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Meta-analyses

The effect of post-oral bitter compound interventions on the postprandial glycemia response: A systematic review and meta-analysis of randomised controlled trials

Zinat Mohammadpour [a, b], Elaheh Heshmati [a, c], Leonie K. Heilbronn [a, c], Gilly A. Hendrie [d], Paige G. Brooker [d], Amanda J. Page [a, c, *]

[a] School of Biomedicine, University of Adelaide, Adelaide, SA 5005, Australia
[b] College of Medicine and Dentistry, James Cook University, Cairns, QLD 4878, Australia
[c] Nutrition, Diabetes and Gut Health, Lifelong Health Theme, SAHMRI, SA 5000, Australia
[d] Health and Biosecurity, Commonwealth Scientific and Industrial Research Organisation (CSIRO), Adelaide 5000, Australia

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SUMMARY

Background & aims: The post-oral sensing of bitter compounds by a family of bitter taste receptors (TAS2Rs) is suggested to regulate postprandial glycemia in humans. However, reports are inconsistent. This systematic review used meta-analysis to synthesise the impact of bitter compound interventions on the postprandial glycaemic response in humans.

Methods: Electronic databases (Medline, PubMed, and Web of Science) were systematically searched from inception to April 2024 to identify randomised controlled trials reporting the effect of interventions utilising post-oral bitter compounds *vs.* placebo on postprandial plasma glucose levels at t = 2 h (2 h-PPG), and area under the curve (AUC) of glucose, insulin, and c-peptide. The random-effect and subgroup analysis were performed to calculate pooled weighted mean differences (WMD), overall and by pre-defined criteria.

Results: Forty-six studies (within 34 articles) were identified; 29 and 17 studies described chronic and acute interventions, respectively. The chronic interventions reduced 2 h-PPG (n = 21, WMD = −0.35 mmol/L, 95%CIs = −0.58, −0.11) but not AUC for glucose or insulin. Subgroup analysis showed the former was particularly evident in individuals with impaired glycemia, interventions longer than three months, or quinine family administration. The acute interventions did not improve the postprandial glycemia response, but subgroup analysis revealed a decrease in AUC-glucose after quinine family administration (n = 4 WMD = −90.40 (nmol × time/L), 95%CIs = −132.70, −48.10).

Conclusion: Chronic bitter compound interventions, particularly those from the quinine family, may have therapeutic potential in those with glycemia dysregulation. Acute intervention of the quinine family may also improve postprandial glucose. Given the very low quality of the evidence, further investigations with more rigorous methods are still required.

1. Introduction

"Bitter compounds" is an overarching term describing a broad range of chemical compounds mediating bitter taste [1]. Bitter compounds can be naturally found in plants (e.g., caffeine in coffee) and plant extracts (e.g., quinine in the extracts of the cinchona tree). They can also be generated during food processing (e.g., epigallocatechin gallate originated from catechin in green tea). In addition, many chemically synthesised compounds (e.g., hydroxychloroquine) taste extremely bitter [1]. The diverse structures of bitter compounds (e.g., phenols, esters, fatty acids, hydroxy fatty acids, amines, and flavonoids, among many others) indicate the wide range of bitter chemotypes [2,3]. However, almost all bitter compounds are detected by at least one of 25 subtypes of the bitter taste receptor family (taste 2 receptors, TAS2Rs) [4].

Evidence suggests that activation of TAS2Rs by bitter compounds in the gastrointestinal (GI) lumen impacts the glycaemic response [5,6]. For example, reports from the Amish Family Diabetes Study confirmed that a functionally compromised TAS2R is

* Corresponding author. School of Biomedicine, University of Adelaide, Adelaide, SA 5005, Australia.
E-mail address: amanda.page@adelaide.edu.au (A.J. Page).

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associated with disrupted postprandial blood glucose and insulin during an oral glucose tolerance test (OGTT) [7]. Although not fully established, it is suggested that bitter compound-induced activation of TAS2Rs on GI enteroendocrine cells initiates an intracellular signalling cascade culminating in gut hormone secretion and subsequent slowing of gastric emptying [6]. Moreover, TAS2Rs on GI smooth muscle cells are reportedly involved in gastric emptying [8].

Given the above, bitter compounds seem likely to regulate postprandial glycemia. The postprandial glucoregulatory effect is particularly important for individuals with impaired glycaemia, with chronically elevated blood glucose levels contributing to the progression of type 2 diabetes mellitus (T2DM) [9]. Impaired glycaemia also causes microvascular and macrovascular complications, which ultimately increase the risk of developing cardiovascular disease [10]. Therefore, interventions regulating postprandial glycemia, such as bitter compounds, may have therapeutic potential in preventing and managing these conditions [11,12]. It was highlighted in previous systematic reviews and meta-analyses that caffeine and green tea catechins may reduce the insulin sensitivity index [13] and fasting blood glucose levels [14], respectively. However, these studies focused solely on the oral administration of individual bitter compounds as a drink. Moreover, other evidence is inconsistent regarding factors such as bitter compound type, duration (e.g., the day of study or over time), and route of administration (e.g., oral, intragastric, or intraduodenal). Therefore, the purpose of this systematic review and meta-analysis was to investigate and statistically evaluate the randomised controlled trials (RCTs) reporting the effect of post-oral bitter compounds *vs.* placebo on (i) postprandial plasma glucose level at t = 2 h (2 h-PPG); (ii) area under the curve (AUC) [15] of postprandial plasma level of glucose (AUC-glucose); (iii) insulin (AUC-insulin); and (iv) c-peptide (AUC-c-peptide), an endogenous insulin secretion marker.

2. Materials & methods

2.1. Protocol and registration

This review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) 2020 statement [16] and was prospectively registered with the International Prospective Register of Systematic Reviews (PROSPERO; CRD42022358876).

2.2. Search strategy and study selection

The eligibility criteria and search strategy were developed using the following population, intervention, comparison, outcome (PICO) framework [17]: (P) adults (aged >18 y) who are not pregnant or lactating, (I) post-oral administration (capsule or infusion) of bitter compounds or plant extracts containing bitter compounds more than 90%, (C) compared to administration of placebo, (O) 2 h-PPG, AUC-glucose, AUC-insulin, or AUC-c-peptide.

A systematic literature search of three electronic databases (Medline, PubMed, and Web of Science) was performed to identify relevant articles published in English from the database inception to April 2024. A combination of MeSH (medical subject headings) terms and free-text keywords were used to search for relevant interventions (bitter compounds), outcomes (postprandial glycemia), and study type (RCT) (see supp table S1 for the full search strategy). Citation chaining was used to search for additional articles not captured in the systematic search.

Two investigators (ZM & EH) independently screened articles by title/abstract and full text using Covidence [18]. Disagreements were resolved by discussion between the investigators in the presence of a third investigator (AP).

2.3. Data extraction

The following data was extracted from each full-text article:

- General information, including the name of the first author, year of publication, and number of individuals
- Main outcomes, including the mean and standard deviation (SD) of post-intervention status (for treatment and placebo groups) of 2 h-PPG (mmol/L), AUC-glucose (mmol × time/L), AUC-insulin (nmol × time/L), and AUC-c-peptide (pmol × time/L) (preferably during the first 120 min of OGTT or a mixed meal tolerance test (MMTT))
- Predefined criteria, including individuals' sex (male, female, or both male and female), weight status (body mass index (BMI) less than or greater than 25 kg/m^2, interpreted as lean or overweight/obese [19]), glycaemia status (normal or impaired glycemia (prediabetes/T2DM); if mentioned in the study), intervention route (treatment was delivered via intragastric (capsule), intragastric (infusion), or intraduodenal (infusion)), intervention duration (acute or chronic if treatment was applied in the day of study or over time, respectively), intervention duration for the chronic studies (less or more than three months [20,21], interpreted as short-term chronic or long-term chronic, respectively), and the type of bitter compounds

If studies reported standard error of the mean (SEM), SD was calculated using the equation "SD = SEM × sqrt (sample size)" [22]. A web-based program (WebPlotDigitiser accessible via https://apps.automeris.io/wpd/) was used to estimate data from figures [23].

If eligible studies did not report the interested data, the corresponding author of the study was contacted by email twice within one month. Studies were excluded if the intervention was not identified as bitter by BitterDB [24] or if other interventions, such as exercise or diet, were simultaneously applied in the study.

Data extraction was performed by an investigator (ZM) and checked by another investigator (EH). Conflicts were resolved through discussion.

