Received: 28 July 2020 | Revised: 21 April 2021 | Accepted: 18 May 2021

DOI: 10.1002/ptr.7183

REVIEW

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The effect of cocoa/dark chocolate consumption on lipid profile, glycemia, and blood pressure in diabetic patients: A meta-analysis of observational studies

Mina Darand[1] | Masoomeh Hajizadeh Oghaz[2] | Amir Hadi[3] | Masoumeh Atefi[1] | Reza Amani[1]

[1]Department of Clinical Nutrition, School of Nutrition and Food Science, Food Security Research Center, Isfahan University of Medical Sciences, Isfahan, Iran

[2]Department of Nutrition and Health Sciences, College of Education and Human Sciences, University of Nebraska-Lincoln, Nebraska

[3]Department of Clinical Nutrition, School of Nutrition and Food Science, Isfahan University of Medical Sciences, Isfahan, Iran

Correspondence
Reza Amani, Department of Clinical Nutrition, School of Nutrition and Food Science, Isfahan University of Medical Sciences, Isfahan, Iran.
Email: r_amani@nutr.mui.ac.ir

Abstract

Due to the increasing rate of cardiovascular disease and related risk factors in the worldin recent decades, the present meta-analysis was performed to investigate the effects ofcocoa/chocolate consumption on lipid profile, glycemia, and blood pressure control in diabetic patients. A systematic search of the databases PubMed, Scopus, Web of Science, and Cochran Library was performed up to July 2020. All randomized controlled trials (RCTs) using cocoa/dark chocolate in diabetic patients were included in the study. The search results were limited to English-language publications. Eight RCTs, including 433 participants, were selected for this meta-analysis. Pooled analysis indicated a significant reduction in low-density lipoprotein cholesterol LDL-c levels (WMD: −15.49 mg/dl; 95% CI: −24.56, −6.42, $p = .001$) and fasting blood sugar (FBS) concentrations (WMD: −6.88 mg/dl; 95% CI: −13.28, −0.48, $p = .03$) following cocoa/dark chocolate consumption. The analysis of papers included in current study indicates that the consumption of cocoa/dark chocolate reduced the serum fasting blood glucose (FBS) and LDL cholesterol concentrations. However, further high quality trials are essential for confirming the clinical efficacy of cocoa/dark chocolate consumption on complete metabolic profile.

KEYWORDS
blood pressure, cocoa, dark chocolate, diabetic patients, lipid profile, meta-analysis

1 | INTRODUCTION

The prevalence of diabetes mellitus is on the rise around the world and it is currently considered as the eighth leading cause of death (World Health Organization, 2016). It has been projected that 366 million individuals will suffer from Type 2 diabetes mellitus (T2DM) in 2030 (Wild, Roglic, Green, Sicree, & King, 2004), and this could lead to an epidemic of cardiovascular disease (CVD) as well (NCD Risk Factor Collaboration, 2016). Meanwhile, more than 50% of diabetic patients deal with hypertension which is a crucial comorbidity of diabetes (Lastra, Syed, Kurukulasuriya, Manrique, & Sowers, 2014). Hypertension and diabetes have many common pathophysiological mechanisms, including complex interactions among sodium, renin-angiotensin-aldosterone system (RAAS), autonomic nervous system, kidney disease, and obesity (Libianto, Batu, MacIsaac, Cooper, & Ekinci, 2018). Individuals with T2DM have poor glycemic control which contributes to CVD and other diabetic comorbidities. Relying upon measures of glycosylated hemoglobin (HbA1c) and fasting glucose cannot accurately reflect glycemic control, since they do not represent what happens after meals and throughout the day in free-living conditions (Libianto et al., 2018).

Diet is one of the key lifestyle factors involved in the genesis, prevention, and control of glycemia, lipid profile, and blood pressure in hypertensive diabetic patients. Cocoa products are known as a good

source of dietary flavanols, and the health benefits of cocoa can be attributed to them. However, the flavanol profile and content vary according to their cultivars and fermentation procedure (Lin et al., 2016). Flavanols could cause a reduction in glucose excursion, a mechanism that helps patients with metabolic disorders maintain glucose homeostasis by antagonizing digestive enzymes and glucose transporters. Also, Cocoa may have a positive impact on insulin signaling, possibly by relieving insulin-signaling pathways from oxidative stress and inflammation and/or via an increased incretin response (Strat et al., 2016). Moreover, cocoa and its products, such as cocoa-rich chocolate, have been known for their good taste. Recent experimental and observational studies have found that dietary intake of flavanol-rich cocoa products, such as dark chocolate, are associated with reduced risk of cardiometabolic diseases, including CVD (Zhang, Xu, & Liu, 2013), hypertension (Grassi et al., 2008), metabolic syndrome (Gu & Lambert, 2013), and diabetes (Grassi, Desideri, & Ferri, 2013). Ibero-Baraibar, Suárez, Arola-Arnal, Zulet, and Martinez (2016) found that the daily consumption of a meal enriched with 1.4 g of cocoa extract (415 mg flavanols), by overweight/obese middle-aged subjects for 4-weeks resulted in a greater reduction of postprandial area under the curve of systolic blood pressure (SBP) compared to the effects of energy-restricted diet alone independently of weight loss. Moreover, a meta-analysis by Jafarnejad, Salek, and Clark (2020) demonstrated a significant inverse association between cocoa consumption and systolic and diastolic blood pressure in middle-aged and elderly subjects. On the other hand, a study by Dicks et al. (2018) reported daily intake of 2.5 g of flavanol-rich, unsweetened, and strongly defatted cocoa powder did not improve blood pressure and glucose metabolism in stably treated patients with T2DM and hypertension in a fasting state. Furthermore, a meta-analysis indicated that chocolate/cocoa has improved fasting insulin and insulin resistance (Hooper et al., 2012). Also, in a parallel, double-blind, and placebo-controlled trial, Konya, Sathyapalan, Kilpatrick, and Atkin (2019) showed that the addition of cocoa powder to soy protein with isoflavones had no beneficial effects on insulin resistance and low-density lipoprotein cholesterol (LDL-c). Due to the high prevalence of diabetes in the world and its complications, as well as the existing contradictions, we carried out a meta-analysis of the scientific literature to evaluate the effects of cocoa/dark chocolate consumption on lipid profile, glycemia, and blood pressure in diabetic patients. The results of our analysis could be incorporated into a targeted dietary program as part of public health policy to improve lifestyle of patients with T2DM.

2 | METHODS

2.1 | Search strategy

We followed preferred reporting items for systematic reviews and meta-analyses (PRISMA) in the design and reporting of the methods for this meta-analysis (Moher et al., 2009). PubMed (MeSh terms), Scopus, Web of Science (ISI), and Cochrane Library databases were searched from inception to July 2020 for randomized controlled trials (RCTs) examining the effects of cocoa/dak chocolate on metabolic syndrome factors in patients with T2DM. We searched different combination of keywords in Pumbed as follows: Cocoa [ti/ab] OR Cacao [ti/ab] OR Chocolate [ti/ab]), Diabetes [ti/ab], Metabolic Syndrome [ti/ab], High-density lipoprotein [ti/ab] OR "HDL" [ti/ab], Triglycerides [ti/ab] OR "TG" [ti/ab], Hypertension [ti/ab] OR High-blood pressure [ti/ab] OR blood pressure [ti/ab], Fasting Blood Sugar [ti/ab] OR Fasting Blood Glucose [ti/ab] OR "FBG" [ti/ab] OR "FBS" [ti/ab], and Obes* [ti/ab] OR waist* [ti/ab] OR Body mass index [ti/ab] OR "BMI" [ti/ab]. Possible Medical Subject Headings in addition to free-text search terms were also used in the search. The search results were limited to English-language publications. In addition, references of the selected studies and relevant review articles were screened to identify eligible trials that were not found through the database search.

