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Research article

Effects of *Momordica charantia* L. supplementation on glycemic control and lipid profile in type 2 diabetes mellitus patients: A systematic review and meta-analysis of randomized controlled trials

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ABSTRACT

Background and aims: Momordica charantia L. (*M. charantia*) has been traditionally utilized as a medicinal intervention for managing type 2 diabetes mellitus (T2DM). The current study was designed to offer a GRADE-assessed systematic review and meta-analysis of randomized controlled trials (RCTs) examining the impact of *M. Charantia* intake on glycemic indexes and the lipid profile of patients with T2DM.

Methods: A comprehensive search was conducted across several databases, including PubMed, EMBASE, Web of Science, and Cochrane Library, from the inception of each database until April 22, 2023. The Hartung-Knapp adjustment was applied to ensure conservative summary estimates with broad confidence intervals.

Results: A total of eight trials involving 423 patients with T2DM were included in this study. Compared to the control group, the intake of *M. charantia* supplementation resulted in significant reductions in fasting blood glucose (FBG) (WMD: −0.85 mmol/L; 95%CI: −1.44, −0.26; $p = 0.005$; $I^2 = 73.4$ %), postprandial glucose (PPG) (WMD: −2.28 mmol/L; 95%CI: −3.35, −1.21; $p = 0.000$; $I^2 = 66.9$ %), glycosylated hemoglobin A1c (HbA1c) (WMD: −0.38 %; 95%CI: −0.53, −0.23; $p = 0.000$; $I^2 = 37.6$ %), and total cholesterol (TC) (WMD: −0.38 mmol/L; 95%CI: −0.70, −0.07; $p = 0.017$; $I^2 = 63.6$ %). These results remained statistically significant even after applying the Hartung-Knapp adjustment. However, no significant differences were observed in terms of triglyceride (TG), high-density lipoprotein (HDL), and low-density lipoprotein (LDL).

Conclusions: The findings of this study suggest that *M. charantia* could serve as a potential alternative for individuals with T2DM, particularly those with elevated total cholesterol levels. However, further high-quality studies are necessary to validate these results.

1. Introduction

The global incidence of diabetes has been progressively increasing in recent decades. Estimates show that the number of individuals affected by diabetes was 285 million in 2009, which rose alarmingly to 463 million by 2019 and is projected to continue reaching 578

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million by 2030 and surpass 700 million by 2045 [1,2]. Notably, the prevalence of diabetes is higher among urban (10.8 %) and high-income (10.4 %) countries as compared to rural (7.2 %) and low-income (4.0 %) countries [1]. In 2017, diabetes caused an estimated four million global deaths and the global health expenditure on diabetes reached USD 727 billion [3]. Moreover, T2DM accounts for nearly 90 % of all diabetes cases and approximately 95 % of the global diabetes burden [1,4]. Diabetic dyslipidemia, which is identified by elevated triglyceride levels, low HDL, and increased small-dense LDL cholesterol, constitutes a common risk factor for cardiovascular disease in T2DM individuals [5].

Lifestyle modification and pharmacologic therapy are common strategies for managing T2DM. Oral medication is generally preferred over injection medication for treating type 2 diabetes [6]. Commonly used oral hypoglycemic medications include metformin, sulfonylureas, glinides, thiazolidinediones, dipeptidyl peptidase-4 inhibitors, and sodium-glucose cotransporters-2 inhibitors [7]. However, these oral hypoglycemic medications may contribute to certain adverse effects such as hypoglycemia, gastrointestinal side effects, and genital mycotic infections [8]. As a result of these potential side effects and the limited efficacy of traditional pharmaceutical treatments, medicinal plant-based therapies have gained significant attention and have been applied extensively to treat type 2 diabetes [9–11].

Momordica charantia L., a member of the Cucurbitaceae family, is an annual climbing plant widely recognized by names such as bitter gourd, bitter melon, or karela. *M. charantia* is widely grown and consumed in Asia, Africa, and the Americas, across tropical, subtropical, and temperate regions [12,13]. *M. charantia* has traditionally been utilized to treat diabetes in China, India, Brazil, and Peru [14,15]. However, clinical trials assessing its efficacy in treating T2DM have generated contradictory outcomes [16–19]. A meta-analysis study has reported that *M. charantia* supplementation reduced the levels of FPG, PPG, and HbA1c in patients with T2DM [20]. That study included fewer studies and lacked research on the effect of *M. charantia* supplementation on lipid profiles in patients with T2DM. Consequently, we conducted a systematic review and meta-analysis to determine the impact of *M. charantia* supplementation on glycemic indices and lipid profiles in patients with T2DM.

2. Methods

This study adhered to the guidelines outlined in the Cochrane Handbook for Systematic Reviews of Interventions and followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement [21]. The registration number of the study protocol in PROSPERO was CRD42023421984.

2.1. Search strategy

We conducted a systematic search for relevant literature on randomized controlled trials (RCTs) from inception to April 22, 2023, by searching multiple databases including PubMed, EMBASE, Web of Science, and Cochrane Library. We employed a variety of search terms such as "*Momordica charantia*", "bitter melon", "bitter gourd", "diabetes mellitus, type 2", "T2DM", "type 2 diabetes mellitus", "type 2 diabetes", "diabetes, type 2", "NIDDM", and "MODY", without imposing any language restriction. We combined search terms within or between groups using boolean operators of "or" and "and". In addition, we screened the references of included studies and review articles for supplementary citations. Document management was performed using Endnote x9.2. The comprehensive search strategy employed for databases is detailed in Table S1.

