Effectiveness of chia (*Salvia hispanica L.*) as an adjuvant therapy for Type 2 diabetes mellitus: A systematic review and meta-analysis

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Abstract

Introduction Salba-chia (Salvia hispanica L.) is a popular functional food containing high levels of protein, total dietary fiber, and is an excellent source of α-linolenic acid. Chia seeds significantly decreases weight, suppresses appetite, and has a potential benefit in the management of Type 2 diabetes mellitus (T2DM). This study aimed to determine the effectiveness of chia seeds as an adjuvant treatment for T2DM.
Methods Randomized controlled trials from 1990 onwards involving Type 2 diabetic patients given chia seed were included. PubMed, Cochrane, ClinicalKey, Google Scholar, and Hinari were searched systematically using MeSH terms "chia", "*Salvia hispanica*", "dietary supplement", and "diabetes". The quality of trials was assessed using the Cochrane Collaboration tool. Data on the study design, blinding status, characteristics of participants, medications taken by participants, chia seed intervention, comparator, duration of intake, and interval of assessment were extracted. The percent change of outcome from baseline was compared between the chia and control groups.
Results Four randomized trials with a total of 213 diabetic patients were enrolled in the treatment group using ground salba-chia or the control group using bran. The supplementation of chia resulted in a statistically significant decrease in fasting glucose (-2.90 mmol/L; 95% CI, -3.08, -2.72; $p < 0.001$), waist circumference (-2.49 cm; 95% CI -2.81, -2.17; $p < 0.001$), total cholesterol (-2.72 mmol/L; 95% CI -3.68, -1.74; $p < 0.001$), HDL (-3.69 mmol/L; 95% CI -3.95, -3.42; $p < 0.001$), LDL (-3.22 mmol/L; 95% CI -4.08, -2.36; $p < 0.001$); and an increase adiponectin levels (6.50 mg/L; 95% CI 6.25, 6.25; $p < 0.001$).
Conclusion Intake of chia seeds resulted in a statistically significant decrease in fasting blood glucose, waist circumference, total cholesterol levels, HDL and LDL cholesterol levels, and increased adiponectin. Chia seeds are generally safer and have lesser side effects compared to the placebo. Chia is effective as adjunctive treatment for Type 2 diabetic patients.

Key words: Chia, Type 2 diabetes, glycemic control, appetite suppression, dietary supplement, adjunct, adjuvant

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There is an increasing popularity of chia seeds in the Philippine market as a possible therapeutic option for a variety of common diseases such as diabetes, obesity, and cardiovascular problems. Chia seeds contain high levels of protein (16-26%) and total dietary fiber (23-41%). It is an excellent source of polyunsaturated fatty acids such as α-linolenic (60%) and linoleic (20%) acids.[1,2] Studies have shown that these nutrients have a significant effect in weight

control and in some cases, in improving cardiovascular disease risk factors.

A literature search showed one meta-analysis on dietary supplementation with chia seed covering all health conditions.[3] Two previous reviews summarized the evidence on the effects of chia seed but used very broad inclusion criteria (i.e., non-human studies and non-clinical trials) and evaluated the cardiovascular risk factors only.[4,5] The objective of this study is to determine the effectiveness of chia seeds as an adjuvant treatment for Type 2 diabetes mellitus in terms of reduction or improvement of glycemic control, waist circumference, and its effect on the lipid profile, and safety through a systematic review of available clinical evidence in humans.

Methods

This meta-analysis was performed in accordance with the principles outlined in the Cochrane Handbook for Systematic Reviews of Interventions and is reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement.[6,7] The studies for inclusion were randomized clinical trials from 1990 onwards in English involving patients with Type 2 diabetes mellitus - not limited by age, sex, and race - whose interventions used chia seeds (in any functional form) as an adjuvant therapy directly compared with another drug or supplement or placebo, and whose outcome of treatment success included but was not limited to reduction or improvement of glycemic control, weight loss, and reduction of waist circumference.

