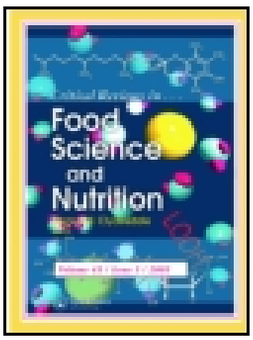

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The effects of tocotrienols intake on obesity, blood pressure, inflammation, liver and glucose biomarkers: a meta-analysis of randomized controlled trials

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REVIEW

The effects of tocotrienols intake on obesity, blood pressure, inflammation, liver and glucose biomarkers: a meta-analysis of randomized controlled trials

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ABSTRACT

The objective of this study is to accomplish a systematic review and meta-analysis of all randomized controlled trials that dissected the influence of tocotrienol supplementation on various anthropometric and cardiometabolic indices in all individuals, irrespective of health condition. This research was carried out in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement guidelines. 17 eligible articles were included in the final quantitative analysis. Current study revealed that tocotrienol consumption was not associated with CRP, WC, MDA, BMI, IL-6, HbA1C, ALT, AST, creatinine TNF-α, FPG, BW, DBP, and SBP. We did observe an overall increase in BW (SMD: 0.063 kg, 95% CI: −0.200, 0.327, $p = 0.637$) and DBP (SMD: 0.249 mmHg, 95% CI: 0.053, 0.446, $p = 0.013$). In addition, a significant reduction in SBP was observed (SMD: −0.616 mmHg, 95% CI: −1.123, −0.110, $p = 0.017$). In summary, our meta-analysis revealed that tocotrienol consumption was associated with increase in BW and DBP and decrease in SBP. Significant associations were not observed for other outcomes.

KEYWORDS

Tocotrienol; Vegetable oils; BMI; Blood Pressure; Inflammation; Liver

Introduction

Hypertension, obesity, and diabetes mellitus are frequent cardiometabolic disorders worldwide (Global, regional, and national 2018). Recent literature emphasize the importance of nutritional habits as pivotal determinants of health (Mozaffarian 2016; Miranda et al. 2019; Rahimlou, Ahmadnia, and Hekmatdoost 2015). Nowadays, nutritional supplementation plays a central role in prevention and management of such cardiometabolic disorders (Mozaffarian 2016; Miranda et al. 2019).

Vitamin E belongs to a family of fat-soluble micronutrients. It is comprised of two major phytochemicals, known as tocopherols and tocotrienols. Each phytochemical is comprised of four isoforms, known as alpha, beta, gamma, and delta (Aggarwal et al. 2010). Delta-tocotrienol is recognized as the most potent isoform of vitamin E (Vasanthi, Parameswari, and Das 2012) and correlates with better bioavailability when administered at higher doses (Qureshi et al. 2016). From a structural perspective, tocopherols and tocotrienols are differentiated based on the presence of saturated and polyunsaturated side chains, respectively (Aggarwal et al. 2010). The presence of polyunsaturated side chains in tocotrienols is advantageous as it facilitates easier penetration into tissues (Ahsan et al. 2014).

Tocotrienol supplementation has been shown to demonstrate various broad-ranging useful properties, including cardiometabolic-protective effects, in addition to anti-cancer, anti-inflammatory and anti-oxidant effects (Ahsan et al. 2014; Pervez et al. 2018). Additionally, tocotrienols possess antidiabetic properties, primarily ascribed to their insulinotropic (Kim et al. 2016; Chia et al. 2016) and insulin-sensitizing activities (Kim et al. 2016; Fang, Kang, and Wong 2010).

Multiplicity of randomized controlled trials have been performed to explore the efficacy of tocotrienol supplementation on various anthropometric and cardiometabolic indices (Stonehouse et al. 2016; Heng et al. 2015; Tan et al. 2018; Baliarsingh, Beg, and Ahmad 2005; Goon et al. 2017; Chin et al. 2011; Rasool et al. 2006; Rasool et al. 2008; Pervez et al. 2018; Shen et al. 2018; Daud et al. 2013; Schuchardt, Heine, and Hahn 2015; Haghighat et al. 2014; Vafa et al. 2015; Gopalan et al. 2014; Wan Nazaimoon et al. 1996; Nesaretnam et al. 2010). Nonetheless, the results were not consistent and limited by the relative small sample size, dissimilar supplementation dosage, and variable underlying health status. Up to the present time, no comprehensive meta-analysis has been done to gather evidence from randomized controlled trials to endorse solid nutritional conclusions regarding efficacy of tocotrienol supplementation.

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Hence, the objective of this study is to accomplish a systematic review and meta-analysis of all randomized controlled trials that dissected the influence of tocotrienol supplementation on various anthropometric and cardiometabolic indices in all individuals, irrespective of health condition.

Methods

This research was carried out in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement guidelines (Moher et al. 2009).

Search strategy

The present systematic literature search was implemented over online databases including SCOPUS, Web of Science, PubMed/Medline, Embase, and Google Scholar from inception to 20 July 2020. The effects of tocotrienol supplementation on obesity, blood pressure, inflammation, liver, and glucose biomarkers were identified using MeSH and non-MeSH terms: (("Tocotrienol" OR "Tocotrienols") AND ("Clinical Trials" OR "RCT" OR "controlled trial" OR "randomized" OR "random" OR "intervention" OR "Trial" OR "Intervention Studies" OR "randomized" OR "placebo"). A step-wise and rigorous systematic database search was augmented with manual searches of gray literature (reference lists from all the relevant articles). Following the initial identification of relevant articles, titles and abstracts were screened for inclusion, removing any duplicates.

Eligibility criteria

Inclusion criteria included: (i) original trials with RCT designs (parallel/crossover), and (ii) RCTs that evaluated the influence of tocotrienol on one or more outcome measures including body weight (BW), body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), fasting blood sugar (FBS), waist circumference (WC), c reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), fasting plasma glucose (FPG), glycated hemoglobin A1C (HbA1C), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and creatinine. Exclusion criteria included: (i) case-control studies/series (ii) preclinical studies, (iii) retrospective studies, (iv) reviews, letters, editorials, and commentaries, (v) duplicated studies, (vi) studies investigating the impacts of tocotrienol in combination with other medications, (vii) studies not reporting outcomes of interest, (viii) tocotrienol intake with other supplements, and (ix) gray literature (theses, congress proceedings, and technical reports).

Data extraction

Data were extracted independently by two investigators. Any disagreements between the two investigators were resolved by the heading author until an agreement was obtained. Extracted data included the following: (i) study design, (ii) characteristics of the studied sample (age of participants, gender, and health status), (iii) tocotrienol dosage, (iv) study details (study author, year of publication, sample size, trial duration), (v) study location, and (vi) post-supplementation outcome measures (biochemical parameters and obesity indices) mean and standard deviation (SD).

Quality assessment

The Cochrane Collaboration's tool for assessing risk of bias in randomized trials was applied for evaluating the risk of bias using the following criteria: (i) allocation concealment, (ii) random sequence generation, (iii) blinding of healthcare personnel and participants, (iv) blinding of outcome data, (v) selective reporting, (vi) incompleteness of outcome data, and (vii) other sources of bias and attrition bias. A qualitative degree was assigned for each item (no, yes or unclear) and an final judgment of high risk, low risk, or unknown risk was recognized for included studies (Borenstein et al. 2011).

Data synthesis and statistical analysis

Raw data in the format of a mean and SD for outcome measures pre- and post-supplementation (WC, BW, BMI, SBP, DBP, CRP, IL-6, TNF-α, FBS, HbA1C, AST, ALT, and creatinine) were used to compute the effect size. The random-effects model was used to calculate weighted mean differences (WMDs) or standardized weighted differences (SMDs) and 95% confidence intervals (95% CIs). When the SD of a mean difference was not described in a study, standardized formulas were applied to derive the mean and SD (Borenstein et al. 2011; Hozo, Djulbegovic, and Hozo 2005). Estimation of publication bias was evaluated by visual inspection of the funnel plot and Egger's regression test (Egger et al. 1997). Where publication bias was detected, it was rectified by the "trim and fill" method to estimate potentially missing studies (Palmer et al. 2008). Assessment of between-study heterogeneity was employed Higgin's I-square (I^2) statistic. Statistical analyses were performed using STATA software.

