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# Combined effect of interventions with pure or enriched mixtures of (poly)phenols and anti-diabetic medication in type 2 diabetes management: a meta-analysis of randomized controlled human trials

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## Abstract

**Purpose** (Poly)phenols have been reported to confer protective effects against type 2 diabetes but the precise association remains elusive. This meta-analysis aimed to assess the effects of (poly)phenol intake on well-established biomarkers in people with type 2 diabetes or at risk of developing diabetes.

**Methods** A systematic search was conducted using the following selection criteria: (1) human randomized controlled trials involving individuals with prediabetes and type 2 diabetes; (2) one or more of the following biomarkers: glucose, glycated haemoglobin (HbA1c), insulin, pro-insulin, homeostatic model assessment of insulin resistance (HOMA-IR), islet amyloid polypeptide (IAPP)/amylin, pro-IAPP/pro-amylin, glucagon, C-peptide; (3) chronic intervention with pure or enriched mixtures of (poly)phenols. From 488 references, 88 were assessed for eligibility; data were extracted from 27 studies and 20 were used for meta-analysis. The groups included in the meta-analysis were: (poly)phenol mixtures, isoflavones, flavanols, anthocyanins and resveratrol.

**Results** Estimated intervention/control mean differences evidenced that, overall, the consumption of (poly)phenols contributed to reduced fasting glucose levels ( $-3.32$  mg/dL; 95% CI  $-5.86, -0.77$ ;  $P=0.011$ ). Hb1Ac was only slightly reduced ( $-0.24\%$ ; 95% CI  $-0.43, -0.044$ ;  $P=0.016$ ) whereas the levels of insulin and HOMA-IR were not altered. Subgroup comparative analyses indicated a stronger effect on blood glucose in individuals with diabetes ( $-5.86$  mg/dL, 95% CI  $-11.34, -0.39$ ;  $P=0.036$ ) and this effect was even stronger in individuals taking anti-diabetic medication ( $-10.17$  mg/dL, 95% CI  $-16.59, -3.75$ ;  $P=0.002$ ).

**Conclusions** Our results support that the consumption of (poly)phenols may contribute to lower glucose levels in individuals with type 2 diabetes or at risk of diabetes and that these compounds may also act in combination with anti-diabetic drugs.

**Keywords** Antidiabetic therapy · Diabetes · Glucose · Hb1Ac · Insulin · Polyphenol

## Introduction

Type 2 diabetes mellitus (hereafter referred as diabetes) affects hundreds of millions of people worldwide, being projected that by 2040 the number of individuals with diabetes will reach 642 million [1]. The International Diabetes

Federation estimated that 12% of global health expenditure is spent on diabetes [1] and, despite the advances in both modern medicine and knowledge of the disease, it remains one of the leading causes of death globally.

It is generally considered that diabetes results from the combination of genetic and environmental factors. Different loci have been put forward as risk factors for diabetes [2], however, lifestyle factors such as obesity, lack of physical exercise, calorie-rich diets, and smoking have been considered the greatest players in the disease [3]. These are potentially modifiable factors which can delay the disease onset and progression. Together with proper monitoring

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and medication, lifestyle and dietary changes are essential to control diabetes and avoid its comorbidities [4].

Glucose homeostasis results from a controlled system in which the rise of blood glucose is compensated by the increase of insulin secretion. In healthy states, this tightly regulated feedback loop guarantees that glucose levels remain within the normal range. Insulin resistance and impaired insulin secretion are the major pathological processes associated with diabetes development. Insulin resistance precedes diabetes onset and occurs when cells fail to respond to physiological levels of insulin, mainly in the liver and in the muscles [5]. Impaired insulin secretion is characterized by the lack of proper secretion of insulin by the  $\beta$ -cells in response to glucose as a result of decreased  $\beta$ -cell function and mass [6, 7]. This can also lead to the release of an immature form of insulin, before C-peptide cleavage pro-insulin [8, 9]. These mechanisms culminate in hyperglycaemia, the major clinical symptom of diabetes. Another established hallmark of diabetes, yet clinically unexplored, is the formation of pancreatic deposits of islet amyloid polypeptide (IAPP) or amylin [10], which are associated with  $\beta$ -cell failure. IAPP is co-secreted with insulin by pancreatic  $\beta$ -cells and plays a role in glucose homeostasis by regulating satiety and gastric emptying [8]. Failure of  $\beta$ -cell processing machinery during diabetes is also associated with secretion of pro-IAPP forms [11, 12]. Locally subjected to high levels of insulin,  $\alpha$ -cells release increased levels of glucagon, thus hyperglucagonemia is also commonly found in diabetes [13].

(Poly)phenols comprise a large class of phytochemicals present in diverse sources in the diet, such as fruit, vegetables, red wine, and cocoa [14]. They are known to exhibit a variety of biological activities targeting different molecular mechanisms and cellular pathways [15]. The beneficial health effects of (poly)phenols have been associated with protection against cardiovascular diseases (e.g., promoting endothelial function and inhibiting platelet aggregation), cancer (via the reduction of cell proliferation, induction of cell cycle arrest or apoptosis) [16], neurological disorders such as Parkinson's and Alzheimer's diseases and diabetes (e.g., modulating oxidative stress and anti-inflammatory responses) [17, 18]. Particularly, human studies have shown the correlation between (poly)phenol-rich food consumption and reduced risk of developing diabetes [19, 20]. For example, the prospective examination of the associations between (poly)phenols intake on the risk of incident diabetes in the PREDIMED study revealed a 28% reduction in new-onset diabetes in the highest compared with the lowest tertile of total (poly)phenol intake (Hazard Ratio—HR 0.72; 95% CI 0.52, 0.99;  $P$ -trend = 0.05). Notably, a high intake of (poly)phenols was inversely associated with diabetes in elderly persons at high risk of cardiovascular disease [21]. Also, dietary (poly)phenols were inversely associated with metabolic syndrome in adults of the HAPIEE study, as individuals in

the highest quartile of (poly)phenol intake were less likely to develop the syndrome (Odds Ratio—OR 0.80; 95% CI 0.64, 0.98 and OR 0.70; 95% CI 0.56, 0.86 for both men and women, respectively) [22]. Additionally, isoflavone-rich soy-based foods were reported to reduce significantly the risk of diabetes (OR for the highest versus the lowest intake: 0.31; 95% CI 0.21, 0.46;  $P < 0.001$ ) [23]. (Poly)phenols are also thought to contribute to the control of this disease [24] as exemplified by flavonoid-rich berries and oolong tea consumption that improved post-prandial hyperglycaemia [25, 26]. Animal studies further support the beneficial effects of (poly)phenol-enriched mixtures and pure extracts intake against altered glucose metabolism. A study using the flavonoid kaempferol reported improved insulin resistance in a diabetes rat model potentially through the reduction of hepatic inflammation by the inhibition of the NF- $\kappa$ B pathway [27]. Another report showed a significant reduction of hyperglycaemia and insulin resistance in diabetes rats as well as a modulation of inflammation following treatment with ellagic acid [28]. Different (poly)phenols such as resveratrol and the ellagitannin pentagalloyl-glucose have also been described to prevent the aggregation of IAPP and to reduce its cellular toxicity using in vitro models [29, 30].