2.2 | Screening and study selection

Screening was performed independently by two investigators (M.H. and M.D.). Any disagreement was resolved by consensus. To exclude irrelevant studies, the researchers first screened and filtered the titles and abstracts of studies obtained through preliminary search. Then, researchers independently screened the full text of results. Studies that did not meet our inclusion criteria were removed and the remaining studies were selected for further analysis.

2.3 | Eligibility criteria

The PICO for this meta-analysis included: P: Patients with Type 2 diabetes, I: Consuming cocoa OR dark chocolate, C: Not consuming cocoa OR dark chocolate, O: Changes in factors including blood pressure, glycemia and lipid profile. Also, articles were included for analysis if they conformed to the following inclusion criteria: (a) were a peer reviewed RCT study; (b) provided original data on the effect of cocoa/dark chocolate consumption on glycemia, lipid profile, and blood pressure in diabetic patients; (c) were published in English; (d) were done on human subjects; (e) had full text available, and (f) provided a comparison group.

2.4 | Data extraction

We recorded study characteristics as follows: first author's last name, publication year; location of the study, design details, including whether they were parallel or crossover; study duration; number of participants; and daily dose of intervention. Participant characteristics including health status, mean age, gender, and mean body mass index (BMI) were also recorded. When aforesaid characteristics were not reported in available publications, we contacted the corresponding author to obtain the necessary data. Two of the authors (A.H. and M.D.) independently performed the data extraction including the screening of studies, selection, and validation. Disagreements in the assessment of data were resolved by discussion and consensus was reached in all cases.

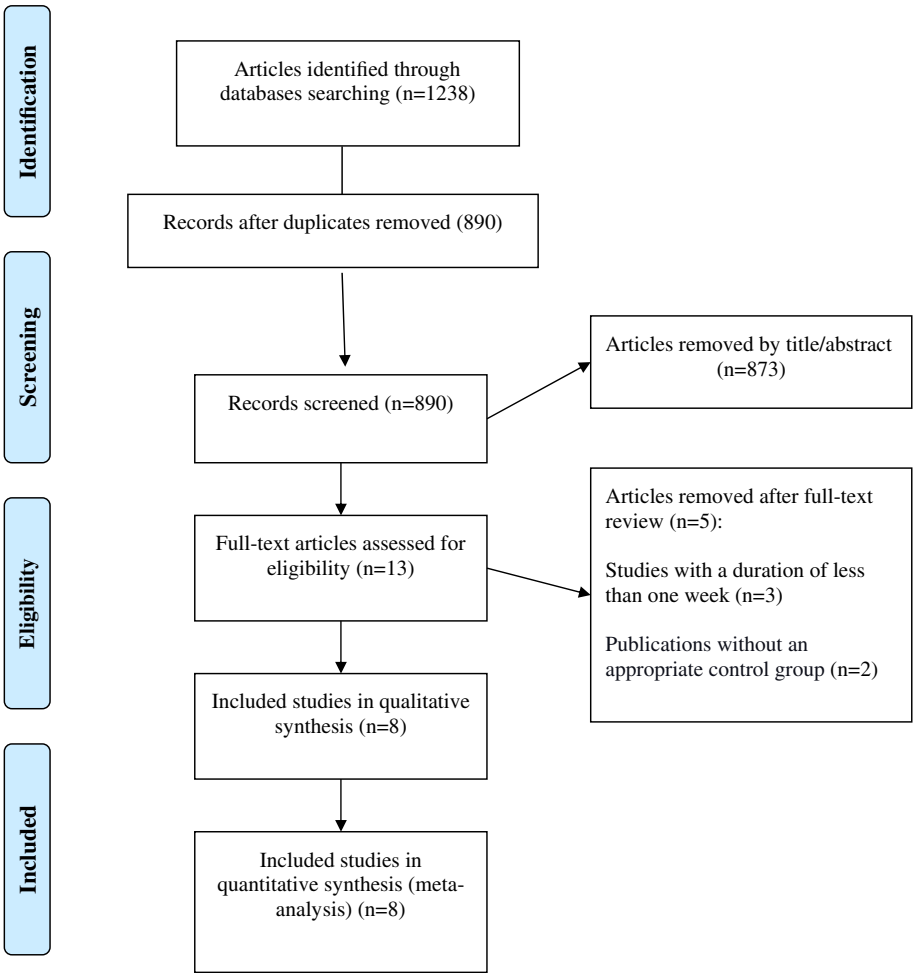


FIGURE 1 Preferred reporting items for meta-analysis flow diagram of study selection process [Colour figure can be viewed at wileyonlinelibrary.com]

2.5 | Quality assessment of studies

Two reviewers (A.H. and M.D.) who were blinded to authors and results independently assessed the quality of each study according to the Cochrane risk of bias (Higgins et al., 2011). This scale involves seven criteria to assess the risk of bias which are as follows: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases. Bias is assessed as a judgment (high [+], low [−], or unclear for individual elements, that are interpreted as high risk, low risk, and unknown risk, respectively. Finally, the overall quality of the studies was categorized into weak, fair, or good, if ≤3, 3, or ≥4 domains were rated, respectively.

2.6 | Data synthesis and analysis

Data were analyzed using Stata version 12.0 software (StataCorp, College Station, TX). The effect size of each study was calculated from mean and standard deviation (*SD*) of the outcomes pre- and post-intervention and presented as weighted mean difference (WMD) with 95% confidence intervals (CI). In studies in which the change values were not directly reported, the mean change was calculated by following formula: (measure at the end of follow-up in the treatment group – measure at baseline in the treatment group) – (measure at the end of follow-up in the control group – measure at baseline in the control group), where correlation coefficient (*R*) was considered as 0.5 (Borenstein, Hedges, Higgins, & Rothstein, 2011). Also, their SDs were calculated as follows: [SD = square root [(SD pre-treatment)^2 + (SD post-treatment)^2 − (2R × SD pre-treatment × SD post-treatment)]. Due to the fact that selected RCTs were carried out in different settings, the random-effects model was employed to calculate the overall effect from the effect sizes. Heterogeneity was examined using the I-squared (I^2) index. An I^2 value >50% was considered to indicate substantial heterogeneity between trials. To explore the source of heterogeneity, as well as the possible influences of study designs and participant characteristics on combined effect sizes, we further conducted pre-specified subgroup analyses stratified by trial duration, baseline BMI values, participants' mean age and intervention dosage. Sensitivity analysis was also carried out to explore the robustness of pooled estimates by sequentially excluding studies from meta-analysis and comparison the overall effect. The presence of publication bias was tested using Egger's regression asymmetry test. All tests were two-sided. p Values <.05 were considered statistically significant, except where otherwise specified.