Results

Study selection

In the first stage, a total of 1524 articles was identified through electronic search, 917 of which were similar. After screening throughout title and abstract, 57 articles met our eligible criteria and underwent full-text evaluation. Finally, full-text screening included 17 articles (Stonehouse et al. 2016; Heng et al. 2015; Tan et al. 2018; Baliarsingh, Beg, and Ahmad 2005; Goon et al. 2017; Chin et al. 2011; Rasool et al. 2006; Rasool et al. 2008; Pervez et al. 2018; Shen et al. 2018; Daud et al. 2013; Schuchardt, Heine, and Hahn 2015; Haghighat et al. 2014; Vafa et al. 2015; Gopalan et al. 2014; Wan Nazaimoon et al. 1996; Nesaretnam et al. 2010) with 24 arms for the analyses (Figure 1).

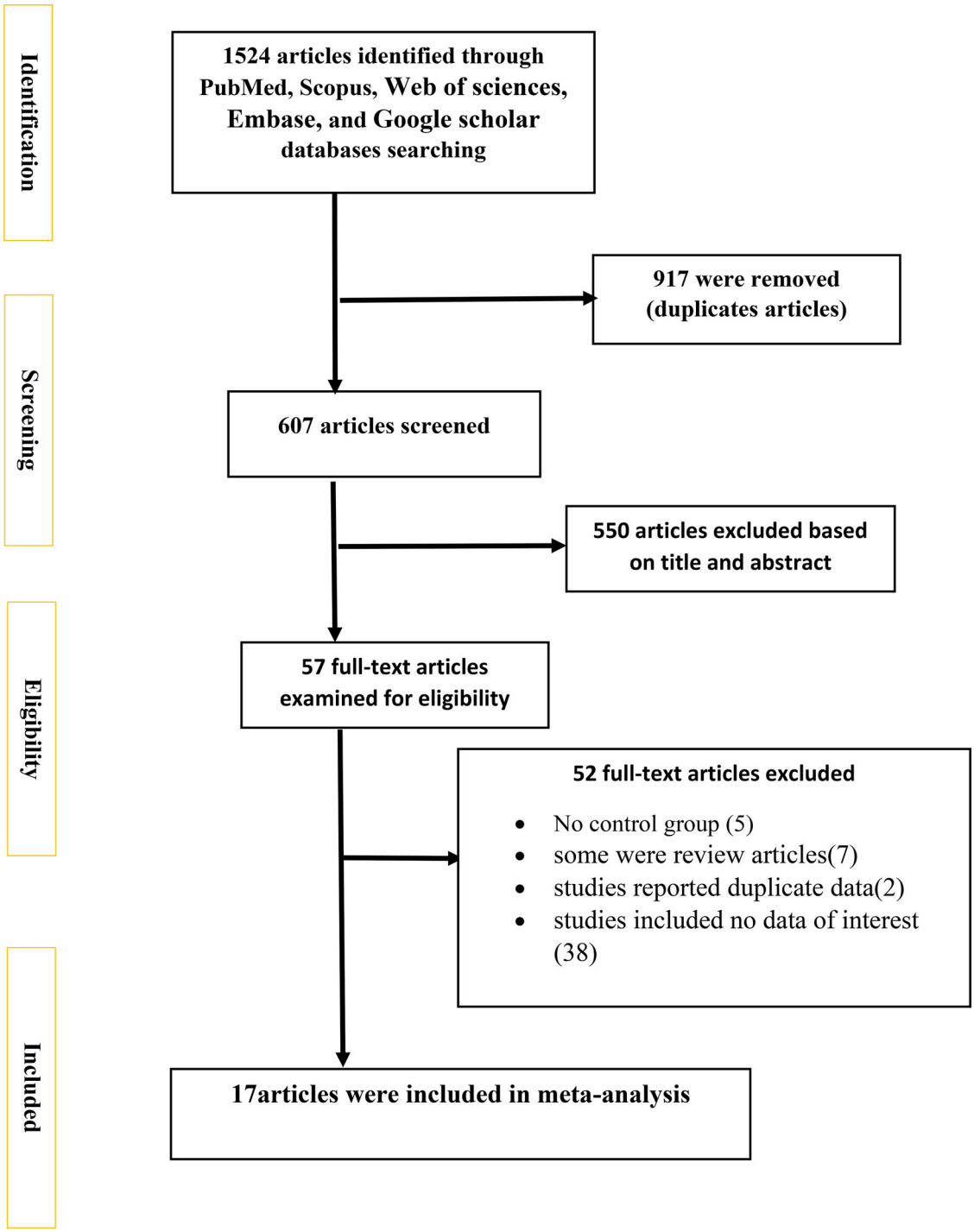

Figure 1. Flow chart for study examined and included into the meta-analysis.

Characteristics of the included studies

Characteristics of the included studies are summarized in Table 1. This study included articles published between 1991 and 2018 and conducted in Malaysia (Heng et al. 2015; Tan et al. 2018; Goon et al. 2017; Rasool et al. 2006; Rasool et al. 2008; Chin et al. 2011; Gopalan et al. 2014; Wan Nazaimoon et al. 1996; Nesaretnam et al. 2010), Pakistan (Pervez et al. 2018), Australia (Stonehouse et al. 2016), India (Baliarsingh, Beg, and Ahmad 2005), Iran (Haghighat et al. 2014; Vafa et al. 2015), Germany (Schuchardt, Heine, and Hahn 2015), and USA (Daud et al. 2013; Shen et al. 2018). Sample size ranged from 18 (Rasool et al. 2008; Rasool et al. 2006) to 240 (Nesaretnam et al. 2010) participants and intervention duration varied from 60 days (Baliarsingh, Beg, and Ahmad 2005) to 5 years (Nesaretnam et al. 2010). Daily dosage of tocotrienol differed from 27 mg (Schuchardt, Heine, and Hahn 2015) to 860 mg (Shen et al. 2018). Six arms (two studies) enclosed male subjects only (Rasool et al. 2008; Rasool et al. 2006) and three articles encompassed only female subjects (Shen et al. 2018; Goon et al. 2017; Nesaretnam et al. 2010). Participants with various diseases were contained in eligible studies, including type 2 diabetes (Baliarsingh, Beg,

Table 1. Demographic characteristics of the included studies.

Author	Study design	Target population	duration	gender	Mean age (years)	Sample size	Intervention dosage	outcomes	Jaded score
Pervez et al. (2018)	Randomized, double-blind, placebo-controlled pilot	Fatty liver disease	12 weeks	Both	>20	64	300 mg twice daily	Weight BMI/ WC CRP/MDA/AST/ALT	3
Tan et al. (2018)	Randomized, double-blinded, placebo-controlled	type 2 diabetes	8 weeks	Both	18–80	46	200 mg twice a day	Weight/DBP SBP/A1C AST/ALT/Creatinine	5
Shen et al. (2018)	Double-blinded, placebo-controlled, randomized	postmenopausal women with osteopenia	12 weeks	Female	>45	87	430 mg/day 860 mg/day	Weight/BMI AST/ALT FPG/Creatinine	3
Heng et al. (2015)	Randomized, placebo-controlled, double-blind	Metabolic syndrome	16 weeks	Both	20–60	71	400 mg/day	BMI/WC/DBP/SBP TNF/IL-6/CRP/FPG	3
Goon et al. (2017)	Randomized, double-blinded, placebo-controlled trial.	Healthy adults	6 months	Both	50–55	47	150 mg/day	BMI/DBP/SBP/MDA FPG	2
Vafa et al. (2015)	Double-blinded, placebo-controlled, randomized trial	type 2 diabetes	8 weeks	Both	35–60	45	200 mg/day	MDA/FPG	4
Daud et al. (2013)	Randomized, double-blind, placebo-controlled	chronic hemodialysis	16 weeks	Both	–	81	180 mg/day	BMI/IL-6/CRP	3
Chin et al. (2011)	Randomized, placebo-controlled, double-blind	Healthy adults	6 months	Both	35–49 > 50	62	160 mg/day	BMI/DBP/SBP/MDA FPG	2
Stonehouse et al. (2016)	Randomized, placebo-controlled, double-blind	type 2 diabetes	8 weeks	Both	18–70	87	420 mg/day	DBP/SBP/TNF/IL-6 CRP/A1C/	5
Rasool et al. (2006)	Randomized, blinded end-point, placebo-controlled	Healthy adults	2 months	Male	21–30	36	80/160/320 mg/day	SBP	1
Rasool et al. (2008)	Randomized, placebo controlled, blinded	Healthy adults	2 months	Male	23.9 ± 0.39	36	50/100/200 mg/day	DBP/SBP	1
Baliarsingh, Beg, and Ahmad (2005)	Randomized, double blind, placebo-controlled	type 2 diabetes hypercholesterolemia	60 days	Both	–	19	3 mg/kg body weight twice	DBP/SBP/A1C Creatinine/FPG	2
Schuchardt, Heine, and Hahn (2015)	Double-blind, placebo-controlled	hypercholesterolemia	12 weeks	Both	18–75	204	12 mg/day 27 mg/day	CRP	2
Haghighat et al. (2014)	Double-blinded, placebo-controlled, randomized trial	type 2 diabetes	8 weeks	Both	35–60	44	200 mg /day	CRP/Creatinine	4
Gopalan et al. (2014)	Randomized, double-blind, and placebo-controlled	CVD	2 years	Both	52 ± 8.5	121	200 mg/day twice	CRP	4
Wan Nazaimoon et al. (1996)	Randomized, double-blind cross-over	type 2 diabetes	60 days 60 days washout	Both	31–70	64	300 mg/day 6 cap	MDA	2
Nesaretnam et al. (2010)	Double-blinded, placebo-controlled pilot	Breast cancer	5 years	Female	40–60	240	200 mg/day Twice	ALT	2

