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Emanuel L. Peter, Félicien Mushagalusa Kasali, Serawit Deyno, Andrew Mtewa, Prakash B. Nagendrappa, Casim Umba Tolo, Patrick Engeu Ogwang, Duncan Sesaazi



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***Momordica charantia* L. lowers elevated glycaemia in Type 2 Diabetes Mellitus**

Patients: Systematic review and Meta-analysis

Emanuel L. Peter,^{a,1*} Félicien Mushagalusa Kasali,^{a,2} Serawit Deyno,^{a,3} Andrew Mtewa,^{a,4}
Prakash B. Nagendrappa,^b Casim Umba Tolo,^a Patrick Engeu Ogwang,^a , Duncan Sesaaizi^{a,c}

^aPharm-BioTechnology and Traditional Medicine Center (PHARMBIOTRAC), World Bank-Africa Center of Excellence (ACE II), Mbarara University of Science and Technology, Uganda

^bSchool of Integrative Health Sciences, Trans-disciplinary University, 74/2, Jarakabande Kaval, Post Attur Via Yelahanka Bengaluru – 560 064 India

^cDepartment of Pharmaceutical Sciences, Faculty of Medicine, Mbarara University of Science and Technology, Uganda

Permanent address

¹Department of Innovation, Technology Transfer & Commercialization, National Institute for Medical Research, Barack Obama drive, P.O. Box 9653, 2448, Dar Es Salaam, Tanzania

²Department of Pharmacy, Faculty of Medicine and Pharmacy, Official University of Bukavu, PO. Box 570 Bukavu, Republic Democratic of Congo

³Department of Pharmacology, School of Medicine, College of Medicine and Health Sciences, Hawassa University, P. O. Box 1560 Hawassa, Ethiopia

⁴Chemistry Section, Department of Applied Sciences, Malawi Institute of Technology, Malawi University of Science & Technology, P. O. Box 5196, Limbe

epeter@std.must.ac.ug/epeterlyimo@gmail.com

FMK: felicienkasali@gmail.com

fmushagalusa@std.must.ac.ug

SD: dserawit@std.must.ac.ug

dserawit@gmail.com

AM: amtewa@must.ac.mw

andrewmtewa@yahoo.com

PBN: bn.prakash@tdu.edu.in

CUT: tolocas@must.ac.ug

PEO: pogwang@must.ac.ug

DS: dsesaazi@must.ac.ug

***Corresponding Author** Pharm-BioTechnology and Traditional Medicine Center (PHARMBIOTRAC). World Bank-Africa Center of Excellence (ACE II), Mbarara University of Science and Technology, P.O. Box 1410 Mbarara, Uganda Phone number: +255 764932508

Abstract

Ethnopharmacological relevance

Momordica charantia Linn (Cucurbitaceae) has been extensively used traditionally as food and herbal medicine for type 2 diabetes mellitus in Asia, Brazil, and East Africa. *Invitro* and *invivo* studies suggest its glycemic control potential; however, clinical studies produced conflicting results.

Aim of the study

To evaluate the efficacy of *M. charantia* preparations in lowering elevated plasma glucose level in prediabetes and type 2 diabetes mellitus patients.

Methods

Electronic search of the Cochrane library, PubMed®, CINAHL, and SCOPUS databases was done from 1st January 1970 to 30th April 2018 without language restriction. Two independent reviewers extracted data and assessed risk of bias of articles. Revman var. 5.3 software was used for data synthesis in meta-analysis. Heterogeneity was assessed using Chi-square and I^2 tests. Treatment effect was estimated using mean difference in outcome measures between *M. charantia* preparations and placebo or oral hypoglycemic agents control group. The protocol of this study has a registration number PROSPERO CRD42018083653.

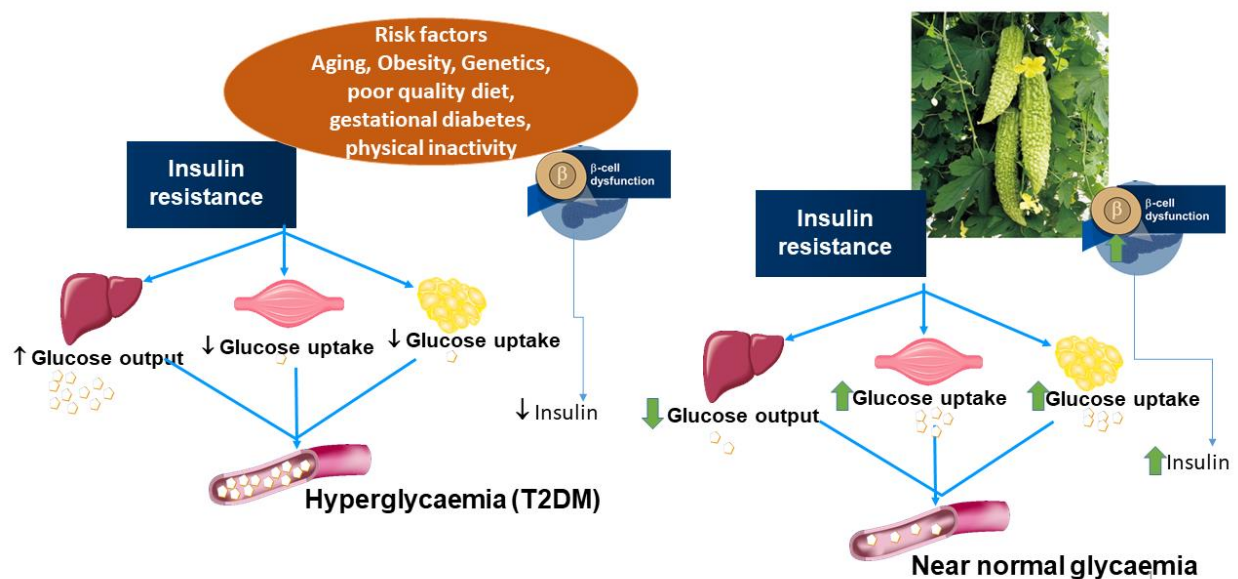
Results

Ten studies of type 2 diabetes mellitus (n = 1,045) were included in the meta-analysis. They had 4 to 16 weeks follow up and overall moderate to high risk of bias. Compared to placebo, *M. charantia* monoherbal formulation significantly reduces FPG, PPG and HBA_{1c} with mean difference of **-0.72** mmol/L, (95% CI: -1.33, -0.12), $I^2 = 14\%$, **-1.43** mmol/L, (95% CI: -2.18, -0.67), $I^2 = 0$, **-0.26** %, (95% CI: -0.49, -0.03), $I^2 = 0$ respectively. *M. charantia* also lowered FPG in prediabetes (mean difference -0.31 mmol/L, n= 52); the evidence was downgraded to low quality because the study had unclear risk of bias and inadequate sample size. No serious adverse effects were reported.

Conclusion

M. charantia adjunct preparations improved glycemic control in T2DM patients. However, this conclusion based on low to very low quality evidences for the primary outcomes and sparse data for several safety outcomes, thus, warrant further research. Particularly needed are the researches that focus on standardizing *M. charantia* formulation and determine its efficacy and safety in clinical trials with adequate sample size, designed with random sequence generation, allocation concealment of intervention and blinding of both research personnel and participants.

Graphical Abstract:



Key words

Bitter gourd, Type 2 Diabetes Mellitus, Efficacy, Safety, Meta-analysis, Prediabetes

1 Introduction

Diabetes mellitus is a group of metabolic disorders characterized by elevated blood glucose level. Type 2 diabetes mellitus (T2DM) is the most common form of diabetes mellitus, accounting for over 90% of all diabetes cases (IDF, 2017; WHO, 2016). It is commonly seen in older adults, but increasingly seen in children, adolescents and younger adults due to rising level of obesity, physical inactivity and poor quality diet.

Diabetes mellitus has been recognized as an important cause of morbidity and permanent disability in adults which overwhelms social and economic welfare of all nations irrespective of their level of economy. The international diabetes federation (IDF)'s diabetes atlas estimates that, about 425 million adults aged 20-79 years were living with diabetes in 2017 globally, and projected to increase to 629 million in 2045 with developing nations disproportionately burdened (IDF, 2017). The increase in diabetes mellitus is predominantly linked to rapid increasing urbanization, population ageing, obesity, ethnicity, family history of diabetes (WHO, 2016), and history of gestation diabetes (Bellamy et al., 2009). Other modifiable factors contributing to the increase include physical inactivity (Whiting et al., 2011), poor quality diet, and prediabetes (Ley et al., 2014).

Treatment of T2DM involves the use of oral hypoglycemic agents (OHAs) singly or combined in order to achieve controlled hyperglycemia (Ghadge and Kuvalekar, 2016; Simo and Hernandez, 2002). The sustained reduction in hyperglycemia reduces the risk of microvascular diseases among T2DM (Gaster and Hirsch, 1998). However, the OHAs are; expensive (Justin-Temu et al., 2009; Smith-Spangler et al., 2012); have adverse effects such as severe hypoglycemia, lactic acidosis, idiosyncratic liver cell injury, permanent neurological deficit, digestive discomfort, headache, dizziness, and even death (Singh et al., 2017; Okayasu et al., 2012); and increasingly

associated with failure rate (Alhadramy, 2016; Banerjee et al., 2002). In light of the above, herb based therapies have become alternative to mainstream western medical treatment because herbs are known to have few adverse effects and readily accessible to majority of patients (Naja et al., 2015; WHO, 2002).

