Nutritional intervention and impact of polyphenol on glycohaemoglobin (HbA1c) in non-diabetic and type 2 diabetic subjects: systematic review and meta-analysis

Susana A. Palma-Duran [1] Antonis Vlassopoulos [1] Mike Lean [1] Lindsay Govan [2] Emilie Combet [1]*

Short running title: Dietary plant polyphenols on glycohaemoglobin

Address

Human Nutrition, New Lister Building, School of Medicine, college of Medical, veterinary and Life Sciences, University of Glasgow, Alexandra Parade, Glasgow G31 2ER, UK

Public Health and Health Economics and Health Technology Assessment, University of Glasgow, 1 Lilybank Gardens, Glasgow G12 8QQ, UK

Corresponding author: Emilie Combet, Human Nutrition, New Lister Building, School of Medicine, college of Medical, veterinary and Life Sciences, University of Glasgow, Alexandra Parade, Glasgow G31 2ER, UK. Telephone: +44 141 201 8527, email: Emilie.CombetAspray@glasgow.ac.uk

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Abstract

Polyphenols have been extensively studied for their antioxidant and anti-inflammatory properties. Recently, their antiglycative actions by oxidative stress modulation have been linked to prevention of diabetes and associated complications. This paper assesses the evidence for polyphenol interventions on glycohaemoglobin (HbA1c) in non-diabetic, pre-diabetic and type 2 diabetes mellitus (T2DM) subjects. A systematic review of polyphenols clinical trials on HbA1c in humans was performed according to the Preferred Reporting Items for Systematic Review and Meta-Analysis. Thirty-six controlled randomized trials with HbA1c values were included. Polyphenols (extracts, supplements, foods), were supplemented (28 mg to 1.5g) for 0.7 to 12 months. Combining all subjects (n=1954, mean baseline HbA1c=7.03%, 53 mmol/mol), polyphenol supplementation significantly ($p<0.001$) lowered HbA1c% by -0.53±0.12 units (-5.79±0.13 mmol/mol). This reduction was significant ($p<0.001$) in T2DM subjects, specifically (n=1426, mean baseline HbA1c=7.44%, 58 mmol/mol), with HbA1c% lowered by -0.21±0.04 units (-2.29±0.4 mmol/mol). Polyphenol supplementation had no significant effect ($p>0.21$) in the non-diabetic (n=258, mean baseline HbA1c=5.47%, 36 mmol/mol) and the pre-diabetic subjects (n=270, mean baseline HbA1c=6.06%, 43 mmol/mol) strata: -0.39±0.27 HbA1c% units (-4.3±0.3 mmol/mol), and -0.38±0.31 units (-4.2±0.31 mmol/mol), respectively. In conclusion, polyphenols can successfully reduce HbA1c in T2DM, without any intervention at glycaemia, and could contribute to the prevention of diabetes complications.

Introduction

Hyperglycaemia is clearly recognized as the primary factor in the onset and progression of diabetes. Both acute and chronic hyperglycemia enhance the formation of early, intermediate and advanced glycation endproducts (AGEs), leading to a series of pathogenic complications (Jakuš et al., 2004). AGEs are complex, heterogeneous, and chemically stable which progressively accumulate on the tissue and organs developing chronic complications of diabetes, such as retinopathy, nephropathy, neuropathy, micro and macrovasculopathies (Jakuš et al., 2004). Glycohaemoglobin (HbA1c) is an early glycation product and a marker of chronic glycaemia from the preceding 2 to 3 months (Singh et al., 2001; Diagnosis and classification of diabetes mellitus 2012). HbA1c correlates with both micro and macrovascular complications and is considered as the standard biomarker for glycaemic management (Diagnosis and classification of diabetes mellitus 2012).

Conceding that glycated products are involved in the pathogenesis of diabetes, anti-glycation treatments may assist in the prevention of diabetes and their complications. Nutritional interventions, especially those involving plant foods and beverages or specific phytochemicals, have attracted attention for the management diabetes and its complications. Polyphenols are one of these major classes of phytochemicals. Ubiquitous in plant foods, they have a wide range of chemical structures usually comprising at least one aromatic ring with hydroxyl groups (Xie et al., 2013; Crozier et al., 2009). This wide structural variation, including their substituents, has given to polyphenols their different levels of anti-AGEs and anti-diabetic activities demonstrated *in vivo* and *in vitro* studies (Xie et al., 2013; Klein et al., 2011b). While the original paradigm indicated the antiglycative effect of polyphenols was due to their free radical scavenging potential, new evidence of scavenging-independent protection has emerged (Vlassopoulos et al., 2013; Sadowska-Bartosz et al., 2014; Mandeville et al., 2009).

HbA1c has a higher positive predictive value to identify people at risk of diabetes and cardiovascular complications. Hence, concentrations in the range of 5.5 to 6% are appropriate to initiate preventive interventions (Diagnosis and classification of diabetes mellitus 2012). Nutrition is a potential tool in regulating glucose metabolism, and it has been reported that dietary polyphenol might be protective (Hanhineva et al., 2010). There are several studies and reviews addressing the beneficial effects of polyphenols on humans and animal as well as *in vitro* models on the glycaemic control and cardiovascular risk factors in patients with diabetes (Rosenow et al., 2012; Overman et al., 2011; Chuang et al., 2011; Biesalski 2007). However, the results of human clinical trials investigating the effects of polyphenols on glycation have presented inconsistent results, with some of them presenting short intervention periods that cannot reflect any change during this time frame. Therefore, the present systematic review aimed to evaluate the current published randomized controlled trials related to polyphenol supplementation on HbA1c concentrations in non-diabetic, pre-diabetic and type 2 diabetes mellitus (T2DM) subjects.

Methods

The present systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guideline (Moher et al., 2009). A literature research was carried out on PubMed (http://www.ncbi.nlm.nih.gov/pubmed/), and ISI Web of Knowledge for randomized clinical trials that examined the effects of polyphenols on glycohaemoglobin conducted in human subjects. The database search included all studies published before February 2014. The following search terms were used to identify relevant studies: phenol, polyphenol, phytoestrogen, resveratrol, ellagitan, elligitan, catechin,

flavan, flavon, fruit, vegetable, spice, tea, cocoa, coffee or juice, which were paired with treatment, intervention, or supplementation. The terms glycation, glycated, haemoglobin, HbA1c or glycohaemoglobin were used as well. The wild-card term "*" was used to improve the sensitivity of the search by increasing the number of matches. The references of all relevant trials and reviews were hand-searched for additional studies.

Study Selection

Studies were chosen for analysis if they met the following criteria: (1) the systematic review was restricted to the reports of clinical trials conducted in non-diabetic, pre-diabetic and diabetic subjects without any diabetic complications; (2) the articles were published in English or the abstracts were available in English; (3) studies were controlled parallel or cross-over randomized trials supplemented with polyphenols in form of supplements (oral capsules, extracts, powders), or specific foods and beverages; (4) the baseline and endpoint of glycohaemoglobin values or their differences were available with SDs, SEs, or 95% confidence intervals (CIs); and (5) a concurrent control group was included for the polyphenol group where the only difference between them was the polyphenol supplementation. Studies were excluded when polyphenols were given as part of multicomponent treatment. When data were insufficient, the authors were contacted to obtain additional study details and confirm their eligibility.

