Received: 24 February 2020 | Revised: 21 July 2020 | Accepted: 26 July 2020

DOI: 10.1002/ptr.6853

Check for updates

WILEY

REVIEW

The safety and efficacy of *Momordica charantia* L. in animal models of type 2 diabetes mellitus: A systematic review and meta-analysis

Emanuel L. Peter[1,2] | Prakash B. Nagendrappa[3] | Anita Kaligirwa[4] | Patrick Engeu Ogwang[1] | Crispin Duncan Sesaazi[5]

[1]Department of Pharmacy, Faculty of Medicine, Mbarara University of Science and Technology, Mbarara, Uganda

[2]Department of Innovation, Technology Transfer & Commercialization, National Institute for Medical Research, Dar Es Salaam, Tanzania

[3]Centre for Local Health Traditions & Policy, Trans-Disciplinary University (TDU), Bengaluru, India

[4]Department of Pharmacology, Faculty of Medicine, Mbarara University of Science and Technology, Mbarara, Uganda

[5]Department of Pharmaceutical Sciences, Faculty of Medicine, Mbarara University of Science and Technology, Mbarara, Uganda

Correspondence
Emanuel L. Peter, Department of Pharmacy, Faculty of Medicine, Mbarara University of Science and Technology, P.O. Box 1410, Mbarara, Uganda.
Email: epeterlyimo@gmail.com, epeter@std.must.ac.ug

Funding information
Mbarara University of science and technology; World Bank

Type 2 diabetes mellitus is a chronic hyperglycemic condition due to progressively impaired glucose regulation. *Momordica charantia* L. could potentially improve hyperglycemia because its fruit extracts can alleviate insulin resistance, beta-cell dysfunction, and increase serum insulin level. We evaluated the effect of *M. charantia* L. in comparison with a vehicle on glycemic control in animal models of type 2 diabetes mellitus. MEDLINE, Web of Science, Scopus, and CINAHL databases were searched without language restriction through April 2019. About 66 studies involving 1861 animals that examined the effect of *M. charantia* L. on type 2 diabetes mellitus were included. Fruits and seed extracts reduced fasting plasma glucose (FPG) and glycosylated hemoglobin A1c in comparison to vehicle control: (42 studies, 815 animals; SMD, −6.86 [95% CI; −7.95, −5.77], 3 studies, 59 animals; SMD; −7.76 [95% CI; −12.50, −3.01]) respectively. Also, the extracts have hepato-renal protective effects at varying doses and duration of administration. Despite the observed significant glycemic control effect, poor methodological quality calls for future researches to focus on standardizing extract based on chemical markers and adopt measures to improve the quality of preclinical studies such as sample size calculation, randomization, and blinding.

KEYWORDS
bitter gourd, efficacy, meta-analysis, preclinical, safety, type 2 diabetes mellitus

1 | INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a chronic hyperglycemic condition in response to progressively impaired glucose regulation as a result of insulin resistance and beta-cell dysfunction. The chronicity of hyperglycemia causes microvascular complications in the retina, renal glomerulus, and peripheral nerves (Olokoba, Obateru, & Olokoba, 2012). It also increases the risk of accelerated atherosclerosis and premature death (Chawla, Chawla, & Jaggi, 2016). In addition to that, it is implicated in dementia, sexual dysfunction, depression, and lower-limb amputations (Cukierman, Gerstein, & Williamson, 2005; Forbes & Cooper, 2013; Nouwen et al., 2011).

People with T2DM use oral hypoglycemic agents (OHAs) to control elevated glycemia and ameliorate diabetes complications. However, the OHAs have in recent years been linked to intolerable side effects and high failure rate (Banerjee, Sinharoy, & Singh, 2002). This leaves the majority of people with T2DM to use *Momordica charantia* L. (Family: Cucurbitaceae) as an alternative therapy. The plant is well known in African, Ayurveda, and traditional Chinese systems of medicine for its use in diabetes mellitus. It is also a vital market vegetable in southern and eastern Asia, and most of the African countries (Englberger, 2009; USDA, 2017).

The antidiabetic activity of *M. charantia* L. has been investigated in several animal models of T2DM (Rohajatien, Harijono, & Sri

 © 2020 John Wiley & Sons Ltd

Wahyuni, 2018). The majority of these studies used chemically induced T2DM in rats, mice, or rabbits. Then, they assessed the improvement of hyperglycemia, insulin resistance, beta-cell dysfunction, serum insulin level, and dyslipidemia (Aswar & Kuchekar, 2012; Chaing et al., 2012; Fernandes, Lagishetty, Panda, & Naik, 2007; Salimifar, Fatehi-Hassanabad, & Fatehi, 2013). These features are also crucial in the clinical evaluation of the efficacy of antidiabetic activity of herbal products as reported in the previous meta-analysis based on randomized clinical trials (Peter et al., 2018; Phimarn, Sungthong, Saramunee, & Caichompoo, 2018).

In vitro and in vivo studies indicated that *M. charantia* L. improved histological architecture of the islets of Langerhans and beta-cell regeneration (Mahmoud et al., 2017), had insulin secretagogue activity (Platel & Srinivasan, 1995), enhanced peripheral glucose utilization, inhibited glucose-6-phosphatase and fructose biphosphatase glucogenic enzymes (Abdollahi, Zuki, Goh, Rezaeizadeh, & Noordin, 2010), increased adiponectin release (Roffey et al., 2007), 11β-hydroxysteroid dehydrogenase type 1 inhibition (Blum, Loerz, Martin, Staab-weijnitz, & Maser, 2012), α-amylase, and α-glucosidase inhibition (Yue, Xu, Cao, Zhang, & Zhao, 2017).

Despite the preclinical studies performed each year continuing to increase, and our understanding of the mechanism of action is improving, a recent meta-analysis of randomized clinical trials of *M. charantia* L. established a very low certainty of the evidence of its glucose-lowering effect (Peter et al., 2018). There is also a lack of consensus on the proposed mode of action due to contradictory findings of existing preclinical studies. This could indicate the existing challenges in translating animal studies into clinical practice. Given the sheer volume of preclinical experiments of the safety and efficacy of treatment with *M. charantia* L. in T2DM, a structured process is needed to objectively evaluate and provide robust, informative summaries of these studies. Therefore, this systematic review of animal studies aimed to evaluate the evidence of the safety and efficacy of treatment with *M. charantia* L. on animal models of type 2 diabetes mellitus. We also described the impact of study design methodological features, publication bias, and suggested future researches to reliably predict clinical efficacy.

2 | MATERIALS AND METHODS

This systematic review and meta-analysis is based on registered protocol number CRD42019119181 (Peter, Mtewa, Nagendrappa, Kaligirwa, & Sesaazi, 2020). We reported results according to the PRISMA guidelines, the PRISMA abstract checklist, and guidelines for reporting systematic review and meta-analysis of animal studies (Beller et al., 2013; Moher et al., 2009; Sena, Currie, McCann, Macleod, & Howells, 2014).

2.1 | Information source and search strategy

Review authors searched MEDLINE through PubMed platform, Web of Science through a web of knowledge platform, CINAHL, and Scopus. The authors also searched gray literature to include conference papers, technical reports, thesis and Dissertations in Google Scholar, OpenGrey, ProQuest Dissertations & Theses, and British Library EThos. Review authors searched each database through April 2019. They also screened reference lists of included studies and reviews for additional eligible studies not retrieved by the search.

The search strategy involved a combination of MeSH terms and keywords. The search terms were divided into three components that is, the population component with the following words; "animals," "animal," "animals model," "preclinical studies," "experimental animals," "experimental animal," "laboratory animal," "laboratory animals," "rodents," "rodent," "rabbits," "rabbit," "rats," "rat," "diabetic rats," "animal disease model," "mice," "mouse." The intervention component's terms were "*M. charantia*," "bitter melon," "bitter gourd," and "karela." The last component had "diabetes mellitus, type 2," "non-insulin dependent diabetes mellitus," "NIDDM," "glucose metabolic disorders," "metabolic diseases," "hyperlipidemia," "hyperglycemia," "insulin resistance," and "glucose intolerance" terms. The three search components were combined with the boolean logic term "AND" while the keywords within each component were combined with "OR." Search filters for the identification of preclinical studies in PubMed were applied to increase search efficiency (Hooijmans, Tillema, Leenaars, & Ritskes-Hoitinga, 2010). Review authors did not restrict language during the search and identification of studies. The final searches for each database were re-run just before the final analyses to retrieve the most recent studies eligible for inclusion: The supplementary material (S1) elaborated search strategy and their results for PubMed, Scopus, and CINAHL databases (S1).

2.2 | Study design and animal models eligibility

The authors included preclinical randomized or non-randomized controlled designed studies. Furthermore, the original full article and those conducted in animal models of T2DM were considered. The authors assessed animal models carefully to include those with insulin resistance and β-cells failure to ensure construct validity. Our review also included all sex, age, species, and strain of animals. However, studies done in a human, in vitro, ex vivo, and in silico designs, and before–after studies without a description of the control group were excluded.

2.3 | Intervention and comparison eligibility

The intervention group included animals from studies that evaluated the efficacy or safety of the treatment with *M. charantia* L. preparations (whole extract or fraction of any part of the *M. charantia* L.) in any dosing, dosage forms, and frequency. The included studies should have induced T2DM in animals before administered the preparations. On the other hand, comparison groups were animals from studies that induced T2DM and treated with vehicle or saline. Untreated healthy animal control was also included to establish the extent of T2DM induction.

But, the authors excluded studies that evaluated the efficacy of polyherbal preparations of *M. charantia* L. or isolated pure compounds, concurrent treatment with OHAs or insulin, and control treated with any other drug.

2.4 | Study records

2.4.1 | Study selection and data management

Authors pooled retrieved articles into Mendeley software var. 2.1 (Elsevier). After deduplication, two authors (ELP & AK) screened the titles and abstracts of studies independently. Then, they retrieved full-texts of eligible articles and independently assessed them against predetermined inclusion criteria. Disagreement over the eligibility of particular studies was resolved through consensus.

2.4.2 | Data items and collection process

Two authors extracted data independently from the included studies using a pilot-tested data collection form. Discrepancies between the authors were identified and resolved through consensus. Corresponding authors of included studies were contacted via email to obtain numerical data of studies that had data presented graphically, missing, or when additional data were required.

We extracted both primary outcome; fasting plasma glucose level and secondary outcomes; glycosylated hemoglobin A1c (HBA1c), Homeostatic Model Assessment of Insulin Resistance (HOMA-IR), Homeostatic model assessment for assessing β-cell function (HOMA-B), serum insulin level, number of insulin-positive cells, triglycerides (TGs), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c), liver glycogen, weight, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (GGT), urea, and serum creatinine.

2.5 | Taxonomical assessment

The taxonomical and nomenclatural accuracy was assessed by comparing reported taxonomical information with existing standards in an open botanical database accessible at www.theplantlist.org. Analysis of potential taxonomical errors was done according to methods proposed by Rivera and colleagues (Rivera et al., 2014). Articles received "A" grade if full information about the species of plant, identification of specimen, and deposited voucher specimen presented, while grade "B" for those which did not present information on identification of specimen and a voucher specimen and those with inaccurate taxonomic information. Finally, the authors rated "C" to studies with incomplete or not presented at all information about the species of plant, or identification of specimens and a voucher specimen.

2.6 | Methodological quality and risk of bias assessment

We used SYRCLE's risk of bias tool to assess the risk of bias for each included study (Hooijmans et al., 2014). The tool assessed domains of random sequence generation, baseline characteristics, allocation concealment, random housing, blinding of investigators/caregivers, random outcome assessment, blinding of assessor, incomplete outcome data, selective outcome reporting, and other sources of bias. Each criterion was assigned value as high, low, or unclear risk of bias.

Besides, a modified CAMARADES checklist was used to assess the methodological quality of the included studies. According to this checklist, the quality indicators are based on 10 criteria: (1) peer-reviewed publication, (2) statement of control of temperature, (3) random allocation to treatment or control, (4) blinded caregiver/investigator, (5) blinded assessment of outcome, (6) use of co-interventions/co-morbid, (7) appropriate animal model (age, sex, species, strain), (8) sample size calculation, (9) compliance with animal welfare regulations and (10) statement of potential conflict of interests (Dalgleish et al., 2007). Each study was given a quality score out of a possible total of 10 points. Finally, the authors calculated mean score and categorized studies into "low-quality" for mean score 1–5 and "high quality" for mean score 6–10.

2.7 | Data synthesis

Quantitative data were pooled in a statistical meta-analysis using Review Manager (RevMan) software 5.3 (Copenhagen: The Nordic Cochrane Centre). Meta-analysis included studies with data on; FPG, HbA1c, serum insulin level, number of insulin-positive cells, TGs, TC, HDL-c, LDL-c, liver glycogen, ALT, AST, ALP, urea, serum creatinine, and weight. Since the same outcomes reported on the different measurement scales, we used the standardized mean difference (SMD) to evaluate the effect of *M. charantia* L. in comparison to vehicle control. The inverse of variance-weighted method was used to attribute the relative contribution of each included study to the pooled SMD effect of *M. charantia* L. and its 95% confidence intervals. The authors used the random effects model for pooling effect estimates because the effect sizes from animal studies were more likely to differ due to the difference in design characteristics.

Qualitative data were summarized in the form of a table. We used signs (+) and (–) to indicate the direction of increased or decreased effect respectively. Variables analyzed qualitatively were HOMA-IR, HOMA-B, morphological structure of islet of Langerhans, number of beta-cells, and number of insulin secretory granules.

2.8 | Heterogeneity assessment

We used the I^2 statistic to quantify heterogeneity in primary studies (Higgins & Thompson, 2002). The I^2 of 75 or more was considered as indicative of substantial heterogeneity (Borenstein, Hedges, Higgins, & Rothstein, 2010). Subgroup analysis was done to examine potential

factors that influence heterogeneity on the primary outcome (FPG). For this analysis, we considered the risk of bias score, methodological quality score, study design (randomized and non-randomized design), duration of treatment, dose, mode of preparation of *M. charantia* L., animal species (mouse, rat, rabbit, dog, other), animal strains (Wistar, Long-Evans, KK mice, C57BL/6J mice, others), animal age, sex (male, female), and model of induction of type 2 diabetes mellitus (chemical, genetic, surgical, high-fat diet).

