] Guevara-Cruz et al (2012)[30] Nieman et al (2012)[31,c] Toscano et al (2014)[28,d] Vuksan et al (2017) (a)[32]	**(−0.15, 0.18)** **I^2 = 0.0%, P = 0.819**
	Fasting blood insulin (pmol/L)	Vuksan et al (2007)[5] Guevara-Cruz et al (2012)[30] Brissette (2013)[24]	**4.63 (−9.88, 19.13)** **I^2 = 0.0%, P = 0.734**
	Postprandial blood glucose (iAUC [min × mmol/L, total of 2 h])	Vuksan et al (2010)[8] (high dose) Guevara-Cruz et al (2012)[30] (low dose) Ho et al (2013)[6] (high dose) Vuksan et al (2017) (b)[7] (high dose)	**−24.10 (−53.08, 4.87)** **I^2=67.9%, P =0.025**
Inflammation	C-reactive protein (mg/L)	Vuksan et al (2007)[5] Guevara-Cruz et al (2012)[30] Nieman et al (2012)[31,c] Toscano et al (2014)[28,d] Vuksan et al (2017) (a)[32]	**−0.61 (−1.36, 0.14)** **I^2 = 0.0%, P = 0.913**
	Interleukin 6 (pg/mL)	Nieman et al (2009)[25] Nieman et al (2012)[31,c] Nieman et al (2015)[26]	**<0.001 (−0.01, 0.02)** **I^2 = 0.0%, P = 0.876**
	Interleukin 8 (pg/mL)	Nieman et al (2012)[31,c] Nieman et al (2015)[26]	**−0.73 (−2.57, 1.10)** **$I2$=0.0%, P = 0.677**
	Interleukin 10 (pg/mL)	Nieman et al (2012)[31,c] Nieman et al (2015)[26]	**−0.28 (−2.23, 1.66)** **$I2$=0.0%, P = 0.812**
	TNF-α (pg/mL)	Nieman et al (2009)[25] Nieman et al (2012)[31,c] Nieman et al (2015)[26]	**<0.001 (<−0.001, 0.01)** **I^2 = 0.0%, P = 0.452**
	von Willebrand factor (IU/mL)	Vuksan et al (2007)[5] Brissette (2013)[24]	**−0.09 (−0.32, 0.14)** **I^2 = 25.2%, P = 0.247**
	Acid glycoprotein (mg/dL)	Toscano et al (2014)[28,d]	2.00 (−10.47, 14.47)
	Factor VIII (IU/mL)	Vuksan et al (2007)[5]	−0.21 (−0.46, 0.04)
	Fibrinogen (g/L)	Vuksan et al (2007)[5]	−0.26 (−0.69, 0.17)
	Leukocytes (10^9/L)	Nieman et al (2015)[26]	−0.180 (−2.401, 2.041)
	Plasma monocyte chemotactic protein (pg/mL)	Nieman et al (2009)[25]	0.04 (−0.05, 0.13)

(continued)

Table 4 **Continued**

Outcome category	Outcome (unit of measurement)	References	Mean difference (95%CI)[a]
Lipid	Total cholesterol (mmol/L)	Vuksan et al (2007)[5]	**−0.07 (−0.30, 0.15)**
		Nieman et al (2009)[25]	**I^2 = 0.0%, P = 0.773**
		Guevara-Cruz et al (2012)[30]	
		Nieman et al (2012)[31,c]	
		Brissette (2013)[24]	
		Toscano et al (2014)[28,d]	
	Low-density lipoprotein (mmol/L)	Vuksan et al (2007)[5]	**−0.01 (−0.24, 0.21)**
		Nieman et al (2009)[25]	**I^2 = 0.0%, P = 0.879**
		Guevara-Cruz et al (2012)[30]	
		Brissette (2013)[24]	
		Toscano et al (2014)[28,d]	
	High-density lipoprotein (mmol/L)	Vuksan et al (2007)[5]	**−0.05 (−0.11, 0.02)**
		Nieman et al (2009)[25]	**I^2 = 11.7%, P = 0.339**
		Guevara-Cruz et al (2012)[30]	
		Brissette (2013)[24]	
		Toscano et al (2014)[28,d]	
	Triglyceride (mmol/L)	Vuksan et al (2007)[5]	**−0.08 (−0.32, 0.17)**
		Nieman et al (2009)[25]	**I^2 = 4.1%, P = 0.384**
		Guevara-Cruz et al (2012)[30]	
		Brissette (2013)[24]	
		Toscano et al (2014)[28,d]	
	Very low-density lipoprotein (mg/dL)	Toscano et al (2014)[28,d]	−2.00 (−22.25, 18.25)
Blood pressure	Diastolic blood pressure (mmHg)	Vuksan et al (2007)[5]	**−3.37 (−7.43, 0.70)**
		Guevara-Cruz et al (2012)[30]	**I^2 = 64.8%, P = 0.036**
		Brissette (2013)[24]	
		Toscano et al (2014)[28,d]	
	Systolic blood pressure (mmHg)	Vuksan et al (2007)[5]	**−2.57 (−6.70, 1.55)**
		Nieman et al (2009)[25]	**I^2 = 38.3%, P = 0.151**
		Guevara-Cruz et al (2012)[30]	
		Nieman et al (2012)[31,c]	
		Brissette (2013)[24]	
		Toscano et al (2014)[28,d]	
Liver	Aspartate aminotransferase (U/L)	Vuksan et al (2007)[5]	**−0.10 (−3.29, 3.08)**
		Brissette (2013)[24]	**I^2 = 0.0%, P = 0.828**
	Alanine aminotransferase (U/L)	Vuksan et al (2007)[5]	**3.39 (−1.82, 8.60)**
		Vuksan et al (2017) (a)[32]	**I^2 = 20.2%, P = 0.263**
	Alkaline phosphatase (U/L)	Brissette (2013)[24]	−0.20 (−11.17, 10.77)
Renal	Creatinine (μmol/L)	Vuksan et al (2007)[5]	**−1.37 (−7.42, 4.69)**
		Vuksan et al (2017) (a)[32]	**I^2 = 0.0%, P = 0.989**
	Blood urea nitrogen (mmol/L)	Vuksan et al (2007)[5]	**−0.28 (−1.30, 0.74)**
		Vuksan et al (2017) (a)[32]	**I^2 = 54.9%, P = 0.137**
Athletic performance	Time to exhaustion (min)	Nieman et al (2015)[26]	−3.00 (−13.54, 7.54)
	Distance to exhaustion (km)	Nieman et al (2015)[26]	−0.60 (−2.23, 1.03)
	Volume of oxygen consumption (mL/[kg × min])	Nieman et al (2015)[26]	0.30 (−0.42, 1.02)
	Heart rate (beats/min)	Nieman et al (2015)[26]	−2.00 (−3.61, −0.39)[e]
	Ventilation (L/min)	Nieman et al (2015)[26]	1.20 (−1.15, 3.55)
	Rating of perceived exertion (NR)	Nieman et al (2015)[26]	0.20 (−0.31, 0.71)
	Respiratory exchange ratio (NA)	Nieman et al (2015)[26]	0.00 (0.00, 0.00)
	Plasma volume shift (%)	Nieman et al (2015)[26]	2.10 (−1.07, 5.27)
	Lactate (mmol/L)	Nieman et al (2015)[26]	−0.15 (−0.49, 0.19)
	Glucose (mmol/L)	Nieman et al (2015)[26]	−0.24 (−0.80, 0.32)
	Time to complete 15-km trial (min)	Nieman & Meaney (2016)[27]	0.02 (−1.02, 1.06)
	Average power output (watts)	Nieman & Meaney (2016)[27]	4.00 (−12.81, 20.81)
Hemostasis	Activated partial thromboplastin time (s)	Brissette (2013)[24]	−0.30 (−1.77, 1.17)
	Prothrombin time (s)	Vuksan et al (2017) (a)[32]	−0.30 (−0.58, −0.02)[e]
	International normalized ratio (no unit)	Brissette (2013)[24]	< 0.001 (−0.03, 0.03)

(continued)

Table 4 **Continued**

Outcome category	Outcome (unit of measurement)	References	Mean difference (95%CI)[a]
Appetite	100 mm visual analog scale (appetite rating) (iAUC [(min × mm, total of 2 h])	Vuksan et al (2010)[8] (low dose)	< −0.001 (< −0.001, 518.94)
		Vuksan et al (2010)[8] (medium dose)	< −0.001 (< −0.001, 240.44)
		Vuksan et al (2010)[8] (high dose)	< −0.001 (< −0.001, −2.98)[e]
	100 mm visual analog scale (appetite rating) (mm)	Vuksan et al (2017) (b)[7] (nonactive comparator ["without chia seed"])	−13.00 (−26.86, 0.86)
		Vuksan et al (2017) (b)[7] (active comparator [flax seed])	−6.00 (−19.86, 7.86)
Satiety/glucose regulation	Leptin (μg/L)	Guevara-Cruz et al (2012)[30]	−2.20 (−9.25, 4.85)
	Adiponectin (mg/L)	Guevara-Cruz et al (2012)[30]	**< 0.001 (< −0.001, < 0.001)**
		Vuksan et al (2017) (a)[32]	**I^2=0.0%, P = 0.795**
	Ghrelin (pg/mL)	Vuksan et al (2017) (a)[32]	−211.40 (−361.83, −60.97)[e]
	Peptide tyrosine tyrosine (pg/mL)	Brissette (2013)[24]	−5.10 (−31.56, 21.36)
Oxidative stress	Malondialdehyde (μmol/L)	Toscano et al (2014)[28,d]	0.40 (−0.99, 1.79)
Other	Cortisol (nmol/L)	Nieman et al (2015)[26]	61.00 (−1.31, 123.31)
	Nitrite (μmol/L)	Toscano et al (2014)[28,d]	−6.20 (−19.56, 7.16)