Momordica charantia Linn. (Family; Cucurbitaceae) has been widely used and extensively studied herb for its glycemic control effect in T2DM (Ooi et al., 2012; Yin et al., 2014). It is a tropical and subtropical vine, commonly found in Brazil, Asia, and some parts of east Africa including Tanzania (Garau et al., 2003; Krawinkel and Keding, 2006). Since ancient times, *M. charantia* has been used as a nutritional food and a medicinal herb for T2DM. Although efficacy and safety of *M. charantia* has been studied in randomized and non-randomized controlled clinical trials, results are still contradictory. This uncertain situation continues to put doubt on safety and efficacy of *M. charantia* for treatment of T2DM patients, challenging the recommendation of this alternative therapy for T2DM (Efird et al., 2014). The inconsistent and contradictory findings called for urgent need to review and synthesize data from studies that evaluated *M. charantia* preparation in prediabetes and T2DM. Therefore, this study systematically reviewed and synthesized evidences on the safety and efficacy of *M. charantia* preparations in lowering elevated plasma glucose in prediabetes and T2DM patients. The results of this study provided objective evaluation of clinical efficacy and safety of *M. charantia* for clinical decision making and set up directions for future research with regards to *M. charantia* and T2DM.

2 Methods

2.1 Study design

This is a systematic review based on manual and electronic databases search of literatures. The systematic review and meta-analysis was designed according to the preferred reporting items for systematic reviews and meta-analysis (PRISMA) guidelines (Moher et al., 2009). The study was conducted according to the registered protocol number PROSPERO CRD42018083653 (Peter et al., 2018).

2.2 Search strategy

A three-step search strategy was adopted. Initially PubMed[®], SCOPUS, CINAHL and the cochrane library were searched using the keywords; *Momordica charantia*, bitter gourd, bitter melon, type 2 diabetes, NIDDM, clinical trial, human, adult, prospective studies, combined using boolean logic terms 'AND', 'OR' and 'NOT'. Analysis of the text words contained in the title and abstract, and of the index terms used to describe article was done. A second search using all identified keywords and index terms was undertaken across all included databases. Thirdly, the reference lists of all identified reports and articles after full text screening were searched for additional studies. University digital library systems, Google, Google Scholar, OpenGrey, ProQuest dissertations & Theses and British Library EThos were searched for unpublished studies. Also search was done through <https://www.clinicaltrials.gov> for data from ongoing clinical trials or unpublished trials. Research teams were also contacted for additional data. No language restriction was imposed during identification of studies. Syntax for each database was generated and set for weekly update alert. In PubMed, an NCBI (National Center for Biotechnology Information) account was created and password shared among reviewers. All

identified articles were pooled into Mendeley software, later citations were imported into Covidence an online systematic review platform accessible via <https://www.covidence.org>. The Covidence online software handled duplicates, screen titles and abstracts, carry out full text screen of the uploaded PDF files and data extraction.

Two independent reviewers (ELP & SD) conducted the title and abstract screening in duplicate to identify eligible articles using predefined criteria. Full texts of the eligible articles were obtained and assessed against the inclusion and exclusion criteria. Any disagreements between the reviewers during full text assessment was resolved by discussion and consensus, when no resolution reached, a third reviewer (AM) was involved in a decision.

2.3 Study selection

The systematic review included randomized controlled trials (RCTs) and non-randomized clinical trials conducted in adult prediabetes or T2DM patients, aged 18 years and older of either sex from different countries. The diagnosis of prediabetes and T2DM was based on American diabetes association (ADA) or WHO standard diagnostic criteria (ADA, 2017, 2011, 2010, 2003; Eastman and Vinicor, 1997; WHO, 1985). Studies with follow up duration of at least four weeks for both primary and secondary outcomes were considered. Since clinical studies have indicated that this is the minimum period of time required for treatments to produce meaningful changes in glucose control as assessed by HbA_{1c} concentration (Sidorenkov et al., 2011). This systematic review excluded cross-sectional studies, case series and case reports studies as well as studies conducted on patients with concomitant endocrinopathies affecting their blood glucose levels such as T2DM with hypothyroidism.

2.4 Data extraction

Data from selected studies were extracted using standardized data extraction tool from Joanna Briggs institute meta-analysis of statistics assessment and review instrument (JBI-MASARI). The data extracted included specific details about the interventions; consisted of mono and polyherbal formulation of whole fruit, seeds or pulp of *M. charantia* in different dosage form administered orally, alone or in combination with OHAs for treatment groups while, control groups were either placebo or treatment with standard OHAs. Other details were the outcomes of interest for the review which were categorized into primary —fasting plasma glucose levels (FPG), 2 h post-prandial plasma glucose level (PPG) and glycosylated hemoglobin A1c (HbA_{1c}); and secondary ones —incidence and severity of adverse effects, total cholesterol (TC), body weight, body mass index (BMI), serum creatinine, alanine aminotransferase (ALT) and aspartate aminotransferase (AST). The specific details about population and study methods were also extracted.

2.5 Quality assessment of included studies

Selected articles were assessed by two independent reviewers (ELP and SD) for methodological validity prior to inclusion in the review using standardized cochrane risk of bias tool for clinical trials (Higgins, 2011). The bias was graded as low, unclear or high. Non-randomized trials were assessed using “risk of bias in non-randomized studies - of interventions” ROBINS-I (Sterne et al., 2016). In non-randomized studies, overall judgement of risk of bias for each outcome was reached by assessing each of the seven bias domains guided by set of signaling questions and disagreements between the two primary reviewers was resolved through discussion with a third reviewer (AM).

2.6 Statistical analysis

Quantitative data was pooled in statistical meta-analysis using RevMan var. 5.3 software (cochrane collaboration). The mean changes in FPG, PPG and HbA_{1c} between study groups at follow up were treated as continuous variables. The inverse of variance-weighted method was used for pooling the weighted mean differences and its 95% confidence intervals (Whitehead and Whitehead, 1991). Outcome data were extracted as analyzed in that specific study without any additional adjustment for potential losses to follow-up. Where statistical pooling was not possible, the findings were presented in narrative form. Clinical and methodological heterogeneity were assessed statistically using Chi-square test and I^2 tests (Higgins et al., 2011). If significant heterogeneity was observed random effect model was used, otherwise fixed effect model was used for analysis. Sensitivity analysis was performed by restricting study methodological quality. Publication bias was not evaluated because of the limited number of studies included in a meta-analysis.

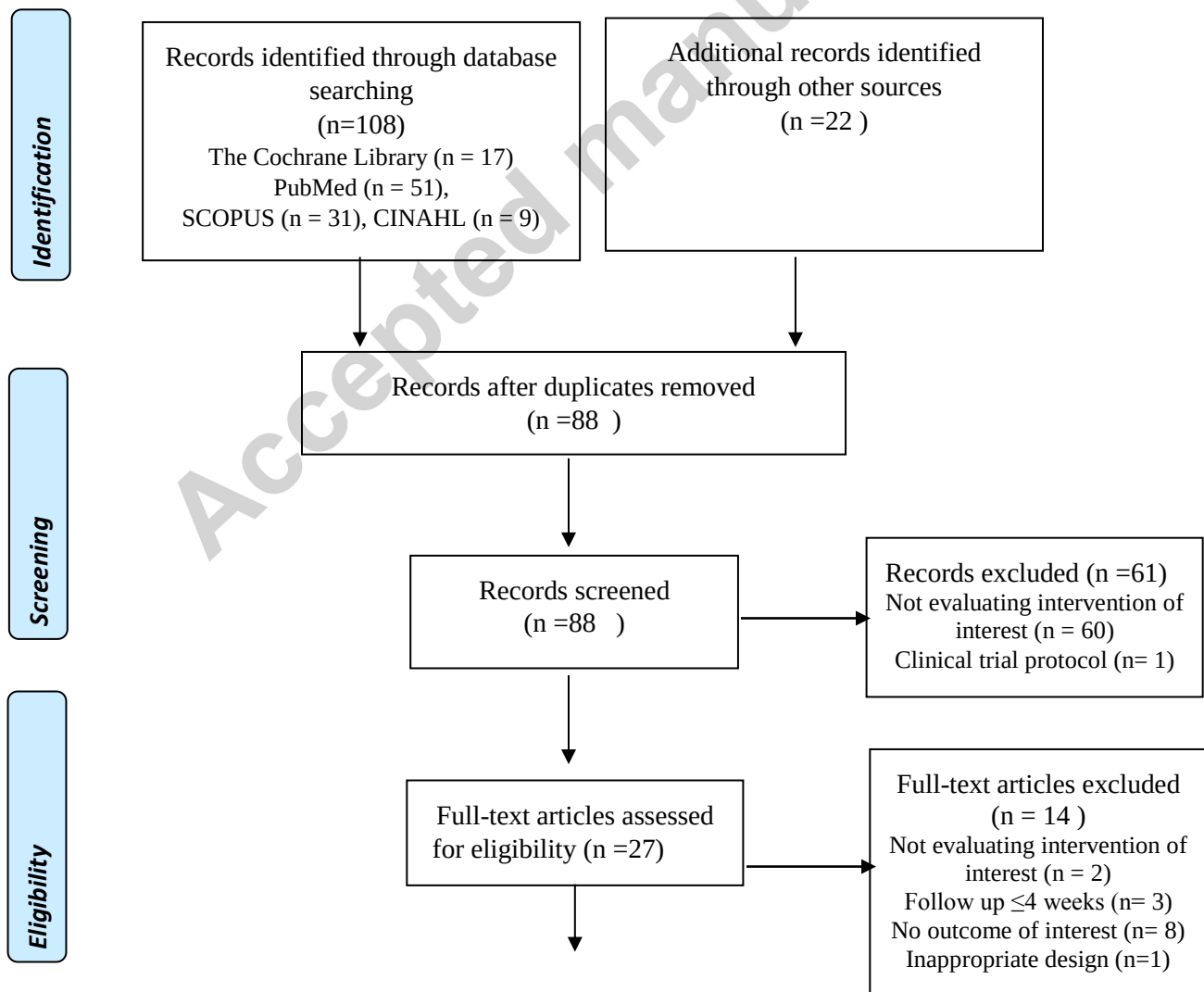
Two independent reviewers (ELP and SD) used GRADE pro software to assess quality of evidence of three outcome measures; FPG, PPG and HbA_{1c} level. The reviewers downgraded a starting rating of 'high quality' evidence by one level for serious concerns (or by two levels for very serious concerns) about risk of bias, inconsistency, indirectness, imprecision or publication bias.