2.4. Study risk of bias assessment

Version 2 of the Cochrane Risk of Bias tool for randomized trials (RoB 2) [25] was used to assess the risk of bias. Studies were evaluated in five domains to identify potential bias in the (i) randomisation process, (ii) deviations from intended interventions, (iii) missing outcome data, (iv) measurement of the outcome, and (v) selection of the reported results. Each domain, and subsequently each study, was judged to have a 'low' or 'high' risk of bias or expressed as having 'some concerns'. Two investigators (ZM & EH) independently assessed the bias risk, and discussions resolved discrepancies.

2.5. Quality of evidence assessment

The quality of the evidence was assessed for each outcome using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE), considering the risk of bias, inconsistency, indirectness, imprecision, and publication bias of the included studies [26]. The overall certainty was identified as 'high', 'moderate', 'low', or 'very low' quality [27].

Two investigators (ZM & EH) independently evaluated the overall certainty of the evidence, and discrepancies were resolved through discussion.

2.6. Statistical analysis

StataMP17 (Stata Corp, College Station, TX) was used to compute the meta-analysis. Random-effect analysis using the DerSimonian and Laird method was performed to calculate weighted mean differences (WMD) between studies [28]. When comparing the results, 95% confidence intervals (CIs) were considered to measure the precision of the findings [29]. It should be noted that very wide CIs, reflecting uncertainty around the effect estimate, and a null value (e.g., WMD = 0.0) can result in a lower weight assigned to the study in the meta-analysis. In the case of a weight of 0.00, the study did not contribute to the overall WMD [29,30]. The variation in WMD attributable to heterogeneity was assessed by I^2 and Cochran's Q test (significance of $p < 0.1$), and I^2 thresholds were interpreted according to the Cochrane Handbook [30]. Subgroup analysis (Random-effect analysis by pre-defined criteria) was performed to find the potential source of heterogeneity and estimate the precise effect of each subgroup on the overall WMD [29,30]. Subgroup analyses were performed for individuals' sex, weight status, glycemia status, intervention duration, type of bitter compound, route of bitter compound administration, and the studies' risk of bias if more than three studies were available in each group for comparison [28]. A sensitivity analysis (by removing selected studies from the analysis) was also performed to find the impact of studies with very wide CIs and/or weight of 0.00 on overall WMD and address the conflicts between findings [29]. Egger's test was conducted to show potential publication bias, with a significant p-value ($p>|t| < 0.1$) suggesting the presence of publication bias [30,31]. Studies with chronic and acute interventions were analysed separately.

3. Results

3.1. Study selection

The study selection process guided by PRISMA [16] is summarised in Fig. 1. Of the 747 unique articles found through database searching, 677 were excluded after screening by title/abstract. In the full-text screening phase, 35 articles did not meet the inclusion criteria (e.g., three used plant extract interventions containing less than 90% bitter compound) and were excluded. After identifying seven articles [32–38] by backward reference searching, 42 articles [39–73] were selected for data extraction. However, eight eligible articles [66–73] did not report the interested data. Seven articles reported trial effects from more than one eligible study arm [33,39,41,45,51,56,57]. Finally, 46 included studies were identified from 34 eligible articles [32–65], and data were appraised for meta-analysis.

3.2. Characteristics of the included studies

The characteristics of the included studies are summarised in Table 1. The total sample size across the studies was 1520 individuals (range 7 [65] to 122 [41]). A range of bitter compounds were used across the studies. Compounds from the quinine family were most commonly used (16 studies within 7 articles included quinine hydrochloride [39,56,57], chloroquine [33], hydroxychloroquine [35,41,44])), followed by caffeine (9 studies within 9 articles [37,40,59–65]) and resveratrol (8 studies within 8 articles [32,34,38,43,46,47,50,52]). Other bitter compounds included epigallocatechin gallate (6 studies within 4 articles [36,45,55,58]), genistein (2 studies within 2 articles [42,51]), and thiamine hydrochloride (1 study [54]). Three studies (within 3 articles) used a mixture of bitter compounds (including resveratrol & hesperetin [50] and epigallocatechin gallate & resveratrol [48,53]). While seven studies (within 4 articles) used intragastric [56,57]) or intraduodenal [39,56] intubation for bolus delivery of treatments, the remainder used capsules for intragastric administration.

Most studies (n = 38) were judged to be 'low risk' of bias, seven studies (reported in six articles [35,38,44,57,59,62]) had 'some concern', and one study [60] was judged to be 'high risk' of bias. The domains of recruitment of individuals in a cluster-randomized trial (D1b), deviations from the intended interventions (D2a), and measurement of the outcome (D4) were the main sources of bias of the included studies (see supp table S2 for more details).

In total, 17 studies (within 13 articles [36,37,39,56–65]) used acute interventions (treatment was applied on the day of study), and 29 (within 22 articles [32–35,38,40–55]) applied chronic interventions (treatment was delivered over time). This meta-analysis reported the results separately for studies with acute and chronic interventions.

3.3. The effect of bitter compounds on postprandial glucose level at t = 2 h (2 h-PPG)

3.3.1. Chronic interventions

Pooling effect sizes from 21 studies (within 15 articles [34,35,38,40–42,44,45,49–55]) with 1346 individuals revealed that chronic intervention with bitter compounds resulted in a greater mean reduction in 2 h-PPG compared to that of the placebo group (WMD = −0.346 mmol/L, 95%CIs = −0.580, −0.112) (Table 2 and Fig. 2). After applying subgroup analysis, results remained significant for studies with male and female (n = 13, WMD = −0.427 mmol/L, 95%CIs = −0.817, −0.038), lean (n = 5, WMD = −0.937 mmol/L, 95%CIs = −1.472, −0.403), overweight/obese weight status (n = 15, WMD = −0.238 mmol/L, 95% CIs = −0.482, −0.007), and individuals with impaired glycemia (n = 11, WMD = −0.685 mmol/L, 95%CIs = −1.153, −0.217). Significance was also observed with interventions longer than three months (n = 19, WMD = −0.300 mmol/L, 95%CIs = −0.547, −0.053) and treatment with bitter compounds from the quinine family (n = 5, WMD = −0.860 mmol/L, 95%CIs = −1.476, −0.243) (Table 3). The overall quality of this outcome was judged to be 'very low' (Table 2) due to substantial heterogeneity between studies (I^2 = 88.1%, $p < 0.1$). However, subgroup analysis identified none of the predefined criteria as a potential source of heterogeneity (supp table S3). Moreover, Egger's test revealed publication bias due to small-study effects ($p>|t|$ 0.018).

3.3.2. Acute intervention

Combining the effect sizes of 15 studies (within 9 articles [37,39,57,59–63,65]) with 406 individuals did not show any differences between bitter compound and placebo interventions for 2 h-PPG (WMD = −0.074 mmol/L, 95%CIs = −0.220, 0.071) (Table 2 and Fig. 2). Subgroup analysis did not change the results (Table 3). There was also no important heterogeneity between studies (I^2 = 0%) or evidence of publication bias ($p>|t|$ 0.714) (Table 2). However, the overall quality of this outcome was judged to be 'moderate' (Table 2) as there was a serious risk of bias.

3.4. The effect of bitter compounds on the area under the curve for glucose (AUC-glucose)

3.4.1. Chronic intervention

Pooling effect sizes from 15 studies (within 11 articles [32,33,42,43,46,47,49–52,55]) with 912 individuals failed to show