2.9 | Publication bias

Publication bias for each outcome was assessed by testing the asymmetry of the funnel plot using Egger's test (Egger, Davey Smith, Schneider, & Minder, 1997). For the publication bias assessment, we only considered meta-analysis of 10 or more studies because test power is generally too low to distinguish chance from real asymmetry when it includes a smaller number of the primary studies (Egger et al., 1997; Sterne et al., 2011). When publication bias was detected, the trim and fill method was used to correct the probable publication bias by imputing missed studies and adjusted the effect size (Duval & Tweedie, 2000).

2.10 | Assessment of confidence in cumulative evidence

The authors used "The Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach" as a framework to rate the certainty in the evidence of preclinical studies (Leeflang et al., 2018; Wei et al., 2016). The authors rated the certainty for each outcome by considering the risk of bias (as assessed by SYRCLE'S risk of bias tool), inconsistency (as assessed by heterogeneity tests, confidence intervals, and *p* values), imprecision, publication bias, and indirectness as proposed by Leeflang and colleagues (Leeflang et al., 2018). After considering all factors, the authors rated evidence as high, moderate, low, or very low-quality.

3 | RESULTS

3.1 | Results of the search

We identified 443 articles through electronic and manual searching. After removing duplications and screening the articles based on the titles and abstracts, 181 articles remained. The full-texts of these articles were examined for eligibility, consequently, 115 articles were further excluded because; one was a thesis for which a published article retrieved, 12 were only abstracts, 16 were inappropriately designed, 45 had not induced T2DM before administering the *M. charantia* L., 18 had no outcomes of interest, 16 did not investigate the intervention of interest and seven were duplicate publications. For each set of duplicate publications, we included one article which had most data. Only one contacted corresponding author shared full text. Therefore, we included 66 studies in qualitative analysis and 48 studies in meta-analysis. A PRISMA flow diagram is presented to show the screened, excluded, and included articles (Figure 1).

3.2 | Description of included studies

The majority of included studies 51 (77.3%) used rats, whereas 12 (18.2%) used mice and only 3 (4.5%) used rabbits. Regarding the strains of animal species; 29 (43.9%) used Wistar albino rats, 11 (16.7%) Sprague–Dawley rats and the remaining 14 different strains used are as shown in Table 1. However, three of the included studies did not specify any strains used.

A total of 37 (56.1%) used male animals, six used only female animals (9.1%), 12 (18.2%) used equal numbers of male and female animals, and the remaining studies did not provide information on the sex of the animals used.

About 32 (48.5%) studies used alloxan monohydrate, 27 (40.9%) studies used Streptozotocin (STZ) whereas two studies each used a high-fat diet and nicotinamide + STZ. One study each used remaining induction materials; cyproheptadine, genetically induced model, and high-fat diet + STZ.

The dose of STZ used ranges from a minimum of 35 mg/kg to a maximum of 200 mg/kg. The average dose was 77.59 ± 44.9 mg/kg. On the other hand, alloxan monohydrate used at a minimum dose of 32 and a maximum dose of 150 mg/kg with an average of 104.75 ± 35.447 mg/kg. The time taken to confirm stable T2DM after exposure to induction material was between one and 90 days. The majority of studies used models of T2DM with FPG levels at baseline ≥11.1 mmol/L, while three studies had models with ≥6 mmol/L (Hafizur et al., 2011; Saha et al., 2012; Shih et al., 2008).

Thirty-two (32) of these studies used an aqueous extract of fresh or dried fruits, and 17 used an alcoholic extract. The remaining studies used acetone extract, hydroalcoholic extract, petroleum ether extract, supernatant aqueous extract, and powdered dried fruits.

About 62 studies used fruits of *M. charantia* L., three used leaves, and one used seeds. Saifi et al., 2014 is the only study that described quality control measures of the intervention; the remaining studies did not describe quality control measures. The studies administered the *M. charantia* L. between 7 days and 90 days. Table 1 summarized the characteristics of the included studies.

3.3 | Taxonomical assessment of included studies

All 66 included studies used the scientific names; however, the majority 57 (86.1%) of the scientific names were not correct. The most recurrent type of error was missing plant authority names 39 (68.4%) and missing plant family names 25 (43.9%). Table 2 illustrates the different types of errors identified.

Four (4) out of 66 studies were given taxonomical validation score of "A" because they presented full information about plant

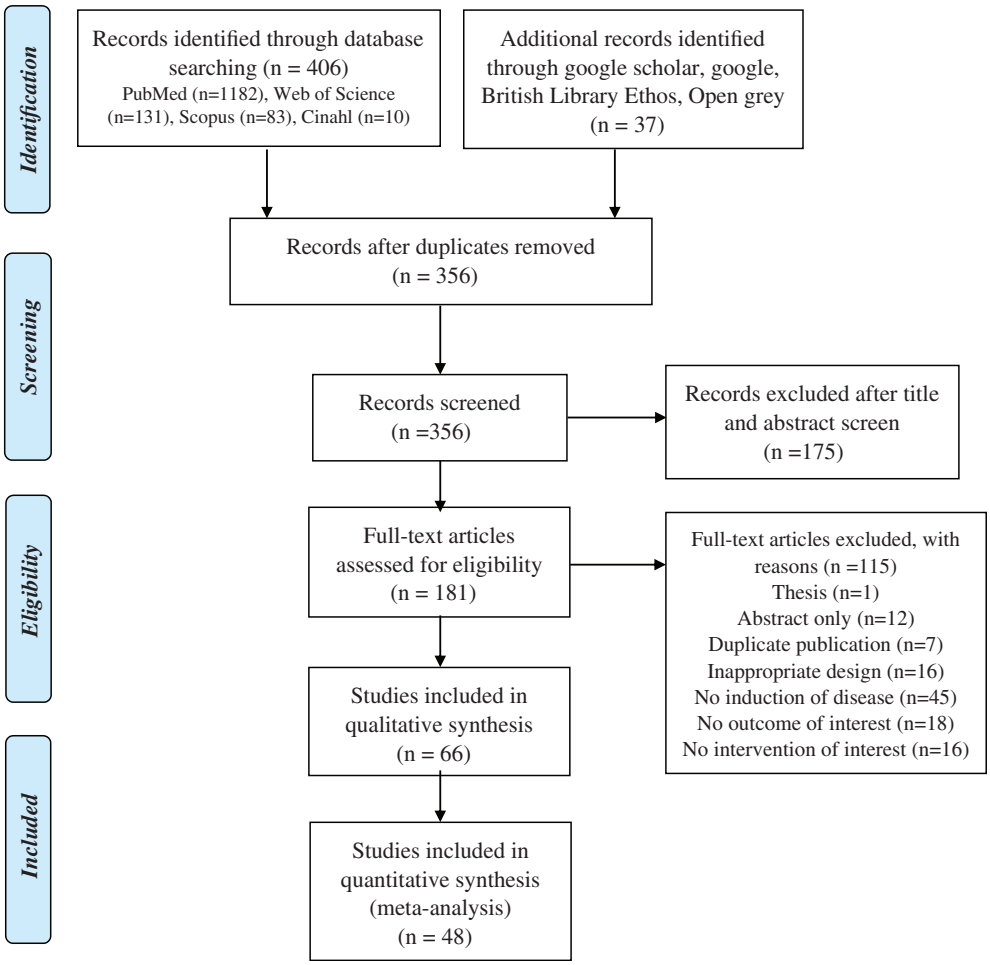

FIGURE 1 Flow diagram for screened included and excluded studies [Colour figure can be viewed at wileyonlinelibrary.com]

name, identification of specimens, and voucher specimen deposited. On the other hand, 10 studies were given a score of "B" since only partial information about plant name and identification of specimen was present. It is worth noting that, the majority of included studies (52) had inadequate or no information about taxonomical identification of plant species (S2).

3.4 | Methodological quality

The quality score of the majority of studies in this analysis 51 (77.3%) was between 2 and 3 with a median score of 3 (interquartile range 1). To put it succinctly, these studies had poor methodological quality. Interestingly, all 66 studies reported publication in peer-reviewed journals. However, none of these studies described the method of random allocation of animals to the treatment or control group, blinded caregiver/investigator, blinded assessment of outcome, and sample size calculation. Only one study described co-interventions of animal models used at baseline (Hossain et al., 2014). About 25 studies reported compliance with animal welfare regulations while 21 studies reported a statement of maintaining a constant temperature, and only 14 studies provided a statement of potential conflict of interest. Supplementary material (S3) summarizes the methodological quality assessment of studies included in the analysis.

3.5 | Risk of bias assessment

Our results indicated that all studies did not perform allocation concealment, random animal housing, blinding of animal caregivers and investigators, random outcome assessment and blinding of outcome assessment. This could mean that these studies were prone to systematic errors due to the design flaw that could overestimate the effect of the *M. charantia* L. Four studies were given unclear risk of bias concerning random sequence generation because we found an inadequate description of the method used for random sequence generation (Aswar & Kuchekar, 2012; Ayoub et al., 2013; Rezaeizadeh et al., 2011; Singh & Gupta, 2007). Summary of the risk of bias across all studies and risk of bias of each included study is provided in Figure 2 and supplementary (S4) respectively.

3.6 | Effect of intervention

3.6.1 | Primary outcome; fasting plasma glucose (FPG)

About 42 preclinical studies (n = 815) had data on FPG. The pooled estimate indicated moderate quality evidence that *M. charantia* L. significantly reduced FPG compared with a vehicle control group,

TABLE 1 Characteristics of the included studies

Study	Country	Species/ Strain	Sex	Age (weeks)/ Weight (g)	Animal model (*n*)	Induction			Nature/Dose of extract	Duration of treatment (days)
						(Dose mg/kg)	Time (days)	FPG (mmol/L)		
(Abas, Othman, & Thent, 2014)	Malaysia	Rat/Sprague–Dawley	M	nm/200–300	N (6), V (6), A (6), T (6)	STZ (60)	30	>8	Aqueous extract of fresh fruit/1.5 g/kg	28
(Abdollahi, Zuki, Goh, Rezaeizadeh, & Noordin, 2011)	Malaysia	Rat/Sprague–Dawley	Both	12/200–250	N (7), V (7), A (7), T (7)	STZ (85)	90	>11	Aqueous extract of fresh fruit/20 mg/kg	30
(Ahmed, Adeghate, Cummings, Sharma, & Singh, 2004)	UAE	Rat/Wistar albino	M	12/200–300	N (10), V (10), T (10)	STZ (60)	nm	>16.7	Supernatant aqueous extract of fresh fruit/10 ml/kg	70
(Ahmed, Adeghate, Sharma, Pallot, & Singh, 1998)	UAE	Rat/Wistar albino	M	nm/200–250	N (5), V (5), T (5)	STZ (60)	7	>16.7	Supernatant aqueous extract of fresh fruit/10 ml/kg	63
(Akhter, Rasel, & Islam, 2018)	Bangladesh	Rat/mixed albino	M	8–12/200–300	N (12), V (12), T (12)	Alloxan (100)	10	>8.3	Aqueous extract of fresh fruit/300 mg/kg	21
(Castellanos-campos et al., 2016)	Mexico	Rat/Wistar albino	M	nm/150–250	N (6), V (6), T (30)	Alloxan (150)	3	>8.3	Aqueous extract of fresh leaves[a]/10–160 mg/kg	30
(Almarzooq, 2009)	S/Arabia	Mice/Swiss albino	Both	8/20–25	N (10), V (10), T (10)	Alloxan (50)	nm	nm	Supernatant aqueous extract of fresh fruit/10 ml/kg	90
(Aswar & Kuchekar, 2012)	India	Rat/Wistar albino	M	nm/160–200	N (6), V (6), A (6), T (12)	Alloxan (120)	2	nm	Aqueous extract of fresh fruit/250 and 500 mg/kg	7
(Ayoub et al., 2013)	India	Rat/Wistar albino	F	nm/170–210	N (10), V (10), A (10), T (20)	STZ (45)	3	>11.1	Alcoholic extract of fresh fruits/100 & 200 mg/kg	45
(El Batran et al., 2006)	Egypt	Rat/Sprague–Dawley	Both	nm/120–150	V (6), T (12)	Alloxan (150)	nm	nm	70% ethanolic extract of fresh fruits/2.1–9.2 mg/100 g[a]	30
(Bhat et al., 2018)	India	Rat/Wistar albino	M	8–12/200–250	V (6), T (6)	STZ (50)	30	>11.1	Aqueous extract of fresh fruit/300 mg/kg	28
(Cakici et al., 1994)	Turkey	Mice/albino	M	nm/20–40	N (5), V (8), A (4), T (5)	CH (45)	8	>13.9	50% ethanolic extract of fresh fruits[a]/0.5 g/kg	7
(Chandra, Mahdi, Singh, Mahdi, & Chander, 2008)	India	Rat/Sprague–Dawley	M	Adult/180–200	N (6), V (6), A (6), T (6)	STZ (65)	3	10–11.1	Supernatant aqueous extract of fresh fruit/500 mg/kg	30
(Chandru et al., 2016)	India	Rat/Wistar albino	Both	12–16/170–250	N (6), V (6), A (6), T (6)	STZ (55)	3	>13.9	Aqueous extract of fresh fruit/6 ml/kg	28
(Chaturvedi, 2005)	Botswana	Rat/Horts men	M	nm/200–250	N (5), V (5), T (5)	Alloxan (60)	nm	nm	70% methanolic extract of fresh fruits/80, 100 &120 mg/kg	45
(Day, Cartwright, Provost, & Bailey, 1990)	UK	Mice/Theiller origin	M	Adult/	N (5), V (5), T (5)	STZ (200)	nm	nm	Aqueous extract of fresh fruits/20 mg/ml	7
(Fernandes et al., 2007)	India	Rat/Wistar albino	Both	72/150–200	N (8), V (8), A (8), T (24)	Alloxan (100)	6	>13.9	Ethanol extract of fresh fruits/ 150 & 300 mg/kg	30
(Grover, Vats, Rathi, & Dawar, 2001)	India	Mice/albino	Both	nm/30–50	N (6), V (6), T (6)	STZ (150)	10	>16.7	Aqueous extract of fresh fruits/200 & 400 mg/kg	40