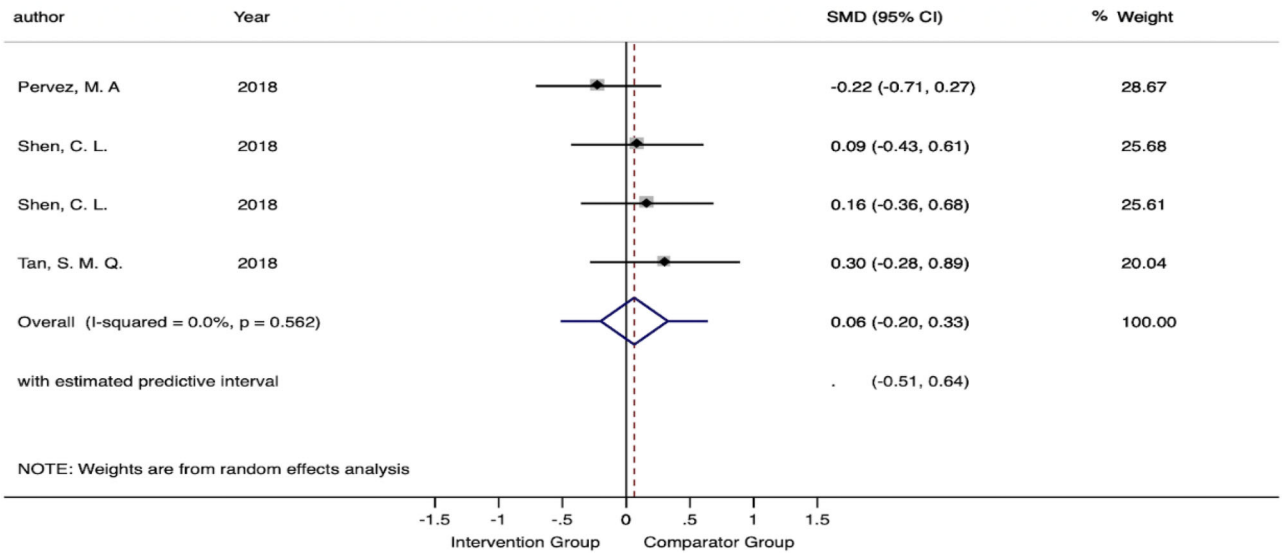

Figure 2. Forest plot displaying standardized mean difference and 95% confidence intervals for the effect of tocotrienol supplementation on body weight.

and Ahmad 2005; Vafa et al. 2015; Haghighat et al. 2014; Tan et al. 2018; Stonehouse et al. 2016; Wan Nazaimoon et al. 1996), hyperlipidemia (Baliarsingh, Beg, and Ahmad 2005; Schuchardt, Heine, and Hahn 2015), osteopenia (Shen et al. 2018), fatty liver disease (Pervez et al. 2018), breast cancer (Nesaretnam et al. 2010), chronic hemodialysis (Daud et al. 2013), cardiovascular disease (Gopalan et al. 2014), and healthy patients (Goon et al. 2017; Chin et al. 2011; Rasool et al. 2006; Rasool et al. 2008).

Meta-analyses

Effects of tocotrienol supplementation on weight

Overall, weight was reported in four studies comprising 194 participants (intervention group = 82, control group= 112). Pooled results suggested that tocotrienol supplementation caused an insignificant change in weight (SMD: 0.063 kg, 95% CI: −0.200, 0.327, $p = 0.637$). Pooled analysis was homogenous ($I^2 = 0.0\%$, $p = 0.562$) (Figure 2).

Effects of tocotrienol supplementation on BMI

Eight papers evaluated BMI with a total of 427 individuals (intervention group = 247 and control group= 180). Pooled effect sizes showed that tocotrienol intervention did not result in a significant difference on BMI (SMD: −0.065 kg/m^2, 95% CI: −0.258, 0.129, $p = 0.512$) (Figure 3). Pooled analysis was homogeneous ($I^2 = 14.1\%$, $p = 0.320$).

Effects of tocotrienol supplementation on WC

WC was reported in two studies including 121 participants (intervention group = 60 and control group= 61). Summary results demonstrated no statistically significant difference between both tocotrienol and placebo groups (SMD: − 0.337 cm, 95% CI: −0.696, 0.022, $p = 0.066$) (Figure 4). Pooled analysis was homogeneous ($I^2 = 0.0\%$, $p = 0.978$).

Effects of tocotrienol supplementation on DBP

Diastolic blood pressure was investigated in ten studies comprising 355 individuals (intervention group = 204 and control group= 151). Tocotrienol supplementation resulted in a significant increased diastolic blood pressure (SMD: 0.249 mmHg, 95% CI: 0.053, 0.446, $p = 0.013$) (Figure 5). Pooled analysis was homogeneous ($I^2 = 0.0\%$, $p = 0.904$). Subgroup analysis based on population (healthy and T2DM) showed significant increase on DBP in healthy population (SMD: 0.20 mmHg, 95% CI: −0.09, 0.50, $p = 0.034$) compared with T2DM patients (SMD: 0.28 mmHg, 95% CI: 0.02, 0.54, $p = 0.176$).

Effects of tocotrienol supplementation on SBP

Combining findings from thirteen studies with 391 participants (intervention group = 231 and control group= 160), a significant decrease was observed in SBP after tocotrienol supplementation (SMD: −0.616 mmHg, 95% CI: −1.123, −0.110, $p = 0.017$) (Figure 6). Pooled analysis was heterogeneous ($I^2 = 83.3\%$, $p = 0.000$) and we performed a subgroup analysis to resolve heterogeneity based on the length of intervention to detect the source of heterogeneity. When the length of intervention declined (2 months), a greater reduction in SBP was demonstrated after tocotrienol intervention (SMD: −1.14 mmHg, 95% CI: −2.01, −0.28, $I^2 = 87.3$). Subgroup analysis based on population (healthy and T2DM) showed significant reduce on SBP in healthy population (SMD: −1.04 mmHg, 95% CI: −1.80, −0.28, $p = 0.007$) compared with T2DM patients (SMD: 0.19 mmHg, 95% CI: −0.53, 0.56, $p = 0.947$).

Effects of tocotrienol supplementation on CRP

Findings on CRP levels were reported in eight studies with a total of 593 participants (intervention group = 333 and control group= 260). Combined results revealed no significant reduction in CRP levels following tocotrienol

