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Efficacy and safety of *Coccinia grandis* (L.) Voigt on blood glucose and lipid profile: An updated systematic review and meta-analysis

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ABSTRACT

Introduction: *Coccinia grandis* has been shown to improve blood glucose and lipids. The results of earlier clinical studies on the effects of *C. grandis* on blood sugar and lipid profile are debatable. This meta-analysis aimed to evaluate, using randomized controlled trials (RCTs), the effects of consuming *C. grandis* on lipid profiles and blood glucose levels.

Methods: Thai and English articles by two independent authors were searched in PubMed, ScienceDirect, Scopus, and ThaiJo up to November 2023 for a systematic review. The keywords were developed based on MeSH terms as follows: (*Coccinia grandis* OR *Coccinia cordifolia* OR *Coccinia indica*) AND (fasting blood glucose OR FBS OR fasting plasma glucose OR FPG OR HbA1C OR postprandial glucose OR PPG OR lipid profile OR low-density lipoprotein OR LDL OR high-density lipoprotein OR HDL OR total cholesterol OR TC OR triglyceride OR TG). The Laird and DerSimonian random-effect model was used to pool the findings. Seven trials with 595 individuals and 1–90-day treatments were included.

Results: The combined data revealed a noteworthy decline in fasting blood sugar (FBS); standardized mean difference (SMD) by -1.99 mg/dL (P<0.001), 1-hour postprandial glucose (PPG) by -0.99 mg/dL (P<0.001), 2-hour PPG by -0.69 mg/dL (P=0.004) and triglycerides (TG) by -0.46 mg/dL (P=0.001). However, there were no significant differences in hemoglobin A1C (HbA1C), low-density lipoprotein (LDL), high-density lipoprotein (HDL), and total cholesterol (TC). No major intervention side effects were recorded.

Conclusion: Our investigation found that *C. grandis* reduced FBS, PPG, and TG. The treatment's long-term advantages and safety are unknown.

Implication for health policy/practice/research/medical education:
This meta-analysis indicates that the consumption of *Coccinia grandis* has the potential to reduce FBS, PPG, and TG. This therapeutic modality is an adjunctive therapy for patients diagnosed with diabetes mellitus and hyperlipidemia.

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Introduction

Cardiometabolic risk factors represent a paramount global cause of mortality, exerting a profound and pervasive impact annually (1,2). Moreover, empirical data substantiates the disconcerting reality that over 60% of fatalities stemming from diverse chronic ailments can be attributed to the pernicious influence of cardiovascular risk factors (3). Cardiometabolic risk factors significantly burden the healthcare system (4).

Previous studies have consistently shown a relationship between elevated blood glucose, hemoglobin A1C (HbA1C), and postprandial plasma glucose (PPG) levels and the morbidity of cardiovascular disease (CVD) (5). Furthermore, the increased levels of triglycerides (TG), total cholesterol (TC), and low-density lipoprotein cholesterol (LDL-C) increase the risk of CVD, but

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high-density lipoprotein cholesterol (HDL-C) provides protection (6,7). Another study has demonstrated that attempts to lower blood glucose levels effectively decreased cardiovascular problems (8). Furthermore, the incidence of ischemic heart disease among participants decreased by 12%–20% throughout the five-year follow-up when LDL levels were reduced by about 10% (9).

These risk factors are intimately linked with impaired glucose metabolism, insulin resistance, and dyslipidemia, which significantly elevate the risk of various chronic ailments, including diabetes, obesity, hepatic steatosis, and CVDs (10). Managing blood glucose and lipid profiles can be achieved through the adoption of appropriate dietary patterns, serving as preventive or control measure for diabetes and related conditions (11). Intriguingly, the realm of non-pharmacological strategies, encompassing health-focused diets and functional foods, such as herbal medicine, has garnered considerable attention as providing valuable approaches in addressing these challenges (12,13).

Coccinia grandis (L.) Voigt, a perennial climber belonging to the Cucurbitaceae family, is indigenous to tropical regions of Asia, notably prevalent in Thailand, Sri Lanka, India, and Pakistan. The leaf extract of *C. grandis* holds a venerable position in Ayurvedic medicine as an adjunctive therapy for the management of diabetes mellitus (14). Beyond this, the plant's leaves are recognized for their multifaceted therapeutic properties, encompassing antioxidative and anti-inflammatory attributes (15,16). In streptozotocin-induced diabetic rats and normoglycemic rats, Attanayake's study has examined the acute hypoglycemia potential of an alcoholic extract of *C. grandis* (17). Likewise, methanolic leaf extract's impact on lipid profiles and liver enzymes in streptozotocin-induced diabetic rats has been investigated (18). Moreover, in rats with diabetes induced by alloxan, there have been reports of *C. grandis* aqueous leaf extract's hypolipidemic properties.

