Effects of tea or tea extract on metabolic profiles in patients with type 2 diabetes mellitus: a meta-analysis of 10 randomized controlled trials

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Abbreviations

ADPN	Adiponectin
CRE	Creatinine
CRP	C-reaction protein
DBP	Diastolic blood pressure
EC	Epicatechin
ECG	Epicatechin-3-gallate
EGC	Epigallocatechin
EGCG	Epigallocatechin gallate
FBG	Fasting blood glucose
FBI	Fasting serum insulin
SBP	Systolic blood pressure
T2DM	Type 2 diabetes mellitus
UA	Uric acid

ABSTRACT:

Background: As consumption of tea has been confirmed as a protective factor for type 2 diabetes mellitus (T2DM), it would be interesting to know if T2DM patients could benefit from tea. Because of small sample sizes and inconsistent results of previous studies, we performed this meta-analysis to reevaluate the effects of tea or tea extract on all available outcomes in patients with T2DM.

Methods: We systematically searched electronic databases of PubMed, Cochrane Library and EMBASE to identify randomized controlled trials of tea in T2DM patients up to January 2015. Weight mean differences for the changes in all outcomes were pooled by Review manager 5.2.

Results: A total of 10 trials including 608 subjects were identified. The meta-analysis found that tea could alleviate the decrease of fasting blood insulin [1.30 U/L, 95% CI (0.36, 2.24)], and reduced waist circumference only in more than 8 weeks intervention [-2.70 cm, 95% CI (-4.72, -0.69)], whereas there were no statistically significant differences with regard to HOMA-IR 0.38 (-0.18, 0.95), fasting blood glucose -0.05 mmol/L (-0.51, 0.40), LDL-c 0.07 mmol/L (-0.15, 0.29), HDL-c 0.01 mmol/L (-0.08, 0.09), BMI -0.15 kg/m^2 (-0.50, 0.21), SBP 0.35 mmHg (-3.54, 4.24), DBP -1.02mmHg (-3.53, 1.48), TG -0.11mmol/L (-0.28, 0.05), and TC -0.05mmol/L (-0.20, 0.11) in patients with T2DM, and leptin, ADPN, CRE, and UA were also non-significant.

Conclusions: The intervention of tea or tea extraction could maintain a stable fasting blood insulin and reduce waist circumference in the T2DM patients, however, the effects on other outcomes were not significant.

Keywords: tea; T2DM; metabolic profile; meta-analysis

INTRODUCTION

Over the past decades, there has been a rapidly raise in the prevalence of type 2 diabetes mellitus (T2DM) in the world (1). WHO estimations had predicted that 350 million people worldwide will suffer diabetes by the year 2030 (2). For diabetes is the fifth leading cause of death in the world, entailing related morbidity and mortality, useful preventive strategies for the complication of diabtes are urgently needed (3).

As oxidative stress is regarded as an underlying mechanism in the progress of insulin resistance, impaired blood glucose and lipid metablism and β-cell dysfunction in T2DM (4-6), many anti-oxidative stress agents were investigated for the protection of diatetic complications. Tea, derived from the plant *Camellia sinensis*, is one of the most widely consumed beverages in the world next to water (7). Depending on the level of fermentation, tea can be classified into three types: green tea (unfermented), oolong tea (partially fermented) and black tea (complete fermented). Green tea contains more catechins, including epigallocatechin gallate (EGCG), epicatechin-3-gallate (ECG), epigallocatechin (EGC), and epicatechin (EC) (8). Black tea and oolong tea contain more theaflavins and thearubigins (9).

Tea could reduce the risk for T2DM, which has been reported many cohort studies and meta-analyses (10-12). Green tea polyphenols have been shown to scavenge free radicals, decrease lipid peroxidation by increasing the activity of superoxide dismutase and glutathione, and also have anti-diabetic effects (13). Recent meta-analyses reported that green tea beverages or extracts could significantly reduce serum TC and LDL-cholesterol concentrations (14), and reduce FBG in the mixed population of RCT studies (15). Based on current beneficial effects of tea in general population, it would be important to determine if favorable effects of tea still exist in patients with T2DM. A number of RCT studies have reported the beneficial effects of tea or its extract (16-22), but not all (23-25).