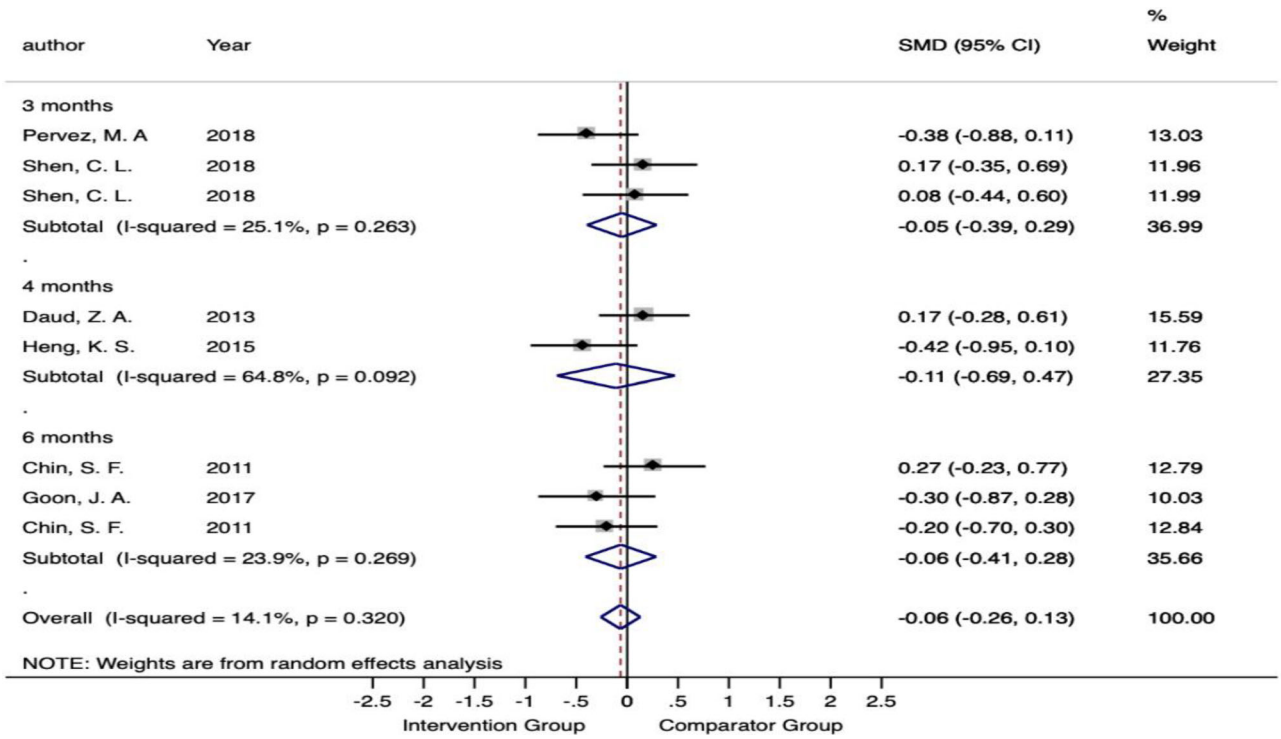

Figure 3. Forest plot displaying standardized mean difference and 95% confidence intervals for the effect of tocotrienol supplementation on BMI.

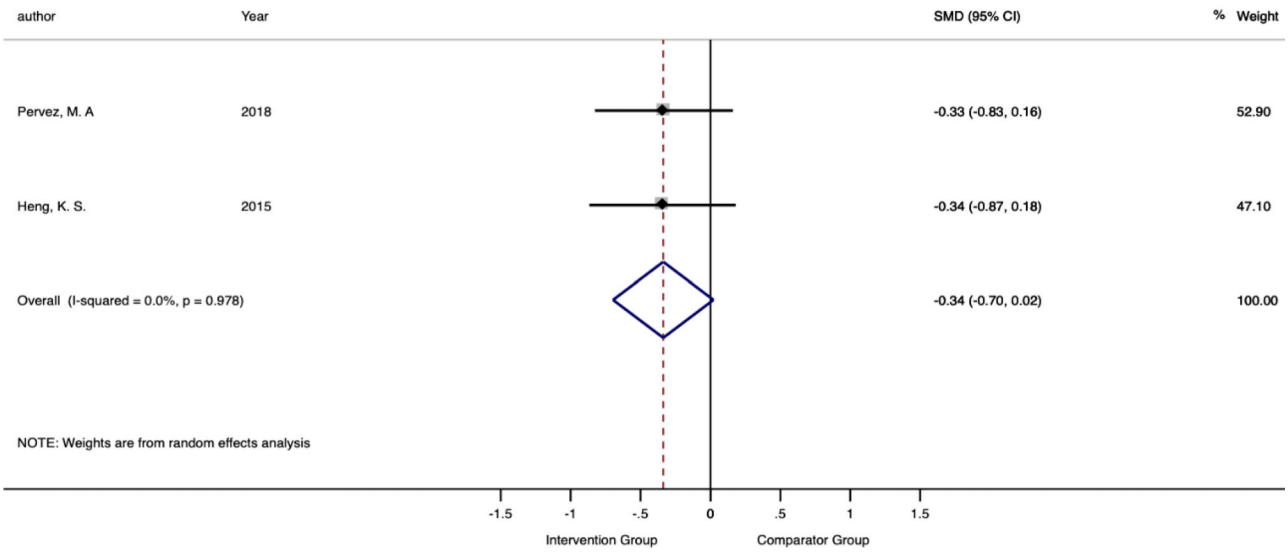

Figure 4. Forest plot displaying standardized mean difference and 95% confidence intervals for the effect of tocotrienol supplementation on WC.

supplementation (SMD: −0.077 mg/l, 95% CI: −0.309, 0.156, $p = 0.519$) (Figure 7). Pooled analysis was heterogeneous ($I^2 = 54.2\%$, $p = 0.033$). Source of heterogeneity was not identified by performing subgroup analysis.

Effects of tocotrienol supplementation on malondialdehyde (MDA)

MDA levels were evaluated in six studies with 314 individuals (intervention group = 174 and control group= 140). Combined results from random-effects model showed no significant association between tocotrienol consumption and MDA levels (SMD: −0.447 nmol/ml, 95% CI: −1.061, 0.167, $p = 0.153$) (Figure 8). Pooled analysis was heterogeneous ($I^2 = 86.9\%$, $p = 0.000$). Length of intervention was found as a source of heterogeneity.

Effects of tocotrienol supplementation on IL-6

Three studies with a total of 192 participants (intervention group = 97 and control group= 95) reported IL-6 levels. Pooled results showed that IL-6 levels did not significantly differ in tocotrienol consumers compared with control group (SMD: −0.031 pg/ml, 95% CI: −0.380, 0.319, $p = 0.864$) (Figure 9). Pooled analysis was homogeneous ($I^2 = 33.3\%$, $p = 0.223$).

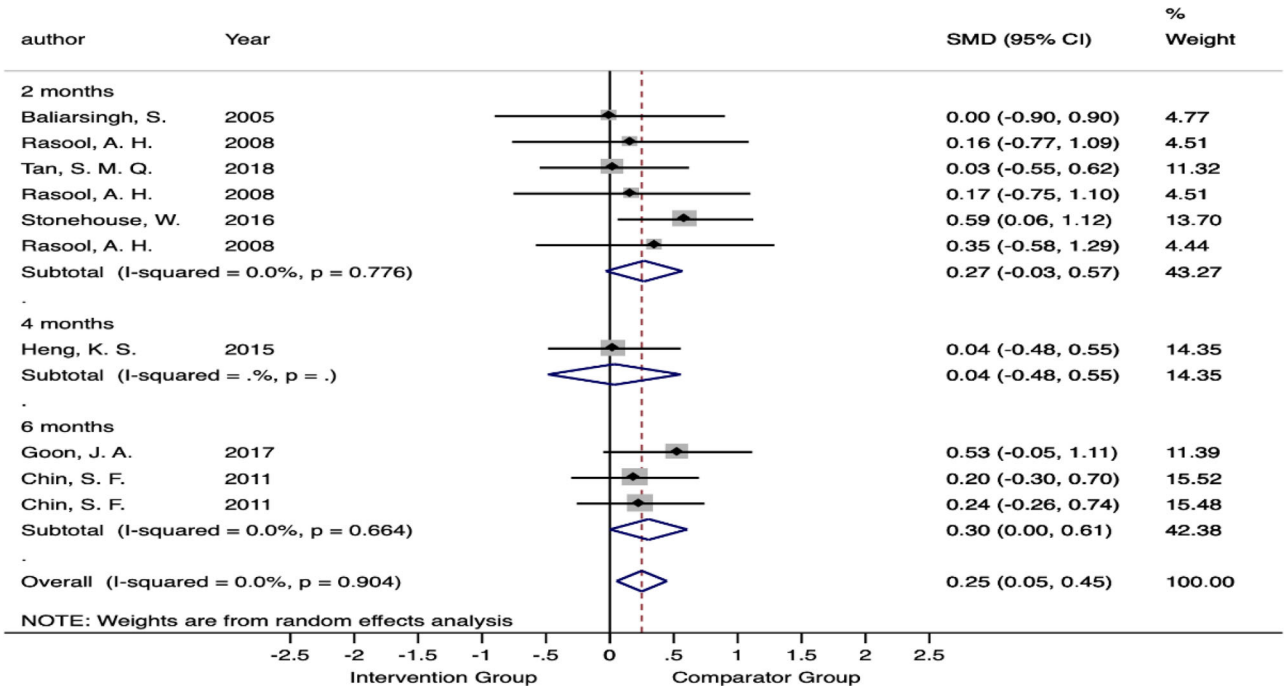

Figure 5. Forest plot displaying standardized mean difference and 95% confidence intervals for the effect of tocotrienol supplementation on DBP.