3 Results

3.1 Results of the search

A total of 130 articles were identified through electronic and manual searching. After removal of duplicates and screened the articles based on the titles and abstracts, 27 articles remained. The 27

full-texts were examined for eligibility. Fourteen articles were further excluded because eight of them did not have outcome of interest (Ahamad et al., 2014; Akhtar, 1982; Inayat-ur-Rahman et al., 2009; Leatherdale et al., 1981; Salam et al., 2015; Tsai et al., 2012; Yadav et al., 2014; Welihinda et al., 1986), three articles had follow up duration of less than 4 weeks (Lim et al., 2010; Selvakumar et al., 2017; Tongia et al., 2004), two did not evaluate intervention of interest (Baldwa et al., 1977; Sharma and Patki, 2010) and one study had inappropriate control group (Dash et al., n.d.). Thirteen studies with a follow up duration between 4 to 16 weeks were then included in the qualitative review. Finally, ten studies (n = 1,045) were included in quantitative analysis. A PRISMA diagram is presented to show the screened, excluded and included articles (Fig. 1).



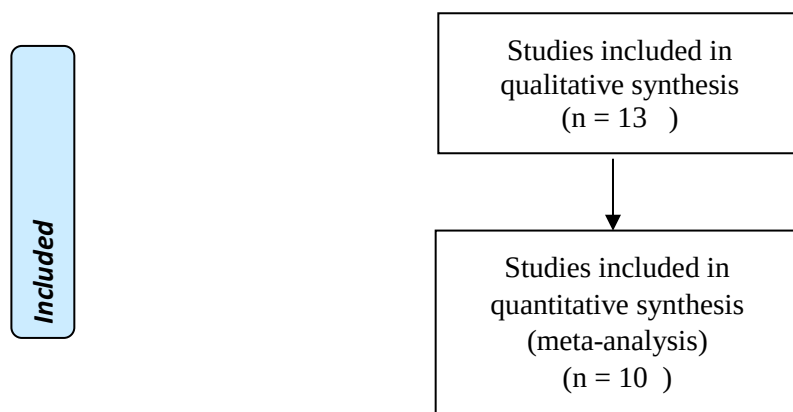


Fig. 1: Flow diagram of study screened, included and excluded studies

3.2 Description of included studies

3.2.1 Heterogeneity

Among the 13 included studies in the systematic review, twelve (12) were randomized controlled trials (Azam et al., 2016; Cortez-Navarrete et al., 2018; Dans et al., 2007; Fuangchan et al., 2011; Hsia et al., 2004; John et al., 2003; Krawinkel et al., 2018; Rahman et al., 2015; Suthar et al., 2016a; 2016b; Trakoon-osot et al., 2013; Zanker et al., 2012) while one was non-randomized controlled clinical trial (Anas et al., 2011).

Regarding nature of intervention evaluated, three studies assessed glycemic control of *M. charantia* polyherbal formulation in adults T2DM (Anas et al., 2011; Azam et al., 2016; Hsia et al., 2004). While the remaining studies assessed glycemic control of *M. charantia* monoherbal formulation. Majority of studies (n=6) used powdered whole fruits (seeds and fruits pulp) of *M. charantia* (Cortez-Navarrete et al., 2018; Dans et al., 2007; Fuangchan et al., 2011; Trakoon-osot et al., 2013; Krawinkel et al., 2018; John et al., 2003) while dry standardized fruit juice powder were used by three studies (Azam et al., 2016; Suthar et al., 2016a; 2016b). Only one study use *M. charantia* seeds in a polyherbal formulation (Hsia et al., 2004). However, two studies did not mention part of *M. charantia* used for intervention they evaluated (Anas et al., 2011; Zanker et al., 2012). Majority of studies (n = 7) had only partial information about the botanical material

and preparation's composition used while only one study had full information about the botanical material used including a voucher specimen and adequate details on the preparation's compositions (table 3). Capsules were the most common herb dosage form used by most studies (Dans et al., 2007; Fuangchan et al., 2011; Rahman et al., 2015; Suthar et al., 2016a; Trakoonosot et al., 2013; Zanker et al., 2012), whereas tablet was the less frequently used formulation (John et al., 2003).

One study used prediabetes adult participants (Krawinkel et al., 2018) whereas the remaining studies involved adult T2DM patients either on OHAs or recently diagnosed T2DM not on any OHAs. The included studies used either placebo (Anas et al., 2011; Cortez-Navarrete et al., 2018; Dans et al., 2007; Hsia et al., 2004; John et al., 2003; Krawinkel et al., 2018; Suthar et al., 2016a; Trakoonosot et al., 2013; Zanker et al., 2012) or active control with either glibenclamide (Azam et al., 2016; Rahman et al., 2015) or metformin (Fuangchan et al., 2011; Suthar et al., 2016b); table 1 and 2 summarized characteristics of included studies. When studies with data on outcome of interest were pooled in a meta-analysis, the I^2 test statistic was less than 25%, all p -value > 0.05 which indicate heterogeneity may be low.

Table 1 and 2. Baseline characteristics of the included studies

Table 3. Taxonomical identification and preparation methods for study interventions

3.2.2 Risk of bias in included randomized clinical trials

Overall, more than 50% of the studies included had high risk of bias. The results indicated that, majority of studies included failed to conceal allocation sequence, blind outcome assessment and personnel (Fig. 2).

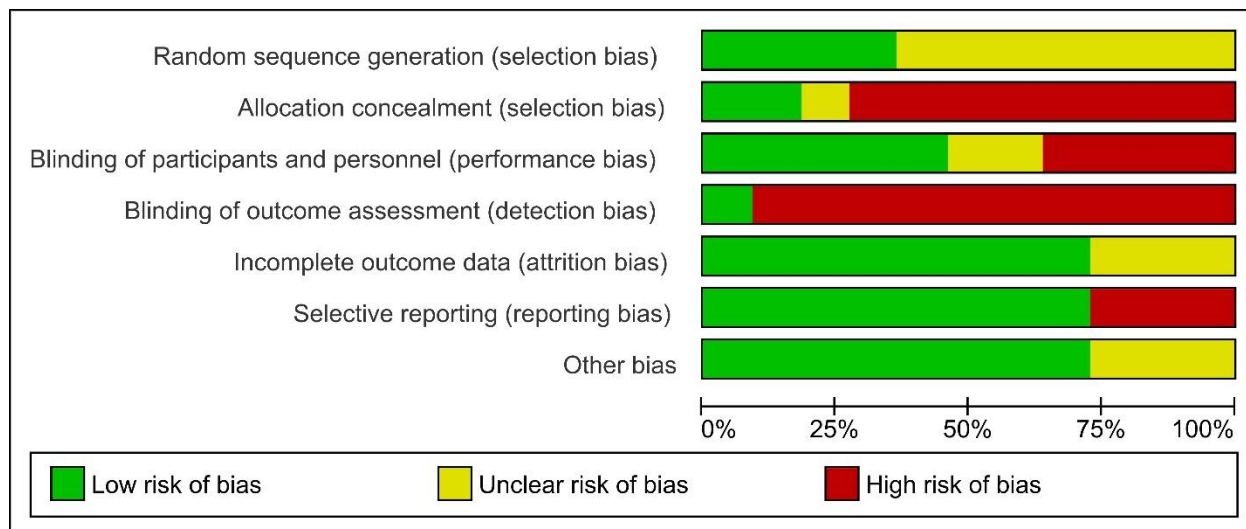


Fig. 2: Risk of bias assessment presented as percentages across all RCTs

3.2.2.1 *Random sequence generation*

More than 50% of included studies had unclear risk of bias due to random sequence generation (Fig. 2 & 3). Four studies described specific methods for random sequence generation which included; use of simple number list (Cortez-Navarrete et al., 2018), computer generated random sequence (Dans et al., 2007), random numerical code (Hsia et al., 2004) and Mersenne Twister random number generator (Krawinkel et al., 2018). These studies were given low risk of bias. Unclear risk of bias was given to eight studies that randomized participants into different study groups without adequately described methods used to generate random sequence (Azam et al., 2016; Fuangchan et al., 2011; John et al., 2003; Rahman et al., 2015; Suthar et al., 2016a; Suthar et al., 2016b; Trakoon-osot et al., 2013; Zanker et al., 2012).

