Effect of sour tea (*Hibiscus sabdariffa* L.) on arterial hypertension: a systematic review and meta-analysis of randomized controlled trials

Corina Serban[a,*], Amirhossein Sahebkar[b,c,*], Sorin Ursoniu[d], Florina Andrica[e], and Maciej Banach[f]

Background: *Hibiscus sabdariffa* L. is a tropical wild plant rich in organic acids, polyphenols, anthocyanins, polysaccharides, and volatile constituents that are beneficial for the cardiovascular system. *Hibiscus sabdariffa* beverages are commonly consumed to treat arterial hypertension, yet the evidence from randomized controlled trials (RCTs) has not been fully conclusive. Therefore, we aimed to assess the potential antihypertensive effects of *H. sabdariffa* through systematic review of literature and meta-analysis of available RCTs.

Methods: The search included PUBMED, Cochrane Library, Scopus, and EMBASE (up to July 2014) to identify RCTs investigating the efficacy of *H. sabdariffa* supplementation on SBP and DBP values. Two independent reviewers extracted data on the study characteristics, methods, and outcomes. Quantitative data synthesis and meta-regression were performed using a fixed-effect model, and sensitivity analysis using leave-one-out method. Five RCTs (comprising seven treatment arms) were selected for the meta-analysis. In total, 390 participants were randomized, of whom 225 were allocated to the *H. sabdariffa* supplementation group and 165 to the control group in the selected studies.

Results: Fixed-effect meta-regression indicated a significant effect of *H. sabdariffa* supplementation in lowering both SBP (weighed mean difference −7.58 mmHg, 95% confidence interval −9.69 to −5.46, $P < 0.00001$) and DBP (weighed mean difference −3.53 mmHg, 95% confidence interval −5.16 to −1.89, $P < 0.0001$). These effects were inversely associated with baseline BP values, and were robust in sensitivity analyses.

Conclusion: This meta-analysis of RCTs showed a significant effect of *H. sabdariffa* in lowering both SBP and DBP. Further well designed trials are necessary to validate these results.

Keywords: antioxidants, arterial hypertension, flavonoids, *Hibiscus sabdariffa* L., polyphenols

Abbreviations: ACE, angiotensin-converting enzyme; CI, confidence interval; CMA, comprehensive meta-analysis; NOS, nitric oxide synthase; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis; RCTs, randomized controlled trials; WMD, weighed mean difference

INTRODUCTION

Considering the high prevalence of hypertension, its control, therapy, complications, and the side effects of drugs used for its treatment [1,2], the natural compounds rich in phytochemicals should be always considered as an attractive alternative for control and prevention of this disease [3].

There are more than 300 species of *Hibiscus* around the world. One of them is *Hibiscus sabdariffa* Linn. – a member of the Malvaceae family – commonly used due to its cardioprotective properties in experimental and clinical studies [4–7]. *Hibiscus sabdariffa* is used in many countries as a food, cold and hot beverages, wine, jam, and ice cream, chocolates, as a flavoring agent in the food industry, and as a medicinal herb [8]. *Hibiscus sabdariffa* beverages are also known as *Hibiscus* tea, bissap, roselle, red sorrel, agua de Jamaica, Lo-Shen, Sudan tea, sour tea, or karkade [9], and are widely used to treat hypertension, atherosclerosis [10], obesity, inflammation [11], pyrexia, and liver disorders [12]. The main constituents of *H. sabdariffa* are organic acids such as citric acid, hydroxycitric acid, *Hibiscus* acid, malic and tartaric acids, oxalic and ascorbic acid; anthocyanins such as delphinidin-3-sambubioside (hibiscin), cyanidin-3-sambubioside (gossypicyanin), cyanidin-3,5-diglucoside, and delphinidin (anthocyanidin); polysaccharides such as arabinose, galactose, glucose, and rhamnose; and smaller amounts of galacturonic acid, glucuronic acid, manose, and xylose; and flavonoids such as hibiscitrin (hibiscetin-

Journal of Hypertension 2015, 33:1119–1127

[a]Department of Functional Sciences, Discipline of Pathophysiology, 'Victor Babes' University of Medicine and Pharmacy, Timisoara, Romania, [b]Biotechnology Research Center, Mashhad University of Medical Sciences, Mashhad, Iran, [c]Metabolic Research Centre, Royal Perth Hospital, School of Medicine and Pharmacology, University of Western Australia, Perth, Australia, [d]Department of Functional Sciences, Discipline of Public Health, [e]Faculty of Pharmacy, Discipline of Pharmaceutical Chemistry 'Victor Babes' University of Medicine and Pharmacy, Timisoara, Romania and [f]Department of Hypertension, Chair of Nephrology and Hypertension, Medical University of Lodz, Poland

Correspondence to Professor Maciej Banach, MD, PhD, FNLA, FAHA, FESC, FASA, Head, Department of Hypertension, WAM University Hospital in Lodz, Medical University of Lodz, Zeromskiego 113, 90-549 Lodz, Poland. Tel: +48 42 639 37 71; fax: +48 42 639 37 71; e-mail: maciejbanach@aol.co.uk

*Drs Corina Serban and Amirhossein Sahebkar contributed equally to the writing of this article.

Received 27 August 2014 **Revised** 4 March 2015 **Accepted** 4 March 2015

DOI:10.1097/HJH.0000000000000585

3-glucoside), sabdaritrin, gossypitrin, gossytrin, and other gossypetin glucosides, quercetin and luteolin [13]. Since *H. sabdariffa* is an aromatic plant, it also contains volatile constituents as described elsewhere [14].

Among the medicinal properties of *H. sabdariffa*, reduction of blood pressure (BP) has been the most widely investigated [15–17]. Different studies have compared the efficacy of *H. sabdariffa* to some antihypertensive drugs. As for example, the standardized extract of *H. sabdariffa* (containing 9.6 mg total anthocyanins) was compared with captopril 50 mg/day, and the results revealed comparable hypotensive effect, and tolerability in hypertensive patients [15]. In another study, dried extract of *H. sabdariffa* calyxes containing 250 mg total anthocyanins was compared to 10 mg of lisinopril [16]. The exerted antihypertensive effects with a wide margin of tolerability and safety in patients with stage I or II of hypertension were observed, though the efficacy was lower than for lisinopril [16]. *Hibiscus sabdariffa* has also diuretic capacity owing to its antioxidant properties and high potassium content, causing BP reduction that is comparable with that of furosemide [18].

Many experimental and clinical studies have evaluated *H. sabdariffa* efficiency as a medication for arterial hypertension therapy based on the ethnomedicinal, pharmacological, and phytochemical properties [9,15,18,19]. However, the results of these studies were based on relatively small sample sizes, and are not fully conclusive. Therefore, the precise effect of *H. sabdariffa* supplementation has not been still established. The purpose of this meta-analysis was to investigate the impact of *H. sabdariffa* supplementation on SBP and DBP. As far as we are aware, this is the first systematic review and meta-analysis on this topic.