Data Extraction and Quality Assessment

Search, data collection, and quality assessment were carried out independently by two reviewers, divided into non-diabetics (including pre-diabetic trials), and T2DM trials according to the inclusion criteria. Title and abstracts were inspected for potential inclusion and duplicates were removed. Full-text articles were attained for further screening of suitability, reference lists were also screened for inclusion. Data on treatment, study design, subjects' characteristics, number of participants, year of publication, period of intervention, and effect of intervention on glycation

were extracted from all the acquired articles. All the authors reviewed the collected data before conducting the statistical analyses. For any discrepancy between them a discussion was held until a consensus was reached. If HbA1c values were reported multiple times in different stage during the trial, only final values were included in the meta-analysis. Additionally, all HbA1c concentrations were dually reported as % and mmol/mol. HbA1c concentrations were converted between NGSP (National Glycohemoglogin Standardization Program) values in percentage to IFCC (International Federation of Clinical Chemistry) values in mmol/mol using the equation NGSP = [0.09148 * IFCC] + 2.152).

The quality of the included articles was estimated using the following criteria: (1) randomization, (2) minimal risk of bias during patient allocation, (3) blinding, (4) report of the number of withdraws and explanation for withdrawal, (5) comparability of control and polyphenol supplemented group at baseline, (6) intention-to-treat analysis, (7) a clearly describe intervention procedure (Higgins 2008). Authors (SP, AV) scored the articles, attributing one point per each criteria addressed in the study design, toward a possible score of 0 (lowest quality) to 7 (highest quality). Studies receiving a score ≥5 were deemed to be of high quality, whereas those with a score <5 were considered of low quality.

Statistical Analysis

The meta-analysis was performed using NCSS 2007 version: 07.1.20, 2010 (Hintze, J. 2009, NCSS, LLC. Kaysville, Utah) and Comprehensive Meta-analysis (Biostat Inc, 2009, Englewood USA). Studies were stratified according to health status as non-diabetic, pre-diabetic and T2DM for analysis. Diabetes mellitus and other categories classification was established according to the report of WHO consultation; Diagnosis and Classification of Diabetes Mellitus and Use of glycated haemoglobin in diagnosis of diabetes mellitus: abbreviated report of a WHO consultation (Consultation 1999; Organization 2011). HbA1c was presented as % at baseline and

at the end of the polyphenol supplementation. When not directly available, SDs were calculated from SEs or 95% CIs. To avoid double-counting of subjects, and unit-of-analysis error, the control group, in trials with more than one treatment arm, was divided according to the number of subgroups within the trial. Meta-analysis was performed using a correlation coefficient (R)=0.5 between groups to allow the calculation of variance used to weight each study and estimate the variance of the combined effects, as described by Follmann (Follmann et al., 1992). Difference in mean ± SE were calculated for net difference in HbA1c%, presented along 95% CIs, with equivalence for the net change in mmol/mol ± SE. The effect of heterogeneity of treatment between studies was tested using the Cochran's Q test (study-by-treatment interaction, P <0.1). Additionally, the I^2 statistic was also examined, I^2 > 50% was considered as an indicator of heterogeneity among trials. A random-effects model was used if a significant heterogeneity was presented. The results of meta-analysis were explained by forest plot of the mean difference (95% CI). Moreover, to evaluate the influence of each study on the effect size, a sensitivity analysis was accomplished using the one-study remove approach. To examine potential publication bias, Egger regression test and funnel plots were assessed. Following the meta-analysis, the pooled effect size (ES) was calculated using the equation ES= mean difference/ (√N x SE of the difference).

Results

Study selection

The flow diagram of the identification process for eligible studies is shown in **Figure 1**. Initially, 926 potential eligible studies were identified through PubMed and Web of Knowledge. After exclusion of non-clinical trials, publications not written in English or irrelevant to the purpose of

the review, 83 articles were assessed for full-text eligibility. After full-text review, 36 randomized control trials (RCT) were excluded due to lack of HbA1c measurement, HbA1c measurement not reported, only HbA1c baseline concentrations reported, HbA1c measurements not published despite measurement, authors not replying to emails, or polyphenols provided as part of a multicomponent treatment. Finally, 36 studies were selected for inclusion in the systematic review.

Study characteristics

The identified trials were divided as non-diabetic, pre-diabetic and T2DM. The characteristics of the trials are shown in **Table 1, 2** and **3** for non-diabetic, pre-diabetic, and T2DM, respectably. A total of 1954 subjects were included in our study; 528 non-diabetics and 1426 T2DM. Some trials included non-diabetic and T2DM subjects and these studies were divided for the analysis. HbA1c concentrations for each stratum are presented in **Table 4** in % and mmol/mol.

A variety of polyphenols were given, more often as extracts or powders, obtained from polyphenol-rich foods and offered as capsules for ingestion (n=27 studies). The principal sources of polyphenols were green tea, juice, cinnamon, and chocolate bar. The total amount of polyphenol supplement given ranged from 28 mg to 1.5 g per day. The intervention studies lasted from under one month to one year, with three months the most common duration. Most studies (20 out of 36) were double blind trials. The trials varied in size from 18 to 95 subjects for non-diabetic, 19 to 123 subjects for pre-diabetic, and from 12 to 114 subjects for T2DM interventions. Study settings were diverse, with 15 studies from Asia, 9 from the US, 8 from Europe, and 4 from elsewhere (Australia, Brazil, Canada and Mauritius). Subjects in the T2DM trial group were conventionally medicated, most of them with metformin while non-diabetic subject were not medicated.

Data quality

Study quality was evaluated for all trials and the results are presented in **Table 1, 2** and **3**. Most trials (n=32) were classified as high quality (≥5), with only four trials classified as low quality (<5). High quality trials presented adequate minimal risk of bias during patient selection and reported use of random allocation number for the subjects. Details regarding withdrawals were reported in 28 trials. Only three of the trials analysed data according to the intention-to-treat principle, achieving the highest score of 7.

Effect of polyphenol intake on HbA1c

Results of polyphenol supplementation on HbA1c% reduction are presented in the Forest plot in **figure 2** to **4** (difference in mean and 95% CI) according to health status. The meta-analysis of polyphenol intervention on the population as a whole (all three strata) significantly lowered HbA1c %: -0.53±0.12, 95% CI: -0.77 to -0.29 units HbA1c% (-5.79 ± 1.3 mmol/mol, 95% CI: -8.4 to -3.2), compared with the control group ($p<0.001$, effect size=0.09).

