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Hibiscus sabdariffa L. in the treatment of hypertension and hyperlipidemia: a comprehensive review of animal and human studies

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Abstract

The effectiveness of *Hibiscus sabdariffa* L. (HS) in the treatment of risk factors associated with cardiovascular disease is assessed in this review by taking a comprehensive approach to interpreting the randomized clinical trial (RCT) results in the context of the available ethnomedical, phytochemical, pharmacological, and safety and toxicity information. HS decoctions and infusions of calyxes, and on occasion leaves, are used in at least 10 countries worldwide in the treatment of hypertension and hyperlipidemia with no reported adverse events or side effects. HS extracts have a low degree of toxicity with a LD50 ranging from 2,000 to over 5,000 mg/kg/day. There is no evidence of hepatic or renal toxicity as the result of HS extract consumption, except for possible adverse hepatic effects at high doses. There is evidence that HS acts as a diuretic, however in most cases the extract did not significantly influence electrolyte levels. Animal studies have consistently shown that consumption of HS extract reduces blood pressure in a dose dependent manner. In RCTs, the daily consumption of a tea or extract produced from HS calyxes significantly lowered systolic blood pressure (SBP) and diastolic blood pressure (DBP) in adults with pre to moderate essential hypertension and type 2 diabetes. In addition, HS tea was as effective at lowering blood pressure as the commonly used blood pressure medication Captropril, but less effective than Lisinopril. Total cholesterol, low-density lipoprotein cholesterol (LDL-C), and triglycerides were lowered in the majority of normolipidemic, hypolipidemic, and diabetic animal models, whereas high-density lipoprotein cholesterol (HDL-C) was generally not affected by the consumption of HS extract. Over half of the RCTs showed that daily consumption of HS tea or extracts had favorable influence on lipid profiles including reduced total cholesterol, LDL-C, triglycerides, as well as increased HDL-C. Anthocyanins found in abundance in HS calyxes are generally considered the phytochemicals responsible for the antihypertensive and hypocholesterolemic effects, however evidence has also been provided for the role of polyphenols and hibiscus acid. A number of potential mechanisms have been proposed to explain the hypotensive and anticholesterol effects, but the most common explanation is the antioxidant effects of the anthocyanins inhibition of LDL-C oxidation, which impedes atherosclerosis, an important cardiovascular risk factor. This comprehensive body of evidence suggests that extracts of HS are promising as a treatment of hypertension and hyperlipidemia, however more high quality animal and human studies informed by actual therapeutic practices are needed to provide recommendations for use that have the potential for widespread public health benefit.

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Keywords

Hibiscus sabdariffa L.; Roselle; hypertension; cholesterol; randomized clinical trials; ethnopharmacology

1. Introduction[1]

Hibiscus sabdariffa L. (HS) (Malvaceae) tea is in widespread use across the world as a beverage and as a treatment for hypertension and hyperlipidemia. Two systematic reviews have been published on the effectiveness of HS for the treatment of hypertension [1, 2]. However Ngamjarus and colleagues [2] excluded all randomized clinical trials (RCTs) as being of too low quality, and Wahabi and colleagues [1] established the quality of studies using the Jadad scale, a scale which focuses exclusively on randomization, blinding and participant withdrawals [3–6]. Both reviews determined that the evidence available at the time of review was inconclusive.

However, subsequent to the publication of these two previous reviews, expanded criteria allowing for a more comprehensive evaluation of the totality of evidence related to the medicinal use of botanicals have been proposed by Fonnebo and colleagues [7]. This review applies these updated and expanded criteria to assess data related to the use of HS for hypertension, including data from a high quality study published subsequent to earlier reviews [8]. Furthermore, to obtain a more complete view of potential protective effects of HS as relates to cardiovascular disease, evidence related to HS effects on cholesterol metabolism are also reviewed. These data are reviewed in the context of ethnomedicinal information on HS use, preparation, and dosage and updated phytochemical, pharmacological, and toxicological information on HS, which was last reviewed by Ali and colleagues in 2005 [9].

