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SYSTEMATIC REVIEWS AND META-ANALYSES

A comprehensive overview on the effects of green tea on anthropometric measures, blood pressure, glycemic and lipidemic status: An umbrella review and meta meta-analysis study

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Abstract *Aim:* The aim of this meta-review was to establish the effects of green tea (GT) intake on some cardiometabolic risk factors including anthropometric measures, blood pressure as well as blood glucose and lipids using evidence from previous systematic reviews and meta-analyses.
Data synthesis: Articles were identified via searches in PubMed, Embase, and the Cochrane Library, Web of Knowledge database from the index date of each database through January 31, 2021. A total of 13 meta-analyses were finally included in the synthesis. Meta-meta-analysis revealed significant effects of GT on weight and waist circumference with weighted mean difference (WMD) of −0.89 (95% CI -1.43 to −0.34, $p < 0.001$) and −1.01 (95% CI -1.63 to −0.39, $p < 0.001$), systolic and diastolic blood pressure, with WMDs of −1.17 (95% CI -2.18 to −0.16) and −1.24 (95% CI -2.07 to −0.4), respectively. There was similar effect on fasting blood glucose (WMD, −1.3, 95% CI -2.09 to −0.51, $p < 0.001$) but not on other glycemic indicators. The findings also revealed a significant effect size of total cholesterol and LDL-C (WMD -4.93; 95% CI -6.41 to −3.46, $p < 0.001$, WMD -4.31; 95% CI -6.55 to −2.07, $p < 0.001$, respectively).
Conclusion: Regular consumption of GT and probably its bioactive constituents as supplements have beneficial effects on different health aspects including weight, blood pressure, blood glucose and lipids. However, these effects might be influenced by several factors such as the amount and frequency of consumption, health/disease condition and life style including dietary habits and physical activity.

1. Introduction

Different varieties of tea including non-fermented green tea; semi-fermented oolong tea; and fully fermented black tea are among the widely consumed beverages around the world. Green tea (GT) is not just a refreshing drink since it contains large amounts of bioactive compounds such as flavonoid-like polyphenols, proteins, including enzymes, antioxidants, minerals, and vitamins

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[1]. Polyphenolic compounds representing 36% of dry weight of GT, exert a variety of physiological actions. The main polyphenolic secondary metabolites (flavonoids) present in GT are catechins, which include epicatechin (EC), epicatechin-3-gallate (ECG), epigallocatechin (EGC) and epigallocatechin-3-gallate (EGCG), gallocatechin (GC), catechin gallate (CG), and gallocatechin gallate (GCG) [2]. These compounds are, at least in part, responsible for GT health benefits including decrease in cardiovascular disease (CVD) risk [3,4]. A community study showed that subjects who were drinking three to five cups of GT a day had a 41% lower CVD mortality compared with GT non-drinkers [5]. These findings were further supported by recent studies indicating that tea polyphenols including EGCG may lower CVD risk [6–8] via multiple mechanisms including inhibition of oxidation, vascular inflammation, thrombogenesis, improvement in blood lipid profile and also alteration of the gut microbiota [9–11].

CVD is a leading cause of global morbidity, mortality and disability and will continue to dominate mortality trends in the future [12]. Hypertension, dyslipidemia, diabetes, obesity, sedentary lifestyle and poor dietary habits are major modifiable risk factors linked to detrimental changes in cardiometabolic health [13]. Most public health actions have targeted modifiable risk factors to reduce the burden of CVD, as preventing or treating major modifiable risk factors has proven to be effective in reducing mortality from CVD [14]. Considering the beneficial role of GT consumption in reducing the risk of these risk factors (hypertension, dyslipidemia, diabetes obesity) and high consumption of this beverage in all communities even small effects in humans could have large implications for public health [15]. Several systematic review and meta-analysis (SRM) studies have reported the effects of GT consumption on CVD risk factors to date. However, with increasing number of these reports, the information end-users (service providers and policymakers) would be overwhelmed with too many of them. Umbrella reviews summarize the existing systematic reviews relevant to a question so that decision makers do not need to integrate the results of multiple systematic reviews by themselves [16]. Thus, the aim of this meta-review was to establish the effects of GT intake on some cardiometabolic risk factors (lipid profile, blood pressure, glycemic and anthropometric markers) using evidence from previous systematic reviews and meta-analyses.

1.1. Objectives

The objectives of this study were to summarize evidence from systematic reviews and meta-analyses of GT consumption on (i) anthropometric measures including weight, body mass index (BMI) and waist circumference (WC); (ii) systolic blood pressure (SBP) and diastolic blood pressure (DBP); (iii) glycemic outcomes including fasting blood glucose (FBG), fasting serum insulin, hemoglobin (Hb) A1c and Homeostatic Model Assessment of Insulin Resistance (HOMA-IR); and blood lipid profile including total cholesterol (TC), low density lipoprotein-cholesterol (LDL-C), high density lipoprotein-cholesterol (HDL-C) and triglycerides.

2. Methods

This overview was conducted using methods presented in The Cochrane Handbook for Systematic Reviews of Interventions [17]. Also, recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) were followed. The protocol of the study was registered at PROSPERO 2021: CRD42021253230. An umbrella review and meta-meta-analysis were conducted to identify the effect of GT on cardiometabolic risk factors. Umbrella reviews (also called overview of systematic reviews) represent an effective way of SRM reports on a specific research topic.

2.1. Criteria for selecting reviews for inclusion

In this overview of systematic reviews (SRs), we included SRs and meta-analyses containing randomized controlled trials (RCTs) and/or controlled clinical trials (CCTs) that assessed the effects of GT intake on cardiometabolic risk factors as a primary or secondary outcome of the review.

2.2. Types of participants

From the eligible SRs, we included results from trials that contained adults only.

2.3. Types of interventions

We included reviews comparing the intake of GT as beverage or supplement with placebo or no intervention.

2.4. Types of outcome measures

The primary outcomes were cardiometabolic risk factors including (i) anthropometric measures (weight, BMI, waist circumference), (ii) blood pressure (systolic, diastolic), (iii) glycemic indicators (fasting blood sugar, fasting insulin, HOMA-IR, HbA1c), and (iv) lipid profile (triglycerides, TC, LDL-C, HDL-C).