Abbreviations: NA, not applicable NR; not reported.
[a]Boldface estimates are pooled estimates, while non-boldface estimates are from a single trial.
[b]Result for intervention group combined with results for participants who took and who did not take antihypertensive medication (as the separated result was not available).
[c]Result for intervention group for whole chia seed only (excluding participants who took ground chia seed) to maximize comparability.
[d]Result for intervention group participants who took antihypertensive medication.
[e]Result showing a significant difference between chia seed group and comparator group.

participants who received chia seed and the control group. These included pooled MDs for the following: (1) glycated hemoglobin (HbA1c), 0.02% (95%CI, −0.37 to 0.41; 2 trials; GRADE low),[5,32] (2) fasting blood glucose, 0.01 mmol/L (95%CI, −0.15 to 0.17; 6 trials; GRADE low),[5,25,28,30–32] and (3) fasting blood insulin, 4.63 pmol/L (95%CI, −9.88 to 19.13; 3 trials; GRADE low),[5,24,30] all with no or minimal heterogeneity ($I^2 = 0.0\%$, $P > 0.10$). Postprandial blood glucose was also nonsignificantly different, with a pooled MD of −24.10 incremental area under the curve (iAUC) (mmol/L × 2 h) (95%CI, −53.08 to 4.87; 4 trials; $I^2 = 67.9\%$, P =0.025; GRADE very low).[6–8,30] Of all the subgroup analyses, the one assessing the reduction of postprandial blood glucose was found to be significantly different for the following: (1) high and medium doses of chia seed, (2) participants with a healthy body mass index, and (3) Salba chia seed (Table 5). Moreover, 2 additional subgroup analyses were conducted on postprandial blood glucose for trials using diet control[7,30] or not[6,8] and for trials using different times of assessment.[6–8,30] The reduction in postprandial blood glucose was not significant for trials that did not report whether the participants' diet was controlled or not[6,8] as well as for trials that reported controlled diets.[7,30] However, the reduction in postprandial blood glucose was significant for trials that assessed the effect within the same day (−38.15 iAUC [mmol/L × 2 h]; 95%CI, −74.37 to −1.93; $I^2 = 46.6\%$, P=0.154)[6–8] compared with the trial that assessed postprandial blood glucose 60 days after the consumption of chia seed.[30]

Markers of inflammation. There were no significant differences in any of the markers of inflammation between participants who received chia seed and the control group. These included pooled MDs with no heterogeneity ($I^2 = 0\%$, $P > 0.10$) for the following: (1) C-reactive protein, −0.61 mg/L (95%CI, −1.36 to 0.14; 5 trials; GRADE low),[5,28,30–32] (2) interleukin 6: < 0.001 pg/mL (95%CI, −0.01 to 0.02; 3 trials; GRADE low),[25,26,31] (3) interleukin 8: −0.73 pg/mL (95%CI, −2.57 to 1.10; 2 trials; GRADE low),[26,31] (4) interleukin 10, −0.28 pg/mL (95%CI, −2.23 to 1.66; 2 trials; GRADE low),[26,31] and (5) tumor necrosis factor α, < 0.001 pg/mL (95%CI, < −0.001 to 0.01; 3 trials; GRADE low).[25,26,31] The pooled MD was also not significant for von Willebrand factor: −0.09 IU/mL (95%CI, −0.32 to 0.14; 2 trials; GRADE low),[5,24] with minimal heterogeneity of $I^2 = 25.2\%$, $P = 0.247$. Other MDs of inflammatory markers, including acid glycoprotein, factor VIII, fibrinogen, leukocytes, and plasma monocyte chemotactic protein, reported by single trials were all not significant and were assessed as GRADE low (Table 4). The lack of statistical significance remained unchanged in subgroup analysis (Table 5). The additional subgroup analysis on diet control during the trials also did not

Table 5 **Subgroup analyses of the effects of chia seed**

Outcome (unit of measurement)	Mean difference (95%CI)[a]										
	Main analysis	Subgroup analysis 1: chia seed dose		Subgroup analysis 2: participants' health status		Subgroup analysis 3: comparator		Subgroup analysis 4: type of chia seed		Subgroup analysis 5: chia seed form	
Anthropometric											
Body weight (kg)	**0.07 (−0.18 to 0.31) I^2 = 0.0%, P = 0.991 (5 trials)**[5,29–32]	High	**0.07 (−0.17 to 0.32) I^2 = 0.0%, P = 0.975 (3 trials)**[5,29,31]	With health condition; overweight/obese	**0.07 (−0.18 to 0.31) I^2 = 0.0%, P = 0.970 (4 trials)**[5,29,30,32]	Active	**0.07 (−0.18 to 0.31) I^2 = 0.0%, P = 0.964 (4 trials)**[5,29,31,32]	Salba	0.07 (−0.18 to 0.31) I^2 = 0.0%, P = 0.636 (2 trials)[5,32]	Whole	1.00 (−8.92 to 10.92) (1 trial)[31]
		Medium	−1.60 (−8.50 to 5.30) (1 trial)[32]	Healthy; overweight/obese	1.00 (−8.92 to 10.92) (1 trial)[31]	Nonactive	0.10 (−6.25 to 6.05) (1 trial)[30]	Non-Salba	0.07 (−4.83 to 4.98) I^2 = 0.0%, P = 0.973 (3 trials)[29–31]	Ground	**0.07 (−0.18 to 0.31) I^2 = 0.0%, P = 0.970 (4 trials)**[5,29,32]
		Low	−0.10 (−6.25 to 6.05) (1 trial)[30]	Athletes; BMI NR	NA					Unspecified	−0.10 (−6.25 to 6.05) (1 trial)[30]
Body fat mass (%)	**−0.07 (−1.91 to 1.78) I^2 = 0.0%, P = 0.457 (4 trials)**[29–32]	High	**0.32 (−3.21 to 3.86) I^2 = 0.0%, P = 0.581 (2 trials)**[29,31]	With health condition; overweight/obese	**−0.49 (−2.88 to 1.90) I^2 = 14.2%, P = 0.312 (3 trials)**[29,30,32]	Active	**−1.04 (−3.72 to 1.65) I^2 = 0.0%, P = 0.437 (3 trials)**[29,31,32]	Salba	−2.90 (−7.03 to 1.23) (1 trial)[32]	Whole	0.90 (−3.18 to 4.98) (1 trial)[31]
		Medium	−2.90 (−7.03 to 1.23) (1 trial)[32]	Healthy; overweight/obese	0.90 (−3.18 to 4.98) (1 trial)[31]	Nonactive	0.80 (−1.74 to 3.34) (1 trial)[30]	Non-Salba	**0.64 (−1.43 to 2.70) I^2 = 0.0%, P = 0.839 (3 trials)**[29–31]	Ground	**−0.59 (−3.06 to 1.87) I^2 = 0.0%, P = 0.839 (3 trials)**[29,30,32]
		Low	0.80 (−1.74 to 3.34) (1 trial)[30]	Athletes; BMI NR	NA					Unspecified	0.80 (−1.74 to 3.34) (1 trial)[45]
BMI (kg/m^2)	**0.04 (−1.58 to 1.66) I^2 = 0.0%, P = 0.868 (2 trials)**[28,30]	High	0.50 (−5.15 to 6.15) (1 trial)[28]	With health condition; overweight/obese	**0.04 (−1.58 to 1.66) I^2 = 0.0%, P = 0.868 (2 trials)**[28,30]	Active	0.50 (−5.15 to 6.15) (1 trial)[28]	Salba	NA	Whole	NA
		Medium	NA	Healthy; overweight/obese	NA	Nonactive	< 0.01 (−1.69 to 1.69) (1 trial)[30]	Non-Salba	**0.04 (−1.58 to 1.66) I^2 = 0.0%, P = 0.868 (2 trials)**[28,30]	Ground	0.50 (−5.15 to 6.15) (1 trial)[28]
		Low	< 0.01 (−1.69 to 1.69) (1 trial)[30]	Athletes; BMI NR	NA					Unspecified	< 0.01 (−1.69 to 1.69) (1 trial)[30]
Waist circumference (cm)	**−1.21 (−4.16, 1.74) I^2 = 0.0%, P = 0.472 (3 trials)**[28,30,32]	High	0.50 (−9.82, 10.82) (1 trial)[28]	With health condition; overweight/obese	**−1.21 (−4.16, 1.74) I^2 = 0.0%, P = 0.472 (3 trials)**[28,30,32]	Active	**−2.70 (−6.79, 1.39) I^2 = 0.0%, P = 0.507 (2 trials)**[28,32]	Salba	−3.30 (−7.76, 1.16) (1 trial)[32]	Whole	NA
		Medium	−3.30 (−7.76, 1.16) (1 trial)[32]	Healthy; overweight/obese	NA	Nonactive	0.40 (−3.85, 4.65) (1 trial)[30]	Non-Salba	**0.41 (−3.52, 4.35) I^2 = 0.0%, P = 0.986 (2 trials)**[28,30]	Ground	**−2.70 (−6.79 to 1.39) I^2 = 0.0%, P = 0.507 (2 trials)**[28,32]
		Low	0.40 (−3.85, 4.65) (1 trial)[30]	Athletes; BMI NR	NA					Unspecified	0.40 (−3.85 to 4.65) (1 trial)[30]
Glycemic											
HbA1c (%)	**0.02 (−0.37 to 0.41) I^2 = 16.9%, P = 0.273 (2 trials)**[5,32]	High	−0.20 (−0.73 to 0.33) (1 trial)[5]	With health condition; overweight/obese	**0.02 (−0.37 to 0.41) I^2 = 16.9%, P = 0.273 (2 trials)**[5,32]	Active	**0.02 (−0.37 to 0.41) I^2 = 16.9%, P = 0.273 (2 trials)**[5,32]	Salba	**0.02 (−0.37 to 0.41) I^2 = 16.9%, P = 0.273 (2 trials)**[5,32]	Whole	NA
		Medium	0.20 (−0.28 to 0.68) (1 trial)[32]	Healthy; overweight/obese	NA	Nonactive	NA	Non-Salba	NA	Ground	**0.02 (−0.37 to 0.41) I^2 = 16.9%, P = 0.273 (2 trials)**[5,32]
		Low	NA	Athletes; BMI NR	NA					Unspecified	NA