Looking into individual strata (Figure. 2), polyphenol treatment showed a favourable reduction of HbA1c concentrations in the supplemented T2DM subjects compared to control subjects: -0.21±0.04, 95% CI: -0.29 to -0.121 units HbA1c% (-2.29±0.4 mmol/mol HbA1c, 95% CI -3.2 to 1.3, $p<0.001$). In contrary, polyphenols treatment in non-diabetic subjects (Figure 3) did not lead to significant ($p=0.15$) reduction in HbA1c: -0.39± 0.27, 95% CI: -0.92 to 0.15 units HbA1c%; (-4.3±3.0 mmol/mol HbA1c, 95% CI: -10.1 to 1.6). Similar results were found for the pre-diabetic subjects: -0.38±0.31, 95% CI: -0.99 to 0.22 units HbA1c% (-4.2±3.4 mmol/mol HbA1c, 95% CI: -10.8 to 2.4, $p=0.21$). Polyphenol interventions had a larger effect size in T2DM group (effect size=0.12) compared to the overall group (effect size=0.09). A significant heterogeneity was found for the changes in HbA1c% for non-diabetic and pre-diabetic trials ($p<0.001$, I^2 =97.5% and 93.2% respectively) and the results are reported with the random-effects model. There was

no significant heterogeneity for the T2DM group (p=0.28; I^2 =10.89), in this case, the results are reported based on the fixed-effects model.

The funnel plots for each group approximated an inverted symmetrical funnel, which suggests limited publication bias (**Figure. 5**). Using Egger regression test, publication bias was found in the combined meta-analyses for all strata (b0= -2.80, p=0.003) indicating that the smaller trials show a more pronounced effect that the larger ones. This was the case for the T2DM stratum, which presented a statistically significant asymmetry (b0= -0.647, p<0.01), but not the non-diabetic trials (b0=5.37, p=0.08) or the pre-diabetic trials (b0=1.46, p=0.37).

Sensitivity analysis to explore heterogeneity was performed using the one-study remove approach. We found no significant change in HbA1c % reduction between treatment groups in each stratum. Similarly, analysis limited to high-quality studies (score ≥5) was performed on the T2DM stratum (where no heterogeneity existed) to determine risk of bias due to poorer quality studies (eliminated trials are listed in table 3). HbA1c% reduction was still significant when analyses were limited to high-quality studies (n=25) and was not changed: -0.27±0.06 units HbA1c%, 95% CI: -0.39 to -0.16 (3.0±0.7 mmol/mol HbA1c, 95% CI: -4.3 to -1.7, p<0.001). This was not performed for the pre-diabetic and non-diabetic strata since few trials (n=8) with a high quality level (except for Banini, 2006) were found.

Additionally, when analysis was restricted to longer trials (≥ 6 and ≥ 12 weeks) on all three stratums combined, reduction in HbA1c became more marked. Including trials lasting 6 weeks or longer led to a reduction of -0.40±0.09 units HbA1c%; 95% CI: -0.57 to -0.22% (-4.4±1.0 mmol/mol, 95% CI: -0.57 to -2.4, p<0.001). Trials lasting 12 weeks or longer led to a reduction of -0.38±0.10 units HbA1c%; 95% CI: -0.59, to -0.18 (-4.2±1.1 mmol/mol, 95% CI: -6.4 to -2.0, p<0.001). The same was for T2DM stratum lasting 12 weeks or longer with a reduction of -

0.27±0.07 units HbA1c%, 95% CI: -0.40 to -0.14 (3.0±0.8 mmol/mol; 95% CI: -4.4 to -1.5, $p<0.001$).

Discussion

Glycated tissue components are recognised as markers of vascular complications, in diabetic as well as non-diabetic subjects (Selvin et al., 2010b). As a widely-used example, HbA1c during the first 3 months after T2DM diagnosis is a strong determinant of cardiovascular death within 5 years and can predict microvascular and macrovascular diseases (Kerr et al., 2011; Mulnier et al., 2006). Fructosamine concentrations have also been associated with cardiovascular mortality (Browner et al., 1999; Mittman et al., 2010). Thereby, lowering glycated concentrations after diagnosis may reduce long-term risks of diabetes complication.

Our meta-analysis showed a significant -0.53±0.12 unit reduction in HbA1c% in the total population (n=1954) irrespective of diabetes status (equivalent to -5.8±1.3 mmol/mol), which was sustained among T2DM individuals (n=1426) but not significant among pre-diabetic and non-diabetic subjects, whose baseline HbA1c was lower.

The ARIC study showed that for every one unit increase in HbA1c% being associated with a 55% risk of stroke (Selvin et al., 2010a). Overall the EPIC, ARIC and AusDiab studies suggested a 18-26% increase in all-cause mortality for each one increase in HbA1c% (Barr et al., 2009; Khaw et al., 2004; Selvin et al., 2010a). Assuming a linear association between HbA1c increase and risk of comorbidities, a reduction of 0.53 units in HbA1c%, as seen in all subjects combined, could result in 14-23% reduction in all-cause mortality and 26% decrease in the risk of stroke. Despite the relatively small effect size of the treatment (0.09 for all strata), there is the potential

for sizeable clinical and public health significance. As most of polyphenol studies are short intervention trials, consequently, long term clinical outcome have not been measure yet.

Our results are in concordance with a previous meta-analysis assessing cinnamon intake on HbA1c (Davis et al., 2011). The six cinnamon trials included by Davis et al. (n= 435 subjects) led to a significant decrease in mean HbA1c (0.09%; 95% CI: 0.04 to 0.14). Another meta-analysis (6 trials, <3 months, n= 348 subjects) (Zheng et al., 2013) quantifying the effect of green tea catechins on glycaemic control failed to observe a significant decrease on HbA1c (-0.04%; 95% CI: -0.15 to 0.08%). The green tea trials were based on short durations (<3 months in half of the trials), similar to several trials included here in the non-diabetic and pre-diabetic strata, and eight trials in the T2DM stratum. Removal of these eight trials in the T2DM stratum did not change the outcome of the meta-analysis, with a reduction of HbA1c highly significant (-0.27%; SE: 0.07%; 95% CI: -0.40 to -0.14; $p<0.001$). Since HbA1c% is a long-term predictor of diabetes complications, any effect should be measured using a marker that reflects a change due to the exposure.

Only 5 trials were found that met the inclusion criteria for non-diabetic and pre-diabetic. Two trials included T2DM subjects and these studies were divided for the analysis. Although there were more trials that declared HbA1c % in their analysis, the reduction after treatment or baseline was not mentioned. This reduced the number of trials included in the meta-analysis. Long-term, high quality, randomized control trials are needed to verify the effects of polyphenols intervention on HbA1c in non-diabetic and pre-diabetic. Moreover, few of the trials included assessed HbA1c concentrations as their primary outcome, so sample sizes were not estimated for this outcome. An increased risk of coronary heart disease, ischemic stroke, and death has been observed even in the normal concentrations of HbA1c (Selvin et al., 2004). The risks of microvascular events can progressively lower down for pre-diabetic individuals when HbA1c

concentrations yield 6.5% (Zoungas et al., 2012). Therefore, even a reduction of HbA1c within the normal values may be useful to reduce the risk of diabetes, vascular diseases and death.

The trials included in this meta-analysis had a variety of polyphenol sources, dosage, presentation, duration of the RCTs, differences in ethnicity, health condition, heterogeneous groups of subjects, and, for T2DM, glucose control level medication, that could have led to a bias among the trials, and therefore to the heterogeneity observed. For instance, in the T2DM trials, polyphenols were presented principally as capsules or extracts, while in the non-diabetic and pre-diabetic trials, the main source of polyphenol was food.