TABLE 1 Characteristics of eligible studies

First author (location; year)	RCT design (blinding)	Population	Mean age	Mean BMI	Sex	Sample size (intervention/placebo)	Duration (weeks)	Outcome	Type of cocoa	Dose of cocoa
Balzer (Germany; 2008)	Double-masked, randomized, controlled trial	T2DM	63.75	31.60	Both genders	21/20	4	No changes in: -Blood pressure -Glycemic control	Cocoa powder	963 mg/day
Mellor (U.K.; 2010)	Double-blind, randomized, controlled trial crossover	T2DM	62.25	29.20	Both genders	12/12	4	With high polyphenol chocolate: ↑HDL-cholesterol ↓Total-cholesterol: HDL ratio No change in: -Glycemic control	High-cocoa solids	38.25 g/day
Curtis (U.K.; 2012)	Double-blind, randomized, controlled trial	T2DM	62.55	32.27	Females	47/46	12	↓Total-cholesterol: HDL-cholesterol ↓LD-cholesterol No changes in: -Glycemic control -Blood pressure -Hemoglobin A1C	Flavonoid-enriched chocolate	950 mg/day
Parsaeyan (Iran; 2014)	Randomized clinical control trial	T2DM	54	28.00	Both genders	50/50	6	↓Blood cholesterol ↓Triglyceride ↓LDL-cholesterol ↓HDL-cholesterol	Cocoa powder	10 g/day
Rostami(Iran; 2015)	Double-blind, randomized, controlled trial	Patients with diabetes and hypertension	57.94	29.77	Both genders	32/28	8	↓Systolic blood pressure ↓Diastolic blood pressure ↓Fasting blood sugar	Dark chocolate	25 g/day
Dicks (Germany; 2018)	Double-blind, randomized, controlled trial	Patients with diabetes and hypertension	64.2	29.75	Both genders	17/18	12	No changes in: -Blood pressure -Glucose metabolism (glucose, hemoglobin A1C) -Lipids (triglycerides, Total-cholesterol, LDL, HDL)	Cocoa powder	2.5 g/day
Jafarirad (Iran; 2018)	Singel-blind, parallel, randomized, clinical trial	T2DM	52.3	27.00	Both genders	21/23	2	↓Fasting blood sugar ↓Hemoglobin A1C ↓LDL ↓Triglyceride ↓Total-cholesterol ↑HDL-cholesterol	Dark chocolate	30 g/day
Konya (a) (U.K.; 2019)	Double-blind, randomized, controlled trial	T2DM	65.185	31.35	Both genders	11/13	8	No changes in: -Fasting blood sugar -Hemoglobin A1C -LDL	Cocoa powder	45 g/day (high-polyphenol chocolate: 16.6 mg)

TABLE 1 (Continued)

First author (location; year)	RCT design (blinding)	Population	Mean age	Mean BMI	Sex	Sample size (intervention/placebo)	Duration (weeks)	Outcome	Type of cocoa	Dose of cocoa
								-Triglyceride -Total-cholesterol -HDL-cholesterol -Systolic blood pressure -Diastolic blood pressure		
Konya (b) (U.K.; 2019)	Double-blind, randomized, controlled trial I	T2DM	65.595	31.84	Both genders	12/13	8	No changes in: -Fasting blood sugar -Hemoglobin A1C -LDL -Triglyceride -Total-cholesterol -HDL-cholesterol -Systolic blood pressure -Diastolic blood pressure	Cocoa powder	45 g/day (low-polyphenol chocolate<2 mg)

Abbreviations: g, gram; HDL, high density lipoprotein; LDL, low density lipoprotein; mg, milligram; NE, no effect; U.K., United Kingdom; T2DM, type 2 diabetes mellitus.

3 | RESULTS

3.1 | Search results

The primary comprehensive database search identified 1238 articles; after eliminating duplicates, 890 articles remained. Then, 873 articles based on initial title and abstract screening were excluded because of the following reasons: (a) irrelevant studies; (b) conducted on the animal; (c) review studies, book section, and (d) other reasons (letter, conference paper, and short survey). Eventually, 13 relevant articles were retrieved for full-text review. We excluded five full-text articles due to the following reasons: (a) publications without an appropriate control group ($n = 2$), and (b) studies with duration of less than 1 week ($n = 3$). Finally, eight articles were considered for this meta-analysis (Figure 1).

3.2 | Study characteristics

The main characteristics of the eight eligible trials with 223 in the intervention group and 210 participants in control group are summarized in Table 1. These studies were carried out between 2008 and 2019. The design of all the included trials was parallel. Out of eight included studies, three studies performed in Iran (Nina, Sima, Hossein, & Alireza, 2018; Parsaeyan, Mozaffari-Khosravi, Absalan, & Mozayan, 2014; Rostami et al., 2015), two in Germany (Balzer et al., 2008; Dicks et al., 2018), and three in the United Kingdom (Curtis et al., 2012; Konya et al., 2019; Mellor, Sathyapalan, Kilpatrick, Beckett, & Atkin, 2010). Participant's age ranged from 30 to 80 years. A study (Curtis et al., 2012) was conducted exclusively on women, and seven were performed on both genders. The dose of cocoa ranged from about 1 to 45 g, and intervention duration ranged from 2 to 12 weeks.

3.3 | Quality assessment

According to the Cochrane risk of bias tool, all trials were classified as good quality. Table 2 presents details on the study quality assessment of the included studies.

3.4 | Meta-analysis results

3.4.1 | Effects of cocoa/dark chocolate consumption on glycemic indicators

A pooled analysis of eight effect sizes showed significant reduction in fasting blood sugar (FBS) concentrations following cocoa/dark chocolate consumption (WMD: −6.88 mg/dl; 95% CI: −13.28, −0.48, $p = .03$) without any heterogeneity among the studies ($I^2 = 0.0\%$, $p = .51$; Figure 2a). After subgroup analysis, this reduction was significant only in studies with dosage >2.5 g/day (WMD: −13.68 mg/dl; 95% CI: −24.61, −2.74, $p = .01$), mean age ≤65 years (WMD:

TABLE 2 Quality assessment

Study	Random sequence generation	Allocation concealment	Blinding of participants personnel	Blinding of outcome assessors	Incomplete outcome data	Selective outcome reporting	Other sources of bias
Curtis et al. (2012)	+	+	+	?	+	−	?
Jafarirad et al. (2018)	+	+	+	?	+	+	?
Dicks et al. (2018)	+	+	+	+	+	+	?
Parsaeyan et al. (2014)	+	+	−	?	+	+	?
Rostami et al. (2015)	+	+	+	+	+	+	?
Konya et al. (2019)	+	+	+	+	−	+	?
Balzer et al. (2008)	+	+	+	?	+	+	?
Mellor et al. (2010)	+	+	+	+	−	−	?

−8.98 mg/dl; 95% CI: −16.07, −1.89, $p = .01$), and participants with BMI ≥30 kg/m^2 (WMD: −10.30 mg/dl; 95% CI: −18.71, −1.88; Table 3). We performed the sensitivity analysis by the one-study omission (leave-one-out) approach, to determine the influence of each study on the combined effect size. The results of this analysis showed that excluding Balzer et al. (2008), Rostami et al. (2015), Dicks et al. (2018), Nina et al. (2018), and Curtis et al. (2012) studies from the analysis alters the overall effect size (WMD: −6.61 mg/dl; 95% CI: −13.49, 0.25), (WMD: −5.71 mg/dl; 95% CI: −12.82, 1.40), (WMD: −7.31 mg/dl; 95% CI: −14.73, 0.11), (WMD: −5.65 mg/dl; 95% CI: −12.21, 0.90), (WMD: −6.04 mg/dl; 95% CI: −13.05, 0.97), respectively. Furthermore, no evidence of publication bias was observed (Egger's test, $p = .56$).