The literature search was conducted from September 9 to 20, 2020 on MEDLINE (PubMed), Cochrane Library (CENTRAL), Clinical Key (Elsevier), Google Scholar, and Hinari. Search strategies for each of these databases were developed using Medical Subject Headings (MeSH) terms, including keywords: "chia", "chia seeds", "salvia", "Salvia hispanica", "salvia and chemistry", "seeds and chemistry", "alpha-linolenic acid and blood", "dietary supplements", "chia supplementation", "supplementation", "adjuvant therapy or adjuvant", "overweight", "obesity and blood", "metabolic", "metabolomics and methods", "hyperlipidemia", "lipid profile and lipid", "LDL", "HDL", "triglyceride, "blood glucose", "lipoproteins and blood", "dietary fats and blood", "effect", "diabetes", "glycemic", "Hba1c", "weight loss", "satiety", "insulin", "chia and adjuvant therapy", "chia and diabetes", and "chia and dietary supplementation". Five pairs of review authors independently screened the titles and abstracts obtained in the search against the inclusion criteria. These were then assessed by the primary investigator and another main author for eligibility. The full reports were then obtained for all titles that met the inclusion criteria or when there was uncertainty. All review authors then screened the full text reports, decided whether these met the inclusion criteria, and then recorded the reasons for exclusion. Disagreements were resolved through discussion. No review authors were blinded to the journal titles or to the study authors or institutions.

Five teams of review authors extracted data independently and in pairs from each eligible study using REVMAN. All review authors utilized a standardized data extraction sheet (i.e., web-based Google Docs Office Suite) to extract the characteristics and results of the clinical trials. Data extracted were the demographic and clinical characteristics of the subjects (mean age, gender, baseline diabetes profile, and medications), trial design, trial size, frequency and duration of treatment, composition and form of chia seed and its comparator used, medications given, daily quantity intake, diet control, duration of intake and duration of follow-up. Whenever possible, results from an intention to treat analysis were used.

Critical appraisal of each article was done using the Center for Evidence-Based Medicine (CEBM) Critical Appraisal Tool to assess the risk of bias. To facilitate the assessment of risk of bias for each study, the researchers collected information using the Cochrane Collaboration tool for assessing the risk of bias which covered sequence generation, allocation concealment, blinding, incomplete outcome data (e.g., dropouts and withdrawals) and selective outcome reporting. All data were encoded using RevMan 5.4.1.

Outcomes of interest included the following: glycemic control based on glycosylated hemoglobin (HbA1c) and fasting blood glucose; effect on waist circumference, lipid profile, and on adiponectin. The percent change of outcome from the baseline was compared between the chia and control groups. The results were expressed as mean differences with 95% confidence intervals. A statistical significance level of $p < 0.05$ was used together with 95% confidence intervals. Relative risk was used to determine the risk of an outcome or side effect in both chia and control groups. A relative risk < 1.00 was deemed to

have a decreased risk of experiencing the side effect. Statistical heterogeneity was evaluated by chi square and I-test. The authors used an I2 > 75% and a $p < 0.01$ for chi-square as indicative of statistical heterogeneity.[8]

Results

The electronic search yielded a total of 166 articles of which 63 were screened. Thirty of the screened articles were deemed relevant and their full texts were retrieved for review. Twenty-six articles were excluded because they included non-diabetic participants (n = 6), did not use chia as adjunct therapy (n = 6), or had inadequate data (n = 14). Thus, only four trials involving 213 participants were included in this review. The flow diagram of study selection is shown in Figure 1.