3.2.2.2 *Allocation (selection bias)*

Blinding allocation was adopted in three studies (Azam et al., 2016; Dans et al., 2007; Hsia et al., 2004) which were given low risk of bias. Unclear risk of bias was given to one study which did not adequately report on allocation concealment (Cortez-Navarrete et al., 2018). The remaining

studies were evaluated as having high risk of bias because reviewers established no evidence of allocation concealment.

3.2.2.3 *Blinding (performance bias)*

Six studies had low risk of bias because they adopted a double blind technique (Cortez-Navarrete et al., 2018; Dans et al., 2007; Fuangchan et al., 2011; Hsia et al., 2004; Rahman et al., 2015b; Zanker et al., 2012) while two studies were single blinded with researchers being aware of intervention groups, hence were given unclear risk of bias (Azam et al., 2016; Krawinkel et al., 2018). Reviewers found no blinding of either personnel or participants or both in the remaining studies which were given high risk of bias.

3.2.2.4 *Blinding of outcome assessment (Detection bias)*

Only one study adequately described blinding of assessors (Dans et al., 2007), hence it was given low risk of bias. The remaining studies had high risk of bias because they did not adequately described blinding of outcome assessment.

3.2.2.5 *Incomplete outcome data (attrition bias)*

Unclear risk of bias was given to one study due to inadequate description of reasons for loss to follow up (Suthar et al., 2016a). In this domain, only one study had high risk of bias because of the significant difference between participants dropped out from the treatment arm (n=8) and control arm (n=3), reviewers believed that, the markedly unmatched dropped out could alter the results of the study (Hsia et al., 2004). Remaining studies had low risk of bias since they adequately reported the drop out and the reasons for drop out were sufficiently given.

3.2.2.6 *Selective reporting (reporting bias)*

Only one protocol for the studies included was located, leaving the majority of studies without their protocols which would have otherwise facilitated assessment of reporting bias. Hence a low risk of bias was given to studies that measured every anticipated outcome related to T2DM. High

risk score was given to one study which did not report some parameters of adverse effects even though they appeared in the methods section (Azam et al., 2016), a study that did not give description of concomitant medicines which would likely influence the effect of intervention (Dans et al., 2007) and two studies that did not adequately describe reasons for drop out (Hsia et al., 2004; John et al., 2003).

3.2.2.7 Other potential sources of bias

There was no sufficient evidence to establish other potential source of bias in the majority of studies included, hence they were given low risk of bias in this domain. However, unclear risk of bias was given to two studies because the role of funding agencies on these studies was not clearly revealed (Hsia et al., 2004; Suthar et al., 2016a). Also, reviewers were not adequately convinced on the influence of carry over effects of two cross over trials (Azam et al., 2016; Krawinkel et al., 2018) which were finally assessed as unclear risk of bias in this domain.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Azam 2016	?	+	?	-	+	-	?
Cortez-Navarrete 2018	+	?	+	-	+	+	+
Dans 2007	+	+	+	+	?	-	+
Fuangchang 2011	?	-	+	-	+	+	+
John 2003	?	-	-	-	?	-	+
Krawinkel 2018	+	-	?	-	+	+	?
Rahman 2015	?	-	+	-	+	+	+
Suthar 2016a	?	-	-	-	?	+	?
Suthar 2016b	?	-	-	-	+	+	+
Trakoon-osot 2013	+	-	-	-	+	+	+
Zänker 2012	?	-	+	-	+	+	+

+ = low risk of bias; - = High risk of bias; ? = Unclear risk of bias

Fig. 3: Summary of risk of bias judgements about each risk of bias item for each RCT.

4 Effect of Interventions

4.1 Effect of interventions on Prediabetes

Only one RCT (n = 44) investigated glycemic control of powder of unripe whole fruit of *M. charantia* on prediabetes (Krawinkel et al., 2018). The RCT was a cross over trial that reported overall changes of FPG and HbA_{1c}% variables as outcome indicators for glycemic control. With regard to the FPG; there was moderate quality evidence that, administration of *M. charantia* preparation reduced elevated FPG (Mean difference -0.31mmol/L, n = 44). The HbA_{1c} level increased (Mean difference 0.05%, n = 44). Confidence interval of estimates and data on each period of crossover were not available (additional file 1).

4.2 Effect of interventions on type 2 diabetes mellitus

4.2.1 Primary outcome

4.2.1.1 Fasting plasma glucose (FPG)

Results indicated low quality evidence that prolonged use of *M. charantia* monoherb formulation at a dose of 2-6 g/day was more effective than placebo in lowering elevated FPG level. (Mean difference -0.72 mmol/L, 95% CI: -1.33 to -0.12, five studies with 231 participants); $I^2 = 14\%$ suggesting heterogeneity between groups may be low (fig. 4).

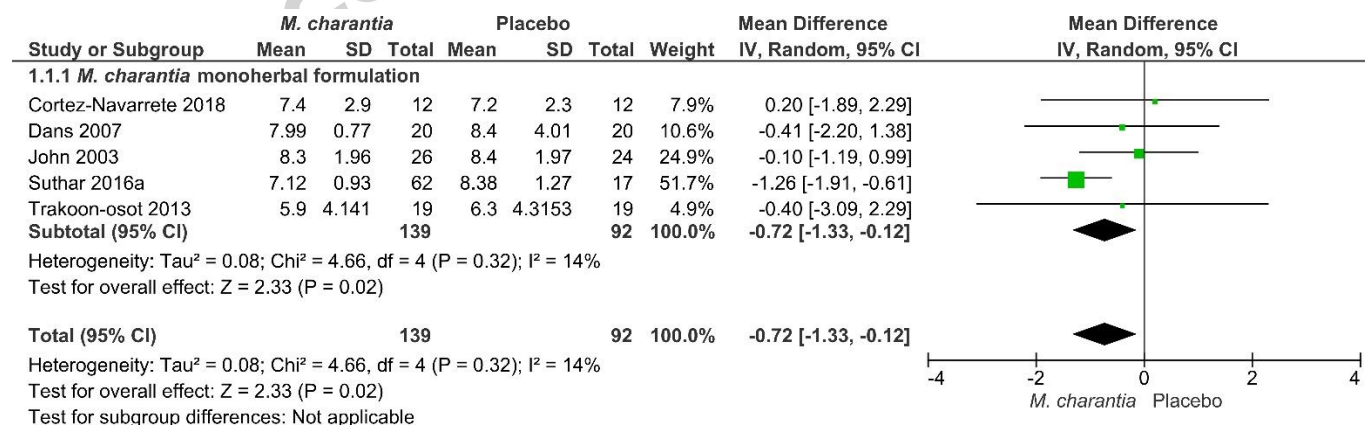


Fig. 4: Effect size of *M. charantia* on FPG level compare to placebo

In another comparison of *M. charantia* and OHAs, three studies (n = 323) provided data for FPG outcome. The OHAs were more effective than *M. charantia* in lowering elevated FPG level (Mean difference 0.76 mmol/L, 95% CI: 0.55 to 0.98), $I^2 = 0$; suggesting that heterogeneity between groups may be low (Fig. 5.).

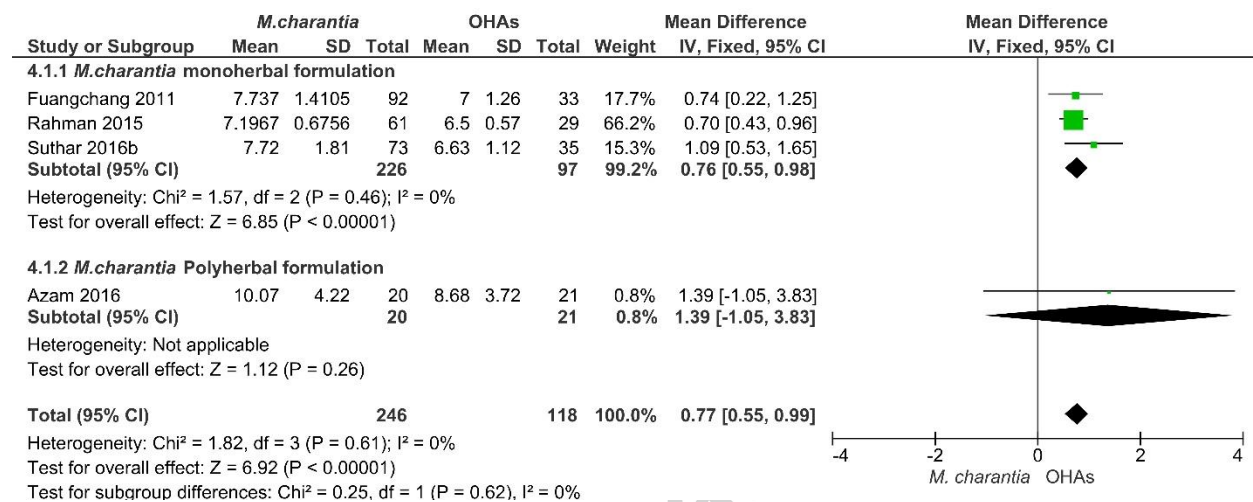


Fig. 5: Effect size of *M. charantia* on FPG level compare to OHAs

4.2.1.2 Postprandial glucose (PPG)

There was low quality evidence that *M. charantia* monoherb formulation compared to placebo was effective in lowering elevated PPG level (Mean difference -1.43 mmol/L, 95% CI: -2.18 to -0.67, n = 153); $I^2 = 0$ suggesting heterogeneity between groups may be low (fig. 6).