Initial investigations have determined that an aqueous *C. grandis* leaf extract, given at a dose of 0.75 g/kg, constitutes an optimally effective and safe therapeutic modality, demonstrating promise as an antihyperglycemic agent in rat models (19). Multiple randomized controlled trials (RCTs) have been undertaken to assess the potential causal relationship between *C. grandis* supplementation and its impact on blood glucose levels and lipid profiles. Hence, the aim of this study was to conduct a comprehensive review of the literature regarding the effects of *C. grandis* supplementation on lipid profiles and blood glucose levels in RCTs, including diabetic patients, and to compile and update the material in a meta-analysis.

Methods

Search strategy

The referred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines were closely followed during the current inquiry, guaranteeing the methodological rigor and transparency of this evaluation (20) and the PROSPERO database has the protocol recorded (CRD42023482144). A thorough and systematic search was executed across the world's most prominent databases including PubMed, Scopus, ScienceDirect, and ThaiJo. This study was conducted up to 30 November 2023. The primary aim of this comprehensive search, conducted in both English and Thai languages, was to identify RCTs examining the impact of *Coccinia grandis* on a spectrum of pertinent clinical parameters. The results that were of particular importance included PPG, fasting blood glucose (FBG), HbA1C, and the lipid profile parameters, which included TG, TC, HDL, and LDL.

Medical Subject Headings (MeSH) was used as part of the search strategy for this investigation in order to carefully query the databases. The MeSH terms used were as follows: (*Coccinia grandis* OR *C. grandis* OR *Coccinia cordifolia* OR *C. cordifolia* OR *Coccinia indica* OR *C. indica*) AND (blood glucose OR fasting blood glucose OR FBS OR fasting plasma glucose OR FPG OR HbA1C OR postprandial glucose OR PPG OR lipid profile OR Low-density Lipoprotein OR LDL OR High-Density Lipoprotein OR HDL OR total cholesterol OR TC OR triglyceride OR TG). Furthermore, in an endeavor to ensure a comprehensive review of the pertinent literature, a thorough examination was conducted on the reference lists of the recovered and reviewed studies. This supplementary method was pursued to identify any relevant articles that might have eluded our initial search, due to various factors. Such articles were evaluated through a manual review process. It is imperative to note that the eligibility of all potential abstracts and titles was independently assessed by two reviewers, namely WP and CT, to confirm that the analysis contained only studies that met the eligibility requirements.

Selection criteria

The present authors conducted a thorough review of the literature, independently identifying pertinent articles. Duplicate articles were eliminated through careful screening of titles, abstracts, and full-text contents. Trials were included if they met the following pre-established criteria: 1) randomized study design with participants aged 18 years or older, 2) comprehensive details on the *C. grandis* product, 3) comparative analysis between *C. grandis* and a placebo, and 4) baseline measurements, outcomes of interest, and documentation of any adverse events. To ensure the robustness of the analysis, non-randomized controlled trials and animal research were omitted. Lipid profiles and blood glucose levels were evaluated as the main outcomes of interest in this investigation. Secondary outcomes included liver and renal function tests, and potential adverse effects.

Data extraction

Two independent reviewers (WP and CT) extracted relevant data from the full manuscripts of eligible studies into an electronic database. Extracted data included patient characteristics, study design, intervention, number of participants in each group, and outcomes. A third reviewer (BS) reconciled any disagreements. When necessary, the original authors were contacted for clarification or additional data.

Information extraction

This meta-analysis extracted the following data from relevant studies: mean and standard deviation (SD) of primary outcomes (FBS, HbA1C, PPG, LDL, HDL, TC, and TG) before and after intervention, liver function tests, renal function tests, and the number of adverse events. The following information was also extracted: the name of the authors, the year the work was published, the country, the number of participants in the intervention and control groups, the sex, age (years), and state of the participants' health, the duration of the intervention, and the extract dosage.

Quality measurement

Two authors independently used the Cochrane Risk of Bias Tool for Randomized Controlled Trials to assess the potential for bias in the included studies (21). This tool assesses the following domains: random sequence generation, blinding, allocation concealment, partial result data, and other potential sources of bias. The degree of bias was rated as low, high, or unclear for each domain. Any inconsistencies or differences in the information extraction or risk assessment were resolved by a third author.

Data synthesis and statistical analysis

Statistical analysis was performed using Review Manager (RevMan®, v. 5.3; Cochrane Collaboration) and Stata software version 15.0 (StataCorp, College Station, TX, USA). Utilizing the standardized mean difference (SMD) with a 95% confidence interval (CI), the effectiveness was evaluated. Heterogeneity was examined using the Q-statistic with I^2 results. $I^2 \geq 50\%$ ($P < 0.10$) indicated statistical heterogeneity. The random-effects model was used for all outcomes. To make sure robustness, the sensitivity analyses with fixed-effect models were carried out. Subgroup analyses were conducted based on the study design and treatment duration. Funnel plots were used to evaluate publication bias. Safety outcomes were descriptively reported.