(continued)

Table 5 **Continued**

Outcome (unit of measurement)	Mean difference (95%CI)[a]										
	Main analysis	Subgroup analysis 1: chia seed dose		Subgroup analysis 2: participants' health status		Subgroup analysis 3: comparator		Subgroup analysis 4: type of chia seed		Subgroup analysis 5: chia seed form	
Fasting blood glucose (mmol/L)	**0.02 (−0.15 to 0.18) I^2 = 0.0%, P = 0.82 (6 trials)**[5,25,28,30–32]	High	**0.04 (−0.21 to 0.29) I^2 = 0.0%, P = 0.542 (4 trials)**[5,25,28,31]	With health condition; overweight/obese	**−0.01 (−0.22 to 0.20) I^2 = 0.0%, P = 0.618 (4 trials)**[5,28,30,32]	Active	**0.04 (−0.21 to 0.29) I^2 = 0.0%, P = 0.707 (5 trials)**[5,25,28,31,32]	Salba	**−0.61 (−1.71 to 0.49) I^2 = 0.0%, P = 0.509 (2 trials)**[5,32]	Whole	**0.06 (−0.21 to 0.32) I^2 = 0.0%, P = 0.585 (2 trials)**[25,31]
		Medium	0.20 (−3.19 to 3.59) (1 trial)[32]	Healthy; overweight/obese	**0.06 (−0.21 to 0.32) I^2 = 0.0%, P = 0.585 (2 trials)**[25,31]	Nonactive	< 0.001 (−0.22 to 0.22) (1 trial)[30]	Non-Salba	**0.03 (−0.14 to 0.20) I^2 = 0.0%, P = 0.871 (4 trials)**[25,28,30,31]	Ground	**(−0.39 to 0.41) I^2 = 0.0%, P = 0.610 (4 trials)**[5,28,32]
		Low	< 0.01 (−0.22 to 0.22) (1 trial)[30]	Athletes; BMI NR	NA					Unspecified	< 0.001 (−0.22 to 0.22) (1 trial)[30]
Fasting blood insulin (pmol/L)	**4.63 (−9.88 to 19.13) I^2 = 0.0%, P = 0.734 (3 trials)**[5,24,30]	High	8.80 (−14.76 to 32.36) (1 trial)[5]	With health condition; overweight/obese	**4.63 (−9.88 to 19.13) I^2 = 0.0%, P = 0.734 (3 trials)**[5,24,30]	Active	**3.60 (−11.35 to 18.56) I^2 = 0.0%, P = 0.576 (2 trials)**[5,24]	Salba	**3.60 (−11.35 to 18.56) I^2 = 0.0%, P = 0.576 (2 trials)**[5,24]	Whole	NA
		Medium	0.10 (−19.25 to 19.45) (1 trial)[24]	Healthy; overweight/obese	NA	Nonactive	21.00 (−38.81 to 80.81) (1 trial)[30]	Non-Salba	21.00 (−38.81 to 80.81) (1 trial)[30]	Ground	**3.60 (−11.35 to 18.56) I^2 = 0.0%, P = 0.576 (2 trials)**[5,24]
		Low	21.00 (−38.81 to 80.81) (1 trial)[30]	Athletes; BMI NR	NA					Unspecified	21.00 (−38.81 to 80.81) (1 trial)[30]
Postprandial blood glucose (iAUC [min × mmol/L, total of 2 h])	**−24.10 (−53.08 to 4.87) I^2 = 67.9%, P = 0.025 (4 trials)**[6–8,30,b,c]	High[b,c,d]	**−51.60 (−79.64 to −23.56)**[e] **I^2=31.5%, P = 0.232 (3 trials)**[6,8,30]	With health condition; overweight/obese[b,c,f]	−2.60 (−6.12 to 0.92) (1 trial)[30]	Active[a,b,f]	−22.46 (−78.97 to 34.05) (1 trial)[7]	Salba[b,c,f]	**−38.15 (−74.37 to −1.93)**[e] **I^2 = 46.3%, P = 0.155 (3 trials)**[6–8]	Whole[c,f,g]	**−21.67 (−50.09 to 6.76) I^2 = 0.0%, P = 0.620 (2 trials)**[6,8]
		Medium[b,c,d]	**−33.95 (−61.85 to −6.05)**[e] **I^2 = 0.0%, P = 0.647 (2 trials)**[6,8]	Healthy; overweight/obese[b,c,f]	−16.40 (−51.63 to 18.83) (1 trial)[6]	Nonactive[a,b,f]	**−24.10 (−53.08 to 4.87) I^2 = 67.9%, P = 0.025** (4 trials)[6–8,30]	Non-Salba[b,c,f]	−2.60 (−6.12 to 0.92) (1 trial)[30]	Ground[c,f,g]	**−44.69 (−110.09 to 20.71) I^2 = 74.6%, P = 0.047 (2 trials)**[6,7]
		Low[b,c,d]	**−2.89 (−6.38 to 0.61) I^2 = 0.0%, P = 0.378 (3 trials)**[6,8,30]	Healthy; BMI normal[b,c,f]	**−54.53 (−104.23 to −4.83)**[e] **I^2 = 43.9%, P = 0.182 (2 trials)**[7,8]					Unspecified	−2.60 (−6.12 to 0.92) (1 trial)[30]
Inflammation											
C-reactive protein (mg/L)	**−0.61 (−1.36 to 0.14) I^2 = 0.0%, P = 0.913 (5 trials)**[5,28,30–32]	High	**−0.66 (−1.79 to 0.47) I^2 = 0.0%, P = 0.730 (3 trials)**[5,28,31]	With health condition; overweight/obese	**−0.65 (−1.44 to 0.13) I^2 = 0.0%, P = 0.844 (4 trials)**[5,28,30,32]	Active	**−0.75 (−1.65 to 0.16) I^2 = 0.0%, P = 0.875 (4 trials)**[5,28,31,32]	Salba	**−0.95 (−1.98 to 0.08) I^2 = 0.0%, P = 0.924 (2 trials)**[5,32]	Whole	−0.09 (−2.80 to 2.62) (1 trial)[31]
		Medium	−0.90 (−2.41 to 0.61) (1 trial)[32]	Healthy; overweight/obese	−0.09 (−2.80 to 2.62) (1 trial)[31]	Nonactive	−0.30 (−1.66 to 1.06) (1 trial)[30]	Non-Salba	**−0.21 (−1.32 to 0.89) I^2 = 0.0%, P = 0.976 (3 trials)**[28,30,31]	Ground	**−0.75 (−1.65 to 0.15) I^2 = 0.0%, P = 0.881 (4 trials)**[5,28,31,32]
		Low	−0.30 (−1.66 to 1.06) (1 trial)[30]	Athletes; BMI NR	NA					Unspecified	−0.30 (−1.66 to 1.06) (1 trial)[30]

(continued)

