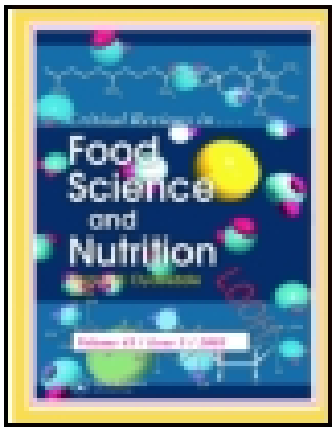

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Camellia Sinensis in Asymptomatic Hyperuricaemia: A Meta-analysis of Tea or Tea Extract Effects on Uric Acid Levels

Ilaria Peluso[a], Alessia Teichner[a], Husseen Manafikhi[a] & Maura Palmery[a]
[a] Department of Physiology and Pharmacology "V. Erspamer", "Sapienza" University of Rome, P.le Aldo Moro 5, 00185 Rome, Italy.
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Camellia sinensis in asymptomatic hyperuricaemia: a meta-analysis of tea or tea extract effects on uric acid levels

Ilaria Peluso[1], Alessia Teichner[1], Husseen Manafikhi[1] and Maura Palmery[1]*

[1]*Department of Physiology and Pharmacology "V. Erspamer", "Sapienza" University of Rome, P.le Aldo Moro 5, 00185 Rome, Italy.*

***Address for correspondence:**

Maura Palmery, Prof.

Department of Physiology and Pharmacology "V. Erspamer"

"Sapienza" University of Rome ,

P.le Aldo Moro 5, 00185 Rome, Italy.

maura.palmery@uniroma1.it

Phone +39-06-49912573; Fax: +39-06-49912480

Short title for the running head: Camellia sinensis in asymptomatic hyperuricaemia

Abstract

Flavanols of Camellia sinensis exhibit uric acid (UA) lowering effect, through the modulation of both xanthine oxidase and urate excretion. In order to investigate the potential benefit of Camellia Sinenis products in asymptomatic hyperuricaemia, a meta-analysis of long-term Randomized Controlled Trials (RCT) with tea or tea extract has been conducted. From 20 human intervention studies selected only 5 RCT (13 interventions) were suitable for meta-analysis (n=472).

The current "normal" range set for hyperuricaemia fails to identify patients with potential metabolic disorders. Therefore on the basis of the literature data, we fixed cut off limits for UA baseline levels of 4.5 mg/dl for women, 6.1 mg/dl for men and 5.5 mg/dl for studies involving mixed populations.

Statistically significant effects were not found, but subgroup analysis revealed that the Pooled Estimate effect was different in subjects with baseline levels under [MD (95% CI): 0.1078 (-0.0528 to 0.2684)] and over the cut off [MD (95% CI): -0.0239 (0.3311 to 0.2833)].

However, due to the low number of RCT and to the lack of data on bioavailability, it is difficult to draw any firm conclusion and more studies are needed to establish if tea flavanols could be useful in asymptomatic hyperuricaemia treatment.

Keywords: long term intervention, meta-analysis, uric acid, xanthine oxidase, urate transport.

INTRODUCTION

Black tea (BT) and green tea (GT) are very different due to the processing or harvesting times of the leaves and leaf buds of the Camellia sinensis, which lead to a different composition in phenolic compounds (Serafini et al., 2011a). In the case of GT, the leaves are steamed quickly after harvesting to prevent oxidation of polyphenols and the major flavonoids present are the flavanols epicatechin and its gallate derivatives (Serafini et al., 2011a). These flavonoids are present in lower amounts in BT where they are converted, during the "fermentation" period, to complex condensation products such as theaflavins and thearubigins (Serafini et al., 2011a). Despite the role of uric acid (UA) in Plasma Non-Enzymatic Antioxidant Capacity (Serafini et al., 2011b), some of the protective effects of Epigallocatechin-3-gallate (EGCG) have been ascribed to its capability to reduce excessive UA level (Yokozawa et al., 2004). Accordingly, the latter can also be a dangerous signal for immune system (Shi et al., 2003), and hyperuricaemia has been associated to oxidative stress (Lahera et al., 2006).

Hyperuricaemia is an elevated UA level in blood that is most often mild and remains asymptomatic (Kanellis et al., 2004; Mikuls et al., 2005; Zoppini et al., 2011). However, chronic asymptomatic hyperuricaemia may be complicated by gout, urolithiasis and possibly nephropathy. Gout is an inflammatory response to deposition of monosodium urate crystals in and around joints (Mandell, 2008; Tausche et al., 2009; Fink et al., 2013; Wang et al., 2012). Therapy of hyperuricaemia and gout has to depend on pathogenesis and stage of the disease. Guidelines of management for gout recommend that serum urate concentration should be maintained below 6 mg/dl to promote crystal dissolution leading to prevention of recurrent gouty

attack (Mandell, 2008; Tausche et al., 2009). In the presence of renal impairment, allopurinol, an analogue of hypoxanthine, is the treatment of choice for urate lowering therapy (Fink et al., 2013; Wang et al., 2012).