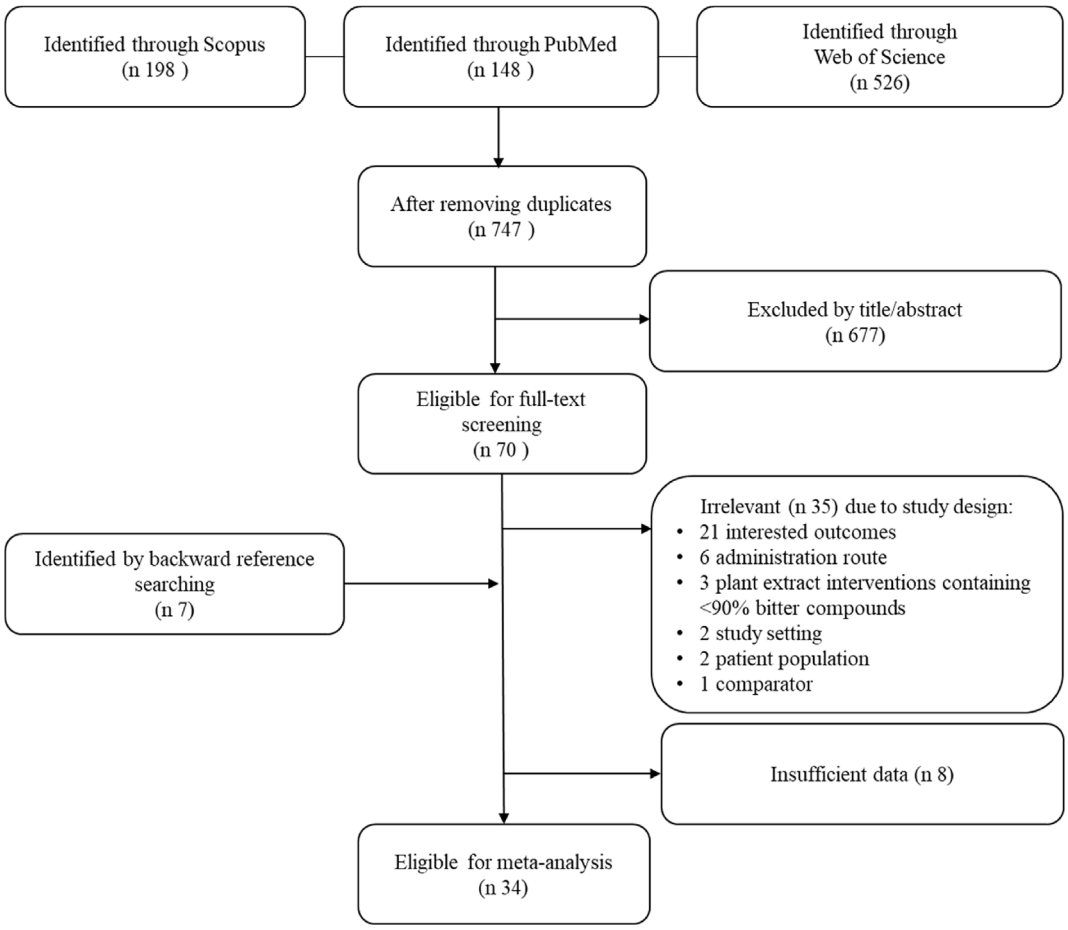

Fig. 1. Flow diagram of study selection up to April 2024.

any effect of bitter compounds on AUC-glucose (WMD = 0.176 (mmol × time/L), 95%CIs = −0.445, 0.796) (Table 2 and Fig. 3). The results did not change by subgroup analysis (Table 3). Heterogeneity between studies was not important (I^2 = 7.7%) and there was no publication bias (p>|t| = 0.515) (Table 2). The overall quality of this outcome was also judged to be 'high' (Table 2).

3.4.2. Acute intervention

Data from 11 studies (within 9 articles [37,39,57,59–63,65]) with 290 individuals did not show any difference in AUC-glucose between bitter compound and placebo treatments (WMD = −2.273 (mmol × time/L), 95%CIs = 3.454, 3.491) (Table 2 and Fig. 3). However, applying subgroup analysis showed a significant reduction by quinine family administration (WMD = −90.393 (mmol × time/L), 95%CIs = −132.705, −48.082) (Table 3). The overall quality of this outcome was judged to be 'low' (Table 2) due to the small pooled sample size (n < 400). Moreover, there was substantial heterogeneity between studies (I^2 = 78.7%, p < 0.1), and the type of bitter compound was disclosed as the potential source of heterogeneity (supp table S3). There was no publication bias (p>|t| = 0.361) (Table 2).

3.5. The effect of bitter compounds on the area under the curve for insulin (AUC-insulin)

3.5.1. Chronic intervention

Combining data from 11 studies (within 8 articles [32,33,42,45–47,51,52]) with 646 individuals did not show any effect of bitter compounds on AUC-insulin (WMD = 147.726 (nmol × time/L), 95%CIs = −94.313, 389.765) (Table 2 and Fig. 4). Subgroup analysis revealed a significant effect of bitter compounds on females for AUC-insulin (n = 6, WMD = 313.529 (nmol × time/L), 95%CIs = 32.129, 594.929) (Table 3). There was no important heterogeneity between studies (I^2 = 39.7%, p > 0.1) and no publication bias (p>|t| = 0.311) (Table 2). The overall quality of this outcome was judged to be 'high' (Table 2).

3.5.2. Acute intervention

Results from 11 studies (within 9 articles [39,57,59–65]) with 280 individuals revealed no difference between bitter compound and placebo treatments on AUC-insulin (WMD = 12.348 (nmol × time/L), 95%CIs = −11.870, 36.567) (Table 2 and Fig. 4). The results did not change after subgroup analysis (Table 3). There was no important heterogeneity between studies (I^2 = 23.4%, p > 0.1) (Table 2). The overall quality of this outcome was judged to be 'low' (Table 2) due to the small pooled sample size (n < 400). Moreover, the publication bias test revealed some small-study effects (p>|t| = 0.095) (Table 2).

3.6. The effect of bitter compounds on the area under the curve for c-peptide (AUC-c-peptide)

3.6.1. Chronic intervention

There was only one study [33] with chronic intervention reporting AUC-c-peptide, therefore no analysis was performed. Results of this study [33] with 107 individuals revealed no

Table 1
Characteristics of included studies.

Study					Participant					Intervention				Tolerance test		Interested outcomes
	Ref	First author	Year	Country	Design	n	Sex	Age	BMI	Condition[b]	Bitter compound	Dose (daily)	Route	Duration (weeks)	Method	Duration (min)	
Chronic intervention																	
1	[40]	Van Schaik	2022	Australia	cross-over	8	male	22	23	no	caffeine	100 mg	IG-capsules	1	MMTT	120	2 h-PPG[a]
2	[41]	Chakravarti A	2021	India	parallel	122	male & female	53	24	T2DM	hydroxychloroquine	200 mg	IG-capsules	12	MMTT	120	2 h-PPG
3	[41]	Chakravarti B	2021	India	parallel	122	male & female	52	25	T2DM	hydroxychloroquine	300 mg	IG-capsules	12	MMTT	120	2 h-PPG
4	[41]	Chakravarti C	2021	India	parallel	122	male & female	53	25	T2DM	hydroxychloroquine	400 mg	IG-capsules	12	MMTT	120	2 h-PPG
5	[32]	de Ligt	2020	Netherlands	parallel	41	male & female	62	29	no	resveratrol	150 mg/day	IG-capsules	24	OGTT	120	AUC-Glucose[a] AUC-Insulin[a]
6	[42]	Guevara Cruz	2020	Mexico	parallel	45	male & female	20 −60	30 −40	no	genistein	50 mg	IG-capsules	8	OGTT	120	AUC-Glucose AUC-Insulin
7	[33]	McGill A	2019	USA	cross-over	45	male & female	55	35	MS, not diabetic	chloroquine	Weekly 80 mg	IG-capsules	3	OGTT	120	AUC-Glucose
8	[33]	McGill B	2019	USA	cross-over	45	male & female	55	35	MS, not diabetic	chloroquine	80 mg	IG-capsules	3	OGTT	120	AUC-Glucose
9	[33]	McGill C	2019	USA	cross-over	25	male & female	55	35	MS, not diabetic	chloroquine	250 mg	IG-capsules	3	OGTT	120	AUC-Glucose
10	[33]	McGill D	2019	USA	parallel	107	male & female	55	35	MS, not diabetic	chloroquine	250 mg	IG-capsules	48	OGTT	120	AUC-Glucose AUC-Insulin AUC-c peptide
11	[43]	Walker	2019	Switzerland	cross-over	28	male	48	34	MS	resveratrol	200 mg	IG-capsules	4	OGTT	120	2 h-PPG AUC-Glucose
12	[44]	Baidya	2018	India	parallel	100	male & female	49	28	T2DM	hydroxychloroquine	400 mg	IG-capsules	24	OGTT	120	2 h-PPG
13	[34]	Kantartzis	2018	Germany	parallel	105	male & female	18 −70	≥27	some impaired glycaemia	resveratrol	150 mg/day	IG-capsules	12	OGTT	120	2 h-PPG
14	[35]	Townsend	2018	USA	parallel	39	male & female	55	ND	T2DM	hydroxychloroquine	400 mg	IG-capsules	24	OGTT	120	2 h-PPG
15	[45]	Dostal A	2017	USA	parallel	20	female	61	28	postmenopausal	epigallocatechin gallate	843 mg	IG-capsules	48	MMTT	120	2 h-PPG[a] AUC-Insulin
16	[45]	Dostal B	2017	USA	parallel	20	female	61	28	postmenopausal	epigallocatechin gallate	843 mg	IG-capsules	48	MMTT	120	AUC-Insulin
17	[45]	Dostal C	2017	USA	parallel	20	female	61	28	postmenopausal	epigallocatechin gallate	843 mg	IG-capsules	48	MMTT	120	2 h-PPG[a] AUC-Insulin
18	[46]	Pollack	2017	USA	cross-over	30	male & female	67	35	prediabetic	resveratrol	2000 −3000 mg	IG-capsules	6	MMTT	180	AUC-Glucose AUC-Insulin
19	[47]	van der Made	2017	Netherland	cross-over	45	male & female	61	28	no	resveratrol	150 mg	IG-capsules	4	MMTT	240	2 h-PPG
20	[48]	Most	2016	Netherlands	cross-over	38	male & female	38	30	no	epigallocatechin gallate & resveratrol	282 mg & 80 mg	IG-capsules	12	MMTT (high fat)	120	2 h-PPG[a] AUC-Glucose
21	[49]	Thazhath	2016	Australia	cross-over	14	male & female	67	28	T2DM	resveratrol	1000 mg	IG-capsules	5	MMTT	240	2 h-PPG[a] AUC-Glucose
22	[50]	Xue	2016	UK	parallel	32	male & female	45	30	no	resveratrol & hesperetin	90 mg & 120 mg	IG-capsules	8	OGTT	90	2 h-PPG AUC-Glucose
23	[51]	Ye A	2015	China	parallel	109	female	56	24	T2DM, no treatment required	daidzein	50 mg	IG-capsules	24	OGTT	180	2 h-PPG AUC-Glucose AUC-Insulin
24	[51]	Ye B	2015	China	parallel	110	female	56	24	T2DM, no treatment required	genistein	50 mg	IG-capsules	24	OGTT	180	2 h-PPG AUC-Glucose AUC-Insulin