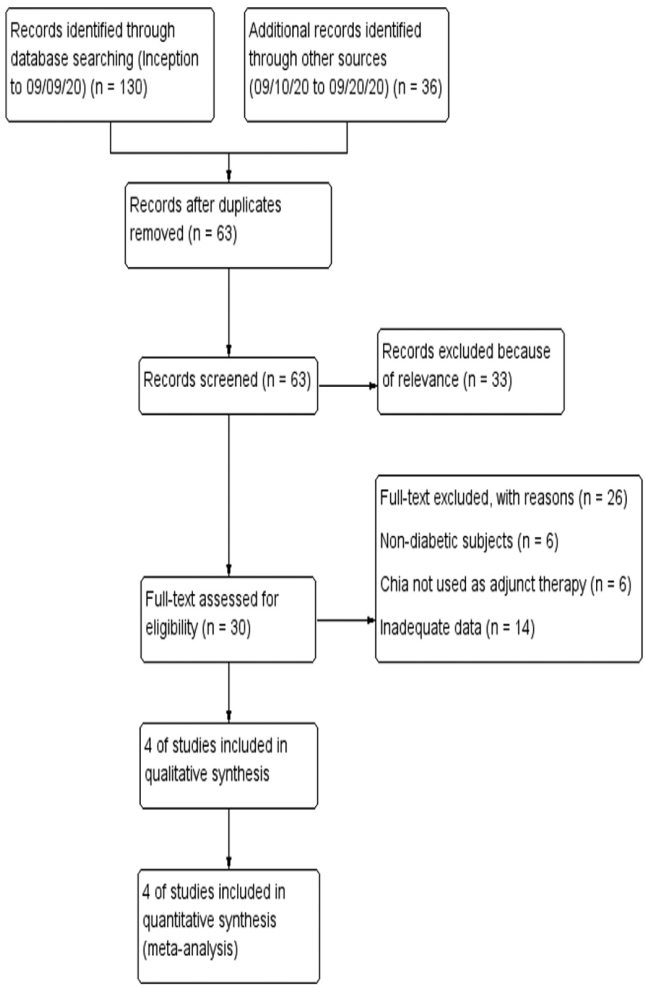

Figure 1. Flow diagram of the article screening and selection process.

The characteristics of the four included studies are summarized in Table 1. All trials were conducted in Canada. Three studies utilized a double-blind parallel design and their primary inclusion criteria consisted of those with Type 2 diabetes mellitus of one year with baseline HbA1c levels between 6.5 and 8.0%.[9,10,11] One study used a single-blind cross-over design and included those who had Type 2 diabetes mellitus of at least six months duration.[12] All studies required that the participants be treated with diet and/or oral hypoglycemic medications. Medications received concomitantly by the participants were either single or combined oral hypoglycemic agents such as insulin secretagogues, metformin, pioglitazone, HMG-CoA reductase inhibitors, atorvastatin, and simvastatin. Ground salba-chia was the main form of treatment for all studies. The control in three studies was oat-bran while one study used wheat-bran.

Most studies had a low overall low risk of bias as shown in Figure 2. The risk was low except for attrition bias as all four studies had attrition rates of 25%, 26%, 32%, and 26%, making them high risk, as shown in Figure 3. Vuksan's 2007 study did not do an intention-to-treat analysis (Figure 3).

There was a statistically significant decrease in the fasting glucose level of 2.90 mmol/L (95% CI -3.08%, -2.72%; $p < 0.001$; $I^2 = 0\%$, $x^2 = 0.81$) in the studies of Brisette and Vuksan (2007) as shown in Figure 4. Two out of three studies showed an increase in HbA1c levels; however, the overall effect was not statistically significant (1.03%; 95% CI -1.43, 3.50; $p = 0.41$; $I^2 = 100\%$, $x^2 < 0.001$) as shown in Figure 5. Two studies showed a significant mean decrease in body weight and two showed an increase. The result was an overall 0.64 kg (95% CI (-1.85, 0.57; $p = 0.30$) decrease which was not statistically significant. Three studies showed a significant mean decrease in the waist circumference ranging from 2.40 to 3.10 cm. The overall decrease of -2.49cm (95% CI (-2.81, -2.17; $p < 0.00$; $I^2 = 0\%$, $x^2 = 0.42$) was statistically significant, as shown in Figure 6. Brisette and Vulcan (2007) showed a statistically significant decrease in the total cholesterol of 2.72 mmol/L (95% CI -3.69, -1.74; $p < 0.001$; $I^2 = 0\%$, $x^2 = 0.67$), as shown in Figure 7. The summary data of both studies showed a statistically significant decrease in the HDL (-3.69 mmol/L (95% CI -3.95, -3.42; $p < 0.001$; $I^2 = 65\%$, $x^2 = 0.09$) and LDL-C levels (-3.22 mmol/L; 95% CI (-4.08, -2.36; $p < 0.001$; $I^2 = 0\%$, $x^2 = 0.80$), as shown in Figures 8 and 9. Brisette and Vuksan (2016) demonstrated a statistically significant

Table 1. Characteristics of included studies (n = 4).