Results

Upon conducting a comprehensive screening of the available literature, the initial search across established databases yielded a total of 1256 articles, as illustrated in Figure 1. After meticulous removal of the duplicate articles, this number was substantially reduced to 371 studies. Subsequent refinement of the selection criteria, undertaken through a judicious review of titles and abstracts, led to the exclusion of 309 articles. The remaining studies, deemed potentially pertinent, underwent further scrutiny based on a thorough examination of their full texts. Within this phase, one article was excluded as it represented a duplication. Ultimately, in alignment with the stringent criteria outlined for our investigation, a total of seven trials (22-28) met the inclusion criteria and were thus subjected to a comprehensive analysis. These seven studies collectively furnished a comprehensive evaluation of *C. grandis*' impact on blood sugar levels. Furthermore, within this cohort, three studies were identified which specifically addressed the influence of *C. grandis* on lipid profiles.

Study characteristics

Table 1 lists the characteristics of the pooled studies. Three studies were conducted in India (22,23,26), two studies performed in Sri Lanka (24,27), one trial in Thailand (25) and one study in Australia (28). Our meta-analysis contained only RCTs. Four trials (23,24,27,28) were double blinded RCTs. The duration of studies varied from one to ninety days. Four studies (23,25,27,28) examined the effects of 500 mg/d *C. grandis* extract. Six trial were performed in DM type 2 patients (22-27) and one trial performed in prediabetes participants (28). The study participants' ages ranged from 37 to 70 years.

Quality assessment

Considering the methods reported for generating randomization sequences, it was discerned that merely two out of the seven studies exhibited an elevated risk of bias (23,25). The remaining studies predominantly exhibited an elevated or indeterminate risk of bias, primarily attributed to concerns regarding allocation concealment and participant blinding. In terms of selective reporting, the majority of studies provided comprehensive descriptions. Based on a comprehensive evaluation, the Cochrane Handbook for Systematic Reviews of Interventions' criteria were generally met, with the included studies' quality being judged at a noteworthy level (20) (Figure 2).

Meta-analysis

Blood glucose

A random-effect meta-analysis revealed a significant reduction in FBS with *C. grandis* (SMD -1.99 mg/dL; 95% CI -2.95, -1.04; $P < 0.001$). Additionally, there were significant reductions in 1-hour and 2-hour PPG (SMD -0.99 mg/dL; 95% CI -1.79, -0.19; $P < 0.001$ and SMD -0.72 mg/dL; 95% CI -0.93, -0.50; $P = 0.004$, respectively). However, *C. grandis* did not significantly reduce HbA1c