2.2. Study selection

Two independent investigators (Zhang and Zhao) screened all the relevant articles using pre-established inclusion and exclusion guidelines. The criteria were that the studies needed to be original RCTs on adult T2DM patients (years of age >18) taking *M. charantia* or extract supplementation. The control group was to receive a placebo. The chosen studies had to report outcomes including FBG, PPG, HbA1c, TC, TG, HDL, and LDL. In the event of any disagreement between the two reviewers, the third researcher (Song) was responsible for conflict resolution. Studies that did not meet our criteria, such as animal or in vitro studies; reviews, meta-analyses, or comments; herbal formulas rather than *M. charantia* supplementation; or those with insufficient data or lacking information, were excluded.

2.3. Data extraction

Two reviewers (Zhang and Zhao) independently employed a structured data collection form to extract relevant and crucial information from each of the included studies. The information gathered contained study-related particulars such as the author's name, year of publication, and geographical location of the clinical trial, study design parameters, group-specific sample sizes, intervention-related details including dose, formulation, and duration, placebo composition details, as well as the demographic characteristics of subjects such as age, gender, and body mass index (BMI). Moreover, baseline levels and post-supplementation values of FBG, PPG, HbA1c, TC, TG, HDL, and LDL and their SDs were also noted. Any differences of opinion during data collection were reviewed and resolved by the third reviewer (Song).

2.4. Quality assessment

Two individual reviewers (Zhang and Zhao) employed the Cochrane Collaboration risk of bias tool [22] to assess the risk of bias.

The effectiveness of outcomes was verified by employing the GRADE (Grading of Recommendations Assessment, Development and Evaluation) criteria [23], which classified evidence into one of four qualifiers, ranging from high quality to very low quality. Any divergent opinions between the two reviewers were addressed and resolved by consulting with a third reviewer (Song).

2.5. Statistical analysis

Stata 17.0 was utilized to conduct the meta-analysis. The "splitting the shared group" approach was used for multi-arm trials [24]. Quantitative analysis of FBG, PPG, HbA1c, TC, TG, HDL, and LDL utilized the mean change and its standard deviation (SD) between pre-and post-intervention. The SD of mean change was calculated using the equation [25]: $SD^2_{change} = (SD^2_{pre\text{-}intervention} \times SD_{after\text{-}intervention}{}^2) - (2R \times SD_{pre\text{-}intervention} \times SD_{after\text{-}intervention})$, assuming R = 0.5 when studies did not report this parameter. If necessary, the standard error (SE) and sample size (N) of outcome measures were utilized to calculate SD using the equation $SD = SE \times \sqrt{N}$ [26]. The random-effects model and fixed-effects model were applied to calculate the weighted mean difference (WMD) and 95 % confidence intervals (95%CI) of the outcome effects. Heterogeneity among studies was estimated by the numerical value of I^2 and p-value. Statistically significant heterogeneity was defined as $I^2 > 50$ % and $p < 0.05$ [27]. If $I^2 > 50$ %, the random-effects model was used. The units for FBG, PPG, TC, TG, HDL, and LDL were converted from mg/dl to mmol/L. HbA1c was analyzed as a percentage. Subgroup analysis was conducted based on intervention duration (<12w and ≥12w) and intervention dosage (<2 g/d and ≥2 g/d). Sensitivity analysis was performed to evaluate the impact of each included study on the overall effect size. Egger's and Begg's tests were performed to investigate the publication bias. A p-value <0.05 was considered statistically significant. Funnel plots were not constructed to detect publication bias due to their limited accuracy when the number of included trials is less than 10 [28].

3. Results

3.1. Characteristics of included studies

218 articles were obtained through the database and literature review, of which 67 were initially removed due to duplication (Fig. 1). Following the initial screening based on title and abstract, a total of 136 articles were excluded. Subsequently, the remaining 15 studies underwent thorough examination by scrutinizing their full texts. Out of these, 8 studies were chosen for inclusion in this study. Seven studies were excluded after a thorough examination of their full texts due to the absence of a placebo-controlled group (n = 5) or the lack of interest parameters (n = 2).

The eight studies included in this analysis were published from 2003 to 2022 [17–19,29–33]. Among these, seven studies were conducted in Asia [17–19,29–31,33], while one study was conducted in North America [32]. One study [30] followed an open-label, randomized, active-controlled, phase II trial. One study [31] was a single-blind RCT, while the remaining seven studies [17–19,29,30,32,33] were double-blind RCTs. The eight included studies were conducted with both genders, and the total sample size was 423. The maximum and minimum sample sizes were 90 [19] and 20 [32], respectively.