Overall, (poly)phenols have been widely substantiated by pre-clinical evidence as compounds with metabolic regulatory effects that may contribute to prevent or delay the onset of type-2 diabetes but the evidences in humans are still limited. There are only a few meta-analyses of randomized controlled human trials evaluating the effects of (poly)phenols on diabetes biomarkers or incidence, and some of those report ambiguous results [31–36]. For instance, effects on biomarkers such as blood glucose, fasting insulin or HbA1c are reported to be changed by a certain (poly)phenol in one meta-analysis and not altered in another [32, 33]. In addition, and despite that most individuals with diabetes are under medication, very few of these studies have contemplated a possible combined effect between (poly)phenols and anti-diabetic drugs. Overall, the protective role of dietary (poly)phenols towards diabetes is not yet understood. In the present study, we systematically reviewed published randomized controlled trials investigating the impact of (poly)phenol consumption on diabetes biomarkers. Our main aim was to analyse the reported effects on a selection of biomarkers associated with the disorder, i.e., blood glucose, glycated haemoglobin (HbA1c), insulin, pro-insulin, insulin resistance (HOMA-IR), IAPP/amylin, pro-IAPP/pro-amylin, glucagon and C-peptide. The influence of factors that may be responsible for inter-individual variability in the response to (poly)phenol consumption was also examined, including sex, BMI, health status and prescribed medication. The influence of type of (poly)phenol, dose and duration of treatment was also investigated.

## Methods

### Search strategy, study selection and data extraction

This systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines [37], and the Cochrane Handbook for Systematic Reviews of Interventions [38]. A systematic search was conducted by two of the authors in Medline, SCOPUS, Web of Knowledge and ClinicalTrials.gov in November 2016 and updated on January 2018, to select randomized clinical trials that studied the effects of pure (poly)phenols on diabetes.

Search terms in titles and abstracts included (the wild card “\*” was used to increase the number of matches): polyphenol\* OR flavonoid\* OR anthocyani\* OR flavanol OR flavonol OR flavone OR flavanone OR ellagitannin OR proanthocyani\* OR "phenolic acid" OR resveratrol, AND diabet\* OR prediabet\* NOT rat AND clinical trial (MeSH terms were used in PubMed). The search was restricted to English language.

After removal of duplicates, studies were screened by two independent authors, and double-checked by a third author to reach consensus of selected studies for full paper eligibility. Selected studies were limited to human randomized controlled trials, which (1) had a chronic intervention (4 weeks or more), with a pure (poly)phenol or an enriched fraction of (poly)phenols and a control group receiving a placebo and (2) measured one or more of the following outcomes: blood glucose, HbA1c, insulin, pro-insulin, HOMA-IR, IAPP/amylin, pro-IAPP/pro-amylin, glucagon and C-peptide.

Data extraction was performed independently by two authors using a standardized data extraction form and crosschecked by a third author. Extracted data included: (1) publication details: name of first author, year of publication, title, name and e-mail of corresponding author; (2) study characteristics: study design, arm number and description, washout duration, treatment duration, number of participants under (poly)phenol supplementation, number of participants receiving the placebo, number of participants completing the study, composition of (poly)phenol supplement and placebo, dose and mode of administration; (3) sample characteristics: country, number of male and female participants, age mean and age range, ethnicity, health status (diabetes, moderate risk—overweight, obesity, first-degree relatives with diabetes or peripheral insulin resistance—and high risk—metabolic syndrome or impaired glucose), menopausal status, smoking, medication, baseline BMI, diet (assessment method, baseline diet and diet during study), physical activity level; (4) information on reported outcomes: type of sample (fasted or

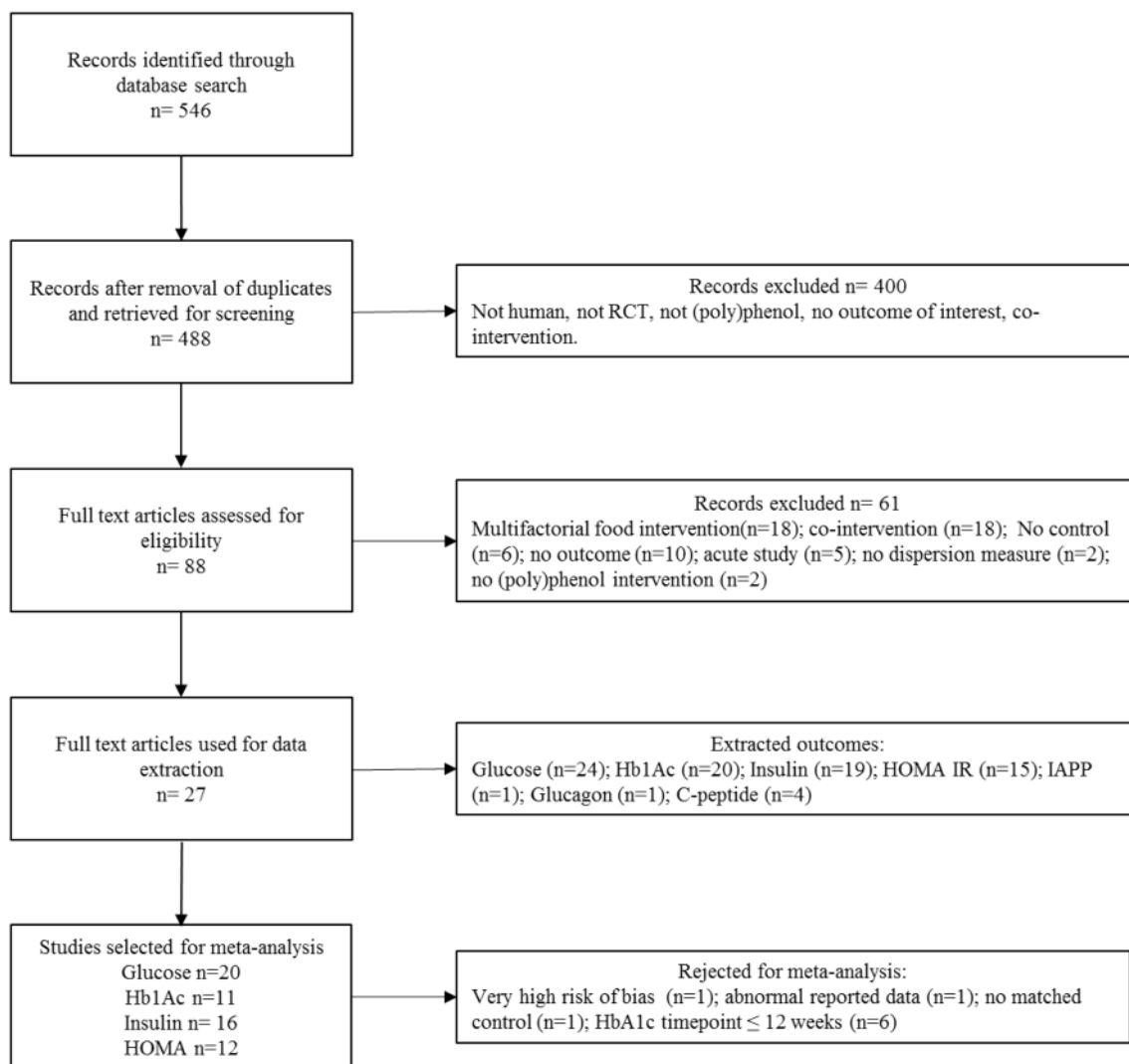
post-prandial), changes or values before and after intervention (central measure, dispersion measure and *P* value when available); (5) Outcomes: glucose, HbA1c, insulin, pro-insulin, HOMA-IR, IAPP/amylin, pro-IAPP/pro-amylin, glucagon, and C-peptide. Before analysis, glucose and insulin units were converted to the most commonly used units in the clinical environment (mg/dL for glucose and  $\mu$ IU/mL for insulin).