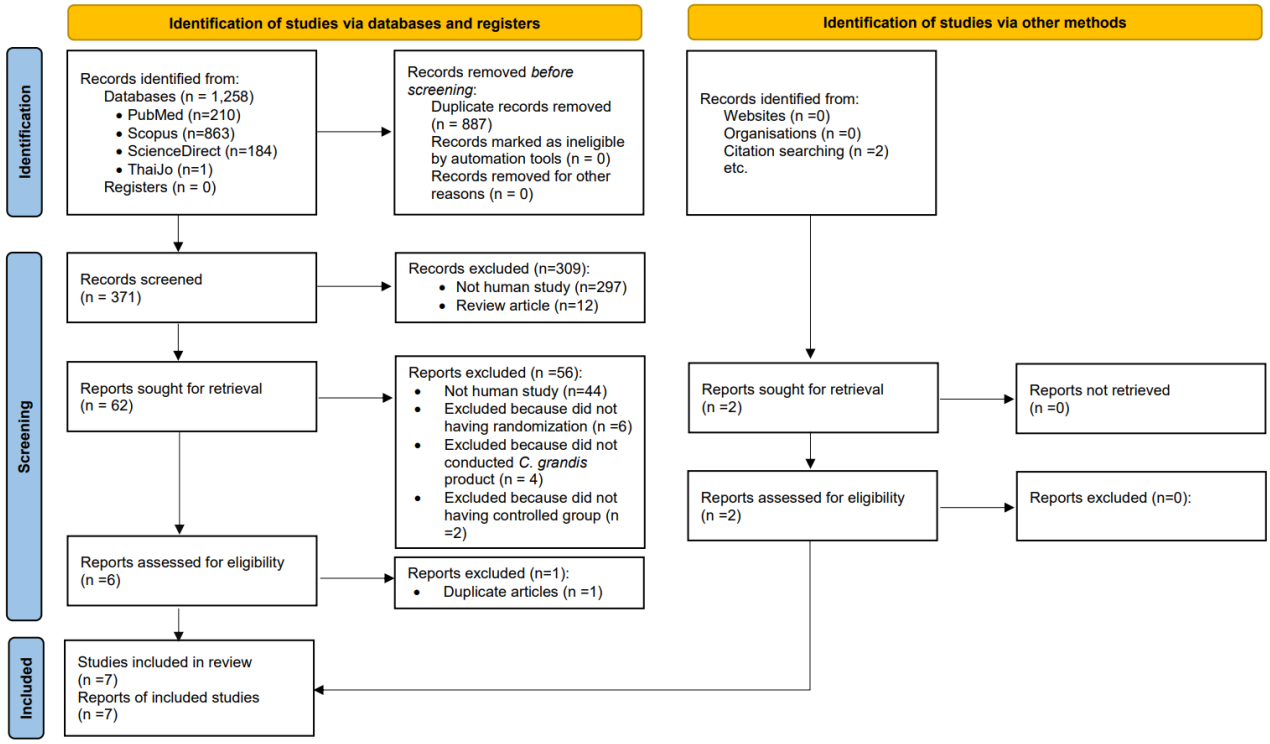

Figure 1. Flow diagram showing how the studies considered in this analysis were chosen

(SMD -0.71%; 95% CI -1.44, 0.01; $P=0.05$). There was a significant heterogeneity in these outcomes ($I^2 \geq 50\%$). The model was changed from a random effect model to a fixed effect model in a sensitivity analysis. HbA1c was significant with -0.77% (-0.99, -0.54; $P<0.001$); however, the results for FBS and PPG outcomes remained unchanged (Table 2).

Lipid profile

A pooled data analysis showed no significant improvement

Table 1. Study attributes that were part of the meta-analysis

Study, year	Country	Study design	Participants	Age (mean) or range (year)	Intervention	Control	Duration	Outcomes
Khan et al. 1998	India	RCT	DM	N/A	Freeze-dried leaves of *C. grandis* tablets (n=61)	Placebo tablets (n=61)	42 days	FBS, PPG
Kuriya, et al. 2008	India	DRCT	DM type 2	47.05±6.0	*C. grandis* extract 500 mg/d (n=30)	Maltodextrin capsules 500 mg/d (n=29)	90 days	FBS, PPG, HbA1C, LDL, HDL, TC, TG
Munasinghe, et al. 2011	Sri Lanka	DRCT	DM type 2	35±11.5	*C. grandis* leaves 20 g/d (n=61)	Placebo 20 g/d (n=61)	1 day	FBS, PPG
Leeprakon, et al. 2017	Thailand	RCT	DM type 2	46-70	*C. grandis* 500 mg/d (n=28)	Placebo (n=28)	60 days	FBS, HbA1C
Wasana, et al. 2021	Sri Lanka	DRCT	DM type 2	48.64±7.09	*C. grandis* 500 mg/d (n=79)	Corn starch 500 mg/d (n=79)	90 days	FBS, HbA1C, LDL, HDL, TC, TG, renal function test, liver function test
Junaid, et al. 2020	India	RCT	DM type 2	30-60	*C. grandis* 360 g/d (n=15)	Barley flour (n=15)	30 days	FBS, HbA1C, PPG
Pickering, et al. 2023	Australia	DRCT	Pre-DM	27-73	*C. grandis* extract 500 mg/d (n=25)	Maltodextrin 500 mg (n=23)	48 days	FBS, HbA1C, PPG, LDL, HDL, TC, TG, renal function test, liver function test

Abbreviations: RCT, randomized controlled trial; DRCT, double blind randomized controlled trial; DM, diabetes mellitus; FBS, fasting blood sugar; PPG, postprandial glucose; HbA1C, Hemoglobin A1C; LDL, low-density lipoprotein; HDL, high-density lipoprotein; TC, total cholesterol; TG, triglyceride; N/A, not available.

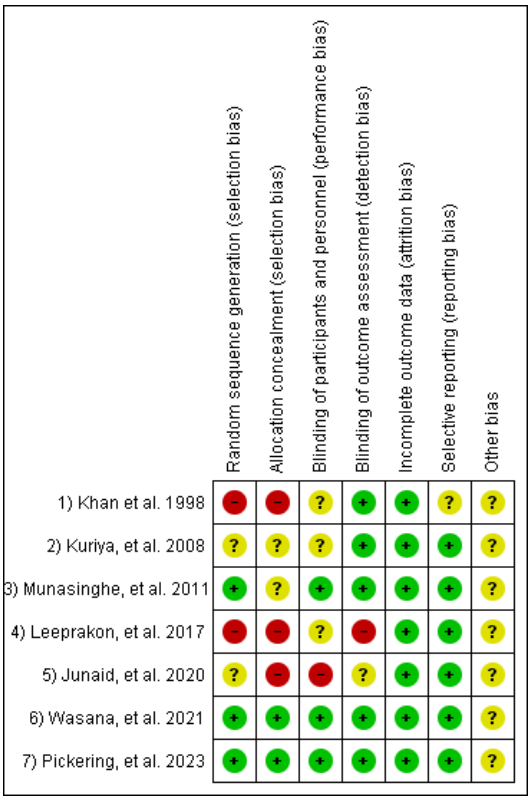

Figure 2. Reporting risk of bias assessment of each defining element of the recruited studies. +: low risk; −: high risk; ?: unclear.