Not all polyphenols have the same properties, and relatively few have been fully assessed for their bioavailability and metabolic fate after ingestion, or for effect of the food matrix and background dietary compositions (Crozier et al., 2009). This heterogeneity inherent to nutritional interventions probably introduces substantial variance in outcomes and should be taken in consideration (even for the T2DM stratum) when interpreting the results and drawing conclusions. In fact, polyphenol urinary concentration or other biomarkers of intake should be measured to indicate compliance and to demonstrate that an increase of polyphenol has been achieve during the intervention. And so forth, relate the change in HbA1c concentration to an increase in polyphenols intake. In this case, only 7 (Balzer et al., 2008; Curtis et al., 2012; Fenercioglu et al., 2010; Kudolo et al., 2005; Pan et al., 2007; Toolsee et al., 2013; Vinson et al., 2012) of the trial included in the meta-analysis included polyphenol metabolites analysis or antioxidant capacity assay.

A dose-response effect between polyphenol and HbA1c was not included in the meta-analysis given the variability of trials. Dietary approaches included in this meta-analysis supplemented the diets with 28 to 1500 mg/day polyphenols. Polyphenol rich extracts had a more marked effect in reducing HbA1c among the trials. The isoflavonoids extracts doses (125 mg/d) used in the

supplements can be achieved with the ingestion of soy products (Song et al., 1998; Rau De Almeida Callou et al., 2010). Similarly, a daily intake of 1-3g of cinnamon (27 mg/d of coumarin) can be feasible to reduce HbA1c concentrations (He et al., 2005; Shan et al., 2005). On the other hand, resveratrol dose (250 mg/d) could be achieve with extracts since red wine, with the highest resveratrol content, presents around 3 mg/100 ml (Lamikanra et al., 1996). In terms of physiological relevance, a strict and well-designed dietary intervention should be able to deliver similar doses of certain polyphenols as those obtained by supplements. It is however still unclear how the food matrix and downstream cascade of physiological events associated with food (and meal) structure can impact on the biological activity of food bioactives, including polyphenols. A Western diet is able to deliver between 109mg to 313mg of polyphenol per day, 820mg and 1.3g for a Mediterranean diet (Sowers et al., 2006; Zamora-Ros et al., 2013; Dilis et al., 2010; Tresserra-Rimbau et al., 2013; Touvier et al., 2013).

In summary, the results of the meta-analysis showed that polyphenol supplementation is associated with a significant reduction in HbA1c (%) in the total population. This effect is more profound in subjects with T2DM, whereas in pre- and non-diabetic subjects the relatively small number of published trials, the low study quality and the small effect size of the interventions did not allow for the detection of a significant effect. Despite the small effect size of the polyphenol supplementation trials, the meta-analysis shows a good potential of such intervention in terms of clinical and public health significance that needs further investigation. Importantly, the doses supplemented are achievable through dietary modification and offer a large range of opportunities for intervention. More long-term controlled trials of high quality are needed especially in populations free (but at risk) of diabetes (e.g. those with overweight, high blood pressure, or impaired glucose tolerance).

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S.P. wrote the manuscript, conducted research and analysed data. A. V. conducted research, contributed to discussion and reviewed the manuscript. M. L. reviewed/edited the manuscript and contributed to discussion. L. G. reviewed the manuscript and contributed to the statistical analysis. E. C. designed research, supervised the project, reviewed/edited the manuscript and contributed to discussion. All authors read and approved the final manuscript.

S.P. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

The authors declare no conflict of interest.

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Table 1. Characteristics of the trials carried out with non-diabetic individuals, that were included in the analysis

							HbA1c ± SD			
							Polyphenol		Control	
Study	**Quality score**	**Country**	**Design**	**No. subjects**	**Polyphenol intervention**	**Duration (m)**	**Pre**	**Post**	**Pre**	**Post**
Non-diabetic										
Banini, 2006 (Banini et al., 2006)	3	US	RCT	23	Muscadine grape juice (150 mL/d)	<1	5.5 ± 0.28	5.8 ± 0.85	5.5 ± 1.61	5.2 ± 0.77
Brown, 2009 (Brown et al., 2009)	6	UK	RDBCT	88	Tea (800mg EGCG/d) capsule	2	5.28 ± 0.43	5.31 ± 0.05	5.12 ± 0.32	5.22 ± 0.05
Dallas, 2013 (Dallas et al., 2013)	6	France	RDBCT	95	Polyphenol-rich fruit extract (900mg/d) capsule	3	5.64 ± 0.10	5.95 ± 0.08	5.55 ± 0.10	6.79 ± 0.05
Ogawa, 2013 (Ogawa et al., 2013)	6	Japan	RDBCT	34	1000mg/d of acacia polyphenol tablet	2	5.4 ± 0.41	5.4 ± 0.41	5.5 ± 0.41	5.6 ± 0.41
Vinson, 2012 (Vinson et al., 2012)	5	US	RCoT	18	6-8 Purple majesty Potatoes	1	5.6 ± 0.40	5.0 ± 0.40	5.6 ± 0.40	4.7 ± 0.40

HbA1c % is expressed as mean ± standard deviation. B, blind; C, controlled; Co, crossover; D, double; EGCG, epigallocatechin gallate; R, randomized; S, single; T, trial. High quality score ≥ 5.

Table 2. Characteristics of the trials carried out with pre-diabetic individuals, that were included in the analysis

							HbA1c ± SD			
							Polyphenol		Control	
Study	**Quality score**	**Country**	**Design**	**No. subjects**	**Polyphenol intervention**	**Duration (m)**	**Pre**	**Post**	**Pre**	**Post**
Pre-diabetic										
Evans, 2012 (Evans et al., 2012)	5	US	RDBCT	19	Diabetinol 1500mg/d (nobiletin and tangeretin) capsule	3	6.52 ± 0.75	6.42 ± 0.63	6.39 ± 0.70	6.45 ± 0.47
Cho, 2012 (Cho et al., 2012)	5	Korea	RDBCT	99	Sajabalssuk (3000mg/d) and Pinitol (Positive control: 1140mg/d) capsule	2.3	6.28 ± 0.75	5.63 ± 0.57	6.19 ± 1.61	6.51 ± 1.26
					Pinitol (Positive control: 1140mg/d) capsule		5.54 ± 1.03	6.05 ± 1.03		
Klein, 2011 (Klein et al., 2011a)	6	Brazil	RSBCT	29	Mate Tea (19800mg/d)	2	6.1 ± 0.80	5.7 ± 0.86		
					Mate Tea (19800mg/d) and Diet intervention		5.7 ± 0.47	5.30 ± 0.41	5.97 ± 0.59	5.88 ± 0.81
Toolsee, 2013 (Toolsee et al., 2013)	6	Mauritius	RBGCT	123	Green tea infusion (6000mg/d) male	3.5	6.0 ± 0.18	5.9 ± 0.15	6.0 ± 0.14	5.9 ± 0.20
					Green tea infusion (6000mg/d) female		6.1 ± 0.19	5.95 ± 0.16	6.0 ± 0.12	5.9 ± 0.12

HbA1c % is expressed as mean ± standard deviation. B, blind; C, controlled; Co, crossover; D, double; G, gender; R, randomized; S, single; T, trial. High quality score ≥ 5.