There is still no consensus on the treatment of individuals with asymptomatic hyperuricaemia (Kanellis et al., 2004; Mikuls et al., 2005; Zoppini et al., 2011). However, the latter is an important etiological factor in common morbidities such as arterial hypertension, cardiovascular disease (CVD) and type 2 diabetes mellitus (T2D) (Kanellis et al., 2004; Zoppini et al., 2011; Becker and Jolly, 2006; Strazzullo and Puig, 2007; 15. Hwu and Lin, 2010). Urate lowering drug treatment is normally not indicated in asymptomatic hyperuricaemic individuals, considering that the allopurinol hypersensitivity syndrome has been reported (Markel, 2005). For this reason Febuxostat, a more tolerable xanthine oxidase (XO) inhibitor has received attention (Tayar et al., 2012).

In this context, also theaflavins and catechins inhibit XO to produce UA and theaflavin-3,3'-digallate, the most potent inhibitor of XO among these compounds, acts as a competitive inhibitor (Lin et al., 2000; Dew et al., 2005). Moreover, EGCG (Yin et al., 2009; Palermo et al., 2005; Han et al., 2012; Park and Dong 2003; Nomura et al., 2000) and theaflavins (Park and Dong 2003; Nomura et al., 2000; Łuczaj and Skrzydlewska, 2005) inhibit the nuclear factor κB (NF-κB) (Park and Dong 2003; Nomura et al., 2000; Łuczaj and Skrzydlewska, 2005) and the aryl hydrocarbon receptor (AhR) EGCG (Yin et al., 2009; Palermo et al., 2005; Han et al., 2012) response pathways, key regulators of XO (Martinez-Hervas et al., 2010; Sugihara et al., 2001). Flavonoids have been proposed as alternative of uricosuric agents (e.g. benzbromarone) in allopurinol-allergic patients (Yu et al., 2007). Renal urate transporter (URAT) (Yu et al., 2007;

Hu et al., 2012; Wang et al., 2010), organic anion transporters (OAT) (Hu et al., 2012; Wang et al., 2010; Sekine et al., 2006), multidrug resistance-associated proteins (MRP) (Sekine et al., 2006; El-Sheikh et al., 2008) and uromodulin (Hu et al., 2012), play important roles in renal urate excretion and are regulated by both flavonoids (Yu et al., 2007; Hu et al., 2012; Wang et al., 2010) and hyperuricaemic drugs (Yu et al., 2007; El-Sheikh et al., 2008). In particular tea catechins (Roth et al., 2011; Fuchikami et al., 2006; Vaidyanathan and Walle, 2001) interact with OAT (Roth et al., 2011; Fuchikami et al., 2006) and MRP (Vaidyanathan and Walle, 2001). Moreover allopurinol and flavonoids reversed dys-regulations of OAT and URAT and attenuate hyperuricaemia and renal dysfunction in rats induced by fructose intake (Hu et al., 2009). Besides, it has been suggested that the inhibitory effect of green tea on calcium oxalate urolithiasis is most likely due to antioxidative effects (Itoh et al., 2005). Contrarily to teas, other antioxidant beverages, such as orange juice and pink grapefruit juice, were shown to promote XO activity (Dew et al., 2005). Moreover, cocoa beverage significantly increase calcium and oxalic acid excretion and also leafy vegetable foods contain oxalate (Hesse et al., 1993). This could be critical in hyperuricaemia considering that increases in calcium and oxalate excretion promote kidney stones (Taylor and Curhan, 2006).

Accordingly to the urate lowering effect of Camellia sinensis, despite the evidence showing that reducing soft-drink consumption decreased recurrent symptomatic stone risk (Fink et al., 2013), observational studies have found that tea consumption reduces the risk of stone formation (Taylor and Curhan, 2006).

Therefore, the objective of this meta-analysis was to investigate the effect of Camellia sinensis products on hyperuricaemia. To this aim, in the absence of specific Randomize Controlled Trials

(RCT), a systematic review and meta-analysis of chronic intervention studies with BT, GT or extracts and UA concentrations has been conducted in this work.