in LDL (SMD -0.17 mg/dL; 95% CI: -0.41, 0.07; $P=0.16$), HDL (SMD 0.10 mg/dL; 95% CI: -0.23, 0.43; $P=0.56$), or TC (SMD -0.11 mg/dL; 95% CI: -0.35, 0.13; $P=0.38$) after *C. grandis* treatment. However, *C. grandis* significantly decreased triglyceride levels (SMD -0.46 mg/dL; 95% CI: -0.74, -0.18; $P=0.001$). There was no significant heterogeneity in these outcomes ($I^2<50.0\%$). After changing the model from a random effect model to a fixed effect model in a sensitivity analysis, all of the outcomes' conclusions remained unchanged (Table 2).

Adverse event

Munasinghe et al (24) reported that the adverse events of *C. grandis* administration were nausea (1.7%), headache (5%), and drowsiness (29%). A study in Thailand (25) found that the adverse events of *C. grandis* were dizziness (3.57%), insomnia (3.57%), and rash (1.78%). Two studies assessed other safety profiles using renal and liver function test parameters (27,28). The meta-analysis showed that *C. grandis* significantly altered AST and ALT levels, but not renal function tests (Table 3).

Subgroup analysis

Subgroup analysis by study design, *C. grandis* extraction method, and treatment duration revealed that the double-blinded RCTs (DRCTs) improved FBS and 1-hour PPG, and both RCTs and DRCTs significantly decreased 2-hour PPG. *C. grandis* extraction significantly reduced FBS and 2-hour PPG. Treatment duration longer than or equal to 90 days improved FBS, 1-hour PPG, and 2-hour PPG (Table 4).

Publication bias

To evaluate publication bias in the meta-analysis, a funnel plot was employed (Figure 3). The funnel plot was symmetrical, suggesting no significant publication bias.

Discussion

A comprehensive review and meta-analysis was conducted to ascertain the efficacy of *C. grandis* in reducing FBS, PPG, and triglyceride. Although the meta-analysis comprised seven studies, the sample size, research methodologies, and outcomes were not all the same. Based on an evaluation of the studies' quality using the Cochrane Risk of Bias Tool for Randomized Controlled Trials (21), it was discovered that the majority of the studies had a high risk of bias. This study demonstrated a statistically significant reduction in post-FBS, HbA1c, and post-meal blood sugar at 60 minutes. Blood glucose levels after eating at 60 and

Table 2. The main analysis outcomes and sensitivity analysis

Outcomes	Main analysis N; SMD [95%CI]; I^2	Sensitivity analysis N; SMD [95%CI]; I^2	References
Blood glucose			
FBS	299; -1.99 [-2.95, -1.04]; 95.0%*	296; -1.15 [-1.34, -0.97]; 95.0%*	(22-28)
HbA1C	176; -0.71 [-1.44, 0.01]; 89.0%	174; -0.77 [-0.99, -0.54]; 89.0%*	(23,25-28)
1-Hour PPG	162; -0.99 [-1.79, -0.19]; 90.0%*	160; -0.51 [-0.74, -0.29]; 90.0%*	(22,24,26,28)
2-Hour PPG	177; -0.69 [-1.16, -0.21]; 78.0%*	174; -0.72 [-0.93, -0.50]; 78.0%*	(22-24,28)
Lipid profile			
LDL	133; -0.17 [-0.41, 0.07]; 0.0%	132; -0.17 [-0.41, 0.07]; 0.0%	(23,27,28)
HDL	133; 0.10 [-0.23, 0.43]; 38.0%	132; 0.07 [-0.17, 0.32]; 38.0%	(23,27,28)
Total cholesterol	133; -0.11 [-0.35, 0.13]; 0.0%	132; -0.11 [-0.35, 0.13]; 0.0%	(23,27,28)
Triglyceride	133; -0.46 [-0.74, -0.18]; 18.0%*	132; -0.47 [-0.72, -0.23]; 18.0%	(23,27,28)

Abbreviations: FBS, fasting blood sugar; PPG: postprandial glucose; HbA1C, Hemoglobin A1C; LDL, low-density lipoprotein; HDL, high-density lipoprotein; SMD, standardized mean difference.
* $P \leq 0.05$ compared to the control group.