METHODS

Data sources

The present study was designed in conformity to the guidelines of the 2009 Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement [20]. Our literature search included MEDLINE, Cochrane Library, Scopus, and EMBASE databases, and was limited to randomized controlled trials (RCTs) investigating the efficacy of sour tea (*H. sabdariffa*) supplementation on arterial hypertension that were published up to 1 July 2014. The references in all retrieved articles were searched for additional relevant publications. Each search strategy included keywords related to *H. sabdariffa* and search terms of interest, including systolic or diastolic arterial hypertension. Two reviewers (C.S. and S.U.) assessed each article independently to diminish the probability of duplication, analyzing reviews, case studies, and uncontrolled trials. Disagreements were resolved by consensus and discussion with a third party (M.B.). Studies were excluded if they were uncontrolled or their results did not consider the main goals of the analysis.

Study selection

Inclusion criteria

Study design had to meet the following criteria: randomized, placebo-controlled parallel or cross-over trial; population enrolled: adults at least 18 years; SBP and DBP data at baseline and after consumption of *H. sabdariffa* preparations were available.

Exclusion criteria

Studies were excluded under the following conditions: compared sour tea with different drugs; no numerical values were provided regarding SBP and/or DBP at baseline or study end; the study did not include a control group; and ongoing trials.

Quality assessment

The quality of involved studies in this meta-analysis was evaluated using Jadad scale [21]. This scale includes randomization (0–2 points), blinding (0–2 points), and dropouts and withdrawals (0–1 point). The overall score of a study in accordance with this scale varies among 0–5, with greater scores as a measure of better quality [21].

Quantitative data synthesis

Meta-analysis was conducted using the Cochrane Program Review Manager Version 5.1 (Cochrane Collaboration, Oxford, UK). Since all studies used the same methods for the BP measurement, weighed unstandardized mean difference 95% confidence interval (CI) was used as a summary statistic. Mean difference in measurements was calculated as follows: (measure at end of follow-up in the treatment group — measure at baseline in the treatment group) — (measure at end of follow-up in the control group — measure at baseline in the control group). SDs of the mean difference were calculated using the following formula: SD = square root $(\text{SDpre-treatment})^2 + (\text{SDpost-treatment})^2 - (2R \times \text{SDpre-treatment} \times \text{SDpost-treatment})$, assuming a correlation coefficient (R) = 0.5 [22,23]. A fixed-effect model and the generic inverse variance method were used for quantitative data synthesis. Pooled effect size was expressed as unstandardized weighed mean difference (WMD) with 95% CI. In order to evaluate the influence of each study on the overall effect size, sensitivity analysis was conducted using the one-study remove (leave-one-out) approach [22,24]. The proportion of inconsistency across the included studies, which is not attributable to chance (heterogeneity), was quantified using Cochran Q test and I^2 indices [22,25]. In order to avoid double-counting of patients and consequent unit-of-analysis error in the trials with more than one treatment arm, the control group was evenly (when possible) divided into two sections. In case the values were only presented as graph, the software GetData Graph Digitizer 2.24 (http://getdata-graph-digitizer.com/) was applied to digitize and extract the data.

Meta-regression

Fixed-effect meta-regression was performed to assess the potential impact of baseline SBP and DBP values on the WMD calculated for each respective parameter [22,26]. Meta-regression analysis was performed using comprehensive meta-analysis (CMA) V2 software (Biostat, New Jersey, USA) [27].

Assessment of publication bias

Presence of publication bias was explored graphically using funnel plots of precision (1/standard error) by study effect

size (mean difference). Asymmetric funnel plots were further assessed for publication bias using Duval and Tweedie 'trim-and-fill' and 'fail-safe N' methods, as well as Begg's rank correlation and Egger's weighted regression tests [22,27]. All publication bias analyses were performed using CMA V_2 software (Biostat) [26].

RESULTS

A summary of the study selection process is shown in Fig. 1. The initial screening for potential relevance excluded articles whose titles and/or abstracts were clearly irrelevant. After removing the trials not assessing the effects of *H. sabdariffa* extracts on arterial hypertension, only seven RCTs met the inclusion criteria and the full texts were obtained. Two trials that compared *H. sabdariffa* with captopril and lisinopril were excluded from the final meta-analysis [15,16]. After assessment, five articles met the inclusion criteria and were selected for the final meta-analysis [3,4,9,28,29].

Description of studies

In total, 390 participants were randomized, of whom 225 were allocated to the *H. sabdariffa* supplementation group and 165 to the control group in the five selected studies [3,4,9,28,29]. The number of participants in these trials ranged from 53 to 124. Included studies were published between 1999 and 2013, and were conducted in the United States, Mexico and Iran (three studies). A range of doses from 3.75 g/day to two spoonfuls or 100 mg of aqueous *H. sabdariffa* extract were administered in the included trials. Duration of supplementation with sour tea ranged between 15 days and 6 weeks. All trials were designed as parallel-group studies. One trial [4] had three arms comparing *H. sabdariffa* extract powder vs. diet in healthy individuals, *H. sabdariffa* extract powder vs. diet in patients with metabolic syndrome, and *H. sabdariffa* extract powder + diet vs. diet in patients with metabolic syndrome. Demographic and baseline parameters of the included studies are shown in Table 1. *Hibiscus sabdariffa* was safe and well tolerated in all the RCTs included in this review, with no report of serious adverse events.

Quantitative data synthesis

As mentioned above, five studies met the inclusion criteria to be included in the meta-analysis. One of the trials [4] had three treatment arms; therefore, the final analyses were performed with seven treatment arms. Pooled estimates of effect size for the impact of sour tea on SBP (WMD −7.58 mmHg, 95% CI −9.69 to −5.46, $P < 0.00001$) and DBP (WMD −3.53 mmHg, 95% CI −5.16 to −1.89, $P < 0.0001$) were both significant. Forest plots detailing the meta-analysis of trials on SBP and DBP are presented on Figs. 2 and 3.

The strength of the estimated effect sizes for the impact of sour tea on SBP and DBP was robust in sensitivity analyses and did not significantly differ according to the characteristics of the original studies. The results of sensitivity analysis are shown in Tables 2 and 3.

Meta-regression

Meta-regression analysis was performed to evaluate the potential impact of SBP and DBP on the calculated net effects of sour tea supplementation on each respective parameter. Fixed-effect meta-regression indicated a significant inverse association between baseline SBP and SBP-lowering (slope −0.27, 95% CI −0.43 to −0.20, $P = 0.0005$), and baseline DBP and DBP-lowering (slope −0.27, 95% CI −0.44 to −0.10, $P = 0.002$) effects of *H. sabdariffa* supplementation. Meta-regression plots are presented in Figs. 4 and 5.