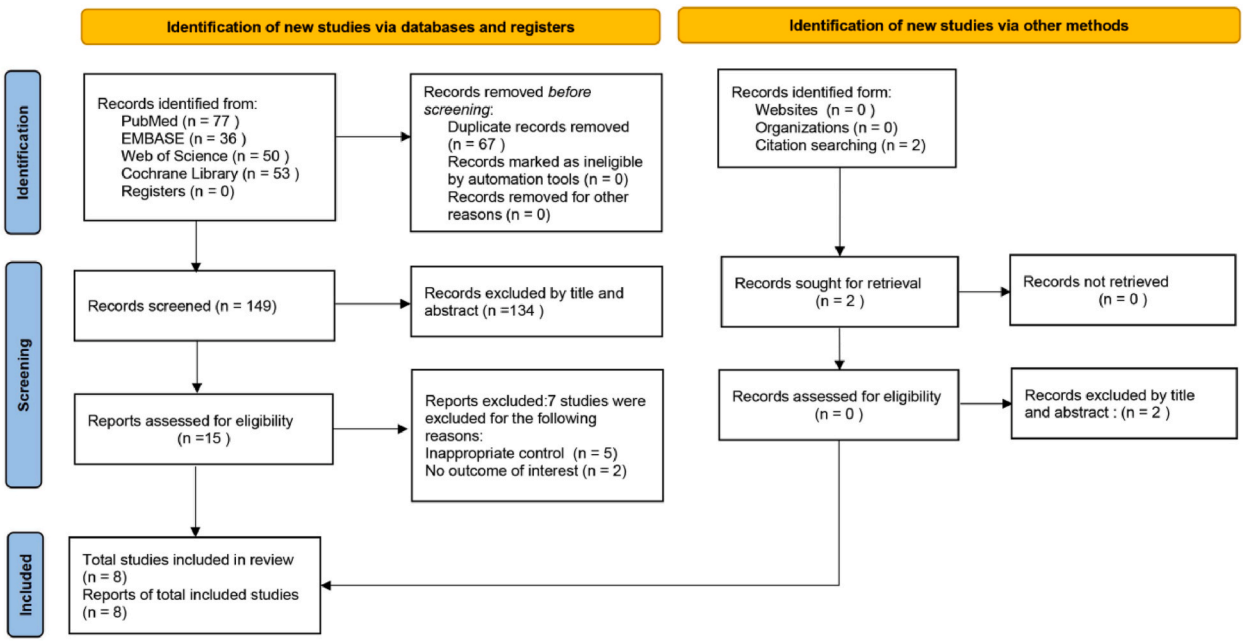

Fig. 1. Flowchart of included studies selection.

Table 1
Baseline characteristics of the included studies in this study.

Study		John2003	Dans2007	Trakoon-osot2013	Suthar2016	Kumari2018a	Kumari2018b	Cortez-Navarrete2018	Kim2020	Yang2022
Geographic location		India	Philippine	Thailand	India	India	India	Mexico	Korea	China
Study design		RCT	RCT	RCT	RCT	RCT	RCT	RCT	RCT	RCT
Population		T2DM	T2DM	T2DM	T2DM	T2DM	T2DM	T2DM	T2DM	T2DM
Mean age (year)	I	52.23 (7.50)	58.70 (9.81)	57.2 (8.8)	41.33 (7.59)	NR	NR	50.1 (7.3)	58.1 (6.9)	58.3 (12.7)
mean (SD)	C	53.41 (10.10)	59.76 (10.04)	58.7 (7.0)	41.31 (6.88)	NR	NR	47.0 (7.4)	60.3 (7.6)	58.6 (13.9)
Mean BMI (kg/m^2)	I	NR	26.37 (4.75)	25.04 (3.69)	NR	26.3 (3.7)	27.95 (3.2)	29.1 (2.4)	25.3 (3.8)	26.0 (4.2)
mean (SD)	C		26.00 (3.94)	26.37 (6.04)	NR	28.9 (5.4)	28.9 (5.4)	28.8 (3.9)	26.6 (5.1)	26.3 (4.5)
Sample size (M/F)	I	7 M/19F	7 M/13F	3 M/16F	39 M/23F	NR	NR	5 M/7F	38 M/24F	6 M/14F
	C	9 M/15F	8 M/12F	8 M/11F	10 M/7F	NR	NR	3 M/9F	12 M/16F	5 M/15F
Sample size for analysis	I	22	20	19	64	25	25	10	62	20
	C	19	20	19	19	12	13	10	28	20
Type of supplementation/control	I	Tablet	Capsule	Capsule	Capsule	Tablet	Tablet	Capsule	Capsule	Capsule
	C	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo
Dose		6 g/d	1 g/d	6 g/d	1.2 g/d	1 g/d	1.5 g/d	2 g/d	2.38 g/d	0.6 g/d
Duration of treatment		4w	12w	16w	12w	8w	8w	12w	12w	12w
FBG (mmol/L)	I	8.34 (1.49)	8.40 (2.24)	6.53 (1.79)	8.33 (1.96)	8.80 (1.11)	8.03 (1.01)	8.2 (1.4)	8.10 (1.92)	9.58 (1.72)
mean (SD)	C	8.65 (1.39)	8.14 (2.36)	6.58 (0.91)	8.26 (1.93)	8.66 (0.68)	8.66 (0.68)	7.1 (1.9)	7.28 (1.34)	9.41 (1.53)
HbA1c (%)	I	NR	7.92 (0.59)	7.47 (1.03)	7.87 (1.00)	7.60 (0.70)	7.30 (0.47)	7.8 (0.8)	7.0 (0.5)	7.8 (0.6)
mean (SD)	C	NR	8.07 (0.77)	7.32 (0.70)	7.83 (1.10)	7.1 (0.49)	7.1 (0.49)	7.6 (0.6)	6.9 (0.4)	7.9 (0.6)
PPG (mmol/L)	I	14.69 (1.82)	NR	NR	11.24 (3.15)	12.16 (1.29)	12.72 (1.11)	17.1 (3.7)	NR	NR
mean (SD)	C	14.10 (1.63)	NR	NR	10.57 (3.01)	12.30 (1.32)	12.30 (1.32)	14.9 (4.7)	NR	NR
TC (mmol/L)	I	NR	5.25 (1.46)	NR	3.95 (0.71)	5.37 (0.47)	4.99 (0.40)	4.89 (0.73)	4.02 (0.74)	NR
mean (SD)	C	NR	5.08 (1.09)	NR	3.99 (0.78)	4.88 (0.47)	4.88 (0.47)	4.41 (0.75)	4.12 (0.71)	NR
TG (mmol/L)	I	NR	NR	NR	1.26 (0. 24)	1.53 (0.41)	1.95 (0.20)	2.31 (1.25)	1.55 (0.94)	NR
mean (SD)	C	NR	NR	NR	1.22 (0.26)	1.51 (0.27)	1.51 (0.27)	2.19 (0.76)	1.32 (0.63)	NR
HDL (mmol/L)	I	NR	NR	NR	1.26 (0. 15)	1.14 (0. 17)	1.04 (0. 10)	1.13 (0.18)	1.28 (0.31)	NR
mean (SD)	C	NR	NR	NR	1.26 (0. 15)	1.18 (0. 13)	1.18 (0. 13)	1.04 (0.23)	1.40 (0.30)	NR
LDL (mmol/L)	I	NR	NR	NR	2.12 (0. 63)	3.18 (0. 55)	3.06 (0. 36)	2.69 (0.80)	2.46 (0.67)	NR
mean (SD)	C	NR	NR	NR	2.18 (0. 65)	2.95 (0. 44)	2.95 (0. 44)	2.35 (0.64)	2.44 (0.64)	NR