Therefore, in this study, we included all the RCT studies to combine the data and evaluate more precise effects of tea or its extract on body weight, blood glucose, lipids, insulin, insulin sensitivity and inflammation in T2DM patients.

METHODS

Literature search

Relevant studies were searched from electronic databases, including PubMed, EMBASE, and Cochrane Library up to January 2015. Search terms included 'tea' and 'diabetes', 'diabetes mellitus', 'diabetic', 'T2DM', or 'DM' and 'population' or 'trial'. In addition, the reference in retrieved articles were further hand-scanned to add potential eligible studies.

Study selection

All eligible studies should meet the following criteria: (1) The studies must be RCTs; (2) The patients with T2DM; (3) The intervention was tea or tea extract and placebo or water was applied as comparison of intervention; (4) Articles reported at least one of the outcomes: body weight, body mass index (BMI), waist circumference, systolic blood pressure (SBP), diastolic blood pressure (DBP), fasting blood glucose (FBG), fasting serum insulin (FBI), glycosylated hemoglobin (HbA1c), homeostasis model of insulin resistance (HOMA-IR) index, triglycerides (TG), fasting cholesterol (TC), HDL-cholesterol, LDL-cholesterol, leptin, adiponectin (ADPN), ghrelin, creatinine (CRE), uric acid (UA), and C-reaction protein (CRP). Two authors (Y-C. L. and R-N. F.) did the searching and extraction independently and disagreements were resolved by a third author (C. W.).

Quality and evidence level assessment

The methodological quality of the included studies were evaluated. We determined the risk of bias according to the Cochrane Handbook from the Cochrane collaboration guideline (26). We classified items of sequence generation, concealment of allocation, blinding, incomplete outcome data, selective outcome reporting and other sources of bias as: yes, no or unclear. According to the Grading of Recommendations Assessment Development and Evaluation approach, the quality of evidence for each outcome was graded as high, moderate, low and very low with regard to study limitations, inconsistency of results, indirectness of evidence, imprecision and publication bias (27).

Data extraction

Data extraction was conducted by two authors (Y-C. L. and R-N. F.) independently and in duplicate. All of these items, including the first author's name, year of publication, country and study design, demographic characteristics of the participants, sample sizes of treatment and control groups, dosage of tea or tea extract, duration of treatment and outcomes. The data were compared and the disagreements were resolved by a third author (C.W.).

Statistical analysis

REVMAN 5.2 (Cochrane Collaboration, Oxford, England) was employed for data analysis. The area of the black square in forest plots indicates the weight contributed by each study. Heterogeneity was estimated through the I^2-test statistic, which estimated the extent of variability across studies. Substantial heterogeneity exists when values I^2 exceeds 50% or $P < 0.05$, the random-effect model were used, otherwise, fixed-effect model was applied. To evaluate the influence of each single study on the combined results, the stability of the results were evaluated through one-leave-out and publication bias were evaluated through funnel plots. *P*-values were two-tailed and $P<0.05$ was considered as statistical significance.

RESULTS

Literature search and study selection

Figure 1 presents a flow chart showing the detailed process of study selection. The primary search found a total of 622 relevant articles. After further screening the titles of all achieved articles briefly, 121 articles were identified for further screening and 501 articles that were apparently not relevant to current studies were excluded. Then we screened titles and abstracts of each articles and 16 articles were remained for further full-text evaluation. Of these articles, 5 articles were excluded for the reasons as follows: duplicate study (n=1), no target outcomes reported (n=3), no controls (n=1), not only tea extracts as intervention (n=1). Finally, 10 eligible studies were included in our study (16-25).

The characteristics of the studies included

The characteristics of the studies included are presented in Table 1. The 10 articles included involving 608 participants. The duration of intervention ranged from 4 to 16 weeks. Of the 10 included studies, 2 studies reported sequence generation using either computer-generated numbers or a table of random numbers; 4 trials mentioned the details method of blinding.

Methodological quality

Of the 10 included studies, 2 articles reported sequence generation using random numbers (24) or computer generated numbers (20). No articles mentioned allocation concealment. 5 articles described the details of blinding (18, 20, 22, 24, 25). Other information is provided in Table S1.