Table 3. Renal and liver function test parameters of *Coccinia grandis* vs comparators

Outcomes	Main analysis N; SMD [95%CI]; I^2	Sensitivity analysis N; SMD [95%CI]; I^2	References
Renal function			
Serum creatinine	104; 0.26 [-0.04, 0.55]; 7.0%	102; 0.26 [-0.01, 0.54]; 7.0%	(27,28)
GFR	25; 0.11 [-0.46, 0.68]; N/A	23; 0.11 [-0.46, 0.68]; N/A	(28)
Liver function test			
AST	104; 0.35 [0.08, 0.63]; 0.0%	102; 0.35 [0.08, 0.63]; 0.0%	(27,28)
ALT	104; 0.51 [-0.15, 1.17]; 75.0%	102; 0.37 [0.09, 0.64]; 75%	(27,28)
GGT	104; -0.00 [-0.66, 0.65]; 76.0%	102; 0.13 [-0.14, 0.41]; 76.0%	(27,28)
ALP	104: -0.22 [-0.50, 0.05]; 0.0%	102; -0.22 [-0.50, 0.05]; 0.0%	(27,28)

Abbreviations: GFR, glomerular filtration rate; AST, aspartate transaminase; ALT, alanine transaminase; GGT, gamma-glutamyl transferase; ALP, alkaline phosphatase; SMD, standardized man difference; N/A, not available

120 minutes were also statistically significantly reduced.

Coccinia grandis is a plant species that possesses a wide range of bioactive phytochemicals in its leaves and aerial parts. Rutin, quercetin, and kaempferol are present in the ethanolic extract and rutin, kaempferol, and kappacontane in the methanolic extract (29,30). Moreover, the fruit extract in question is made up of several different substances, such as undecanol, β-sitosterol acetate, tocopherol, stigmatosterol, ethisteron, campoesterol, and campesterol (31). It is worth mentioning that flavonoids

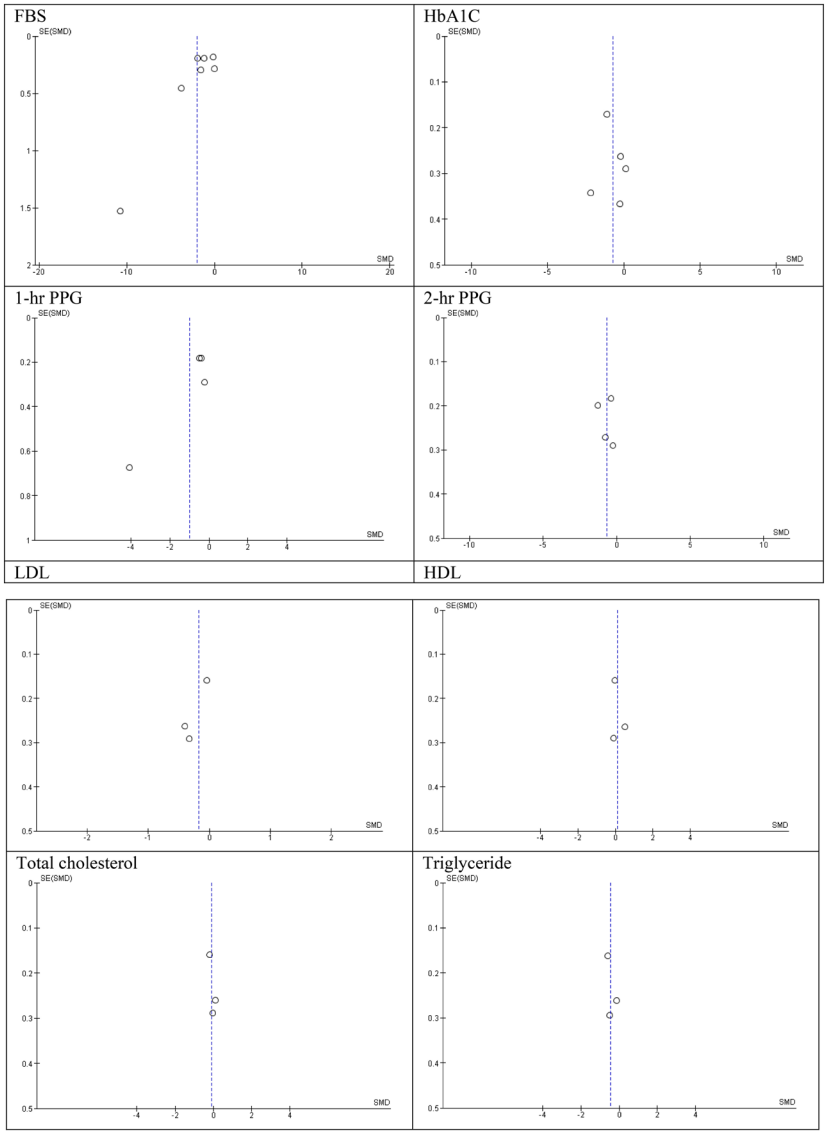

Figure 3. Funnel plots detailing publication bias. Abbreviations: FBS, fasting blood glucose; HbA1C, hemoglobin A1C; PPG, postprandial glucose; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

Table 4. Analyzing randomized controlled trial (RCT) subgroups to assess the impact of *Coccinia grandis* on clinical results