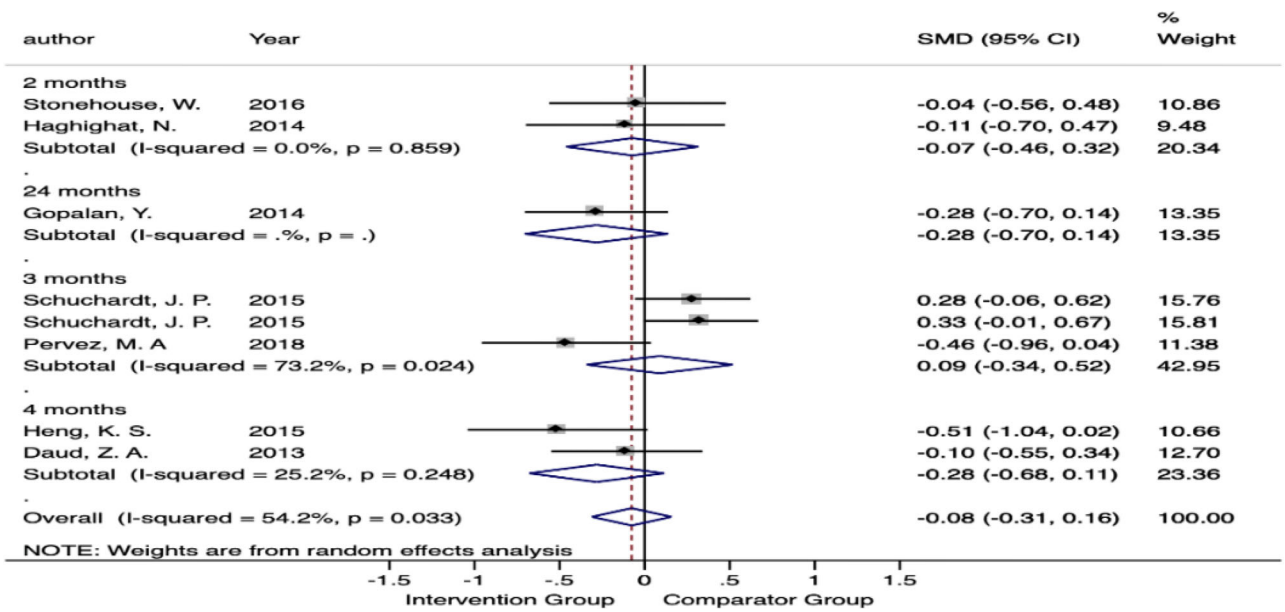

Figure 6. Forest plot displaying standardized mean difference and 95% confidence intervals for the effect of tocotrienol supplementation on SBP.

Effects of tocotrienol supplementation on TNF-α

Two studies with 114 participants (intervention group = 57 and control group= 57) assessed TNF-α levels. Pooled effect sizes presented no significant alteration in TNF-α levels after tocotrienol supplementation (SMD: −0.136 pg/ml, 95% CI: −0.504, 0.232, $p = 0.468$) (Figure 10). Pooled analysis was homogeneous ($I^2 = 0.0\%$, $p = 0.544$).

Effects of tocotrienol supplementation on FPG

Eight studies investigated the FPG levels with a total of 349 participants (intervention group = 209 and control group= 140). Combined effect sizes revealed that FPG levels were not under the influence of tocotrienol supplementation (SMD: −0.045 mg/dl, 95% CI: −0.258, 0.168, $p = 0.681$) (Figure 11). Pooled analysis was homogeneous ($I^2 = 14.5\%$, $p = 0.316$). Subgroup analysis based on population (T2DM, healthy adults, and post-menopausal women with osteopenia) dis not show significant impact in different populations.

Effects of tocotrienol supplementation on HbA1C

HbA1C was reported in three studies with 121 individuals (intervention group = 60 and control group= 61). Combining results indicated no significant relationship

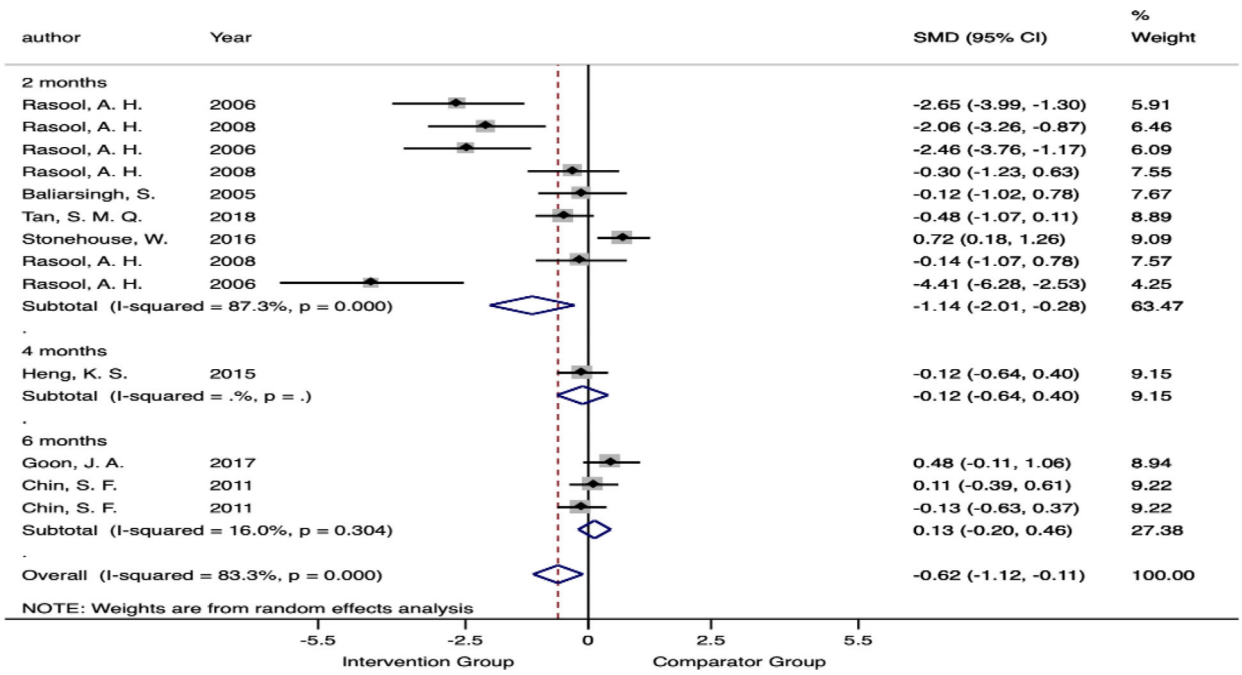

Figure 7. Forest plot displaying standardized mean difference and 95% confidence intervals for the effect of tocotrienol supplementation on CRP.

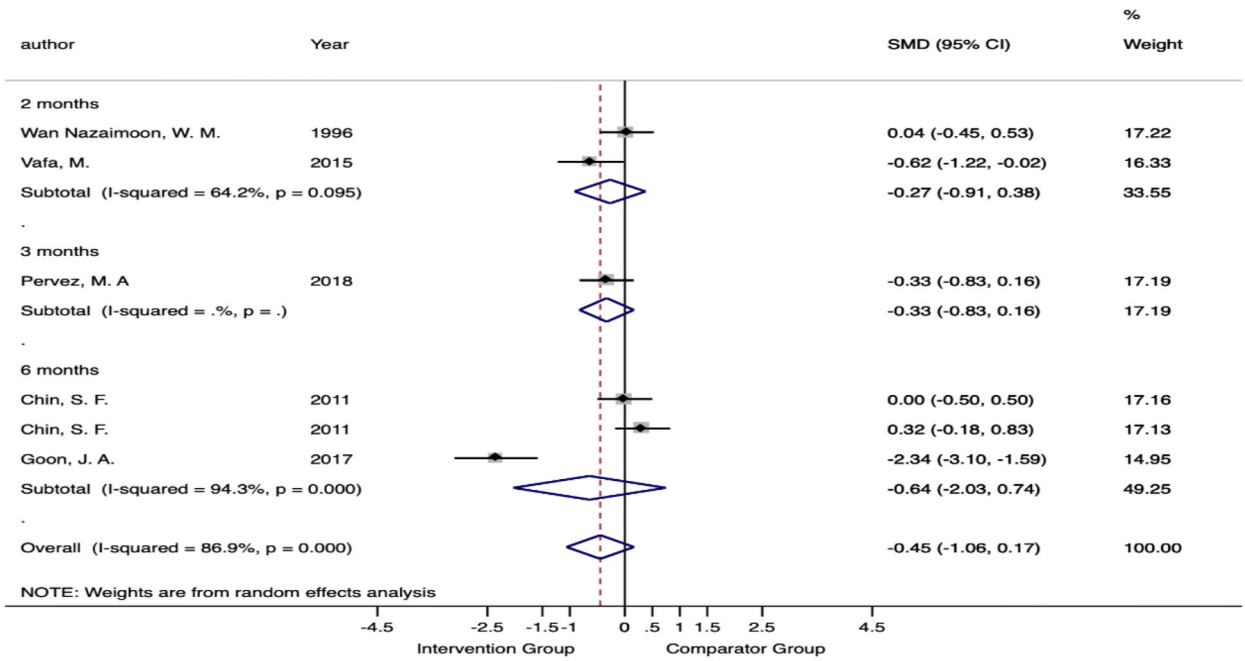

Figure 8. Forest plot displaying standardized mean difference and 95% confidence intervals for the effect of tocotrienol supplementation on MDA.