### Assessment of bias

A systematic assessment of the risk of bias for each of the included studies was based on the Cochrane Collaboration measurement with some modifications [38]. The specific items used for the assessments of each study are those used in a previous meta-analysis [39]: (1) selection bias—random sequence generation, allocation concealment (in each item, yes = 1; no = 0, unclear = 0); (2) performance bias—blinding (yes = 1 for each participants, researchers and statisticians, no = 0, unclear = 0), measurement of compliance (1 for biomarker measure, 0.5 if compliance information was collected by counting non-used capsules or recipients, or by self-reporting, 0 if no measurement of compliance was done or the information was insufficient); (3) attrition bias—flow of participants (1 if flow of participants was explained in detail, including number of withdrawals and reasons, 0 if there was no information or insufficient information); (4) other bias—baseline comparability between test and control groups (yes = 1, no = 0, unclear = 0), data report (1 if pre- and post-data or change was reported in a table with central measure and spread for placebo and treatment groups, and sample size in each group, 0 if anything was missing), industry funding (0 if any commercial source provided some or all monetary funding for the trial, if a company carried out a study “in house”, if any of the authors was employed by a relevant industry or if it was unclear that there was any kind of industry funding, 1 if there was no funding from industry or if the only involvement of a company was to provide some ingredients for the intervention). Studies were rated as low risk of bias when total score was 8–10, moderate risk of bias when total score was > 5 and < 8, and high risk of bias when total score was > 2 and  $\leq$  5. Studies with total score  $\leq$  2 were rejected.

### Data analysis

Data for each outcome were analysed using the Comprehensive Meta-Analysis Software, version 3.3 (Biostat, Englewood, NJ, USA). Fixed or random effect meta-analyses were conducted to assess test/placebo differences across studies, with effect size measured as difference in means (DM) and 95% confidence intervals (CI). In studies with more than one time point, only the longest time point



**Fig. 1** Flow diagram of the studies selection process for meta-analysis

was included in the analysis, except for the comparative analysis of duration subgroups. Studies with participants receiving different types of supplementation (different doses or types of (poly)phenols) were considered as sub-studies and the data of sub-studies treated as independent studies. The heterogeneity of studies was assessed using the Cochran's  $Q$  statistic (a Chi-squared test with  $n - 1$  degrees of freedom), and the inconsistency index  $I^2$  (the proportion of total variation contributed by between-study variability), where  $I^2$  values equal to 25%, 50% and 75% were considered as low, moderate and high heterogeneity, respectively [40]. Random effect meta-analysis was used when moderate to high heterogeneity across studies was present and  $P$  value for Cochran's  $Q$  statistic was lower than 0.1. Publication bias was assessed visually with funnel plots and statistically by applying the Egger's regression test.

Statistical comparisons between subgroups were performed by applying a random-effects analysis and calculation of the between-categories  $Q$  statistic and corresponding  $P$  values. A  $P$  value  $< 0.05$  was considered statistically significant.

## Results

### Description of the included studies

The study selection process is shown in Fig. 1. A total of 546 studies were retrieved from the electronic reference databases. After initial screening of 488 references, 88 trials met inclusion criteria for full text review. Detailed full text analysis led to exclusion of 61 studies, ending with 27 trials selected for data extraction. Quality analysis pinpointed

one RCT [41] with a very high risk of bias (score  $\leq 2$ ) and thus it was also excluded from the meta-analysis. Only one study referred to IAPP [42] and glucagon [43] and three studies measured C-peptide [43–45]. Neither pro-insulin nor pro-IAPP were further evaluated due to the lack of studies. All RCTs with duration between 4 weeks and 1 year were included for the meta-analysis of glucose (20 RCTs), insulin (16 RCTs) and HOMA-IR (12 RCTs). As Hb1Ac represents the average level of blood glucose for the past 3 months, only RCTs with duration of 12 weeks or longer were included in the meta-analysis of this biomarker (11 RCTs).

The individuals included in the studies had an average age of 55.5 years, with no predominance of either sex. These individuals presented an average BMI of 28.9, corresponding to overweight. In terms of health status, there were 12 studies with individuals with diagnosed diabetes, 3 studies with individuals classified as at high risk of developing diabetes (participants with metabolic syndrome or impaired glucose tolerance) [46–48], and 5 studies with individuals classified as moderate risk of developing diabetes (overweight, obesity, first-degree relatives with diabetes or peripheral insulin resistance) [43, 49–52]. From the studies including individuals with diabetes the duration of the disease ranges from 2 to 22 years. Individuals from 10 of the 20 studies were undergoing medication for diabetes, antihypertensive drugs, cholesterol-lowering drugs or a combination of these.

Characteristics of the studies included in the meta-analysis are shown in Table 1. Most RCTs were from European countries [43, 44, 46, 47, 49–51, 53–56], seven in Asian countries [45, 48, 52, 57–60], one was performed in North America [61] and one in Australia [62]. The present meta-analysis evaluated the results from RCTs that studied the effect of pure or enriched (poly)phenol extracts intake on individuals with diabetes or at risk of diabetes: six studies used a mixture of (poly)phenols from passion fruit, grape, pine tree bark, among others (doses of 125–2093 mg/day); five studies used isoflavones (doses of 33–100 mg/day); four studies used flavanols (doses of 560–1270 mg/day); one study used anthocyanins (392 mg/day); and five studies used resveratrol (doses of 40–1500 mg/day) (Table 1).<sup>1</sup>

### Effect of (poly)phenol supplementation on measures of glucose, Hb1Ac, insulin, and HOMA-IR

Glucose meta-analysis included 20 RCT studies (two of the RCTs included two sub-studies), with 1200 participants: 681 treated with (poly)phenol supplement and 519 on placebo.

<sup>1</sup> The total number of studies is equal to 21 because one of the studies depicts results from 2 interventions (a (poly)phenol mixture and resveratrol).

Meta-analysis showed a statistically significant reduction in fasting plasma glucose after supplementation with a pure (poly)phenol or enriched extract (DM =  $-3.50$  mg/dL; 95% CI =  $-6.28, -0.73$ ;  $P=0.013$ ) (Table 2). Sensitivity analysis by removal of one study [60] with high risk of bias had no impact on effect size or significance (DM =  $-3.32$  mg/dL; 95% CI =  $-5.86, -0.77$ ;  $P=0.011$ ) (Fig. 2). There was moderate heterogeneity across the 19 studies with low and moderate risk of bias ( $I^2=47.96\%$  and  $P$  value for  $Q$  test =  $0.007$ ), but no evidence of publication bias ( $P$  value for Egger's weighted regression =  $0.408$ ).

Meta-analysis on Hb1Ac with all the 11 studies (including two sub-studies) with 12 or more weeks of intervention (340 participants treated with (poly)phenol and 276 controls) also showed a statistically significant but moderate reduction after supplementation with (poly)phenols (DM =  $-0.24$  mg/dL, CI =  $0.430, -0.044$ ;  $P=0.016$ ) (Table 2). However, when the high risk of bias study [60] was excluded, significance was lost (DM =  $-0.171$  mg/dL, CI =  $0.409, 0.066$ ;  $P=0.158$ ) (Fig. 3).