The objective of this review is to:

- Examine the evidence of the effectiveness of HS on cardiovascular risk factors based on ethnomedicinal, safety and toxicity, pharmacological, phytochemical information

2. Methods

2.1. Information Sources

The following databases were searched from commencement to November 14, 2012: AGRICOLA, AMED, BIOSIS Previews, Cochrane Library, International Pharmaceutical Abstracts, ISI Web of Knowledge, MEDLINE, Pubmed, Natural Medicines Comprehensive Database. We also used other resources, such as Clinical Trials.gov and Current Controlled Trials, WorldWideScience.org, OpenGrey, hand searching of journals and reference lists of all papers and relevant reviews identified, to find any additional studies that were not captured in the databases. Additionally, original articles were retrieved from existing reviews [1, 2, 9] and re-reviewed.

RCT, randomized clinical trial; HS, *H. sabdariffa*, *Hibiscus sabdariffa* L.; AST, aspartate aminotransferase; ALT, alanine aminotrasferase; HCTZ, hydrocholorthiazide; GAE, gallic acid equivalents; CGE, cyanidin glucoside equivalents; ORAC, oxygen radical absorbance capacity; ACE, angiotensin I converting enzyme; PI3-K, phosphoinositol 3-kinase; LDL, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; CTGF, connective tissue growth factor; RAGE, receptor of advanced glycation end product; HMG-CoA, 3-hydroxy-3-methylglutaryl-coenzyme A; LD50, median lethal dose; CONSORT, Consolidated Standards of Reporting Trials; SBP, systolic blood pressure; DBP, diastolic blood pressure

2.2. Search

We used the search terms of Hibiscus or *Hibiscus sabdariffa* and hypertension or cholesterol. Using the additional search terms of the common names for HS, including Sour Tea, Roselle, Red Sorrel, Karkade, Jamaica, or Flor de Jamaica, or herbal tea or herbal medicine in combination with high blood pressure, elevated blood pressure, hypertension, pre-hypertension, mild hypertension, or dyslipidemia, hypercholesterolemia, lipid profiles, hypolipidemic effect, hyperlipidemic, or atherosclerosis did not yield any further results.

The literature search using keywords “hypertension” and “hibiscus” resulted in the retrieval of 154 titles, 70 of which were duplicates and 28 were regarding species or conditions not focused on in this review. After removing irrelevant articles, 77 articles remained for review, of which 5 were RCTs [8, 10–13]. In the second literature search “hibiscus” was kept as a keyword and “hypertension” was replaced with “cholesterol”. The search yielded 167 total titles, of which 58 duplicates and 30 articles were removed because they focused on irrelevant species or conditions. The remaining 79 articles were reviewed, 5 of which were RCTs [14–18].

2.3. Data Collection Process and Data Items

The articles identified using the aforementioned search strategy were sorted into the following categories: ethnobotany, safety and toxicity, pharmacology, with animal and human studies in separate categories, and phytochemistry. The data from the RCT studies were extracted and categorized by two authors (AH and ML) and presented in appropriate sections. The quality of trial and herbal intervention reporting in the RCTs was assessed by the same authors through determining the percentage of items reported from herbal interventions elaboration of the 2001 Consolidated Standards of Reporting Trials (CONSORT) statement, as these reflect the industry standard for the minimum information necessary for reporting RCTs at the time most of the trials in this review were carried out [4, 19, 20].

3. Ethnomedicinal Uses and Preparation

HS is consumed as a beverage in the United States [8], Mexico [11, 13, 16], Nigeria and other West African countries [21–25], Egypt [26], Iran [10, 14, 18], India [17, 27, 28], Thailand [29], and Tawian [15, 30, 31], among other countries. Ethnomedicinal studies have reported the use of HS for the treatment of various cardiovascular risk factors including hypertension in Egypt, Jordan, and Trinidad and Tobago [32–35], hypotension in Jordan and Iraq [34, 36], hyperlipidemia in Jordan, Greece, Brazil, and Trinidad and Tobago [33, 35, 37, 38], and obesity in Iraq, Greece, and Brazil [36–38].