between HbA1C and tocotrienol intervention (SMD: −0.282, 95% CI: −0.676, 0.111, $p = 0.160$) (Figure 12). Pooled analysis was homogeneous ($I^2 = 12.9\%$, $p = 0.317$).

Effects of tocotrienol supplementation on AST

Four trials including a total of 196 participants (intervention group = 112 and control group= 84) reported AST levels. Pooled analysis demonstrated that AST levels did not undergo a significant change following tocotrienol consumption (SMD: −0.195 U/L, 95% CI: −0.460, 0.071, $p = 0.151$) (Figure 13). Pooled analysis was homogeneous ($I^2 = 1.0\%$, $p = 0.387$).

Effects of tocotrienol supplementation on ALT

Pooled effect sizes from five studies on ALT concentration, with a total of 436 participants (intervention group = 232

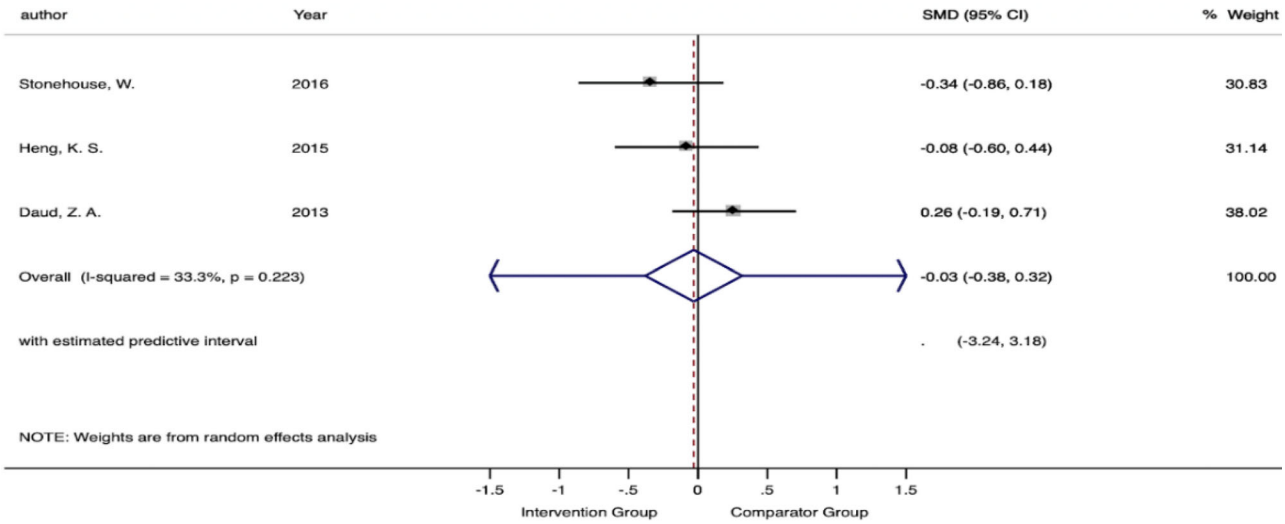

Figure 9. Forest plot displaying standardized mean difference and 95% confidence intervals for the effect of tocotrienol supplementation on IL-6.

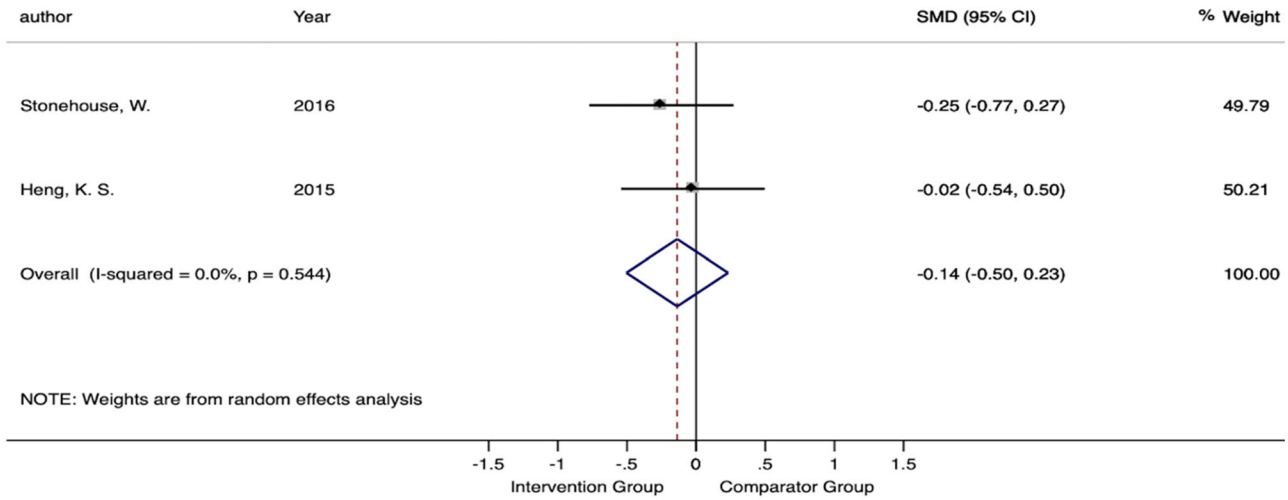

Figure 10. Forest plot displaying standardized mean difference and 95% confidence intervals for the effect of tocotrienol supplementation on TNF-α.

and control group= 204) showed that ALT levels remained unchanged after tocotrienol supplementation (SMD: −0.183 U/L, 95% CI: −0.534, 0.169, $p = 0.309$) (Figure 14). Pooled analysis was heterogeneous ($I^2 = 66.3\%$, $p = 0.018$) and the source of heterogeneity could not be clarified.

Effects of tocotrienol supplementation on creatinine

Combined findings from five articles on creatinine levels, including 196 participants (intervention group = 114 and control group= 82) reported no significant effect of tocotrienol intervention on creatinine levels (SMD: −0.133 mg/dl, 95% CI: −0.606, 0.339, $p = 0.580$) (Figure 15). Pooled analysis was heterogeneous ($I^2 = 66.6\%$, $p = 0.017$) and the source of heterogeneity could not be identified ($I^2 = 66.6\%$, $p = 0.017$). Subgroup analysis based on population (T2DM and post-menopausal women with osteopenia) showed significant reduce on creatinine in T2DM (SMD: −0.49 mmHg, 95% CI: −0.95, −0.02, $p = 0.038$) compared with post-menopausal women with osteopenia (SMD: 0.26 mmHg, 95% CI: −0.10, 0.63, $p = 0.161$).