2.5. Search methods for identification of reviews

Relevant English language articles were identified via searches in PubMed, Embase, and the Cochrane Library, Web of Knowledge database from the index date of each database through January 31, 2021 and reference lists of relevant articles using the text keywords (“systematic review” OR “meta-analysis”) and (“green tea”) and (“fasting blood sugar” OR “insulin” OR “HbA1c” OR “HOMA” OR “triglyceride” OR “cholesterol” OR “LDL” OR “HDL” OR

"systolic blood pressure" OR "weight" OR "BMI" OR "waist circumference"). Articles were initially screened on the basis of title and abstract reading. The full texts of potentially eligible articles were then independently scrutinized by two investigators (BN, TN).

2.6. Data collection and analysis

The methodology for data collection and analysis is based on Chapter 22, 'Overviews of Reviews' in the Cochrane Handbook of Systematic Reviews of Interventions [17].

2.7. Selection of reviews

Two overview authors independently assessed all systematic reviews for potential inclusion. Titles and abstracts were screened. Full texts of all potentially relevant documents were retrieved and then methods section of reviews were assessed to ensure those with the appropriate population and pre-specified outcome were selected.

2.8. Data extraction and management

Data extraction was performed independently by two investigators. Any existing discrepancies were resolved in consensus meetings. The following data were extracted: (i) descriptive characteristics of SRs, (ii) the number of trials in the review, (iii) risk of bias of the included trials, (iv) interventions and comparisons, and (v) the outcome data. In cases where data were not available, we accessed the original published papers of the studies for further details.

2.9. Data synthesis

The quantitative and qualitative approaches were used to summarize the estimates of the included SRs. Stata version 16.0 software (StataCorp, TX USA) was applied for the quantitative analyses. Data were summarized using effect size (EF), 95% confidence intervals (CIs), and numbers of studies and participants contributing data to each pooled effect from comparisons and for the outcome relevant to this overview.

For all pooled effect estimates, the accompanying I^2 values were reported and represent the degree of statistical heterogeneity between the trials. Degree of heterogeneity was classified into low (I^2<25%), moderate (25%≤ I^2<50%) and large (50%≤ I^2) [17]. Fixed-effects models were used if the level of heterogeneity was <50%. Otherwise, the pooled estimates were calculated using the random-effects model. Egger's test was used to evaluate publication bias and small-study effect, and a p value < 0.1 in the test confirmed the bias and small-study effect.

To evaluate the impact of the overlap in the inclusion of the same primary studies, the degree of overlap between reviews was measured to generate a citation matrix and also to calculate the corrected cover area (CCA), a metric that provides a percentage of overlap of the primary studies. A CCA value lower than five indicates slight overlap, whereas values greater than or equal to 15 can be considered as a very high [18].

The results from meta-analyses with CCA <15, but no shared authorship team, were reported and compared as separate reviews. In the case of very high overlap in primary study, the most recent meta-analysis or best quality was considered (Tables 2–5).

2.10. Quality of included reviews

Two reviewers independently assessed the methodological quality of included reviews using the validated AMSTAR2 (A Measurement Tool to Assess Systematic Reviews 2) instrument [19,20] and disagreements were resolved through consensus. AMSTAR assessments are presented in the results and tables. AMSTAR2 includes the following critical areas: registered protocol; adequacy of literature search; rationalization for excluded studies; risk of bias for included studies; appropriateness of meta-analytic methods; consideration of risk of bias when interpreting results; and assessing of publication bias. The tool provides guidance to rate the overall confidence in the results of a review (high, moderate, low or critically low depending on the number of critical flaws and/or non-critical weaknesses).

2.11. Risk of bias of primary studies included in the reviews

The risk of bias of included studies during reviews was not re-assessed but reported study risk of bias according to the review's authors' assessment was considered, instead.

2.12. Quality of evidence in included reviews

An overall assessment of the quality of evidence for each intervention of interest was performed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach. The GRADEpro includes five criteria: risk of bias, consistency, directness, imprecision and publication bias [21]. Assessing and combining these components determined evidence quality as: high: further research is very unlikely to change confidence in the estimate of the effect; moderate: further research is likely to have an important impact on confidence in the estimate of effects and may change the estimate; low: further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate; or very low: any estimate of the effect is very uncertain.

Also, the signs were used to link the estimated effects of review and our confidence in the available data as follows:

- Clear evidence of benefit (moderate- or high-quality evidence with confidence intervals (CIs) not crossing line of no effect): ↗
- Clear evidence of harm (moderate- or high-quality evidence with CIs not crossing line of no effect): ×
- Clear evidence of no effect or equivalence (moderate- or high quality evidence with narrow CIs crossing the line of no effect): =

- Possible benefit (low-quality evidence with clear benefit, or moderate- or high-quality evidence with wide CIs crossing the line of no effect): +
- Possible harm (low-quality evidence with clear harm, or moderate- or high-quality evidence with wide CIs crossing the line of no effect):
- Unknown benefit or harm (low-quality evidence with wide CIs crossing the line of no effect or very low-quality evidence): ?

2.13. Ethical consideration

The present study was done using data extracted from published studies. Hence, no study participants' consent or ethical approval was required.

3. Results

The database search provided a total of 1204 articles, of which 259 were excluded because of having narrative design not meta-analysis that was the main inclusion criterion of the present study. After screening the titles and reviewing the abstracts and full-texts, a total of 19 studies were included in the qualitative synthesis of current umbrella review (Fig. 1). Due to the requirement of CCA> 15, six additional meta-analyses were excluded so that 13 meta-analyses were finally included in the quantitative synthesis.

3.1. Description of the included reviews

All included systematic reviews comprised randomized clinical trials on the effect of GT as beverage or supplement vs. placebo and were published between 2009 and 2020. Studies that were included in this overview had focused on glycemic indicators (n = 5), lipid profiles (n = 6), blood pressure (n = 5) and anthropometric measurements (n = 5). They included a total of 317 studies, providing a total sample of 24,482 adults. The range of number of studies per SRM were from seven [22,23] to 31 [24]. The number of participants in the included reviews ranged from 480 [22] to 3321 [24]. Further details of the included reviews can be found in Table 1.