The flowers, or more specifically the calyxes, are typically prepared using an aqueous decoction or infusion [32, 33, 36, 38]. However, the Bedouins in the North Badia region of Jordan use the leaves, as well as the flowers, and they drink the infusions hot when treating high blood pressure and cold when treating low blood pressure [34]. In Trinidad and Tobago only the leaves are used to treat high blood pressure and the flower and seeds are used to treat high cholesterol [35]. Dosing was only described in 1 [36] of the 7 ethnobotancial studies reviewed. Mati and colleagues [36] discovered that herbalists in the Kurdistan Autonomous Region of Iraq recommend drinking 1 cup/day of an infusion of 1 tsp (1/2 tsp when ground) of HS flowers in 1 cup warm water for the treatment of hypotension and 2 cups/day of a decoction of 2 tsp of the HS flowers in 1/2 L of water or 1 cup/day of a decoction of 50 g in 2 cups of water for the treatment of obesity.

4. Phytochemical Properties

The main compounds found in HS flowers are organic acids, mainly citric and malic acids, anthocyanins, a myriad of flavonoids and glycosides, and fiber [9, 39–41]. The calyxes have the same organic acid and anthocyanin constituents, but the presence of flavonoids and glycosides is minimal [9]. Anthocyanins, particularly delphinidin-3-sambubioside and cyanidin-3-sambubioside, are generally believed to be the active constituents responsible for the antihypertensive, antioxidant, and hypocholesterolemic effects of HS, possibly because they are found in high relative quantities in aqueous extracts [8, 11, 13, 16]. However, Yang [42] compared a polyphenol rich (74%) extract containing protocatechuic acid (24.2%), catechin (2.7%), gallocatechins (2.4%), caffeic acid (19.9%), and gallocatechin gallates (30.0%) with an aqueous extract of HS containing anthocyanins (2.5%), polyphenolic acid (1.7%) and flavonoids (1.4%) and determined that the phenol rich extract exhibited a greater ability to decrease total cholesterol and LDL-C cholesterol and increased HDL-C cholesterol dose-dependently suggesting the importance of polyphenols in inducing anti-cholesterol effects. Hibiscus acid may also be playing a role in lower blood pressure and cholesterol [43].

The plant parts used, the color of the parts, the harvesting practices and the preparation method greatly influence the volatile composition of the extract and influence dosing [9]. The HS varieties with deeper red calyxes exhibited greater antioxidant activity as compared to lighter red or white varieties [44, 45]. Greater antioxidant activity was found in flowers that were harvested at 35 days after flowering as compared to less mature flowers [45]. Ethanol extractions of calyxes exhibited the highest antioxidant activity as compared to ethanol extractions of leaves and aqueous extractions of both plant parts [28]. However, aqueous extractions are appropriate for studies interested in testing the effectiveness of traditional preparation practices and capturing the broad public health implications of this herbal treatment.

Very little research has been done on the bioavailability of HS extract. McKay and colleagues [8] provide the only exception in their clinical trial where they brewed HS tea by steeping 1,250 mg of dried HS in 240 mL of boiled water, administering one such serving three times a day. No anthocyanins were detected in the urine within one hour of consumption of this HS tea, which contained 22 mg gallic acid equivalents (GAE) total phenols, 7 mg cyanidin glucoside equivalents (CGE) total anthocyanins, 4 mg CGE delphinidin-3-sambubioside, 0.02 mg CGE cyanidin-3-sambubioside, and 1950 μmol trolox equivalents/g oxygen radical absorbance capacity (ORAC).

5. Safety and Toxicity

Studies carried out in animals and humans have primarily demonstrated either no change or decreases in measures related to function of the liver (AST and ALT liver enzymes [16, 46, 47]) or kidney (creatinine [16, 18, 22, 23, 31, 46, 48], blood urea nitrogen [18, 31], and urea [16]) function (Table 1). However, at doses of 300 mg/kg/day of HS over a 3 month period, an adverse effect on liver enzymes was observed, suggesting that at very high doses the extract could be hepatotoxic [46]. Uric acid levels were reported to be elevated in rodents given extremely high doses of HS, a potential adverse effect that could exacerbate or contribute to the development of gout [23].