Risk of bias in included studies

Visual inspection of funnel plot asymmetry suggested potential publication bias for the effects of sour tea on

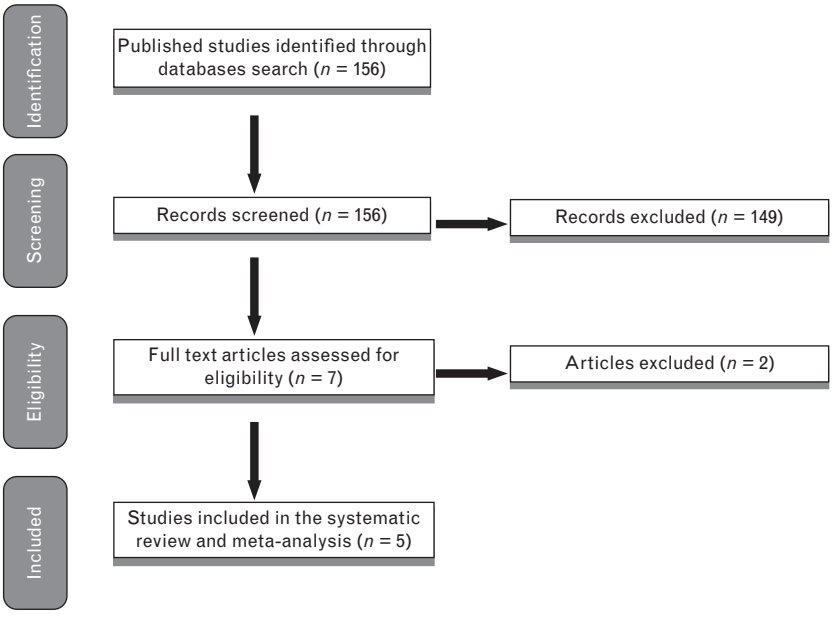

FIGURE 1 Flow diagram for study selection.

TABLE 1. Demographic characteristics of the included studies

		Haji Faraji and Haji Tarkhani [3]	Gurrola-Diaz *et al.* [4]			McKay *et al.* [9]	Mozaffari-Khosravi *et al.* [28]	Mozaffari-Khosravi *et al.* [29]
Year		1999	2010			2010	2009	2013
Jadad score		2	2			5	3	2
Location		Iran	Mexico			USA	Iran	Iran
Design		Randomized controlled parallel trial	Factorial, randomized follow-up study with 3 treatment arms			Randomized double-blind placebo-controlled parallel trial	Randomized double-blind placebo-controlled parallel trial	Randomized open-label placebo-controlled parallel trial
Duration of trial		15 days	4 weeks			6 weeks	4 weeks	4 weeks
Inclusion criteria		SBP of 160–180 mmHg and/or a DBP of 100–114 mmHg, use of two or fewer antihypertensive drugs, and absence of secondary hypertension and underlying diseases such as cardiovascular abnormalities, thyroid disease or diabetes	Volunteers of either sex with and without metabolic syndrome			Nonsmoking men and women, age 30–70 years, with SBP 120–150 mmHg, DBP ≤95 mmHg, and BMI of 18.5–35 kg/m^2, not taking BP-lowering medications	Type 2 diabetes mellitus for more than 5 years, showing mild hypertension according to JNC-VI criteria SBP [30]	Age range of 30–60 years with a 5-year history of diabetes; blood pressure of 120–139/80–89 mmHg, absence of nephropathy and other expressive symptoms, lack of use of insulin; absence of consumption of antioxidant complements, vitamins, minerals, and fish oil 6 months prior to intervention
Sour tea intervention		2 spoonfuls daily	100 mg of HS extract daily			3 bags (each containing 1.25 g HS) daily	2 bags (each containing 2 g HS) daily	3 bags (each containing 3 g HS) daily
Participants	Case	31	11[a]	18[b]	22[c]	35	27	46
	Control	23	27	26	20	30	26	48
Age (years)	Case	52.6±7.9	NS[a]	NS[b]	NS[c]	54.2±10.6	55.37±8.6	6±52.1[d]
	Control	51.5±10.2	NS	NS	NS	54.3±11.3	50.42±8.56	6.7±52.2[d]
Male (%)	Case	NS	NS[a]	NS[b]	NS[c]	57.1	22.2	19.6
	Control	NS	NS	NS	NS	56.7	7.7	25
BMI (kg/m^2)	Case	NS	NS[a]	NS[b]	NS[c]	27.4±3.7	28.28 ± 3.8	3.8 ± 28.3[d]
	Control	NS	NS	NS	NS	28.3 ± 3.8	28.35 ± 4.8	5.6 ± 28[d]
SBP (mmHg)	Case	NS	122.8 ± 7.6[a]	131.0 ± 11.6[b]	136.4 ± 11.4[c]	129.4 ± 4.8	134.4 ± 11.8	123.1 ± 15.5
	Control	NS	119.8 ± 11.2	121.6 ± 12.1	112.8 ± 12.1	129.8 ± 6.9	118.6 ± 14.9	119.4 ± 15.1
DBP (mmHg)	Case	NS	74.2 ± 4.6[a]	83.8 ± 9.3[b]	86.2 ± 11.3[c]	78.9 ± 7.7	80.2 ± 6.1	79.4 ± 11.1
	Control	NS	76.3 ± 11.3	77.57 ± .9	81.0 ± 9.0	79.6 ± 5.5	76.7 ± 7.6	78.9 ± 8.3

Values are expressed as mean ± SD or median (min–max) unless otherwise stated. HS, *Hibiscus sabdariffa*; NA, not applicable; NS, not stated.
[a]Denotes HS extract powder vs. diet in healthy individuals.
[b]Denotes HS extract powder vs. diet in patients with metabolic syndrome.
[c]Denotes HS extract powder + diet vs. diet in patients with metabolic syndrome.
[d]Mean and SD of the difference.