(Continues)

TABLE 1 (Continued)

Study	Country	Species/ Strain	Sex	Age (weeks)/ Weight (g)	Animal model (*n*)	Induction			Nature/Dose of extract	Duration of treatment (days)
						(Dose mg/kg)	Time (days)	FPG (mmol/L)		
(Gupta, Kant, Johri, & Saxena, 2007)	India	Rat/Charles Foster	M	nm/120–140	N (6), V (6), T (6)	STZ (35)	2	>7.8	95% alcoholic extract of fresh fruits/250 mg/kg	7
(Hafizur, Kabir, & Chishti, 2011)	Pakistan	Rat/Wistar albino	nm	4/nm	N (11), V (8), A (8), T (8)	STZ (100)	60	6.1–9.4	Hydroalcoholic extract of fresh fruits/400 mg/kg	28
(Hossain, Asadujjaman, Khan, Ahmed, & Islam, 2011)	Bangladesh	Rat/Long-Evans	M	8/150–180	N (5), V (5), A (5), T (5)	Alloxan (110)	2	>11.1	Petroleum ether fraction of fresh fruit/150 mg/kg	7
(Hossain, Mostofa, Awal, Chowdhury, & Sikder, 2014)	Bangladesh	Rat/Long-Evans	nm	nm/150–200	N (6), V (6), A (6), T (18)	STZ (55)	7	13.3–13.9	Aqueous extract of fresh fruits/250, 500 & 750 mg/kg	90
(Ibrahem & Al-Abassi, 2010)	Iraq	Rat/Wistar albino	M	8/150–200	N (10), V (10), A (10), T (10)	Alloxan (150)	7	>13.9	Aqueous extract of seeds/150 mg/kg	30
(Jafri, Ismail, & Zaman, 2015)	India	Rat/Wistar albino	Both	nm/200–300	N (15), V (15), T (15)	Alloxan (100)	7	7.8–9.4	Aqueous extract of dried fruits/1 g/kg	60
(Kolawole, Abiona, Kolawole, Ayankunle, & Olaniran, 2011)	Nigeria	Rat/Wistar albino	M	nm/180–250	N (5), V (5), A (5), T (15)	Alloxan (120)	8	>7.8	Methanol extract of fresh fruits/200, 400 & 600 mg/kg	28
(Kumar et al., 2013)	India	Mice/Swiss albino	F	8/28–32	N (6), V (6), T (6)	Alloxan (150)	nm	nm	Aqueous extract of dried fruits/100 mg/kg	21
(Lal, Gupta, Poonam, & Awanish, 2011)	India	Rat/Wistar albino	nm	Adult/110–160	N (5), V (5), A (5), T (5)	STZ (50)	2	≥11.1	Aqueous extract of dried fruits/20 ml/kg	28
(Ma, Yu, Xiao, & Wang, 2017)	China	Rat/SPF-grade CD	M	nm/nm	N (8), V (8), A (8), T (24)	HFD + STZ (25)	7	≥11.1	70% ethanol extract of fresh fruits[a]/100, 200 & 400 mg/kg	60
(Mahdi et al., 2003)	India	Rat/albino	M	nm/150–200	N (6), V (6), A (6), T (6)	STZ (65)	3	nm	Aqueous extract of fresh fruits/10 ml/kg	30
(Mahmoud et al., 2017)	Egypt	Rat/albino	M	6–8/150–200	N (6), V (6), T (6)	STZ (45)	7	>11.1	Supernatant aqueous extract of fresh fruit/10 ml/kg	21
(Matheka, Alkizim, Kiama, & Bukachi, 2012)	Kenya	Rat/Sprague–Dawley	F	24/200–250	V (7), T (7)	Alloxan (125)	27	>7.1	Aqueous extract of fresh fruits/10 ml/kg	28
(Miura et al., 2001)	Japan	Mice/KK-ay	M	12/22–25	V (5), T (5)	Genetic	na	16.7	Aqueous extract of fresh fruits/100 mg/kg	21
(Mohammady, Elattar, Mohammed, & Ewais, 2012)	Egypt	Rat/albino	M	nm/120–160	N (10), V (10), A (10), T (10)	Alloxan (100)	nm	10–16.7	Aqueous extract of fresh fruits/300 mg/kg	30
(Mushtaq et al., 2016)	Pakistan	Rabbit/ *O. cuniculus*	F	nm/1000–2000	N (5), V (5), A (5), T (10)	Alloxan (55)	15	≥16.7	Ethanolic extract of fresh fruits/1 & 3 mg/kg	15
(Nagy, Bastawy, & Abdel-Hamid, 2012)	Egypt	Rat/Sprague–Dawley	M	17/150–200	N (10), V (10), T (10)	STZ (60)	7	8.9	Supernatant aqueous extract of fresh fruits/400 mg/kg	56

(Continues)

TABLE 1 (Continued)

Study	Country	Species/ Strain	Sex	Age (weeks)/ Weight (g)	Animal model (*n*)	Induction			Nature/Dose of extract	Duration of treatment (days)
						(Dose mg/kg)	Time (days)	FPG (mmol/L)		
(Nivitabishekam, Asad, & Prasad, 2009)	India	Rat/Sprague–Dawley	M	nm/180–250	N (5), V (5), A (5), T (5)	NAM + STZ (120 + 60)	7	8.3	Methanolic extract of fresh fruits[b]/500 mg/kg	28
(Nkambo et al., 2013)	Uganda	Rat/Wistar albino	M	nm/150–180	N (6), V (6), A (6), T (12)	Alloxan (65)	5	>11.1	Methanolic extract of fresh fruits[a]/125 &375 mg/kg	7
(Parmar et al., 2011)	India	Rat/Wistar albino	nm	12/7–10	N (6), V (6), T (12)	STZ (90)	90	>7.8	Supernatant aqueous extract of fresh fruits/10 mg/kg	56
(Platel & Srinivasan, 1995)	India	Rat/Wistar albino	M	Adult/150–160	N (12), V (12), T (12)	STZ (50)	15	nm	Freeze dried powder of fresh fruit/nm	48
(Rathi, Grover, Vikrant, & Biswas, 2002)	India	Rat/Wistar albino	nm	nm/nm	N (8), V (8), T (24)	Alloxan (32)	2	>9.7	Aqueous extract of fresh fruits/200 mg/kg	21
(Reyes et al., 2006)	Philippines	Rat/Sprague–Dawley	F	nm/140–150	N (5), V (5), T (5)	Alloxan (125)	4	>16.7	Aqueous extract of fresh fruits/20 ml/kg	27
(Rezaeizadeh et al., 2011)	Malaysia	Rat/Sprague–Dawley	nm	12/nm	N (7), V (7), A (7), T (7)	STZ (85)	90	>11	Aqueous extract of fresh fruits/20 ml/kg	30
(Rohajatien et al., 2018)	Indonesia	Rat/*R. norvegicus*	M	8–12/nm	N (6), V (6), T (6)	STZ + NA (65 + 20)	5	>11.1	Fresh fruits feeding/ 71.1 mg/kg	30
(Saha et al., 2012)	Bangladesh	Rat/Long-Evans	M	nm/142–170	N (5), A (5), T (10)	Alloxan (125)	3	>6	Aqueous extract of fresh fruits/36 & 21 g/kg	21
(Saifi, Namdeo, Chauhan, & Dwivedi, 2014)	India	Rat/Wistar albino	Both	nm/150–200	N (6), V (6), A (6), T (6)	Alloxan (120)	2	>11.1	70% hydroalcoholic extract of fresh fruits[c]/300 mg/kg	21
(Sani, Atiku, & Imam, 2015)	Nigeria	Rat/	nm	nm/100–150	N (5), V (5), T (15)	Alloxan (100)	2	>11.1	Aqueous extract of fresh leaves[a]/200, 400 & 600 mg/kg	30
(Sathishsekar & Subramanian, 2005)	India	Rat/Wistar albino	M	nm/160–180	N (6), V (6), A (6), T (12)	STZ (55)	7	>13.9	Aqueous extract of fresh fruits/150 mg/kg	30
(Sharma et al., 2014)	India	Mice/Swiss albino	nm	16–24/28–32	N (6), V (6), T (12)	Alloxan (150)	21	>11.1	Aqueous extract of fresh fruits/100 & 250 mg/kg	21
(Shibib, Khan, & Rahman, 1993)	Bangladesh	Rat/Wistar albino	M	nm/180–250	N (5), V (4), T (4)	STZ (65)	3	nm	Ethanolic extract of fresh fruits/200 mg/kg	7
(Shih, Lin, & Lin, 2008)	Taiwan	Mice/ C57BL/ 6J	M	5/nm	N (9), V (9), T (18)	HFD	60	6.7	Aqueous extract of fresh fruits/500 & 1,000 mg/kg	30
(Singh et al., 1989)	India	Rat/Wistar albino	Both	nm/100–150	N (18), V (18), T (54)	Alloxan (60)	nm	nm	Acetone extract of fresh fruits/25 mg/100 g	30
(Singh & Gupta, 2007)	India	Rat/Wistar albino	nm	nm/nm	N (6), V (6), T (18)	Alloxan (60)	8	nm	Acetone extract of fresh fruits/25, 50 and 75 mg/100 g	30

(Continues)

TABLE 1 (Continued)

Study	Country	Species/ Strain	Sex	Age (weeks)/ Weight (g)	Animal model (*n*)	Induction			Nature/Dose of extract	Duration of treatment (days)
						(Dose mg/kg)	Time (days)	FPG (mmol/L)		
(Singh, Gupta, Sirohi, & Varsha, 2008)	India	Rat/Wistar albino	nm	7–8/100–150	N (18), V (18), T (54)	Alloxan (60)	nm	nm	Alcoholic extract of fresh fruits/25, 50 and 75 mg/100 g	nm
(Sitasawad, Shewade, & Bhonde, 2000)	India	Mice/Balb/c	M	6–8/nm	N (?), V (?), A (?), T (?)	STZ (200)	nm	nm	Supernatant aqueous extract of fresh fruits/10 ml/kg	nm
(Srivastava, Venkatakrishna-Bhatt, & Verma, 1988)	India	Rat/Charles Foster	Both	nm/150–200	N (10), V (10), T (30)	Alloxan (120)	3	8.3	Aqueous extract of fresh fruits/4 g/kg	20
(Srivastava, Venkatakrisna-Bhatt, Verma, Venkaiah, & Raval, 1993)	India	Rat/Charles Foster	Both	nm/150–200	N (20), V (10), T (10)	Alloxan (120)	3	8.3	Aqueous extract of fresh fruits/4 g/kg	21
(Tahira & Hussain, 2014)	Pakistan	Rabbit/	M	nm/1000–1,500	N (7), V (7), A (5), T (7)	Alloxan (80)	nm	>11.1	Alcoholic extract of fresh fruits/100 mg/kg	14
(Tarkang & Ofogba, 2012)	Nigeria	Rat/Wistar albino	M	nm/180–200	N (4), V (4), T (4)	Alloxan (120)	10	>13.9	Aqueous extract of fresh fruits/400 mg/kg	28
(Tripathi & Chandra, 2010)	India	Rat/Wistar albino	M	nm/120–150	N (5), V (5), T (5)	Alloxan (150)	4	>15.6	Aqueous extract of fresh fruits/13.33 g/kg	30
(Vangoori et al., 2013)	India	Rabbit/albino	Both	Adult/1000–4,000	V (5), A (5), T (15)	Alloxan (150)	nm	12.2–27.8	Ethanolic extract of fresh fruits/0.5, 1 & 1.5 g/kg	35
(Wehash et al., 2012)	Egypt	Rat/Sprague–Dawley	M	nm/200–220	N (6), V (6), T (6)	STZ (50)	3	>13.9	95% ethanolic extract of fresh fruits/500 mg/kg	30
(Han, Hui, & Wang, 2008)	China	Mice/ Kunming strain	nm	nm/20–22	N (12), V (12), T (36)	Alloxan (75)	2	>11.1	Aqueous extract of fresh fruits/nm	10
(Wang et al., 2014)	Taiwan	Mice/KK/HIJ	M	6/19–22	N (8), V (8), T (8)	HFD	60	nm	Aqueous extract of fresh fruits	60
(Yousaf, Hussain, Rehman, Aslam, & Abbas, 2016)	Pakistan	Mice/nm	F	6–8/21–23	N (?), V (?), A (?), T (?)	STZ (150)	nm	>10.5	Aqueous extract of fresh fruits/nm	nm
(Chowdhury et al., 2012)	Bangladesh	Rat/Long-Evans	M	nm/nm	N (5), V (5), A (5), T (5)	STZ (60)	nm	16.20 ± 0.90	95% ethanolic extract of fresh fruits/100 mg/kg	7
(Karunanayake, Jeevathayaparan, & Tennekoon, 1990)	Sri-Lanka	Rat/Sprague–Dawley	M	nm/195 ± 21	V (18), T (20)	STZ (50)	3	nm	Supernatant aqueous extract of fresh fruits/10 ml/kg	30

Abbreviations: A, active treatment group; CH, cyproheptadine; F, female; M, male; N, normal control group; na, not applicable; NAM + STZ, nicotinamide+streptozotocin; nm, not mentioned; S/Arabia, Saudi Arabia; T, intervention group; Time, time taken to confirm stable T2DM induced; UAE, United Arabs Emirates; UK, United Kingdom; V, vehicle/saline control group; ?, no number of animals.

[a]Investigated dose–response relationship.

[b]Standardized dose based on chemical markers.

[c]Quality control data available.