Table 3. Characteristics of the trial carried out with Type 2 Diabetes Mellitus patients, that were included in the analysis

Study	Quality score	Country	Design	No. subjects	Medication	Polyphenol intervention	Duration (m)	HbA1c ± SD Polyphenol Pre	HbA1c ± SD Polyphenol Post	HbA1c ± SD Control Pre	HbA1c ± SD Control Post
Balzer, 2008 (Balzer et al., 2008)	6	US	RDBCT	41	H	High Flavonols (963mg/d) vs Low (75mg/d) dose cocoa drink	1	7.0 ± 0.9	6.9 ± 0.90	7.5 ± 1.2	7.5 ± 1.2
Banini, 2006 (Banini et al., 2006)	3	US	RCT	29	NS	Muscadine grape juice (150mL/d)	<1	8.4 ± 2.21	8.3 ± 2.21	5.5 ± 1.61	5.2 ± 0.77
						Muscadine grape wine (150mL/d)		7.4 ± 1.58	6.8 ± 2.53		
						Dealcoholized-Wine (150mL/d)		7.6 ± 1.50	7.5 ± 1.20		
Basu, 2013 (Basu et al., 2013)	2	US	PCS	17	H	Pomegranate Polyphenol extracts (1506mg/d) capsule	1	7.51 ± 0.75	7.31 ± 0.53	6.45 ± 0.76	6.45 ± 0.85
Bhatt, 2012 (Bhatt et al., 2012)	5	India	RCT	57	H(M/Gl)	Resveratrol capsule (250mg/d)	3	13.7 ± 2.0	13.1 ± 1.9	11.4 ± 1.90	11.7 ± 1.7
Blevins, 2007 (Blevins et al., 2007)	7	US	RDBCT	57	M/Th/HGMCR	Cinnamon capsule (1500mg/d)	3	7.2 ± 0.30	7.4 ± 0.10	7.1 ± 0.20	7.2 ± 0.2
Campbell, 2011(Campbell-Tofte et al., 2011)	7	Denmark	RDBCT	23	M/Ht/Ch	Rauvolfia-Citrus Tea (750mL/d) drink	4	6.5 ± 1.1	6.1 ± 1.20	6.8 ± 1.00	6.7 ± 1.00
Curtis, 2012 (Curtis et al., 2012)	6	UK	RDBCT	93	Statin	Flavonoid-enriched Chocolate (27000mg/d: 90mg epicatechin + 100mg isoflavones aglycone equivalents)	12	7.13 ± 0.96	7.22 ± 1.03	7.25 ± 1.01	7.44 ± 1.15
Fenercioglu, 2010 (Fenercioglu et al., 2010)	5	Turkey	RDBCT	114	M/A	Pomegranate extract (500mg), Green tea extract (300mg) and vitamin C (60mg) capsule	3	7.36 ± 1.78	7.00 ± 0.98	7.71 ± 2.33	7.1 ± 2.13
Fukino, 2005 (Fukino et al., 2005)	4	Japan	RCT	66	-	Green tea extract/powder (544mg polyphenol)	2	6.2 ± 1.9	6.0 ± 1.90	6.1 ± 1.30	6.4 ± 1.40
Fukino, 2008 (Fukino et al., 2008)	5	Japan	RCoNBNWT	60	H	Green tea extract/powder (544mg polyphenol + 102 mg caffeine)	4	6.2 ± 2.0	5.8 ± 1.70	6.1 ± 1.30	5.9 ± 1.40
Howes, 2003 (Howes et al., 2003)	6	Australia	RDBCoT	19	M/Su/A	Isoflavone tablet (50mg/d formononetin, 5mg/d biochanin, with genistein and daidzein)	3	7.16 ± 0.63	7.12 ± 2.97	7.16 ± 0.63	7.11 ± 2.67
Hsu, 2011 (Hsu et al., 2011)	6	Taiwan	RDBCT	68	H	Decaffeinated green tea extract (1500mg/d; 856 mg/d of EGCG and other catechins) capsule	4	8.4 ± 2.1	8.00 ±	8.4 ± 1.80	8.2 ± 1.9

								2.00		
Hussain, 2007 (Hussain 2007)	5	Iraq	RDB CT	59	H (Gl)	Silymarin (200mg/d + glibenclamide) capsule, Control (10 mg/d glibenclamide)	4	8.91 ± 0.76	7.45 ± 0.81	8.78 ± 0.50	8.74 ± 0.46
						placebo capsule (+ glibenclamide)		8.76 ± 0.67	8.71 ± 0.63		
Jayawardena, 2005 (Jayawardena et al., 2005)	5	Sir Lanka	RDB CoT	51	H (M/Gl)	Kothala Himbutu Tea infusion	6	6.8 ± 0.9	6.29 ± 1.02	6.7 ± 0.90	6.65 ± 1.04
Klein, 2011 (Klein et al., 2011a)	6	Brazil	RSBCT	29	H (M/Su)	Mate Tea (19800mg/d)	2	7.6 ± 2.99	6.7 ± 2.65	6.5 ± 0.60	6.4 ± 0.60
						Mate Tea (19800mg/d) and Diet intervention		6.8 ± 0.90	6.7 ± 1.20		
Kudolo, 2005 (Kudolo et al., 2005)	4	US	RCT	19	H (M/Gly)	*Ginkgo biloba* extract tablet (120mg/d) in normal and high cholesterol T2DM subjects	3	6.9 ± 0.90	7.30 ± 1.60	7.30 ± 1.40	7.20 ± 2.00
Lu, 2012 (Lu et al., 2012)	6	China	RDB CT	66	Gli	Low-dose cinnamon tablets(120mg/d)	3	8.9 ± 1.24	8.23 ± 0.99	8.93 ± 1.14	8.93 ± 1.04
						high-dose cinnamon tablets (360mg/d)		8.92 ± 1.35	8.00 ± 1.00		
MacKenzie, 2007 (Mackenzie et al., 2007)	6	US	RDB CT	49	H (M/Gly)	Tea extract (375mg/d: 150mg green tea catechins + 75mg black tea theaflavins + 150mg others tea Polyphenols) capsule	3	7.2 ± 0.80	7.5 ± 0.90	7.1 ± 0.80	7.5 ± 0.92
						Tea extract (750mg/d: 300mg green tea catechins and 150mg black tea theaflavins, 300mg other tea polyphenols) capsule		7.1 ± 0.9	7.6 ± 1.15		
Mang, 2006 (Mang et al., 2006)	6	Germany	RDB CT	65	M/Su/Th	3 capsule/d of cinnamon extract (112mg aqueous purified extract with <0.1% coumarins and <0.1%essential oil) capsule	4	6.86 ± 1.00	6.83 ± 0.83	6.71 ± 0.73	6.68 ± 0.70
Mellor, 2010 (Mellor et al., 2010)	5	UK	RDB CoT	12	M/Statin	3 bars/d of high Polyphenol Chocolate (16.6mg/d epicatechins) vs low polyphenol chocolate (<2mg)	4	6.4 ± 0.49	6.5 ± 0.49	6.40 ± 0.20	6.4 ± 0.50
Mirzaei, 2010 (Mirzaei et al., 2010)	5	Iran	RDB CT	72	-	Green tea extract (150mg/d: 150 mg caffeine, 240 mg polyphenols) capsule	2	7.21 ± 1.63	7.25 ± 1.87	7.61 ± 2.04	8.17 ± 2.09
Movahed, 2013 (Movahed et al., 2013)	6	Iran	RGDBCT	64	H (M/Gl/Statin)	Resveratrol capsule (100mg/d)	1.5	8.6 ± 1.39	7.60 ± 1.32	8.30 ± 2.37	8.50 ± 2.46
Nagao, 2009 (Nagao et al., 2009)	6	Japan	RDB CoT	43	Su/Th	Catechin green tea (catechin: 582.8mg/d) vs green tea (catechin: 96.3mg/d) drink	3	6.68 ± 0.77	6.31 ± 0.77	6.59 ± 0.90	6.58 ± 1.03