METHODS

Data source and study selection

We performed a systematic search (Figure 1) up to October 2013. Any study that met the following criteria was selected for meta-analysis: randomized long term placebo-controlled trials where the plasma levels of UA were measured before and after placebo and treatment and that appear in an edited English journal. All human chronic studies were included if they met the above criteria regardless of the dose of BT, GT or extract and of the healthy status of subjects. First trials were identified through title or abstract. Duplicates and irrelevant references have been removed from our search and from result eligible studies were included through full text and reviewed by two independent authors (I.P. and H.M.). Discrepancies were resolved by discussion with a third reviewer (M.P.).

A total of 20 intervention studies after tea or tea extracts administration were identified as suitable and were retrieved for complete review. Figure 1 depicts the flow of studies in this review and the four-phase diagram of meta-analysis, according to the PRISMA Statement (Moher et al., 2009).

Of the reviewed studies, we excluded studies referring to bolus administration (Henning et al., 2005; Jówko et al., 2012; Leenen et al., 2000; Müller et al., 2010; Natella et al., 2002; Rabovsky et al., 2006; Van Amelsvoort et al., 2001), not placebo-controlled trials (Gomikawa et al., 2008;

Kimura et al., 2002; Sone et al., 2011) and papers reporting post-treatment but not pre-treatment values (Panza et al., 2008), not shown data (Chow et al., 2003; Maron et al., 2003; Rondanelli et al., 2009) or figures (Li et al., 2010).

The remaining 5 studies (Bahorun et al., 2010; Hsu et al., 2008; Hsu et al., 2011; Princen et al., 1998; van het Hof et al., 1997), reporting 8 intervention with BT from 3 references and 5 data from 4 RCT with GT or green tea extract (GTE), met our inclusion criteria and could provide data for the analyses (Figure 1).

Data extraction

A data extraction form including quality characteristics was used and a quality score was assigned as previously described (Peluso et al., 2013). All data extraction and quality assessment were performed independently by two reviewers (I.P. and A.T.) to ensure uniformity, and all data were entered by these reviewers, who checked the extracted data and validity criteria against the original published report. Discrepancies were resolved by discussion with a third reviewer (M.P.).

Hyperuricaemia is defined as serum values of UA $\geq$ 6.8 and $\geq$ 5.4 mg/dL for men and women, respectively (Rodrigues et al., 2012). However, the current "normal" range set for hyperuricaemia often fails to identify patients with potential metabolic disorders (Zhang et al., 2013). The association of serum UA with CVD risk factor (Rodrigues et al., 2012), metabolic syndrome (Rodrigues et al., 2012; Zhang et al., 2013), T2D (Kawamoto et al., 2013) and nonalcoholic fatty liver disease (Hwang et al., 2011) is gender-specific and more pronounced in women.

Therefore, on the basis of the literature data, we fixed a cut off of 5.5 mg/dl for studies involving mixed population of male and females (Rodrigues et al., 2012; Hwang et al., 2011), and of 4.5 mg/dl and 6.1 mg/dl, respectively for women and men, when reported (Rodrigues et al., 2012; Zhang et al., 2013; Kawamoto et al., 2013) (Figure 1).

Accordingly with these cut off limits we have found 8 and 5 interventions from 3 (Bahorun et al., 2010; Princen et al., 1998; van het Hof et al., 1997) and 3 (Bahorun et al., 2010; Hsu et al., 2008; Hsu et al., 2011) studies for UA in normal range and over the limits associated with diseases risk, respectively (Figure 1).

Meta-analysis

For the meta-analysis, we calculated the mean change of plasma UA concentrations from baseline to follow-up for each intervention and control group, if not reported, and the SD of delta concentration was estimated as previously described (Peluso et al., 2013). All values were converted to mg/dl, if necessary. For each study with more than one intervention group, we divided the control group evenly according to the number of intervention groups (Peluso et al., 2013). When the data were presented as SEMs, SD was obtained by multiplying SEM by the square root of the sample size.

Statistical heterogeneity, the presence of publication bias, Mean difference (MD) and confidence intervals 95% (CI 95%) were evaluated as previously described (Peluso et al., 2013).

To explore the effects of modifier factors on the primary outcomes, subgrouping was used when data from ≥ three studies and ≥ five interventions were included. These factors were the type of

intervention (BT or GT/GTE) and baseline levels of UA. Meta regression was not performed because less than ten studies were available (Peluso et al., 2013).

RESULTS

Description of included studies

Studies characteristics and the results of the assessment of risk of bias of the included trials (quality assessment) are shown in Table 1. The ingested dose ranged from 600 ml to 900 ml of tea and from 1.2 g to 3.6 g of GTE; the latter was equivalent to the consumption of 18 cups of GT per day (Princen et al., 1998).