We failed to find any significant effect of cocoa/dark chocolate consumption on HbA1c percentage (WMD: −0.02%; 95% CI: −0.24, 0.21, $p = .87$, $I^2 = 0.0\%$; Figure 2b), insulin levels (WMD: −0.31 Hedges's; 95% CI: −0.91, 0.28, $p = .30$, $I^2 = 78.1\%$; Figure 2c). Subgroup analysis on the participant mean age, baseline BMI, study duration, and intervention dose did not change the findings for the effects of cocoa consumption on HbA1c percentage and insulin levels (Table 3). Overall meta-analysis result for the aforementioned indicators was not sensitive to individual studies. Furthermore, no evidence of publication bias was also observed (HbA1c: Egger's test, $p = .76$; insulin: Egger's test $p = .86$).

3.4.2 | Effects of cocoa/dark chocolate consumption on blood pressure

The effect of cocoa consumption on blood pressure was examined in four clinical trials with five effect sizes. Summarizing these effect sizes, we found that cocoa consumption caused a non-significant reduction in the SBP (WMD: −2.53 mm/Hg; 95% CI: −6.70, 1.64, $p = .23$, $I^2 = 1.6\%$; Figure 3a), and diastolic blood pressure (DBP; WMD: −1.91; 95% CI: −5.58, 1.75, $p = .30$, $I^2 = 26.0\%$; Figure 3b). After subgroup analysis, a significant reduction in SBP was detected comparing cocoa consumption to control in studies with cocoa dosage ≥2.5 g/day (WMD: −4.79 mm/Hg; 95% CI: −9.51, −0.006, $p = .04$). However, subgroup analysis based on other factors, including participants' mean age, baseline BMI, and study duration, did not provide additional information (Table 3). Sensitivity analysis revealed that no individual study had a sensible effect on the overall results. Furthermore, no evidence of publication bias was also observed (SBP: Egger's test, $p = .07$; DBP: Egger's test $p = .06$).

3.4.3 | Effects of cocoa/dark chocolate consumption on lipid profile

Combining findings from eight studies with nine arms, a significant reduction in LDL-C levels (WMD: −15.49 mg/dl; 95% CI: −24.56, −6.42, $p = .001$) was detected after cocoa consumption than the controls, with a significant between-study heterogeneity ($I^2 = 93.8\%$, $p < .001$; Figure 4a). Subgroup analysis based on cocoa dosage (>2.5 g/day; $I^2 = 40.7\%$, $p = .16$), baseline BMI (<30 kg/m^2; $I^2 = 36.1\%$, $p = .18$), and study duration (<8 weeks; $I^2 = 0.0\%$, $p = .80$) decreased the heterogeneity. However, this reduction was significant only in studies with dosage >2.5 g/day (WMD: −16.19 mg/dl; 95% CI: −25.20, −7.17, $p < .001$), duration >8 weeks (WMD: −20.08 mg/dl; 95% CI: −22.45, −17.71, $p < .001$), mean age ≤65 years (WMD: −11.77 mg/dl; 95% CI: −21.04, −2.50, $p = .01$), and participants with BMI <30 kg/m^2 (WMD: −15.43 mg/dl; 95% CI: −23.51, −7.35, $p < .001$; Table 3). Overall meta-analysis result for LDL-C was not sensitive to individual studies. Furthermore, no evidence of publication bias was also observed (Egger's test, $p = .40$).

Pooled results (eight studies with nine arms) revealed that cocoa/dark chocolate consumption has no significant effects on total cholesterol (TC) concentrations (WMD: −0.31; 95% CI: −11.22, −10.60, $p = .95$). There was significant heterogeneity between the effect sizes of included studies ($I^2 = 92.3\%$, $p \leq .001$; Figure 4b). Subgroup analysis based on cocoa dosage (≤2.5 g/day; $I^2 = 0.0\%$, $p = .78$), baseline BMI (<30 kg/m^2; $I^2 = 0.0\%$, $p = .66$), mean age (>65; $I^2 = 0.0\%$, $p = .67$), and study duration (≥8 weeks; $I^2 = 0.0\%$, $p = .89$) disappeared the

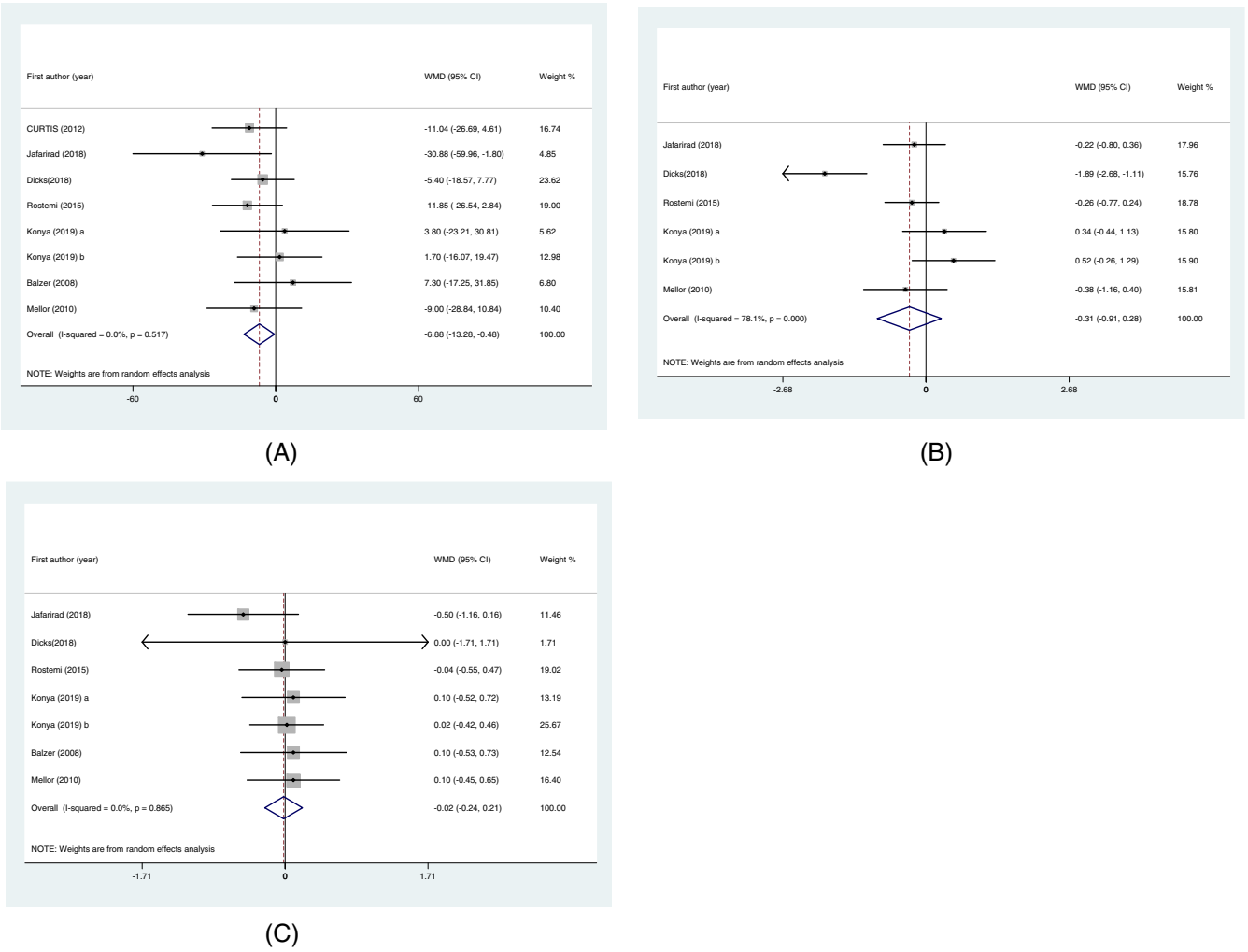


FIGURE 2 (a) Effects of cocoa/dark chocolate consumption on fasting blood sugar. (b) Effects of cocoa/dark chocolate consumption on HbA1c percentage. (c) Effects of cocoa/dark chocolate consumption on insulin levels [Colour figure can be viewed at wileyonlinelibrary.com]