Reference	RCT design; blinding status (stated by the author)	Total no. of participants (ITT; completed trial)	Characteristics, mean age (years) and age range of participants	Medications taken by 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
Vuksan, et al (2016) Canada	Randomized, double-blind, parallel design, Intention-to-treat analysis	77: 54	Presence of type 2 diabetes mellitus of 1 year (HbA1c between 6.5 and 8.0%) 55 (35 – 75)	Metformin (MET), MET + Sulfonylurea (SU), Metformin + Thiazolidinedione (TZD), Metformin + dipeptidyl peptidase 4 (DPP4), MET + SU +TZD, SU + DPP-4, SU + DPP4 Meglitinides (MIG) + TZD	Ground salba-chia	Oat-bran based control; no	30g/1000kcal/ day Yes	6 months
Vuksan, et al (2007) Canada	Randomized, placebo-controlled, single-blind, cross-over	27: 20	Stable type 2 diabetes (HbA1C,6.0% to 8.5%; fasting plasma glucose, 6.4-8.5mmol/L) of at least 6 months duration 64 (18 – 75)	Insulin secretagogues, Metformin, Pioglitazone	Ground form added to bread for both groups	Wheat bran; no	37 +/- 4g Yes	12 weeks (84 days)
Brisette (2013) Canada	Randomized, double-blind, parallel study Intention-to-treat analysis	78:58	Stable type 2 diabetes (HbA1C,6.0% to 8.5%; fasting plasma glucose, 6.4-8.5mmol/L) at least 1 year 55 (35 – 75)	Antihyperglycemic agents biguanides (Metformin), sulphonylureas (Glyburide, Glipizide) thiazolidinediones (Pioglitazone), dipeptidyl peptidase-4 inhibitors (Sitagliptin) and combinations of these (Janumet)	Ground salba	Oat bran, inulin, maltodextrin; no	7.5g Yes	24 weeks or 168 days
Choleva (2011) Canada	Randomized, double-blind, placebo-controlled, parallel design Intention-to-treat analysis	41: 20	T2DM for at least 1 year (treated with diet and/or oral hypoglycemic medications) (HbA1c between 6.5% and 8.0%) 55y (35 - 75)	Anti-hyperglycemic medications included biguanides (Metformin), sulphonylureas (Glyburide, Glipizide) thiazolidinediones (Pioglitazone), dipeptidyl peptidase-4 inhibitors (Sitagliptin) and combinations of these (Janumet).	Ground Salba and Salba enriched bread	Oat bran, inulin, maltodextrin; no	30g of Salba/1000kcal intake Yes	24 weeks or 168 days