(*continued on next page*)

Table 1 (*continued*)

Study					Participant					Intervention				Tolerance test		Interested outcomes
	Ref	First author	Year	Country	Design	n	Sex	Age	BMI	Condition[b]	Bitter compound	Dose (daily)	Route	Duration (weeks)	Method	Duration (min)	
25	[52]	Méndez-del Villar	2014	Mexico	parallel	24	male & female	40	35	MS, not T2DM	resveratrol	1500 mg	IG-capsules	12	OGTT	120	2 h-PPG AUC-Glucose AUC-Insulin
26	[53]	Most	2014	Netherlands	cross-over	18	male & female	35	29	no	epigallocatechin gallate & resveratrol	282 mg & 200 mg	IG-capsules	3 days	MMTT (high fat)	120	2 h-PPG[a]
27	[54]	Alaei-Shahmiri	2013	Australia	cross-over	12	male & female	57	29	T2DM	thiamine hydrochloride	300 mg	IG-capsules	6	OGTT	120	2 h-PPG[a]
28	[38]	Timmers	2011	Netherlands	cross-over	10	male	52	31	no	resveratrol	150 mg	IG-capsules	4	MMTT	120	2 h-PPG[a]
29	[55]	Brown	2009	UK	parallel	88	male	51	31	no	epigallocatechin gallate	800 mg	IG-capsules	8	OGTT	120	2 h-PPG AUC-Glucose
Acute intervention																	
1	[39]	Rezaie A	2023	Australia	cross-over	13	male	26	23	no	quinine hydrochloride	600 mg	ID-bolus delivery	–	MMTT	120	2 h-PPG[a] AUC-Glucose AUC-Insulin AUC-c peptide
2	[39]	Rezaie B	2023	Australia	cross-over	13	female	27	22	no	quinine hydrochloride	600 mg	ID-bolus delivery	–	MMTT	120	2 h-PPG[a] AUC-Glucose AUC-Insulin AUC-c peptide
3	[39]	Rezaie C	2023	Australia	cross-over	13	female	27	22	no	quinine hydrochloride	300 mg	ID-bolus delivery	–	MMTT	120	2 h-PPG[a]
4	[56]	Rose A	2021	Australia	cross-over	14	male	25	22	no	quinine hydrochloride	600 mg	IG-bolus delivery	–	MMTT	120	2 h-PPG[a]
5	[56]	Rose B	2021	Australia	cross-over	14	male	25	22	no	quinine hydrochloride	600 mg	ID-bolus delivery	–	MMTT	120	2 h-PPG[a]
6	[57]	Bitarafan A	2020	Australia	cross-over	14	male	26	23	no	quinine hydrochloride	275 mg	IG-bolus delivery	–	MMTT	120	2 h-PPG AUC-Glucose AUC-Insulin
7	[57]	Bitarafan B	2020	Australia	cross-over	14	male	26	23	no	quinine hydrochloride	600 mg	IG-bolus delivery	–	MMTT	120	2 h-PPG AUC-Glucose AUC-Insulin
8	[58]	de Morais Junior	2020	Brazil	cross-over	14	female	21	21	no	epigallocatechin gallate	800 mg	IG-capsules	–	MMTT (high fat)	120	2 h-PPG
9	[36]	Fernandes	2018	Brazil	cross-over	22	female	24	21	no	epigallocatechin gallate	752 mg	IG-capsules	–	MMTT	120	2 h-PPG
10	[37]	Schubert	2014	Australia	cross-over	12	male & female	26	23	no	Caffeine	4 mg/kg	IG-capsules	–	MMTT	270	AUC-Glucose
11	[59]	Battram	2007	Canada	cross-over	14	male & female	45	ND	tetraplegia	Caffeine	4 mg/kg	IG-capsules	–	OGTT	120	2 h-PPG[a] AUC-Glucose AUC-Insulin AUC-c peptide
12	[60]	Dekker	2007	Canada	cross-over	12	male	22	23	no	Caffeine	5 mg/kg	IG-capsules	–	OGTT	120	2 h-PPG[a] AUC-Glucose AUC-Insulin AUC-c peptide
13	[61]	Lane	2004	USA	cross-over	14	male & female	62	ND	T2DM	Caffeine	375 mg	IG-capsules	–	MMTT	120	AUC-Glucose AUC-Insulin
14	[62]	Petrie	2004	Canada	cross-over	9	male	31	34	no	Caffeine	5 mg/kg	IG-capsules	–	OGTT	120	2 h-PPG[a] AUC-Glucose AUC-Insulin AUC-c peptide

15 [63] Robinson	2004	Canada	cross-over	12	male	49	32	T2DM	Caffeine	5 mg/kg	IG-capsules	–	OGTT	180	2 h-PPG[a] AUC-Glucose AUC-Insulin AUC-c peptide
16 [64] Thong	2002	Canada	cross-over	7	male	24	23	no	Caffeine	5 mg/kg	IG-capsules	–	OGTT	120	2 h-PPG[a] AUC-Insulin AUC-c peptide
17 [65] Graham	2001	Canada	cross-over	18	male	18 –33	ND	no	Caffeine	5 mg/kg	IG-capsules	–	OGTT	120	2 h-PPG[a] AUC-Glucose AUC-Insulin AUC-c peptide

ND, not determined; T2DM, type 2 diabetes mellitus; MS, metabolic syndrome; IG, intragastric; ID, intraduodenal; OGTT, oral glucose tolerance test; MMTT, mixed meal/drink tolerance test; 2 h-PPG, postprandial plasma glucose at t = 2 h; AUC, area under the curve.

[a] Calculated from image.

[b] Participants diagnosed with prediabetes or T2DM were identified as impaired glycaemia in this study.

difference between bitter compound and placebo treatments on AUC-insulin (WMD = 0.70 (nmol × time/L), 95%CIs = −1.100, 1.500).

3.6.2. Acute intervention

Pooling effect sizes from 8 acute studies (within 7 articles [39,59,60,62–65]) showed a significant increase in AUC-c-peptide in response to bitter compound vs placebo (WMD = 43.534 (pmol × time/L), 95%CIs = 26.749, 60.320) (Table 2 and Fig. 5), without heterogeneity between studies (I^2 = 0%, p < 0.1) (supp table S3). After subgroup analysis, the results remained significant in all subgroups. There was no publication bias (p>|t| = 0.792) (Table 2). However, the overall quality of this outcome was judged to be 'moderate' (Table 2) due to the small pooled sample size (n < 400).