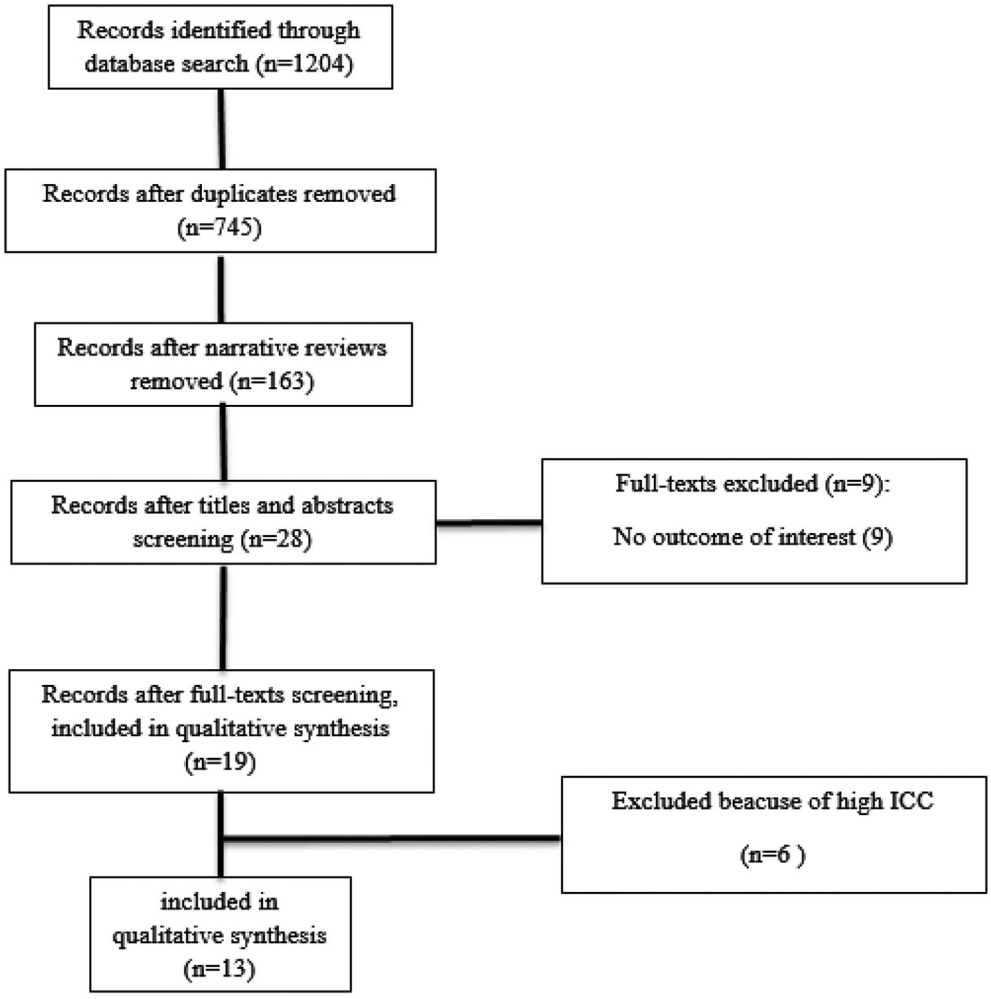

Fig. 1 PRISMA flow diagram for studies included in and excluded from the meta-meta-analysis.

Table 1 Characteristics of included reviews.

First author, Year	participants	Number of studies (number of subjects)	Intervention vs. placebo	Outcome	Effect size (95%CI) MD	Credibility Assessment	Effect on outcome	subgroups	AMSTAR2 score
Asbaghi, 2020a	type 2 diabetes	14 (879)	green tea and green tea extract vs. placebo	FBG, FBI, Hb A1c, HOMA-IR.	FBG: 1.79 (−7.89, 4.31) FBI: 0.27 (−0.51, 1.04) HbA1c: 0.14 (−0.38, 0.1) HOMA: 0.16 (−0.17, 0.49)	Low Low Low Low	? ? ? ?	Duration, Catechins dose,	14/16 Moderate
Asbaghi, 2020b	type 2 diabetes	7 (480)	green tea and green tea extract vs. placebo	TC, LDL, HDL, TG	TC (mg/dL): 6.81 (−15.13, 1.52) LDL (mg/dL): 0.37 (−4.13, 3.4) HDL (mg/dL): 3.1 (−10.16, 3.95) TG (mg/dL): 12.79 (−24.71, −0.84)	Low Moderate Very low Low	? ? ? ?	Dose, duration	14/16 Moderately
Asbaghi, 2020c	type 2 diabetes	11 (687)	green tea and green tea extract vs. placebo	Wt, BMI, WC, BF	Wt (kg): 0.4 (−0.64, −0.16) BMI: 0.05 (−0.1, −0) WC (cm): 1.22 (−2.81, 0.36) BF (%): 0.56 (−0.73, 0.38)	Moderate Moderate Moderate Moderate	 ? = =	Duration, dose, overweight,	14/16 Moderate
Hursel, 2009	adults	11 (1226)	green tea and green tea extract vs. placebo	Wt	Wt (kg): 1.31 (−2.05, −0.57)	Low	+	Ethnicity, habitual caffeine intake	12/16 low
Jurgens, 2012	overweight or obese adults	14 (1562)	green tea and green tea extract vs. placebo	Wt, BMI, WC, WHR	Wt (kg): 0.95 (−1.76, −0.14) BMI: 0.2 (−0.5, 0.1) WC (cm): 0.99 (−1.76, −0.22) WHR: 0 (−0.02, 0.01)	Moderate Moderate Moderate Moderate	↙ = ↙ =	with or without caffeine,	16/16 High
Kim, 2011	Adults	20 (1415)	green tea and green tea extract vs. placebo	TC, LDL, HDL, TG	TC (mg/dL): 5.46 (−9.59, −1.32) LDL (mg/dL): 5.3 (−9.99, −0.62) HDL (mg/dL): 0.27 (−1.62, 1.09) TG (mg/dL): 3.0 (−2.73, 8.73)	High High Moderate Moderate	↙ ↙ = +	Beverage/capsule Dose, hyperlipidemia/ healthy	16/16 high
Khalesi, 2014	Adults	13 (768)	green tea and green tea extract vs. placebo	SBP, DBP, TC, TG, LDL, HDL, FBG, BMI	SBP (mmHg): 2.05 (−3.06, −1.05) DBP (mmHg): 1.71 (−2.86, −0.56) TC: 5.8 (−10.44, −0.77) TG: 8.8 (−11.5, 28.34) LDL: 6.18 (−8.5, −3.48) HDL: 0.38 (−1.93, 2.32) FBG: 0.14 (−0.37, 0.09) BMI: 0.06 (−0.43, 0.31)	Moderate Moderate Moderate Very Low Moderate Low Very Low Low	↙ ↙ + ? + ? ? ?	Beverage/capsule Dose, SBP <130/ <130 mmHg, BMI >30/<30	13/16 low