Outcomes	No. of trials	SMD	95% CI	I^2 (%)	P^a	P^b
FBS						
Study design						
RCT	3	-4.73	-7.82, -1.64	97.0	0.003	<0.001
DRCT	4	-0.93	-1.15, -0.71*	95.0	<0.001	<0.001
Extraction						
Non	3	-2.58	-4.34, -0.82*	97.0	0.004	<0.001
Extracted	4	-1.78	-2.99, -0.57*	95.0	0.004	<0.001
Duration						
<90 days	5	-2.29	-3.66, -0.93*	96.0	0.001	<0.001
≥90 days	2	-1.81	-2.12, -1.49*	1.0	<0.001	0.32
HbA1C						
Study design						
RCT	2	-1.22	-3.13, 0.70	93.0	0.21	<0.001
DRCT	3	-0.41	-1.19, 0.37	88.0	0.30	<0.001
Extraction						
Non	1	-0.24	-0.95, 0.48	N/A	0.52	N/A
Extracted	4	-0.82	-1.68, 0.03	91.0	0.06	<0.001
Duration						
<90 days	3	-0.76	-2.18, 0.66	93.0	0.29	<0.001
≥90 days	2	-0.66	-1.53, 0.21	88.0	0.14	<0.001
1-hr PPG						
Study design						
RCT	2	-2.22	-5.73, 1.30	96.0	0.22	<0.001
DRCT	2	-0.35	-0.65, -0.05*	0.0	0.02	0.63
Extraction						
Non	3	-1.34	-2.44, -0.25*	93.0	0.02	<0.001
Extracted	1	-0.23	-0.80, 0.33	N/A	0.42	N/A
2-hr PPG						
Study design						
RCT	1	-1.27	-1.66, -0.88*	N/A	<0.001	N/A
DRCT	3	-0.46	-0.72, -0.20*	0.0	<0.001	0.38
Extraction						
Non	2	-0.83	-1.69, 0.02	90.0	0.06	<0.001
Extracted	2	-0.53	-1.04, -0.02*	41.0	0.04	0.19
Duration						
<90 days	3	-0.66	-1.30, -0.02*	85.0	0.04	<0.001
≥90 days	1	-0.78	-1.31, -0.25*	N/A	0.004	N/A
LDL						
Duration						
<90 days	1	-0.32	-0.90, 0.25	N/A	0.26	N/A
≥90 days	2	-0.16	-0.48, 0.16	24.0	0.33	0.25
HDL						
Duration						
<90 days	1	-0.10	-0.66, 0.47	N/A	0.73	N/A
≥90 days	2	0.19	-0.31, 0.69	64.0%	0.45	0.10
Total cholesterol						
Duration						
<90 days	1	-0.02	-0.59, 0.54	N/A	0.93	N/A
≥90 days	2	-0.12	-0.39, 0.15	2.0%	0.37	0.31
Triglyceride						
Duration						
<90 days	1	-0.51	-1.09, 0.06	N/A	0.08	N/A
≥90 days	2	-0.40	-0.86, 0.06	59.0%	0.09	0.12

Abbreviations: FBS, fasting blood sugar; DRCT, double-blinded randomized controlled trials; SMD, standardized mean difference; CI, confidence interval; PPG, post prandial glucose; LDL, low-density lipoprotein; HDL, high-density lipoprotein; N/A, not applicable.

[a] *P* value of effect size; [b] *P* value of heterogeneity; *$P \leq 0.05$ compared to the control group.

constitute the predominant phenolic group in *C. grandis* and have been recognized for their potential antidiabetic properties (32,33).

Coccinia grandis may reduce hyperglycemia by increasing β-cell proliferation, stimulating insulin secretion, reducing apoptosis, and controlling liver glucose metabolism (34). The most prevalent flavonoid in *C. grandis*, quercetin, has been demonstrated to have antidiabetic effects via a variety of pathways. Quercetin reduced the absorption of glucose and fructose in human intestinal Caco-2 cells by 75% and inhibited the glucose transporter 2 (GLUT2) (35). Additionally, quercetin inhibits α-amylase and α-glucosidase, two hydrolytic enzymes that convert carbs into simple sugars. This can improve blood glucose regulation after a meal and slow down the digestion of carbohydrates (36,37). Quercetin protects pancreatic β-cells from oxidative stress, which is implicated in β-cell damage and diabetes. Quercetin has been shown to protected pancreatic β-cells from damage in streptozotocin (STZ)-induced diabetic rats by directly reducing nitric oxide and malondialdehyde levels and indirectly increasing antioxidant enzyme activity. It also increased insulin secretion in these rats (38). When *Vaccinium vitis-idaea* produced quercetin glycosides, which were given to STZ-induced diabetic rats, the 5' adenosine monophosphate-activated protein kinase (AMPK) pathway was seen to be activated (39). In diabetic rats, quercetin increased the expression of glucose transporter 4 (GLUT4). This increase in GLUT4 expression led to increased glucose absorption into the muscle cells (40).