3.7. Sensitivity analysis

When conducting random effect analysis to find the overall WMDs, the following studies revealed a very wide 95%CIs:

- Thazhath-2016 [49] for AUC- glucose outcome in chronic intervention
- Guevara Cruz-2020 [42] and Méndez-del Villar- 2014 [52] for AUC-insulin outcome in chronic intervention
- Battram-2007 [59], Dekker-2007 [60], Robinson-2004 [63] for AUC-insulin outcome in acute intervention
- Battram-2007 [59] and Petrie-2004 [62] for AUC-c-peptide outcome in acute intervention.

We tried to highlight the potential reasons leading to these very wide CIs by considering the study sample size, participants' status (sex, age, condition, BMI), type and duration of the interventions and the methods used for extraction/calculation of the mean and SD of the outcomes. However, we could not pinpoint any specific reason. It should be noted that very wide CIs lead to a minimal weight for the study.

Although the studies with small weights have a meagre impact on overall WMD, sensitivity analysis was performed by removing the studies with very wide CIs and the ones with a weight of 0.00. The results confirmed the same pattern of results with and without sensitivity analysis. Supplementary table S4 provides detailed information about studies considered in the sensitivity analysis and the related results.

To address the conflicts between results, the random effect analysis was repeated for chronic 2 h-PPG and chronic AUC-glucose, with only studies reporting both 2 h-PPG and AUC-glucose (n = 8). Similar sensitivity analysis was performed for acute AUC-insulin and acute AUC-c-peptide, only analysing studies reporting both AUC-insulin and AUC-c-peptide (n = 8). Results did not show any difference between the bitter compound and placebo treatments for both chronic 2 h-PPG (WMD = −0.088 mmol/L, 95%CIs = −0.534, 0.358) and chronic AUC-glucose (WMD = −0.320 (mmol × time/L), 95%CIs = −2.197, 1.558). No differences were observed in the results for both acute AUC-insulin (WMD = 8.902 nmol/L, 95%CIs = −12.684, 30.487) and acute AUC-c-peptide (WMD = 43.534 (mmol × time/L), 95% CIs = 26.749, 60.320).

4. Discussion

This meta-analysis confirmed that chronic interventions with bitter compounds reduced 2 h-PPG, overall and in subgroups of individuals with impaired glycemia, intervention longer than three months, and quinine family administration. However,

Table 2
Summary of the results for the effect of bitter compound intervention on the postprandial glycemia response.

	Studies (n)	Sample size (n)	WMD (95% CIs)	Heterogeneity (95% CIs)	p>|t|	Evidence quality[b]	How to GRADE[b]
***2h-PPG* (mmol/L)**							
chronic intervention	21	1346	−0.346 (−0.580, −0.112) [a]	88.1% (0.0%, 96.5%) [a]	0.018 [a]	⊕○○○Very Low	Risk of bias: no Inconsistency: very serious [c] Indirectness: no Imprecision: no Publication bias: suspected [d]
acute intervention	15	406	−0.074 (−0.220, 0.071)	0% (0.0%, 39.6%)	0.714	⊕⊕⊕○Moderate	Risk of bias: serious [e] Inconsistency: no Indirectness: no Imprecision: no Publication bias: no
AUC-glucose (mmol × time/L)							
chronic intervention	15	912	0.176 (−0.445, 0.796)	7.7% (0.0%, 50.6%)	0.515	⊕⊕⊕⊕High	Risk of bias: no Inconsistency: no Indirectness: no Imprecision: no Publication bias: no
acute intervention	11	290	−2.273 (−8.345, 3.799)	78.7% (0.0%, 94.9%) [a]	0.361	⊕⊕○○ Low	Risk of bias: no [e] Inconsistency: serious [f] Indirectness: no Imprecision: serious [g] Publication bias: no
AUC-insulin (pmol × time/L)							
chronic intervention	11	646	147.726 (−94.313, 389.765)	39.7% (0.0%, 72.6%)	0.311	⊕⊕⊕⊕High	Risk of bias: no Inconsistency: no Indirectness: no Imprecision: no Publication bias: no
acute intervention	11	280	12.348 (−11.870, 36.567)	23.4% (0.0%, 66.8%)	0.095[a]	⊕⊕○○ Low	Risk of bias: no Inconsistency: no Indirectness: no Imprecision: serious [g] Publication bias: suspected [d]
AUC- c-peptide (nmol × time/L)							
acute intervention	8	196	43.534 (26.749 60.320) [a]	0% (0.0%, 52.4%)	0.791	⊕⊕⊕○Moderate	Risk of bias: no [h] Inconsistency: no Indirectness: no Imprecision: serious [g] Publication bias: no

There was only one study on AUC-c-peptide in chronic intervention; therefore, an analysis was not performed.
WMD, weighted mean differences; CIs, confidence intervals; p>|t|, test of small-study effects; 2 h-PPG, postprandial plasma glucose at t = 2 h; AUC, area under the curve; GRADE, Grading of Recommendations Assessment, Development, and Evaluation.
[a] p-value was statistically significant for test of WMD (95% CIs did not include zero), test of heterogeneity (with significance of < 0.1), or p > |t| (with significance of < 0.1).
[b] Quality of the evidence was assessed for each outcome according to GRADE (26) and below are the reasons to downgrade each criteria:
[c] There was substantial heterogeneity between studies and subgroup analysis could not disclose the source of heterogeneity.
[d] Small-study effect was detected.
[e] Four studies had 'some concern' and one study had a 'high risk' of bias, but subgroup analysis revealed the result was driven from studies with 'low risk' of bias.
[f] There was substantial heterogeneity between studies and subgroup analysis disclosed the source of heterogeneity.
[g] The pooled sample size was less than 400.
[h] Two studies had 'some concern' and one study had a 'high risk' of bias, but subgroup analysis revealed the result was driven from studies with 'low risk' of bias.

chronic bitter compound administration did not affect AUC-glucose and AUC-insulin. Acute intervention of bitter compounds did not improve postprandial glucose outcomes but decreased AUC-glucose in the studies with quinine family intervention. The overall AUC-insulin did not change after acute interventions. Compared to placebo, there was a small and likely clinically insignificant increase in AUC-c-peptide following acute intervention of bitter compounds.

There are consistent reports from preclinical studies that bitter compounds decrease postprandial blood glucose [74,75]. For instance, compared to placebo, acute IG administration of denatonium benzoate has been reported to lower postprandial glucose in *db/db* mice, an animal model for diabetes [74]. Daily IG administration of isocohumulone for two weeks, compared with placebo, was reported to improve postprandial glucose during OGTT in wild-type mice [75]. This meta-analysis also suggested that chronic interventions with bitter compounds may improve postprandial glycemia in human studies, albeit with the quality of evidence assessed as 'very low'.

The potential underlying mechanisms are through the interaction between bitter compounds and TAS2Rs which are well-reviewed elsewhere [5,6]. Briefly, bitter taste receptors, TAS2Rs, are located on enteroendocrine cells in the gut wall. When activated, these receptors can induce glucoregulatory gut hormone secretion, such as glucagon-like peptide-1 (GLP-1) [6]. This can subsequently stimulate insulin secretion from the pancreas [76] and slow gastric emptying via vagal afferent-mediated central mechanisms [77,78]. In addition, activation of TAS2Rs on gastric smooth muscle cells can directly inhibit gastric phase III contractions and slow gastric emptying, leading to decreased blood glucose [8,79]. Given that chronic interventions failed to increase AUC-insulin in this meta-analysis, the gastric emptying-related pathway is more plausible. Further, the potential impact of circulating bitter compounds on reducing lipid accumulation [80] and suppressing hedonic food intake [81] might also play a role in improving the postprandial glycaemic response. This effect is particularly notable in interventions longer than three months. It is also plausible that, although there is a lack of effect on AUC-insulin,