Changes of treatment group after intervention

We extracted 16 anthropometry or biochemistry indexes, including body weight, BMI, waist circumference, FBG, FBI, HbA1c, HOMA-IR, TG, TC, HDL-cholesterol, LDL-cholesterol, leptin, ADPN, ghrelin, CRE, and UA. The results of all the variables were inconsistent among the studies.

Pooled effects of overall tea or tea extract on variables of body weight, blood lipid, glucose and insulin sensitivity and inflammation

We conducted a systematically meta-analysis on 16 anthropometry and metabolic profile indexes (Table 2, 3 and S2). Results of these analysis showed that tea or tea extract alleviated the decrease of FBI (1.30 [0.36, 2.24], $P = 0.005$; number of studies = 7). For the analysis in more than 8 weeks intervention studies, overall tea or tea extract reduced waist (-2.70 [-4.72, -0.69], $P = 0.009$; number of studies = 5). However, it showed no significant differences of changes in other variables between treatment groups and control groups. Considering of phenolic compounds in green and black tea are markedly different, we analyzed data of green tea or green tea extracts separately (Table 4 and Figure 2). Results showed that green tea or green tea extract alleviated the decrease of FBI (1.51 [0.05, 2.97], $P = 0.04$; number of studies = 6).

Publication Bias

No significant publication biases were detected in the graphed funnel plots of the our meta-analyses, which were provided in Figure S1.

Sensitive Analysis

To determine the influence of each single study on the combined results, we assessed the stability of the results through one-leave-out. After excluding each of the studies, the mean differences between treatment and control groups ranged in a small section, but there were no studies observed to have significant effect on the result of current meta-analysis, which further strengthened our findings before. Data were provided in Table S3.

DISCUSSION

To the best of our knowledge, this meta-analysis firstly comprehensively evaluated the effect of tea or tea extract on metabolic profiles in patients with T2DM from all available RCTs. Tea or tea extract alleviated the decrease of FBI. And in more than 8 weeks intervention studies, overall tea or tea extract reduced waist. However, the pooled data showed non-significant or clinically meaningful effects of tea or tea extracts on body weight, BMI, FBG, HbA1c, HOMA-IR, TG, TC, HDL-c, LDL-c, leptin, ADPN, CRE, and UA.

Effects of tea or tea extract on glycemic control and insulin sensitivity

Many researches have investigated the molecular mechanisms of positive effect of tea or tea extracts on glucose metabolism. EGCG as the most abundant compound of catechin in green tea is known with beneficial effects on human health (28). EGCG could remit the status of insulin resistance by inhibiting the proliferation and differentiation in 3T3-L1 adipocyte cells (29), increasing fatty acids oxidation (30), and expression of GLUT-4 in adipose tissue (31). It also has been reported that the protective function of EGCG for β-cell destruction induced by inflammatory cytokine through inhibition of nuclear factor-κB activation (32). In our previous study, we also found that EGCG could extend lifespan in healthy rats by protecting liver and kidney damage and alleviating age-associated inflammation and oxidative stress through the

inhibition of NF-kappaB signaling by stimulating the longevity factors FoxO3a and SIRT1(33).

In present meta-analysis, a significant alleviated decrease trend of fasting insulin was observed in the tea or tea extract group, which indicates tea or tea extract may have beneficial effects on secretory ability of pancreatic islets. Insulin secretory ability, insulin content and glucose-stimulated insulin secretion was decreased in patients of T2DM (34). As catechins could protect pancreatic β-cells from inflammation throungh inhibiting activation of nuclear factor-κB (32), and based on current meta-analysis, tea or catechins ingestion might protect pancreas islets against damage and maintain insulin secretory ability of pancreatic β-cells in diabetic patients.

The effects of tea on weight loss and weight maintenance

This meta-analysis including 10 articles reported that catechins or an EGCG-caffeine mixture have a mild positive effect on weight reduction and weight maintenance (35). The inhibition in several enzymes may explain the mechanisms tea induced weight loss. Catechins could inhibit the catechol O-methyltransferase and caffeine could inhibit phosphodiesterase; as the degradation of these enzymes, norepinephrine and cAMP rise will be blocked; consequently, parasymphatic activity will be increased (36). Moreover, two 24h-intervention studies (36, 37) showed a significant increase in energy expenditure and fatty acid oxidation could be induced by tea or tea extract. However, our study did not found significant effects of tea on body weight in patients with T2DM. However, we speculated that the different of metabolic disorder between healthy subjects and T2DM patients or short period intervention might be the reason.