Two studies that compared *M. charantia* and OHAs had data on postprandial glucose level (Fuangchan et al., 2011; Rahman et al., 2015). However, due to large methodological and clinical heterogeneity pooling such data was not possible. In one study (Fuangchan et al., 2011), the results showed no significant mean difference in PPG level between *M. charantia* and metformin group ($p = 0.1$). Similar none significant mean difference was observed in another study (Rahman et al., 2015a).

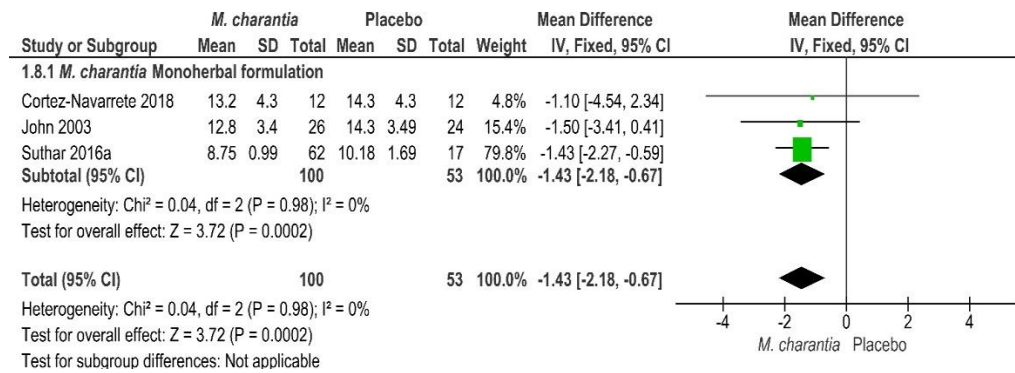


Fig. 6: Effect size of *M. charantia* on PPG level compared to placebo

4.2.1.3 Glycosylated hemoglobin A1c (HbA1c)

Data for HbA_{1c} level was pooled from five studies ($n = 243$). There was very low quality evidence that *M. charantia* monoherb formulation was more effective than placebo in lowering elevated HbA_{1c} (Mean difference -0.26% , 95% CI: -0.49 to -0.03); $I^2 = 0$, suggesting heterogeneity between groups may be low. *M. charantia* polyherb formulation also lowers elevated HbA_{1c} when compared to placebo (Mean difference -0.66% , 95% CI: -1.26 to -0.06 , $n = 50$) (Fig. 7). Two studies that compared *M. charantia* and OHAs had data on HbA_{1c} level (Rahman et al., 2015; Suthar et al., 2016b). Due to large methodological and clinical heterogeneity pooling such data was not possible. The results of these study showed that *M. charantia* had a weaker hypoglycemic effect when compared to OHAs. However, *M. charantia* was able to reduce risk factors of cardiovascular diseases as compared to glibenclimide (Rahman et al., 2015a).

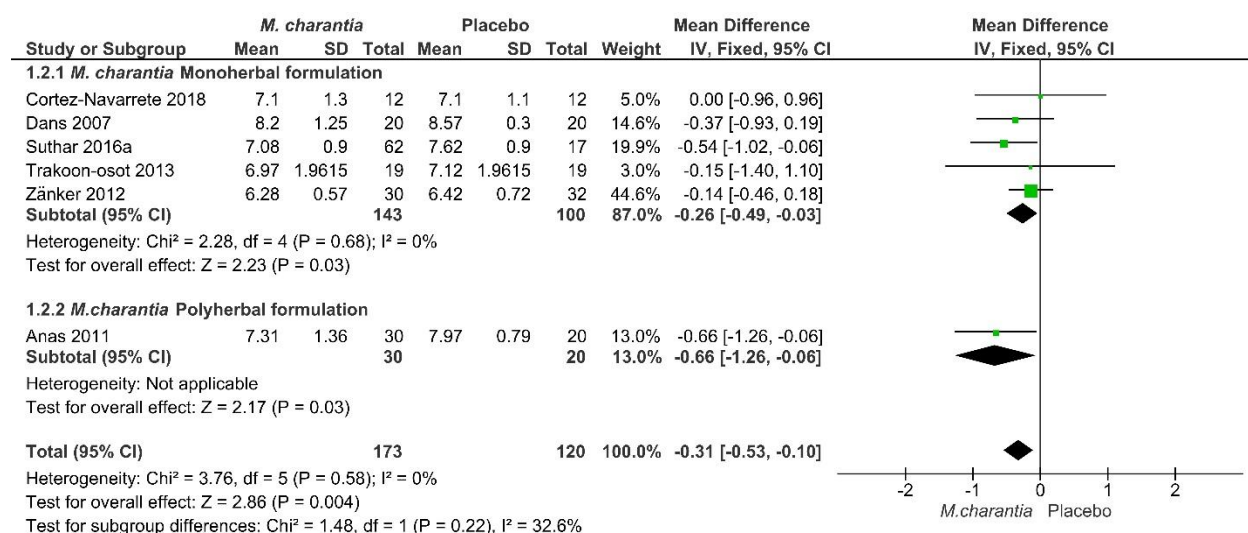


Fig. 7. Effect size of *M. charantia* on HbA1c level when compared to placebo

4.3 Sensitivity analysis

The sensitivity analysis was performed in a subgroup of *M. charantia* monoherbal formulation compared with placebo by excluding studies with high risk of bias in allocation concealment and blinding (Participants and/ or assessor). The results changed to none significant effect of *M. charantia* formulation in lowering FPG; (mean difference -0.15 mmol/L, 95% CI: -1.51 to 1.21, two studies n = 64); PPG; (mean difference -1.1 mmol/L, 95% CI: -4.54 to 2.34, one study n = 24); and HbA_{1c}; (mean difference -0.28%, 95% CI: -0.76 to 0.21, two studies n = 64).

4.3.1 Secondary outcomes

4.3.1.1 Incidence and severity of adverse effects

Frequently reported adverse effects were related to gastrointestinal tract which included hyperacidity/heartburn, nausea and/or vomiting, diarrhea, abdominal discomfort, enhanced appetite, constipation and flatulence which were reported by five studies (Cortez-Navarrete et al., 2018; Dans et al., 2007; Krawinkel et al., 2018; Rahman et al., 2015; Trakoon-osot et al., 2013). One such study established that, frequency of diarrhea and flatulence in the *M. charantia* group was significantly higher than the placebo group ($p = 0.046$ and $p = 0.027$, respectively). These

symptoms were transient and was classified as grade 1 according to common terminology criteria for adverse events severity scale (Trakoon-osot et al., 2013). Similarly, another study noted that symptoms such as loose stools, diarrhea, flatulence, stomach rumbling, nausea or vomiting were more commonly reported by the *M. charantia* group than the placebo group; however, causal relationship between these common symptoms and the use of *M. charantia* was not established (Krawinkel et al., 2018).

Three studies reported central nervous system related adverse effects; headache and dizziness (Cortez-Navarrete et al., 2018; Rahman et al., 2015; Suthar et al., 2016b). Other less frequently occurred adverse effects were skin rash (Rahman et al., 2015b), sore throat (Hsia et al., 2004) and hypotension (Suthar et al., 2016b). We identified one study that did not give sufficient descriptions of adverse effects despite being assessed because authors concluded that they were not significant and unrelated to the intervention (Suthar et al., 2016a). However, three studies did not report any adverse effect related to the use of *M. charantia* either in monoherbal or polyherbal (Anas et al., 2011; Azam et al., 2016; John et al., 2003). No study reported any serious adverse effect. Adverse effects markers for liver and kidney function were reported by only four studies (Table 4). These studies indicated no significant difference in changes of ALT, AST and creatinine between *M. charantia* groups and control groups; however, these limited data although are not significantly different between groups but point out a direction in which *M. charantia* consistently lower raised liver enzymes as compared to placebo (Cortez-Navarrete et al., 2018; Dans et al., 2007; Trakoon-osot et al., 2013).

5 Discussion

5.1 Summary of main findings

Our findings suggest that *M. charantia* monoherbal and polyherbal preparations taken orally at a dose of 2 to 6g/day for at least four weeks significantly reduces elevated FPG level, PPG and HbA_{1c} among adult T2DM patients. *M. charantia* monoherbal also reduces elevated FPG in prediabetes, indicating that *M. charantia* preparations could be used as adjunct therapy for glycemic control and thus could reduce risk for microvascular complications in T2DM patients.

It is possible that, the observed hypoglycemic effect of *M. charantia* preparations may be due to presence of concentrated mixture of phytochemicals with hypoglycemic activity in unripe fruit, seeds, and fruit pulp used. It is well established that immature green variety of *M. charantia* have high amount of saponin, total lipids and fatty acids with hypoglycemic activity (Habicht et al., 2011). Some isolated phytochemicals from *M. charantia* fruit are; charantin, polypeptide-p (p-insulin), momordicoside Q, R, S and T, conjugated linolenic acid, linoleic acid, conjugated linoleic acid and cucurbitane-type triterpene glycosides known as saponins. These phytochemical compounds were investigated in animals and human studies and shown significant hypoglycemic activity (Ahamad et al., 2014; Chida and Sakawa, 2006; Chuang et al., 2006; Keller et al., 2011; Ma et al., 2010; Pitipanapong et al., 2007; Prabhu N, Ismail M, 2015; Tan et al., 2008; Yue et al., 2017).