Average length is 4-16 weeks and the number of participants in individual trials ranged from 45 to 232. Participant withdrawal rate from the trial was between 4 and 22% and 3 studies (Bahorun et al., 2010; Princen et al., 1998; van het Hof et al., 1997) involved multiple interventions in parallel design.

Age ranged between 16 and 65 years (Table 1) and one study selected only females (Hsu et al., 2008). The remaining trials included percentage of female participants from 41% to 65% and the characteristics and comorbidity status of the participants varied (Table 1). Only one study recruited healthy participants (van het Hof et al., 1997), whereas the remaining RCT evaluated the effect of the intervention among subjecs with CVD (Bahorun et al., 2010), diabetes (Hsu et al., 2011) or risk factors such as smoking habit (Princen et al., 1998) and obesity (Hsu et al., 2008).

None of the trials measured bioavailability and the more frequent limitations were the absence of double blinding (3/5), food antioxidant intake in subjects selection criteria (3/5) and wash out/run-in period (3/5). Only one study presented a high weight bias because randomization generated baseline levels for treated subjects and controls more different than the observed effect after follow up (Hsu et al., 2011). All studies adequately evaluated compliance but, as expected, blinding of subjects have been obtained only in studies with GTE (Hsu et al., 2008; Hsu et al., 2011).

Meta-analysis

The number of subjects was 472 of which 309 received BT, GT or GTE and 163 placebo.

No significant difference was detected with meta-analysis for the change of plasma concentration of UA between tea or extracts ingestion and control (Fig. 2A). The Pooled Estimate effect size was the same in fixed and random effect models (Fig. 2A) and similar in quality effect model [MD (95%CI): 0,0824 (-0,0866 to 0,2514)]. Low statistical heterogeneity was found (I2 0%, t2 0, Q 15%, Egger intercept -0.0135, p = 0.9798), Funnel plot showed no asymmetric distribution of results and Trim-and-fill analysis did not suggest potential publication bias (Fig. 2B).

A no significant decrease and increase, respectively, were detected with meta-analysis for the change of plasma concentration of UA between tea or extracts ingestion and control in subjects with baseline concentration over and under the cut off in fixed, random and quality effect models (Table 2). Also subgrouping for type of treatment revealed no significant effect size in fixed, random and quality effect models (Table 2). Furthermore, the exclusion of the study conducted

on healthy participants (van het Hof et al., 1997) did not significantly change (Table 2) the results obtained with meta analysis (Fig. 2A).

CONCLUSION

In our meta-analysis, statistical significance has not been found, probably by reason of the low number of subjects, but different results have been found, after teas or tea extracts chronic consumption, in subjects with normal baseline levels and with hyperuricaemia, where increased and decreased UA levels have been observed, respectively (Table 2).

These opposite effects could be due to the dual effect on UA concentration of polyphenols of tea. The latter could prevent oxidation (Serafini et al., 2011a) but may also decrease the production and increase the excretion of UA (Roth et al., 2011; Fuchikami et al. 2006; Vaidyanathan and Walle 2001). Despite the higher effect of theaflavins as XO inbibitors in vitro (Lin et al., 2000; Dew et al., 2005), no significant differences have been observed in the effect size between BT or GT and GTE subgroups (Table 2).

However, out of one studies had UA as secondary outpoint; therefore only this RCT (Bahorun et al., 2010) reported data for men and women separately, stratifying them for baseline levels.

This study with BT showed decreases of UA only in subjects (especially women) with high baseline levels and in men with baseline UA concentrations above 8mg/dl, the latter lowered after wash-out (BT 7.3 ± 1.7 mg/dl and water 8.0 ± 2.0 mg/dl) (Bahorun et al., 2010), suggesting an inhibitory effect on XO that persists after discontinuation of consumption. Accordingly to this hypothesis also in an uncontrolled trial GTE decreased UA after 7 days of wash-out, subsequent

to 7 days of supplementation, when catechins went down to pre-treatment concentrations (Kimura et al., 2002). Panza et al. (2008), reported a decrease of UA levels, after 7 days of ingestion of GT (600ml), and an inhibition of the exercise-induced activation of XO.

However, only one of the studies in bolus administration of tea or tea extracts, reported decreases in UA concentration (Rabovsky et al., 2006), whereas in the others increased (Henning et al., 2005; Natella et al., 2002) or unchanged (Jówko et al., 2012; Leenen et al., 2000; Müller et al., 2010; Van Amelsvoort et al. 2001; Kimura et al., 2002) UA levels were found. Moreover, Bahorun et al. (2010) in women observed decreases in UA after wash-out also in controls, suggesting differential gender effects of a high fluid intake.