Table 5 **Continued**

Outcome (unit of measurement)	Mean difference (95%CI)[a]										
	Main analysis	Subgroup analysis 1: chia seed dose		Subgroup analysis 2: participants' health status		Subgroup analysis 3: comparator		Subgroup analysis 4: type of chia seed		Subgroup analysis 5: chia seed form	
Interleukin 6 (pg/mL)	**< 0.01 (−0.01 to 0.02) I^2 = 0.0%, *P* = 0.876 (3 trials)**[25,26,31]	High	**<0.01 (−0.01, 0.02) I^2 = 0.0%, *P* = 0.876 (3 trials)**[25,26,31]	With health condition; overweight/obese	NA	Active	**< 0.01 (−0.01 to 0.02) I^2 = 0.0%, *P* = 0.785 (2 trials)**[25,31]	Salba	NA	Whole[g]	**<0.001 (−0.01 to 0.02) I^2 = 0.0%, *P* = 0.785 (2 trials)**[25,31]
		Medium	NA	Healthy; overweight/obese	**< 0.01 (−0.01 to 0.02) I^2 = 0.0%, *P* = 0.785 (2 trials)**[25,31]	Nonactive	−0.74 (−4.08 to 2.60) (1 trial)[26]	Non-Salba	**< 0.01 (−0.01 to 0.02) I^2 = 0.0%, *P* = 0.876 (3 trials)**[25,26,31]	Ground[g]	0.51 (−1.22 to 2.24) (1 trial)[31]
		Low	NA	Athletes; BMI NR	−0.74 (−4.08 to 2.60) (1 trial)[26]					Oil	−0.74 (−4.08 to 2.60) (1 trial)[26]
Interleukin 8 (pg/mL)	**−0.73 (−2.57 to 1.10) I^2 = 0.0%, *P* = 0.677 (2 trials)**[26,31]	High	**−0.73 (−2.57 to 1.10) I^2 = 0.0%, *P* = 0.677 (2 trials)**[26,31]	With health condition; overweight/obese	NA	Active	−0.46 (−2.70 to 1.78) (1 trial)[31]	Salba	NA	Whole[g]	−0.46 (−2.70 to 1.78) (1 trial)[31]
		Medium	NA	Healthy; overweight/obese	−0.46 (−2.70 to 1.78) (1 trial)[31]	Nonactive	−1.29 (−4.50 to 1.92) (1 trial)[26]	Non-Salba	**−0.73 (−2.57 to 1.10) I^2 = 0.0%, *P* = 0.677 (2 trials)**[26,31]	Ground[g]	0.04 (−1.40 to 1.48) (1 trial)[31]
		Low	NA	Athletes; BMI NR	−1.29 (−4.50 to 1.92) (1 trial)[26]					Oil	−1.29 (−4.50 to 1.92) (1 trial)[26]
Interleukin 10 (pg/mL)	**−0.28 (−2.23 to 1.66) I^2 = 0.0%, *P* = 0.812 (2 trials)**[26,31]	High	**−0.28 (−2.23 to 1.66) I^2 = 0.0%, *P* = 0.812 (2 trials)**[26,31]	With health condition; overweight/obese	NA	Active	−0.27 (−2.22 to 1.68) (1 trial)[31]	Salba	NA	Whole[g]	−0.27 (−2.22 to 1.68) (1 trial)[31]
		Medium	NA	Healthy; overweight/obese	−0.27 (−2.22 to 1.68) (1 trial)[31]	Nonactive	−4.39 (−38.31 to 29.53) (1 trial)[26]	Non-Salba	**−0.28 (−2.23 to 1.66) I^2 = 0.0%, *P* = 0.812 (2 trials)**[26,31]	Ground[g]	−0.53 (−2.67 to 1.61) (1 trial)[31]
		Low	NA	Athletes; BMI NR	−4.39 (−38.31 to 29.53) (1 trial)[26]					Oil	−4.39 (−38.31 to 29.53) (1 trial)[26]
TNF-α (pg/mL)	**<0.001 (< −0.001, 0.01) I^2 = 0.0%, *P* = 0.452 (3 trials)**[25,26,31]	High	**<0.001 (< −0.001, 0.01) I^2 = 0.0%, *P* = 0.452 (3 trials)**[25,26,31]	With health condition; overweight/obese	NA	Active	**< 0.01 (< −0.01, 0.01) I^2 = 0.0%, *P* = 0.567 (2 trials)**[25,31]	Salba	NA	Whole[g]	**< 0.001 (< −0.001 to 0.01) I^2 = 0.0%, *P* = 0.567 (2 trials)**[25,31]
		Medium		Healthy; overweight/obese	**< 0.01 (−0.01, 0.01) I^2 = 0.0%, *P* = 0.567 (2 trials)**[25,31]	Nonactive	−0.33 (−0.91 to 0.25) (1 trial)[26]	Non-Salba	**< 0.001 (< −0.001, 0.01) I^2 = 0.0%, *P* = 0.452 (3 trials)**[25,26,31]	Ground[g]	−0.31 (−2.08 to 1.46) (1 trial)[31]
		Low		Athletes; BMI NR	−0.33 (−0.91 to 0.25) (1 trial)[26]					Oil	−0.33 (−0.91 to 0.25) (1 trial)[26]
von Willebrand factor (IU/mL)	**−0.09 (−0.32 to 0.14) I^2 = 25.2%, *P* = 0.247 (2 trials)**[5,24]	High	−0.24 (−0.58 to 0.09) (1 trial)[5]	With health condition; overweight/obese	**−0.09 (−0.32 to 0.14) I^2 = 25.2%, *P* = 0.247 (2 trials)**[5,24]	Active	**−0.09 (−0.32 to 0.14) I^2 = 25.2%, *P* = 0.247 (2 trials)**[5,24]	Salba	**−0.09 (−0.32 to 0.14) I^2 = 25.2%, *P* = 0.247 (2 trials)**[5,24]	Whole	NA
		Medium	< 0.01 (−0.24 to 0.24) (1 trial)[24]	Healthy; overweight/obese	NA	Nonactive	NA	Non-Salba	NA	Ground	**−0.09 (−0.32 to 0.14)I^2 = 25.2 , *P* = 0.247 (2 trials)**[5,24]
		Low	NA	Athletes; BMI NR	NA					Unspecified	NA

(continued)

Table 5 **Continued**

Outcome (unit of measurement)	Mean difference (95%CI)[a]									
	Main analysis	Subgroup analysis 1: chia seed dose		Subgroup analysis 2: participants' health status		Subgroup analysis 3: comparator		Subgroup analysis 4: type of chia seed		Subgroup analysis 5: chia seed form	
Lipid											
Total cholesterol (mmol/L)	**−0.07 (−0.30 to 0.15) I^2 = 0.0%, P = 0.773 (6 trials)**[5,24,25,28,30,31]	High	**0.06 (−0.26 to 0.38) I^2 = 0.0%, P = 0.863 (4 trials)**[5,25,28,31]	With health condition; overweight/obese	**−0.21 (−0.50 to 0.08) I^2 = 0.0%, P = 0.945 (4 trials)**[5,24,28,30]	Active	**(−0.25 to 0.28) I^2 = 0.0%, P = 0.901 (5 trials)**[5,24,25,28,31]	Salba	**−0.13 (−0.53 to 0.27) I^2 = 0.0%, P = 0.825 (2 trials)**[5,24]	Whole	**0.14 (−0.23 to 0.50) I^2 = 0.0%, P = 0.865 (2 trials)**[25,31]
		Medium	−0.10 (−0.58 to 0.38) (1 trial)[24]	Healthy; overweight/obese	**0.14 (−0.23 to 0.50) I^2 = 0.0%, P = 0.865 (2 trials)**[25,31]	Nonactive	−0.30 (−0.73 to 0.13) (1 trial)[30]	Non-Salba	**−0.05 (−0.32 to 0.23) I^2 = 0.0%, P = 0.500 (4 trials)**[25,28,30,31]	Ground	**−0.11 (−0.45 to 0.24) I^2 = 0.0%, P = 0.990 (4 trials)**[5,24,28,31]
		Low	−0.30 (−0.73 to 0.13) (1 trial)[30]	Athletes; BMI NR	NA					Unspecified	−0.07 (−0.28 to 0.15) (1 trial)[30]
Low-density lipoprotein (mmol/L)	**−0.01 (−0.24 to 0.21) I^2 = 0.0%, P = 0.879 (5 trials)**[5,24,25,28,30]	High	**0.03 (−0.33 to 0.38) I^2 = 0.0%, P = 0.603 (3 trials)**[5,25,28]	With health condition; overweight/obese	**−0.06 (0.32 to 0.19) I^2 = 0.0%, P = 0.917 (4 trials)**[5,24,28,30]	Active	**−0.02 (−0.30 to 0.27) I^2 = 0.0%, P = 0.755 (4 trials)**[5,24,25,28]	Salba	**−0.10 (−0.48 to 0.28) I^2 = 0.0%, P = 1.000 (2 trials)**[5,24]	Whole	0.16 (−0.30 to 0.62) (1 trial)[25]
		Medium	−0.10 (−0.58 to 0.38) (1 trial)[24]	Healthy; overweight/obese	0.16 (−0.30 to 0.62) (1 trial)[25]	Nonactive	< 0.01 (−0.37 to 0.37) (1 trial)[30]	Non-Salba	**0.04 (−0.24 to 0.32) I^2 = 0.0%, P = 0.652 (3 trials)**[25,28,30]	Ground	**−0.13 (−0.49 to 0.24) I^2 = 0.0%, P = 0.870 (3 trials)**[5,24,28]
		Low	< 0.01 (−0.37, 0.37) (1 trial)[30]	Athletes; BMI NR	NA					Unspecified	< 0.001 (−0.37 to 0.37) (1 trial)[30]
High-density lipoprotein (mmol/L)	**−0.05 (−0.11 to 0.02) I^2 = 11.7%, P = 0.339 (5 trials)**[5,24,25,28,30]	High	**−0.10 (−0.20 to −0.01)**[e] **I^2 = 0.0%, P = 0.403 (3 trials)**[5,25,28]	With health condition; overweight/obese	**−0.01 (−0.08 to 0.05) I^2 = 0.0%, P = 0.724 (4 trials)**[5,24,28,30]	Active	**−0.07 (−0.15 to 0.01) I^2 = 6.4%, P = 0.361 (4 trials)**[5,24,25,28]	Salba	**−0.04 (−0.15 to 0.06) I^2 = 0.0%, P = 0.369 (2 trials)**[5,24]	Whole	**−0.15 (−0.28 to −0.02)**[e] **(1 trial)**[25]
		Medium	< 0.01 (−0.14 to 0.14) (1 trial)[24]	Healthy; overweight/obese	−0.15 (−0.28 to −0.02) (1 trial)[25]	Nonactive	< 0.01 (−0.10 to 0.10) (1 trial)[30]	Non-Salba	**−0.05 (−0.16 to 0.06) I^2 = 46.3%, P = 0.155 (3 trials)**[25,28,30]	Ground	**−0.03 (−0.13 to 0.07) (3 trials) I^2 = 0.0%, P = 0.566**[5,24,28]
		Low	< 0.01 (−0.10 to 0.10) (1 trial)[30]	Athletes; BMI NR	NA					Unspecified	< 0.001 (−0.10 to 0.10) (1 trial)[30]
Triglyceride (mmol/L)	**−0.08 (−0.32 to 0.17) I^2 = 4.1%, P = 0.384 (5 trials)**[5,24,25,28,30]	High	**−0.03 (−0.47 to 0.40) I^2 = 39.6%, P = 0.191 (3 trials)**[5,25,28]	With health condition; overweight/obese	**−0.19 (−0.47 to 0.09) I^2 = 0.0%, P = 0.558 (4 trials)**[5,24,28,30]	Active	**−0.07 (−0.37 to 0.22) I^2 = 26.5%, P = 0.253 (4 trials)**[5,24,25,28]	Salba	**−0.13 (−0.44 to 0.19) I^2 = 0.0%, P = 0.544 (2 trials)**[5,24]	Whole	0.19 (−0.24 to 0.63) (1 trial)[25]
		Medium	−0.20 (−0.59 to 0.19) (1 trial)[24]	Healthy; overweight/obese	0.19 (−0.24 to 0.63) (1 trial)[25]	Nonactive	−0.20 (−1.07 to 0.67) (1 trial)[30]	Non-Salba	**−0.13 (−0.70 to 0.43) I^2 = 43.5%, P = 0.170 (3 trials)**[25,28,30]	Ground	**−0.19 (−0.49 to 0.12) I^2 = 3.4%, P = 0.355 (3 trials)**[5,24,28]
		Low	−0.20 (−1.07 to 0.67) (1 trial)[30]	Athletes; BMI NR	NA					Unspecified	−0.20 (−1.07 to 0.67) (1 trial)[30]