M. charantia preparations possess a diverse mode of glucose-lowering action which are insulin secretagogue effect, enhance glucose uptake into C2C12 myocytes and 3T3-L1 adipocytes (Yibchok-anun et al., 2006), increase insulin sensitivity in the skeletal muscle through inhibition of protein tyrosine phosphatase 1B (PTP1B) (Sridhar et al., 2008; Yue et al., 2017) and decrease intestinal glucose absorption through inhibition of α -glucosidase (Yue et al., 2017). Other

pathways include increase glycogen synthesis by the liver (Sarkar et al., 1996), depress glucose-6-phosphatase and fructose-1,6 biphosphatase, and accelerate rate of glucose metabolism through the pentose phosphate Pathway (Shibib et al., 1993), decrease gluconeogenesis through selective inhibition of 11 β - hydroxysteroid dehydrogenase type 1 (11 β - HSD1) microsomal enzyme (Blum et al., 2012) and recovery/renewal of partially destroyed pancreatic beta cells (Ahmed et al., 1998). The multiple active ingredients and the rich diversity of mode of actions could have contributed to the observed significant blood glucose lowering ability in T2DM; possibly through synergistic effect. These interesting findings strongly justify the use of *M. charantia* whole extracts rather than isolated active compounds.

5.2 Quality of the evidence

Certainty of evidence was assessed using GRADE approach (Additional file 2). Overall, the quality of evidence of all primary outcomes were found to be low or very low primarily due to risk of bias, inconsistency and imprecision. The heterogeneity test using I^2 for all meta-analysis was not significant though variation in studies were observed due to different formulation, study design, population and dosage. Only one study provided a full information about the botanical material used including a voucher specimen and adequate details on the preparation's compositions. However, majority of remaining studies had only partial information about the botanical material and preparation's composition or inadequate information on the preparation's compositions and overall taxonomically inadequate (Table 3). Lack of proper standardization of preparations and wide dosage range used could have contributed to the observed inconsistent results in individual trials. Small sample size in all trials included and large clinical and methodological heterogeneity limit generalization of the findings of this study and calls for additional clinical trials to determine the efficacy of *M. charantia* standardized preparation in

T2DM. This systematic review and meta-analysis provide empirical evidence which underscore the argument that trials which do not perform concealment of intervention and blinding (participants and/or assessor) tend to have statistically significant effect size. The significant effect size could be due to performance bias; when investigators being aware of groups participants belong are likely to treat each participant differently resulting into overestimating the effect of intervention.

A major omission was noted in the majority of included studies failed to adequately report safety data on liver and kidney function after exposure to intervention. Although the sparse data of liver and kidney function were summarized, largely absence of these safety indicators limit the ability to fully assess the extent of adverse effects which could have been caused by the intervention. The lack of specific clinical detail of other adverse effects prevented the reviewers from thoroughly evaluating the safety of *M. charantia* preparations in treatment of T2DM. It is worth noting that, the high risk of bias of the studies included in this systematic review and the small sample size of some indicators lead to poor statistical power which requires caution while interpreting and generalizing these findings.

6 Conclusions

M. charantia unripe fruits, seeds or fruit pulp preparations taken orally at a dose of 2-6g/day for at least 4 weeks lowered elevated FPG, PPG and HbA_{1c} level in type 2 diabetes mellitus. However, this conclusion should be considered in light of unclear to high risk of bias of included studies and low to very low level of certainty of evidence in all primary outcomes. Therefore, further research is needed in the aspect of standardizing *M. charantia* formulation and conduct high quality clinical trials to answer specific questions on the safety, efficacy, specific dose required to achieve optimal glycemic control and duration of treatment of *M. charantia*

preparations in T2DM patients. The quality clinical trials needed are those that will have adequate sample size, designed to ensure important methodological features (random sequence generation, allocation concealment of intervention, blinding of both participants and assessors) are properly addressed.

7 Competing interests

The authors have no competing interests.

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10 Authors' contributions

ELP conceived and drafted earlier version of the manuscript and a guarantor of the manuscript. FMK, SD and AM revised the draft of manuscript. DS, PBN, CUT, PEO mentored, revised and edited the manuscript. All authors read and approved the final manuscript.

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Table 1. Baseline characteristics of the included studies

Study, Year	Time	Method, Country	Age M(SD), M:F	Intervention (n) Control (n)	Inclusion criteria	Exclusion criteria
Dans, 2007	12	RCT, Philippine	58.70 (9.81), 7:13	I= Mc seed+fruits powder 500mg Cap; two caps. t.i.d and p.c for 3 months, (20)	Type 2 diabetes mellitus patients, ≥ 18 years.	ALT or AST > 3 times the upper limit of normal, allergic to any part of the plant, severe chronic illness, acute illness, illness limiting life expectancy, drug or alcohol abuse or psychiatric problems, inability to attend follow-up clinic, recipient of another investigational product 3 months prior the study and pregnancy or lactation
			59.76 (10.04), 8:12	C=Placebo; two caps. t.i.d and p.c for 3 months, (20)	HbA1c of 7%-9% On OHAs or dietary or newly diagnosed	
Fuangchan, 2011	4	RCT, Thailand	52.2 (8.3), 8:25	I ₁ = Mc fruit pulp 500mg; one cap. o.d for 4 weeks (33)	Newly diagnosis with Type 2 diabetes mellitus, age between 35 and 70 years	ALT, AST, total bilirubin or alkaline phosphatase > 2.5 times the upper limit of normal, Serum cr. > 1.8 mg/dL, Hb < 11 g/dL for
			50.6(10.5), 6:26	I ₂ = Two caps. o.d for 4 weeks (32)		
			52.0 (9.1), 11:20	I ₃ = Four caps. o.d for 4 weeks (31)		

			52.5 (9.2), 9:24 (33)	C= Metformin tabs.; 1000mg daily for 4 weeks		male and <10g/dL for female, severe angina, moderate- severe heart failure with left ventricular hypertrophy (LVH), pregnant and lactating women, on insulin or OHAs, participation in another clinical trial within 30 days of screening, long-term diabetic complications, BMI < 18 or > 38; or a body weight variation more than 10% during the screening period.
John, 2003	4	RCT, India	52.3 (8.55), 7:19	I=Mc fruit powder 1g; two tabs. t.i.d and p.c for 4 weeks (26)	Adults Type 2 diabetes mellitus	Type 1 DM, FPG >200 mg/dl and PPG >300 mg/dl. Diabetic patients with infection or with diabetic related complications,
			54.25 (9.2), 9:15	C=Placebo as riboflavin; two tabs. t.i.d and p.c for 4weeks (24)	patients	

						Pregnant women, lactating mothers and patients on insulin for sugar control
Suthar, 2016a	13	RCT, India	41.33 (7.59), 39:23	I= Mc fruit juice powder cap 400mg; One AM and two PM half an hour before meal for 90 days (64)	T2DM, male and female, > 30 and < 70 years, on OHAs, FPG $\geq$ 110 mg/dl, PPG 250 mg/dl, HbA1c > 7%, but < 10%	Pregnant or lactating women, women of childbearing potential and men not agreeing to use adequate contraception methods during study, type 1 DM, secondary DM, and clinically significant cardiac disease, endocrine abnormalities other than stable thyroid disease or requiring insulin therapy and serum creatinine level >1.5 mg/dl.
			41.31 (6.88), 10:7	C=Placebo caps; One AM and two caps PM half an hour before meal for 90 days (21)		
Suthar, 2016b	15	RCT, India	49.43 (9.26), 46:37	I= Mc dried unripe fruit juice 400mg cap; one b.i.d and p.c for 15 weeks (83)	Male and female of age $\geq$ 30 and $\leq$ 65 years, diagnosed	Type 1 DM, secondary diabetes mellitus, pregnant or

			47.70 (9.11) 23:17	C= Tab. Metformin 500mg; one b.i.d and p.c for 15 weeks (40)	with T2DM, FPG ≥ 110 mg/dL and ≤ 250 mg/dL; and HbA1c $\geq 7\%$ and $\leq 10\%$	lactating women, cardiac disease, endocrine abnormalities other than stable thyroid disease, on insulin, serum cr of ≥ 1.5 mg/dL, AST and ALT ≥ 2.5 upper limit of normal, taking any other herbal products, dietary supplements, or medications during the past 8 weeks that could affect plasma glucose and/or body weight.
Zänker, 2012	16	RCT, German	63.5 (7.76), 21:9 62.8 (8.53), 26:9 61.5 (7.26), 23:9	I ₁ =Mc dried aq. Extract 0.5g cap.; one b.i.d p.c for 4 months (38) I ₂ = MC 0.5g dried aq. xtract+Cr+Zn; one b.i.d p.c for 4 months (42) C=Placebo; two caps. b.i.d and p.c for 4 months (44)	T2DM, ≥ 40 years, both sex, on diet, education, exercise therapy and/or OHA	T1DM, on insulin, thyroid diseases, coagulation disorders, administration of anticoagulants, on dietary supplements containing; chromium/zinc, bitter melon, or other nutritional

						supplements that lowers blood sugar, concomitant therapy past 3 months, GIT diseases on laxatives, anemia, renal insufficiency, tumorous diseases, allergic, pregnant, lactating, alcoholic, on other intervention study.
Rahman, 2015	10	RCT, Pakistani	51.9(10.5) , 21:9 52 (11.4), 20:11 52.2(8.70) , 18:11	I ₁ =Mc powder; 2g caps/day (30) I ₂ =Mc powder; 4g caps/day (31) C=Glibenclamide ; tab 5mg daily (29)	T2DM, age 30-70 years, male and FPG 126- 240 mg/dl, normal Renal and liver Function Tests	Previous use of antidiabetic drugs, cancer, Menopausal status or pregnancy, Use of contraceptives, Use of anticancer drugs, Hormonal therapy and Diabetic complications.
Trakoon-osot, 2013	16	RCT, Thailand	57.2 (8.8), 3:16	I= Mc dried fruit pulp powder 400mg Cap; 6g/day (19)	T2DM, age ≥ 20 years, HbA1C >6.5%,	Type 1 DM, on insulin, allergic to Mc pregnancy or