TABLE 2 The common type of errors in scientific name identified in the included studies

Particulars	*N* (%)	Study
Use of the scientific name		
Correct name	9 (13.6)	(Cakici et al., 1994; Day et al., 1990; Karunanayake et al., 1990; Kolawole et al., 2011; Ma et al., 2017; Miura et al., 2001; Mushtaq et al., 2016; Shih et al., 2008; Sitasawad et al., 2000)
Incorrect name	57 (86.4)	
Type of errors in incorrect names		
Misspelling of genus or species	3 (5.3)	(Rathi et al., 2002; Sani et al., 2015; Srivastava et al., 1988)
Inconsistent use of italics	6 (10.5)	(Aswar & Kuchekar, 2012; Fernandes et al., 2007; Lal et al., 2011; Nagy et al., 2012; Rohajatien et al., 2018; Srivastava et al., 1988)
Inappropriate capitalization	3 (5.3)	(Abdollahi et al., 2011; Chandru et al., 2016; Sathishsekar & Subramanian, 2005)
Missing author	39 (68.4)	(Abas et al., 2014; Abdollahi et al., 2011; Ahmed et al., 1998; Akhter et al., 2018; Almarzooq, 2009; Ayoub et al., 2013; Bhat et al., 2018; Castellanos-campos et al., 2016; Chandra et al., 2008; Chandru et al., 2016; Chaturvedi, 2005; Chowdhury et al., 2012; Grover et al., 2001; Hafizur et al., 2011; Han et al., 2008; Hossain et al., 2011; Ibrahem & Al-Abassi, 2010; Jafri et al., 2015; Kumar et al., 2013; Lal et al., 2011; Mahdi et al., 2003; Matheka et al., 2012; Mohammady et al., 2012; Nagy et al., 2012; Parmar, Patel, Patel, Patel, & Patel, 2011; Platel & Srinivasan, 1995; Rathi et al., 2002; Reyes et al., 2006; Rezaeizadeh et al., 2011; Saha et al., 2012; Sharma et al., 2014; Shibib et al., 1993; Singh et al., 2008, 1989; Tarkang & Ofogba, 2012; Tripathi & Chandra, 2010; Vangoori et al., 2013; Wehash et al., 2012; Yousaf et al., 2016)
Non-standard author abbreviation	13 (22.8)	(Fernandes et al., 2007; Gupta et al., 2007; Hossain et al., 2014; Mahmoud et al., 2017; Nivitabishekam et al., 2009; Saifi et al., 2014; Sani et al., 2015; Sathishsekar & Subramanian, 2005; Singh & Gupta, 2007; Srivastava et al., 1988, 1993; Tahira & Hussain, 2014; Wang et al., 2014)
Missing of a period of abbreviation	5 (8.8)	(Ahmed et al., 2004; El Batran et al., 2006; Nivitabishekam et al., 2009; Nkambo, Anyama, & Onegi, 2013; Rohajatien et al., 2018)
No family name	25 (43.9)	(Akhter et al., 2018; Bhat et al., 2018; Chandra et al., 2008; Chandru et al., 2016; Chaturvedi, 2005; Fernandes et al., 2007; Hafizur et al., 2011; Ibrahem & Al-Abassi, 2010; Jafri et al., 2015; Lal et al., 2011; Mahdi et al., 2003; Matheka et al., 2012; Mohammady et al., 2012; Nagy et al., 2012; Nivitabishekam et al., 2009; Platel & Srinivasan, 1995; Saha et al., 2012; Sharma et al., 2014; Shibib et al., 1993; Singh & Gupta, 2007; Srivastava et al., 1988; Tarkang & Ofogba, 2012; Vangoori et al., 2013; Wehash et al., 2012; Yousaf et al., 2016)
Misspelling of family	8 (14.0)	(Abdollahi et al., 2011; Ahmed et al., 1998; Rezaeizadeh et al., 2011; Rohajatien et al., 2018; Sani et al., 2015; Sathishsekar & Subramanian, 2005; Singh et al., 2008; Srivastava et al., 1993)

representing −6.86 of SMD (95% CI; −7.95, −5.77), I^2 = 90. Interestingly, all studies consistently favored *M. charantia* L. (Figure 3).

3.6.2 | Secondary outcomes

Glycosylated hemoglobin A1c (HbA1c)

The data from three preclinical studies were pooled for assessment of HbA1c (Figure 4). There was moderate quality evidence that *M. charantia* L. significantly lowered HbA1c level in a treated group (*n* = 34) compared to the vehicle control group (*n* = 25); −7.76 of SMD (95% CI; −12.5, −3.01). The I^2 = 82%; indicating the presence of heterogeneity in individual studies.

Serum insulin

Results indicated very low-quality evidence that serum insulin level observed in *M. charantia* L. treated group (*n* = 132) was significantly increased compared with the vehicle control group (*n* = 85); 4.28 of SMD (95% CI; 2.35, 6.22). The I^2 of 93% was indicating the presence of heterogeneity. Only one study (Shih et al., 2008) had a significant

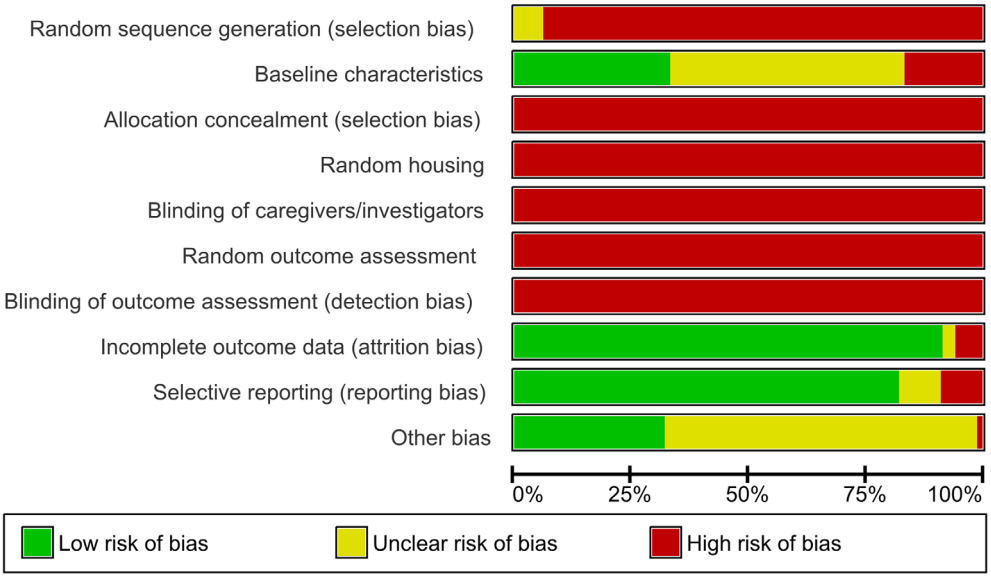

FIGURE 2 Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies [Colour figure can be viewed at wileyonlinelibrary.com]

effect size in the opposite direction (Figure 4). The authors downgraded the evidence to very low-quality due to a severe risk of bias and imprecision, serious inconsistency, and strongly suspected publication bias (S5).

Insulin-positive cells

There was an increase in the number of insulin-positive cells in the *M. charantia* L. treated group (n = 32) compared to the vehicle control group (n = 22); 3.25 of SDM (95% CI; −0.21, 6.70). Although such an increase was not statistically significant, all three studies favored the intervention (Figure 4). The I^2 was 93% indicated the presence of heterogeneity in the individual study.

Liver glycogen

The pooled data from four studies indicated that there was no statistically significant increase in liver glycogen in the *M. charantia* L. treated group (n = 56) compared to the vehicle control group (n = 36); 1.11 of SDM (95% CI; −3.20, 5.43). The I^2 of 97% indicated the presence of heterogeneity. Two studies favored *M. charantia* L., and another two studies favored the vehicle control group (Figure 5).

Triglycerides (TGs)

The data from 13 preclinical studies were pooled for the assessment of triglycerides (Figure 6). Results showed a very low-quality evidence that *M. charantia* L. significantly lowered TGs level in treated group (n = 142) compared to vehicle control group (n = 87); −9.12 of SMD (95% CI; −11.76, −6.49). The I^2 was 92% indicated the presence of substantial heterogeneity in individual studies.

Total cholesterol (TC)

Figure 6 showed that *M. charantia* L. treated group (n = 216) had a significantly reduced level of total cholesterol compared with the vehicle control group (n = 125) with SMD of −10.38 (95% CI; −13.04, −7.73). The I^2 was 95% indicated the heterogeneity. The certainty of this evidence was assessed as low (S4 Appendix).

High-density lipoprotein cholesterol (HDL-c)

The HDL-c was assessed by integrating data from eight studies (Figure 6). There was low-quality evidence that the HDL-c level in *M. charantia* L. treated group (n = 72) increased compared to the vehicle control group (n = 50), 4.37 SDM (95% CI; 2.29, 6.45). The I^2 was 89% indicated the presence of heterogeneity.

Low-density lipoprotein cholesterol (LDL-c)

The LDL-c level in the *M. charantia* L. treated group (n = 72) was significantly decreased compared to that observed in the vehicle control group (n = 50). The SMD of −6.71 (95% CI; −9.06, −4.36). The I^2 was 89% indicated the presence of heterogeneity (Figure 6).

Alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphate (ALP)

There was a significant reduction of ALT (SMD; −5.14; [95% CI; −7.33, −2.95]), AST (SMD; −3.60; [95% CI; −4.95, −2.25]), and ALP (SMD; −3.58; [95% CI; −4.94, −2.22]) in the *M. charantia* L. treated groups compared with the vehicle control groups. The I^2 were 77, 64 and 82% respectively; indicated the presence of significant heterogeneity (Figure 7).

Serum creatinine and plasma urea

There was a significant reduction of serum creatinine (SMD; −4.52; [95% CI; −6.42, −2.61]) and plasma urea (SMD; −2.68; [95% CI; −4.13, −1.22]) in the *M. charantia* L. treated groups compared with the vehicle control groups. The I^2 was 84% and 89% respectively; indicated the presence of significant heterogeneity.

Effect of M. charantia *L. on body weight*

About 14 preclinical studies provided quantitative data on weight. We reported a significant increase in body weight in the *M. charantia* L. treated groups (n = 148) compared with the vehicle control groups (n = 114). The SMD was 2.96 (95% CI; 1.63, 4.29), and I^2 was 56% which indicates the presence of moderate heterogeneity in individual studies.

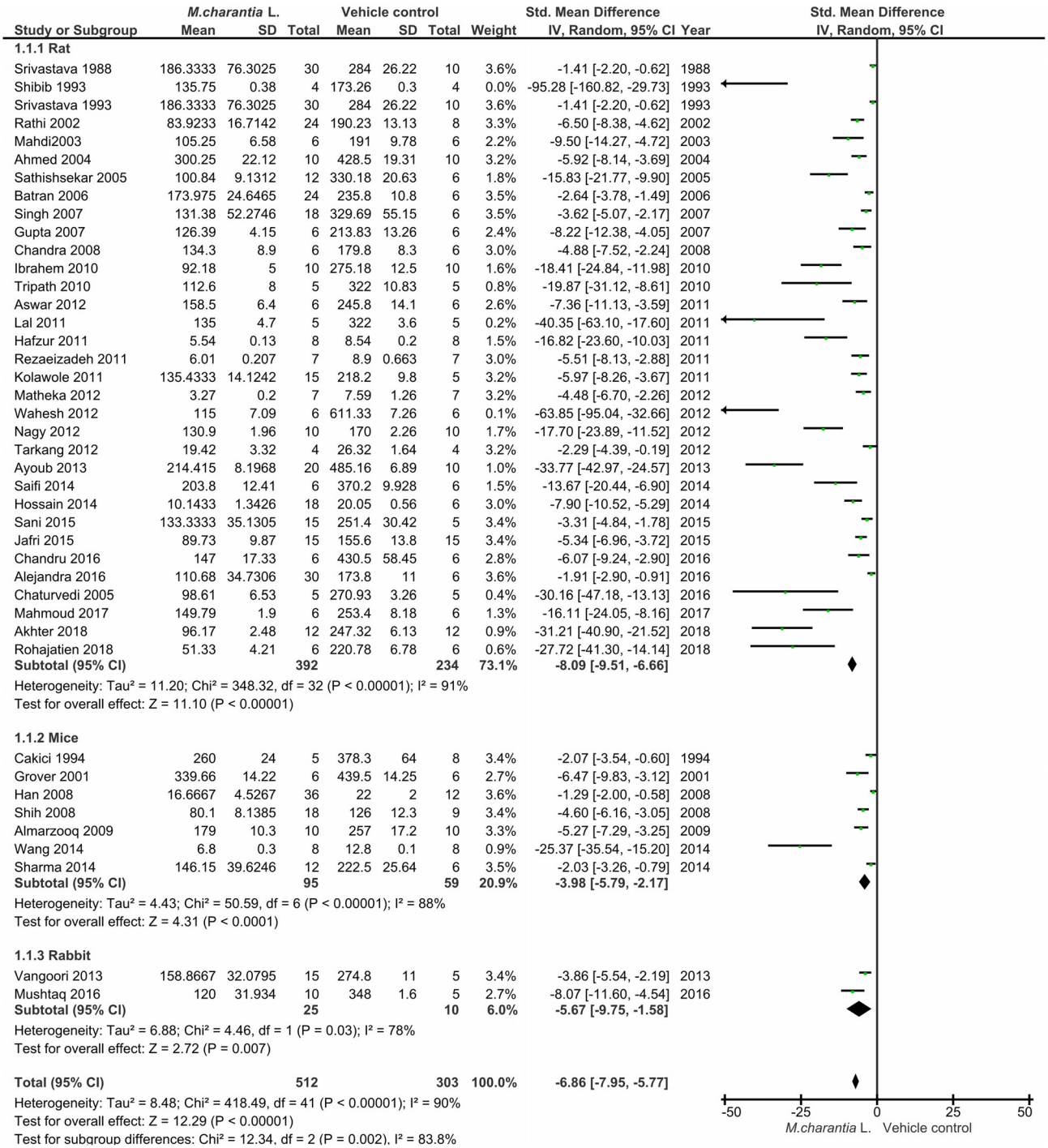

FIGURE 3 Forest plot of preclinical studies comparing *M. charantia* L. and vehicle control; measuring fasting plasma glucose [Colour figure can be viewed at wileyonlinelibrary.com]

3.6.3 | Subgroup analysis

The authors considered subgroup analysis for *M. charantia* L. versus vehicle control on FPG level for rats, mice, and rabbits' species (Figure 4). The test for subgroup analysis suggested that there was a statistically significant subgroup effect (p = .002), I^2 = 83.8%, that is, animal species significantly modified the effect of *M. charantia* L. in comparison to vehicle control. The treatment effect favored *M. charantia* L. across all three species. However, the treatment effect was higher for rats than mice and rabbits. Hence the subgroup effect is quantitative. Heterogeneity between results in studies within subgroup requires further exploration.