BMI: body mass index; FBG: fasting blood glucose; PPG: postprandial glucose; HbA1c: glycosylated hemoglobin A1c; TC: Total cholesterol; TG: triglyceride; HDL: high-density lipoprotein; LDL: low-density lipoprotein; M: male; F: female; I: intervention; C: control; RCT: randomized clinical trial; NR: not reported; T2DM: type 2 diabetes mellitus.

The intervention group utilized various parts of *M. charantia*, including dried powder of fresh whole fruit [17,19], extraction from the fruits and seeds [18], dried powder of fruit pulp [29,32], dried powder of fruit juice [30], and peptides extracted from *M. charantia* [33]. One study did not provide information on the specific part used [31]. Capsules were the dosage form employed in six studies [18,19,29,30,32,33], while tablets were used in the remaining two studies [17,31].

Among the eight studies, the average age of participants ranged from 41.3 [30] to 60.3 years [19], with one study only providing age ranges (40–60 years) instead of mean age [31]. The intervention group received doses ranging from 0.6 g/d [33] to 6 g/d [17,29], with Kumari's study having two different intervention dose arms (1 g/d and 1.5 g/d) and a placebo arm, referred to as Kumari2018a and Kumari2018b respectively. The treatment duration ranged from 4 [17] to 16w [29], although most studies had a 12-week intervention period [18,19,30–33]. Six studies maintained participants' usual diet, anti-diabetic medications, and physical activities while providing *M. charantia* supplementation [17,18,29,31–33], while two studies did not report this information [19,30]. Table 1 shows the main characteristics of the included studies.

3.2. Risk of bias assessment

A majority of the included studies [17,19,29–31] failed to implement allocation concealment, blinding of participants and personnel, and blinding of outcome assessment. Two studies [17,18] evaluated a high risk of bias in the selective reporting domain because they did not report detailed information about concomitant medication or the reasons for dropout. Consequently, the overall risk of bias in these studies was evaluated to be high. (Fig. 2).

3.3. Findings from the systematic review

Three studies [19,30,31] demonstrated a significant reduction in FBG levels following *M. charantia* supplementation compared to the placebo group, whereas the remaining five studies [17,18,29,32,33] did not observe this effect. Regarding PPG, three studies [30–32] reported a significant effect of *M. charantia* supplementation, while one study [17] showed no significant change. In terms of HbA1c levels, four studies [29,31–33] indicated a significant reduction with *M. charantia* supplementation, while three studies [18,19,30] did not find such an effect. Five studies [18,19,30–32] reported a reduction in TC after the intervention. Four studies [19,30–32] reported the outcomes of TG, HDL, and LDL, while no significant alterations were observed for these parameters.

Two studies [17,31] did not report safety assessments. According to the reports of included studies, *M. charantia* supplementation was well-tolerated. No serious adverse events related to *M. charantia* supplementation intake were reported. The most commonly reported adverse events were gastrointestinal complaints, such as diarrhea, flatulence, nausea, and constipation [18,19,29,32]. However, these symptoms were not attributed to the treatment, as they were also observed in the placebo group. Additionally, no adverse events were found in the other two studies [30,33] among all subjects.