Supplementation with (poly)phenols had no statistically significant effect on insulin and HOMA-IR measures. All studies used for meta-analysis were low and moderate risk of bias and sensitivity analysis by removal of one study had no impact on effect size or  $P$  value (Table 2, Figs. 4, 5). There was low heterogeneity among studies (Table 2) and no evidence of publication bias ( $P$  value for Egger's weighted regression was  $0.705$  for insulin and  $0.163$  for HOMA-IR).

### Subgroup analyses for identification of factors impacting plasma glucose reduction

To explore the factors that could influence the inter-individual variability of response to (poly)phenol intake, subgroup analyses were performed only on blood glucose. As recommended in Cochrane Handbook for Systematic Reviews of Interventions [38], the study with high risk of bias was excluded from the subgroup analysis [60] to decrease heterogeneity among subgroups and prevent misleading results. The other outcomes were not considered for subgroup analysis due to the low number of studies.

#### Influence of type of (poly)phenol, dose and duration

Subgroup analysis on type of (poly)phenol was performed with four subgroups: (poly)phenol mixtures, isoflavones, flavanols, and resveratrol (Table 3). Only one study used anthocyanins as the intervention (poly)phenol [59] and thus, it was excluded from this subgroup analysis. The analysis of the intervention with each separate group of (poly)phenols showed no statistically significant effect. There was no evidence of heterogeneity between subgroups (Table 3).

**Table 1** Characteristics of selected RCTs examining the effect of (poly)phenol supplementation on biomarkers of diabetes

First author, year, country [ref]	(Poly)phenol Design	Dose (/day)	Duration	Measured outcomes	Risk of bias (Quality score)	$N_T/N_C$ Health status	Sex (F/M/mixed) Age (mean $\pm$ SD) BMI (mean $\pm$ SD)	Medication (yes/no) Type of medication (anti-diabetic/other)
Zibadi, 2008, USA [61]	(Poly)phenol mixture Parallel	125 mg	12 weeks	Glucose, Hb1Ac	Moderate 6.5	24/24 Diabetes	Mixed 59.9 $\pm$ 10.4 NR	Yes Anti-diabetic
Bozzetto, 2015, Italy [46]	(Poly)phenol mixture Parallel	2093 mg	8 weeks	Glucose, insulin, HOMA-IR	Moderate 6.5	20/20 High Risk	Mixed 54.5 $\pm$ 8.8 31.8 $\pm$ 3.3	No
Tomé-Carneiro a, 2013, Spain [53]	(Poly)phenol mixture Parallel	302 mg	52 weeks	Glucose, Hb1Ac	Moderate 7.5	9/13 Diabetes	Male 60.0 $\pm$ 10 32.2 $\pm$ 5.1	Yes Other
Tomé-Carneiro b, 2013, Spain [53]	Resveratrol	302 + 16.2 mg	52 weeks	Glucose, Hb1Ac	Moderate 7.5	9/13 Diabetes	Male 63 $\pm$ 12 31 $\pm$ 5.1	Yes Other
Hokayem, 2013, France [49]	(Poly)phenol mixture Parallel	2000 mg	8 weeks	Glucose, insulin, Hb1Ac	Low 8.5	20/18 Moderate risk	Mixed 49.1 $\pm$ 8.5 29.2 $\pm$ 2.8	No
Raju, 2013, India [60]	(Poly)phenol mixture Parallel	220 mg	16 weeks	Glucose, Hb1Ac	High 5	19/21 Diabetes	Mixed 51.5 $\pm$ 10.9 NR	Yes Anti-diabetic
Woerdeman, 2018, Netherlands [50]	(Poly)phenol mixture Parallel	600 mg	8 weeks	Glucose, insulin	Moderate 6.5	14/15 Moderate risk	Mixed 39.0 $\pm$ 12.5 NR	No
Jayagopal, 2002, UK [54]	Isoflavones Crossover	132 mg	12 weeks	Glucose, insulin, Hb1Ac, HOMA-IR	Moderate 7.5	32/32 Diabetes	Mixed 62.5 $\pm$ 6.77 32.2 $\pm$ 5	No
Setchell, 2013, Italy [55]	Isoflavones Crossover	33 mg	8 weeks	Glucose, insulin	Moderate 6	10/10 Diabetes	Mixed 62.7 $\pm$ 2.3 28.8 $\pm$ 1	No
Squadrito, 2013, Italy [47]	Isoflavones Parallel	54 mg	52 weeks	Glucose, insulin, HOMA-IR	Low 9	55/53 High risk	Female 56.5 $\pm$ 4.70 31.8 $\pm$ 5	Yes Anti-diabetic
Gonzalez, 2007, UK [56]	Isoflavones Crossover	132 mg	12 weeks	Glucose, insulin, Hb1Ac, HOMA-IR	Moderate 6.5	26/26 Diabetes	Female NR 30.9 $\pm$ 6	No
Liu a, 2010, China [48]	Isoflavones Parallel	100 mg	24 weeks	Glucose, insulin, HOMA-IR	Moderate 7.5	60/60 High Risk	Female 56.4 $\pm$ 4.7 24.1 $\pm$ 3.8	Yes Other
Liu b, 2010, China [48]	Isoflavones Parallel	100 mg	24 weeks	Glucose, insulin, HOMA-IR	Moderate 7.5	60/60 High Risk	Female 56.0 $\pm$ 4.4 24.75 $\pm$ 3.8	Yes Other

**Table 1** (continued)

First author, year, country [ref]	(Poly)phenol Design	Dose (/day)	Duration	Measured outcomes	Risk of bias (Quality score)	$N_T/N_C$ Health status	Sex (F/M/mixed) Age (mean $\pm$ SD) BMI (mean $\pm$ SD)	Medication (yes/no) Type of medication (anti-diabetic/other)
Brown, 2009, UK [51]	Flavanols Parallel	800 mg	8 weeks	Glucose, insulin, Hb1Ac, HOMA-IR	Low 8.5	46/42 Moderate risk	Male 51.4 $\pm$ 6.5 31.1 $\pm$ 2.6	No
Hsu, 2011, Taiwan [57]	Flavanols Parallel	1272 mg	16 weeks	Glucose, insulin, Hb1Ac, HOMA-IR	Low 8.5	35/33 Diabetes	Mixed 51.4 $\pm$ 9.2 29.8 $\pm$ 4	N/D
Nagao, 2009, Japan [58]	Flavanols Parallel	53 mg	12 weeks	Glucose, insulin, Hb1Ac	Moderate 6.5	23/20 Diabetes	Mixed 63.9 $\pm$ 1.9 24.8 $\pm$ 0.9	Yes Anti-diabetic
Shoji, 2017, Japan [52]	Flavanols Parallel	600 mg	12 weeks	Glucose, insulin, Hb1Ac, HOMA-IR	Moderate 7	17/15 Moderate risk	Mixed 50.9 $\pm$ 1.2 23.4 $\pm$ 0.6	No
Liu, 2015, China [59]	Anthocyanin Crossover	392 mg	24 weeks	Glucose, insulin, Hb1Ac, HOMA-IR	Low 8	29/29 Diabetes	Mixed 57.9 $\pm$ 2.9 24.1 $\pm$ 3.3	Yes Other
Bo 1, 2016, Italy [44]	Resveratrol Parallel	40 mg	24 weeks	Glucose, insulin, Hb1Ac, HOMA-IR	Moderate 7.5	59/58 Diabetes	Mixed 64.9 $\pm$ 8.6 29.5 $\pm$ 3.8	Yes Anti-diabetic
Bo 2, 2016, Italy [44]	Resveratrol Parallel	500 mg	24 weeks	Glucose, insulin, Hb1Ac, HOMA-IR	Moderate 7.5	62/58 Diabetes	Mixed 65.0 $\pm$ 7.6 28.8 $\pm$ 3.9	Yes Anti-diabetic
Poulsen, 2013, Denmark, [43]	Resveratrol Parallel	1500 mg	4 weeks	Glucose, insulin, Hb1Ac, HOMA-IR	Moderate 7.5	12/12 Moderate risk	Male 38.3 $\pm$ 15.7 34.2 $\pm$ 3.3	No
Thazhath, 2016, Australia [62]	Resveratrol Crossover	1000 mg	5 weeks	Glucose, Hb1Ac	Moderate 7.5	28/28 Diabetes	Mixed 67.5 $\pm$ 8.5 27.7 $\pm$ 7.4	No
Goh, 2014, China [45]	Resveratrol Parallel	500 mg	12 weeks	Glucose, insulin, Hb1Ac, HOMA-IR	Moderate 7.5	5/5 Diabetes	Male 56.3 $\pm$ 6.4 26.9 $\pm$ 5.4	Yes Anti-diabetic