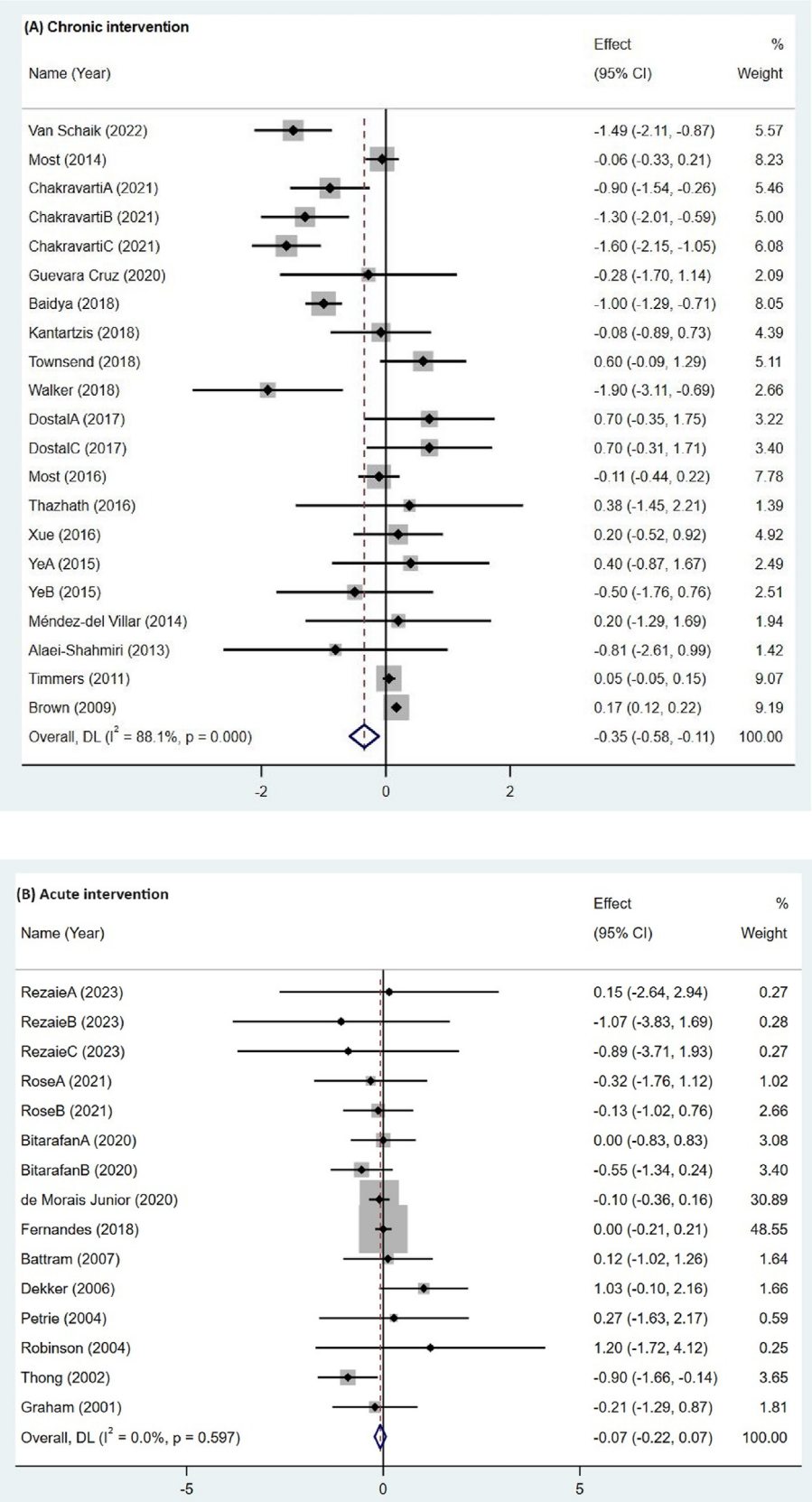

Fig. 2. Forest plot for the pooled weighted mean differences of bitter compound interventions on the postprandial plasma level of glucose at t = 2 h (2 h-PPG; mmol/L) using random-effect model; (A) chronic and (B) acute interventions.

Table 3
Subgroup analysis using the random-effect model for the effect of bitter compound intervention on the postprandial glycemia response.

	2h-PPG (mmol/L)			*AUC-glucose (mmol × time/L)*			*AUC-insulin (pmol × time/L)*			*AUC- c-peptide (nmol × time/L)*		
	n	*WMD*	*95%CIs*	*n*	*WMD*	*95%CIs*	*n*	*WMD*	*95%CIs*	*n*	*WMD*	*95%CIs*
Chronic intervention												
Overall	**21**	**−0.346**[a]	**−0.580 −0.112**	**15**	**0.176**	**−0.445 0.796**	**11**	**147.726**	**−94.313 389.765**			
Individuals' sex												
male	4	−0.246	−0.554 0.063	2			0					
female	4	0.400	−0.164 0.965	2			5	313.529	32.129 594.929			
male and female	13	−0.427[a]	−0.817 −0.038	11	0.079	−0.581 0.740	6	29.664	−363.369 422.697			
Individuals' weight												
lean	5	−0.937[a]	−1.472 −0.403	2			2					
overweight/obese	15	−0.238	−0.482 −0.007	13	0.152	−0.532 0.836	9	160.659	−102.009 423.327			
not determined	1			0			0					
Individuals' glycemia[b]												
normal	10	−0.020	−0.206 0.166	10	0.411	−0.204 1.026	8	204.981	−75.045 485.008			
impaired	11	−0.685[a]	−1.153 −0.217	5	−1.348	−2.971 0.274	3					
Intervention duration												
short term (≤3 months)	2			3			0					
long term (>3 months)	19	−0.300[a]	−0.547 −0.053	12	−0.162	−1.090 0.766	11	147.726	−94.313 389.765			
Bitter compound												
quinine family	5	−0.860[a]	−1.476 −0.243	4	0.265	−0.492 1.021	1					
epigallocatechin gallate	3			1			3					
caffeine	1			0			0					
resveratrol	5	−0.248	−0.889 0.392	6	−1.363	−2.985 0.259	4	−44.763	−844.922 755.395			
genistein/daidzein	3			3			3					
other or mixture	4	−0.067	−0.266 0.132	1			0					
Risk of bias in the studies												
low	19	−0.338	−0.644[a] −0.033	14	−0.111	−0.745 0.522	11	147.726	−94.313 389.765			
some concern/high	2	−0.406	−1.552 0.741	1			0					
Acute intervention												
Overall	**15**	**−0.074**	**−0.220 0.071**	**11**	**−2.273**	**−8.345 3.799**	**11**	**12.348**	**−11.870 36.567**	**8**	**43.534**[a]	**26.749 60.320**
Individuals' sex												
male	10	−0.198	−0.564 0.168	7	1.412	−60.367 63.190	8	8.077	−3.257 19.411	6	43.475[a]	26.676 60.275
female	4	−0.045	−0.208 0.117	1			1			1		
male and female	1			3			2			1		
Individuals' weight												
lean	11	−0.103	−0.289 0.083	6	−43.110	−103.083 16.864	6	207.432	−628.709 1043.573	4	47.219[a]	18.977 75.460
overweight/obese	2			2			2			2		
not determined	2			3			3			2		
Individuals' glycemia[b]												
normal	14	−0.077	−0.223 0.068	9	−27.464	−73.443 18.514	9	8.547	−8.788 25.883	7	43.063[a]	26.123 60.004
impaired	1			2			2			1		
Bitter compound												
quinine family	7	−0.276	−0.716 0.163	4	−90.393[a]	−132.705−48.082	4	438.393	−1.303 2147.978	2		
epigallocatechin gallate	2			0			0			0		
caffeine	6	0.024	−0.668 0.715	7	0.263	−2.118 2.643	7	10.088	−7.526 27.703	6	43.449[a]	26.642 60.255
Administration route												
intragastric (capsule)	8	−0.061	−0.309 0.186	7	0.263	−2.118 2.643	7	10.088	−7.526 27.703	6	43.449[a]	26.642 60.255
intragastric (infusion)	3			2			2			0		
intraduodenal (infusion)	4	−0.241	−1.022 0.539	2			2			2		
Risk of bias in the studies												
low	10	−0.085	−0.239 0.069	6	−1.267	−6.635 4.100	6	90.346	−65.110 245.803	5	45.233[a]	27.763 62.703
some concern/high	5	0.057	−0.473 0.587	5	−6.114	−79.601 67.374	5	7.451	−17.051 31.953	3		

There was only one study on AUC-c-peptide in chronic intervention; therefore, an analysis was not performed. n, number of studies; CIs, confidence intervals; 2 h-PPG, postprandial plasma glucose at t = 2 h; AUC, area under the curve; WMD, weighted mean differences

[a] Test of WMD for subgroups was statistically significant (95% CIs did not include zero).

[b] Participants diagnosed with prediabetes or type 2 diabetes were identified as impaired glycaemia in this study.

chronic bitter compound interventions might have improved insulin sensitivity in skeletal muscle [42] and liver [33].