Due to the limited number of studies, the major limitation of this meta-analysis is that we could not investigate sex, age, healthy status and body mass index differences between subjects or dose and duration of treatment effects. However, concerning the excluded studies both decreased (Kimura et al., 2002; Panza et al., 2008) or unchanged (Gomikawa et al., 2008; Li et al., 2010) UA levels have been reported after long term GT (Gomikawa et al., 2008; Panza et al., 2008) or GTE Kimura et al., 2002; Li et al., 2010) consumption in healthy subjects. The decreases were observed after 7 day of consumption (Kimura et al., 2002; Panza et al., 2008), while treatment of 2 weeks (Gomikawa et al., 2008) or 16 weeks (Li et al., 2010) were unable to change the UA concentration. Moreover, in an uncontrolled trial have been observed decreases of UA after 9 weeks of GT (100mg/day of total catechins) and increases of UA with catechin-enriched GT (400mg/day of total catechins), but these effects did not reach statistical significance (Sone et al., 2011). Therefore, longer or higher consumptions seem to be not related with higher effects.

Tea polyphenols could regulate gut microbioma (Axling et al., 2012), as well as phase I, II and III metabolism/transport systems (Chow et al., 2006; Chow et al., 2007; Vischini et al., 2011); all involved in their metabolism (Serafini et al., 2011; Henning et al., 2011).

From there, a critical point of this meta-analysis is that none of the selected studies reported data of tea flavanols or metabolites after the intervention. Besides, bioavailability in healthy and dys-metabolic subjects could profoundly differ because metabolic diseases and obesity are associated with dysbiosis (Hooper et al., 2012; Tremaroli and Bäckhed, 2012) and low grade chronic inflammation (Calder et al., 2011) and inflammatory cytokines modulate cytochrome P450 (Liptrott et al., 2009) and MRP (Kimura et al., 2006).

These evidence could be taken into account in the interpretation of data of these meta-analysis, considering that the subgroup with UA levels above the cut off comprise studies involving subjects with CVD (Bahorun et al., 2010) diabetes (Hsu et al. 2011) or obesity (Hsu et al., 2008). Of these studies only one, which reported better results on the effect on hyperuricaemia, recruited patients under treatment with drugs against hypertension or diabetes (Bahorun et al., 2010). Therefore, we cannot exclude a possible interaction of tea with other drugs at the level of the MRP (Vaidyanathan and Walle, 2001), involved in renal urate excretion (Sekine et al., 2006; El-Sheikh et al., 2008).

Hyperuricaemia is often associated with other diseases (Becker and Jolly, 2006; Hwu and Lin, 2010; Kanellis et al., 2004; Strazzullo and Puig, 2007; Zoppini et al., 2011), therefore considering that our data suggest that tea or tea extracts exerted differential effects in subjects with high or low UA concentration, RCT with UA levels and bioavailability as primary end

point, considering separately men and women with asymptomatic hyperuricaemia are needed in order to establish if tea flavonols could be useful in these subjects.

Conflict-of-interest disclosure: All authors declare that they have no conflicts of financial and commercial interest.

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Table 1. RCT included in the meta-analyses

Reference	Subjects	Treatment (duration)	Baseline UA (reported effect)	Bias (Score range 0 - 1)
Bahorun 2010	CVD n= 232, W 41% D 12% BMI n.r., Y 25-60	600ml BT (12 weeks)	(a) 4.4 mg/dl M (↔) (b) 6.1 mg/dl M (↔) (c) 8.4 mg/dl M (↓) (d) 3.4 mg/dl W (↔) (e) 5.1 mg/dl W (↔) (f) 6.7 mg/dl W (↓)	No food antioxidant intake in subjects selection criteria, No wash out/run-in period, No double blinding. (0.8)
Hsu 2008	Obeses n= 100, W 100% D 22% BMI >26 Y 16-60	1.2g GTE (12 weeks)	5.7 mg/dl W (↔)	No dietary record, No food antioxidant intake in subjects selection criteria, No wash out/run-in period. (0.79)
Hsu 2011	T2D n= 68, W 65%	1.5g GTE (16 weeks)	5.6 mg/dl M/W (↔)	No baseline comparability, No dietary record,