(continued)

Table 5 **Continued**

Outcome (unit of measurement)	Mean difference (95%CI)[a]									
	Main analysis	Subgroup analysis 1: chia seed dose		Subgroup analysis 2: participants' health status		Subgroup analysis 3: comparator		Subgroup analysis 4: type of chia seed		Subgroup analysis 5: chia seed form
Blood pressure										
Diastolic blood pressure (mmHg)	**−3.37 (−7.43 to 0.70) I^2 = 64.8%, P = 0.036 (4 trials)**[5,24,28,30]	High	**−7.14 (−11.08 to −3.19)**[e] **I^2 = 0.0%, P = 0.508 (2 trials)**[5,28]	With health condition; overweight/obese	**−3.37 (−7.43 to 0.70) I^2 = 64.8%, P = 0.036 (4 trials)**[5,24,28,30]	Active	**−4.33 (−10.12 to 1.46) I^2 = 74.7%, P = 0.019 (3 trials)**[5,24,28]	Salba	**−2.44 (−8.99 to 4.11) I^2 = 75.1%, P = 0.045 (2 trials)**[5,24]	Whole	NA
		Medium	0.70 (−3.30 to 4.70) (1 trial)[24]	Healthy; overweight/obese	NA	Nonactive	−1.20 (−5.56 to 3.16) (1 trial)[30]	Non-Salba	**−4.64 (−11.96 to 2.69) I^2 = 74.1%, P = 0.050 (2 trials)**[28,30]	Ground	**−4.33 (−10.12 to 1.46) I^2 = 74.7%, P = 0.019 (3 trials)**[5,24,28]
		Low	−1.20 (−5.56 to 3.16) (1 trial)[30]	Athletes; BMI NR	NA					Unspecified	−1.20 (−5.56 to 3.16) (1 trial)[30]
Systolic blood pressure (mmHg)	**−2.57 (−6.70 to 1.55) I^2 = 38.3%, P = 0.151 (6 trials)**[5,24,25,28,30,31]	High	**−5.41 (−11.47 to 0.64) I^2 = 38.7%, P = 0.180 (4 trials)**[5,25,28,31]	With health condition; overweight/obese	**−3.99 (−10.58 to 2.60) I^2 = 62.4%, P = 0.046 (4 trials)**[5,24,30,31]	Active	**−3.38 (−8.82 to 2.05) I^2 = 49.8%, P = 0.092 (5 trials)**[5,24,25,28,31]	Salba	**−4.77 (−19.83 to 10.28) I^2 = 84.4%, P = 0.011 (2 trials)**[5,24]	Whole[g]	**−1.17 (−6.44 to 4.09) I^2 = 0.0%, P = 0.975 (2 trials)**[25,31]
		Medium	2.40 (−3.92 to 8.72) (1 trial)[24]	Healthy; overweight/obese	**−1.17 (−6.44 to 4.09) I^2 = 0.0%, P = 0.975 (2 trials)**[25,28]	Nonactive	−1.00 (−7.00 to 5.00) (1 trial)[30]	Non-Salba	**−1.94 (−5.69 to 1.81) I^2 = 38.7%, P = 0.639 (4 trials)**[25,28,30,31]	Ground[g]	**−5.50 (−13.51 to 2.51) I^2 = 61.2%, P = 0.052 (4 trials)**[5,24,28,31]
		Low	−1.00 (−7.00 to 5.00) (1 trial)[30]	Athletes; BMI NR	NA					Unspecified	−1.00 (−7.00 to 5.00) (1 trial)[30]
Liver										
Aspartate aminotransferase (U/L)	**−0.10 (−3.29 to 3.08) I^2 = 0.0%, P = 0.828 (2 trials)**[5,24]	High	0.21 (−4.05 to 4.47) (1 trial)[5]	With health condition; overweight/obese	**−0.10 (−3.29 to 3.08) I^2 = 0.0%, P = 0.828 (2 trials)**[5,24]	Active	**−0.10 (−3.29 to 3.08) I^2 = 0.0%, P = 0.828 (2 trials)**[5,24]	Salba	**−0.10 (−3.29 to 3.08) I^2 = 0.0%, P = 0.828 (2 trials)**[5,24]	Whole	NA
		Medium	−0.50 (−5.29 to 4.29) (1 trial)[24]	Healthy; overweight/obese	NA	Nonactive	NA	Non-Salba	NA	Ground	**−0.10 (−3.29 to 3.08) I^2 = 0.0%, P = 0.828 (2 trials)**[5,24]
		Low	NA	Athletes; BMI NR	NA					Unspecified	NA
Alanine aminotransferase (U/L)	**3.39 (−1.82 to 8.60) I^2 = 20.2%, P = 0.263 (2 trials)**[5,24]	High	0.68 (−5.97 to 7.34) (1 trial)[5]	With health condition; overweight/obese	**3.39 (−1.82 to 8.60) I^2 = 20.2%, P = 0.263 (2 trials)**[5,24]	Active	**3.39 (−1.82 to 8.60) I^2 = 20.2%, P = 0.263 (2 trials)**[5,24]	Salba	**3.39 (−1.82 to 8.60) I^2 = 20.2%, P = 0.263 (2 trials)**[5,24]	Whole	NA
		Medium	6.00 (−0.51 to 12.51) (1 trial)[24]	Healthy; overweight/obese	NA	Nonactive	NA	Non-Salba	NA	Ground	**3.39 (−1.82 to 8.60) I^2 = 20.2%, P = 0.263 (2 trials)**[5,24]
		Low	NA	Athletes; BMI NR	NA					Unspecified	NA

(continued)

Table 5 **Continued**

Outcome (unit of measurement)	Mean difference (95%CI)[a]									
	Main analysis	Subgroup analysis 1: chia seed dose		Subgroup analysis 2: participants' health status		Subgroup analysis 3: comparator		Subgroup analysis 4: type of chia seed		Subgroup analysis 5: chia seed form	
Renal											
Creatinine (μmol/L)	**−1.37 (−7.42 to 4.69) I^2 = 0.0%, P = 0.989 (2 trials)**[5,32]	High	−1.32 (−11.09 to 8.46) (1 trial)[5]	With health condition; overweight/obese	**−1.37 (−7.42 to 4.69) I^2 = 0.0%, P = 0.989 (2 trials)**[5,32]	Active	**−1.37 (−7.42 to 4.69) I^2 = 0.0%, P = 0.989 (2 trials)**[5,32]	Salba	**−1.37 (−7.42 to 4.69) I^2 = 0.0%, P = 0.989 (2 trials)**[5,32]	Whole	NA
		Medium	0.60 (−7.12 to 8.32) (1 trial)[32]	Healthy; overweight/obese	NA	Nonactive	NA	Non-Salba	NA	Ground	**−1.37 (−7.42 to 4.69) I^2 = 0.0%, P = 0.989 (2 trials)**[5,32]
		Low	NA	Athletes; BMI NR	NA					Unspecified	NA
Blood urea nitrogen (mmol/L)	**−0.28 (−1.30 to 0.74) I^2 = 54.9%, P = 0.137 (2 trials)**[5,32]	High	0.24 (−0.74 to 1.22) (1 trial)[5]	With health condition; overweight/obese	**−0.28 (−1.30 to 0.74) I^2 = 54.9%, P = 0.137 (2 trials)**[5,32]	Active	**−0.28 (−1.30 to 0.74) I^2 = 54.9%, P = 0.137 (2 trials)**[5,32]	Salba	**−0.28 (−1.30 to 0.74) I^2 = 54.9%, P = 0.137 (2 trials)**[5,32]	Whole	NA
		Medium	−0.80 (−1.76 to 0.16) (1 trial)[32]	Healthy; overweight/obese	NA	Nonactive	NA	Non-Salba	NA	Ground	**−0.28 (−1.30 to 0.74) I^2 = 54.9%, P = 0.137 (2 trials)**[5,32]
		Low	NA	Athletes; BMI NR	NA					Unspecified	NA
Satiety/glucose-regulating											
Adiponectin (mg/L)	**< 0.001 (< −0.001, < 0.001) I^2 = 0.0%, P = 0.795 (2 trials)**[30,32]	High	NA	With health condition; overweight/obese	**< 0.001 (< −0.001, < 0.001) I^2 = 0.0%, P = 0.795 (2 trials)**[30,32]	Active	< 0.001 (< −0.001, < 0.001) (1 trial)[32]	Salba	< 0.001 (< −0.001, < 0.001) (1 trial)[32]	Whole	
		Medium	< 0.001 (< −0.001, < 0.001) (1 trial)[32]	Healthy; overweight/obese		Nonactive	−0.20 (−1.71 to 1.31) (1 trial)[30]	Non-Salba	−0.20 (−1.71 to 1.31) (1 trial)[30]	Ground	< 0.001 (< −0.001 to < 0.001) (1 trial)[32]
		Low	−0.20 (−1.71 to 1.31) (1 trial)[30]	Athletes; BMI NR						Unspecified	−0.20 (−1.71 to 1.31) (1 trial)[30]

Abbreviations: BMI, body mass index; HbA1c, glycated hemoglobin; iAUC, incremental area under the curve; NA, not applicable; NR, not reported; TNF-α, tumor necrosis factor α.
Boldface estimates are pooled estimates, while non-boldface estimates are from a single trial.
[a]One trial assessed the effect using both active and nonactive comparators.
[b]Based on the whole form of chia seed.
[c]Based on a nonactive comparator.
[d]Two trials assessed the effect of 3 different doses (low, medium, and high) of chia seed.
[e]Result showing a significant difference between chia seed group and comparator group.
[f]Based on low dose and whole form of chia seed.
[g]One trial assessed the effect of both whole and ground chia seed.