The inconsistency between 2 h-PPG and AUC-glucose results reflects the difference in the studies included in the analysis for these outcomes. According to sensitivity analysis, a reduction in 2 h-PPG was mainly driven by studies without AUC-glucose measurements. These studies mostly used bitter compounds from the quinine family, particularly hydroxychloroquine. In contrast, most studies without AUC-glucose measurements did not use bitter compounds from the quinine family. Further, subgroup analysis revealed that the reduction in 2 h-PPG was in studies where bitter compounds from the quinine family were administered. This is consistent with the results of two other meta-analyses, which reported improved postprandial glycemia after hydroxychloroquine administration in patients with and without diabetes [82,83]. The inconsistency in the results where chronic interventions decreased 2 h-PPG only in studies on males and females, but in the studies on either males or females, might also be due to the bitter compounds used. None of the studies undertaken on males or females used bitter compounds from the quinine family and, therefore, failed to lower 2 h-PPG. The higher efficacy of the quinine family might be due to their ability to activate a relatively higher number of TAS2R subtypes (9 out of 25) compared to other bitter compounds [2].

The postprandial glycemia-lowering effects of chronic interventions were also more pronounced in individuals with

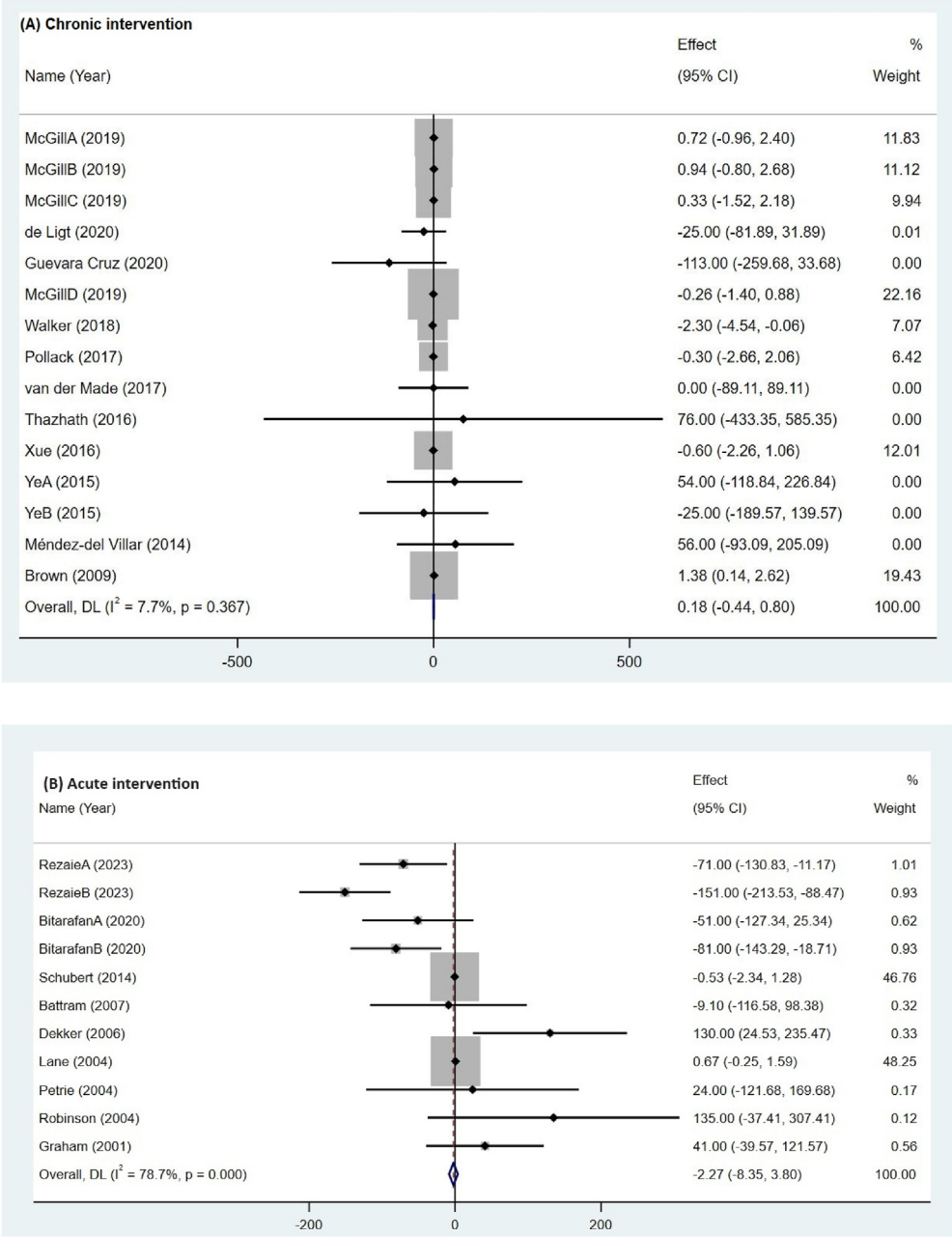

Fig. 3. Forest plot for the pooled weighted mean differences of bitter compound interventions on the area under the curve level for postprandial plasma level of glucose (AUC-Glucose; mmol × time/L) using random-effect model; (A) chronic and (B) acute interventions.

impaired glycemia. This is most likely because of the increased capacity to reduce higher blood glucose levels in individuals with impaired glycemia.

Despite the glucoregulatory results from chronic interventions with bitter compounds, acute interventions did not impact postprandial glycaemia. A recent systematic review by Hassan *et al.* also failed to draw a solid conclusion about the effects of acute bitter compound interventions on appetite and related GI hormone secretion [84]. There were also differences in populations and the bitter compounds used in the chronic and acute intervention studies. Most acute studies delivered caffeine to individuals with normal glycemia. In contrast, the glucoregulatory results in the chronic studies were mainly driven by the administration of bitter compounds from the quinine family to individuals with impaired glycemia. This was especially evident from the subgroup analysis, where the acute intervention of bitter compounds from the quinine family was revealed to reduce acute AUC-glucose.

Although AUC-c-peptide was increased by acute interventions of bitter compounds, no overall effect was seen on AUC-insulin. Moreover, whilst the sub-group analysis showed an increase in the AUC-insulin levels (<8 pmol × time/L), this is unlikely to be of clinical significance [85].

4.1. Implications for practice

The reduction in 2 h-PPG from this meta-analysis is clinically important. Postprandial glucose is a stronger risk factor for developing cardiovascular disease and diabetes-related complications