Another subgroup analysis considered for *M. charantia* L. versus vehicle control on FPG level was animal strain; Wistar albino rats,

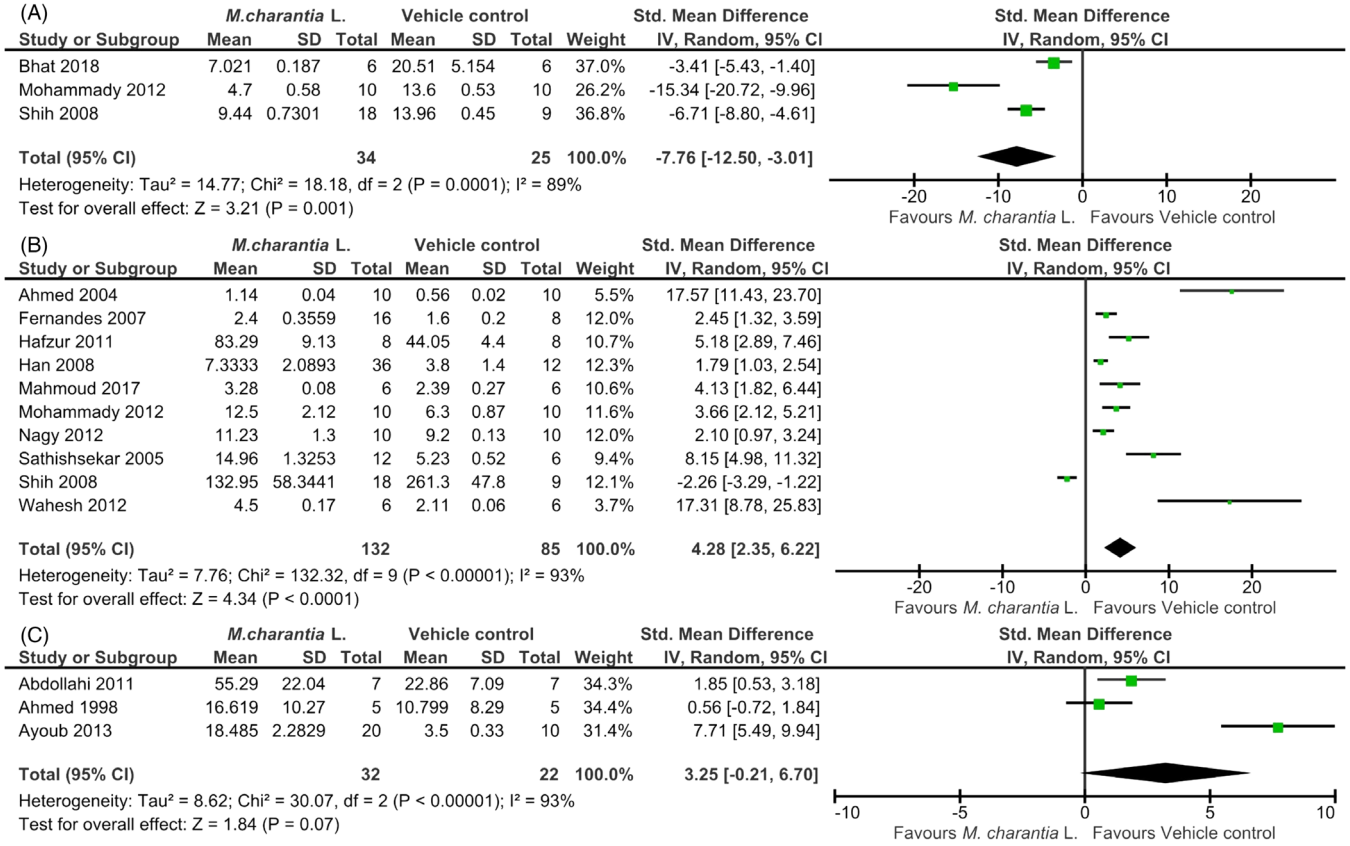

FIGURE 4 Forest plot of preclinical studies comparing *M. charantia* L. and vehicle control; measuring (A) HBA1c, (B) Serum insulin level, (C) Insulin-positive cells in pancreases [Colour figure can be viewed at wileyonlinelibrary.com]

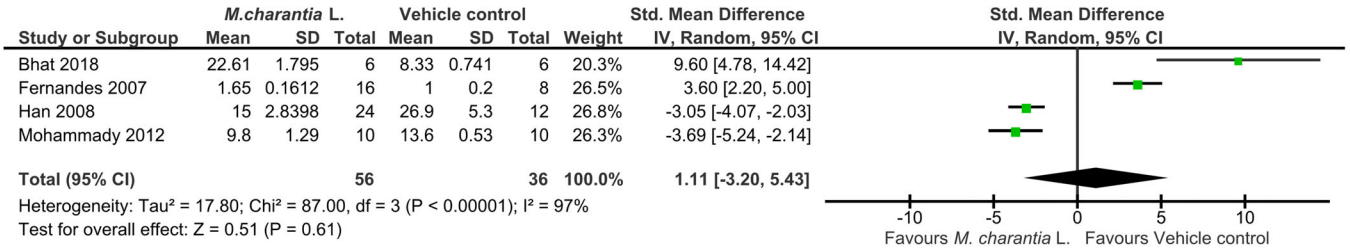

FIGURE 5 Forest plot of preclinical studies comparing *M. charantia* L. and vehicle control; measuring liver glycogen [Colour figure can be viewed at wileyonlinelibrary.com]

Sprague–Dawley rats, and Charles Foster rats. The test for subgroup differences indicated that there was a statistically significant subgroup effect ($p \leq .00001$), $I^2 = 85.4\%$, in other words, animal strains significantly modified the effect of *M. charantia* L. in comparison to vehicle control. The treatment effect favored *M. charantia* L. over vehicle control for all animal strains; therefore, the subgroup effect is quantitative. It is interesting to note that effect size was greater for Wistar albino rats (SMD; −10.29, 95% CI; −12.55, −8.03), $I^2 = 90\%$ than for Sprague–Dawley rats (SMD; −6.71, 95% CI; −10.02, −3.40), $I^2 = 88\%$, and Charles Foster rat (SMD; −2.15, 95% CI; −3.69, −0.60), $I^2 = 80\%$. This analysis indicated a substantial unexplained heterogeneity between the studies with each subgroup as indicated by their I^2. It is also important to note that the subgroup analysis could not detect subgroup effects of other animal stains (Horts men rats, Long-Evans rats, Swiss albino mice, Kunming mice, C57BL/6J and KK/HIS mice) because a small number of studies contributed the data.

3.7 | Evaluation of publication bias

We assessed publication bias for *M. charantia* L. versus vehicle control on FPG, TC, TGs, serum insulin and body weight by visually assessing funnel plots. Egger's tests for funnel plot asymmetry suggested that there was a statistically significant publication bias for FPG, TC, TGs,

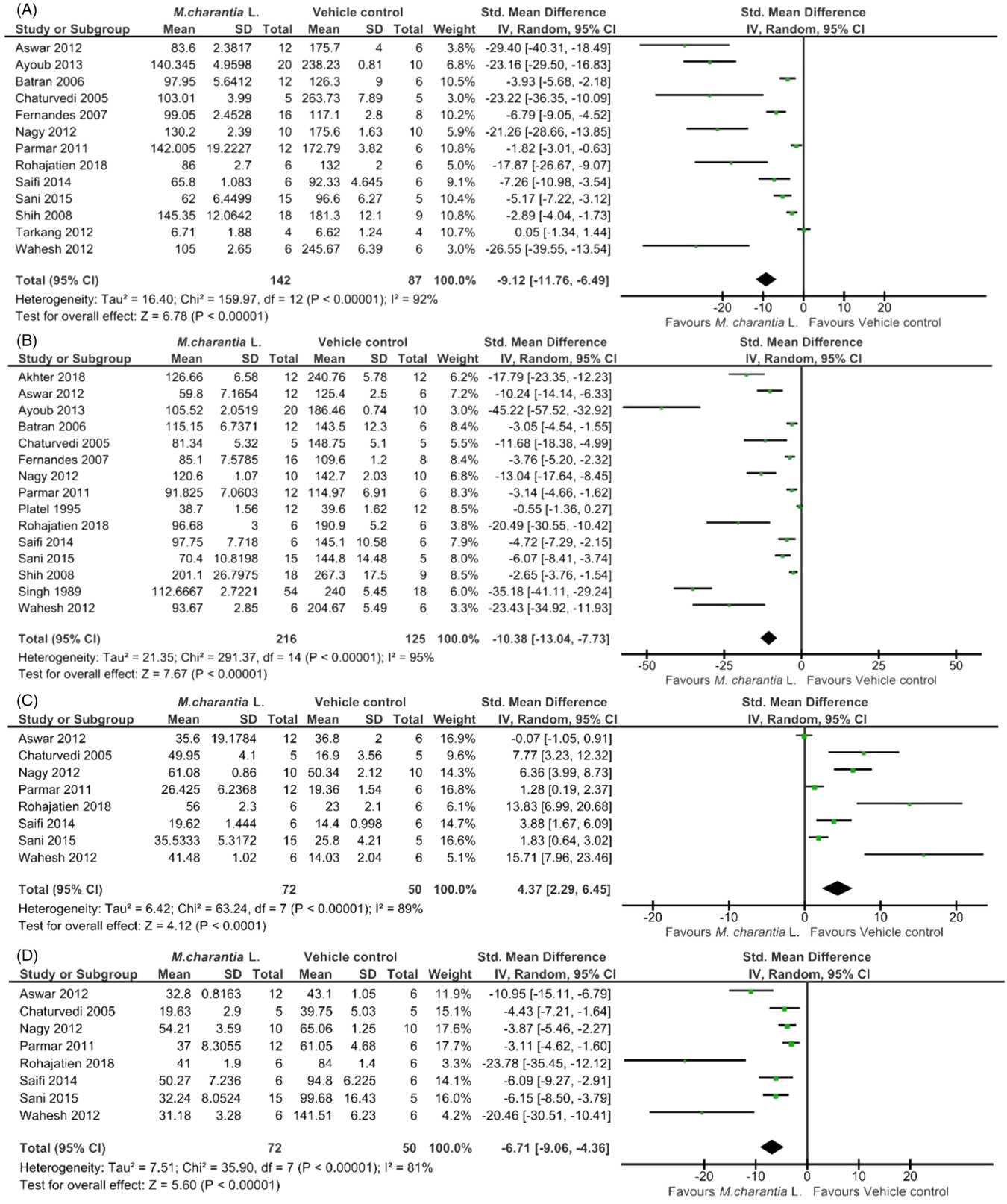

FIGURE 6 Forest plot of preclinical studies comparing *M. charantia* L. and vehicle control; measuring (A) TGs, (B) TC, (C) HDL-c, (D) LDL-c [Colour figure can be viewed at wileyonlinelibrary.com]

and serum insulin ($p < .0001$). However, there was no evidence of publication bias for the weight ($p = .062$).