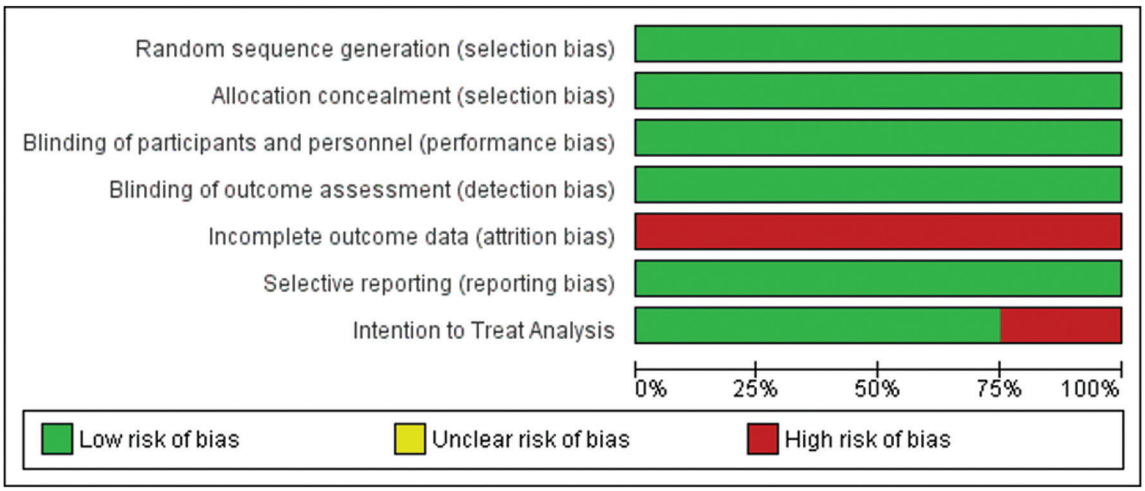

Figure 2. Risk of bias graph for all studies.

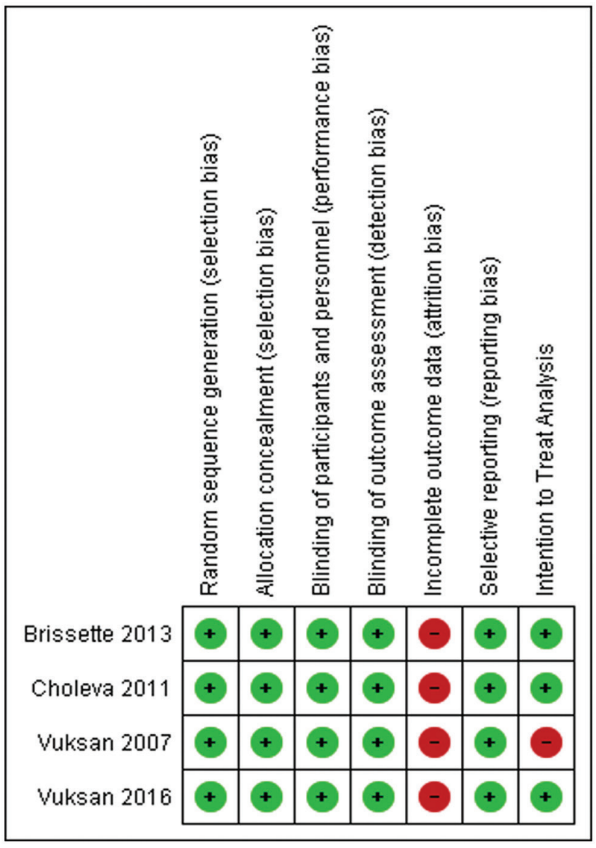

Figure 3. Risk of bias summary for individual studies.

6.50 mg/L increase in the adiponectin levels (95% CI 6.25, 6.75; $p < 0.001$; $I^2 = 0\%$, $x^2 = 1.00$) as shown in Figure 10.

Bristte, Choleva and Vuksan (2007), but not Vuksan (2016) found a decreased risk of gastrointestinal symptoms; the overall effect was a statistically significant lower risk of experiencing bloating, belching, diarrhea, flatulence, constipation, nausea, and abdominal pain (RR = 0.37, 95% CI 0.25, 0.55; $I^2 = 0\%$, $x^2 = 0.45$) as shown in Figure 11. Brisette and Choleva showed a decrease in the risk of renal symptoms that was not statistically significant (RR = 0.38, 95% CI 0.06, 2.34; p = 0.30). The same studies also showed a decrease in the risk of neurologic symptoms that was not statistically significant (RR = 0.60, 95% CI 0.32, 1.13; p = 0.11).