SBP (Fig. 6). The 'trim-and-fill' method imputed two theoretically missing studies, leading to an imputed effect size (WMD −9.48 mmHg, 95% CI −11.54 to −7.43) that was larger but not statistically significant from the initial estimate. The 'fail-safe N' test showed that 50 theoretically missing studies would be needed to add to the analysis of the effect of sour tea on SBP in order to yield a statistically nonsignificant overall effect. Consistently, Begg's rank correlation test (Kendall's Tau with continuity correction = 0.48, Z value = 1.50, two-tailed P value = 0.13) and Egger's linear regression test (intercept = 6.39, 95% CI −3.43 to 16.20, t value = 1.67, DF = 5.00, two-tailed P = 0.16) suggested no evidence of publication bias. The funnel plot for the impact of sour tea on DBP was not asymmetric (Fig. 7). The 'trim-and-fill' method did not impute any study, and the 'fail-safe N' test suggested a need to add 20 theoretically missing studies in order to yield a statistically nonsignificant overall effect. Likewise, there was no evidence of publication bias

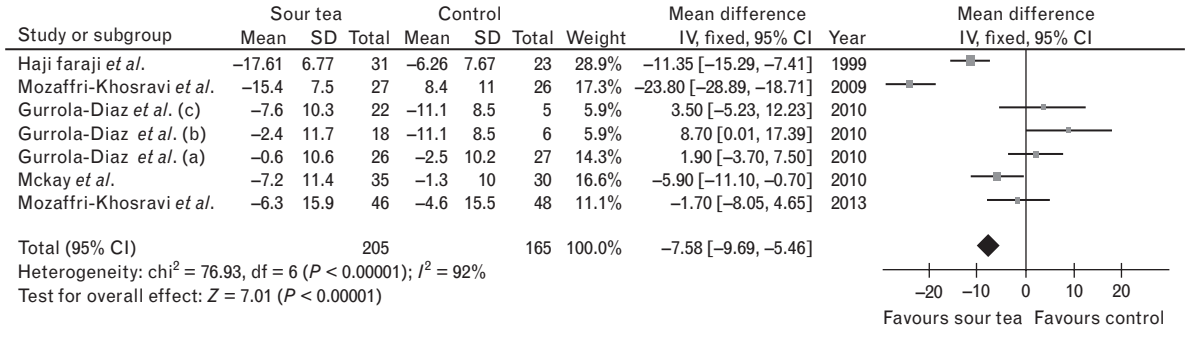

FIGURE 2 Forest plot detailing weighted mean difference and 95% CI for the impact of sour tea supplementation on SBP. Gurrola-Diaz *et al.* [4] (a) Sour tea vs. diet in healthy individuals; (b): sour tea vs. diet in patients with metabolic syndrome; (c) sour tea + diet vs. diet in patients with metabolic syndrome. CI, confidence interval.

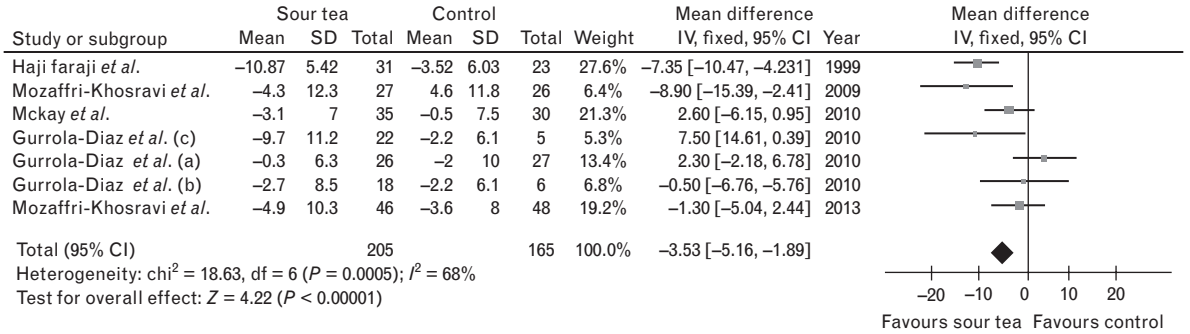

FIGURE 3 Forest plot detailing weighted mean difference and 95% CI for the impact of sour tea supplementation on DBP. Gurrola-Diaz *et al.* [4] (a) sour tea vs. diet in healthy individuals; (b) sour tea vs. diet in patients with metabolic syndrome; (c) sour tea + diet vs. diet in patients with metabolic syndrome. CI, confidence interval.

according to the results of Begg's rank correlation test (Kendall's Tau with continuity correction = 0.10, Z value = 0.30, two-tailed P value = 0.76) and Egger's linear regression (intercept = 0.18, 95% CI −5.07 to 5.44, t value = 0.09, DF = 5.00, two-tailed P = 0.93) test.

DISCUSSION

In this systematic review and meta-analysis, we summarized published evidence from five RCTs (comprising seven treatment arms) that investigated the effects of supplementation with *H. sabdariffa* in SBP and DBP-lowering. The results indicated a significant antihypertensive effect of sour tea supplementation on both SBP and DBP.

The exact mechanisms responsible for these effects of *H. sabdariffa* are not completely understood. An experimental study [31] investigated the effect of the water extract of the dried calyx of *H. sabdariffa* and anthocyanins on the left ventricular myocardial capillary length and surface area in spontaneously hypertensive rats. The extract significantly reduced SBP and left ventricular mass in a dose-dependent fashion, and increased surface area and length density of the myocardial capillaries [31]. The inhibition of calcium (Ca^{2+})-influx into vascular smooth muscle cells and the vasodilator effect mediated through the endothelium-derived nitric oxide-cyclic guanosine monophosphate (cGMP)-relaxant pathway could be responsible for the antihypertensive effect of *H. sabdariffa* in the isolated aortic rings of hypertensive rats [32]. Polyphenols from *H. sabdariffa* crude extracts induced an endothelium-dependent relaxant effect via stimulation of nitric oxide synthase (NOS) enzyme by phosphatidylinositol-3-kinase/protein kinase B pathway in the isolated thoracic aorta of rats [32]. The nonendothelium-dependent relaxation was a direct smooth muscle activation resulting from activation of smooth muscle potassium channels [33]. Furthermore, aqueous *H. sabdariffa* extract containing delphinidin-3-O-sambubioside and cyanidin-3-O-sambubioside anthocyanins inhibited the angiotensin-converting enzyme (ACE) activity, causing an additional antihypertensive effect [34]. Histopathological examinations also showed that *H. sabdariffa* extract reduces foam cell formation and inhibits smooth muscle cell migration and calcification in the blood vessel of rabbits [12]. The hypotensive activity of *H. sabdariffa* may be also outlined by a decrease of blood viscosity via the inhibitory activity of cyclooxygenase [35], and inhibition of the differentiation of adipocytes via the modulation of phosphoinositide-3-kinase–protein kinase B/*Akt* (PI3-K/Akt) and extracellular-signal-regulated kinase (ERK) pathway [11].