Li, 2015	overweight and obese adults	14 (971)	green tea and green tea extract vs. placebo	SBP, DPB	SBP (mmHg): 1.42 (−2.47, −0.36) DBP(mmHg): 1.42 (−2.47, −0.36)	High Moderate	↙ ↙	Dose, duration, overweight/obese, sex, with or without comorbidity, with or without hypertension, with or without caffeine,	14/16 Moderate
Liu, 2013	Adults	17 (1133)	green tea and green tea extract vs. placebo	FBG, FBI, Hb A1c, HOMA-IR.	FBG (mmol/L): 0.09 (−0.15, −0.03) FBI (μIU/mL): 0.4 (−1.27, 0.46) HbA1c (%): 0.3 (−0.37, −0.22) HOMA: 0.04 (−0.67, 0.59)	High Moderate High Moderate	↙ = ↙ =	Metabolic syndrome risk/healthy, with or without caffeine, Duration, Catechins dose	14/16 Moderate
Lin, 2020	adults	22 (2357)	green tea and green tea extract vs. placebo	Wt, BMI, WC	Wt (kg): 1.78 (−2.8, −0.76) BMI: 0.65 (−1.05, −0.25) WC: 1.5 (−3.19, 0.19)	Moderate Moderate Low	= = ?	Overweight or obese, dose, duration	14/16 Moderate
Onakpoya, 2014	adults	20 (1536)	green tea supplement vs. placebos	SBP, DBP, TC, LDL, HDL, TG	SBP (mmHg): 1.94 (−2.95, −0.93) DBP (mmHg): 0.98 (−2.14, 0.18) TC (mmol/L): 0.13 (−0.2, −0.07) LDL (mmol/L): 0.19 (−0.3, −0.09) HDL (mmol/L): 0.01 (−0.08, 0.06) TG (mmol/L): 0.02 (−0.16, 0.12)	Moderate Moderate Moderate Moderate Moderate Moderate	↙ ? ↙ ↙ ? ?	Men of women, with or without dyslipidemia,	13/16 Low
Peng, 2014	adults	13 (1367)	green tea and green tea extract vs. placebo	SBP, DBP	SBP (mmHg): 1.98 (−2.94, −1.01) DBP (mmHg): 1.92 (−3.17, −0.68)	Moderate Moderate	↙ +	Stage 1 hypertension or prehypertension, with or without caffeine, duration, dose	13/16 low
Phung, 2011	adults	15 (1243)	green tea and green tea extract vs. placebo	Wt, BMI, WC, WHR	Wt (kg): 0.14 (−1.45, 1.16) BMI: 0.06 (−0.54, 0.42) WC (cm): 0.31 (−2.1, 2.72) WHR: 0.01 (−0.11, 0.13)	High High High High	? = ? ?	with or without caffeine,	14/16 Moderate
Wang, 2014	type 2 diabetes/ at risk of type 2 diabetes	7 (510)	green tea or green tea extract or EGCG vs. placebo	FBG, FBI, Hb A1c, HOMA-IR.	FBG: 0.04 (−0.15, 0.24) FBI: 0.09 (−0.3, 0.11) HbA1c (%): 0.01 (−0.13, 0.33) HOMA: 0.06 (−0.35, 0.23)	Low Moderate Very low Moderate	? ? ? ?	With or without diabetes,	13/16 Low
Xu, 2020a	adult	27 (2194)	green tea or green tea extract vs. placebo	FBG, FBI, Hb A1c, HOMA-IR.	FBG (mg/dL): 1.44 (−2.26, −0.62) FBI (μIU/mL): 0.46 (−1.1, 0.17) Hb A1c (%): 0.06 (−0.12, 0.01) HOMA: 0.15 (−0.39, 0.10)	High Moderate High High	↙ = = =	Beverage/capsule Duration Catechins dose with or without caffeine, Fasting blood glucose	14/16 Moderately

(*continued on next page*)

Table 1 (*continued*)

First author, Year	participants	Number of studies (number of subjects)	Intervention vs. placebo	Outcome	Effect size (95%CI) MD	Credibility Assessment	Effect on outcome	subgroups	AMSTAR2 score
Xu, 2020b	Adults	31 (3321)	green tea and green tea extract vs. placebo	TC, LDL, HDL, TG	TC (mg/dL): 4.66 (−6.36, −2.96) LDL (mg/dL): 4.55 (−6.31, −2.8) HDL (mg/dL): 3.77 (−8.9, 1.37) TG (mg/dL): 3.77 (−8.9, 1.37)	High High Moderate High	↙ ↙ = =	Beverage/capsule Dose, duration, with or without caffeine, overweight, obese/ normal	15/16 Moderately
Xu, 2020c	adults	24 (1697)	green tea and green tea extract vs. placebo	SBP, DBP	SBP (mmHg): 1.17 (−2.18, −0.16) DBP (mmHg): 1.24 (−2.07, −0.4)	High High	↙ ↙	Beverage/capsule, duration, dose, with or without caffeine, with or without cardiovascular, hypertension or healthy	14/16 moderate
Zheng, 2011	Adults	15 (1136)	green tea and green tea extract vs. placebo	TC, LDL, HDL	TC (mg/dL): 7.2 (−8.19, −6.21) LDL (mg/dL): 2.19 (−3.16, −1.21) HDL (mg/dL): 0.25 (−0.73, 1.23)	High High High	↙ ↙ =	Beverage/capsule Dose, With cardiovascular risks/ healthy, duration,	14/16 Moderately
Zheng, 2013	Adults	22 (1584)	GTCs with or without caffeine vs. placebo	FBG, FBI, Hb A1c, HOMA-IR.	FBG (mg/dL): 1.48 (−2.57, −0.4) FBI (μIU/mL): 0.04 (−0.36, 0.45) Hb A1c (%): 0.04 (−0.15, 0.08) HOMA: 0.05 (−0.37, 0.26)	High Moderate Moderate Moderate	↙ = = =	Duration, Ethnicity, Catechin dose, with or without caffeine, BMI, Baseline glucose concentration	13/16 Low