Discussion

Four studies with 213 participants were included in this systematic review and meta-analysis. The parameters investigated in this study included glycemic control, waist circumference, lipid profile, and satiety hormones. In summary, chia seeds as adjuvant treatment led to statistically significant decreases in fasting blood glucose, waist circumference, total cholesterol, HDL and LDL and a statistically significant increase in adiponectin. Except for the decrease in HDL, all these outcome parameters favor the use of chia seeds as an adjuvant treatment for diabetes. Side effects noted in this study included symptoms referrable to the gastrointestinal tract, kidneys, and central nervous system. There was a statistically significant reduced risk of experiencing gastrointestinal symptoms (i.e., bloating, belching, diarrhea, flatulence, constipation,

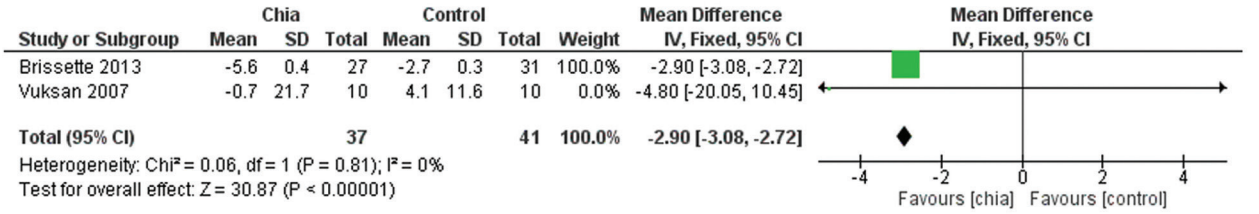

Figure 4. Forest plot of the effect of chia seeds on fasting blood glucose.

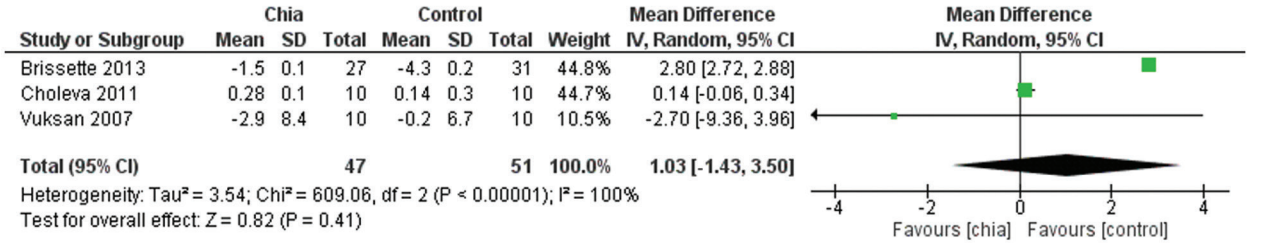

Figure 5. Forest plot of the effect of chia seeds on HbA1c.

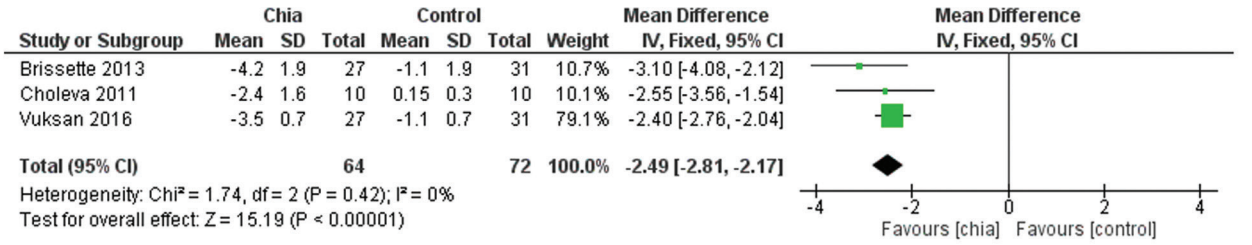

Figure 6. Forest plot of the effect of chia seeds on waist circumference.

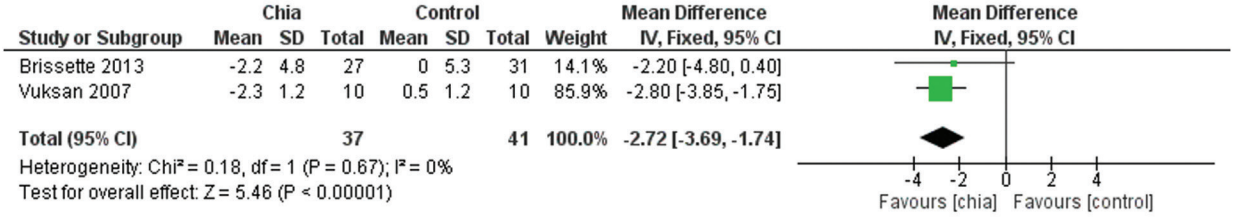

Figure 7. Forest plot of the effect of chia seeds on total cholesterol.