Discussion

This comprehensive systematic review and meta-analysis scrutinized the efficacy of tocotrienol supplementation on various anthropometric indices and cardiometabolic risk factors. We included 17 randomized placebo-controlled trials, comprising 24 different supplementation arms and 1354 individuals. The methodological quality of the included RCTs was equally split into good (Jadad score ≥3, n = 9) and poor (Jadad score <3, n = 8) quality. Our findings portrayed only statistically significant effects on blood pressure parameters. Specifically, tocotrienol supplementation favorably reduced SBP, but unfavorably increased DBP. No statistically significant changes were identified between tocotrienol and placebo groups with regard to anthropometric (body weight, body mass index, and waist

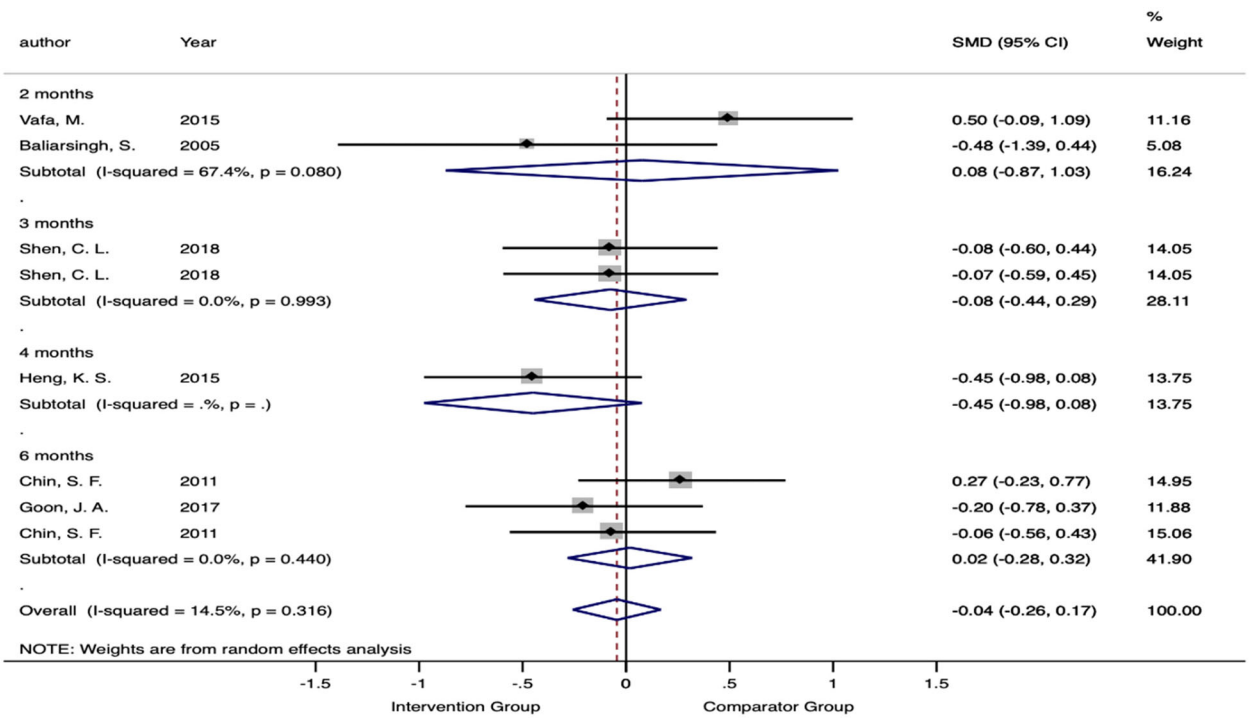

Figure 11. Forest plot displaying standardized mean difference and 95% confidence intervals for the effect oftocotrienol supplementation on FPG.

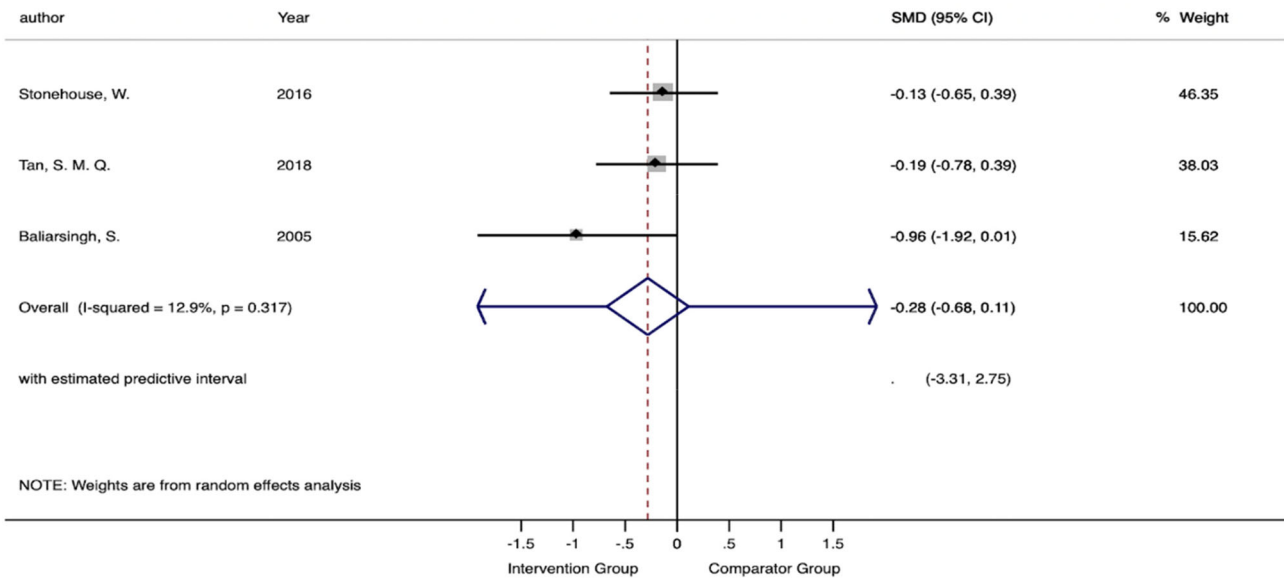

Figure 12. Forest plot displaying standardized mean difference and 95% confidence intervals for theeffect of tocotrienol supplementation on A1C.

circumference), inflammatory (CRP, IL-6, TNF-alpha, and MDA), hepatic (AST, ALT, and creatinine), and glucose (FBG and HbA1c) parameters.

Our pooled analysis established useful reduced SBP effects in individuals who received tocotrienol supplementation. Preclinical studies using spontaneously hypertensive rats (SHRs) delineated the mechanisms of blood pressure-lowering effects of tocotrienol supplementation. Such mechanisms included the upregulation of total antioxidant status (Newaz and Nawal 1999), superoxide dismutase activity (Newaz and Nawal 1999), and vasorelaxant prostacyclin production (Koba et al. 1992). Additionally, Newaz and colleagues (Newaz et al. 2003) revealed that SHRs had lower endothelial nitric oxide synthase activity when compared to the normotensive Wister Kyoto (WKY) rats. Antioxidant tocotrienol supplementation significantly enhanced the nitric oxide synthase activity and nitric oxide production in SHRs, contributing to the favorable decreased blood pressure effects, mostly for the SBP. Moreover, lipid peroxidation is a process that induces oxidative damage to lipids (Ayala, Muñoz, and Argüelles 2014) and has been depicted to play pivotal roles in the pathophysiology of primary hypertension in humans (Kumar and DAS 1993). Tocotrienol supplementation has been disclosed to favorably downregulate lipid

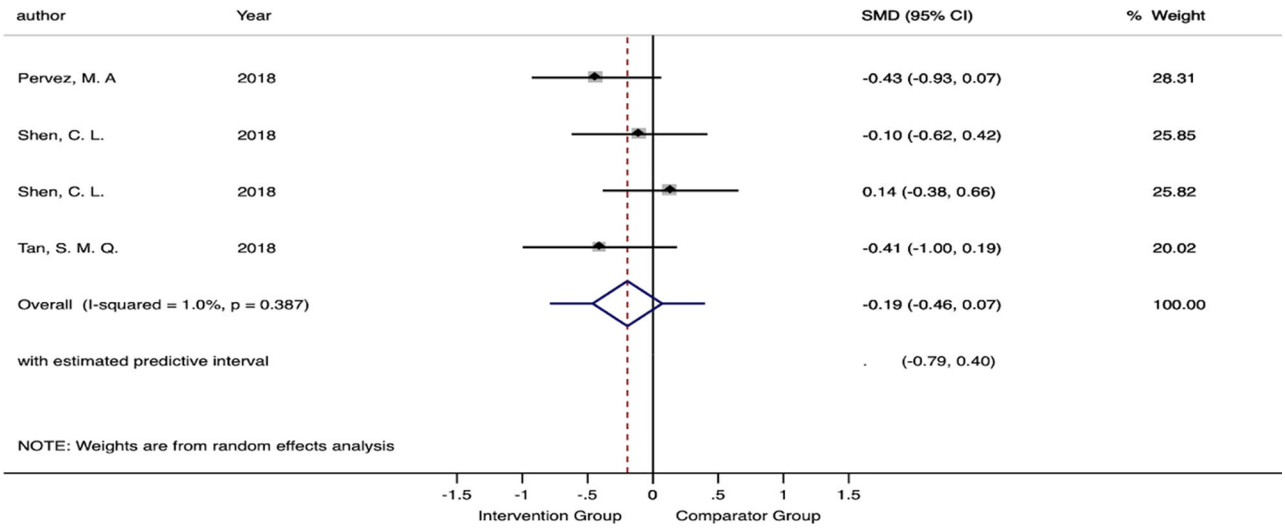

Figure 13. Forest plot displaying standardized mean difference and 95% confidence intervals for the effect oftocotrienol supplementation on AST.