heterogeneity. Furthermore, a significant reduction in TC concentrations was detected comparing cocoa consumption to control in studies with cocoa dosage ≤2.5 g/day (WMD: −3.88 mg/dl; 95% CI: −5.48, −2.28, $p < .001$), baseline BMI ≥30 kg/m^2 (WMD: −3.90 mg/dl; 95% CI: −5.51, −2.30, $p < .001$), trials with duration ≥8 weeks (WMD: −3.76 mg/dl; 95% CI: −5.36, −2.15, $p < .001$; Table 3). Excluding Parsaeyan et al. study from the analysis altered the overall effect size (WMD: −3.88 mg/dl; 95% CI: −5.47, −2.28. Furthermore, no evidence of publication bias was also observed (Egger's test, $p = .38$).

The effect of cocoa/dark chocolate consumption on triglycerides (TG) concentrations was examined in eight clinical trials with nine effect sizes. Summarizing these effect sizes, we found that cocoa consumption caused a nonsignificant reduction in the TG (WMD: −0.99 mg/dl; 95% CI: −17.89, 15.91, $p = .90$). There was significant heterogeneity between the effect sizes of the included studies ($I^2 = 93.5\%$, $p \leq .001$; Figure 4c). Subgroup analysis based on baseline BMI (≥30 kg/m^2; $I^2 = 0.0\%$, $p = .94$), and mean age (>65; $I^2 = 0.0\%$, $p = .79$) decreased the heterogeneity. Furthermore, a significant reduction in TG concentrations was detected comparing cocoa consumption to the control in participants with the baseline BMI ≥30 kg/m^2 (WMD: −8.95 mg/dl; 95% CI: −13.08, −4.81, $p < .001$; Table 3). Sensitivity analysis revealed that no individual study had a great effect on the overall results. Furthermore, no evidence of publication bias was also observed (Egger's test, $p = .60$).

The meta-analysis revealed that there were no significant differences between the effects of cocoa/dark chocolate and control treatment on high density lipoprotein cholesterol (HDL-c) levels (WMD: 1.21 mg/dl; 95% CI: −0.71, 3.13, $p = .21$). The heterogeneity between studies was high ($I^2 = 71.8\%$, $p < .001$; Figure 4d). Subgroup analysis based on cocoa dosage (≤2.5 g/day; $I^2 = 6.4\%$, $p = .37$), study duration ≤8 weeks; $I^2 = 0.0\%$, $p = .60$), baseline BMI (≥30 kg/m^2; $I^2 = 0.0\%$, $p = .51$), and mean age (>65; $I^2 = 0.0\%$, $p = .67$) decreased the heterogeneity. Furthermore, a significant reduction in HDL-c concentrations was detected comparing cocoa consumption to control in participants with baseline BMI ≥30 kg/m^2 (WMD: 1.45 mg/dl; 95% CI: 0.63, 2.26, $p = .001$), trials with duration ≥8 weeks (WMD: 1.55 mg/dl; 95% CI:

TABLE 3 Result of subgroup analysis of included studies in meta-analysis

Sub-grouped by	No. of trials	Effect size[a]	P for effect size	95% CI	I^2 (%)	*p* for heterogeneity	*p* for between subgroup heterogeneity[b]
FBS							
Baseline BMI							0.22
≥30 kg/m[b]	4	−2.18	0.66	−12.04, 7.68	0.0	0.53	
<30 kg/m[b]	4	−10.30	0.01	−18.71, −1.88	0.0	0.47	
Intervention duration							0.75
≥8 weeks	5	−6.34	0.08	−13.59, 0.91	0.0	0.69	
<8 weeks	3	−9.58	0.33	−29.01, 9.58	48.3	0.14	
Cocoa dosage							0.83
≤ 2.5 g/day	5	−3.34	0.40	−11.23, 4.56	0.0	0.67	
>2.5 g/day	3	−13.68	0.01	−24.61, −2.74	0.0	0.44	
Mean age							0.17
≤65 years	6	−8.98	0.01	−16.07, −1.89	0.0	0.49	
>65 years	2	2.33	0.75	−12.51, 17.18	0.0	0.89	
HbA1c							
Baseline BMI							0.48
≥30 kg/m[b]	3	0.06	0.70	−0.25, 0.37	0.0	0.96	
<30 kg/m[b]	4	−0.10	0.54	−0.42, 0.22	0.0	0.57	
Intervention duration							0.70
≥8 weeks	4	−0.02	0.90	−0.27, 0.31	0.0	0.99	
<8 weeks	3	−0.07	0.70	−0.45, 0.30	11.9	0.32	
Cocoa dosage							0.48
≤2.5 g/day	4	0.06	0.71	−0.25, 0.36	0.0	0.99	
>2.5 g/day	3	−0.10	0.53	−0.43, 0.22	0.0	0.37	
Mean age							0.65
≤65 years	5	−0.06	0.68	−0.34, 0.23	0.0	0.68	
>65 years	2	0.05	0.79	−0.31, 0.41	0.0	0.83	
Insulin							
Baseline BMI							0.003
≥30 kg/m[b]	2	0.43	0.12	−0.12, 0.98	0.0	0.76	
<30 kg/m[b]	4	−0.65	0.06	−1.35, 0.04	78.4	0.003	
Intervention duration							0.93
≥8 weeks	4	−0.32	0.51	−1.28, 0.64	86.8	<0.001	
<8 weeks	2	−0.28	0.24	−0.74, 0.19	0.0	0.73	
Cocoa dosage							0.83
≤2.5 g/day	3	−0.34	0.65	−1.86, 1.17	91.2	<0.001	
>2.5 g/day	3	−0.27	0.12	−0.61, 0.07	0.0	0.94	
Mean age							0.003
≤65 years	4	−0.65	0.06	−1.34, 0.04	78.4	0.003	
>65 years	2	0.43	0.12	−0.12, 0.98	0.0	0.76	
SBP							
Baseline BMI							0.09
≥30 kg/m[b]	2	−6.71	0.07	−5.12, 18.53	0.0	0.52	
<30 kg/m[b]	3	−3.90	0.26	−8.22, 0.42	0.0	0.80	
Cocoa dosage							0.08
≤2.5 g/day	3	3.34	0.40	−4.58, 11.26	0.0	0.73	
>2.5 g/day	2	−4.79	0.04	−9.51, −0.06	0.0	0.49	

TABLE 3 (Continued)