Analyzing all flavonoids that may be founded in *H. sabdariffa* extracts, quercetin has been shown to be the most powerful antihypertensive agent in different experimental and clinical studies [36,37]. The potential responsible mechanisms underlying the antihypertensive effect of quercetin are vasodilation, reactive oxygen species

TABLE 2. Leave-one-out sensitivity analysis of the effect of sour tea supplementation on SBP

Study	Ref.	Quantitative data synthesis: Sour tea group (*n*)	Control group (*n*)	Effect size	95% CI	*Z* value	*P* value	Heterogeneity analysis: *Q*	DF (*Q*)	I^2
Overall effect		205	165	−7.58	−9.69 to −5.46	7.01	<0.00001	76.93	6	92%
Leave-one-out sensitivity analysis										
Gurrola-Diaz *et al.*	[4][a]	179	138	−9.15	−11.44 to −6.87	7.85	<0.00001	64.12	5	92%
Gurrola-Diaz *et al.*	[4][b]	187	159	−8.60	−10.79 to −6.42	7.72	<0.00001	62.60	5	92%
Gurrola-Diaz *et al.*	[4][c]	183	160	−8.27	−10.45 to −6.09	7.43	<0.00001	70.37	5	93%
Haji Faraji and Haji Tarkhani	[3]	174	142	−6.04	−8.55 to −3.53	4.72	<0.00001	71.97	5	93%
McKay *et al.*	[9]	170	135	−7.91	−10.23 to −5.59	6.69	<0.00001	76.45	5	93%
Mozaffari-Khosravi *et al.*	[28]	159	117	−8.31	−10.56 to −6.07	7.25	<0.00001	73.23	5	93%
Mozaffari-Khosravi *et al.*	[29]	178	139	−4.18	−6.51 to −1.85	3.52	<0.0004	29.68	5	83%

CI, confidence interval; DF, degrees of freedom.
[a]Sour tea vs. diet in healthy individuals.
[b]Sour tea vs. diet in patients with metabolic syndrome.
[c]Sour tea + diet vs. diet in patients with metabolic syndrome.

TABLE 3. Leave-one-out sensitivity analysis of the effect of sour tea supplementation on DBP

Study	Ref.	Quantitative data synthesis						Heterogeneity analysis		
		Sour tea group (*n*)	Control group (*n*)	Effect size	95% CI	*Z* value	*P* value	*Q*	DF (*Q*)	I^2
Overall effect		205	165	−3.53	−5.16 to −1.89	4.22	<0.0001	18.63	6	68%
Leave-one-out sensitivity analysis										
Gurrola-Diaz *et al.*	[4][a]	179	138	−4.42	−6.18 to −2.66	4.93	<0.00001	11.14	5	55%
Gurrola-Diaz *et al.*	[4][b]	187	159	−3.75	−5.45 to −2.05	4.33	<0.0001	17.67	5	72%
Gurrola-Diaz *et al.*	[4][c]	183	160	−3.30	−4.99 to −1.62	3.85	0.0001	17.36	5	71%
Haji Faraji and Haji Tarkhani	[3]	174	142	−2.07	−3.99 to −0.14	2.10	0.04	10.64	5	53%
McKay *et al.*	[9]	170	135	−3.78	−5.62 to −1.93	4.01	<0.0001	18.30	5	73%
Mozaffari-Khosravi *et al.*	[28]	159	117	−4.06	−5.88 to −2.23	4.36	<0.0001	16.94	5	70%
Mozaffari-Khosravi *et al.*	[29]	178	139	−3.16	−4.85 to −1.47	3.66	0.0003	15.82	5	68%

CI, confidence interval; DF, degrees of freedom.
[a]Sour tea vs. diet in healthy individuals.
[b]Sour tea vs. diet in patients with metabolic syndrome.
[c]Sour tea + diet vs. diet in patients with metabolic syndrome.

scavenger effect, inhibition of nicotinamide adenine dinucleotide phosphate-oxidase, modulator of the endothelial function, vascular smooth muscle cells [37]. It has been shown that quercetin generates a gradual, continued, and dose-dependent decrease in BP when it is offered chronically in generally all experimental models of hypertension, separately of the status of the nitric oxide, oxidative stress, or renin–angiotensin system [38,39]. It was showed that an increased dose of quercetin decreased BP in stage 1 hypertensive patients [40]. Another component of *H. sabdariffa* – the protocatechuic acid – inhibits the oxidation of low-density lipoprotein induced by either copper or a nitric acid donor [41]. Furthermore, cyanidin-3-sambubioside and delphinidin-3-sambubioside – known as competitor inhibitors of ACE activity – could be also responsible for the BP-lowering effect of *H. sabdariffa* [33,42].

In another meta-analysis, the authors included 4 RCTs and 390 patients, and evaluated the efficiency and safety of *H. sabdariffa* in primary hypertensive patients [43]. *Hibiscus sabdariffa* decreased BP higher than black tea, but not as much as ACE inhibitors. However, the short-term and not enough quality of evaluated RCTs did not offer enough proofs to indicate *H. sabdariffa* for the treatment of primary BP [43].

Several experimental and clinical studies have shown that oxidative stress plays an important role in arterial hypertension by adversely affecting vascular endothelial and smooth muscle cell functions [44,45]. The ability of *H. sabdariffa* to decrease global oxidative stress is an important mechanism by which this natural product exerts its beneficial effects against arterial hypertension [46–48]. *Hibiscus sabdariffa* is rich in polyphenolic antioxidants, and polyphenols are known to improve endothelial function and decrease BP through regulating nitric oxide bioavailability [49]. Moreover, polyphenols and hibiscus acid from *H. sabdariffa* calyxes have been suggested as phytochemicals responsible for the antihypertensive effects of this plant [19].

In experimental studies, aqueous extracts of *H. sabdariffa* calyxes and petals at doses ranging from 1 to 1000 mg/kg/day were effective in decreasing BP [17,50]. There has been no evidence of hepatic or renal toxicity due to *H. sabdariffa* extract consumption, except for possible adverse hepatic effects at high doses of 300 mg/kg per day of *H. sabdariffa* over a 3-month period [19,51]. However, caution should be exercised in concomitant ingestion of *H. sabdariffa* along with antihypertensive drugs. An experimental study revealed a possible herb–drug interaction between hydrochlorothiazide (10 mg/kg) and *H. sabdariffa* extract (20–40 mg/kg). Administration of both the extract and the drug produced a significant increase in the volume of urine excreted and decreased the concentrations of sodium, bicarbonate, chloride ions, and pH of urine [52].

Positive results of this meta-analysis support multifaceted and likely synergistic mechanisms that could be

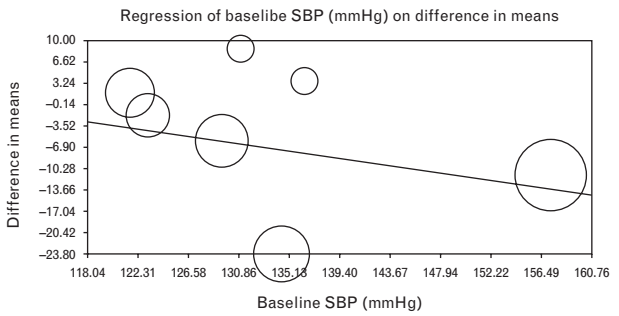

FIGURE 4 Fixed-effect meta-regression analysis of the impact of baseline values on net change in SBP. The size of each circle is inversely proportional to the variance of change.