The effects of tea on serum lipid profile

The effects of green tea and green tea extract on serum lipid profiles has been investigated in both animals and humans by many studies. Hsu et al. have confirmed that green tea could significantly decrease LDL-cholesterol and markedly increase of HDL-cholesterol (38). Other studies showed that green tea consumption could reduce serum cholesterol (39, 40), but not all (41). In our study, we find no significant

influence of tea or tea extract on serum lipid profile of T2DM patients. Thus, further studies on this issue is needed to investigate in T2DM patients.

The effects of tea on blood pressure

The meta-analyses of observational studies had reported the significant inverse relationships between green tea and blood pressure, stroke, coronary artery disease and myocardial infarction (42-44). However, our conclusion failed to find a significant association between green tea and blood pressure in T2DM patients. This conclusion could compromise by each study designing for diabetic ourcomes, but may not fully controled potential confounding factors or it is true that tea did not influence the blood pressure in diabetic patients. Therefore, more RCT studies on this issue are needed to clarify in patients with diabetes.

Limitation of current study

Tea is the most widely consumed beverages worldwide, and many people start drinking tea at an early age and continue this habit for a lifetime. The effects of tea on body weight, body fat, insulin sensitivity and glycemic control may be too mild to show significant effects in individuals during a limited period of intervention in diabetic patients. Long period cohort studies may clarify the tea consumption effects on glucose control, insulin sensitivity, body weight management and complicate of T2DM. On another hand, the ingredient of tea is complicated, the accurate effects of certain substance should be further investigated. For example, green tea derives from steamed fresh leaves and produced in an unfermented process, which release more catechins, including EGCG, ECG, EGC, and EC. Black and oolong tea contain more theaflavins and thearubigins. Although we could analyze the effects of green tea, we could not further separate the effects of above particular substance.

CONCLUSION

According to current meta-analysis, the intervention of tea or tea extracts might be of benefit for maintain a stable fasting blood insulin and reduce waist circumference. However, it did not show significant effect on other metabolic profiles of T2DM patients. Because of limited duration of intervention, longer duration and high-quality

RCTs are needed to further investigate the effects of different teas on multiple metabolic profiles in patients with T2DM.

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Duality of interest

The authors declare that there is no duality of interest associated with this manuscript.

Contribution statement

Conceived and designed the experiments: R-N. F. and C-H. S. Acquisition, analysis and interpretation of data: Y-C. L., R-N. F. and C. W. Wrote the paper: Q-J. H., Y-C. L. and C-H. S. Revising the manuscript: Q-J. H and F-C. G. and L-Y. L.

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Table 1 Characteristics of 10 randomized controlled trials included in analysis

Trials	Location	Design	Participant	Age	Intervention(dosage)	Comparison	Number (T/C)	Treatment duration
Hosoda (2003)	China	cross-over RCT	T2DM	61.2	oolong tea (1500 ml + 15 g tea leaf)	water	10/10	4 weeks
Ryu (2006)	South Korea	cross-over RCT	T2DM	53.9	green tea (900 ml water + 9 g green tea)	water	55/55	4 weeks
MacKenzie (2007)	America	parallel RCT	T2DM	65	extract of green and black tea (375, or 750 mg per day)	water	17/16/16	3 months
Fukino (2008)	Japan	cross-over RCT	T2DM	32~73	green tea extract powder daily containing 544 mg polyphenols (456 mg catechins)	water	29/31	2 months
Nagao (2008)	Japan	parallel RCT	T2DM	64.9/62.8	catechin (582.8 mg per day)	catechin (96.3 mg per day)	23/20	12 weeks
Mirzaei (2009)	Iran	parallel RCT	T2DM	⩾40	GTE capsule (240 mg polyphenols; 150 mg caffeine)	placebo	26/46	8 weeks
Neyestani (2010)	Iran	parallel RCT	T2DM	57.0/55.4	black tea extract (150, 300, 450 and 600 ml per day during week 1, 2, 3, 4)	black tea extract (150 ml per day)	23/23	4 weeks
Hsu (2011)	China	parallel RCT	obese T2DM	20~65	green tea extract (500 mg, three times daily)	placebo (cellulose)	35/33	16 weeks
Mousavi (2013)	Iran	parallel RCT	T2DM	35~65	two or four cups of green tea per day	water	25/24/14	8 weeks
Liu (2014)	China	parallel RCT	T2DM	20~65	green tea extract EGCG (500 mg, three times daily)	placebo (cellulose)	39/38	16 weeks