	D 15% BMI >26 Y 20-65			No food antioxidant intake in subjects selection criteria, No wash out/run-in period. (0.49)
Princen 1998	Smokers n= 64, W 50% D 8% BMI < 28 Y 22-46	3.6 g GTE 900 ml BT 900 ml GT (4 weeks)	4.5 mg/dl M/W (↔) 4.4 mg/dl M/W (↔) 4.4 mg/dl M/W (↔)	No double blinding, Supported by Unilever Research, Products provided by T.J. Lipton. (0.86)
van het Hof 1997	Healthy n=45, W 46% D 4% BMI < 26 Y 37-52	900ml BT 900ml GT (4 weeks)	4.9 mg/dl M/W (↔) 4.8 mg/dl M/W (↔)	No double blinding. (0.9)

UA, uric acid; n, number of subjects (M: men, W: women); D: dropout (when not reported it has been calculated confronting the numbers in methods and in results); BMI: Body Mass Index (kg/m^2); Y: years; CVD: Cardiovascular Disease; T2D: Type 2 Diabetes; BT: Black Tea; GT: Green Tea; GTE: Green Tea Extract. ↔, no change; ↓, decrease. n.r, not reported.

Table 2. Combined Effect Estimate on UA of studies sub-grouped for treatment and baseline levels.

	Studies/intervention (subjects)	Fixed effect MD (95%CI) p (I^2%)	Random effect MD (95%CI) p (τ^2)	Quality effect MD (95%CI) p (Q%)
BT	3/8 (266)	0.1186 (-0.0765 to 0.3136)	0.1186 (-0.0765 to 0.3136)	0.1246 (-0.1056 to 0.3550)
		0.2337 (0%)	0.2337 (0)	0.2484 (15%)
GT/GTE	4/5 (206)	0.0351 (-0.1730 to 0.2433)	0.0351 (-0.1730 to 0.2433)	0.0340 (-0.2131 to 0.2810)
		0.2433 (0%)	0.2433 (0)	0.7688 (15%)
Baseline UA under cut off	3/8 (224)	0.1078 (-0.0528 to 0.2684)	0.1078 (-0.0528 to 0.2684)	0.1078 (0.0771 to 0.2926)
		0.1884 (0%)	0.1884 (0)	0.2188 (12%)
Baseline UA over cut off	3/5 (248)	-0.0239 (0.3311 to 0.2833)	-0.0239 (0.3311 to 0.2833)	-0.0262 (-0.4416 to 0.3892)
		0.8788 (0%)	0.8788 (0)	0.885 (25%)

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Diseases or risk factors	4/11 (427)	0.0602 (-0.1333 to 0.2537) 0.5419 (0%)	0.0602 (-0.1333 to 0.2537) 0.5419 (0%)	0.0634 (-0.1793 to 0.3062) 0.5648 (20%)

MD: mean difference, CI 95%: confidence intervals 95%. Cut off limits for UA baseline levels of 4.5 mg/dl for women, 6.1 mg/dl for men and 5.5 mg/dl for studies involving mixed populations.