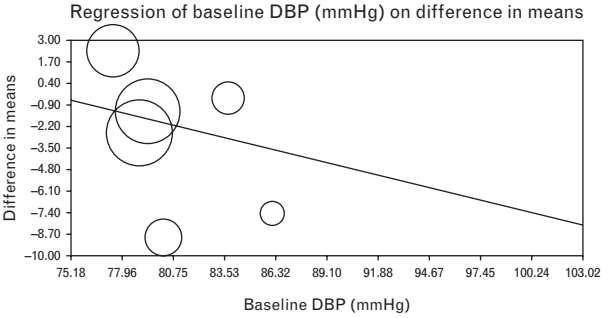

FIGURE 5 Fixed-effect meta-regression analysis of the impact of baseline values on net change in DBP. The size of each circle is inversely proportional to the variance of change.

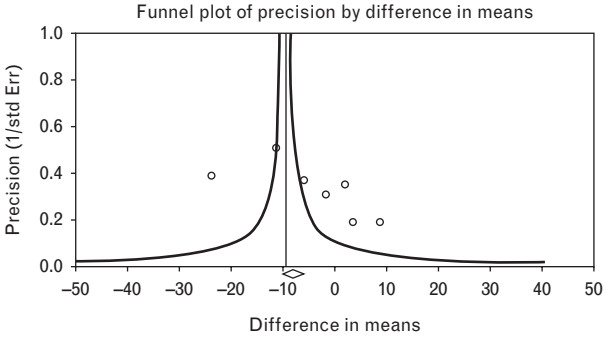

FIGURE 6 Funnel plots detailing publication bias in the studies reporting the impact of *Hibiscus sabdariffa* supplementation on SBP. Open circles represent observed published studies; closed circles represent imputed unpublished studies.

responsible for the hypotensive action of polyphenol-rich *H. sabdariffa*, and provide further evidence to the traditional use of the plant as a potential antihypertensive agent. The inverse association between baseline BP and magnitude of reduction in BP associated with daily sour tea consumption might have a particular implication for the management of high optimal BP (prehypertension) – a condition with increasing global prevalence that might predispose to hypertension incidence and related cardiovascular outcomes [53,54]. The public health effects of daily consumption of *H. sabdariffa* could be crucial, since a small decrease in population-wide BP can be related to the prevention of progression of high optimal BP (prehypertension) to overt hypertension, of considerable decrease of cardiovascular risk in hypertensive patients [53,54]. Furthermore, a reduction of 7.6/3.5 mmHg might have important cardiovascular implications since the results of Heart Outcome Evaluation study demonstrated that a 3.3/1.4 mmHg reduction was associated with a 22% decrease of relative risk of myocardial infarction, stroke, and cardiovascular mortality [55].

Drugs are obviously the primary treatment for hypertension, but the adherence to drug regimens is essentially decreased (∼50%) [56]. Poor adherence to antihypertensive drugs and side effects of them could be significant factors contributing to uncontrolled BP [56]. Therefore, *H. sabdariffa* might be utilized as a possible new effective and safe supplementary option to better prevent and control hypertension.

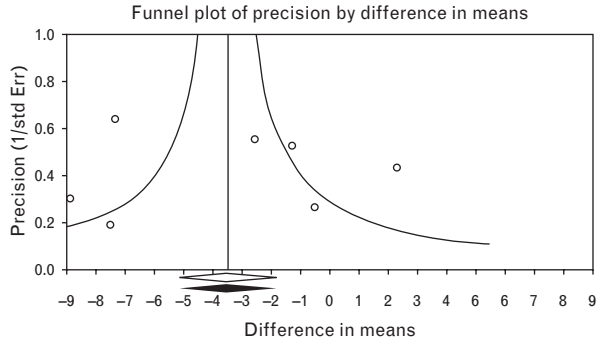

FIGURE 7 Funnel plots detailing publication bias in the studies reporting the impact of *Hibiscus sabdariffa* supplementation on DBP. Open circles represent observed published studies; closed circles represent imputed unpublished studies.

Limitations of the study

The present meta-analysis had several limitations. Most importantly, eligible RCTs involved in this meta-analysis had small populations. It should be also noticed that the control groups differed in the studies included in this meta-analysis; some patients were given black tea [3,28], and others diet [4], green tea [29], and placebo [9]. Furthermore, different effects were observed in the different study populations. The BP-lowering effect was −9.15 mmHg for SBP and −4.42 mmHg for DBP in healthy individuals [4]. SBP was reduced by 5.5% and DBP by 4.0% in prehyrpentensive and mildly hypertensive adults [9]; and by 15.4 and 4.3% in SBP and DBP, respectively, in prehypertension and stage I hypertensive patients [28]. Small numbers of participants was the reason that no additional analyses in the given subgroups were possible to perform. Furthermore, the studies included in this meta-analysis had short durations of follow-up.

Many attributes that differ within studies might be the causes of between-study heterogeneity, such as the year of publication, the type of study, the diagnosis criteria, and conditions of preparation of *H. sabdariffa* (infusion, decoctions, and extraction), the sample size, control group or quality. We used 'leave-one-out' sensitivity analysis under a conservative random-effects model to assess the possibility of some bias such as unclear double-randomization or large unbalanced dropout. Our results clearly indicate that the significance of estimated pooled effect size is not biased by any single study.

In conclusion, the findings of the present meta-analysis, being the first of its kind, confirm the potential effectiveness of supplementation with sour tea in reducing both SBP and DBP. These findings favor the traditional use of this natural, safe, and inexpensive supplement in patients with essential hypertension. However, further large-scale, well designed trials are needed, particularly those in which changes in SBP and DBP are the main outcomes, in order to finally confirm the place of *H. sabdariffa* as an alternative natural treatment for the hypertension management in routine clinical practice. Finally, potential interactions between *H. sabdariffa* supplements and antihypertensive medications, as well as the optimal dose of *H. sabdariffa*, must be still identified in order to optimize combination therapy.

ACKNOWLEDGEMENTS

Funding: This meta-analysis was written independently; no company or institution supported it financially. No professional writer was involved in the preparation of this meta-analysis.

Conflicts of interest

The authors have no relevant interests to declare.

REFERENCES

1. Bielecka-Dabrowa A, Aronow WS, Rysz J, Banach M. The rise and fall of hypertension: lessons learned from Eastern Europe. *Curr Cardiovasc Risk Rep* 2011; 5:174–179.
2. Gluba A, Bielecka-Dabrowa A, Mikhailidis DP, Wong ND, Franklin SS, Rysz J, *et al*. An update on biomarkers of heart failure in hypertensive patients. *J Hypertens* 2012; 30:1681–1689.