Sub-grouped by	No. of trials	Effect size[a]	P for effect size	95% CI	I^2 (%)	*p* for heterogeneity	*p* for between subgroup heterogeneity[b]
Mean age							0.09
≤65 years	3	−3.90	0.07	−8.22, 0.42	0.0	0.52	
>65 years	2	−6.71	0.26	−5.12, 18.53	0.0	0.80	
DBP							0.28
Baseline BMI							
≥30 kg/m[b]	2	0.65	0.84	−6.03, 7.33	0.0	0.51	
<30 kg/m[b]	3	−2.49	0.32	−7.43, 2.46	47.8	0.14	
Cocoa dosage							0.07
≤2.5 g/day	3	0.82	0.73	−3.98, 5.62	0.0	0.80	
>2.5 g/day	2	−3.98	0.17	−9.70, 1.74	44.6	0.17	
Mean age							0.28
≤65 years	3	−2.49	0.32	−7.43, 2.46	47.8	0.14	
>65 years	2	0.65	0.84	−6.03, 7.33	0.0	0.51	
TC							
Baseline BMI							<0.001
≥30 kg/m[b]	4	−3.90	<0.001	−5.51, −2.30	0.0	0.66	
<30 kg/m[b]	5	3.66	0.60	−10.06, 17.39	67.8	0.01	
Intervention duration							<0.001
≥8 weeks	5	−3.76	<0.001	−5.36. -2.15	0.0	0.89	
<8 weeks	4	−1.95	0.86	−24.06, 20.17	82.5	0.001	
Cocoa dosage							<0.001
≤2.5 g/day	5	−3.88	<0.001	−5.48, −2.28	0.0	0.78	
>2.5 g/day	4	4.12	0.62	−12.22, 20.47	71.7	0.01	
Mean age							0.91
≤65 years	7	−0.64	0.91	−12.66, 11.39	94.2	<0.001	
>65 years	2	0.44	0.96	−20.43, 21.31	0.0	0.67	
TG							
Baseline BMI							<0.001
≥30 kg/m[b]	4	−8.95	<0.001	−13.08, −4.81	0.0	0.94	
<30 kg/m[b]	5	6.08	0.52	−12.44, 24.60	73.0	0.005	
Intervention duration							<0.001
≥8 weeks	5	0.46	0.95	−17.33, 18.25	65.3	0.02	
<8 weeks	4	−5.72	0.72	−37.36, 25.94	74.1	0.009	
Cocoa dosage							<0.001
≤2.5 g/day	5	0.07	0.99	−21.26, 21.40	66.3	0.01	
>2.5 g/day	4	−2.84	0.83	−29.69, 24.01	79.1	0.002	
Mean age							0.51
≤65 years	7	−0.47	0.95	−18.40, 17.46	95.1	<0.001	
>65 years	2	−7.10	0.75	−52.28, 38.08	0.0	0.79	
LDL-c							
Baseline BMI							<0.001
≥30 kg/m[b]	4	−23.48	0.05	−47.81, 0.85	86.9	<0.001	
<30 kg/m[b]	5	−15.43	<0.001	−23.51, −7.35	36.1	0.18	
Intervention duration							<0.001
≥8 weeks	5	−16.50	0.05	−33.57, 0.56	82.3	<0.001	
<8 weeks	4	−20.08	<0.001	−22.45, −17.71	0.0	0.80	

(Continues)

TABLE 3 (Continued)

Sub-grouped by	No. of trials	Effect size[a]	P for effect size	95% CI	I^2 (%)	*p* for heterogeneity	*p* for between subgroup heterogeneity[b]
Cocoa dosage							<0.001
≤2.5 g/day	5	−19.43	0.04	−37.99, −0.87	82.5	<0.001	
>2.5 g/day	4	−16.19	<0.001	−25.20, −7.17	40.7	0.16	
Mean age							0.009
≤65 years	7	−11.77	0.01	−21.04, −2.50	94.5	<0.001	
>65 years	2	−44.07	0.23	−116.76, 28.62	92.6	<0.001	
HDL-c							
Baseline BMI							<0.001
≥30 kg/m[b]	4	1.45	0.001	0.63, 2.26	0.0	0.51	
<30 kg/m[b]	5	2.53	0.17	−1.09, 6.14	72.7	0.005	
Intervention duration							<0.001
≥8 weeks	5	1.55	<0.001	0.75, 2.35	0.0	0.60	
<8 weeks	4	1.38	0.53	−3.01, 5.78	71.1	0.01	
Cocoa dosage							<0.001
≤ 2.5 g/day	5	1.49	0.05	−0.01, 2.98	6.4	0.37	
>2.5 g/day	4	1.76	0.35	−1.95, 5.47	70.3	0.01	
Mean age							0.82
≤65 years	7	1.37	0.19	−0.70, 3.45	78.7	<0.001	
>65 years	2	−0.23	0.94	−6.62, 6.16	0.0	0.67	

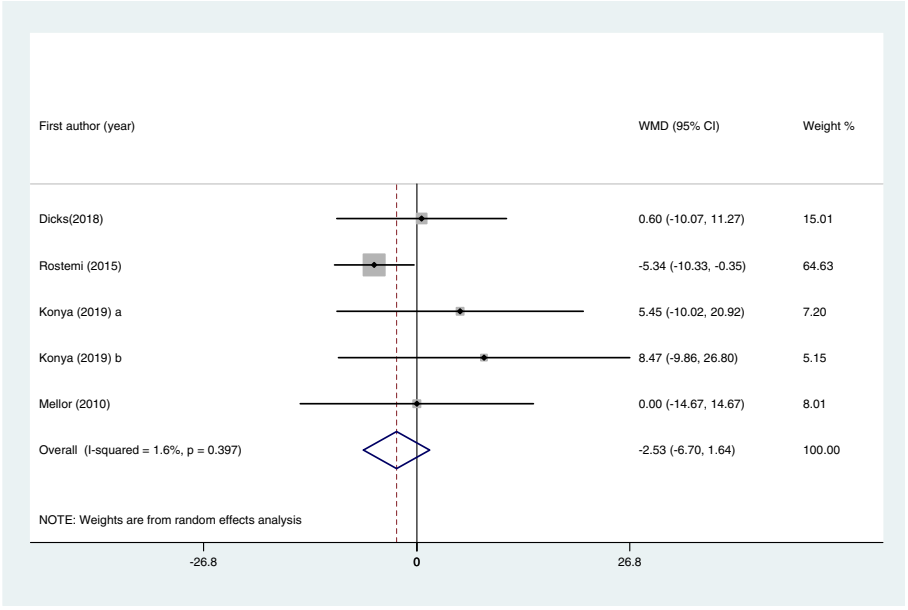
Abbreviations: DBP, diastolic blood pressure; FBS, fasting blood sugar; HbA1c, Hemoglobin A1C; HDL, low-density lipoprotein; LDL, low density lipoprotein; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride.
[a]Calculated by random-effects model.
[b]Calculated by fixed-effects model.

0.75, 2.35, $p < .001$; Table 3). Findings of sensitivity analysis revealed that the observed effects were robust and not dependent on a single study. Based on the Egger's test ($p = .54$), no publication bias existed.