3.2. Quality of the included reviews

We assessed the quality of the systematic reviews through the use of the AMSTAR2 questionnaire (Table 1). The range of scores was from 12 [25,26] to 16 [27,28] out of a maximum score of 16. All reviews presented a comprehensive literature search and a list of included studies. Also, in most reviews, two or more independent reviewers were involved in the study selection and data extraction. The majority of reviews included the components of PICO in their research questions as well. Only two reviews lacked detail on publication bias [25,26]. All reviews explained the methods used to combine findings. Only two reviews reported details on funding of included studies [27,28].

Table 2 Matrix and corrected covered area (CCA) to examine overlap for subsets of glycemic markers.

		Asbaghi, 2020	Zheng, 2013	Liu, 2013	Wang, 2014	Xu, 2020
1	Fukino, 2005	*		*		*
2	Fukino, 2008	*	*	*	*	*
3	Mirzaei, 2009	*	*	*		*
4	Mohammadi, 2020	*				
5	Hsu, 2011	*	*	*	*	*
6	Mousavi, 2013	*				
7	Lasaite, 2014	*				
8	Liu, 2014	*				*
9	Borges, 2016	*				
10	Zandi DarehGharibi, 2018	*				
11	Sobhani, 2019	*				
12	Quezada-Fernandez, 2019	*				
13	Hosseini, 2018	*				
14	Basu, 2011		*		*	*
15	Brown, 2009		*	*		*
16	Brown, 2011		*	*		*
17	Chan, 2006		*	*		*
18	Diepven, 2006		*	*		*
19	Frank, 2009		*			
20	Hase, 2001		*			
21	Hill, 2007		*	*		*
22	Hsu, 2008		*		*	*
23	Hursel, 2009		*			
24	Kovacs, 2004		*			*
25	Nagao, 2005		*	*		
26	Ryu, 2006		*	*	*	*
27	Sone, 2011		*	*		*
28	Stendell-Hollis, 2010		*	*		*
29	Tsuchida, 2002		*		*	
30	Westerterp, 2005		*			
31	Nagao, 2009	*		*		*
32	Wu, 2012			*		*
33	Bogdanski, 2012			*		*
34	Sulibursk a, 2012			*		*
35	Nantz, 2009				*	
36	Chen, 2016					*
37	Dostal, 2016					*
38	Frank, 2009					*
39	Lu, 2016					*
40	Mielgo-Ayuso, 2014					*
41	Miyazaki, 2013					*
42	Tadayon, 2018					*
		N	r	c	CCA	
	Overall	87	42	5	0.26	
	Asbaghi, 2020 vs. Zheng, 2013	36	30	2	0.2	
	Asbaghi, 2020 vs. Liu, 2013			2	0.24	
	Asbaghi, 2020 vs. Wang, 2014			2	0.10	
	Asbaghi, 2020 vs. Xu, 2020			2	0.2	
	Zheng, 2013 vs. Liu, 2013			2	0.56	
	Zheng, 2013 vs. Wang, 2014			2	0.38	
	Zheng, 2013 vs. Xu, 2020			2	0.48	
	Liu, 2013 vs. Wang, 2014			2	0.14	
	Liu, 2013 vs. Xu, 2020			2	0.57	
	Wang, 2014 vs. Xu, 2020			2	0.17	

3.3. Effects of interventions

3.3.1. Anthropometric measures

Of the 5 reviews that assessed the effect of GT on anthropometric measures, one reported data in overweight/obese adults [29] and one included subjects with T2D [28]. All studies (four high/moderate and one low quality evidence) suggested that GT intake might decrease body weight significantly [28–31].

Considering low overlapping among the reviews (Table 5), we included all reviews in quantitative analysis and showed a significant effect on weight, with WMD of −0.89 (95% CI -1.43 to −0.34, $p < 0.001$). There was similar results on waist circumference with WMD of −1.01 (95% CI -1.63 to −0.39, $p < 0.001$) (Table 6).

3.3.2. Blood pressure

In order to evaluate the effect of GT on BP, we found five reviews of which one had reported results of overweight/obese adults [32]. All reviews that regarded as high or moderate quality demonstrated a positive effect of GT consumption on systolic and diastolic blood pressure. Due to very high overlapping among the reviews, we included only most recent reviews in quantitative analysis (Table 4). To do this, we applied citation matrix in subsets and one by one comparison of the reviews. Consequently, we identified 24 trials, covering more than 1697 participants and succeeded to detect a significant effect on SBP and DBP, with WMDs of −1.17 (95% CI -2.18 to −0.16) and −1.24 (95% CI -2.07 to −0.4), respectively (Table 6).

3.3.3. Glycemic outcomes

Data for the effect of GT on glycemic status (overall effect) obtained from five meta-analyses, of which two studies included patients with type 2 diabetes (T2D)/at risk of diabetes. Three reviews showed that the intervention produced a statistically significant benefit, as compared with control, on FBG, all of which had a high quality [33–35]. However, two moderate and low quality evidence that included patients with T2D showed no significant effect on FBG [23,36]. Only one review reported statistical significant effect on HbA1c [33].

Table 2 shows that overall CCA among reviews was very high (28%). Due to the requirement of CCA <15, using citation matrix in subsets and comparison of two individual reviews, two meta-analyses were excluded [33,35] so that three meta-analyses were finally included in the quantitative analysis (Table 2).

Meta-meta-analysis revealed statistically significant effect of GT on FBG (WMD, −1.3, 95% CI -2.09 to −0.51, $p < 0.001$) but not in other glycemic indicators (HbA1c: WMD, −0, 95% CI -0.17 to 0.17, $p = 1.0$, HOMA: WMD, −0,04, 95% CI -0.22 to 0.14, $p = 0.66$, FBI: WMD, −0.28% CI -0.76 to 0.19, $p = 0.24$) (Table 6).