Table 6 **Summary of findings of the effects of chia seed in all indications**

Outcome	Anticipated absolute effects (95%CI)	No. of participants (no. of studies)	Quality of evidence (GRADE[a])
Anthropometric			
Body weight (follow-up: range of 60–168 days	Mean body weight in intervention group was 0.07 kg more (0.18 fewer to 0.31 more)	233 (5 RCTs)	Low[b,c]
Body fat mass (follow-up: range of 60–168 days	Mean body fat mass in intervention group was 0.07% lower (1.91 lower to 1.78 higher)	186 (4 RCTs)	Low[b,c]
BMI (follow-up: range of 60–84 days	Mean BMI in intervention group was 0.04 kg/m^2 higher (1.58 lower to 1.66 higher)	84 (2 RCTs)	Low[b,c]
Waist circumference (follow-up: range of 60–168 days)	Mean waist circumference in intervention group was 1.21 cm lower (4.16 lower to 1.74 higher)	142 (3 RCTs)	Low[b,c]
Hip circumference (follow-up: 168 days)	Mean hip circumference in intervention group was 2.90 cm lower (7.36 lower to 1.56 higher)	58 (1 RCT)	Low[b,c]
Android fat (follow-up: 168 days)	Mean android fat in intervention group was 1.80% lower (4.82 lower to 1.22 higher)	58 (1 RCT)	Low[b,c]
Gynoid fat (follow-up: 168 days)	Mean gynoid fat in intervention group was 5.20% lower (10.24 lower to 0.16 lower)	58 (1 RCT)	Low[b,c]
Glycemic			
HbA1c (follow-up: range of 84–168 days)	Mean HbA1c in intervention group was 0.02% more (0.15 fewer to 0.18 more)	98 (2 RCTs)	Low[b,c]
Fasting blood glucose (follow-up: range of 60–168 days	Mean fasting blood glucose in intervention group was 0.01 mmol/L more (0.16 fewer to 0.17 more)	300 (6 RCTs)	Low[b,c]
Fasting blood insulin (follow-up: range of 60–168 days)	Mean fasting blood insulin in intervention group was 4.63 pmol/L more (9.88 fewer to 19.13 more)	165 (3 RCTs)	Low[b,c]
PPG (follow-up: range of 1–60 days)	Mean PPG in intervention group was 24.10 iAUC (min $\times$ mmol/L for total of 120 min) lower (53.08 lower to 4.87 higher)	145 (4 RCTs)	Very low[b,c,d]
Inflammation			
CRP (follow-up: range of 60–168 days)	Mean CRP in intervention group was 0.61 mg/L lower (1.36 lower to 0.14 higher)	224 (5 RCTs)	Low[b,c]
IL-6 (follow-up: range of 1–84 days)	Mean IL-6 in intervention group was $<$ 0.01 pg/mL higher (0.01 lower to 0.02 higher)	142 (3 RCTs)	Low[b,c]
IL-8 (follow-up: range of 1–70 days)	Mean IL-8 in intervention group was 0.73 pg/mL lower (2.57 lower to 1.10 higher)	80 (2 RCTs)	Low[b,c]
IL-10 (follow-up: range of 1–84 days)	Mean IL-10 in intervention group was 0.28 pg/mL lower (2.23 lower to 1.66 higher)	80 (2 RCTs)	Low[b,c]
TNF-α (follow-up: range of 1–84 days)	Mean TNF-α in intervention group was $<$ 0.01 pg/mL higher ($<$ 0.01 lower to 0.01 higher)	142 (3 RCTs)	Low[b,c]
von Willebrand factor (follow-up: range of 84–168 days)	Mean von Willebrand factor in intervention group was 0.09 IU/mL lower (0.32 lower to 0.14 higher)	98 (2 RCTs)	Low[b,c]
Acid glycoprotein (follow-up: 84 days)	Mean acid glycoprotein in intervention group was 2.00 mg/dL higher (10.47 lower to 14.47 higher)	26 (1 RCT)	Low[b,c]
Factor VIII (follow-up: 84 days)	Mean factor VIII in intervention group was 0.21 IU/mL lower (0.46 lower to 0.04 higher)	20 (1 RCT)	Low[b,c]
Fibrinogen (follow-up: 84 days)	Mean fibrinogen in intervention group was 0.26 g/L lower (0.69 lower to 0.17 higher)	20 (1 RCT	Low[b,c]
Leukocyte count (follow-up: 1 day)	Mean leukocyte count in intervention group was 0.18 $\times$ 10^9/L lower (2.40 lower to 2.04 higher)	24 (1 RCT)	Low[b,c]
Plasma MCP (follow-up: 84 days)	Mean plasma MCP in intervention group was 0.04 pg/mL higher (0.05 lower to 0.13 higher)	76 (1 RCT)	Low[b,c]
Lipid profile			
Total cholesterol (follow-up: range of 60–168 days)	Mean total cholesterol in intervention group was 0.07 mmol/L lower (0.3 lower to 0.15 higher)	300 (6 RCTs)	Low[b,c]
LDL (follow-up: range of 60–168 days)	Mean LDL in intervention group was 0.01 mmol/L lower (0.24 lower to 0.21 higher)	258 (5 RCTs)	Low[b,c]
HDL (follow-up: range of 60–168 days)	Mean HDL in intervention group was 0.05 mmol/L lower (0.11 lower to 0.02 higher)	258 (5 RCTs)	Low[b,c]
Triglyceride (follow-up: range of 60–168 days)	Mean triglyceride in intervention group was 0.08 mmol/L lower (0.32 lower to 0.17 higher)	258 (5 RCTs)	Low[b,c]
VLDL (follow-up: 84 days)	Mean VLDL in intervention group was 2.00 mg/dL lower (22.25 lower to 18.25 higher)	26 (1 RCT)	Low[b,c]

(continued)

Table 6 **Continued**

Outcome	Anticipated absolute effects (95%CI)	No. of participants (no. of studies)	Quality of evidence (GRADE[a])
Blood pressure			
Diastolic BP (follow-up: range of 60–168 days)	Mean diastolic BP in intervention group was 3.37 mmHg lower (7.43 lower to 0.7 higher)	182 (4 RCTs)	Very low[b,c,d]
Systolic BP (follow-up: range of 60–168 days)	Mean systolic BP in intervention group was 2.57 mmHg lower (6.7 lower to 1.55 higher)	300 (6 RCTs)	Very low[b,c,e]
Liver			
AST (follow-up: range of 84–168 days)	Mean AST in intervention group was 0.1 U/L lower (3.29 lower to 3.08 higher)	96 (2 RCTs)	Low[b,c]
ALT (follow-up: range of 84–168 days)	Mean ALT in intervention group was 3.39 U/L higher (1.82 lower to 8.6 higher)	96 (2 RCTs)	Low[b,c]
ALP (follow-up: 168 days)	Mean ALP in intervention group was 0.20 U/L lower (11.17 lower to 10.77 higher)	58 (1 RCT)	Low[b,c]
Renal			
Creatinine (follow-up: range of 84–168 days)	Mean creatinine in intervention group was 1.37 mmol/L lower (7.42 lower to 4.69 higher)	96 (2 RCTs)	Low[b,c]
BUN (follow-up: range of 86–164 days)	Mean BUN in intervention group was 0.28 μmol/L lower (1.3 lower to 0.74 higher)	96 (2 RCTs)	Low[b,c]
Athletic performance			
Time to exhaustion (follow-up: 1 day)	Mean time to exhaustion in intervention group was 3 min lower (13.54 lower to 7.54 higher)	24 (1 RCT)	Low[b,c]
Distance to exhaustion (follow-up: 1 day)	Mean distance to exhaustion in intervention group was 0.60 km lower (2.23 lower to 1.03 higher)	24 (1 RCT)	Low[b,c]
Volume of oxygen consumption (follow up: 1 day)	Mean volume of oxygen consumption in intervention group was 0.30 mL/(kg $\times$ min) higher (0.42 lower to 1.02 higher)	24 (1 RCT)	Low[b,c]
Heart rate (follow-up: 1 day)	Mean heart rate in intervention group was 2.00 beats/min lower (3.61 lower to 0.39 lower)	24 (1 RCT)	Low[b,c]
Ventilation (follow-up: 1 day)	Mean ventilation in intervention group was 1.20 L/min higher (1.15 lower to 3.55 higher)	24 (1 RCT)	Low[b,c]
Rating of perceived exertion (follow-up: 1 day)	Mean rating of perceived exertion in intervention group was 0.20 lower (0.31 lower to 0.71 higher)	24 (1 RCT)	Low[b,c]
RER (follow-up: 1 day)	Mean RER in intervention group was 0.00 (0.00 to 0.00)	24 (1 RCT)	Low[b,c]
Plasma volume shift (follow-up: 1 day)	Mean plasma volume shift in intervention group was 2.10% higher (1.07 lower to 5.27 higher)	24 (1 RCT)	Low[b,c]
Lactate (follow-up: 1 day)	Mean lactate in intervention group was 0.15 mmol/L lower (0.49 lower to 0.19 higher)	24 (1 RCT)	Low[b,c]
Glucose (follow-up: 1 day)	Mean glucose in intervention group was 0.24 mmol/L lower (0.80 lower to 0.32 higher)	24 (1 RCT)	Low[a,b]
Time to complete 15-km trial (follow-up: 14 days)	Mean time to complete 15-km trial in intervention group was 0.02 min higher (1.02 lower to 1.06 higher)	18 (1 RCT)	Low[b,c]
Average power output (follow-up: 14 days)	Mean average power output in intervention group was 4.00 W lower (12.81 lower to 20.81 higher)	18 (1 RCT)	Low[b,c]
Hemostasis			
Activated PTT (follow-up: 168 days)	Mean activated PTT in intervention group was 0.30 s lower (1.77 lower to 1.17 higher)	58 (1 RCT)	Low[b,c]
Prothrombin time (follow-up: 168 days)	Mean prothrombin time in intervention group was 0.30 s lower (0.58 lower to 0.02 lower)	58 (1 RCT)	Low[b,c]
International normalized ratio (follow-up: 168 days)	Mean international normalized ratio in intervention group was $<$ 0.001 lower (0.03 lower to 0.03 higher)	58 (1 RCT)	Low[b,c]
Appetite			
100 mm VAS (low dose) (follow-up: 1 day)	Mean 100 mm VAS (appetite rating) in intervention group was $<$ 0.001 iAUC (min $\times$ mm for total of 2 h) lower ($<$ 0.001 lower to 518.94 higher)	11 (1 RCT)	Low[b,c]
100 mm VAS (medium dose) (follow-up: 1 day)	Mean 100 mm VAS (appetite rating) in intervention group was $<$ 0.001 iAUC (min $\times$ mm for total of 2 h) lower ($<$ 0.001 lower to 240.44 higher)	11 (1 RCT)	Low[b,c]
100 mm VAS (high dose) (follow-up: 1 day)	Mean 100 mm VAS (appetite rating) in intervention group was $<$ 0.001 iAUC (min $\times$ mm for total of 2 h) lower ($<$ 0.001 lower to 2.98 lower)	11 (1 RCT)	Low[b,c]