3. Haji Faraji M, Haji Tarkhani A. The effect of sour tea (*Hibiscus sabdariffa*) on essential hypertension. *J Ethnopharmacol* 1999; 65:231–236.
4. Gurrola-Diaz CM, Garcia-Lopez PM, Sanchez-Enriquez S, Troyo-Sanroman R, Andrade-Gonzalez I, Gomez-Leyva JF. Effects of *Hibiscus sabdariffa* extract powder and preventive treatment (diet) on the lipid profiles of patients with metabolic syndrome (MeSy). *Phytomedicine* 2010; 17:500–505.
5. Aziz Z, Wong SY, Chong NJ. Effects of *Hibiscus sabdariffa* L. on serum lipids: a systematic review and meta-analysis. *J Ethnopharmacol* 2013; 150:442–450.
6. Chang HC, Peng CH, Yeh DM, Kao ES, Wang CJ. *Hibiscus sabdariffa* extract inhibits obesity and fat accumulation, and improves liver steatosis in humans. *Food Function* 2014; 5:734–739.
7. Joven J, March I, Espinel E, Fernandez-Arroyo S, Rodriguez-Gallego E, Aragones G, *et al*. *Hibiscus sabdariffa* extract lowers blood pressure and improves endothelial function. *Mol Nutr Food Res* 2014; 58:1374–1378.
8. Wahabi HA, Alansary LA, Al-Sabban AH, Glasziuo P. The effectiveness of *Hibiscus sabdariffa* in the treatment of hypertension: a systematic review. *Phytomedicine* 2010; 17:83–86.
9. McKay DL, Chen CY, Saltzman E, Blumberg JB. *Hibiscus sabdariffa* L. tea (tisane) lowers blood pressure in prehypertensive and mildly hypertensive adults. *J Nutr* 2010; 140:298–303.
10. Guardiola S, Mach N. Therapeutic potential of *Hibiscus sabdariffa*: a review of the scientific evidence. *Endocrinologia y nutricion* 2014; 61:274–295.
11. Kim JK, So H, Youn MJ, Kim HJ, Kim Y, Park C, *et al*. *Hibiscus sabdariffa* L. water extract inhibits the adipocyte differentiation through the PI3-K and MAPK pathway. *J Ethnopharmacol* 2007; 114:260–267.
12. Chen CC, Hsu JD, Wang SF, Chiang HC, Yang MY, Kao ES, *et al*. *Hibiscus sabdariffa* extract inhibits the development of atherosclerosis in cholesterol-fed rabbits. *J Agric Food Chem* 2003; 51:5472–5477.
13. Sindi HA, Marshall LJ, Morgan MR. Comparative chemical and biochemical analysis of extracts of *Hibiscus sabdariffa*. *Food Chem* 2014; 164C:23–29.
14. Patel S. *Hibiscus sabdariffa*: an ideal yet under-exploited candidate for nutraceutical applications. *Biomed Prevent Nutr* 2014; 4:23–27.
15. Herrera-Arellano A, Flores-Romero S, Chavez-Soto MA, Tortoriello J. Effectiveness and tolerability of a standardized extract from *Hibiscus sabdariffa* in patients with mild to moderate hypertension: a controlled and randomized clinical trial. *Phytomedicine* 2004; 11:375–382.
16. Herrera-Arellano A, Miranda-Sanchez J, Avila-Castro P, Herrera-Alvarez S, Jimenez-Ferrer JE, Zamilpa A, *et al*. Clinical effects produced by a standardized herbal medicinal product of *Hibiscus sabdariffa* on patients with hypertension. A randomized, double-blind, lisinopril-controlled clinical trial. *Planta Medica* 2007; 73:6–12.
17. Mojiminiyi FB, Dikko M, Muhammad BY, Ojobor PD, Ajagbonna OP, Okolo RU, *et al*. Antihypertensive effect of an aqueous extract of the calyx of *Hibiscus sabdariffa*. *Fitoterapia* 2007; 78:292–297.
18. Mojiminiyi FB, Audu Z, Etuk EU, Ajagbonna OP. Attenuation of salt-induced hypertension by aqueous calyx extract of *Hibiscus sabdariffa*. *Nigerian J Physiol Sci* 2012; 27:195–200.
19. Hopkins AL, Lamm MG, Funk JL, Ritenbaugh C. *Hibiscus sabdariffa* L. in the treatment of hypertension and hyperlipidemia: a comprehensive review of animal and human studies. *Fitoterapia* 2013; 85:84–94.
20. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Int J Surg* 2010; 8:336–341.
21. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, *et al*. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996; 17:1–12.
22. Higgins J, Thompson S, Deeks J, Altman D. Statistical heterogeneity in systematic reviews of clinical trials: a critical appraisal of guidelines and practice. *J Health Serv Res Policy* 2002; 7:51–61.
23. Sahebkar A. Are curcuminoids effective C-reactive protein-lowering agents in clinical practice? Evidence from a meta-analysis. *Phytother Res* 2014; 28:633–642.
24. Sahebkar A. Does PPARgamma2 gene Pro12Ala polymorphism affect nonalcoholic fatty liver disease risk? Evidence from a meta-analysis. *DNA Cell Biol* 2013; 32:188–198.
25. Sahebkar A. Effects of resveratrol supplementation on plasma lipids: a systematic review and meta-analysis of randomized controlled trials. *Nutr Rev* 2013; 71:822–835.
26. Borenstein M, Higgins JP. Meta-analysis and subgroups. *Prevent Sci* 2013; 14:134–143.
27. Bolanos Diaz R, Calderon Cahua M. Introduction to traditional meta-analysis. *Revista de gastroenterologia del Peru* 2014; 34:45–51.
28. Mozaffari-Khosravi H, Jalali-Khanabadi BA, Afkhami-Ardekani M, Fatehi F, Noori-Shadkam M. The effects of sour tea (*Hibiscus sabdariffa*) on hypertension in patients with type II diabetes. *J Human Hypertens* 2009; 23:48–54.
29. Mozaffari-Khosravi H, Ahadi Z, Barzegar K. The effect of green tea and sour tea on blood pressure of patients with type 2 diabetes: a randomized clinical trial. *J Diet Suppl* 2013; 10:105–115.
30. Anon. The sixth report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure. *Arch Intern Med* 1997; 157:2413–2446.
31. Inuwa I, Ali BH, Al-Lawati I, Beegam S, Ziada A, Blunden G. Long-term ingestion of *Hibiscus sabdariffa* calyx extract enhances myocardial capillarization in the spontaneously hypertensive rat. *Exp Biol Med* 2012; 237:563–569.
32. Ajay M, Chai HJ, Mustafa AM, Gilani AH, Mustafa MR. Mechanisms of the antihypertensive effect of *Hibiscus sabdariffa* L. calyces. *J Ethnopharmacol* 2007; 109:388–393.
33. Sarr M, Ngom S, Kane MO, Wele A, Diop D, Sarr B, *et al*. In vitro vasorelaxation mechanisms of bioactive compounds extracted from *Hibiscus sabdariffa* on rat thoracic aorta. *Nutr Metab* 2009; 6:45.
34. Ojeda D, Jimenez-Ferrer E, Zamilpa A, Herrera-Arellano A, Tortoriello J, Alvarez L. Inhibition of angiotensin converting enzyme (ACE) activity by the anthocyanins delphinidin- and cyanidin-3-O-sambubiosides from *Hibiscus sabdariffa*. *J Ethnopharmacol* 2010; 127:7–10.
35. Christian K, Nair M, Jackson J. Antioxidant and cyclooxygenase inhibitory activity of sorrel (*Hibiscus sabdariffa*). *J Food Compos Analysis* 2006; 19:778–783.
36. Mckay D. Can hibiscus tea lower blood pressure. *Agro Food Industry Hi-Tech* 2009; 20:40–42.
37. Perez-Vizcaino F, Duarte J, Jimenez R, Santos-Buelga C, Osuna A. Antihypertensive effects of the flavonoid quercetin. *Pharmacol Rep* 2009; 61:67–75.
38. Mackraj I, Govender T, Ramesar S. The antihypertensive effects of quercetin in a salt-sensitive model of hypertension. *J Cardiovasc Pharmacol* 2008; 51:239–245.
39. Duarte J, Pérez-Palencia R, Vargas F, Angeles Ocete M, Pérez-Vizcaino F, Zarzuelo A, *et al*. Antihypertensive effects of the flavonoid quercetin in spontaneously hypertensive rats. *Br J Pharmacol* 2001; 133:117–124.
40. Edwards RL, Lyon T, Litwin SE, Rabovsky A, Symons JD, Jalili T. Quercetin reduces blood pressure in hypertensive subjects. *J Nutr* 2007; 137:2405–2411.
41. Lee M-J, Chou F-P, Tseng T-H, Hsieh M-H, Lin M-C, Wang C-J. Hibiscus protocatechuic acid or esculetin can inhibit oxidative LDL induced by either copper ion or nitric oxide donor. *J Agric Food Chem* 2002; 50:2130–2136.
42. Larson AJ, Symons JD, Jalili T. Therapeutic potential of quercetin to decrease blood pressure: review of efficacy and mechanisms. *Adv Nutr* 2012; 3:39–46.
43. Wahabi H, Alansary L, Al-Sabban A, Glasziuo P. The effectiveness of *Hibiscus sabdariffa* in the treatment of hypertension: a systematic review. *Phytomedicine* 2010; 17:83–86.
44. Gonzalez J, Valls N, Brito R, Rodrigo R. Essential hypertension and oxidative stress: new insights. *World J Cardiol* 2014; 6:353–366.
45. Crowley SD. The cooperative roles of inflammation and oxidative stress in the pathogenesis of hypertension. *Antioxid Redox Signal* 2014; 20:102–120.
46. Frank T, Netzel G, Kammerer DR, Carle R, Kler A, Kriesl E, *et al*. Consumption of *Hibiscus sabdariffa* L. aqueous extract and its impact on systemic antioxidant potential in healthy subjects. *J Sci Food Agric* 2012; 92:2207–2218.
47. Fernandez-Arroyo S, Herranz-Lopez M, Beltran-Debon R, Borras-Linares I, Barrajon-Catalan E, Joven J, *et al*. Bioavailability study of a polyphenol-enriched extract from *Hibiscus sabdariffa* in rats and associated antioxidant status. *Mol Nutr Food Res* 2012; 56:1590–1595.
48. Ajiboye TO, Salawu NA, Yakubu MT, Oladiji AT, Akanji MA, Okogun JI. Antioxidant and drug detoxification potentials of *Hibiscus sabdariffa* anthocyanin extract. *Drug Chem Toxicol* 2011; 34:109–115.
49. Galleano M, Pechanova O, Fraga CG. Hypertension, nitric oxide, oxidants, and dietary plant polyphenols. *Curr Pharmaceut Biotechnol* 2010; 11:837–848.