Figure legends

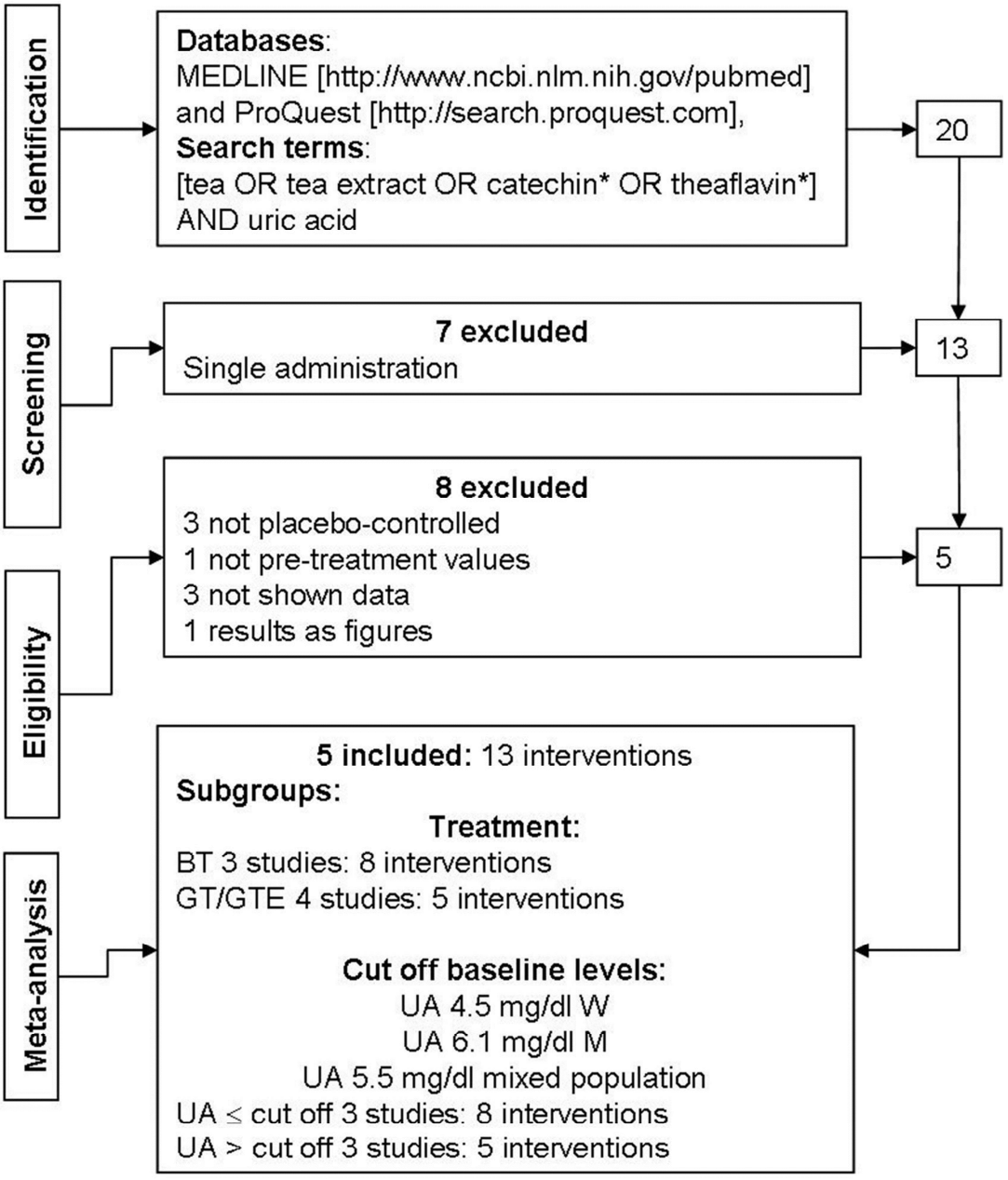
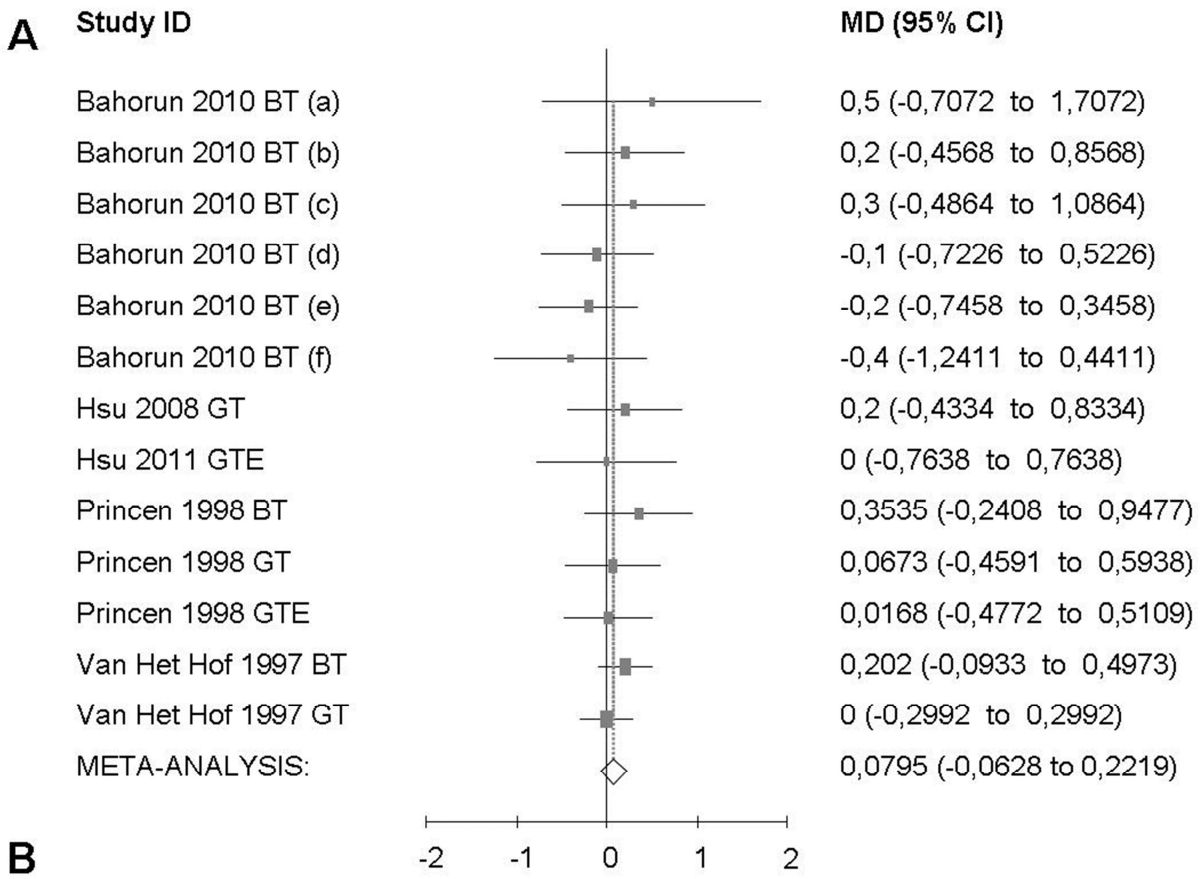