HS extracts administered at 500 mg/kg/day over the course of 3 weeks exhibited diuretic properties in hypertensive animal models. HS consumption in most cases had no significant effect on electrolytes, including magnesium, sodium, potassium, and/or chlorine/chloride [11, 13, 18, 22, 49], although sodium [13] and chlorine levels [11] in humans increased statistically significantly from baseline to final measurement at 30 days of receiving HS

extract. The diuretic behavior of HS extract in these two studies has been compared to the potassium sparing group of diuretic pharmaceuticals, such as Spironolactone or aldosterone antagonists [11, 13].

A few other studies among animals suggest that HS extracts have a low degree of acute toxicity with the median lethal dose (LD50) ranging from 2,000 to over 5,000 mg/kg [23, 46, 49]. In contrast, one studied showed that doses as high as 4,600 mg/kg can be administered for several months in an animal model with no report of mortality, although negative effects on testes and sperm count were found [50]. The variation in these findings may be due to the type of solvents used for extraction, the method and length of administration and the variety of HS used [46].

Herb-drug interactions between HS and hydrochlorothiazide (HCTZ) [49], a commonly prescribed diuretic medication, and acetaminophen [51], an antipyretic-analgesic over-the-counter medication, were examined. Co-administration of HS extract (40 mg/kg) and HCTZ (10 mg/kg) in rats caused a significant increase in the volume of urine excreted, but electrolyte levels were more similar to controls than HCTZ alone [49]. Pharmacokinetics measurements in rabbits suggest that co-administration of HS (20–40 mg/kg) and HCTZ (10 mg/kg) may result in retention of HCTZ, less clearing of HCTZ from the body with increased doses of HS, and slower HCTZ elimination. These results suggest a possible herb-drug interaction and HS should not be used in conjunction with HCTZ. The only pharmacokinetic effect of consumption of HS in adult males before taking acetaminophen was enhanced elimination of the acetaminophen [51]. Based on these findings, acetaminophen should be taken 3–4 hours before drinking HS to avoid shorten its therapeutic effect.

6. HS in the Treatment of High Blood Pressure

6.1. Animal Studies

The results from animal studies presented in table 2 consistently show the beneficial effects of HS extracts on lowering blood pressure [21–23, 52]. Although the same effects on blood pressure occur in normotensive animal models, the positive effects are greater in hypertensive animals [21, 23]. Aqueous extracts of HS calyxes and petals at doses ranging from 1 mg/kg/day through 1,000 mg/kg/day were effective in reducing blood pressure among rodent models [21–23, 52] (Table 2). There is evidence that the positive effects are dose dependent at lower doses [21], but not at extremely high doses [23].

6.2. Human Study

The clinical study populations ranged from pre and mildly hypertensive [8, 10] to stage 1 or 2 hypertensive [11, 12] (Table 3; Table 6 quality of reporting). Only one study chose to recruit people with the additional condition of type 2 diabetes [10]. The study designs included comparing HS to black tea [10], blood pressure medication [11, 13], or a placebo beverage [8]. HS was generally prepared as a tea, but Herrera-Arellano and colleagues [11] prepared it as a standardized aqueous extract. Dried calyxes of HS were used in the tea or extract in those studies (4 of 5) that specified which part of the plant was use [8, 11, 13]. The amount of HS plant part extracted per serving varied from 1.25 g to 10 g with lower doses being administered up to 3 times per day and higher doses being administered only once. The duration of most of the studies was 4 weeks [10, 11, 13], although one study only lasted 12 days [12] and another was 6 weeks long [8].

Systolic blood pressure (SBP) and diastolic blood pressure (DBP) declined with HS treatment in all but one study where DBP did not achieve statistical significance relative to pre-treatment levels [10]. When comparing the results of the HS experimental groups with

the placebo and black tea groups, the decline in SBP and DBP was significantly greater in the HS experimental groups [8, 10, 12]. When comparing effects of HS to those of two commonly used ACE-inhibitors, HS was as effective as Captopril in lowering SBP and DSP in one study [13], but less effective than Lisinopril in another [11].