		58.7 (7.0), 8:11	C=Placebo was made of microcrystalline cellulose grade 102; 6g/day (19)	Consent voluntarily	lactation, AST/ALT > 3 times the upper limit of normal, (Cr) > 1.5 mg/dL), concomitant illness, history of other disorders of oxidative status, currently smoking, taking supplements or functional foods or herbal medicines within 8 weeks prior to the study, psychiatric problems
Krawinkel, 2018	Cross-over RCT, Tanzania	48.2 (8.4), 23:27	I= 2.5g of whole Fruits, freeze- dried powder (28)	Pre- diabetes, 30-65 years, FPG 5.6-6.9 mmol/L	Chronic disease, taking medication regularly, having an identified glucose-6- phosphatase- dehydrogenase (G6PD), deficiency, heavy alcohol consumption, pregnancy, and lactation
		46.6 (9.1), 23:27	C=Placebo (3.25g of cucumber powder) (24)	HbA1c 5.7-7.5% BMI 27-35 kg/m ² , BP 90/60- 160/110 mmHg,	

Anas, 2009	12	Non RCT, India	NR 11:09 NR 9:21	I= Mc powder; 6g b.i.d for 3 months (30) C=Placebo; 1800 Kcal diet/day (20)	Type 2 Diabetes mellitus in	Patients who were young, in whom insulin dependence was suspected, those who had taken insulin in any form at any time, those having ketonuria, and pregnant
Hsia, 2004	12	RCT, USA	47.6 (11.5), 6:17 47.4 (7.0), 4:9	I=Mc mixture; Two caps b.i.d for 3 months (23) C=Placebo; two caps b.i.d for 3 months (13)	T2DM for $\geq$ 1 year, on OHAs, or dietary and lifestyle regimen for ≥ 3 months, age 18-70 years, HbA1c 8% and 12%	On insulin, pregnant, lactating or planning to become pregnant, use of any investigational drug within 30 days, emergency hyperglycemia ≤ 6 months or 2 or more severe hypoglycemic episodes ≤ 6 months; alcohol dependence; cardiac abnormalities, seizures, Cr ≥ 1.4 mg/dL; hepatic enzyme or bilirubin levels ≥ 2 times the upper limit of the normal range; HIV,

						major surgical procedure within 30 days, malignancy other than basal cell skin carcinoma; Hb<11.0 g/L)
Azam, 2016	4	Cross-over RCT, Indonesia	49.8 (6.97), 5:15	I=Mixture extract 22mg/kg o.d before breakfast for a month (22)	Newly diagnosed T2DM, both sex, 30–60 years, RPG < 400mg/dl. Not on insulin therapy. HbA1C; 7-12%	Severe complication, pregnancy, hypoglycemic coma, severe infection and abnormal in complete blood analysis, abnormal liver function test, kidney function test and ECG, received other medication other than those approved by internal medicine team to stop medication temporarily based on medical indication.
Cortez-Navarrete, 2018	12	RCT, Mexico	50.1 (7.3), 5:7	I=500mg caps fruit powder of Mc. Dose: 2 caps b.i.d for 12 weeks (12)	T2DM < 5 years, no treatment for at least 3 months	Pregnant, breastfeeding, on medications known to affect the metabolism

		47.0 (7.4), 3:9	C=Calcined magnesia placebo. Dose: 2 caps b.i.d for 12 weeks (12)	prior, nonsmokers , 35–60 years, BMI; 25.0 - 34.9, FPG <11.6 mmol/L and A1C; 7-9%.	of glucose and insulin, liver or renal disease, hypertension, thyroid or de- compensated cardiovascular disease, TC ≥6.20 mmol/L, TG ≥4.48 mmol/L, liver transaminases ≥2.5 the upper normal limit, or glomerular filtration rate ≤60 mL/min/1.73m 2
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Table 2. Baseline characteristics of the included studies

Study	I/ C	FPG (mmol/L)	HbA1c % mean (SD)	PPG (mmol/L) mean (SD)	TC (mmol/L) mean (SD)	BMI (Kg/m2) mean (SD)	ALT (IU/L)	AST (IU/L)	Creatinine (μmol/L)
Dans, 2007	I C	8.4 (2.24) 8.14 (2.36)	7.92 (0.59) 8.07 (0.077)	NR NR	5.25 (146) 5.08 (1.09)	26.37 (4.75) 26.00 (3.94)	29.87 (21.42) 37.12 (26.26)	NR NR	111.56 (65.11) 100.95 (32.58)
Fuancg han, 2011	I ₁ I ₂ I ₃ C	7.6 (0.99) 8.0 (0.74) 9.2 (0.78) 8 (0.99)	NR NR NR NR	15.1 (2.47) 15.1 (2.8) 13.5 (2.65) 14.6 (4.09)	NR NR NR NR	25.0 (3.4) 25.6 (3.9) 25.4 (3.0) 24.4 (3.1)	29.3 (14.8) 28.8 (14.7) 29.0 (24.4) 32.6 (19.4)	32.5 (14.3) 31.0 (18.8) 31.5 (24.3) 31.3 (16.0)	NR NR NR NR
John, 2003	I C	8.34 (1.49) 8.7 (1.39)	NR NR	14.7 (1.82) 14.1 (1.63)	NR NR	NR NR	NR NR	NR NR	NR NR
Suthar, 2016a	I C	8.33 (1.96) 8.3 (1.93)	7.87 (1.0) 7.83 (1.1)	11.2 (3.15) 10.57 (3.12)	8.5 (1.52) 8.6 (1.67)	NR NR	NR NR	NR NR	NR NR
Zanker, 2012	I ₁ I ₂ C	NR NR NR	6.47 (0.63) 6.69 (0.69) 6.51 (0.65)	NR NR NR	NR NR NR	30.6 (5.97) 28.9 (4.31) 28.5 (4.64)	NR NR NR	NR NR NR	NR NR NR
Rahma n, 2015	I ₁ I ₂ C	8.1 (0.74) 7.9 (0.84) 8.0 (1.02)	8.25 (0.70) 8.30 (0.55) 8.45 (0.60)	13.4 (0.87) 13.7 (1.22) 14.2 (1.46)	12.1 (0.59) 12.6 (0.86) 12.3 (0.62)	25.2 (1.70) 25.7 (2.40) 25 (2.20)	NR NR NR	NR NR NR	NR NR NR
Trakoo n-osot,	I C	6.5 (1.79) 6.6 (0.91)	7.47 (1.03) 7.32 (0.7)	NR NR	NR NR	25.04 (3.69) 26.37 (6.06)	NR NR	NR NR	NR NR

2013									
Anas,	I	5.27 (0.44)	5.85 (0.43)	NR	4.26 (0.91)	29.1 (2.0)	NR	NR	NR
2009	C	5.40 (0.53)	5.85 (0.43)	NR	4.49 (0.98)	30.2 (2.5)	NR	NR	NR
Hsia,	I	NR	8.35 (0.82)	NR	10.9 (1.81)	NR	NR	NR	NR
2004	C	NR	8.6 (0.62)	NR	10.5 (1.74)	NR	NR	NR	NR
Azam,	I	10.3 (4.64)	8.7 (1.63)	13.6 (5.72)	NR	26.6 (4.48)	19.7 (10.45)	NR	96.4 (34.48)
2016	C	11.0 (5.19)	9.2 (1.73)	14.5 (6.33)	NR	26.4 (10.45)	18.8 (8.23)	NR	66.3 (35.36)
Krawinkel,	I	5.3 (0.52)	5.9 (0.43)	NR	NR	29.6 (2.5)	NR	NR	NR
	C	5.2 (0.5)	5.9 (0.4)	NR	NR	29.8 (2.3)	NR	NR	NR
2018									
Suthar,	I	8.6 (1.94)	8.3 (1.02)	NR	NR	27.0 (4.46)	NR	NR	NR
2016b	C	8.2 (1.66)	8.1 (1.01)	NR	NR	27.1 (3.49)	NR	NR	NR
Cortez-Navarr	I	7.1 (1.9)	7.8 (0.8)	17.1 (3.7)	4.9 (0.73)	29.1 (2.4)	35.4 (24.4)	23.1 (11.3)	70.7 (8.84)
ete,	C	8.2 (1.4)	7.6 (0.6)	14.9 (4.7)	4.41 (0.75)	28.8 (3.9)	36 (19.7)	29 (22.4)	61.9 (8.84)
2018									

ALT= alanine aminotransferase, AST= aspartate aminotransferase, b.i.d= twice a day, BMI= body mass index C= control, Caps= capsules, Cr= serum creatinine, DM=diabetes mellitus, EKG=electrocardiogram, FPG=fasting plasma glucose, HbA_{1c}=glycosylated hemoglobin A1c, Hb=hemoglobin, I=intervention Mc=*Momordica charantia*, M: F=male: female, n=number of participants, NR=not reported, OHA=oral hypoglycemic agent, PPG=post-prandial glucose, q= aqueous, RCT=randomized clinical trial, Tabs= tablets. Time= follow up duration in weeks