$N_T$  number of participants supplemented with (poly)phenol,  $N_C$  number of participants receiving placebo,  $BMI$  body mass index,  $Hb1Ac$  glycated haemoglobin, *diabetes* type 2 diabetes mellitus, *HOMA-IR* Homeostatic Model Assessment—Insulin Resistance, *NR* non reported. Notations a and b represent interventions with different (poly)phenols in the same study, and 1 and 2 denote different doses of the same (poly)phenol used in the same study



**Table 2** Overall effect of (poly) phenol supplementation on measures of glucose, Hb1Ac, insulin and HOMA-IR

	Glucose	Hb1Ac	Insulin	HOMA-IR
<b>Effect size</b>				
<i>n</i> ( $N_T/N_C$ )	22 (681/519)	13 (501/429)	18 (601/443)	14 (518/351)
DM	− 3.50 mg/dL	− 0.24%	0.033 $\mu$ IU/mL	0.030
95% CI	− 6.28	− 0.73	− 0.430	− 0.103
<i>P</i> value	0.013	0.016	0.929	0.661
<b>Heterogeneity</b>				
<i>Q</i>	47.41	33.90	21.63	15.107
<i>P</i> value	0.001	0.001	0.199	0.301
<i>I</i> <sup>2</sup>	53.60	64.61	21.41	13.95

All studies were used in the analysis, including the high risk of bias study. Interventions with different concentrations or different (poly)phenols in the same study were counted as different studies

*n* number of studies,  $N_T$  number of participants supplemented with (poly)phenol,  $N_C$  number of participants receiving placebo, *DM* difference in means, *CI* confidence interval, *Q* Chi-squared statistic, *I*<sup>2</sup> inconsistency index, *Hb1Ac* glycated haemoglobin, *HOMA-IR* homeostatic model assessment-insulin resistance

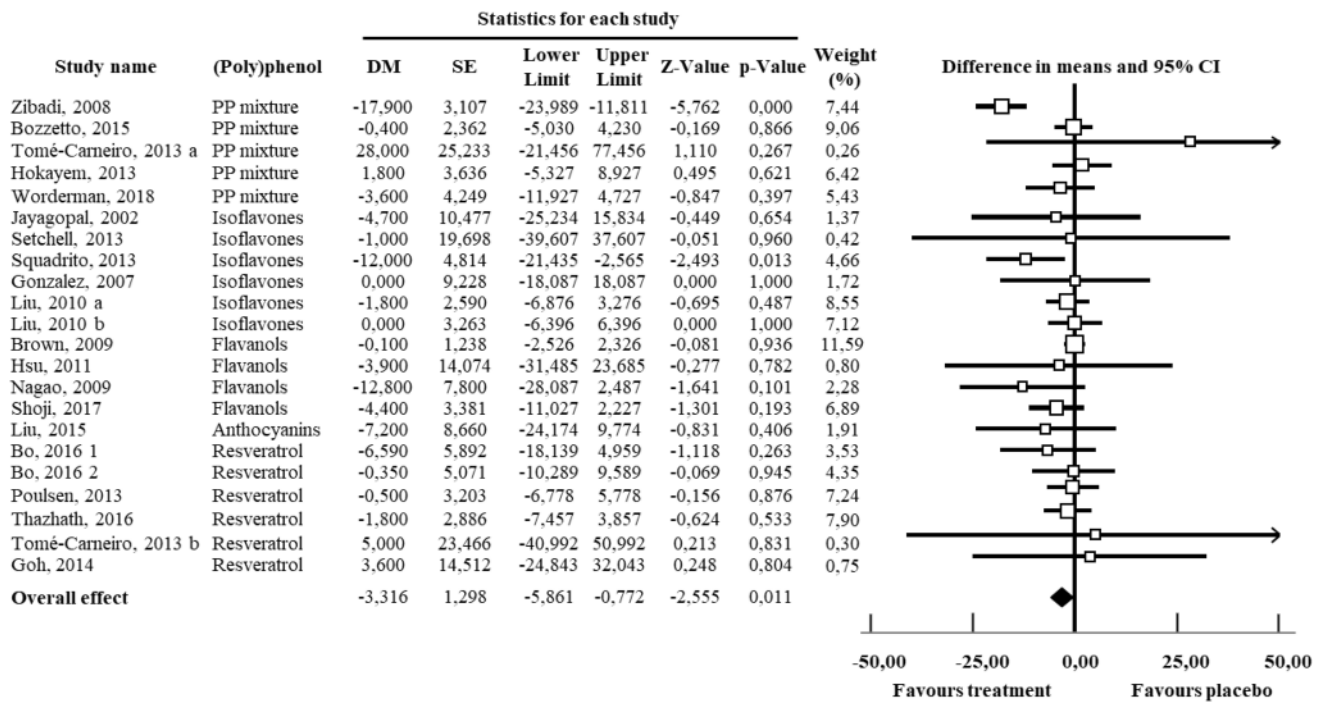
For dose subgroups analysis, 19 studies were separated into three subgroups: low dose ( $\geq 100$  mg/day); medium dose ( $> 100, \geq 500$  mg/day); and high dose ( $> 500$  mg/day) (Table 3). No heterogeneity was evident between dose subgroups. None of the dose subgroups had a statistically significant effect. To assess the impact of study duration, all 32 time points reported across all studies (originated from interventions with different durations and (poly)phenols in the same study) were used for the subgroup analysis. Four subgroups were defined: very short ( $< 8$  weeks), short ( $\geq 8, < 12$  weeks), medium ( $\geq 12, < 24$  weeks) and long ( $\geq 24$  weeks). The levels of glucose were statistically significantly reduced only in the medium duration. (Table 3). Nevertheless, this result was not consistent with meta-regression analysis on dose and duration, which showed no significant impact of covariates dose (covariate coefficient 0.002; 95% CI − 0.001; 0.006;  $P=0.141$ ) or duration (covariate coefficient − 0.002; 95% CI − 0.280; 0.240;  $P=0.880$ ). Furthermore, the meta-regression analysis showed evidence of variance between studies ( $\text{Tau}^2=15.65$ ;  $I^2=52.43\%$ ;  $Q=63.06$ ;  $df=30$ ;  $P=0.0004$ ) from which only 2% could be explained by dose and duration ( $R^2$  analogue = 0.02).