3.4. Findings from the meta-analysis

3.4.1. Fasting blood glucose (FBG)

8 studies were included to investigate the impact of *M. charantia* supplementation on FBG with a total of 423 patients. The findings indicated a significant reduction in FBG among individuals in the intervention group [WMD: −0.85 mmol/L; 95%CI: −1.44, −0.26; *p*

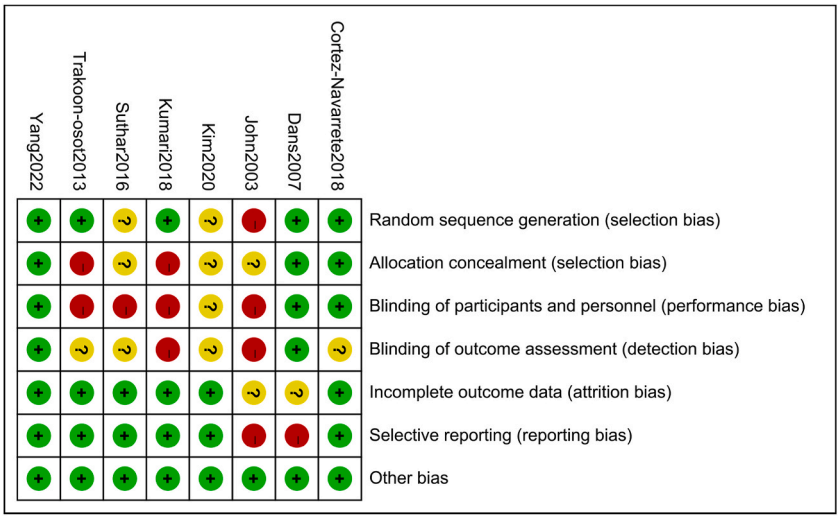

Fig. 2. Risk of bias assessment of included studies. A green dot with a plus indicates low risk, a yellow dot with a question mark suggests an unclear risk of bias, and a red dot with a minus signifies a high risk of bias.

= 0.005; I^2 = 73.4 %] (Fig. 3A). Even after employing the Hartung-Knapp adjustment, statistically significant differences persisted [MD: 0.86 mmol/L; 95%CI: −1.51, −0.22]. Subgroup analysis showed a significant reduction of heterogeneity in intervention duration (≥12w) (Table 2). The quality of evidence for FBG was rated as very low (Table S2).

3.4.2. Postprandial glucose (PPG)

The analysis of PPG levels included 4 studies comprising a total of 215 participants. The findings indicated a significant reduction in PPG levels following *M. charantia* supplementation intake both before [WMD: −2.28 mmol/L; 95%CI: −3.35, −1.21; $p = 0.000$; I^2 = 66.9 %] (Fig. 3B) and after Hartung-Knapp adjustment [MD: 2.27 mmol/L; 95%CI: −3.54, −1.01]. According to subgroup analysis, heterogeneity disappeared in intervention duration (≥12w) and dosage (≥2 g/d). The quality of evidence for the effects of PPG levels was considered to be very low (Table S2).

3.4.3. Glycosylated hemoglobin A1c (HbA1c)

The impact of *M. charantia* supplementation on HbA1c was assessed in 7 studies involving 382 patients. The pooled estimates demonstrated a significant decrease in HbA1c levels in the intervention group compared to the control group [WMD: −0.38 %; 95%CI: −0.53, −0.23; $p = 0.000$; $I^2 = 37.6$ %] (Fig. 3C). The quality of evidence for HbA1c was assessed as low for imprecision and risk of bias (Table S2).

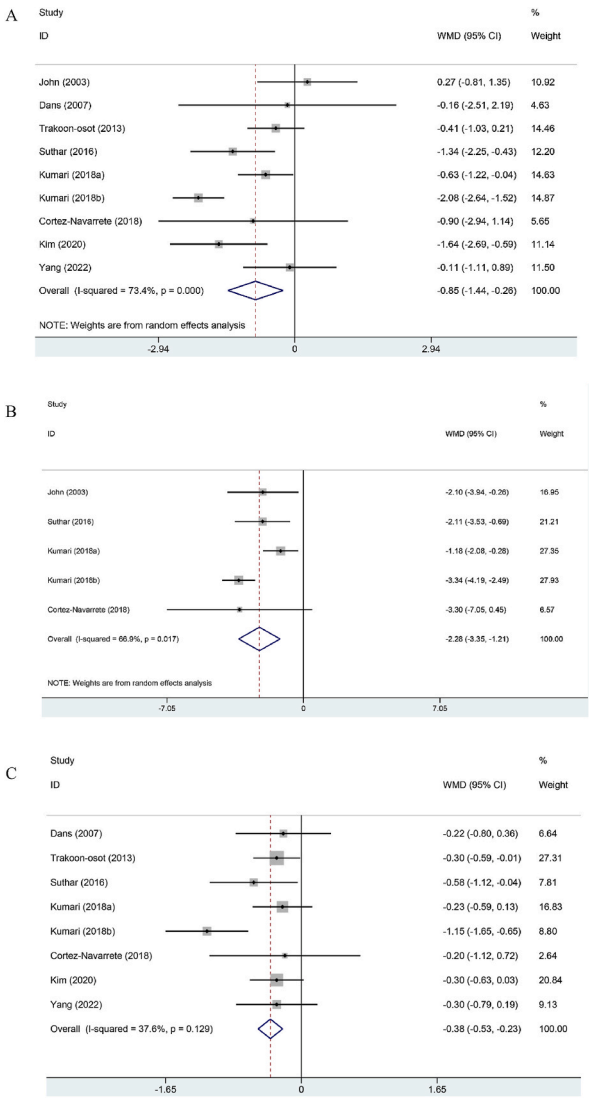

Fig. 3. Forest plot of *M. charantia* supplementation on FBG (A), PPG (B), and HbA1c (C) compared to placebo.

Table 2
Subgroup analysis of the effects of *M. charantia* supplementation on glycemic indices and lipid profile.