7. HS in the Treatment of Elevated Cholesterol

7.1. Animal Studies

The data presented in table 4 indicates that results from studies of the effect of HS extract on animal cholesterol metabolism are varied. Total cholesterol was reduced among healthy rats administered 1.5 mg/kg/day red and green HS petal aqueous extract and 200 mg/kg/day flower alcohol extract ingested over the course of a month, respectively [24, 25], however 200 mg/kg/day calyx alcohol extract administered for over two months showed no effect [30]. High-density lipoprotein cholesterol (HDL-C) was not statistically significantly impacted by HS extract consumption [24, 25, 30] and low-density lipoproteins (LDL-C) was reduced at lower doses [24], but no data was available at higher doses [25, 30]. Triglycerides were significantly reduced at a dose of 200 mg/kg/day HS flower alcohol extract [25].

In hyperlipidemic animal models all of the aqueous calyx and flower extracts reduced total cholesterol regardless of dose or length of administration [29, 53, 54]. Alcohol calyx and leaf extracts also reduced total cholesterol at doses between 200 and 500 mg/kg/day [27, 28, 30]. The majority of the studies indicated that HDL-C levels in hyperlipidemic animal models were unaffected by the consumption of the HS extract [27, 29, 43, 53, 54] but one study reported an increase in HDL-C with consumption of 500 mg/kg/day leaf or calyx alcohol extracts for a month [28]. LDL-C cholesterol was consistently reduced among aqueous and alcohol calyx extracts regardless of dose and duration of administration [27–29, 43, 53, 54]. Alcohol leaf extracts only showed a positive effect at doses between 200 and 500 mg/kg/day [27, 28]. Triglycerides were reduced among lower doses of aqueous calyx extracts [26, 29, 53], but not with extremely high doses [29, 54]. Alcohol calyx extracts were effective at reducing triglycerides at all doses and administration lengths and subjects receiving alcohol leaf extracts responded positively to doses between 200 and 500 mg/kg/day.

In diabetic animal models 100 and 200 mg/kg/day ethanol extracts of HS calyxes administered over the course of approximately 2 months showed a reduction of total cholesterol, LDL-C and triglycerides [30, 31]. An extract of HS flowers using the same doses and extraction method, with a duration of administration half the previously mentioned studies, only exhibited a reduction in total cholesterol in diabetic rats [25]. HDL-C was not significantly changed by HS extract consumption in diabetic animals [25, 31].

7.2. Human Studies

The clinical study populations were diverse and included healthy people as well as those with metabolic syndrome [16], hyperlipidemia [15, 17], hypertension [18], or type 2 diabetes [14] (Table 5; Table 6 quality of reporting). The study designs compared different doses of HS [15] or compared HS to black tea [14, 18], diet and a combination of HS and diet [16], or a placebo [17]. In two studies the dried calyxes of HS were prepared and administered as a tea [14, 18] and in the other studies fresh calyxes [15, 16] or leaves [17] were prepared as a standardized powdered extract and administered in capsules. The doses of HS per serving and the frequency of administration varied from .015 g of dried calyxes prepared in water and administered twice daily [18] to 450 g of dried calyxes prepared in water and administered up to 3 times a day [15]. Alcohol extractions formulated with 500 g of fresh calyxes were administered once daily [16] and alcohol extracts made from 60,000 g

of fresh leaves were administered twice daily [17]. The duration of the studies ranged from 15 days [18] to 90 days [17] with most lasting one month [14–16].

The effect of HS on total cholesterol varied. One brief 15 day study reported a significant increase in total cholesterol among hypertensive patients administered HS [18]. In this same study, HDL-C increased and triglyceride and LDL-C values remained unchanged. Of the remaining 4 studies, one showed no significant change in total cholesterol and the month long studies showed significant decreases in total cholesterol among participants with hypertension, metabolic syndrome and those receiving the two lower doses of HS [14–16]. HS significantly increased beneficial HDL-C levels in participants with and without metabolic syndrome [16] and hypertension [14]. LDL-C was significantly decreased as a result of the consumption of HS in participants with metabolic syndrome [16], hyperlipidemia [17], and type 2 diabetes [14]. Triglyceride levels were significantly decreased by HS in participants with hyperlipidemia [17], type 2 diabetes [14], and without metabolic syndrome [16].