### Influence of health status of the participants and medication

Subgroup analysis shows no influence of sex and BMI in the blood glucose effect. As for the analysis of the influence of the health status of the participants, the 19 selected studies were divided into three groups: participants with diabetes, participants at high risk of diabetes and participants at low risk of diabetes. There were 11 studies (including 2 sub-studies) conducted in participants with diabetes (343 treated with (poly)phenol supplement and 347 controls) [44, 45, 53–59, 61, 62]. Three studies (1 sub-study) included participants at high risk of diabetes: two with metabolic syndrome

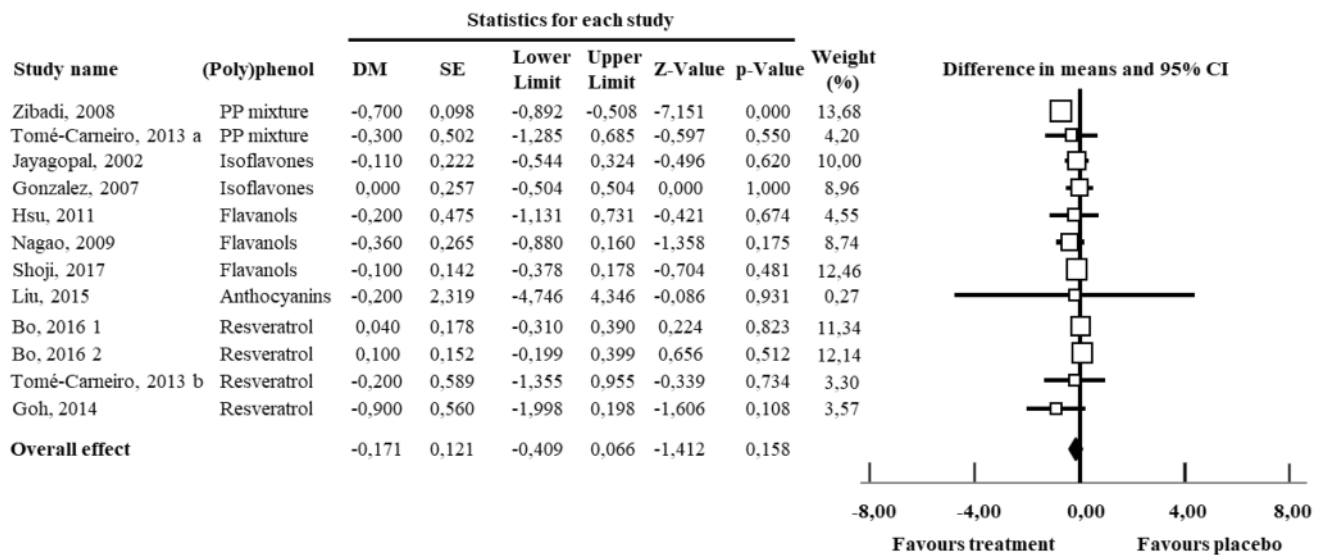
[46, 47] (75 treated and 73 controls) and one with impaired glucose tolerance [48] (360 treated and 180 controls). Lastly, five studies were conducted with volunteers considered at moderate risk of diabetes due to: excess weight, obesity, first-degree relatives of individuals with diagnosed diabetes or peripheral insulin resistance [43, 49–52] (109 treated with (poly)phenol supplement and 102 controls). Comparison between the three subgroups showed a statistically significant effect only in the group with diabetes, with a higher blood glucose reduction than the overall effect (− 5.86 vs − 3.50 mg/dL, 95% CI − 11.34, − 3.89;  $P=0.036$ ) (Table 4). No significant heterogeneity between subgroups was observed. Within the diabetes group, when comparing medicated vs. non-medicated participants, a higher reduction was observed in the medicated participants (− 6.09 mg/dL, 95% CI − 11.35, − 0.82;  $P=0.023$ ) (Table 4). This reduction does not seem to be related with differences in average age (57.75 vs. 53.2 years) and BMI (28.4 vs. 29.4) for medicated and non-medicated individuals, respectively. As we observed a more pronounced plasma glucose reduction in medicated participants, we looked for differences between types of medication and divided medicated participants in two subgroups: anti-diabetic medication (biguanides, sulfonylureas, glitazones, glinides and incretins) and other types of medication (statins, antihypertensive, beta-blockers). Data analysis showed a statistically significant glucose reduction in both subgroups but showed a stronger effect in participants with anti-diabetic medication (− 10.17 mg/dL, 95% CI − 16.59, − 3.75;  $P=0.002$ ) (Table 4).

Meta regression analysis also pointed to an important impact of health status and medication on the blood glucose level response to (poly)phenol supplementation. A statistically significant between-study variance was observed ( $\text{Tau}^2=15.65$ ;  $I^2=52.43\%$ ;  $Q=63.06$ ;  $df=30$ ;  $P=0.0004$ ), with 52% of total between study variance explained by



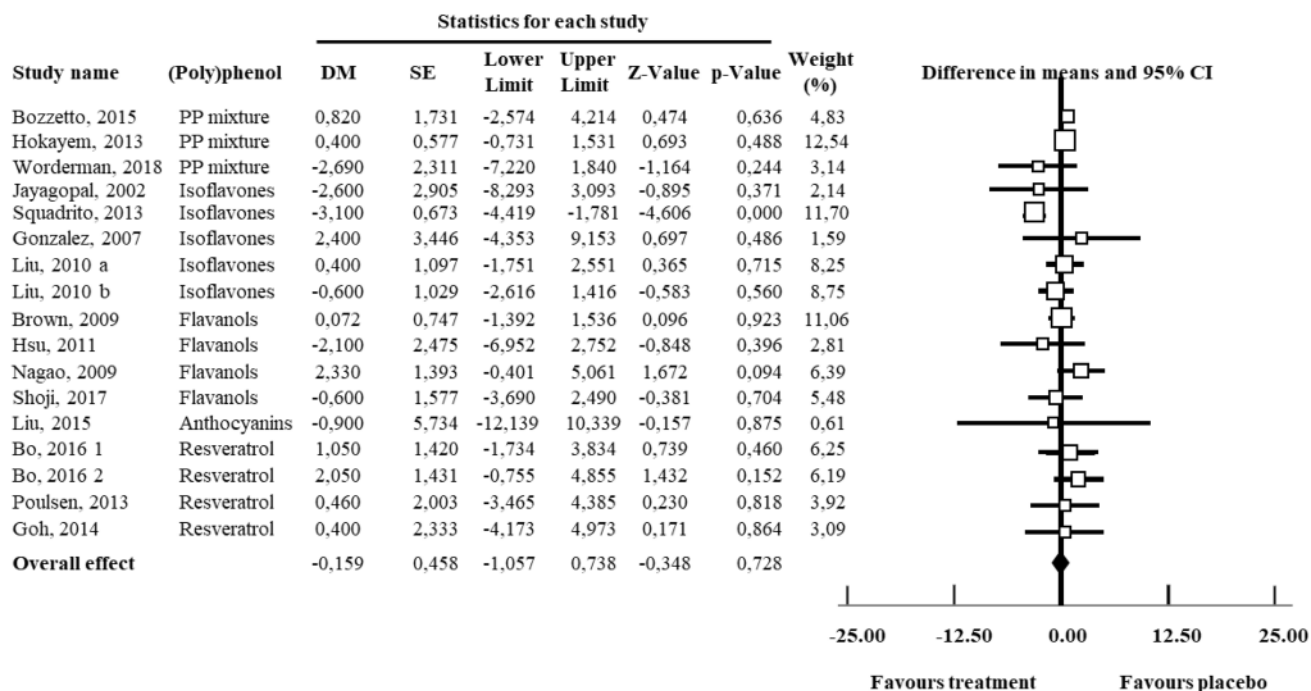
**Fig. 2** Effect of (poly)phenol supplementation on plasma glucose (mg/dL). All studies were used for random effect model meta-analysis. Only low and moderate bias studies are presented. Notations a and b represent interventions with different (poly)phenols in the same