Pan, 2007 (Pan et al., 2007)	6	China	RDBCT	68	H/Ht	Lignan capsule(360mg/d)	3	7.71 ± 1.42	7.06 ± 1.15	7.01 ± 1.29	7.11 ± 1.29
Ryan, 2000(Ryan et al., 2000)	6	Canada	RSBCT	40	H	Herbal tea(Populus tremulides and Heracleum lanatum,250mL/d) vs Placebo Chinese green tea, mint and fennel seed (250mL/d)	< 1	7.5 ± 1.80	7.9 ± 1.60	8.1 ± 1.50	8.30 ± 1.30
Tome-Carneiro, 2013 (Tome-Carneiro et al., 2013)	6	Spain	RTrBCT	35	Ht/Statin /BB/RASB	Green tea extract (350mg/d: 151mg phenolics) capsule	12	7.1 ± 1.30	7.2 ± 1.2	7.0 ± 1.0	7.40 ± 1.00
						Green tea extract (139mg phenolics) + Resveratrol (8.1mg) capsule		7.4 ± 1.60	7.60 ± 1.50		
Vafa, 2012 (Vafa et al., 2012)	5	Iran	RDBCT	37	M/Gli	Cinnamon (3000mg/d) capsule	2	7.35 ± 0.51	6.90 ± 0.77	7.28 ± 0.56	7.18 ± 0.74
Vanschoonbeek, 2006 (Vanschoonbeek et al., 2006)	5	Netherlands	RDBCT	25	M/Su/Th	Cinnamon (1500mg/d) capsule	1.5	7.4 ± 1.04	7.5 ± 1.04	7.1 ± 0.72	7.20 ± 0.72
Zibadi, 2008(Zibadi et al., 2008)	7	US	RDBCT	48	ACE	Pynogenol (125mg/d) capsule	3	7.9 ± 1.47	7.10 ± 0.98	8.1 ± 0.40	8.00 ± 1.96

HbA1c % is expressed as mean ± standard deviation. A, ascarbose; ACE, angiotensin-converting enzyme; B, blind; BB, β-blockers; D, double; C, controlled; Co, crossover; G, gender; Gl, glibenclamide; Gli, gliclazide; Gly, glyburide; H, hypoglycemic agent; HGMCR, hydroxymethylglutaryl-CoA reductase; Ht, hypertensive agent; M, metformin; N, no; PCS, pilot clinical study; R, randomized; S, single; Su, sulphonylureas: T, trial; Th, thiazoledinediones, Tr, triple; W, washout. High quality score ≥ 5.

Table 4. HbA1c concentrations (Mean ± SD) of the subjects included in the analysis

Subjects	Baseline		Endpoint	
	%	mmol/mol	%	mmol/mol
Non-diabetic (n= 258)	5.47 ± 0.40	36.28 ± 4.37	5.76 ± 0.35	39.45 ± 1.31
Pre-diabetic (n= 270)	6.06 ± 0.68	42.73 ± 7.43	5.79 ± 0.63	39.78 ± 4.17
T2DM (n=1426)	7.44 ± 1.19	57.81 ± 8.88	7.33 ± 1.22	56.61 ± 9.26
Treated (n= 1053)	7.59 ± 1.26	59.45 ± 9.51	7.36 ± 1.28	56.94 ± 9.85
Control (n= 901)	6.92 ± 0.99	52.13 ± 7.15	6.94 ± 1.00	52.35 ± 7.24
Total (n= 1954)	7.03 ± 1.03	50.22 ± 10.60	6.94 ± 1.04	49.30 ± 10.70