		Meta-analysis		Heterogeneity		
Study group	Number of studies	WMD(95%Cl)	P-effect	I^2	P-within group	P-between group
FBG						
Intervention duration						0.902
<12w	3	−0.87(-2.16, 0.42)	0.184	90.1 %	0.000	
≥12w	6	−0.79(-1.32, −0.25)	0.004	32.1 %	0.195	
Intervention dosage						
<2 g/d	5	−1.00(-1.83, −0.17)	0.018	78.3 %	0.001	0.509
≥2 g/d	4	−0.61(-1.40, 0.179)	0.129	54.9 %	0.084	
PPG						
Intervention duration						0.972
<12w	3	−2.22(-3.77, −0.68)	0.005	83.0 %	0.003	
≥12w	2	−2.26(-3.59, −0.93)	0.001	0.0 %	0.561	
Intervention dosage						
<2 g/d	3	−2.22(-3.66, −0.79)	0.002	83.0 %	0.003	0.921
≥2 g/d	2	−2.33(-3.35, −1.21)	0.006	0.0 %	0.573	
HbA1c						
Intervention duration						0.194
<12w	2	−0.55(-0.84, 0.25)	0.000	88.1 %	0.004	
≥12w	6	−0.38(-0.49, −0.15)	0.000	0.0 %	0.952	
Intervention dosage						
<2 g/d	5	−0.46(-0.68, 0.25)	0.000	59.9 %	0.041	0.274
≥2 g/d	3	−0.30(-0.51, −0.23)	0.006	0.0 %	0.979	
TC						
Intervention duration						0.000
<12w	2	−0.80(-1.11, −0.50)	0.000	0.0 %	0.457	
≥12w	4	−0.12(-0.34, 0.11)	0.315	0.0 %	0.931	
Intervention dosage						
<2 g/d	4	−0.52(-0.90, −0.13)	0.009	63.5 %	0.042	0.083
≥2 g/d	2	−0.08(-0.38, 0.21)	0.582	0.0 %	0.742	
TG						
Intervention duration						0.279
<12w	2	−0.02(-017, 0.13)	0.810	0.0 %	0.898	
≥12w	3	−0.06(-0.18, −0.00)	0.049	9.2 %	0.332	
Intervention dosage						0.098
<2 g/d	3	−0.06(-016, 0.04)	0.262	0.0 %	0.781	
≥2 g/d	2	−0.36(-0.70, −0.02)	0.040	0.0 %	0.693	
HDL						
Intervention duration						0.191
<12w	2	0.09(-0.05, 0.23)	0.187	76.3 %	0.040	
≥12w	3	−0.01(-0.09, 0.07)	0.746	0.0 %	0.417	
Intervention dosage						
<2 g/d	3	0.06(-0.06, 0.17)	0.327	75.2 %	0.018	0.480
≥2 g/d	2	−0.02(-0.19, 0.15)	0.839	41.2 %	0.192	
LDL						
Intervention duration						0.074
<12w	2	−0.05(-0.96, −0.04)	0.033	81.2 %	0.021	
≥12w	3	−0.04(-0.25, 0.17)	0.705	0.0 %	0.991	
Intervention dosage						0.186
<2 g/d	3	−0.36(-0.76, 0.05)	0.083	81.5 %	0.004	
≥2 g/d	2	−0.03(-0.29, 0.22)	0.797	0.0 %	0.913	

3.4.4. Total cholesterol (TC)

The analysis of TC encompassed 5 studies with a total participant count of 304. The pooled effect sizes revealed a significant decrease in TC levels following the intake of *M. charantia* supplementation before [WMD: −0.38 mmol/L; 95%CI: −0.70, −0.07; $p = 0.017$; $I^2 = 63.6$ %] (Fig. 4A) and after Hartung-Knapp adjustment [MD: −0.40 mmol/L; 95%CI: −0.79, −0.01]. Subgroup analyses revealed a significant reduction of heterogeneity in intervention duration and dosage (≥2 g/d). The quality of evidence for TC was deemed to be very low (Table S2).

3.4.5. Triglyceride (TG)

The combined findings from 4 studies (involving 264 patients) indicated that *M. charantia* supplementation intake had no significant effect on TG [WMD: −0.08 mmol/L; 95%CI: −0.18, 0.01; $p = 0.097$; $I^2 = 0.0$ %] (Fig. 4B). The quality of evidence for TG was estimated as low for imprecision and risk of bias (Table S2).

3.4.6. High-density lipoprotein (HDL)

The analysis of HDL involved 4 studies comprising a total of 264 participants. The combined outcomes indicated that the HDL level