Table 2 Pooled effects of overall tea or tea extracts on metabolic profiles of T2DM patients and subgroup analyses*

Outcomes	Subgroup	Studies	Participants	Statistical method	Effects estimate	*P*
weight	All	12	594	Mean Difference (IV, Fixed, 95% CI)	-0.27 [-1.23, 0.70]	NS
	Asia	10	471	Mean Difference (IV, Fixed, 95% CI)	-0.28 [-1.26, 0.70]	NS
	⩾8 weeks	9	508	Mean Difference (IV, Fixed, 95% CI)	-0.39 [-1.46, 0.69]	NS
BMI	All	13	665	Mean Difference (IV, Fixed, 95% CI)	-0.15 [-0.50, 0.21]	NS
	Asia	11	543	Mean Difference (IV, Fixed, 95% CI)	-0.16 [-0.52, 0.20]	NS
	⩾8 weeks	10	579	Mean Difference (IV, Fixed, 95% CI)	-0.18 [-0.58, 0.22]	NS
waist	All	6	298	Mean Difference (IV, Fixed, 95% CI)	-1.01 [-2.34, 0.32]	NS
	Asia	6	298	Mean Difference (IV, Fixed, 95% CI)	-1.01 [-2.34, 0.32]	NS
	⩾8 weeks	5	263	Mean Difference (IV, Fixed, 95% CI)	-2.70 [-4.72, -0.69]	0.009
SBP	All	9	423	Mean Difference (IV, Fixed, 95% CI)	0.35 [-3.54, 4.24]	NS
	Asia	9	423	Mean Difference (IV, Fixed, 95% CI)	0.35 [-3.54, 4.24]	NS
	⩾8 weeks	7	383	Mean Difference (IV, Fixed, 95% CI)	0.87 [-3.44, 5.19]	NS
DBP	All	9	423	Mean Difference (IV, Fixed, 95% CI)	-1.02 [-3.53, 1.48]	NS
	Asia	9	423	Mean Difference (IV, Fixed, 95% CI)	-1.02 [-3.53, 1.48]	NS
	⩾8 weeks	7	383	Mean Difference (IV, Fixed, 95% CI)	-0.68 [-3.54, 2.18]	NS
TG	All	10	545	Mean Difference (IV, Fixed, 95% CI)	-0.11 [-0.28, 0.05]	NS
	Asia	8	432	Mean Difference (IV, Fixed, 95% CI)	-0.16 [-0.37, 0.06]	NS
	⩾8 weeks	9	499	Mean Difference (IV, Fixed, 95% CI)	-0.08 [-0.26, 0.10]	NS
TC	All	10	552	Mean Difference (IV, Fixed, 95% CI)	-0.05 [-0.20, 0.11]	NS
	Asia	8	432	Mean Difference (IV, Fixed, 95% CI)	-0.07 [-0.23, 0.09]	NS
	⩾8 weeks	9	506	Mean Difference (IV, Fixed, 95% CI)	-0.08 [-0.29, 0.12]	NS
HDL	All	6	381	Mean Difference (IV, Fixed, 95% CI)	0.01 [-0.08, 0.09]	NS
	Asia	4	263	Mean Difference (IV, Fixed, 95% CI)	-0.00 [-0.10, 0.10]	NS
	⩾8 weeks	6	381	Mean Difference (IV, Fixed, 95% CI)	0.01 [-0.08, 0.09]	NS
LDL	All	8	456	Mean Difference (IV, Fixed, 95% CI)	0.07 [-0.15, 0.29]	NS
	Asia	6	340	Mean Difference (IV, Fixed, 95% CI)	0.03 [-0.22, 0.29]	NS
	⩾8 weeks	8	456	Mean Difference (IV, Fixed, 95% CI)	0.07 [-0.15, 0.29]	NS

* Subgroup analyses of metabolic profiles of T2DM patients were stratified by: (1) Asia studies; (2) Study duration longer than 8 weeks.