(continued)

Table 6 **Continued**

Outcome	Anticipated absolute effects (95%CI)	No. of participants (no. of studies)	Quality of evidence (GRADE[a])
100 mm VAS (nonactive comparator, "without chia seed") (follow-up: 1 day)	Mean 100 mm VAS (appetite rating) in intervention group was 13.00 mm lower (26.86 lower to 0.86 higher)	15 (1 RCT)	Low[b,c]
100 mm VAS (active comparator, flax seed) (follow-up: 1 day)	Mean 100 mm VAS (appetite rating) in intervention group was 6.00 mm lower (19.86 lower to 7.86 higher)	15 (1 RCT)	Low[b,c]
Satiety/glucose-regulating			
Leptin (follow-up: 60 days)	Mean leptin in intervention group was 2.20 μg/L lower (9.25 lower to 4.85 higher)	67 (1 RCT)	Low[b,c]
Adiponectin (follow-up: range of 60–168 days)	Mean adiponectin in intervention group was < 0.001 mg/L higher (< 0.001 lower to < 0.001 higher)	121 (2 RCTs)	Low[b,c]
Ghrelin (follow-up: 168 days)	Mean ghrelin in intervention group was 211.40 pg/mL lower (361.83 lower to 60.97 lower)	58 (1 RCT)	Low[b,c]
Peptide tyrosine tyrosine (follow-up: 168 days)	Mean peptide tyrosine tyrosine in intervention group was 5.10 pg/mL lower (31.56 lower to 21.36 higher)	58 (1 RCT)	Low[b,c]
Other			
Malondialdehyde (follow-up: 84 days)	Mean malondialdehyde in intervention group was 0.40 μmol/L higher (0.99 lower to 1.79 higher)	26 (1 RCT)	Low[b,c]
Cortisol (follow-up: 1 day)	Mean cortisol in intervention group was 61.00 nmol/L higher (1.31 lower to 123.31 higher)	24 (1 RCT)	Low[b,c]
Nitrite (follow-up: 84 days)	Mean nitrite in intervention group was 6.20 μmol/L lower (19.56 lower to 7.16 higher)	26 (1 RCT)	Low[b,c]

Abbreviations: ALT, alanine aminotransferase; ALP, alkaline phosphatase; AST, aspartate aminotransferase; BMI, body mass index; BP, blood pressure; BUN, blood urea nitrogen; CRP, C-reactive protein; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; iAUC, incremental area under the curve; IL, interleukin; LDL, low-density lipoprotein; MCP, monocyte chemotactic protein; PPG, postprandial glucose; PTT, partial thromboplastin time; TNF-α, tumor necrosis factor alpha; RCT, Randomized controlled trial; RER, respiratory exchange ratio; VAS, visual analog scale; VLDL, very low-density lipoprotein.

[a]Rating of evidence quality, according to GRADE. *High* represents a high degree of confidence that the true effect lies close to that of the estimate of the effect. *Moderate* represents a moderate degree of confidence in the effect estimate, ie, the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. *Low* represents limited confidence in the effect estimate, ie, the true effect may be substantially different from the estimate of the effect. *Very low* represents very little confidence in the effect estimate, ie, the true effect is likely to be substantially different from the estimate of effect.

[b]All trials with either unclear or high overall risk of bias, as well as some trials with unclear selection bias. This created some uncertainty about the reliability of the results, even though most outcomes assessed were objective outcomes.

[c]The confidence intervals in the outcomes assessed were too wide for a confident estimate of the plausible effect size, mainly because of the small sample size used in each of the outcomes assessed.

[d]Substantial heterogeneity.

[e]Moderate heterogeneity.

change the lack of statistical significance (where the result of 1 trial that did not instruct participants to control their diet[26] was the same trial that included athlete participants, while the 2 trials that did instruct participants to control their diet[25,31] were the same trials that included overweight and obese participants). However, athlete participants who did not control their diet during trials appeared to have a greater reduction in markers of inflammation (interleukins 6, 8, and 10 and tumor necrosis factor α) compared with nonathlete participants who did control their diet (Table 5). Again, however, the findings are based on only 1 trial.[26]

Lipid outcomes. There were no significant differences in any of the lipid parameters between participants who received chia seed and the control group. These included the pooled MDs for the following: (1) total cholesterol, 0.07 mmol/L (95%CI, −0.30 to 0.15; 6 trials; GRADE low),[5,24,25,28,30,31] (2) low-density lipoprotein, −0.01 mmol/L (95%CI, −0.24 to 0.21; 5 trials; GRADE low),[5,24,25,28,30] (3) high-density lipoprotein, −0.05 mmol/L (95%CI, −0.11 to 0.02; 5 trials; GRADE low),[5,24,25,28,30] and (4) triglyceride, −0.08 mmol/L (95%CI, −0.32 to 0.17; 5 trials; GRADE low),[5,24,25,28,30] all with either no or minimal heterogeneity. One trial also assessed the effect of chia seed on very low-density lipoprotein.[28] The MD was not significant: −2.00 mg/dL (95%CI, −22.25 to 18.25; GRADE low). The lack of statistical significance remained unchanged in subgroup analysis, except for the effect of chia seed on high-density lipoprotein (Table 5). The results of 3 trials that used high doses of chia seed and whole chia seed[5,25,28] were significant, with pooled MDs of −0.10 (95%CI, −0.20 to −0.01; $I^2 = 0.0\%$, $P = 0.403$) (3 trials[5,25,28]) and 0.16 (95%CI, −0.30 to 0.62) (1 trial[25]), respectively. On another note, interestingly, when high doses of chia seed were used, the effect appeared to be less favorable on all lipid parameters, ie, increased total cholesterol, low-density lipoprotein, and triglyceride and decreased high-density lipoprotein, than when low or medium

doses were used. In addition, the lipid-lowering effect appeared to be greater for participants with a health condition than for participants without a health condition for all lipid parameters, for Salba chia seed compared with non-Salba chia seed for total cholesterol and low-density lipoprotein, and for ground chia seed compared with whole chia seed for all lipid parameters.

Blood pressure. There were no significant differences for either diastolic blood pressure or systolic blood pressure between participants who received chia seed and the control group. The pooled MD for diastolic blood pressure was −3.37 mmHg (95%CI, −7.43 to 0.70; 4 trials; GRADE very low),[5,24,28,30] with $I^2 = 64.8\%$, $P = 0.036$. Subgroup analysis of different levels of chia seed dose removed the heterogeneity and showed that, when the 2 trials with high doses of chia seed were pooled,[5,28] the MD for diastolic blood pressure was significant at −7.14 mmHg (95%CI, −11.08 to −3.19; $I^2 = 0.0\%$, $P = 0.508$) and was not significant for medium doses (0.70 mmHg [95%CI, −3.30 to 4.70][24]) or low doses (−1.20 mmHg [95%CI, −5.56 to 3.16][30]). Another subgroup analysis for diastolic blood pressure did not change the significance level of the results (Table 5). For systolic blood pressure, the pooled MD was −2.57 (95%CI, −6.70 to 1.55; 6 trials; GRADE very low),[5,24,25,28,30,31] with $I^2 = 38.3\%$, $P = 0.151$. The lack of statistical significance remained unchanged in subgroup analysis (Table 5), although ground chia seed was found to have a greater effect on reduction of systolic blood pressure compared with whole chia seed.

Markers of liver and renal function. There was no significant difference for either liver markers or renal markers between participants who received chia seed and the control group. For liver markers, no parameters were significant, with the pooled MD being −0.10 U/L (95%CI, −3.29 to 3.08; 2 trials; GRADE low; $I^2 = 0\%$, $P > 0.828$)[5,24] and 3.39 U/L (95%CI, −1.82 to 8.60; 2 trials; GRADE low; $I^2 = 20.2\%$, $P = 0.263$) for aspartate aminotransferase[5,24] and alanine aminotransferase,[5,32] respectively. Alkaline phosphatase was also assessed by 1 trial[24]; the MD was nonsignificant and the GRADE low (Table 4). No significant change in findings was found in subgroup analysis.