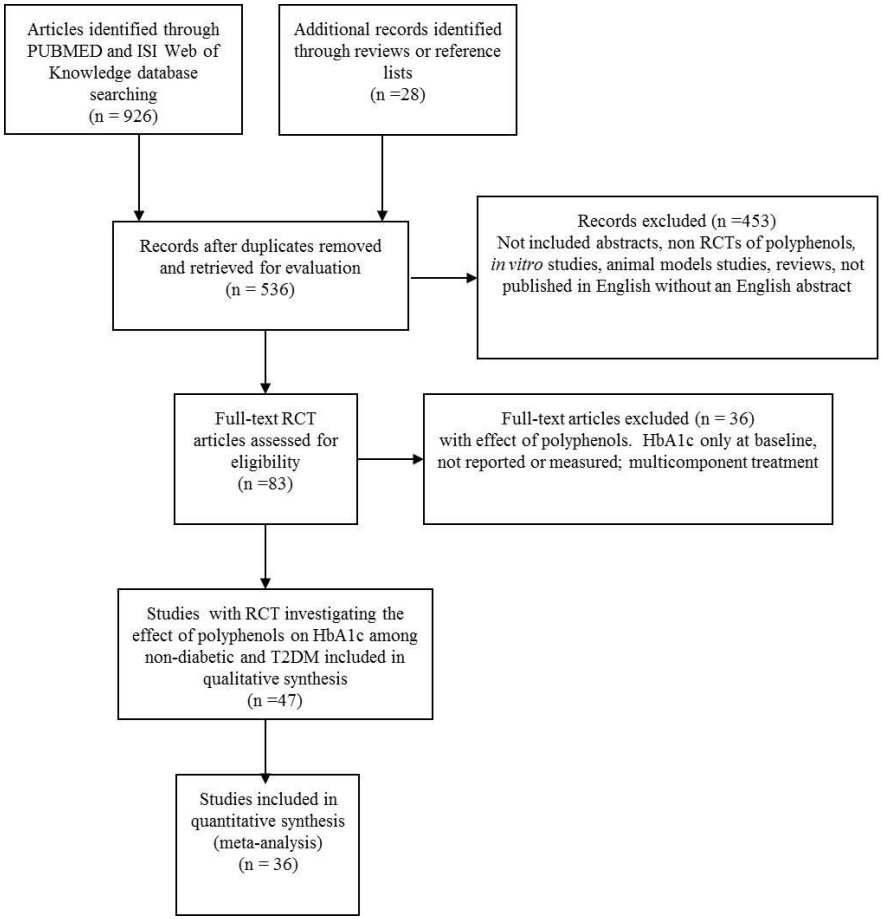

Figure 1. Flow diagram of the study selection process

T2DM Subjects Meta Analysis

Study name	Treatment	Difference in means	SE	Variance	Lower limit	Upper limit	Z-Value	p-Value
Balzer, 2008	High Polyphenol	-0.100	0.330	0.109	-0.747	0.547	-0.303	0.762
Banini, 2006	Dealcoholized-wine	-0.200	0.708	0.501	-1.587	1.187	-0.283	0.777
Banini, 2006	Muscadine grape juice	-0.200	1.056	1.115	-2.269	1.869	-0.189	0.850
Banini, 2006	Muscadine grape wine	-0.300	1.056	1.115	-2.369	1.769	-0.284	0.776
Basu, 2013	Pomegranate	-0.200	0.363	0.131	-0.911	0.511	-0.552	0.581
Bhatt, 2012	Resveratrol	-0.900	0.498	0.248	-1.876	0.076	-1.807	0.071
Blevins, 2007	Cinnamon	-0.100	0.062	0.004	-0.222	0.022	-1.605	0.108
Campbell, 2011	Tea	-0.300	0.452	0.204	-1.186	0.586	-0.664	0.507
Curtis, 2012	Chocolate	-0.100	0.217	0.047	-0.524	0.324	-0.462	0.644
Fenercioglu, 2010	Pomegranate	-0.250	0.361	0.130	-0.958	0.458	-0.692	0.489
Fukino, 2005	Tea	-0.500	0.406	0.165	-1.296	0.296	-1.231	0.218
Fukino, 2008	Tea	-0.200	0.419	0.176	-1.021	0.621	-0.477	0.633
Howes, 2003	Isoflavone	-0.010	1.211	1.466	-2.383	2.363	-0.008	0.993
Hua, 2011	Tea	-0.200	0.475	0.226	-1.131	0.731	-0.421	0.674
Hussain, 2007	Glibenclamide	-0.010	0.224	0.050	-0.450	0.430	-0.045	0.964
Hussain, 2007	Silymarin&Glibenclamide	-1.420	0.274	0.075	-1.958	-0.882	-5.173	0.000
Jayawardena, 2005	Tea	-0.460	0.273	0.075	-0.996	0.076	-1.683	0.092
Klein, 2011	Mate tea	-0.800	1.461	2.134	-3.663	2.063	-0.548	0.584
Klein, 2011	Mate tea & Diet	0.000	0.529	0.280	-1.037	1.037	0.000	1.000
Kudolo, 2005	Ginkgo biloba extract	-0.500	0.731	0.535	-1.933	0.933	-0.684	0.494
Lu, 2012	High dose Cinnamon	-0.920	0.447	0.200	-1.796	-0.044	-2.059	0.040
Lu, 2012	Low dose Cinnamon	-0.670	0.426	0.181	-1.504	0.164	-1.574	0.115
MacKenzie, 2007	High dose tea	-0.100	0.427	0.182	-0.937	0.737	-0.234	0.815
MacKenzie, 2007	Low dose tea	-0.100	0.363	0.132	-0.811	0.611	-0.276	0.783
Mang, 2006	Cinnamon	0.000	0.206	0.042	-0.403	0.403	0.000	1.000
Mellor, 2010	Chocolate	-0.100	0.283	0.080	-0.654	0.454	-0.354	0.724
Mirzaei, 2010	Tea	-0.520	0.482	0.232	-1.464	0.424	-1.080	0.280
Movahed, 2013	Resveratrol	-1.200	0.486	0.236	-2.152	-0.248	-2.469	0.014
Nagao, 2009	Tea	-0.360	0.265	0.070	-0.879	0.159	-1.359	0.174
Pan, 2007	Lignan	-0.210	0.315	0.099	-0.827	0.407	-0.667	0.505
Ryan, 2000	Tea	-0.200	0.495	0.246	-1.171	0.771	-0.404	0.686
Tome-Carneiro, 2013	Tea	-0.300	0.690	0.476	-1.652	1.052	-0.435	0.664
Tome-Carneiro, 2013	Tea & Resveratrol	-0.200	0.755	0.570	-1.679	1.279	-0.265	0.791
Vafa, 2012	Cinnamon	-0.350	0.222	0.049	-0.784	0.084	-1.580	0.114
Vanschoonbeek, 2006	Cinnamon	-0.000	0.355	0.126	-0.696	0.696	-0.000	1.000
Zibadi, 2008	Pynogenol	-0.700	0.480	0.230	-1.640	0.240	-1.460	0.144
Fixed		-0.207	0.044	0.002	-0.293	-0.121	-4.706	0.000
Random		-0.270	0.058	0.003	-0.384	-0.156	-4.646	0.000

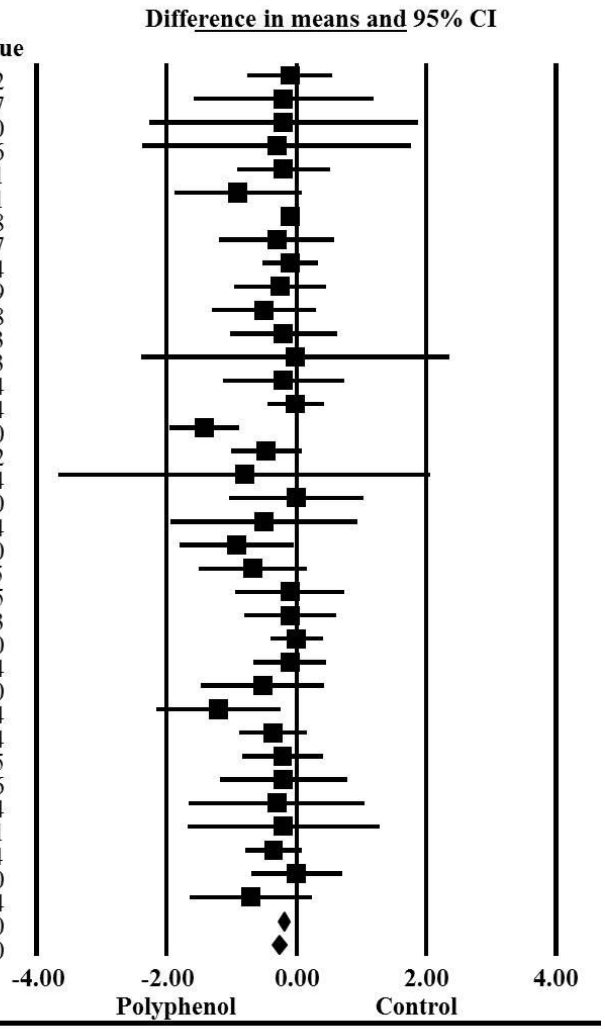

Figure 2. Net change in HbA1c % associated with polyphenol intervention on T2DM subjects. The overall effect size has been estimated from a fixed-effects model

Non-Diabetic Subjects Meta Analysis

Model	Study name	Difference in means	SE	Variance	Lower limit	Upper limit	Z-Value	p-Value
	Banini 2006	-0.600	0.490	0.240	-1.560	0.360	-1.225	0.221
	Brown 2009	-0.070	0.076	0.006	-0.220	0.080	-0.915	0.360
	Dallas 2013	-0.930	0.018	0.000	-0.966	-0.894	-50.844	0.000
	Ogawa 2013	-0.100	0.141	0.020	-0.377	0.177	-0.707	0.480
	Vinson 2012	-0.300	0.200	0.040	-0.692	0.092	-1.500	0.134
Fixed		-0.866	0.018	0.000	-0.901	-0.832	-49.315	0.000
Random		-0.388	0.273	0.075	-0.924	0.147	-1.422	0.155

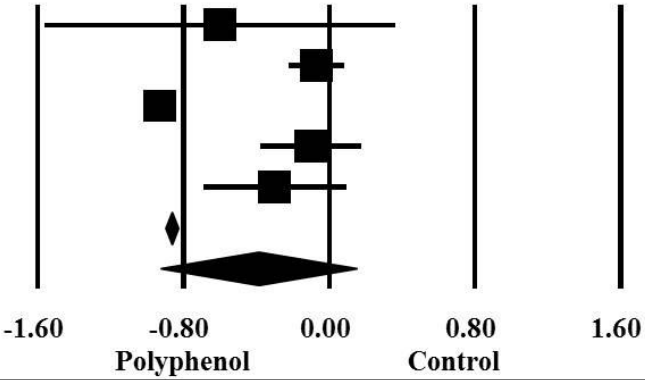

Figure 3. Net change in HbA1c % associated with polyphenol intervention on non-diabetic subjects. The overall effect size has been estimated from a random-effects model.