Table 3 Pooled effects of overall tea or tea extracts on glucuse control and HOMA-IR of T2DM patients and subgroup analyses*

Outcomes	Subgroup	Studies	Participants	Statistical method	Effects estimate	*P*
FBG	All	12	658	Mean Difference (IV, Random, 95% CI)	-0.05 [-0.51, 0.40]	NS
	Asia	10	541	Mean Difference (IV, Random, 95% CI)	-0.12 [-0.85, 0.61]	NS
	⩾8 weeks	10	572	Mean Difference (IV, Random, 95% CI)	-0.00 [-0.29, 0.28]	NS
FBI	All	7	424	Mean Difference (IV, Fixed, 95% CI)	1.30 [0.36, 2.24]	0.005
	Asia	7	424	Mean Difference (IV, Fixed, 95% CI)	1.30 [0.36, 2.24]	0.005
	⩾8 weeks	6	378	Mean Difference (IV, Fixed, 95% CI)	1.51 [0.05, 2.97]	0.04
HbA1c	All	11	602	Mean Difference (IV, Fixed, 95% CI)	-0.07 [-0.19, 0.05]	NS
	Asia	7	424	Mean Difference (IV, Fixed, 95% CI)	-0.26 [-0.57, 0.04]	NS
	⩾8 weeks	10	556	Mean Difference (IV, Fixed, 95% CI)	-0.07 [-0.19, 0.05]	NS
HOMA-IR	All	6	419	Mean Difference (IV, Fixed, 95% CI)	0.38 [-0.18, 0.95]	NS
	Asia	6	419	Mean Difference (IV, Fixed, 95% CI)	0.38 [-0.18, 0.95]	NS
	⩾8 weeks	4	263	Mean Difference (IV, Fixed, 95% CI)	0.28 [-0.86, 1.41]	NS

* Subgroup analyses of metabolic profiles of T2DM patients were stratified by: (1) Asia studies; (2) Study duration longer than 8 weeks.

Table 4 Pooled effects of green tea or green tea extracts on metabolic profiles of T2DM patients and subgroup analyses

Outcomes	Studies	Participants	Statistical method	Effects estimate	P
weight	7	385	Mean Difference (IV, Fixed, 95% CI)	-0.40 [-1.50, 0.69]	NS
BMI	8	457	Mean Difference (IV, Fixed, 95% CI)	-0.20 [-0.60, 0.21]	NS
waist	5	263	Mean Difference (IV, Random, 95% CI)	-1.64 [-3.84, 0.56]	NS
SBP	7	383	Mean Difference (IV, Fixed, 95% CI)	0.87 [-3.44, 5.19]	NS
DBP	7	383	Mean Difference (IV, Fixed, 95% CI)	-0.68 [-3.54, 2.18]	NS
TG	7	386	Mean Difference (IV, Fixed, 95% CI)	-0.11 [-0.36, 0.14]	NS
TC	7	386	Mean Difference (IV, Fixed, 95% CI)	-0.14 [-0.36, 0.09]	NS
HDL	4	263	Mean Difference (IV, Fixed, 95% CI)	-0.00 [-0.10, 0.10]	NS
LDL	6	340	Mean Difference (IV, Fixed, 95% CI)	0.03 [-0.22, 0.29]	NS
FBG	8	455	Mean Difference (IV, Fixed, 95% CI)	-0.07 [-0.60, 0.47]	NS
FBI	6	378	Mean Difference (IV, Fixed, 95% CI)	1.51 [0.05, 2.97]	0.04
HbA1c	6	378	Mean Difference (IV, Fixed, 95% CI)	-0.28 [-0.61, 0.04]	NS
HOMA-IR	5	373	Mean Difference (IV, Fixed, 95% CI)	-0.00 [-0.68, 0.68]	NS