The trim and fill analysis imputed 19 potentially missed studies for FPG, 9 for TC, 5 for TGs, and one missed study for serum insulin. The imputed studies changed the significance or magnitude of the overall pooled effect size for these outcomes. Use of random effects models indicated that FPG changed to non-significant reduction −2.46 SMD, (95% CI; −5.10, 0.17), similarly,

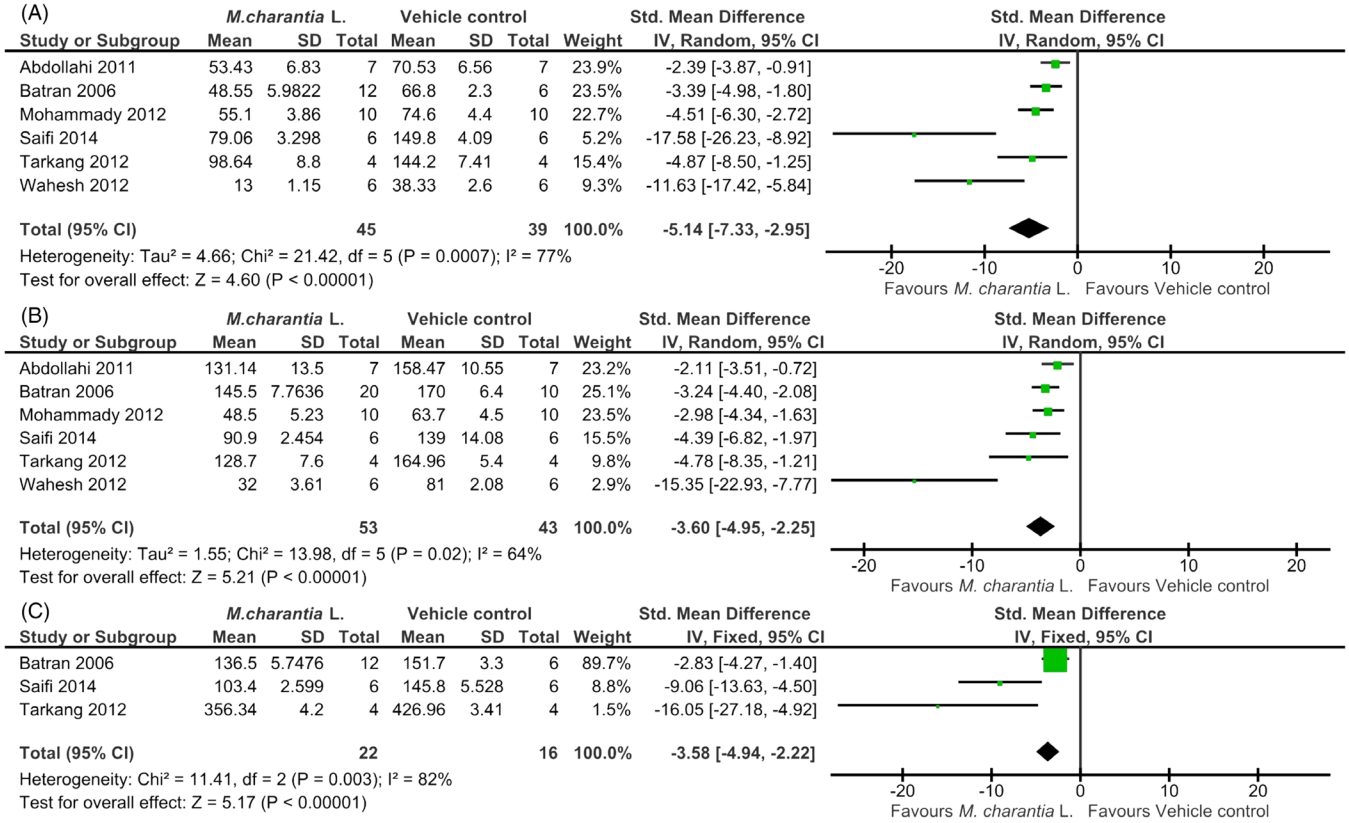

FIGURE 7 Forest plot of preclinical studies comparing *M. charantia* L. and vehicle control; measuring (A) ALT, (B) AST, (C) ALP [Colour figure can be viewed at wileyonlinelibrary.com]

the TGs changed to −1.95 SMD, (95% CI; −8.67, 4.76), while the magnitude of the effect size of TC reduced to −2.22 SMD (95% CI; −2.68, −1.77) from the original analysis, and that of serum insulin increased to 4.58 SMD (95% CI; 0.65, 8.50). The Supplementary Figure S6 illustrates the effect of adjustment by trim and fill analysis.

4 | DISCUSSION

4.1 | Summary of the main findings

This systematic review and meta-analysis is to the best of our knowledge the first to provide quantitative estimates of the effect of *M. charantia* L. on essential attributes of type 2 diabetes mellitus in experimental studies. The cumulative evidence concludes that the administration of *M. charantia* L. to animal models of T2DM can reduce fasting plasma glucose levels. We grade the quality of evidence as moderate because of the very serious risk of bias of included studies, strong evidence of publication bias, and unexplained heterogeneity. The suspected publication bias in our meta-analysis could have impacted on the overall effect of *M. charantia* L. on FPG. About 19 studies deemed missing and adjusted estimate reduced FPG level to non-significant, suggesting that our findings may be inflating *M. charantia* L. efficacy. However, we should consider this interpretation with caution because the authors assessed publication bias only by considering the asymmetric nature of the funnel plot. It should be pointed out that publication bias is not the only explanation for funnel plot asymmetry. Previous studies have established several other factors that could lead to asymmetric funnel plot such as true heterogeneity, poor methodological quality, artefactual, and chance (Egger et al., 1997). With these factors become ubiquitous in preclinical studies, as reported in other assessments (Gupta, 2019; Kilkenny et al., 2009; Pound, Ebrahim, Sandercock, Bracken, & Roberts, 2004), it could be safe to assume their influence on funnel plot asymmetry observed. The finding that publication bias overstated effect size is in line with other systematic review studies (Macleod, O'Collins, Howells, & Donnan, 2004; Sena, Bart van der Worp, Bath, Howells, & Macleod, 2010).

The results of meta-analysis confirmed that administering *M. charantia* L. extracts for at least 3 months could increase serum insulin level, HDL-c, and body weight while significantly reduced HbA1c, triglycerides, total cholesterol, LDL-c, ALT, AST, ALP, urea, and creatinine. The plausible explanation for the increase in serum insulin level could be that *M. charantia* L. works by enhancing insulin release from the partially destroyed beta-cells in the pancreases or increase beta-cell mass or both. The results of the qualitative synthesis supported this argument. Seven studies reported that *M. charantia* L. increases the number of β-cells in the pancreas thereby improving the capability to produce insulin (Abdollahi et al., 2011; Ahmed et al., 1998; Ayoub et al., 2013) and partially restore the healthy cellular population and enlarged size of islets with hyperplasia

(Almarzooq, 2009; Aswar & Kuchekar, 2012; Ayoub et al., 2013; Hafizur et al., 2011; Hossain et al., 2014). The observed decrease in triglycerides, total cholesterol, LDL-c and increase in HDL-c underscore the potential of *M. charantia* L. in controlling type 2 diabetes mellitus and its associated pathologies. The review results further confirm the hepato-renal protective effect of *M. charantia* L. that could partly explain the long history of its use as a nutritional food and herbal medicines for various ailments in local communities in Africa, Asia, and South America (Beloin et al., 2005; Choudhury et al., 2017).

4.2 | Quality of the evidence

Study methodological quality is a critical factor that threatens the validity of preclinical studies. According to the CAMARADES quality score, all studies included in our meta-analysis are of poor methodological quality with an average score of 3. Besides, the SYRCLEs risk of bias tool assessed all studies as having a high risk of bias in the domains of random sequence generation, allocation concealment, random housing, blinding investigators/caregivers, random outcome assessment, and blinding outcome assessment. High risk of bias in these domains means that the studies have poor internal validity. It is now clear that these aspects of experimental design can have a substantial impact on the reported outcome of experiments (Henderson, Kimmelman, Fergusson, Grimshaw, & Hackam, 2013).

Our review found that two studies out of 66 assessed, did not report the number of animals used. While the studies that reported, have no description of the method used to calculate the sample size. Similar findings were reported in another review of animal studies in India (Gupta, 2019). Reporting animal numbers is essential so that the biological and statistical significance of the experimental results can be assessed or the data reanalyzed and is also necessary if the experimental methods are to be repeated (Kilkenny, Browne, Cuthill, Emerson, & Altman, 2013). Appropriate sample size calculation ensures a study designed with sufficient power to detect the true effect of the intervention. Thus, failure to use an adequate sample size can potentially have an impact on science, ethics, and the economy.

The meta-analysis reported higher heterogeneity because included studies used different methodological design features such as; different induction materials for T2DM, different doses of interventions, duration of administration, different types of extracts, different outcome measurement scales, and the small sample size. Of particular concerns is the high dose of STZ and alloxan used to induce T2DM. Although these induction materials are widely used to induce experimental T2DM, alloxan can cause kidney toxicity due to its very narrow effective dose and a higher dose of STZ could completely knock off beta-cells and potentially induce type 1 diabetes mellitus (Gheibi, Kash, & Ghasemi, 2017). The previous study indicated that a single dose of 45 mg/kg STZ leads to hyperglycemia and a higher mortality rate than multiple doses of 30 mg/kg (Zhang, Lv, Li, Xu, & Chen, 2009). Inspired by a growing understanding of disease pathophysiology, researchers have now revealed that a combination of high-fat diet and low dose STZ produce a model of T2DM that closely mimic a natural history of human with T2DM (Reed et al., 2000; Vatandoust et al., 2018). Our findings suggest that the concern about a different model of inducing T2DM varying similarity to humans with the condition is warranted. These design features could potentially be sources of heterogeneity, and by extension, influence constructs validity of the study.

The meta-analysis included studies from at least 20 different countries, meaning that *M. charantia* L. can have varying constituents according to the region of origin, harvesting season, mode of cultivation, or different climatic conditions; thus, could have different therapeutic effects. This geographical variation could mean that standardization of dose based on chemical markers is essential; however, only one study described such a standardization approach. We reported about 86% of the included studies used scientific names incorrectly. Kim and his colleagues reported a similarly high percentage (78.6%) in their systematic review (Kim, Lee, Lee, & Shin, 2014). The incorrect use of names could be the result of insufficient knowledge of taxonomy or negligence in the part of researchers. The erroneous identification is a severe problem that may diminish the utility of research results. Such inappropriate uses of plant names within the literature are a permanent source of confusion for future research, search engines, and databases (Rivera et al., 2014).

The clinical translation of *M. charantia* L and other herbal products from the disciplines of natural product development has been slow and inefficient. The inefficiencies could be partly due to suboptimal research practices that propagate biases that hamper clinical translatability. The biases due to small studies effect, methodological flaws, use of inappropriate animal models of the human condition, use of unstandardized intervention, inappropriate use of statistics, and poor or selective reporting need immediate attention. Together, this systematic review and meta-analysis suggests that previous clinical trials of *M. charantia* L. could have been conducted based on inadequate evidence of efficacy from preclinical studies, and partly this could explain conflicting clinical trial results observed in the meta-analysis (Ooi, Yassin, & Hamid, 2012; Peter et al., 2018).

4.3 | Strength of the study

This is the first and timely systematic review and meta-analysis of *M. charantia* L. using animal studies. We provided a more in-depth insight into the current state and level of available preclinical evidence. We also provided evidence of major methodological, taxonomical flaws, and risk of bias that could potentially threat validity and clinical generalizability of preclinical studies of *M. charantia* L.

5 | CONCLUSION

Momordica charantia L. reduced elevated fasting plasma glucose levels in animal models of type 2 diabetes mellitus. It also significantly reduced glycosylated hemoglobin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphate, urea, serum creatinine, and

several lipid profile parameters. This conclusion must be interpreted in light of strongly suspected publication bias, high risk of bias, and poor methodological quality of primary studies. To enhance clinical generalizability, future researches should focus on standardizing doses of *M. charantia* L. with known chemical markers, provide adequate quality control data, conduct preclinical studies that are designed with random allocation, blinding of investigators and assessors, and power calculation of sample size.

ACKNOWLEDGEMENTS

This work is part of a Ph.D. thesis of ELP. World Bank supports the Ph.D. training through the PHARMBIOTRAC-ACE II fellowship administered at Mbarara University of science and technology. The authors wish to thank the fellowship programme leadership for training support.

CONFLICT OF INTEREST

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

AUTHORS' CONTRIBUTIONS

Conceptualization ELP; Data curation and Formal analysis ELP, AK; Methodology ELP, AK, CDS; Project administration ELP; Supervision CDS, PBN, PEO; validation AK; Writing original draft ELP; Review the drafts for important intellectual content CDS, PBN, AK, PEO. All authors approved the final manuscript.

ORCID

Emanuel L. Peter https://orcid.org/0000-0002-8162-4784

REFERENCES

Abas, R., Othman, F., & Thent, Z. C. (2014). Protective effect of *Momordica charantia* fruit extract on hyperglycaemia-induced cardiac fibrosis. *Oxidative Medicine and Cellular Longevity*, *2014*(429060), 1–8.

Abdollahi, M., Zuki, A. B. Z., Goh, Y. M., Rezaeizadeh, A., & Noordin, M. M. (2010). The effects of *Momordica charantia* on the liver in streptozotocin-induced diabetes in neonatal rats. *African Journal of Biotechnology*, *9*(31), 5004–5012.

Abdollahi, M., Zuki, A. B. Z., Goh, Y. M., Rezaeizadeh, A., & Noordin, M. M. (2011). Effects of *Momordica charantia* on pancreatic histopathological changes associated with streptozotocin-induced diabetes in neonatal rats. *Histology and Histopathology*, *26*(1), 13–21.

Ahmed, I., Adeghate, E., Cummings, E., Sharma, A. K., & Singh, J. (2004). Beneficial effects and mechanism of action of *Momordica charantia* juice in the treatment of streptozotocin-induced diabetes mellitus in rat. *Molecular and Cellular Biochemistry*, *261*(1), 63–70.

Ahmed, I., Adeghate, E., Sharma, A. K., Pallot, D. J., & Singh, J. (1998). Effects of *Momordica charantia* fruit juice on islet morphology in the pancreas of the streptozotocin-diabetic rat. *Diabetes Research and Clinical Practice*, *40*(3), 145–151.

Akhter, R., Rasel, I. H., & Islam, S. M. (2018). Effect of bitter melon and garlic on blood glucose level and blood cholesterol level in rats in diabetic condition. *Research in Agriculture, Livestock and Fisheries*, *5*(3), 359–363.

Almarzooq, M. A. (2009). Hypoglycemic effect of *Momordica charantia* (Karela) on normal and Alloxan diabetic albino mice. *Egyptian Journal of Experimental Biology*, *493*, 487–493.

Aswar, P. B., & Kuchekar, B. S. (2012). Phytochemical, microscopic, antidiabetic, biochemical and histopathological evaluation of *Momordica charantia* fruits. *International Journal of Pharmacy and Pharmaceutical Sciences*, *4*(1), 325–331.

Ayoub, S. M., Rao, S., Byregowda, S. M., Satyanarayana, L., Bhat, N., Shridhar, N. B., & Shridhar, P. B. (2013). Evaluation of hypoglycemic effect of *Momordica charantia* extract in distilled water in Streptozotocin-diabetic rats. *Brazilian Journal of Veterinary Pathology*, *6*(2), 56–64.

Banerjee, S., Sinharoy, K., & Singh, A. K. (2002). Oral hypoglycaemic agent failure. *Journal of the Indian Medical Association*, *100*(7), 452–456.

Beller, E. M., Glasziou, P. P., Altman, D. G., Hopewell, S., Bastian, H., Chalmers, I., … Tovey, D. (2013). PRISMA for abstracts: Reporting systematic reviews in journal and conference abstracts. *PLoS Medicine*, *10*(4), 1–8.