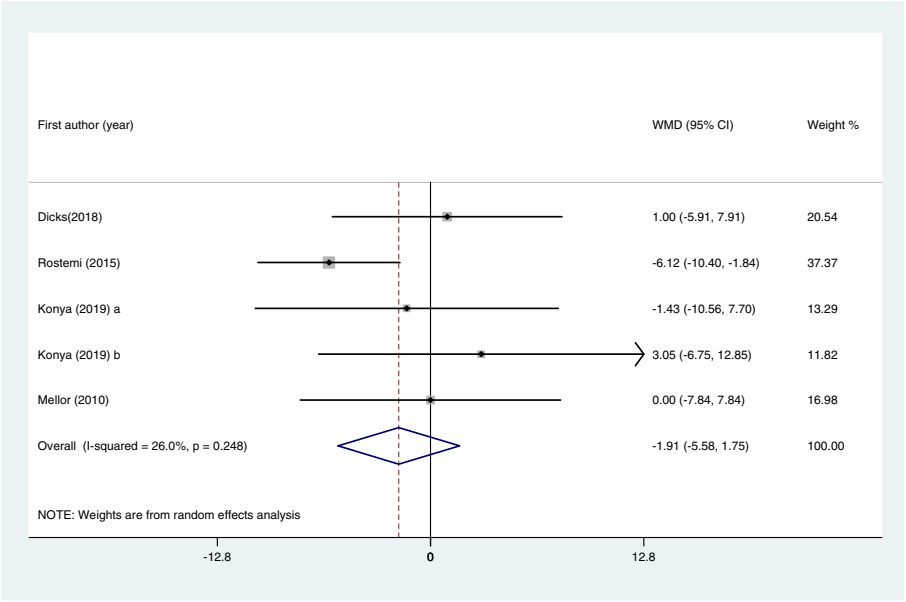
4 | DISCUSSION

To the best of our knowledge, this paper is the first meta-analysis of outcomes from eight RCTs exploring the effects of cocoa powder/dark chocolate on cardiometabolic risk factors in Type 2 diabetic patients. Our meta-analysis results indicate that cocoa/dark chocolate consumption can reduce FBS and LDL-C levels compared to placebo.

The cocoa bean is the seed of the cacao tree (*Theobroma cacao*), a tropical plant indigenous to the Americas' equatorial regions. Cocoa powder is made by pressing cocoa beans and removing butter or fat. Today, cocoa is known for its role in chocolate production (Wood & Lass, 2008). Moreover, Cocoa beans are rich in flavonoids, and the three major groups of polyphenols in cocoa include catechins or flavanols, anthocyanins and proanthocyanins (Sies et al., 2012), which are beneficial to the human body (Jalil & Ismail, 2008). Previous studies have shown the beneficial effects of cocoa-derived products containing flavanols in humans. These benefits include preventing LDL oxidation (Wan et al., 2001) and platelet aggregation (Murphy et al., 2003), improving blood flow (Dinges, 2006), insulin sensitivity (Tomaru et al., 2007), endothelial function (Engler et al., 2004), reducing inflammation (Ramiro et al., 2005), lowering blood pressure (Rostami et al., 2015), promoting brain health, and preventing neurological disorders such as depression (Sokolov, Pavlova, Klosterhalfen, & Enck, 2013). Similar to the studies included in our meta-analysis, several studies have reported a reduction in fasting blood glucose levels after cocoa powder and dark chocolate consumption. For instance, Almoosawi et al. revealed that dark chocolate consumption could reduce blood sugar, SBP, and DBP (Almoosawi, Fyfe, Ho, & Al-Dujaili, 2010). Also, Haghighat et al. demonstrated that consuming 25 g dark chocolate daily (450 mg polyphenols/day) for 8 weeks significantly decreased FBS and HbA1c (Haghighat et al., 2013). Contrary to our study, Mellor et al. showed that the consumption of polyphenols-rich chocolate did not improve fasting glucose and insulin levels in Type 2 diabetic patients (Davison et al., 2010). Overall, our meta-analysis indicates that cocoa consumption did not significantly reduce SBP and DBP. Although the results of the subgroup analysis showed that the consumption of cocoa powder in doses higher than 2.5 g/day reduces SBP, but these results cannot be reliable due to the small number of eligible studies in each subgroup and should be interpreted carefully. The results of previous studies on the effect of cocoa powder on blood pressure are inconsistent. Taubert et al. found that low amounts of cocoa intake (6 g) for 18 weeks reduced SBP by 2.9 mmHg and DBP by 1.9 mmHg (Taubert, Roesen, Lehmann, Jung, &



(A)



(B)

FIGURE 3 (a) Effects of cocoa/dark chocolate consumption on SBP. (b) Effects of cocoa/dark chocolate consumption on DBP. DBP, diastolic blood pressure; SBP, systolic blood pressure [Colour figure can be viewed at wileyonlinelibrary.com]

Schömig, 2007). In another study (Nina et al., 2018), consumption of higher amounts of dark chocolate per day (30 g) was associated with a further reduction in SBP by 6.9 mmHg. In Grassi et al.'s report, consuming higher amounts of dark chocolate (100 g) for 15 days, was associated with a more substantial reduction in SBP by 7.7 mmHg (Grassi, Lippi, Necozione, Desideri, & Ferri, 2005), while Monagas et al. (2009) found no significant association between blood pressure and dark chocolate. Possible causes of discrepancy in the results of available RCTs include differences in the study designs with different intervention periods, cocoa/dark chocolate dosage and different physiological conditions of patients. The result of our study indicates that the consumption of cocoa or dark chocolate significantly reduced LDL-c levels. However, subgroup analysis showed a significant decrease in TC levels by increasing the study time, that is, >8 weeks. Therefore, one reason why some studies did not find any significant results might be the fact that the duration of the studies was not enough to induce the effects. Previous data investigating the impact of cocoa intake on lipid profile is also contradictory. Similar to our study, the results of a meta-analysis study by Tokede et al. showed that cocoa consumption reduced cholesterol and LDL-c levels while no significant change were seen in HDL-c and TG levels (Tokede, Gaziano, & Djoussé, 2011). However, in another meta-analysis study, consumption of cocoa flavonols significantly decreased triglycerides and increased HDL-c levels (Lin et al., 2016). Jia et al.'s study