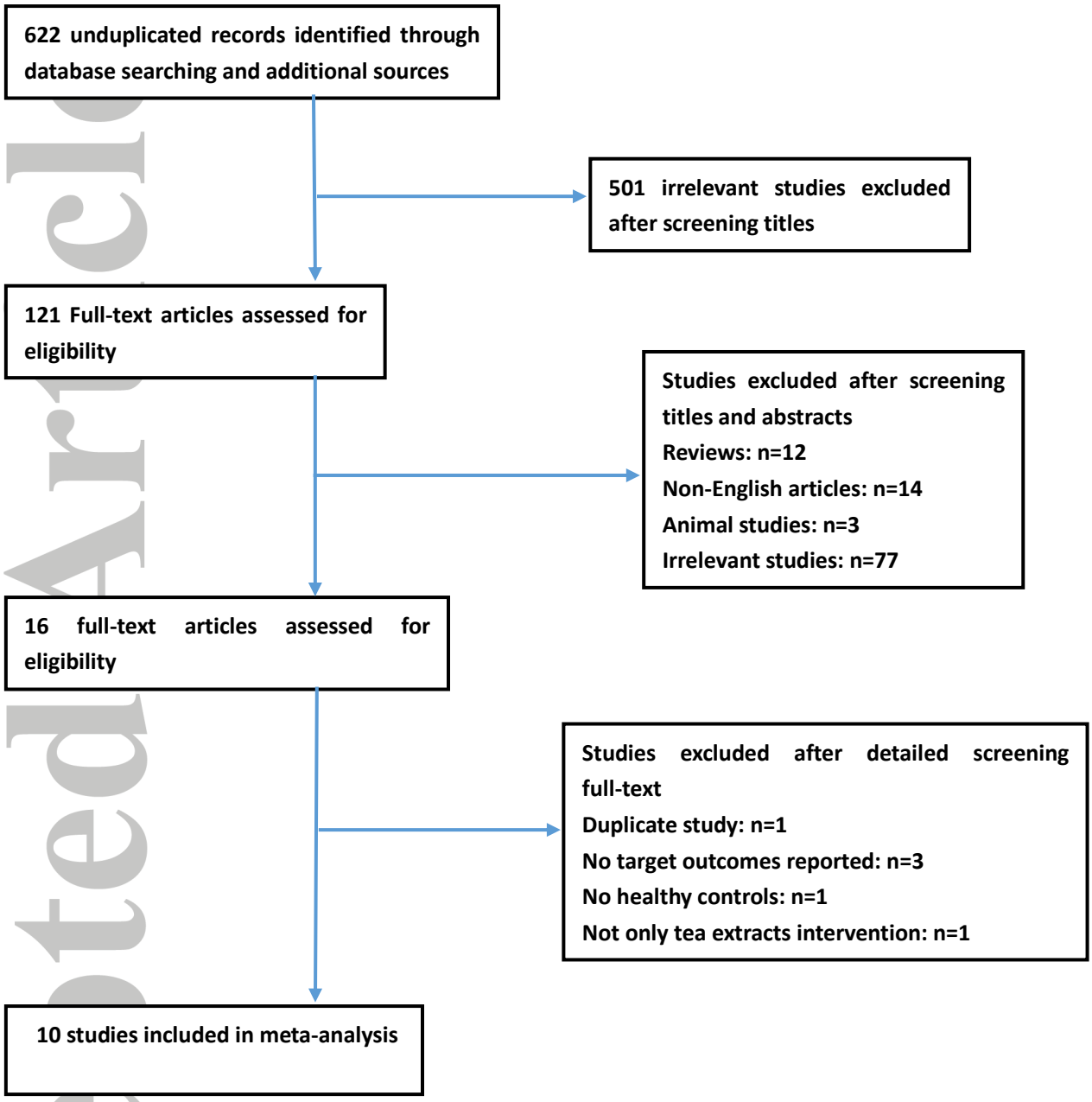
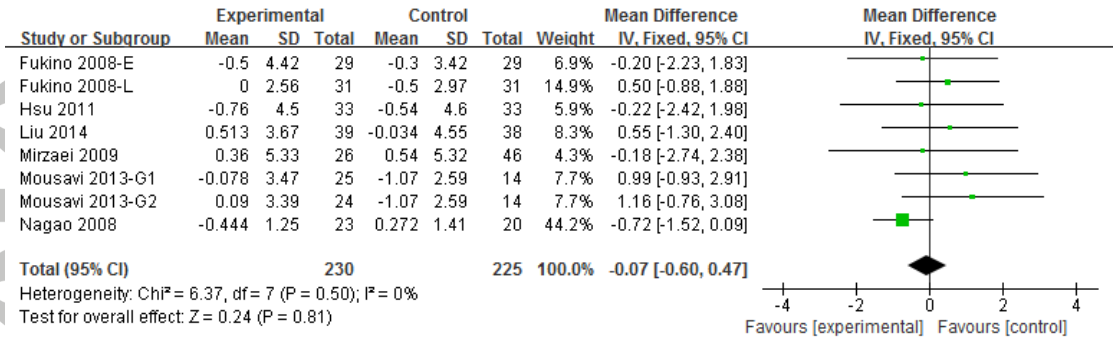
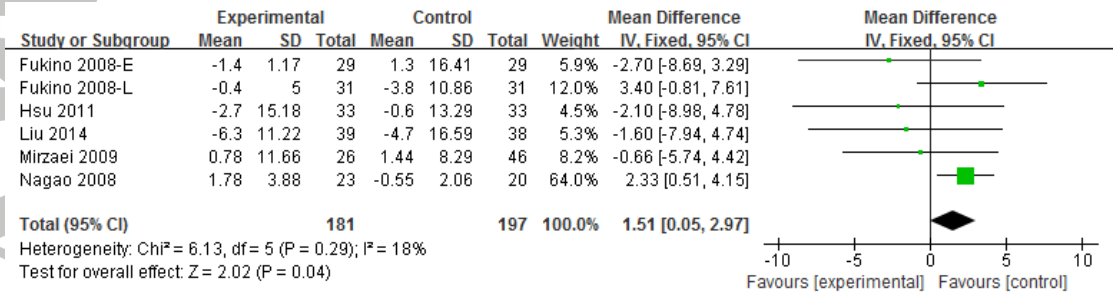