Beloin, N., Gbeassor, M., Akpagana, K., Hudson, J., de Soussa, K., Koumaglo, K., & Arnason, J. T. (2005). Ethnomedicinal uses of Momordicacharantia (Cucurbitaceae) in Togo and relation to its phytochemistry and biological activity. *Journal of Ethnopharmacology*, *96*(1–2), 49–55.

Bhat, G. A., Khan, H. A., Alhomida, A. S., Sharma, P., Singh, R., & Paray, B. A. (2018). GLP-I secretion in healthy and diabetic Wistar rats in response to aqueous extract of *Momordica charantia*. *BMC Complementary and Alternative Medicine*, *18*(1), 162.

Blum, A., Loerz, C., Martin, H., Staab-weijnitz, C. A., & Maser, E. (2012). *Momordica charantia* extract, a herbal remedy for type 2 diabetes, contains a specific 11β-hydroxysteroid dehydrogenase type 1 inhibitor. *Journal of Steroid Biochemistry & Molecular Biology*, *128*, 51–55.

Borenstein, M., Hedges, L. V., Higgins, J. P. T., & Rothstein, H. R. (2010). A basic introduction to fixed-effect and random-effects models for meta-analysis. *Research Synthesis Methods*, *1*(2), 97–111.

Cakici, I., Hurmoglu, C., Tunctan, B., Abacioglu, N., Kanzik, I., & Sener, B. (1994). Hypoglycaemic effect of *Momordica charantia* extracts in normoglycaemic or cyproheptadine-induced hyperglycaemic mice. *Journal of Ethnopharmacology*, *44*, 117–121.

Castellanos-campos, A., Antonio, M., Coronel, G., Treviño, S., Peña-rosas, U., Venegas, B., … Marquez-cabrera, T. (2016). Aqueous extract of *Momordica charantia*, reduces hyperglycemia in Alloxan-induced diabetic Wistar rats. *European Journal of Medicinal Plants*, *17*(3), 1–10.

Chaing, Y.-Y., Hsu, C.-P., Chien, T.-Y., Tsai, C.-H., Kao, Y.-Y., Chao, H.-C., & Huang, H.-Y. (2012). Antidiabetic effects of *Momordica charantia* and *Psidum guajava* extract in type II diabetes rats. *Nutritional Sciences Journal*, *37*(2), 66–74.

Chandra, A., Mahdi, A. A., Singh, R. K., Mahdi, F., & Chander, R. (2008). Effect of Indian herbal hypoglycemic agents on antioxidant capacity and trace elements content in diabetic rats. *Journal of Medicinal Food*, *11*(3), 506–512.

Chandru, S., Vishwanath, P., Devegowda, D., Ramasamudra, S. N., Prashant, A., & Hathur, B. (2016). Evaluation of protein kinase Cβ and PPARγ activity in diabetic rats supplemented with *Momordica charantia*. *Journal of Clinical and Diagnostic Research*, *10*(4), BF01–BF04.

Chaturvedi, P. (2005). Role of *Momordica charantia* in maintaining the normal levels of lipids and glucose in diabetic rats fed a high-fat and low-carbohydrate diet. *British Journal of Biomedical Science*, *62*(3), 124–126.

Chawla, A., Chawla, R., & Jaggi, S. (2016). Microvasular and macrovascular complications in diabetes mellitus: Distinct or continuum? *Indian Journal of Endocrinology and Metabolism*, *20*(4), 546–551.

Choudhury, H., Pandey, M., Hua, C. K., Mu, C. S., Jing, J. K., Kong, L., … Kesharwani, P. (2017). An update on natural compounds in the remedy of diabetes mellitus: A systematic review. *Journal of Traditional and Complementary Medicine*, *8*(3), 361–376.

Chowdhury, A. Z., Hossain, M. I., Hossain, S., Ahmed, S., Afrin, T., & Karim, N. (2012). Antidiabetic effects of *Momordica charantia* (Karela) in male Long Evans rat. *Journal of Advanced Laboratory Research in Biology*, *3*(3), 175–180.

Cukierman, T., Gerstein, H. C., & Williamson, J. D. (2005). Cognitive decline and dementia in diabetes—Systematic overview of prospective observational studies. *Diabetologia*, *48*(12), 2460–2469.

Dalgleish, T., Williams, J. M. G., Golden, A.-M. J., Perkins, N., Barrett, L. F., Barnard, P. J., … Watkins, E. (2007). The CAMARADES 10-item checklist to assess study quality. *Journal of Experimental Psychology: General*, *136*(1), 23–42.

Day, C., Cartwright, T., Provost, J., & Bailey, C. (1990). Hypoglycaemic effect of *Momordica charantia* extracts. *Planta Medica*, *56*, 426–429.

Duval, S., & Tweedie, R. (2000). Trim and fill: A simple funnel-plot-based method. *Biometrics*, *56*(June), 455–463.

Egger, M., Davey Smith, G., Schneider, M., & Minder, C. (1997). Bias in meta-analysis detected by a simple, graphical test. *British Medical Journal (Clinical Research ed.)*, *315*(7109), 629–634.

El Batran, S. A. E. S., El-Gengaihi, S. E., & El Shabrawy, O. A. (2006). Some toxicological studies of *Momordica charantia* L. on albino rats in normal and alloxan diabetic rats. *Journal of Ethnopharmacology*, *108*, 236–242.

Englberger, K. (2009). Invasive weeds of Pohnpei: A guide for identification and public awareness. Available from https://www.cabdirect.org/cabdirect

Fernandes, N. P., Lagishetty, C. V., Panda, V. S., & Naik, S. R. (2007). An experimental evaluation of the antidiabetic and antilipidemic properties of a standardized *Momordica charantia* fruit extract. *BMC Complementary and Alternative Medicine*, *7*(1), 29.

Forbes, J. M., & Cooper, M. E. (2013). Mechanisms of diabetic complications. *Physiological Reviews*, *93*(1), 137–188.

Gheibi, S., Kash, K., & Ghasemi, A. (2017). A practical guide for induction of type-2 diabetes in rat: Incorporating a high-fat diet and streptozotocin. *Biomedicine & Pharmacotherapy*, *95*(24), 605–613.

Grover, J. K., Vats, V., Rathi, S. S., & Dawar, R. (2001). Traditional Indian antidiabetic plants attenuate progression of renal damage in streptozotocin induced diabetic mice. *Journal of Ethnopharmacology*, *76*(3), 233–238.

Gupta, R., Kant, S., Johri, S., & Saxena, A. (2007). Effect of ethanolic extract of *Momordica charantia* on blood sugar level in normal and Streptozotocin induced diabetic rats. *The Journal of Applied Biosciences*, *33*(2), 153–155.

Gupta, S. (2019). A study to assess the methodological quality of in vivo animal experiments published in Indian journal of pharmacology: A retrospective, cross-sectional, observational study. *Indian Journal of Pharmacology*, *51*(1), 11–16.

Hafizur, R. M., Kabir, N., & Chishti, S. (2011). Modulation of pancreatic β-cells in neonatally streptozotocin-induced type 2 diabetic rats by the ethanolic extract of *Momordica charantia* fruit pulp. *Natural Product Research*, *25*(4), 353–367.

Han, C., Hui, Q., & Wang, Y. (2008). Hypoglycemic activity of saponin fraction extracted from *Momordica charantia* in PEG/salt aqueous two-phase systems. *Natural Product Research*, *22*(13), 1112–1119.

Henderson, V. C., Kimmelman, J., Fergusson, D., Grimshaw, J. M., & Hackam, D. G. (2013). Threats to validity in the design and conduct of preclinical efficacy studies: A systematic review of guidelines for in vivo animal experiments. *PLoS Medicine*, *10*(7), e1001489.

Higgins, J. P. T., & Thompson, S. G. (2002). Quantifying heterogeneity in a meta-analysis. *Statistics in Medicine*, *21*(11), 1539–1558.

Hooijmans, C. R., Rovers, M. M., De Vries, R. B. M., Leenaars, M., Ritskes-hoitinga, M., & Langendam, M. W. (2014). SYRCLE's risk of bias tool for animal studies. *BMC Medical Research Methodology*, *14*(1), 1–9.

Hooijmans, C. R., Tillema, A., Leenaars, M., & Ritskes-Hoitinga, M. (2010). Enhancing search efficiency by means of a search filter for finding all studies on animal experimentation in PubMed. *Laboratory Animals*, *44*(3), 170–175.

Hossain, M., Asadujjaman, M., Khan, M., Ahmed, M., & Islam, A. (2011). Antidiabetic and glycogenesis effects of different fractions of methanolic extract of *Momordica charantia* (Linn.) in alloxan induced diabetic rats. *International Journal of Pharmaceutical Sciences and Research*, *2*(2), 404–412.

Hossain, M. A., Mostofa, M., Awal, A. M., Chowdhury, E. H., & Sikder, M. H. (2014). Histomorphological and morphometric studies of the pancreatic islet cells of diabetic rats treated with aqueous extracts of *Momordica charantia* (Karela) fruits. *Asian Pacific Journal of Tropical Disease*, *4*(Suppl 2), s698–s704.

Ibrahem, A. M., & Al-Abassi, N. N. (2010). Study antidiabetic effect of *Momordica charantia* (bitter gourd) seeds on Alloxan induced diabetic rats. *Iraqi Journal of Veterinary Medicine*, *34*(1), 165–170.

Jafri, S., Ismail, M., & Zaman, G. (2015). Effect of *Momordica charantia* (Karela) in alloxan induced diabetic rats. *Pakistan Journal of Science*, *61*(4), 220–222.

Karunanayake, E. H., Jeevathayaparan, S., & Tennekoon, K. H. (1990). Effect of *Momordica charantia* fruit juice on Streptozotocin-induced diabetes in rats. *Journal of Ethnopharmacology*, *30*, 199–204.

Kilkenny, C., Browne, W. J., Cuthill, I. C., Emerson, M., & Altman, D. G. (2013). Improving bioscience research reporting: The arrive guidelines for reporting animal research. *Animals*, *4*(1), 35–44.

Kilkenny, C., Parsons, N., Kadyszewski, E., Festing, M. F. W., Cuthill, I. C., Fry, D., … Altman, D. G. (2009). Survey of the quality of experimental design, statistical analysis and reporting of research using animals. *PLoS One*, *4*(11), e7824.

Kim, J. H., Lee, S., Lee, M. Y., & Shin, H. K. (2014). Therapeutic effect of Soshiho-tang, a traditional herbal formula, on liver fibrosis or cirrhosis in animal models: A systematic review and meta-analysis. *Journal of Ethnopharmacology*, *154*(1), 1–16.

Kolawole, O., Abiona, F., Kolawole, S., Ayankunle, A., & Olaniran, O. (2011). Effect of *Momordica charantia* fruit extract on normal and alloxan-diabetic rats. *International Journal of Pharmacology*, *7*(4), 532–535.

Kumar, A., Sharma, B., Ali, M., Kumar, R., Nath, A., & Jk, S. (2013). *Momordica charantia* protects the liver from hyperglycemia induced toxicity during diabetes in Swiss albino mice. *Open Access Scientific Reports*, *2*(1), 2–4.

Lal, V. K., Gupta, P. P., Poonam, T., & Awanish, P. (2011). Interation of *Momordica charantia* fruit juice with Glibenclamide in Streptozotocin induced diabetic rats. *Pharmacology*, *3*, 853–857.

Leeflang, M. M., Inthout, J., Wever, K. E., Hooft, L., Beer, H. De, Kuijpers, T., … on behalf of the GRADE Working Group (2018). Facilitating healthcare decisions by assessing the certainty in the evidence from preclinical animal studies. *PLoS ONE 13*(1), 1–18. https://doi.org/10.1371/journal.pone.0187271

Ma, C., Yu, H., Xiao, Y., & Wang, H. (2017). *Momordica charantia* extracts ameliorate insulin resistance by regulating the expression of SOCS-3 and JNK in type 2 diabetes mellitus rats. *Pharmaceutical Biology*, *55*(1), 2170–2177.

Macleod, M. R., O'Collins, T., Howells, D. W., & Donnan, G. A. (2004). Pooling of animal experimental data reveals influence of study design and publication bias. *Stroke*, *35*(5), 1203–1208.

Mahdi, A. A., Chandra, A., Singh, R. K., Shukla, S., Mishra, L., & Ahmad, S. (2003). Effect of herbal hypoglycemic agents on oxidative stress and antioxidant status in diabetic rats. *Indian Journal of Clinical Biochemistry*, *18*(2), 8–15.

Mahmoud, M. F., El Ashry, F. E. Z. Z., El Maraghy, N. N., & Fahmy, A. (2017a). Studies on the antidiabetic activities of *Momordica charantia* fruit juice in streptozotocin-induced diabetic rats. *Pharmaceutical Biology*, *55*(1), 758–765.

Matheka, D. M., Alkizim, F. O., Kiama, T. N., & Bukachi, F. (2012). Glucose-lowering effects of *Momordica charantia* (Karela) extract in diabetic rats. *The African Journal of Pharmacology and Therapeutics*, *1*(2), 62–66.

Miura, T., Itoh, C., Iwamoto, N., Kato, M., Kawai, M., Park, S. R., & Suzuki, I. (2001). Hypoglycemic activity of the fruit of the *Momordica charantia* in type 2 diabetic mice. *Journal of Nutritional Science and Vitaminology*, *47*, 340–344.

Mohammady, I., Elattar, S., Mohammed, S., & Ewais, M. (2012). An evaluation of anti-diabetic and anti-Lipidemic properties of *Momordica charantia* (bitter melon) fruit extract in experimentally induced diabetes. *Life Science Journal*, *9*(2), 363–374.

Moher, D., Liberati, A., Tetzlaff, J., Altman, D. G., & PRISMA Group. (2009). Preferred reporting items for systematic reviews and meta-analyses:

The PRISMA statement. *British Medical Journal (Clinical Research ed.)*, *339*(17), b2535.