study and 1 and 2 denote different doses of the same (poly)phenol used in the same study. *DM* difference in means, *SE* standard error, *CI* confidence interval, *PP* (poly)phenol



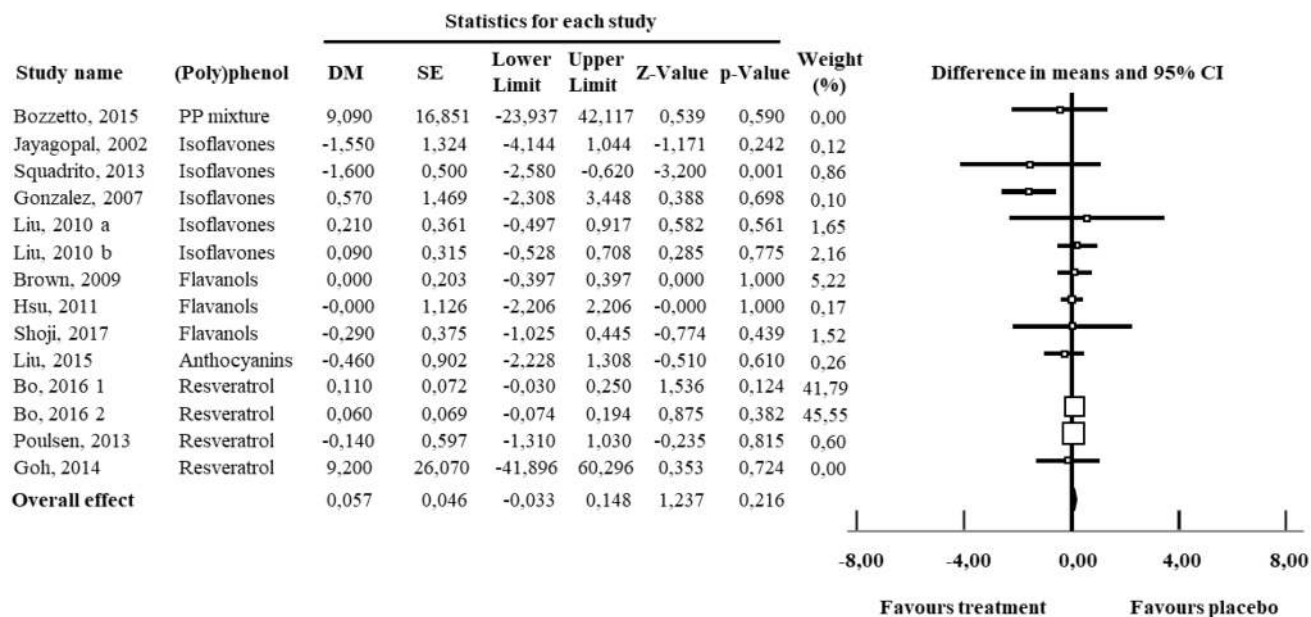
**Fig. 3** Effect of (poly)phenol supplementation on glycated haemoglobin (%). All studies were used for random effect model meta-analysis. Only low and moderate bias studies are presented. Notations a and

b represent different times of intervention in the same study and 1 and 2 denote different doses used in the same study. *DM* difference in means, *SE* standard error, *CI* confidence interval, *PP* (poly)phenol



**Fig. 4** Effect of (poly)phenol supplementation on insulin ( $\mu\text{UI/mL}$ ). All studies were used for random effect model meta-analysis. Only low and moderate bias studies are presented. Notations a and b rep-

resent different times of intervention in the same study and 1 and 2 denote different doses used in the same study. *DM* difference in means, *SE* standard error, *CI* confidence interval, *PP* (poly)phenol



**Fig. 5** Effect of (poly)phenol supplementation on HOMA-IR. Only low and moderate bias studies used for fixed effect model meta-analysis. *DM* difference in means, *SE* standard error, *CI* confidence interval, *PP* (poly)phenol

**Table 3** Subgroup analysis of studies measuring glucose: impact of (poly)phenol type, dose and duration of intervention

	$n$ ( $N_T/N_C$ )	Intervention effect			Heterogeneity between studies	
		DM (mg/dL)	95% CI	$P$ value	$Q$ ; $df$ ; $P$	
<b>(Poly)phenol subgroups</b>						
(Poly)phenol mixtures	5 (97/98)	− 4.08	− 13.13	4.98	0.377	0.710; 4.000; 0.950
Isoflavones	6 (243/147)	− 2.69	− 6.21	0.84	0.135	
Flavanols	4 (137/129)	− 2.04	− 5.97	1.89	0.309	
Resveratrol	6 (175/116)	− 1.52	− 5.14	2.11	0.413	
<b>Dose subgroups<sup>a</sup></b>						
High	8 (231/222)	− 1.00	− 2.78	0.78	0.270	2.553; 3.000; 0.466
Low	5 (260/194)	− 3.48	− 7.65	0.69	0.102	
Medium	8 (206/208)	− 5.03	− 13.92	3.87	0.268	
<b>Duration<sup>b</sup></b>						
Long	9 (334/179)	− 4.14	− 8.66	0.38	0.072	1.501; 3.000; 0.682
Medium	11 (197/195)	− 6.53	− 12.44	− 0.61	0.031	
Short	7 (144/139)	− 2.67	− 6.32	0.97	0.150	
Very short	5 (40/40)	− 2.77	− 5.76	0.22	0.069	

Only low and moderate risk of bias studies were used in the analysis. Interventions with different concentrations of or different (poly)phenols in the same work are counted as different studies. Only the last timepoint was used in the analysis except in the Duration subgroup analysis

$n$  number of studies,  $N_T$  number of participants supplemented with (poly)phenol,  $N_C$  number of participants receiving placebo,  $DM$  difference in means,  $CI$  confidence interval,  $Q$  Chi-squared statistic,  $df$  degree of freedom.