3.3.4. Lipid profile

Lipid profile was the primary outcome of interest in six out of 13 reviews. Only one study included subjects with T2D [22]. Most reviews (five out of six) with high/moderate quality reported that GT might improve serum TC and LDL-C concentrations [24,26,27,37,38]. However, only one review reported that GT might decrease serum TG concentration in the subjects with T2D [22].

After excluding two reviews due to high overlap (Table 3), four reviews were included in quantitative analysis and meta-meta-analysis on effect of GT on serum TC and LDL-C concentrations. The findings revealed a statistically significant effect size (WMD -4.93; 95% CI -6.41 to −3.46, $p < 0.001$, WMD -4.31; 95% CI -6.55 to −2.07, $p < 0.001$, respectively). However, there was no significant effect on circulating HDL-C (WMD 0.13; 95% CI -0.46 to 0.71, $p = 0.67$) and TG (WMD -1.96; 95% CI -8.94 to 5.02, $p = 0.58$) concentrations (Table 6).

4. Discussion

4.1. Summary of the main results

To evaluate the effects of GT consumption on cardiometabolic risk factors as the primary or secondary outcome, this study included 19 reviews comprising 317 randomized controlled trials and 24,482 adults. The estimates of effects and certainty of the estimates for different outcomes varied. Summary of the main findings are as follows:

1. GT consumption has beneficial effects on body weight and waist circumference;
2. GT consumption has beneficial effect on at least one outcome of glycemic status, i.e. FBG, especially in healthy subjects;
3. GT consumption has ameliorating effects on circulating TC and LDL-C concentrations;
4. None of the reviews found evidence for any harm due to GT consumption (defined as a clear increase in the risk of cardiovascular factors);

4.2. Overall completeness and applicability of the evidence

There was broad evidence for the effects of GT on cardiometabolic risk factors. However, there were limited data on subgroups including subjects with diabetes or overweight/obesity. It was, therefore, difficult to draw generalizable conclusions regarding the applicability of the findings to these subgroups.

Evidence of the effects of GT on some other outcomes like body fat was not considered in this overview since eligible systematic reviews were not found. Likewise, there were limited studies that examined the costs and cost-effectiveness of the intervention with GT.

4.3. Quality of the evidence

The quality of the included reviews, as evaluated by AMSTAR tool, was considered “relatively good”. All included reviews had assessed the risk of bias for the included randomized trials. However, the quality of the

Table 3 Matrix and corrected covered area (CCA) to examine overlap for subsets of lipid.

		Asbaghi, 2020	Zheng, 2011	Kim, 2011	Xu, 2020	Khalesi, 2014	Onakpoya, 2014
1	Fukino, 2008	*	*	*	*		
2	Mohammadi, 2010	*					
3	Hsu, 2011	*			*		*
4	Mousavi, 2013	*					
5	Liu, 2014	*			*		
6	Sobhani, 2019						
7	Quezada-Fernandez, 2019	*					
8	Basu, 2011				*	*	
9	Brown, 2009			*	*		*
10	Brown, 2011				*		*
11	Chan, 2006		*	*	*		
12	Diepven, 2006		*		*		*
13	Frank, 2009		*	*	*		*
14	Hsu, 2008		*	*	*	*	*
15	Nagao, 2005		*				
16	Ryu, 2006			*			
17	Nagao, 2009	*	*		*	*	*
18	Wu, 2012				*		
19	Bogdanski, 2012				*	*	*
20	Sulibursk a, 2012				*	*	*
21	Nantz, 2009		*		*	*	
22	Chen, 2016				*		
23	Lu, 2016				*		
24	Mielgo-Ayuso, 2014				*		
25	Miyazaki, 2013				*		
26	Tadayon, 2018				*		
27	Batista, 2009		*	*			*
28	Diplerro, 2009			*			
29	Elchenberger, 2009			*			
30	Makl, 2009		*	*	*		*
31	Bertipaglia de Santana, 2008			*			
32	Matsuyama			*			*
33	Nagao, 2008			*			
34	Akeshita, 2008			*			*
35	Inami, 2007			*			
36	Nagao, 2007		*	*	*	*	*
37	Erba, 2005			*			
38	Maron, 2003		*	*	*		
39	Princen, 1998		*	*	*		
40	Van het Hof, 1997			*			
41	Freese, 1999		*	*			
42	Huang, 2018				*		
43	Kafeshani, 2017				*		
44	Lee, 2016				*		
45	Samvat, 2016				*		
46	Venkatakrishnan, 2018				*		
47	Fukino, 2008	*	*	*	*		
48	Mohammadi, 2010	*					
49	Hsu, 2011	*			*		
50	Mousavi, 2013	*					
51	Liu, 2014	*			*		
52	Sone, 2011					*	*
53	Vieira Senger, 2005					*	
54	Kajimoto, 2003						*
55	Takase,2008						*
56	Widlansky,2007						*
		N	r	c	CCA		
	overall	102	51	6	0.20		
	Asbaghi, 2020 vs. Zheng, 2011	21	19	2	0.1		
	Asbaghi, 2020 vs. Kim, 2011	27	26	2	0.03		
	Asbaghi, 2020 vs. Xu, 2020	38	34	2	0.10		
	Asbaghi, 2020 vs Khalesi, 2014	18	16	2	0.12		
	Asbaghi, 2020 vs Onakpoya, 2014	26	23	2	0.13		
	Zheng, 2011 vs. Kim, 2011	34	25	2	0.36		
	Zheng, 2011 vs. Xu, 2020	45	33	2	0.36		
	Zheng, 2011 vs. Khalesi, 2014	25	20	2	0.25		

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Table 3 (*continued*)

	Asbaghi, 2020	Zheng, 2011	Kim, 2011	Xu, 2020	Khalesi, 2014	Onakpoya, 2014
Zheng, 2011 vs. Onakpoya, 2014	33	25	2	0.32		
Kim, 2011 vs. Xu, 2020	51	42	2	0.21		
Kim, 2011 vs. Khalesi, 2014	31	28	2	0.10		
Kim, 2011 vs. Onakpoya, 2014	39	30	2	0.3		
Xu, 2020 vs. Khalesi, 2014	4	33	2	0.27		
Xu, 2020 vs. Onakpoya, 2014	50	38	2	0.31		
Khalesi, 2014 vs. Onakpoya, 2014	30	21	2	0.42		

trials covered within individual reviews was variable. In general, recent trials tended to report their methodology in more detail.