For renal markers, neither creatinine nor blood urea nitrogen had a significant pooled MD. The MD for creatinine was −1.37 μmol/L (95%CI, −7.42 to 4.69; 2 trials; GRADE low),[5,32] with no heterogeneity, and for blood urea nitrogen −0.28 mmol/L (95%CI, −1.30 to 0.74; 2 trials; GRADE low),[5,32] with substantial heterogeneity of $I^2 = 54.9\%$, $P = 0.137$. In the case of blood urea nitrogen, the source of heterogeneity could be the dose of chia seed, as 1 trial[5] used a high dose of chia seed and another trial[32] used a medium dose. Separating the pooled analysis resulted in nonsignificant MDs for the individual trials (Table 5). The lack of statistical significance remained unchanged in subgroup analysis.

Markers of athletic performance. There was no significant difference for all but one of the athletic-related parameters between participants who received chia seed and the control group. The MDs for time and distance to exhaustion,[26] volume of oxygen consumption,[26] ventilation,[26] rating of perceived exertion,[26] respiratory exchange ratio,[26] plasma volume shift,[26] lactate,[26] glucose,[26] time to complete a 15-km trial,[27] and average power output[27] were all nonsignifcant; only the MD for heart rate was significant (Table 4).[26] Evidence for all parameters was GRADE low. The MD for heart rate was significant, with −2.00 beats per minute (95%CI, −361 to −0.39), GRADE low.[26] It should be noted, however, that the effect estimate of glucose assessed by 1 trial[26] was not combined with the effect estimates of the other 8 trials[5,6,8,24,25,28,30,31] summarized in glycemic parameters, as the regimens employed were intrinsically different.

Other parameters. There were no significant differences between participants who received chia seed and the control group for all other parameters related to hemostasis[24] (except for prothrombin time[24]), for satiety or glucose-regulating hormone[24,30,32] (except for ghrelin[32]), oxidative stress,[28] cortisol,[26] and nitrite,[28] and for appetite measurements[7,8] (except for 1 measurement[8]); evidence in all cases was GRADE low. The MDs for ghrelin and prothrombin time were significant: −211.40 seconds (95%CI, −361.83 to −60.97; 1 trial; GRADE low)[32] and −0.30 seconds (95%CI, −0.58 to −0.02; 1 trial; GRADE low),[24] respectively, while for appetite the MD was less than −0.001 min × mm (total of 2 h) (95%CI, < −0.001 to −2.98; 1 trial; GRADE low)[8] at a high dose (24 g/d) of chia seed intake (Table 4).

Adverse effects. Nine of the 14 included trials[5–7,24,25,28,29,31,32] assessed the adverse effects of chia seed, while the other 5 trials[8,23,26,27,30] did not report whether adverse effects were assessed. Of the 9 trials that assessed adverse effects, 2 reported no adverse effects.[6,7] The other trials reported gastrointestinal adverse effects (5 of 9),[5,24,28,31,32] difficulty in adhering to the regimen (1 of 9),[25] mental adverse effects (1 of 9),[31] and hepatic/renal disorder (1 of 9),[28] all with no significant differences between the participants who received chia seed and the control group. One trial did not report the results of adverse effects assessment.[29]

Sensitivity analysis It was not possible to perform a sensitivity analysis by excluding the data of trials with low

quality from the meta-analysis because a limited number of trials were pooled and because all trials were of low quality (high or unclear risk of bias).

DISCUSSION

To the extent of the authors' knowledge, this is the first systematic review that has included a meta-analysis component to estimate the effect size of chia seed on a number of parameters used to assess human health. The meta-analysis showed the pooled effects of chia seed on all parameters measured to be nonsignificant in main analysis. However, in subgroup analysis, the pooled effects on postprandial blood glucose, high-density lipoprotein, and diastolic blood pressure were significant when higher doses of chia seed were used. There was considerable uncertainty about the magnitude of the possible effects, although it appeared that the effects, if present, were at best modest and were probably not clinically significant. In addition, all trials included in the review employed surrogate markers as outcomes, making the findings less clinically meaningful.

The findings of this review were consistent with the results of a systematic review and meta-analysis of flaxseed, whose high alpha-linolenic acid content is similar to that of chia seed.[34] Like that systematic review and meta-analysis, the current review found that diastolic blood pressure was significantly lower postconsumption. However, in contrast to that systematic review and meta-analysis,[34] the present review showed that the effect of chia seed to reduce systolic blood pressure was not significant. Nevertheless, given the uncertainty about which main active ingredient of chia seed contributes to its health effects, the comparison with flaxseed was only to provide a reference to the food most similar to chia seed.

This review reveals that there was a lack of a suitable comparator used in most of the trials that employed active comparators (including wheat, oat, and poppy seed). This may have resulted in the lack of clinical benefits for the assessment. In addition, a few studies reported "nothing given" in the comparator group, which may have introduced performance bias in the trials by failing to blind the participants. Nevertheless, all trials in this review were assessed to have unclear or high risk of bias, and subgroup analysis was conducted to assess the effect of the use of active and nonactive comparators. Future trials should aim to achieve adequate blinding of participants by including a test to check whether participant blinding was successful.

The subgroup analysis that compared the clinical effects of Salba chia seed with those of conventional chia seed revealed no significant difference between the two. A number of glycemic and lipid parameters, however, showed an increased likelihood for trials that used Salba chia seed to report more favorable effects compared with trials that used conventional chia seed. Since all of the trials that used Salba chia seed had an unclear risk of bias when assessed in the subgroup analysis, it remains uncertain whether the more favorable effects reported with Salba chia seed are attributable to the type of chia seed used or to other factors. Future trials to compare the clinical effects between the two types of chia seeds are warranted. In addition, it is important that future trials report any potential conflict of interest to prevent potential bias.

The subgroup analysis also generated a number of hypotheses, including the possibility that higher doses of chia seed may result in greater clinical effects, including the lowering of postprandial blood glucose (statistically significant and in favor of chia seed) and the increasing of total cholesterol, low-density lipoprotein, and triglyceride and the lowering of high-density lipoprotein (all nonsignificant and not in favor of chia seed). The selection of participants and the dosage of chia seed may also influence the clinical effects of chia seed, as overweight/obese participants had greater body weight gain and greater body fat mass gain compared with those with health conditions who were also overweight/obese, while participants with health conditions showed greater improvement in lipid parameters compared with those without health conditions. Finally, ground chia seed resulted in more favorable outcomes for systolic blood pressure, fasting blood glucose, and anthropometric and lipid parameters compared with whole chia seed; however, only whole chia seed had a significant effect on the reduction of postprandial blood glucose. Importantly, the hypotheses generated were based on single trials or on trials with an unclear or high risk of bias. In addition, while trials were grouped according to homogenous characteristics for one of the specific characteristics, other PICOS parameters may have substantial heterogeneity. Therefore, the hypotheses must be further investigated in rigorously conducted studies.

As with any systematic review and meta-analysis, this review shares the limitations of the original trials. First, a major issue is that all trials were found to have very low quality of evidence (all had either an unclear or a high risk of bias). Results were imprecise when the sample size was less than 400 for all outcomes assessed and the confidence interval included both clinically important benefits and clinical harm, or both clinically important effects and null effects. The overall very low quality of evidence based on the GRADE approach indicates that findings should be interpreted with caution. Other systematic reviews and meta-analyses of herbal[35] and food[36] products have noted similar issues with quality of evidence. In light of this, future trials should aim to improve the methodological quality by ensuring adequate blinding, randomization, and allocation concealment; by clearly reporting any potential

conflict of interest, as highlighted in the risk-of-bias assessment; and by using sample sizes of at least 400 to increase precision.[37] Second, all trials included in this review used only surrogate markers to measure outcomes. Although the use of surrogate markers is more efficient for conducting clinical trials, it may have limited value in predicting clinical benefit, especially for long-term clinical outcomes.[38] Future trials should use clinical events as outcomes or should validate the surrogate markers by demonstrating a clear association with the clinical outcomes.[39] Third, to provide plausible effect estimates and pose new questions about the clinical effects of chia seed with exploratory meta-analysis,[40] the data were pooled from individual studies with broadly similar characteristics in terms of population and intervention.[41] Fourth, although an exhaustive literature search was performed and an effort was made to include gray literature, there might be unpublished studies that were missed. Lastly, publication bias could not be reliably assessed by funnel plots or other means, owing to the small number of included studies.

CONCLUSION

This review provides crucial information for healthcare providers and the public to understand the current evidence regarding health claims for chia seed. The current evidence does not support any health claim for chia seed in any indication. Nevertheless, this systematic review and exploratory meta-analysis has generated hypotheses for future studies to investigate the effects of chia seed on a dose–response gradient. The use of reputable methodological tools for quality assessment (Cochrane Risk of Bias Tool and GRADE) in this review has identified methodological gaps that provide a reference for the design of future high-quality randomized controlled trials to evaluate the clinical effects of chia seed.

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Declaration of interest. V.V. acted as a consultant to Salba Corporation, Buenos Aires, Argentina (2003–2006), and to Core Naturals, Winter Springs, Florida, USA (2007–2008), and received conference travel grants from Salba Smart Natural Products, LLC, Centennial, Colorado, USA (2008 and 2010), and Source Salba, Inc, Toronto, Ontario, Canada (2008). V.V. holds American (no. 7 326 404 B2) and Canadian (no. 2 410 556) patents for the use of viscous fiber blend in diabetes, metabolic syndrome, and cholesterol lowering; received a honorarium for scientific advice from InovoBiologic, Calgary, Alberta, Canada, the producer of the viscous fiber blend PGX that was developed on the basis of V.V.'s patent. All other authors have no conflict of interest related to this manuscript.

Supporting Information

The following Supporting Information is available through the online version of this article at the publisher's website:

Table S1 **PRISMA checklist**

Table S2 **Studies excluded after full-text reading**

Table S3 **Risk-of-bias assessment of trials included in the systematic review**

Figure S1 **Pooled effect estimates for the main analysis on the clinical effects of chia seed.**

Figure S2 **Pooled-effects estimates for subgroup analyses on the clinical effects of chia seed.**

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