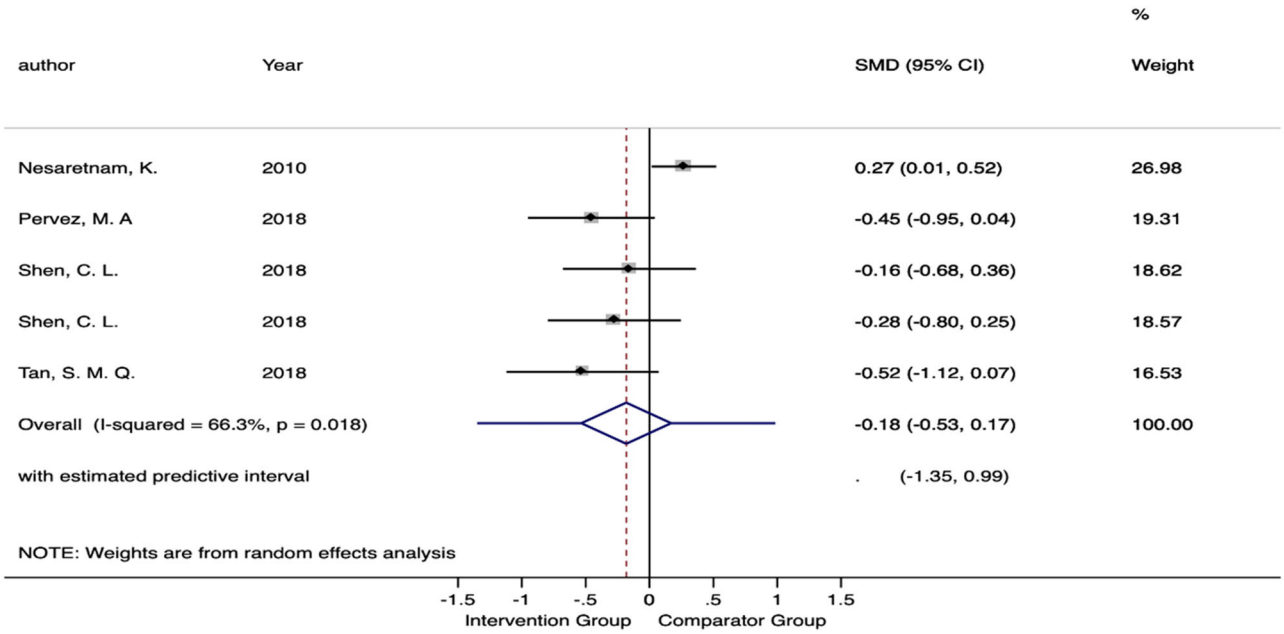

Figure 14. Forest plot displaying standardized mean difference and 95% confidence intervals for the effect oftocotrienol supplementation on ALT.

peroxidation, contributing to blood-pressure lowering effects in SHRs (Newaz and Nawal 1999). Interestingly, our results depicted that tocotrienol supplementation resulted in a statistically significantly higher DBP and this observation cannot be explained.

With respect to anthropometric parameters (BW, BMI, and WC), our results did not reveal statistically useful outcomes from tocotrienol supplementation. Our results were echoed in earlier studies (Shen et al. 2018; Magosso et al. 2013). Magosso and partners (Magosso et al. 2013) reported lack of body composition benefits in patients with nonalcoholic fatty liver disease even after 12 months of continuous tocotrienol supplementation when compared to the placebo group.

Tocotrienols exhibit potent anti-oxidant and anti-inflammatory actions (Koufaki 2016; Kuhad and Chopra 2009). Inflammation is a paramount facet involved in the initiation and progression of cardiometabolic disorders, and it is shown to foretell mortality. Examples of such proinflammatory mediators include CRP (Marsik et al. 2008), TNF-alpha (Zhang et al. 2009), and IL-6 (Volpato et al. 2001). MDA is common marker of oxidative stress damage (Maciejczyk et al. 2018). In our study, although these inflammatory and oxidative markers were decreased in the group who received tocotrienol supplementation, however, they did not yield statistically significant differences when compared to the group who received placebo supplementation.

Our study has several strengths. Importantly, this is the first systematic review and meta-analysis that attempted to investigate the efficacy of tocotrienol supplementation on various body composition and cardiometabolic indices. We considered only RCTs to guarantee inclusion of high-quality studies during data synthesis. The vast majority of assessed outcomes had at least effect sizes pooled from four studies or more. Whenever heterogeneity was present, we attempted to revolve it though sub-group analysis. Nevertheless, our

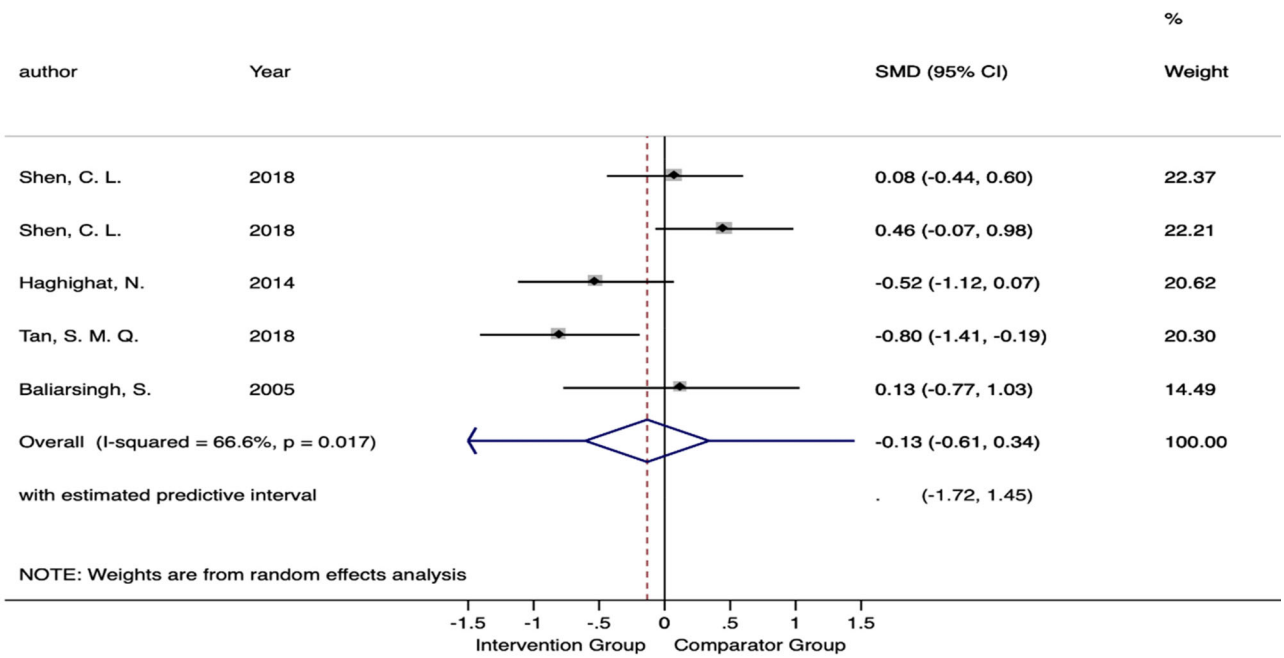

Figure 15. Forest plot displaying standardized mean difference and 95% confidence intervals for the effect oftocotrienol supplementation on creatinine.

study has some limitations. The small number of studies is the main limitation. Furthermore, the included studies exhibited high degrees of variations with regard to clinico-demographics of participants and dosage of tocotrienol supplementation, which could have affected the gauged efficacy results.

Conclusion

This systematic review and meta-analysis showed significantly reduced SBP in favor of the tocotrienol over placebo supplementation. However, no statistically significant changes were identified between tocotrienol and placebo supplementation with regard to the examined anthropometric, inflammatory, hepatic, and glucose indices. As it stands now, this report advocates the beneficial utility of tocotrienol supplementation to lower SBP in select populations. Nonetheless, large-sized, high-quality randomized placebo-controlled trials are warranted to inform concrete conclusions.

Disclosure statement

The authors declare no conflict of interest.

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