Pre-Diabetic Subjects Meta Analysis

Model	Study name	Treatment	Difference in means	SE	Variance	Lower limit	Upper limit	Z-Value	p-Value
	Cho 2012	Pinitol	-0.790	0.357	0.127	-1.490	-0.090	-2.213	0.027
	Cho 2012	Sajabalssuk & Pinitol	-0.370	0.304	0.093	-0.967	0.227	-1.215	0.224
	Evans 2012	Diabetinol	-0.220	0.301	0.091	-0.810	0.370	-0.730	0.465
	Klein, 2011	Mate tea	-0.035	0.472	0.223	-0.960	0.890	-0.074	0.941
	Klein, 2011	Mate tea & Diet	-0.035	0.314	0.099	-0.650	0.580	-0.111	0.911
	Toolsee, 2013	Female	-1.150	0.042	0.002	-1.232	-1.068	-27.616	0.000
	Toolsee, 2013	Male	0.000	0.046	0.002	-0.090	0.090	0.000	1.000
Fixed			-0.616	0.030	0.001	-0.675	-0.556	-20.404	0.000
Random			-0.385	0.310	0.096	-0.994	0.223	-1.241	0.214

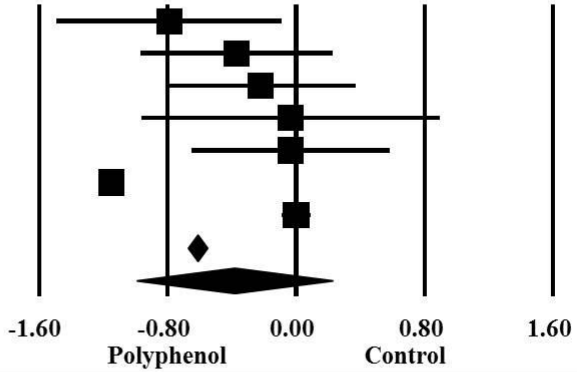

Figure 4. Net change in HbA1c % associated with polyphenol intervention on pre-diabetic subjects. The overall effect size has been estimated from a random-effects model.

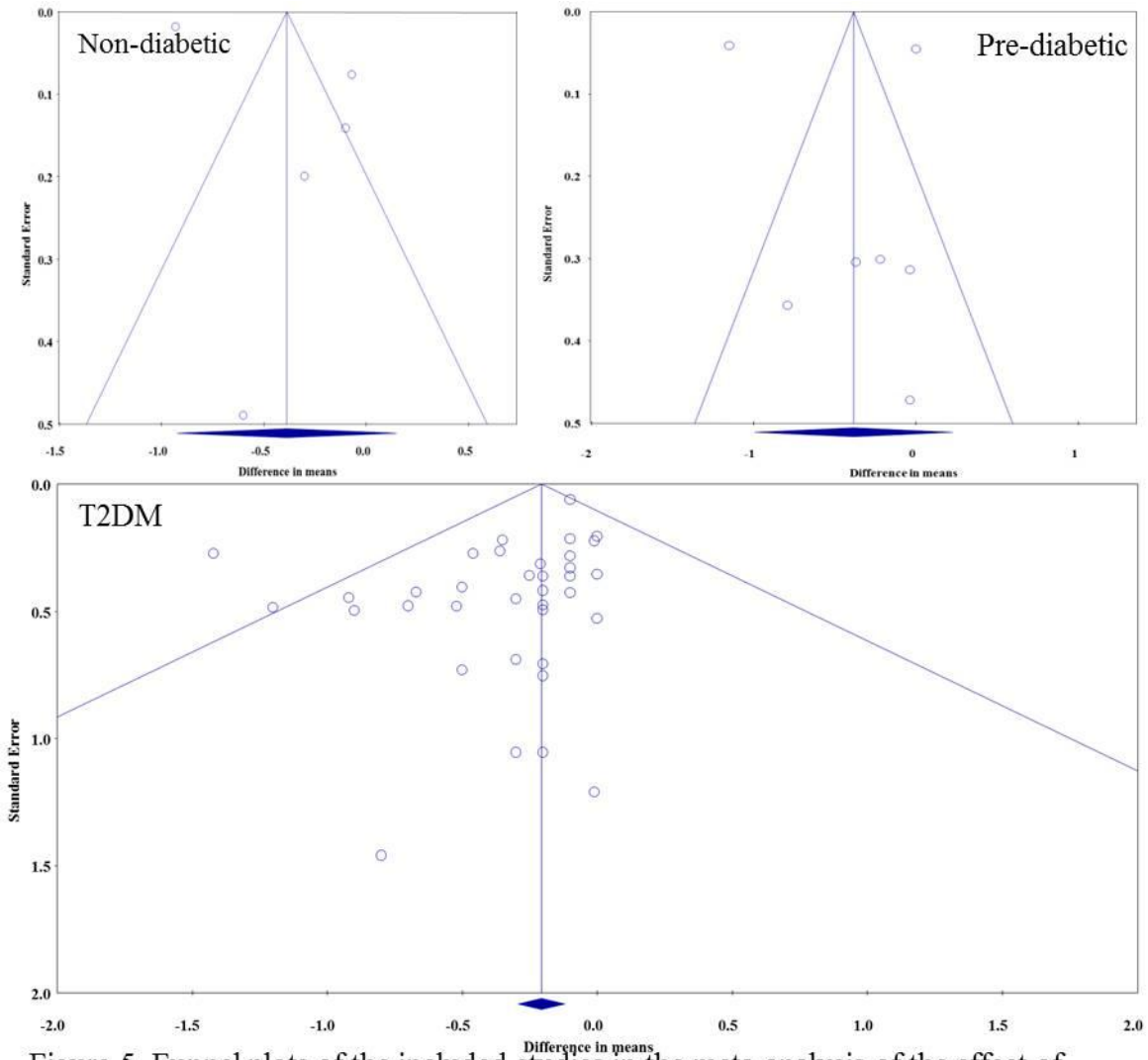

Figure 5. Funnel plots of the included studies in the meta-analysis of the effect of polyphenols on HbA1c%, divided as non-diabetic, pre-diabetic and T2DM (an inverted symmetrical funnel suggests limited publication bias).