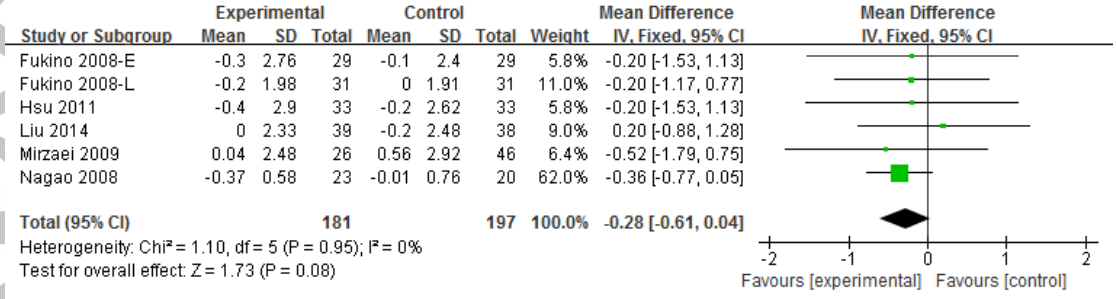
Figure 1. Flow chart of studies included in the meta-analysis



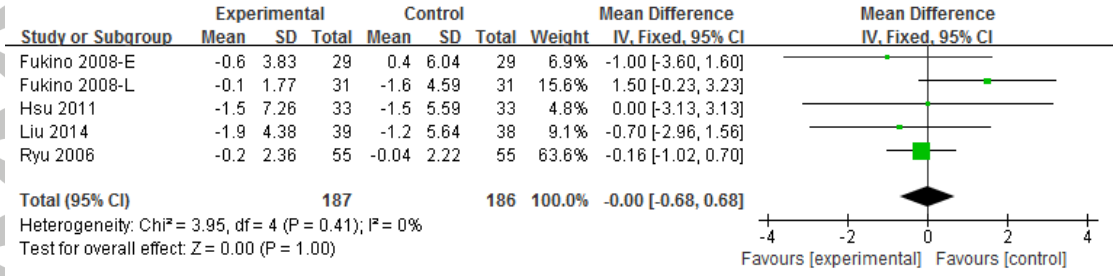
A. The effects of green tea or its extract on FBG



B. The effects of green tea or its extract on FBI



C. The effects of green tea or its extract on HbA1c



D. The effects of green tea or its extract on HOMA-IR

Figure 2. Meta-analysis of the effects of green tea or its extract on blood glucose control and HOMA-IR