8. Quality of RCT Reporting

The studies consistently reported the CONSORT items relevant to all RCTs with scores ranging from 59% [15] of the items reported to 96% [8] (Table 6). The items 1–6 and 12 were reported by most RCTs and included information on eligibility criteria for participants, a description of the intervention, outcome measurements and statistical methods (item 12). Items from the results section including participant flow (item 13), baseline data (item 15), and results from analyses (items 17 and 18) were also generally included. In addition all discussion items, including interpretation of results (item 20) within the context of current evidence (item 22) and external validity (item 21). However, there were several areas where reporting could be improved, including sample size (item 7), randomization sequence allocation (item 8), allocation concealment (item 9), and implementation (item 10), blinding (item 11), recruitment (item 14), numbers analyzed (item 16), and adverse events (item 19).

More specifically, most studies did not make clear the type of RCT being conducted and in many cases there were study design problems. In several RCTs black tea was used as the comparator, as opposed to a placebo, making the results difficult to interpret because of the active pharmacological properties of black tea [10, 12, 14, 18]. McKay and colleagues' [8] in the only placebo-controlled trial to date provided a notable exception to this trend by using a placebo drink that was non-active and is used in the beverage industry to mimic the flavor of HS tea in commercially prepared drinks. In some comparative effectiveness trials it was difficult to compare effectiveness between treatments because the medication was not administered as directed by doctors [11], whereas other trials provided realistic comparators [13, 16]. The results from the study on dose response are difficult to interpret because the baseline values for total cholesterol differed substantially between groups [15].

Additionally, there were several problems specific to the cholesterol RCTs. Differences between groups were impossible to assess because none of the studies included effect sizes or statistical analyses of the between-group differences [14–18]. Another problem with most of the cholesterol trials was short study duration with 4 trials lasting 15 days [18] to 30 days [14–16] and only one trial of a longer 90 day duration [17]. In general, lipid profiles can take up to 2 months to reflect meaningful change in patients given statin medication or modifications to their diet and lifestyle [55, 56]. The hypertension trials selected patient populations with mild to moderate hypertension [8, 11–13] with only one study providing the additional condition of diabetes [10], whereas the patient populations in the cholesterol trials had an array of conditions, many of which did not include elevated cholesterol [14, 16, 18], making it difficult to assess the effectiveness of HS in treating hyperlipidemia.

The quality scores for items specific to the herbal intervention were much lower, ranging from 28% [12] to 67% [8] for the hypertension RCTs and from 33% [18] to 65% [15, 16] for the cholesterol RCTs. Reporting was particularly lacking in the herbal description in the title or abstract (item 1), description of how traditional theories and concepts were maintained, including traditional preparation and dosing practices (item 3), all aspects of the intervention (items 4a, 4c–4f), except characteristics of the herbal product (item 4b), concomitant medications (item 15), interpretation in the light of the product and dosage regimen used (item 20) and how the herbal product and dosage regimen used relates to self-care (item 21).

There were also several problems with the preparation of HS. Many of the studies did not report the part of the plant that was used in the preparation. Kuriyan and colleagues [17] used the leaves in their extract without explanation, whereas the calyxes are most commonly used in HS preparations. In addition, the amount of HS used in preparations and the dose administered varied greatly with Mohagheghi and colleagues [18] choosing to use an extremely small amount of HS calyxes in the preparation per dose and many of the studies failing to include any measure of marker constituents. The absence of information related to product content and the method of preparation and the lack of uniformity of extracts made it difficult to compare findings between studies. In addition, the lack of information regarding ethnobotanical use made it difficult to determine the relationship between the studies and traditional therapeutic use.

9. Biological Mechanisms

In vitro and in vivo studies focused on mechanism of action have determined several potential mechanisms of the HS extracts that may explain the hypotensive activity, including (1) vasodilation mediated through endothelium-derived relaxant pathways and inhibition of calcium influx [9, 57], (2) ACE inhibition [9] by the stimulation of new vessel formation and a reduction of myocardial mass [52] or anthocyanins competing with the substrate for the active site [58], (3) decrease in blood viscosity through cyclooxygenase inhibitory activity [44], and (4) inhibition of adipocyte differentiation through the modulation of PI3-K/Akt and ERK pathway [59].