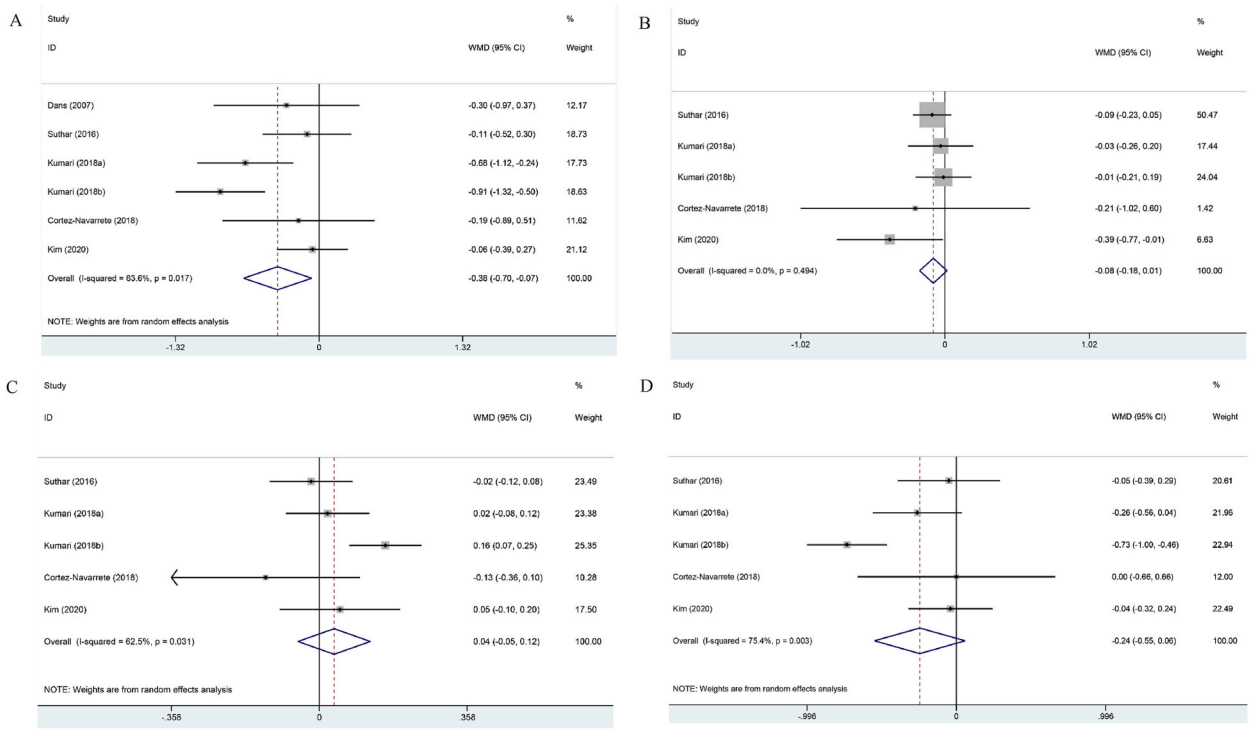

Fig. 4. Forest plot of *M. charantia* supplementation on TC (A), TG (B), HDL (C), and LDL (D) compared to placebo.

of patients was not significantly changed after *M. charantia* supplementation intake [WMD: 0.04 mmol/L; 95%CI: −0.05, 0.12; $p = 0.421$; $I^2 = 62.5$ %] (Fig. 4C). Based on subgroup analysis, heterogeneity significantly decreased in intervention duration (≥12w) and dosage (≥2 g/d). The quality of evidence for HDL was assessed to be of very low quality. (Table S2).

3.4.7. Low-density lipoprotein (LDL)

The impact of *M. charantia* supplementation on LDL was evaluated in four studies involving 264 patients. The combining effects sizes showed that *M. charantia* supplementation intake did not result in a significant change in the LDL levels of participants [WMD: −0.24 mmol/L; 95%CI: −0.55, 0.06; $p = 0.114$; $I^2 = 75.4$ %] (Fig. 4D). When subgroup analysis was conducted, heterogeneity disappeared in intervention duration (≥12w) and dosage (≥2 g/d). The quality of evidence for LDL was assessed as very low (Table S2).

3.5. Sensitivity analysis

A sensitivity analysis was performed to assess the reliability of our findings by omitting one study at a time. Sensitivity analysis for FBG showed that the heterogeneity was changed significantly when Kumari's study was omitted (before omitting $I^2 = 73.4$ %, $p = 0.000$; after omitting $I^2 = 41.7$ %, $p = 0.113$). The omission of Kumari's study also significantly reduced the heterogeneity for PPG and HbA1c (before omitting $I^2 = 66.9$ %, $p = 0.017$ and $I^2 = 37.6$ %, $p = 0.129$; after omitting $I^2 = 0.0$ %, $p = 0.836$ and $I^2 = 0.0$ %, $p = 0.952$, respectively). Additionally, excluding Kumari's study led to a significant alteration in heterogeneity for TC, HDL, and LDL (for TC: before omitting $I^2 = 63.6$ %, $p = 0.017$ and after $I^2 = 0.0$ %, $p = 0.931$; for HDL: before omitting $I^2 = 62.5$ %, $p = 0.031$ and after $I^2 = 0.0$ %, $p = 0.417$; for LDL: before omitting $I^2 = 75.4$ %, $p = 0.003$ and after $I^2 = 0.0$ %, $p = 0.991$). Nonetheless, sensitivity analysis results indicated that the inclusion of Kumari's study did not alter the overall conclusions of FBG, PPG, HbA1c, TC, TG, HDL, and LDL (Fig. S1).

3.6. Publication bias

We performed both Egger's test and Begg's test to identify potential publication bias. The results showed that the *p* values of Egger's test and Begg's test of FBG, PPG, HbA1c, TC, TG, HDL, and LDL were 0.474, 0.602; 0.975, 0.806; 0.538, 0.386; 0.798, 0.707; 0.421, 0.462; 0.288, 0.806; and 0.503, 0.806 respectively. The findings indicated the absence of noteworthy publication bias.