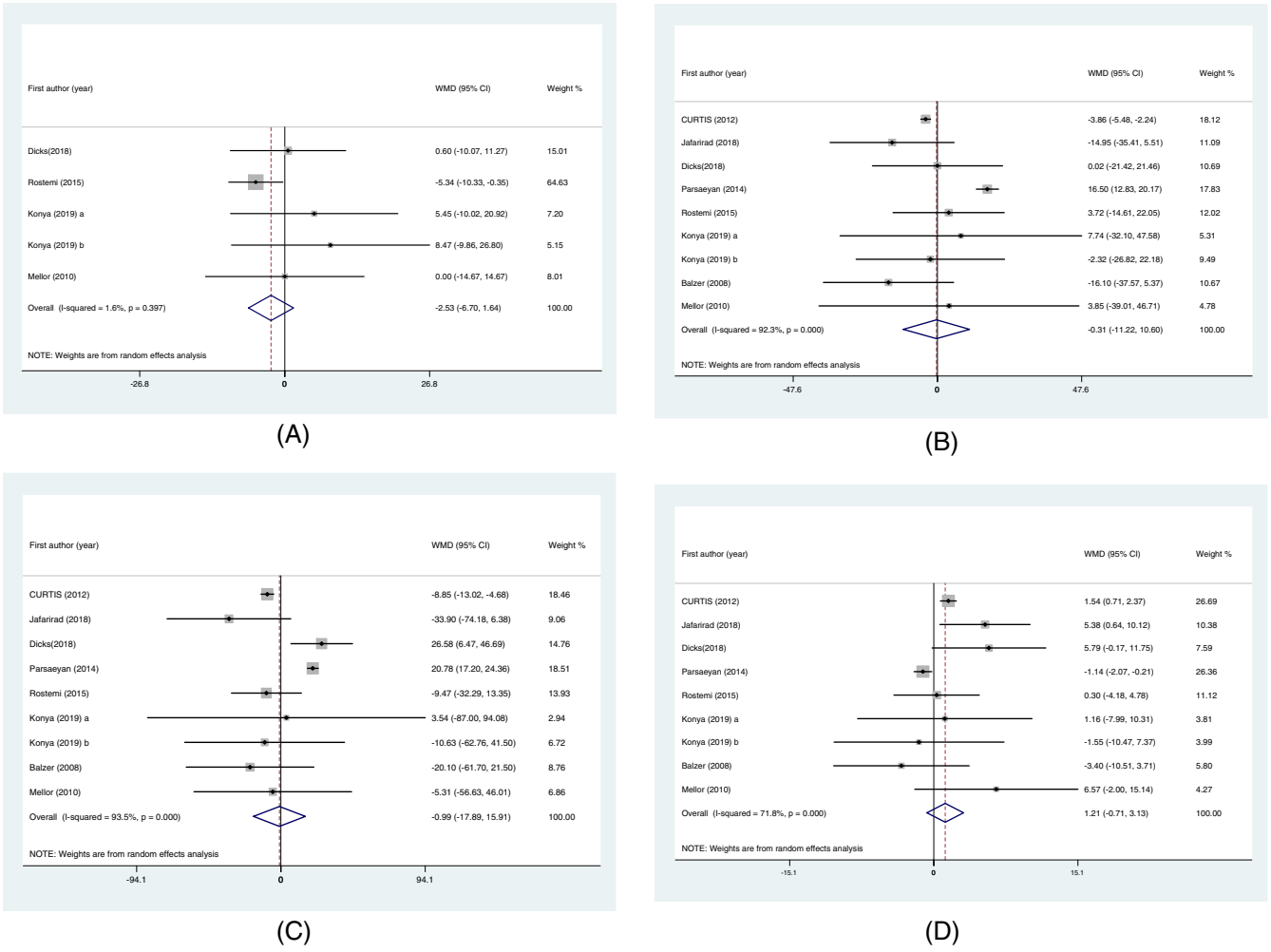


FIGURE 4 (a) Effects of cocoa/dark chocolate consumption on LDL-C levels. (b) Effects of cocoa/dark chocolate consumption on TC. (c) Effects of cocoa/dark chocolate consumption on TG. (d) Effects of cocoa/dark chocolate consumption on HDL-C levels. TC, total cholesterol; TG, triglyceride [Colour figure can be viewed at wileyonlinelibrary.com]

demonstrated that cocoa consumption significantly lowered cholesterol levels in low doses in individuals with cardiovascular risk factors compared to healthy people (Jia et al., 2010). As mentioned earlier, possible causes of conflict in study results include differences in cocoa/dark chocolate dosage, study duration, as well as participants with different physiological conditions including age and BMI. Similar to our meta-analysis, two meta-analysis studies showed that chocolate/cocoa products consumption significantly reduced serum LDL-c levels. At the same time, no significant effects were observed for HDL-c and TG levels (Jia et al., 2010; Tokede et al., 2011).

Insulin resistance plays a vital role in Type 2 diabetes pathogenesis (Kahn, Hull, & Utzschneider, 2006). Increased insulin resistance will result in higher production of VLDLs and lower activity of lipoprotein lipase enzyme, which eventually leads to an increase in total cholesterol and LDL-c levels (Biddinger et al., 2008). One potential mechanism of cocoa polyphenols (catechins and epigallocatechins) is to promote phosphorylation of tyrosine kinase and insulin receptors and to increase the activity of PI3K/AKT pathway and activation of 5′ adenosine monophosphate-activated protein kinase (AMPK; Kang et al., 2019). Activation of AMPK inhibits the breakdown of glycogen stores in hepatocytes by inhibiting hepatic phosphorylase and increasing the activity of enzymes involved in glycogen synthesis, which eventually leads to a decrease in blood glucose (Collins et al., 2007). In addition, AMPK can inhibit hepatic glucose-6-phosphatase activity, which reduces the breakdown of glucose-6-phosphate into glucose and the entry of glucose into the bloodstream. Cocoa consumption also increases glucose uptake into the tissues (Cordero-Herrera, Martín, Goya, & Ramos, 2014). Activated AMPK also regulates lipid metabolism through lowering intracellular cholesterol synthesis in the liver, decreasing lipogenesis and lipolysis in adipose tissue, increasing lipid oxidation in muscle tissue, and reducing circulating fatty acids (Yang, Zhang, Zhang, Huang, & Wang, 2016). Another reason why Type 2 diabetic patients have lower uptakes of glucose is that there is a malfunction in the endothelium (Natali & Ferrannini, 2012). Evidence shows that cocoa or dark chocolate polyphenols will trigger nitric oxide (NO) synthase and increase NO production by blocking free radical production. This will lead to improvements in endothelium function, NO

expansion, and insulin sensitivity (Flammer et al., 2007; Grassi et al., 2015).

There are some strengths and limitations to this meta-analysis. This meta-analysis only includes RCTs and all participants in the trials were in similar health conditions while having Type 2 diabetes. In all eligible RCTs, participants' adherence to the intervention (following up the protocol) was reported to be high. Time was not a limiting factor in searching for articles, but the search results were limited to English-language publications. Significant statistical heterogeneity was found among the eligible studies, which may be due to the difference in the studies design. In the studies, the unit of measurement of metabolic parameters differed from each other, so we tried to match them up together. Due to the limited number of eligible articles in each subgroup, the results of the subgroup analysis on the lipid profile were inconsistent. In addition, there was a possibility that most studies discussed in the present study have not been performed in accordance to a recent consensus document providing a perspective in best practice in pharmacological research on plants bioactive preparations (Heinrich et al., 2020). Also, numerous medicinal plants with pharmacological properties have been introduced to date, However, research projects assessing the effects of such plants on outcomes of interest are very heterogeneous and provide contradictory results and inconsistency in phytotherapy practice. Therefore, there is a need to standardize the use of medicinal plants in clinical practices (Colalto, 2018). Meta-analyses are suggested as a critical approach to draw a preliminary and satisfactory conclusion and provide the uppermost ladders in the hierarchy of evidence (Colalto, 2018; Williamson, Liu, & Izzo, 2020).

5 | CONCLUSION

The present study shows that consumption of cocoa/dark chocolate reduced FBS and LDL cholesterol. Although this reduction in FBG and LDL-c is clinically small, it may be useful alongside lipid-lowering medications and anti-diabetic drugs. More high quality studies are needed to firmly establish the clinical efficacy of the plant-based products.

CONFLICT OF INTEREST

The authors declare there is no conflict of interest.

DATA AVAILABILITY STATEMENT

Data openly available in a public repository that issues datasets with DOIs.

ORCID

Mina Darand https://orcid.org/0000-0003-2636-0963
Masoomeh Hajizadeh Oghaz https://orcid.org/0000-0002-3596-3654

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How to cite this article: Darand, M., Hajizadeh Oghaz, M., Hadi, A., Atefi, M., & Amani, R. (2021). The effect of cocoa/dark chocolate consumption on lipid profile, glycemia, and blood pressure in diabetic patients: A meta-analysis of observational studies. *Phytotherapy Research*, 1–15. https://doi.org/10.1002/ptr.7183