Mushtaq, W., Tariq, M., Ishtiaq, M., Asghar, R., Hussain, T., & Bashir, T. (2016). Role of *Momordica charantia* L. as herbal medicine to cure hyperglycemia in vitro on induced diabetic model animals. *Pakistan Journal of Botany*, *48*(4), 1651–1656.

Nagy, M. A., Bastawy, M. A., & Abdel-Hamid, N. M. (2012). Effects of *Momordica charantia* on Streptozotocin-induced diabetes in rats: Role of insulin oxidative stress and nitric oxide. *Journal of Health Science*, *2*(2), 8–13.

Nivitabishekam, N. S., Asad, M., & Prasad, V. S. (2009). Chemico-biological interactions Pharmacodynamic interaction of *Momordica charantia* with rosiglitazone in rats. *Chemico-Biological Interactions*, *177*, 247–253.

Nkambo, W., Anyama, N. G., & Onegi, B. (2013). In vivo hypoglycemic effect of methanolic fruit extract of *Momordica charantia* L. *African Health Sciences*, *13*(4), 933–939.

Nouwen, A., Nefs, G., Caramlau, I., Connock, M., Winkley, K., Lloyd, C. E., … European Depression in Diabetes Research Consortium. (2011). Prevalence of depression in individuals with impaired glucose metabolism or undiagnosed diabetes: A systematic review and meta-analysis of the European depression in diabetes (EDID) research consortium. *Diabetes Care*, *34*(3), 752–762.

Olokoba, A. B., Obateru, O. A., & Olokoba, L. B. (2012). Type 2 diabetes mellitus: A review of current trends. *Oman Medical Journal*, *27*(4), 269–273.

Ooi, C. P., Yassin, Z., & Hamid, T.-A. (2012). *Momordica charantia* for type 2 diabetes mellitus. *Cochrane Database of Systematic Reviews*, *8*, 1–43.

Parmar, K., Patel, S., Patel, J., Patel, B., & Patel, M. B. (2011). Effects of bittergourd (*Momordica charantia*) fruit juice on glucose tolerance and lipid profile in type-II diabetic rats. *The International Journal of Drug Development and Research*, *3*(2), 139–146.

Peter, E. L., Kasali, F. M., Deyno, S., Mtewa, A., Nagendrappa, P. B., Tolo, C. U., … Sesaazi, D. (2018). *Momordica charantia* L. lowers elevated glycaemia in type 2 diabetes mellitus patients: Systematic review and meta-analysis. *Journal of Ethnopharmacology*, *231*(October 2018), 311–324.

Peter, E. L., Mtewa, A. G., Nagendrappa, P. B., Kaligirwa, A., & Sesaazi, C. D. (2020). Systematic review and meta-analysis protocol for efficacy and safety of *Momordica charantia* L. on animal models of type 2 diabetes mellitus. *Systematic Reviews*, *9*(7), 1–9.

Phimarn, W., Sungthong, B., Saramunee, K., & Caichompoo, W. (2018). Efficacy of *Momordica charantia* L. on blood glucose, blood lipid, and body weight: A meta-analysis of randomized controlled trials. *Pharmacognosy Magazine*, *14*(56), 351.

Platel, K., & Srinivasan, K. (1995). Effect of dietary intake of freeze dried bitter gourd (*Momovdica chavantia*) in streptozotocin induced diabetic rats. *Die Nahrung*, *39*(4), 262–268.

Pound, P., Ebrahim, S., Sandercock, P., Bracken, M. B., & Roberts, I. (2004). Where is the evidence that animal research benefits humans? *British Medical Journal*, *328*(7438), 514–517.

Rathi, S. S., Grover, J. K., Vikrant, V., & Biswas, N. R. (2002). Prevention of experimental diabetic cataract by Indian Ayurvedic plant extracts. *Phytotherapy Research*, *16*(8), 774–777.

Reed, M. J., Meszaros, K., Entes, L. J., Claypool, M. D., Pinkett, J. G., Gadbois, T. M., & Reaven, G. M. (2000). A new rat model of type 2 diabetes: The fat-fed, streptozotocin-treated rat. *Metabolism: Clinical and Experimental*, *49*(11), 1390–1394.

Reyes, B. A. S., Bautista, N. D., Tanquilut, N. C., Anunciado, R. V., Leung, A. B., Sanchez, G. C., … Maeda, K.-I. (2006). Anti-diabetic potentials of *Momordica charantia* and *Andrographis paniculata* and their effects on estrous cyclicity of alloxan-induced diabetic rats. *Journal of Ethnopharmacology*, *105*(1–2), 196–200.

Rezaeizadeh, A., Zakaria, Z. B. A. B., Abdollahi, M., Meng, G. Y., Mustapha, N. M., Hamid, M. B., & Ibrahim, T. A. B. T. (2011). Antioxidant and antihyperglycaemic effects of an aqueous extract from *Momordica charantia* fruit in a type II diabetic rat model. *Journal of Medicinal Plant Research: Planta Medica*, *5*(14), 2990–3001.

Rivera, D., Allkin, R., Obon, C., Alcaraz, F., Verpoorte, R., & Heinrich, M. (2014). What is in a name? The need for accurate scientific nomenclature for plants. *Journal of Ethnopharmacology*, *152*, 393–402.

Roffey, B. W. C., Atwal, A. S., Johns, T., & Kubow, S. (2007). Water extracts from *Momordica charantia* increase glucose uptake and adiponectin secretion in 3T3-L1 adipose cells. *Journal of Ethnopharmacology*, *112*(1), 77–84.

Rohajatien, U., Harijono, T.-E., & Sri Wahyuni, E. (2018). Bitter melon (*Momordica charantia* L.) fruit decreased blood glucose level and improved lipid profile of streptozotocin induced hyperglycemia rats. *Current Research in Nutrition and Food Science*, *6*(2), 359–370.

Saha, S. K., Haque, M. E., Islam, D., Rahman, M. M., Islam, M. R., Parvin, A., & Rahman, S. (2012). Comparative study between the effect of *Momordica charantia* (wild and hybrid variety) on hypoglycemic and hypolipidemic activity of alloxan induced type 2 diabetic Long-Evans rats. *Journal of Diabetes Mellitus*, *02*(01), 131–137.

Saifi, A., Namdeo, K. P., Chauhan, R., & Dwivedi, J. (2014). Evaluation of pharmacognostical, phytochemical and antidiabetic activity fruits of *Momordica charantia* Linn. *Asian Journal of Pharmaceutical and Clinical Research*, *7*(3), 152–156.

Salimifar, M., Fatehi-Hassanabad, Z., & Fatehi, M. (2013). A review on natural products for controlling type 2 diabetes with an emphasis on their mechanisms of actions. *Current Diabetes Reviews*, *9*(5), 402–411.

Sani, F., Atiku, M., & Imam, A. (2015). Effect of oral administration of aqueous leaf extract of *Momordica charantia* (bitter melon) on serum glucose, and lipid profile in Alloxan-induced diabetic rats. *Bayero Journal of Pure and Applied Sciences*, *8*(2), 170–174.

Sathishsekar, D., & Subramanian, S. (2005). Beneficial effects of *Momordica charantia* seeds in the treatment of STZ-induced diabetes in experimental rats. *Biological & Pharmaceutical Bulletin*, *28*(6), 978–983.

Sena, E. S., Bart van der Worp, H., Bath, P. M. W., Howells, D. W., & Macleod, M. R. (2010). Publication bias in reports of animal stroke studies leads to major overstatement of efficacy. *PLoS Biology*, *8*(3), e1000344.

Sena, E. S., Currie, G. L., McCann, S. K., Macleod, M. R., & Howells, D. W. (2014). Systematic reviews and meta-analysis of preclinical studies: Why perform them and how to appraise them critically. *Journal of Cerebral Blood Flow and Metabolism*, *34*(5), 737–742.

Sharma, B., Siddiqui, M. S., Ram, G., Yadav, R. K., Kumari, A., Sharma, G., & Jasuja, N. D. (2014). Rejuvenating of kidney tissues on Alloxan induced diabetic mice under the effect of *Momordica charantia*. *Advances in Pharmaceutics*, *439158*, 1–9.

Shibib, B. A., Khan, L. A., & Rahman, R. (1993). Hypoglycaemic activity of Coccinia indica and *Momordica charantia* in diabetic rats: Depression of the hepatic gluconeogenic enzymes glucose-6-phosphatase and fructose-1,6-bisphosphatase and elevation of both liver and red-cell shunt enzyme glucose-6-phosphate dehydrogenase. *Biochemical Journal*, *292*(1), 267–270.

Shih, C.-C., Lin, C.-H., & Lin, W.-L. (2008). Effects of *Momordica charantia* on insulin resistance and visceral obesity in mice on high-fat diet. *Diabetes Research and Clinical Practice*, *81*(2), 134–143.

Singh, N., & Gupta, M. (2007). Regeneration of β cells in islets of langerhans of pancreas of alloxan diabetic rats by acetone extract of *Momordica charantia* (Linn.) (bitter gourd) fruits. *Indian Journal of Experimental Biology*, *45*(12), 1055–1062.

Singh, N., Gupta, M., Sirohi, P., & Varsha. (2008). Effects of alcoholic extract of *Momordica charantia* (Linn.) whole fruit powder on the pancreatic islets of alloxan diabetic albino rats. *Journal of Environmental Biology*, *29*(1), 101–106.

Sitasawad, S. L., Shewade, Y., & Bhonde, R. (2000). Role of bittergourd fruit juice in stz-induced diabetic state in vivo and in vitro. *Journal of Ethnopharmacology*, *73*(1–2), 71–79.

Srivastava, Y., Venkatakrishna-Bhatt, H., & Verma, Y. (1988). Effect of *Momordica charantia* Linn. Pomous aqueous extract on cataractogenesis in murrin alloxan diabetics. *Pharmacological Research Communications*, *20* (3), 201–209.

Srivastava, Y., Venkatakrisna-Bhatt, H., Verma, Y., Venkaiah, K., & Raval, B. (1993). Antidiabetic and Adaptogenic properties of *Momordica charantia* extract: An experimental and clinical evaluation. *Phytotherapy Research*, *7*, 285–289.

Sterne, J. A. C., Sutton, A. J., Ioannidis, J. P. A., Terrin, N., Jones, D. R., & Lau, J. (2011). Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised. *British Medical Journal*, *342*(d4002), 1–8.

Tahira, S., & Hussain, F. (2014). Antidiabetic evaluation of *Momordica charantia* L. fruit extracts. *The West Indian Medical Journal*, *63*(4), 294–299.

Tarkang, P. A., & Ofogba, C. J. (2012). Evaluation of the hypoglycemic activity and safety of *Momordica charantia* (Cucurbitaceae). *African Journal of Pharmaceutical Sciences and Pharmacy*, *3*(1), 17–29.

Tripathi, U. N., & Chandra, D. (2010). Anti-hyperglycemic and anti-oxidative effect of aqueous extract of *Momordica charantia* pulp and *Trigonella foenum graecum* seed in alloxan-induced diabetic rats. *Indian Journal of Biochemistry*, *47*, 227–233.

USDA. (2017). *Agricultural research service*. USDA Agricultural Research Service: National Plant Germplasm System. Retrieved from https://data.nal.usda.gov/dataset/national-plant-germplasm-system.

Vangoori, Y., Mishra, S., Ambudas, B., Ramesh, P., Meghavani, G., Deepika, K., & Prathibha, A. (2013). Anti-diabetic effect of *Momordica charantia* (bitter melone) on alloxan induced diabetic rabbits. *International Journal of Medical Research & Health Sciences*, *2*(2), 137–142.

Vatandoust, N., Rami, F., Salehi, A. R., Khosravi, S., Dashti, G., Eslami, G., … Salehi, R. (2018). Novel high-fat diet formulation and Streptozotocin treatment for induction of prediabetes and type 2 diabetes in rats. *Advanced Biomedical Research*, *7*(107), 1–5.

Wang, H.-Y., Kan, W.-C., Cheng, T.-J., Yu, S.-H., Chang, L.-H., & Chuu, J.-J. (2014). Differential anti-diabetic effects and mechanism of action of charantin-rich extract of Taiwanese *Momordica charantia* between type 1 and type 2 diabetic mice. *Food and Chemical Toxicology*, *69*, 347–356.

Wehash, F. E., Abpo-Chanema, I. I., & Saleh, R. M. (2012). Some physiological effects of *Momordica charantia* and *Trigonella foenum-graecum* extracts in diabetic rats as compare with cidophage®. *International Scholarly and Scientific Research & Innovation*, *6*(4), 1206–1214.

Wei, D., Tang, K., Wang, Q., Estill, J., Yao, L., & Wang, X. (2016). The use of GRADE approach in systematic reviews. *Journal of Evidence-Based Medicine*, *9*, 98–104.

Yousaf, S., Hussain, A., Rehman, S., Aslam, M. S., & Abbas, Z. (2016). Hypoglycemic and hypolipidemic effects of lactobacillus fermentum, fruit extracts of Syzygium cumini and *Momordica charantia* on diabetes induced mice. *Pakistan Journal of Pharmaceutical Sciences*, *29*(5), 1535–1540.

Yue, J., Xu, J., Cao, J., Zhang, X., & Zhao, Y. (2017). Cucurbitane triterpenoids from *Momordica charantia* L. and their inhibitory activity against α-glucosidase, α-amylase and protein tyrosine phosphatase 1B (PTP1B). *Journal of Functional Foods*, *37*, 624–631.

Zhang, M., Lv, X.-Y., Li, J., Xu, Z.-G., & Chen, L. (2009). The characterization of high-fat diet and multiple low-dose Streptozotocin induced type 2 diabetes rat model. *Experimental Diabetes Research*, *2008*, 1–9.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Peter EL, Nagendrappa PB, Kaligirwa A, Ogwang PE, Sesaazi CD. The safety and efficacy of *Momordica charantia* L. in animal models of type 2 diabetes mellitus: A systematic review and meta-analysis. *Phytotherapy Research*. 2020;1–20. https://doi.org/10.1002/ptr.6853