Table 3. Taxonomical identification and preparation methods for study interventions

Study (reviewer rating)	Type	Botanical identification of the composition				Preparation methods	Quality control measures
		Local name	Taxonomical name (Family)	Voucher	Quantity		
Anas 2011	P	Neem	<i>Melia azadirachta</i> Linn (none)	none	1 part	No description	No description
(C)		Jamun	<i>Syzygium cumini</i> Lam (none)	none	1 part		
		Kalounji	<i>Nigella sativa</i> Linn (none)	none	1 part		

		Karela	<i>Momordica charantina</i> <i>L. (none)</i>	none	1 part		
		Methi	<i>Trigonella foenum</i> <i>graceum Linn (none)</i>	none	1 part		
Azam, 2016 (C)	P	none	<i>Pterocarpus indicus</i> <i>folium (none)</i>	none	20%	Ethanol extraction was	No description
		none	<i>Momordica charantia</i> <i>(none)</i>	none	10%	done. The product was	
		none	<i>Phaseolus vulgaris</i> <i>fructus (none)</i>	none	40%	prepared and packaged by	
		none	<i>Andrographis</i> <i>paniculata Nees (none)</i>	none	30%	PT Njonja Meneer as Diabmeneer®	
Dans, 2007 (C)	M	Ampaya	<i>Momordica charantia</i> <i>(none)</i>	none	None	No description	No description
Fuangchan g 2011 (B)	M	Bitter melon	<i>Momordica charantia</i> <i>(Cucurbitaceae)</i>	none	500 mg	Seeds were removed from unripe fruits. Fruit pulps were dried by hot air oven at 60 °C for 24 h. Dried fruit pulps were powdered.	Charantin was a marker compound. Its content was determined by HPLC as 0.04–0.05% (w/w). Dried pulp were tested for microbial contamination, heavy metal and insecticide.
John 2011 (B)	M	Bitter gourd	<i>Momordica charantia</i> <i>(none)</i>	none	1 g	Shade dried powdered fresh whole fruit. The average size of dried fruit weights around 5g	No description

Suthar 2016a (B)	M	Bitter melon, bitter gourd	<i>Momordica charantia</i> (<i>Cucurbitaceae</i>)	none	400 mg	Unripe green fruits of <i>M.</i> <i>charantia</i> , collected from the fields were authenticated in Piramal Life Sciences Limited (PLSL), Mumbai India. The extraction focuses on the juice expression of whole fruits with seeds, which was then processed and converted into a free- flowing natural green colored powder with a characteristic odor and taste.	Uridine was a chemical marker. Each PDM011011- capsule contain not less than 0.4 mg of Uridine
Suthar 2016b (B)	M	Bitter melon, bitter gourd	<i>Momordica charantia</i> (<i>none</i>)	none	400 mg	The blend was obtained from fresh unripe green bitter melon fruits grown in organic farms. It was authenticated at Piramal Enterprises	Uridine was a chemical marker. Each PDM011011- capsule contain not less than 0.4 mg of Uridine

						Limited, Mumbai, India.	
Zänker 2012 (B)	M	Bitter melon	<i>Momordica charantia</i> (none)	none	0.5 g	Bitter Melon powder with and without chromium/zinc was provided by supplier.	Standardized at 10% charantin (w/v) Checked for ethanol, pesticides, toxins, microbes and a spectrum of modern environmental analysis, including testing the biota for residues
Rahman 2015 (B)	M	Bitter melon	<i>Momordica charantia</i> (none)	none	1000 mg	Unripe bitter melon fresh fruit obtained from agriculture farm Sarai Naurang (Lakki Marwat) was washed thoroughly with water, and seeds removed. The juice was extracted from the fruit pulps by using	Standardized at 0.085% protein and 0.110 mg/g charantin The juice was tested for microbial contamination and/ or the presence of heavy metals.

						electric juicer. The non-contaminated juice (460 ml/Kg) was frozen at -20°C and then freeze dried for 72 h. The yield was 14.5 g powder/460 ml of juice	
Trakoon-osot 2013 (A)	M	Bitter melon, Mara-kheeno k (in Thai)	<i>Momordica charantia</i> (Cucurbitaceae)	WTR-002	400 mg	<i>M. charantia</i> cultivated in Suphan Buri and Kanchanaburi provinces, Thailand were harvested during April-June 2010. The voucher specimen was deposited at department of Pharmacognosy, faculty of pharmacy, Silpakorn University, Thailand. Unripe fruits with seeds removed were collected and	Charantin was an analytical marker. It was analyzed by HPLC method. The content of charantin was 0.42 ± 0.02 mg/capsule. Capsules were tested for weight variation, contaminations of pesticide residues, heavy metals and microorganism s. All tests were acceptable with respect to the criteria of Thai Herbal

						dried under the sun light for 6 h and in hot air oven at 60 °C for another 6 h.	Pharmacopoeia (THP) 2000 and supplement to Thai Herbal Pharmacopoeia (THP Supplement) 2004.
Krawinkel 2018 (B)	M	Bitter gourd	<i>Momordica charantia</i> L (Cucurbitaceae), name checked from http://www.theplantlist.org	none	2.5 g	The bitter gourd variety used was NS1020 from Namdhari Seeds Pvt. Ltd® (India) and was grown and harvested between July and September 2012. Bitter gourd fruits were washed with clean water and dipped into water containing 1–2% hydrogen peroxide. Fruits, including seeds and skin, were chopped, freeze-dried, and ground into powder	No description

						(80 mesh). To mask the bitter taste, 0.75 g alpha- cyclodextrin mixed with 2% lemon peel oil (CAS Number 8008-56-8), 75 mg beta- cyclodextrin, 15 mg steviol glycoside, and 0.75 g cucumber powder were added to the bitter gourd powder	
Hsia, 2004	P	None	<i>Aegle marmelose</i>	None	30	Leaves of A.	Assays
(C)		None	<i>Pterocarpus marsupium</i>	None	30	marmelose, C.	conducted on 7
		None	<i>Syzigium cumini</i>	None	10	tamala and G.	different
		None	<i>Momordica charantia</i>	None	7	sylvestre,	batches of
		None	<i>Gymnema sylvestre</i>	None	5	heartwood of	Pancreas Tonic
		None	<i>Trigonella foenum graecum</i>	None	5	P. marsupium, fruit of S.	from US Botanicals
		None	<i>Azadirachta indica</i>	None	5	cumin, seeds	demonstrated
		None	<i>Ficus racemosa</i>	None	5	of M.	consistent
		None	<i>Tinospora cordifolia</i>	None	2	charantia, T.	percentage
		None	<i>Cinnamomum tamala</i>	None	1	foenum and A. indica, and stem of T. cordifolia were mixed to make a capsule	concentrations of each herbal ingredient across these batches, with coefficients of variation for the percent dry

							weight composition ranging from 1.4% to 7.1% for each of the 10 components of Pancreas Tonic.
Cortez-Navarrete 2018 (C)	M	None	<i>Momordica charantia</i>	None	500mg	The dried powder of the fruit pulp was purchased from Shanghai Kangxi Biotechnology Co. of Shanghai (China). Identification, purification, and pollution tests were performed by the company.	No description

P = Polyherbal, M = Monoherbal

A = Full information about the botanical material is provided including a voucher specimen and adequate details on the preparation's compositions are provided

B = Only partial information about the botanical material and preparation's composition are provided

C = Inadequate information on the preparation's compositions and overall taxonomically inadequate.

Table 4. Secondary outcomes post exposure to intervention for each comparison group

Study	I/C	TC (mmol/L)	BMI (Kg/m ²)	ALT (IU/L)	AST (IU/L)	Creatinine (μmol/L)
		mean (SD)	mean (SD)	mean (SD)	mean (SD)	mean (SD)
Dans, 2007	I	5.08 (1.39)	26.33 (4.87)	26.03 (9.50)	23.12 (7.44)	105.28 (54.83)
	C	5.21 (1.08)	26.04 (3.55)	28.43 (15.33)	24.18 (9.71)	92.33 (22.53)
Fuangchan, 2011	I ₁	-	-	27.8 (19.4)	29.5 (16.3)	78.7 (17.1)
	I ₂			23.5 (13.9)	24.5 (13.1)	79.6 (15.03)
	I ₃			27.1 (25.5)	27.5 (24.2)	82.2 (22.1)
	C			25.2 (14.6)	26.0 (13.5)	81.3 (16.8)
Trakoon-osot, 2013 ^a	I	-	-0.04 (0.08)	-2.37 (21.00)	-3.68 (13.74)	-0.02 (0.07)
	C		-0.07 (0.17)	1.00 (6.38)	2.68 (5.95)	0.01 (0.09)
Anas, 2009	I	172.7 (28.6) *	-	-	-	-
	C	192.45 (30.7)*				
Krawinkel, 2018	I	4.3 (0.8)	29.6 (2.4)	-	-	-
	C	4.4 (1.1)	29.7 (2.4)			
Cortez-Navarrete, 2018	I	4.68 (1.02)	28.3 (1.9)	28.1 (19.4)	23.9 (16.5)	70.72 (35.36)
	C	4.39 (0.52)	28.9 (3.6)	38.2 (18.9)	24.4 (6.7)	79.56 (0.00)

*No SI unit of measurement was specified

^aMean difference between pre and post intervention phase

I = Treatment group, C = Control group