Figure 1. Four-phase flow diagram of systematic review and meta-analysis.



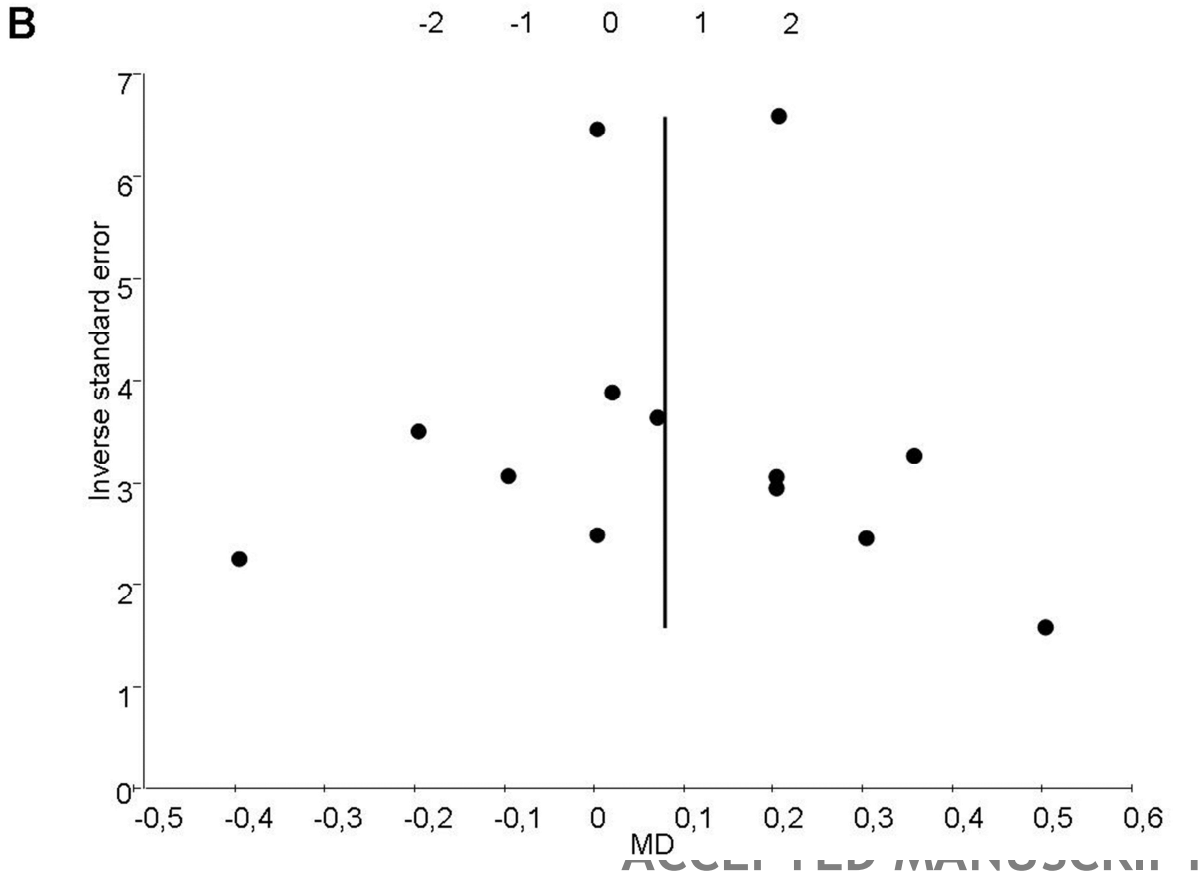


Figure 2. Forest Plot of Fixed Effects estimate after black tea (BT), green tea (GT) and green tea extract (GTE) intervention (A). MD: mean difference. CI 95%: confidence intervals 95%. Trim-and-fill funnel plot (B). The black circles represent actual identified studies. MD, mean difference.