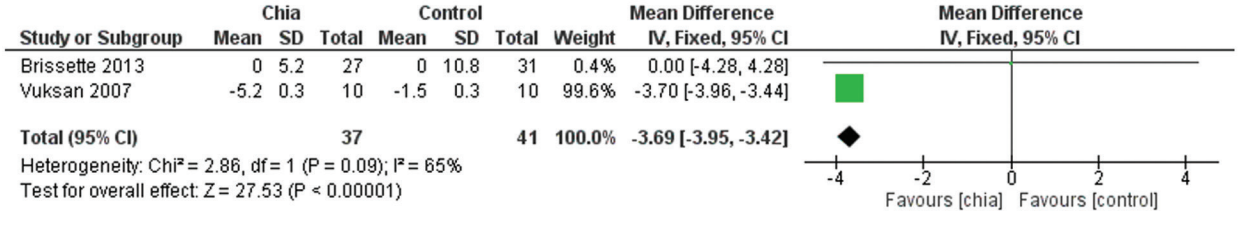

Figure 8. Forest plot of the effect of chia seeds on HDL.

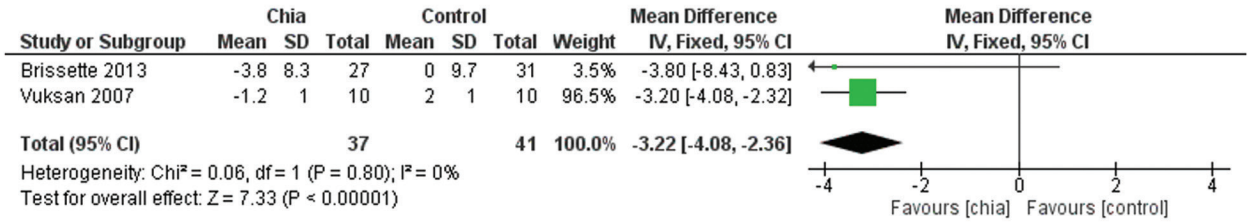

Figure 9. Forest plot of the effect of chia seeds on LDL.

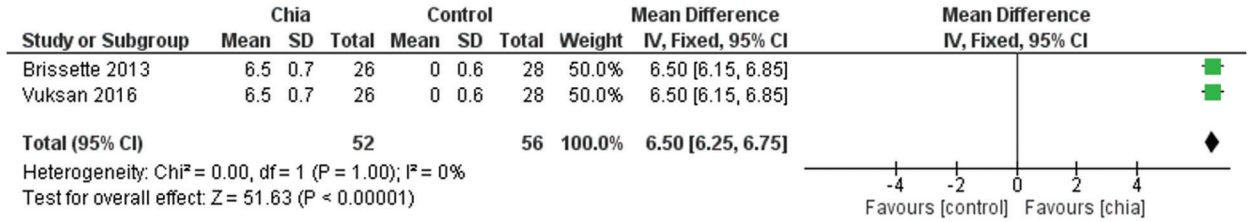

Figure 10. Forest plot of the effect of chia seeds on adiponectin.