4.4. Anthropometric measures

The overview found high and moderate quality evidence of the efficacy of GT on body weight.

The overview found high quality evidence of the efficacy of GT consumption on waist circumference.

High and moderate-quality evidence suggested a benefit of GT intake on weight and waist circumference that was confirmed by the results of the meta-meta-analysis.

Subgroup analysis in high and moderate quality evidence [28,31] showed that GT is effective on body weight

Table 4 Matrix and corrected covered area (CCA) to examine overlap for subsets of BP.

		Khalesi, 2014	Li, 2015	Onakpoya, 2014	Peng, 2014	Xu, 2020
1	Fukino, 2008				*	*
2	Fukino, 2005	*			*	*
3	Hsu, 2011	*	*	*		*
4	Liu, 2014		*			*
5	Basu, 2011	*	*			*
6	Brown, 2009		*	*	*	*
7	Brown, 2011		*	*	*	*
8	Diepven, 2006	*	*	*	*	*
9	Frank, 2009	*	*	*	*	*
10	Hsu, 2008	*	*	*		*
11	Nagao, 2009	*		*	*	*
12	Bogdanski, 2012	*	*	*	*	*
13	Sulibursk, 2012	*	*	*	*	*
14	Nantz, 2009	*	*	*	*	*
15	Chen, 2015					*
16	Miyazaki, 2013					*
17	Batista, 2009			*		
18	Matsuyama			*		
19	Nagao, 2007	*		*	*	*
20	Kafeshani, 2017					*
21	Maki, 2009			*		
22	Sone, 2011	*		*		*
23	Vieira Senger, 2005	*				
24	Hill, 2007		*	*	*	*
25	Takase, 2008		*	*		
26	Takeshita, 2008		*			
27	Kajimoto, 2003			*		
28	Widlansky, 2007			*		
29	Basu, 2010				*	
30	Liu, 2016					*
31	Maeda-Yamamoto, 2018					*
32	Nogueira, 2016					*
33	Takahashi, 2014					*
34		N	r	c	CCA	
	Overall	84	33	5	0.38	
	Khalesi, 2014 vs. Li, 2015	27	19	2	0.42	
	Khalesi, 2014 vs. Onakpoya, 2014	33	22	2	0.5	
	Khalesi, 2014 vs. Peng, 2014	26	17	2	0.52	
	Khalesi, 2014 vs. Xu, 2020	37	25	2	0.48	
	Li, 2015 vs. Onakpoya, 2014	34	23	2	0.47	
	Li, 2015 vs. Peng, 2014	27	19	2	0.42	
	Li, 2015 vs. Xu, 2020	38	26	2	0.46	
	Onakpoya, 2014 vs. Peng, 2014	44	31	2	0.41	
	Onakpoya, 2014 vs. Xu, 2020	37	25	2	0.48	

Table 5 Matrix and corrected covered area (CCA) to examine overlap for subsets of Anthropometric measurements.

		Asbaghi, 2020	Hursel, 2009	Jurgens, 2012	Lin, 2019	Phung, 2011
1	Fukino, 2005	*				*
2	Fukino, 2008	*				
3	Mirzaei, 2009	*				
4	Mohammadi, 2010	*				
5	Hsu, 2011	*				
6	Mousavi, 2013	*				
7	Lasaite, 2014					
8	Liu, 2014	*				
9	Borges, 2016	*				
10	Zandi DarehGharibi, 2018	*				
11	Quezada-Fernandez, 2019	*				
12	Basu, 2011				*	
13	Chan, 2006				*	*
14	Diepven, 2006		*	*	*	*
15	Frank, 2009					*
16	Hase, 2001		*			
17	Hill, 2007			*		*
18	Hsu, 2008		*	*	*	*
19	Hursel, 2009			*		
20	Kovacs, 2004		*	*	*	
21	Nagao, 2005					*
22	Tsuchida, 2002		*	*		*
23	Westerterp-Plantenga, 2005		*	*		
24	Nagao, 2009	*				*
25	Bogdanski, 2012				*	
26	Sulibursk, 2011				*	
27	Nagao, 2001		*			
28	Kozuma, 2005		*	*		
29	Nagao, 2007		*	*		*
30	Auvichayapat, 2008		*	*	*	*
31	Wang, 2008		*			
32	Kajimoto, 2005			*		
33	Kataoka, 2004					
34	Maki, 2009			*		*
35	Suzuki, 2009			*		
36	Takese, 2008					
37	Takashima, 2004			*		
38	Takeshita, 2008			*		
39	Wang, 2010			*		
40	Amozade, 2018				*	
41	Naderi Nabi, 2018				*	
42	Venkatakrishnan, 2018				*	
43	Rostamian, 2017				*	
44	Tabatabaee,2017				*	
45	Mombaini, 2017					
46	Soeizi, 2017				*	
47	Afzalpour, 2016				*	
48	Hovanloo, 2016				*	
49	Janssens,2015				*	
50	Al-Naggar, 2013				*	
51	Toolsee, 2013				*	
52	Aparecida Cardoso, 2012				*	
53	Vieira Senger, 2012				*	
54	Hsu, 2012				*	
55	Di Pierro, 2009				*	
56	Matsuyama, 2008					*
		N	r	c	CCA	
	Overall	78	58	5	0.08	
	Asbaghi, 2020 vs. Hursel, 2009	22	22	2	0	
	Asbaghi, 2020 vs. Jurgens, 2012	27	27	2	0	
	Asbaghi, 2020 vs. Lin, 2019	34	34	2	0	
	Asbaghi, 2020 vs. Phung, 2011	26	24	2	0.08	
	Hursel, 2009 vs. Jurgens, 2012	27	19	2	0.42	
	Hursel, 2009 vs. Lin, 2019	36	30	2	0.2	
	Hursel, 2009 vs. Phung, 2011	26	21	2	0.23	
	Jurgens, 2012 vs. Lin, 2019	41	35	2	0.17	

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Table 5 (*continued*)

	Asbaghi, 2020	Hursel, 2009	Jurgens, 2012	Lin, 2019	Phung, 2011
Jurgens, 2012 vs. Phung, 2011	31	24	2	0.29	
Lin, 2019 vs. Phung, 2011	40	34	2	0.17	

independent of the caffeine content. Two moderate quality reviews reported that GT intake was more effective in overweight/obese subjects. Nonetheless, more evidence is needed.