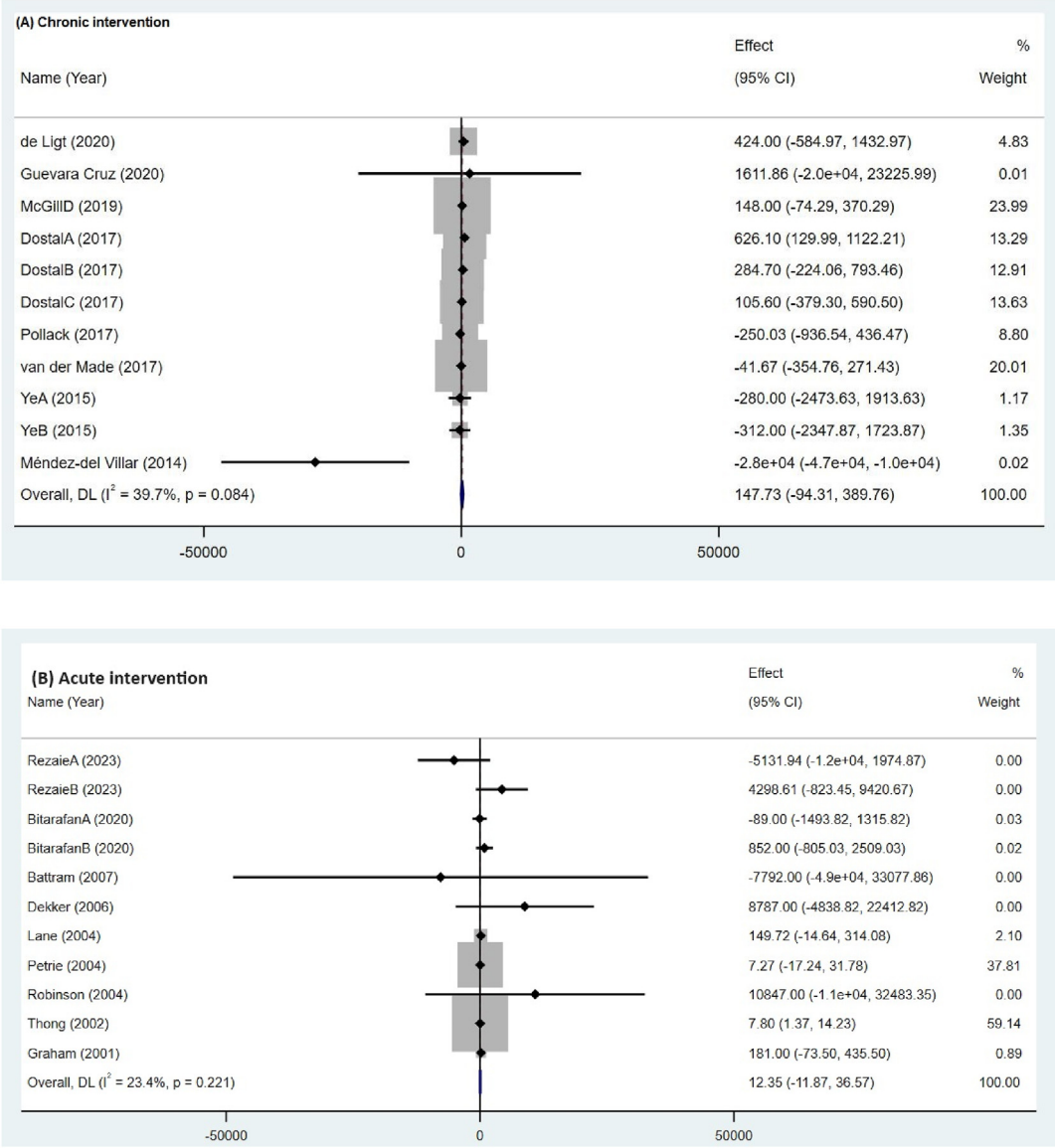

Fig. 4. Forest plot for the pooled weighted mean differences of bitter compound interventions on the area under the curve level for postprandial plasma level of insulin (AUC-Insulin; pmol × time/L) using random-effect model; (A) chronic and (B) acute interventions.

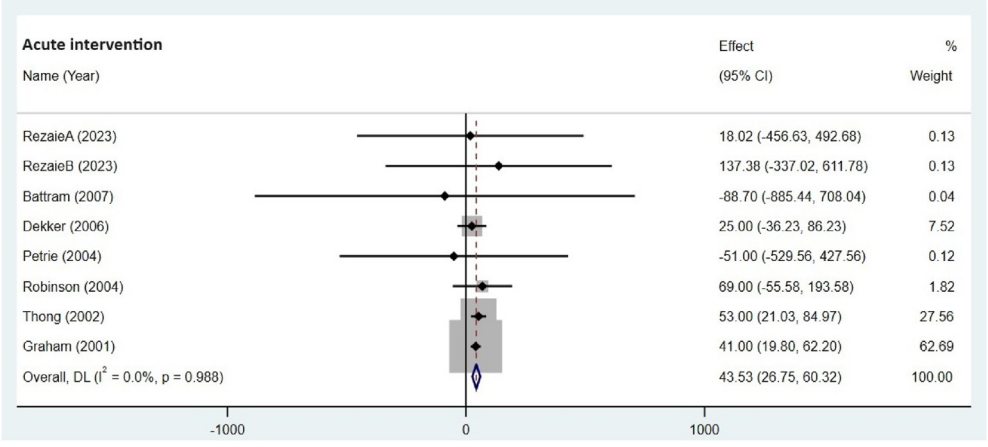

Fig. 5. Forest plot for the pooled weighted mean differences of bitter compound interventions on the area under the curve level for postprandial plasma level of c-peptide (AUC-c-peptide; nmol × time/L) using random-effect model; acute interventions.

than fasting glucose [11]. Moreover, therapies targeting postprandial glucose were reported to improve mean hemoglobin A1c (HbA1c) more effectively than therapies focusing on fasting glucose levels in diabetic patients [12]. However, how much postprandial glucose improvement can be translated into meaningful disease risk reductions is unclear. Results from a Cochrane meta-analysis of nine clinical trials reported 0.46 mmol/L reduction in 2 h-PPG after diet plus physical activity interventions, which can be considered a point of reference [86]. In this case, chronic interventions of bitter compounds have significant clinical impact where the quinine family was administered (−0.86 mmol/L in 2 h-PPG), or bitter compounds were delivered to the individuals with impaired glycemia (−0.69 mmol/L in 2 h-PPG). However, this comparison should be approached with caution since the Cochrane meta-analysis collected data from non-diabetic individuals during OGTT [86], and the current meta-analysis pooled data from healthy individuals and those with impaired glycemia (some reported to be diabetic). In addition, the findings from the current meta-analysis were driven by the 'very low' quality of studies.

4.2. Strengths and limitation

We designed and conducted this study according to the PICO framework [17] and PRISMA 2020 statement [16] to ensure a standardised procedure was followed. To identify bitter compounds administered in the included studies, we used the BitterDB dataset [24]. This dataset provides a chemical structure-based tool for predicting whether a compound is bitter or not [24]. It should be noted that only a few studies investigated the glucoregulatory effects of bitter compounds while considering them as ligands for TAS2Rs (such as [56,57]), whereas most of the studies used bitter compounds without considering their bitterness. In this study, we included studies with plant extract intervention only if the components were clearly described and the concentration of bitter compounds was more than 90%. This selection criterion ensured that our analysis focused exclusively on bitter compounds. To avoid the potential effects of oral bitter taste perception, we only included studies that utilised post-oral bitter compound interventions. We also limited studies to double-blinded RCTs, improving the reliability of the results. While we separated studies with acute and chronic interventions, there were still enough studies and sample sizes to perform the meta-analysis. Only one study had a serious risk of bias, allowing us to interpret the results confidently.

Possible limitations of this study should be acknowledged when considering the findings. While pooling data from RCTs with bitter compound interventions has been previously used in another meta-analysis [84], there is still a concern that compounds may inherently possess functions other than bitterness. Although we tried to include all the studies with bitter compound interventions using our search strategy (using the name of TAS2Rs ligands [2] in the keywords), it is possible some were missed. This might be the case for those studies that used bitter compounds without considering their bitterness. Moreover, the types of bitter compounds widely varied between studies. We addressed this limitation by subgroup analysis based on the type of bitter compound used. The primary outcomes (mean and SD) were extracted from the post-intervention status, as the change from baseline data was unavailable in most of the included studies. The methods to evaluate AUC were inconsistent across studies, lowering the certainty of the estimated effects. A degree of heterogeneity and publication bias due to small-study effects applied to the main finding of this study (2 h-PPG in chronic bitter compound intervention). This can impact the certainty of the findings. In this study, the same comparator group was included more than once in the meta-analysis for the studies with multiple intervention groups [33,39,41,45,51,56,57]. This might contribute to correlated comparisons and erroneous results. There was also a deviation from the study protocol whereby we could not measure AUC- GI hormones due to the limited number of studies reporting related data. Therefore, while this study provided some insights into the glucoregulatory role of bitter compounds, it did not approach the underlying mechanism. Finally, this study exclusively incorporated articles published in English, leading to the omission of studies published in other languages.

5. Conclusion

To our knowledge, this is the first meta-analysis to investigate the effect of bitter compounds on the postprandial glycemia response. The results confirmed that chronic interventions with bitter compounds may produce clinically meaningful reductions in postprandial 2 h glucose levels. However, individuals with impaired glycemia are more likely to benefit from bitter compound interventions, particularly with a treatment regime longer than three months and a bitter compound from the quinine family. Therefore, the quinine family may have potential as therapeutic agents for those with glycemia dysregulation. Given the 'very low' certainty of the evidence, there is still a need to conduct more studies before advising on the potential use of bitter compounds to manage postprandial glycemia in humans. It should be noted that while activating TAS2Rs is a plausible mechanism for bitter compound effects [5,8], the current meta-analysis does not provide direct experimental evidence for this mechanism. Further investigation is required to confirm the role of TAS2Rs and other potential mechanisms.

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Author contributions

All authors contributed to the conception of the research question; ZM performed the systematic search; ZM and EH performed screening, study selection, data extraction, and risk of bias and quality assessment of studies; ZM performed the statistical analysis and prepared the manuscript draft. The manuscript draft was critically reviewed and edited by all authors.

Conflict of interest

None.

Acknowledgement

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2024.09.027.

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