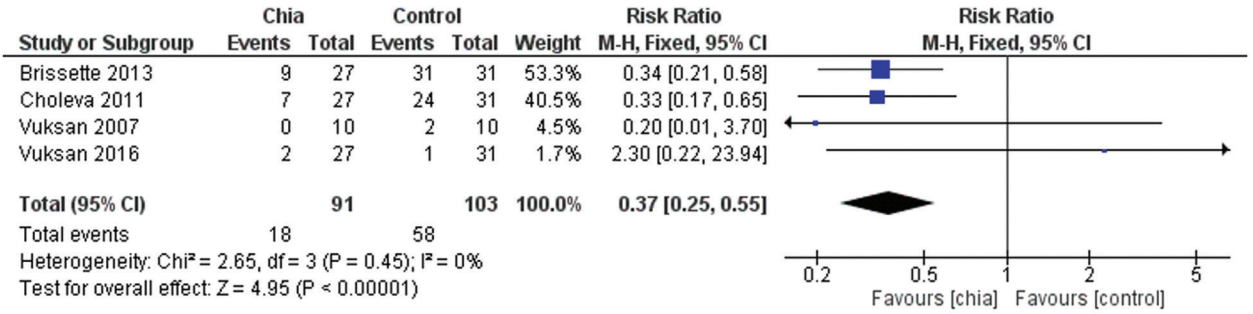

Figure 11. Forest plot of the gastrointestinal side effects of chia seeds.

nausea, and abdominal pain) for those who used chia seeds as adjuvant therapy compared to the control group. There was also a reduced risk of developing renal symptoms (i.e., excessive urination), and CNS symptoms (i.e., headache, dizziness) but the results were not statistically significant.

Although this meta-analysis has shown that chia seeds had a significant effect on fasting blood glucose, waist circumference, total cholesterol, HDL, LDL, and adiponectin, previous meta-analyses did not share the same result. However, the subgroup analysis done by Teoh showed significant effects on postprandial glucose, HDL cholesterol, and diastolic blood pressure when a higher dose of chia seeds was used.[3]

It is postulated that the high fiber content of chia seeds leads to its effect. Chia seeds contain about 23% to 41% dietary fiber, making it a high fiber containing food.[1,2] Fibers are known to induce satiety, causing lower food intake and greater weight changes. The lack of statistical significance for weight loss obtained in this meta-analysis may be attributed to the lack of dietary restrictions noted in the methodology of the studies.[10] In a study where the participants were put in a 500 kcal reduced diet based on the estimated energy requirement using the Harris-Benedict Equation, reduction in weight led to a 58% reduction in the occurrence of T2DM if there was a sustained weight loss of $\geq$ 3.5 kg.[12] Chia seeds with an addition of dietary restriction caused a significant reduction in weight.[9]

In addition to satiety, dietary fiber causes delays in digestion, gastric emptying time and absorption

of carbohydrates that controls hyperglycemia in T2DM patients.[13] Lipid lowering effects by fibers were attributed to the binding of soluble fibers to bile acids and cholesterols during micelle formation. This results in decreased cholesterol levels in the liver causing upregulation of the LDL receptor that enables the clearance of LDL cholesterol.[14] Addition of 4 to 19 grams of fiber supplements in the daily diet improves glycemic control and lowers the risk for cardiovascular events.[15]

Based on the β Cell-Centric Model: Egregious Eleven, there are eleven known pathways that lead to the development of hyperglycemia in diabetes mellitus. These involve the β-cells, incretin, β-cells, brain, liver, muscle, adipose tissue, colon, stomach, small intestine, kidney and the inflammatory response.[16] Chia seeds acts on the gastrointestinal tract, mainly the stomach and small intestine, leading to a decrease in the overall rate of absorption of carbohydrates.[13] Chia seeds' effect on adiponectin, a satiety-regulating hormone often noted to be low among patients with T2DM, is directly correlated to its ability to decrease plasma glucose levels.[17,18] Studies have shown that increasing fiber intake causes an elevation in the plasma adiponectin levels among both diabetic men and women.[18,19] Adiponectin not only increases insulin sensitivity but also decreases risk for atherosclerotic disease.[20] Another study has indicated fiber can increase post-meal insulin and GLP-1 within 15 minutes as compared to a diet without fiber. However, the exact mechanism of action is currently unknown.[21]

A systematic review and meta-analysis of four randomized clinical trials involving 213 participants demonstrated a statistically significant decrease in fasting blood glucose, waist circumference, total cholesterol levels, HDL and LDL cholesterol levels, and an increase in adiponectin. There was lower risk of side effects of those taking chia seeds. Chia is effective as adjunctive treatment for type 2 diabetic patients.

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