4.5. Blood pressure

The overview found moderate quality evidence of the efficacy of GT on SBP and DBP. Moderate and low-quality evidence suggested beneficial effect of GT intake on SBP and DBP.

A low-quality evidence showed the benefit of GT either as beverage or extract only in subjects with baseline SBP> 130 mmHg. Notwithstanding, the moderate quality evidence suggested similar effect in both hypertensive and healthy participants.

4.6. Glycemic status

The overview found moderate quality evidence for effectiveness of the intervention on FBG. No decisive conclusions are possible: low quality evidence,

Table 6 The cardiometabolic risk factors studied in the included reviews.

Cardiometabolic risk factor		Included meta-analysis	Number of Meta-analysis (number of subjects)	Effect size 95% CI	I^2
Glycemic markers	FBS	Asbaghi, 2020a Wang, 2014 Xu, 2020a	3 (3583)	−1.3 (−2.09 to −0.51)	1.11
	HbA1c	Asbaghi, 2020a Wang, 2014 Xu, 2020a	3 (3583)	−0 (−0.17 to 0.17)	84.3
	HOMA-IR	Asbaghi, 2020a Wang, 2014 Xu, 2020a	3 (3583)	−0.04 (−0.22 to 0.14)	8.54
	Fasting serum insulin	Asbaghi, 2020a Wang, 2014 Xu, 2020a	3 (3583)	−0.28 (−0.76 to 0.19)	37.16
Lipid profile	TG	Asbaghi, 2020b Kim, 2011 Xu, 2020b Khalesi, 2014	4 (5984)	−1.96 (−8.94 to 5.02)	62.7
	TC	Asbaghi, 2020b Kim, 2011 Xu, 2020b Khalesi, 2014	4 (5984)	−4.93 (−6.41 to −3.46)	0
	LDL-C	Asbaghi, 2020b Kim, 2011 Xu, 2020b Khalesi, 2014	4 (5984)	−4.31 (−6.55 to −2.07)	57.4
	HDL-C	Asbaghi, 2020b Kim, 2011 Xu, 2020b Khalesi, 2014	4 (5984)	0.13 (−0.46 to 0.71)	0
Blood pressure	SBP	Xu, 2020c	1 (1694)	−1.17 (−2.18 to −0.16)	43
	DBP	Xu, 2020c	1 (1694)	−1.24 (−2.07 to −0.4)	57
Anthropometry	Weight	Asbaghi, 2020c Hursel, 2009 Jurgens, 2012 Lin, 2019 Phung, 2011	5 (7075)	−0.89 (−1.43 to −0.34)	64.4
	BMI	Khalesi, 2014 Asbaghi, 2020c Jurgens, 2012 Lin, 2019 Phung, 2011	5 (6617)	−0.24 (−0.49, −0.0)	72.7
	WC	Asbaghi, 2020c Jurgens, 2012 Lin, 2019 Phung, 2011	4 (5849)	−1.01 (−1.63 to −0.39)	0.0

moderate-quality evidence showed no clear difference or provided insufficient evidence to comment on the efficacy of GT intake on fasting serum insulin, HbA1c and HOMA-IR.

Moderate-quality evidence suggested beneficial effect of GT intake on FBG that was confirmed by results of the meta-meta-analysis.

It is noteworthy that the beneficial effects of GT consumption on FBG were not reported in those reviews that included participants with T2D/at risk of diabetes [23,36]. Interestingly, subgroup analysis in moderate quality evidence showed that GT was effective in lowering FBG just in the subjects with normal FBG at baseline [33–35]. In addition, subgroup analysis in most recent and qualified evidence demonstrated that GT intake was beneficial when consumed with caffeine [34,35] or in a dose of catechin above 450 mg/day [33,35].

Moderate evidence showed no beneficial effect of GT consumption on circulating insulin, HbA1c and HOMA-IR compared with placebo.

4.7. Lipid profile

The overview found moderate quality evidence supporting the efficacy of GT on serum TC and LDL-C concentrations. No decisive conclusions were possible: low quality evidence, moderate-quality evidence showed no clear difference or provided insufficient evidence to comment on the efficacy of GT intake on serum TG and HDL-C concentrations.

High and moderate-quality evidence suggested beneficial effects of GT intake on TC and LDL-C that was confirmed by the results of the meta-meta-analysis.

Subgroup analysis in moderate quality evidence [24,37] showed that GT, apart from its catechin content, is effective in lowering serum TC and LDL-C concentrations.

5. Authors' conclusions

Regular consumption of GT and probably its bioactive constituents as supplements have beneficial effects on different health aspects including weight, blood pressure, blood glucose and lipids. However, these effects might be influenced by several factors such as the amount and frequency of consumption, health/disease condition and life style including dietary habits and physical activity.

5.1. Implication for practice

Prevention of CVD involves modification of life style including healthy diet, weight control and physical activity [39]. Nonetheless, encouragement of the subjects with CVD risk factors, CVD patients and also general population to consume moderate amounts of GT, as a part of healthy diet, may synergistically help lower CVD risk of morbidity and mortality.

5.2. Implication for research

Further high quality studies are needed to evaluate the efficacy of GT on cardiometabolic risk factors in a dose-response manner.

Contributors

TN and **BN** were involved in each of the following points:

1. Design.
2. Data collection.
3. Analysis.
4. Writing manuscript.

Role of the funding source

This research was performed independently of any funding, as part of the institutional activity of the investigators. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit it for publication.

Research involving human participants and/or animals

This article does not contain any studies with human participants or animals performed by any of the authors.

Authorship

BN with the intellectual aid of TN designed the study. BN and TN performed the searches and data extraction. All statistically analyses were done by BN and the results were interpreted by TN and BN. The preliminary manuscript was written by BN and finalized by TN. All authors read and approved the final manuscript.

Declaration of competing interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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