The inhibition of carbohydrate-digesting enzymes within the gastrointestinal tract presents a potentially effective treatment strategy for managing diabetes mellitus, as it has the potential to mitigate postprandial hyperglycemia. Compounds possessing enzyme inhibitory activity have been observed to impede the process of carbohydrate digestion, extending the overall duration of carbohydrate breakdown and resulting in a decrease in the amount of glucose absorption (41). The extract derived from the leaves of *C grandis* has demonstrated significant inhibitory effects on α-amylase and α-glucosidase enzymes. For instance, the methanolic (50% v/v) extract obtained from the leaves of *C. grandis* was shown to inhibit the enzymatic activity of α-amylase (42). In a study conducted by Mohammed et al (43), the ethanolic extract of C. *grandis* leaves exhibited inhibitory action against α-amylase. The IC50 value for this inhibition was determined to be 78.47 ± 0.18 μg/mL. As reported by Pulbutr et al (44), the α-amylase activity of *C. grandis* was found to be strongly inhibited by an aqueous extract obtained from the leaves and stems. The IC_{50} values for the extract were determined to be 8.09 ± 0.72 mg/mL and 8.06 ± 1.27 mg/mL for the leaves and stems, respectively. Additionally, it demonstrated inhibitory effects on α-glucosidase activity, with IC_{50} values of 77.66 ± 9.16 μg/mL and 0.75 ± 0.11 mg/mL for the two corresponding compounds, respectively.

Coccinia grandis significantly reduced the TG levels in a meta-analysis but had no effect on LDL, HDL, or TC. This is interesting because diabetes and dyslipidemia are closely related. The lipid profile of rats is compromised due to the presence of hyperglycemia when they acquire diabetes, leading to disturbances in lipoprotein metabolism. As a result, there is an elevation in the levels of TG, TC, very low-density lipoprotein (VLDL), and LDL, accompanied by a reduction in HDL levels. This can be attributed to the excessive release of adipose tissue fat (45).

Several studies have demonstrated that administering a *C. grandis* extract to diabetic rats enhances their lipid profiles. In diabetic mice caused by alloxan, Manjula and Ragavan (46) reported reductions in blood glucose, TC, TG, VLDL, and LDL upon the administration of an aqueous leaf extract of *C. grandis*. Additionally, Attanayake et al (47) demonstrated that STZ-induced diabetic rats that received oral delivery of *C. grandis* leaf extract in aqueous form for a duration of 30 days exhibited decreased levels of TC, LDL-C, VLDL-C, and TG, while HDL-C levels were elevated.

The reduction in TG observed in the *C. grandis* group in the meta-analysis is consistent with these findings. Potential mechanism of action of *C. grandis* might be reduction of cholesterol by enhancing islet beta cell activity and insulin resistance.

Several studies have investigated the association between reductions in FBS and PPG and the relative risk reduction of CVD. A recent meta-analysis showed that blood glucose control could reduce major adverse cardiovascular events (48). According to Chiasson et al (49), a decrease in PPG with the α-glucosidase inhibitor acarbose for three years was linked to a 49% relative risk reduction in the development of CVDs in patients with impaired glucose tolerance. Nevertheless, the longest treatment period in the studies that made up the meta-analysis was 90 days, which might not be sufficient to produce the previously indicated clinical advantages. Thus, more extensive research is required to assess the clinical advantages and risk mitigation of *C. grandis* in CVD. Although no significant adverse events were linked to *C. grandis* in this systematic review and meta-analysis (24), we looked into the uncommon occurrence of side effects pertaining to hepatic and renal functions. According to this study, when participants started using *C. grandis*, their levels of aspartate aminotransferase and alanine aminotransferase dramatically increased (27,28). The most frequently observed adverse effects involved the central nervous system and gastrointestinal system, but no severe adverse effects were reported (24,27,28).

The studies that were included had excellent methodological standards. It should be highlighted that there were several limitations. Initially, the majority of

trials had a small sample size, which limited statistical power. However, this was mitigated by using appropriate statistical tests for pooled data. Furthermore, although most participants had diabetes, none had abnormal lipid profile. This may have confounded the assessment of the sole effect of *C. grandis* on lipid profiles. Finally, most trials have accessed the factors for a short term.

Conclusion

The existing evidence suggests that various forms of *C. grandis* promote FBS and PPG reduction and improve triglyceride levels. However, the sample sizes of the included trials were mostly small. Large-scale RCTs and long-term evaluation of the effects of *C. grandis* on HbA1c levels and lipid profiles are warranted.

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Authors' contributions

Conceptualization: Wiraphol Phimarn, Chatmanee Taengthonglang and Bunleu Sungthong.
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Writing original draft: Wiraphol Phimarn.
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Conflict of interests

The authors declare that they have no conflict of interest.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication etc.) have been completely observed by the authors. We performed the protocol in accordance with PRISMA guideline.

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