50. Onyenekwe PC, Ajani EO, Ameh DA, Gamaniel KS. Antihypertensive effect of roselle (*Hibiscus sabdariffa*) calyx infusion in spontaneously hypertensive rats and a comparison of its toxicity with that in Wistar rats. *Cell Biochem Function* 1999; 17:199–206.
51. Fakeye TO, Pal A, Bawankule DU, Yadav NP, Khanuja SP. Toxic effects of oral administration of extracts of dried calyx of *Hibiscus sabdariffa* Linn. (Malvaceae). *Phytother Res* 2009; 23:412–416.
52. Ndu OO, Nworu CS, Ehiemere CO, Ndukwe NC, Ochiogu IS. Herb-drug interaction between the extract of *Hibiscus sabdariffa* L. and hydrochlorothiazide in experimental animals. *J Med Food* 2011; 14:640–644.
53. Banach M, Serban C, Aronow WS, Rysz J, Dragan S, Lerma EV, *et al*. Lipid, blood pressure and kidney update 2013. *Int Urol Nephrol* 2014; 46:947–961.
54. Michalska M, Zanchetti A, Wong N, Malyszko J, Rysz J, Banach M. Patients with prehypertension: do we have enough evidence to treat them? *Curr Vasc Pharmacol* 2014; 12:586–597.
55. Sleight P, Yusuf S, Pogue J, Tsuyuki R, Diaz R, Probstfield J. Blood-pressure reduction and cardiovascular risk in HOPE study. *Lancet* 2001; 358:2130–2131.
56. Caligiuri SP, Edel AL, Aliani M, Pierce GN. Flaxseed for hypertension: implications for blood pressure regulation. *Curr Hypertens Rep* 2014; 16:1–13.

Reviewer's Summary Evaluation

Reviewer 1

This is a meta-analysis of randomized controlled trials (RCTs) comparing the effects of *Hibiscus sabdariffa* on blood pressure against placebo. The meta-analysis is based on five RCTs including 390 patients. The results indicate a mean placebo-corrected reduction of blood pressure of 7.6/3.5 mmHg. These data demonstrate a significant antihypertensive effect of sour tea supplementation on both systolic and diastolic blood pressure.

The potential interactions between *Hibiscus sabdariffa* supplements and antihypertensive medications as well as the optimal dose of *Hibiscus sabdariffa* have been not still identified in order to optimize combination therapy. However, the findings of this meta-analysis confirm the potential effectiveness of supplementation with sour tea in reducing blood pressure.