<sup>a</sup>Low dose ( $\leq 100$  mg/day); medium dose ( $> 100, \leq 500$  mg/day); and high dose ( $> 500$  mg/day)

<sup>b</sup>Very short ( $< 8$  weeks), short ( $\geq 8, < 12$  weeks), medium ( $\geq 12, < 24$  weeks); long ( $\geq 24$  weeks)

**Table 4** Subgroup analysis of studies measuring glucose: impact of health status and medication

	$n$	DM (mg/dL)	95% CI	$P$ value	$Q$ ; $df$ ; $P$	
<b>Health status</b>						
Diabetes	13	− 5.86	− 11.34	− 0.39	0.036	3.403; 2.000; 0.182
High risk	4	− 2.29	− 6.22	1.63	0.252	
Moderate risk	5	− 0.58	− 2.57	1.41	0.568	
<b>Medication</b>						
Medicated	12	− 6.09	− 11.35	− 0.82	0.023	3.642; 1.000; 0.056
Non-medicated	10	− 0.69	− 2.42	1.03	0.431	
Anti-diabetic med	6	− 10.17	− 16.59	− 3.75	0.002	
Non-anti-diabetic med	5	− 3.59	− 7.02	− 0.169	0.040	
Non defined	1					

Only low and moderate risk of bias studies were used in the subgroup analysis. Interventions with different concentrations of or different (poly)phenols in the same work are counted as different studies

*Diabetes* type 2 diabetes mellitus,  $n$  number of studies,  $DM$  difference in means,  $CI$  confidence interval,  $Q$  Chi-squared statistic,  $df$  degree of freedom

health status ( $R^2$  analogue = 0.52), and 34% explained by medication ( $R^2$  analogue = 0.34).

## Discussion

This study evaluates and reports the effects of supplementation with various (poly)phenols, whether pure or enriched fractions, excluding interventions using (poly)phenol enriched foods or multifactorial food interventions. The

effects on a range of diabetes biomarkers, specifically those most commonly used in clinical practice—blood glucose and Hb1Ac—and others related with pancreatic function and insulin resistance—insulin and HOMA-IR were evaluated. Overall, the results of this meta-analysis give evidence of a beneficial effect of (poly)phenol supplementation in blood glucose levels of individuals with diabetes and in those at risk of developing the disease.

We also observed a slight reduction in Hb1Ac (0.24%), although statistical significance was lost upon sensitivity

analysis. In addition, given that an alteration of 30 mg/dL in blood glucose reflects 1% change in Hb1Ac marker [63], the 10 mg/dL reduction in blood glucose levels observed in this meta-analysis is not expected to cause a marked change in Hb1Ac. Recent meta-analysis encountered an effect on HbA1c of individuals with diabetes ( $-0.21 \pm 0.04$ ), but not on individuals without diabetes, subjected to nutritional interventions with 0.028–1.5 g of extracts, supplements, or foods for 0.7–12 months [36]. Differences on results may be due to the fact that the authors included interventions with both supplements and foods in their meta-analysis, and we excluded food-based trials from our meta-analysis.

In an attempt to identify some of the factors that may influence the glycaemic response to (poly)phenol intake, we compared the effects of a mixture of (poly)phenols, isoflavones, flavanols and resveratrol on blood glucose. Our analysis shows no statistically significant effects or differences between the four subgroups analysed. Although we cannot discard that these results may be due to the small number of studies per subgroup, it is also plausible that different (poly)phenols may have common and non-specific regulatory effects on the metabolism of glucose. In support of this hypothesis, previous meta-analyses have shown a significant reduction in fasting blood glucose after supplementation with flavonols [39], and a modulation of insulin and HOMA-IR by flavanols present in tea, apple and cocoa [64]. Also, a long-term trial found a correlation between flavan-3-ols and isoflavones intake and the increase in insulin sensitivity [65]. On the other hand, a meta-analysis on the effects of resveratrol has shown a beneficial effect on Hb1Ac (mean effect size = 0.43; SE 0.16; 95% CI 0.10,  $-0.75$ ;  $P < 0.01$ ) but not on blood glucose, insulin and HOMA-IR [66]. Additionally, a recent meta-analysis shows an inverse association between the intake of (poly)phenols and diabetes (HR of 0.56) [35]. These data support the notion that the effector regulators of glucose metabolism at the cellular and organ level may not be the parent compounds supplied to the volunteers. The putative compounds are common low-molecular weight phenolic metabolites of the main classes of (poly)phenols generated in the intestinal tract as the culmination of multiples steps involving gut microbiota metabolism [64, 67–69]. In support of this view, it was recently shown that 2,3-dihydroxybenzoic acid (DHBA), a colonic phenolic acid derived from flavonoid intake, decreases the uptake of glucose and the enzymes responsible for gluconeogenesis in a renal proximal tubular cell line [70], suggesting a possible influence in renal glucose reabsorption and thus, a potential regulatory effect on blood glucose levels.

Of note, our analysis has shown statistical evidence for a higher hyperglycaemia reduction in medicated as compared

to non-medicated individuals with diabetes. Remarkably, the strength of evidence on this reduction was higher for those on medication for diabetes, than on individuals taking other types of medication such as statins, antihypertensive and beta-blockers drugs. This is the first meta-analysis that shows evidence for the impact of the type of medication on the effect of (poly)phenols on glycaemic control in individuals with diabetes. Our data are suggestive of a potential synergistic action of (poly)phenol supplementation and medication mainly for diabetes treatment, opening new venues for the exploitation of (poly)phenol-rich diets as co-adjuvants in diabetes management. This notion is supported by previous animal studies showing an interaction between the intake of (poly)phenol-rich herbs and anti-diabetic medication on glucose control and insulin sensitivity [71, 72].

Monitoring of blood glucose levels is the primary clinical criteria for diabetes diagnosis and control. However, other biomarkers such as glucagon, C-peptide, pro-insulin and IAPP/amylin are also useful to monitor diabetes and pancreatic function. However, only a few studies addressed the impact of (poly)phenols on these parameters. The scarcity of studies investigating the potential protective action of (poly)phenols towards these clinical parameters led to their exclusion of the meta-analysis emphasizing the need of further research in the field.

The main strength of this study is the indication that (poly)phenol consumption may improve glycaemic control in individuals with diabetes, particularly those medicated for the disease. Only clinical trial studies were included in the analysis to eliminate confounding factors that may play a role in nutritional interventions, such as limitations of dietary assessment techniques, displacement of other nutrients or difficulties in assessing baseline dietary status [73]. The detected effects on the major clinical symptom of diabetes, the abnormal levels of blood glucose, makes this study relevant to encourage further investigations towards the use of (poly)phenols together with diabetes medication for an improved glycaemic control.

On the other hand, the reduced number of clinical intervention studies included in this meta-analysis as well as the lack of further information reported in those studies constitutes the main weaknesses of our research. This made impossible to perform further sub-groups analyses and to consider additional factors to those herein analysed. This may also represent the main reason as to why we were not able to detect any other significant results apart from those reported for blood glucose. The timeline of the original search also represents a weakness that may have contributed to these limitations.

## Conclusion

Despite the considerable number of randomized clinical trials that have so far evaluated the health benefits of several (poly)phenols towards biomarkers of diabetes, there is still a clear need for more intervention studies further demonstrating these effects and investigating in depth the factors that influence inter-individual variability in the response to these compounds. The validation of the reduction of blood glucose by these compounds as well as other potential regulatory effects on other biomarkers should be accompanied by mechanistic studies, with a focus on (poly)phenol microbial metabolism for an accurate characterization of their health benefits towards diabetes management and the combined effects with anti-diabetic drugs.

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## Compliance with ethical standards

**Conflict of interest** The authors declare no conflict of interests.


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