4. Discussion

The present study is the first systemic review and meta-analysis to assess the effects of *M. charantia* supplementation on both

glycemic control and lipid profile in T2DM patients. Based on the eight trials in this study, our findings indicated the effectiveness of *M. charantia* supplementation in reducing glycemic indices such as FBG, PPG, and HbA1c in patients with T2DM. However, regarding lipid profile, *M. charantia* supplementation did not significantly affect TG, HDL, and LDL, except for TC, where a significant reduction was observed. Our results on glycemic indices align with previous systematic reviews exploring the effects of *M. charantia* supplementation in individuals with T2DM [20]. They included fewer studies, but the results of glycemic indices (for FBG: MD -0.72 mmol/L, 95%CL: 1.33 to −0.12; for PPG: MD: −1.43 mmol/L, 95%CL: 2.18 to −0.67; for HbA1c: MD: −0.26 %, 95%CL: −0.49 to −0.03) were in accord with our results. Notably, the efficacy of *M. charantia* polyherbal formulation was the synergistic effects of various herbs other than the effect of *M. charantia* alone. Consequently, unlike previous studies, our study only included RCTs that compared the effects of *M. charantia* supplementation with placebos while excluding clinical trials utilizing compound herbal preparations to mitigate the impact of other herbal ingredients. Additionally, given the limited number of included studies, we implemented the Hartung-Knapp adjustment to obtain conservative summary estimates accompanied by wide confidence intervals. In subgroup analyses, a significant reduction of heterogeneity was observed in trials with intervention duration ≥12w and dosage ≥2 g/d. The difference in intervention duration and dosage may cause heterogeneity among studies. The sensitivity analysis results suggest that Kumari's study has led to the observed heterogeneity among studies. This may be related to the experimental design of Kumari's study.

M. charantia contains several functional components such as polysaccharides, protein/peptides, terpenoids, saponins, alkaloids, flavonoids, and other bioactive components [34]. Several bioactive compounds in *M. charantia,* including polypeptides, glycosides, sterols, and alkaloids, have demonstrated antidiabetic effects, with charantin, polypeptide p, and vicine being the main components responsible for hypoglycemic effects [35–37]. The glucose-lowering effects of *M. charantia* are attributed to diverse mechanisms, including enhanced insulin secretion [38], improved insulin resistance through the regulation of mRNA and protein levels of SOCS-3 and JNK [39], glucose uptake regulation [40], increased hepatic glycogen synthesis and glucose utilization [41], inhibited the activity of protein tyrosine phosphatase 1B (PTP1B) and α-amylase [42], and inhibited the activity of 11β-Hydroxysteroid dehydrogenase type 1 (11β-HSD1) [43]. Furthermore, *M. charantia* exhibits significant antioxidant and anti-inflammatory activities, contributing to its anti-hyperglycemic properties [44]. Studies have demonstrated that *M. charantia* fruit powder reduced high-fat diet-induced hyperlipidemia and hyperglycemia in mice [45]. Administration of *M. charantia* juice to diabetic rats resulted in a significant reduction in serum cholesterol and triglyceride levels [46]. However, the present results of this meta-analysis only showed a significant reduction of TC in lipid profile after *M. charantia* supplementation intake. Our findings suggest that *M. charantia* supplementation may be a relatively safe and effective strategy for managing hyperglycemia in T2DM patients.

This meta-analysis has several strengths. This meta-analysis was conducted by the rules of PRISMA to acquire great quality. All the included trials were RCTs without language and publication time restrictions. The GRADE approach and Cochrane Collaboration risk of bias tool were used to conduct the quality assessment for the included studies. Furthermore, no evidence of publication bias was found in Egger's and Begg's tests. However, several limitations exist within the current meta-analysis. Firstly, the number of included trials and their sample sizes were insufficient, therefore the results of the study should be interpreted with caution. Secondly, the high heterogeneity among the effect sizes in studies is another limitation of this study. Additionally, The overall quality of the majority of studies is not high, potentially influencing the assessment of findings to a certain degree.

5. Conclusions

In summary, this meta-analysis suggests that the intake of *M. charantia* supplementation may contribute to the reduction of FBG, PPG, HbA1c, and TC levels in T2DM patients. Nevertheless, it is important to interpret these findings with caution due to the overall high risk of bias found across the included studies and the low quality of evidence available for each parameter. Therefore, further well-designed RCTs with large sample sizes are necessary to establish the efficacy of *M. charantia* supplementation in the management of type 2 diabetes mellitus.

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Ethics declarations

Review and/or approval by an ethics committee was not needed for this study because this study was a meta-analysis.

Data availability statement

The datasets used and analyzed during the current study are available from Mendeley data (https://data.mendeley.com/datasets/f7v2gfz4bw/1).

CRediT authorship contribution statement

Xiaolei Zhang: Writing – review & editing, Writing – original draft, Software, Methodology, Formal analysis, Data curation, Conceptualization. **Yinan Zhao:** Writing – review & editing, Writing – original draft, Software, Data curation. **Yagang Song:** Writing – review & editing, Supervision, Methodology, Data curation. **Mingsan Miao:** Writing – review & editing, Supervision, Project administration, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e31126.

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Abbreviations

BMI: body mass index
C: control
F: female
FBG: fasting blood glucose
GRADE: Grading of Recommendations Assessment, Development and Evaluation criteria
HbA1c: hemoglobin A1c
HDL,: high-density lipoprotein
I: intervention
LDL,: low-density lipoprotein
M: male
M. Charantia: Momordica charantia L
MD: mean difference
MODY: Maturity Onset Diabetes Mellitus
NIDDM: Non-Insulin-Dependent Diabetes Mellitus
NR: not reported
PPG: Postprandial glucose
PRISMA: preferred reporting items for systematic reviews and meta-analyses
RCTs: randomized controlled trials
SD: standard deviation
T2DM: type 2 diabetes mellitus
TC: total cholesterol
TG: triglyceride;
WMD: weighted mean difference