Other potential mechanisms have been tested to explain the positive impact of HS extract on cholesterol metabolism. For example, cholesterol biosynthesis may be reduced by inhibiting HMG-CoA reductase [42, 60]. Decreases in LDL-C may be the result of the inhibition of triacylglycerol synthesis by hibiscus acid racemization [43]. The positive effects of the extract in diabetic animal models may be partially the result of the reduction in the expression of CTGF and RAGE [30]. Additionally, although not directly related to the reduction in cholesterol but beneficial for improving cardiovascular risk factors, HS may hinder atherosclerosis and improve vasoreactivity through (1) impediment of the formation of macrophage-derived foam cells [61] and/or (2) inhibition of LDL-C oxidation due to antioxidant effects of the extract [25, 28, 29, 31, 53, 54].

10. Conclusions

There are many strengths and limitations to the array of evidence considered in this review. Ethnomedicinal studies provide evidence for the widespread use of a tea made with HS calyxes to treat hypertension and hyperlipidemia, but these studies provide little guidance for animal and human studies through their lack of attention to cultivation, preparation, and consumption patterns. HS extracts are generally considered to have a low degree of toxicity. Studies demonstrate that HS consumption does not adversely effect liver and kidney function at lower doses, but may be hepatotoxic at extremely high doses. In addition,

electrolyte levels generally are not effected by ingesting HS extracts despite its diuretic effects.

Animal studies have consistently shown that consumption of HS extract reduces blood pressure in a dose dependent manner. They have also shown that total cholesterol, LDL-C, and triglycerides were lowered in the majority of normolipidemic, hyperlipidemic, and diabetic animal models, whereas HDL-C was generally not affected by the consumption of HS extract.

The daily consumption of HS calyx extracts significantly lowered SBP and DBP in adults with pre to moderate essential hypertension and type 2 diabetes. In addition, HS tea was as effective at lowering blood pressure as Captropril, but less effective than Lisinopril. Over half of the RCTs showed that daily consumption of HS tea or extracts had a favorable influence on lipid profiles including reduced total cholesterol, LDL-C, triglycerides as well as increased HDL-C. Regrettably many of the RCTs were of low quality and did a poor job characterizing the HS extracts and utilized a form that is not widely consumed making it difficult to determine the amount of public health benefit related to HS tea consumption. McKay and colleagues [8] provide a notable exception with their high quality placebo-controlled trial. As the findings related to the effects of HS on blood pressure from lower quality studies are consistent with those of this high quality study, the totality of evidence suggests that HS consumption may have a public health benefit due to its anti-hypertensive effects.

Anthocyanins found in abundance in HS calyxes are generally considered the phytochemicals responsible for the antihypertensive and hypocholesterolemic effects, however evidence has also been provided for the role of polyphenols and hibiscus acid. A number of potential mechanisms have been proposed to explain the hypotensive and anticholesterol effects, but the most common explanation is the antioxidant effects of the anthocyanins inhibit LDL-C oxidation which impedes atherosclerosis, an important cardiovascular risk factor. Research on active compounds in HS and the mechanisms of action are still fairly nascent making it difficult to justify carrying out RCTs using anything other than the whole plant parts used in general practice.

This body of evidence interpreted together suggests that HS has great potential to reduce risk factors associated with cardiovascular disease and merits further study.

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Table 1

Effect of administration of HS extracts on creatinine, urea, AST, ALT, and electrolyte levels in rodents and humans.

Primary author, year, type of study	Plant Part	Extract mode	Dose	End time point	Crea	Urea	AST	ALT	Mg	Na	K	Cl
		A,	50[a],									
		A;	100[a];									
Fakeye, 2008, *	C	W/A	100[a]	7	NS							
Lee, 2009, *	F	A	100[a]	60	NS	Dep						
Lee, 2009, *	F	A	200[a]	60	NS	Dep						
Fakeye, 2009, *	C	W/A	300[a]	90	N/A		N/A	N/A				
Fakeye, 2009, *	C	A	300[a]	90	NS		NS	Ele				
Onyenekwe, 1999, *	P	W	500[a]	60	Dep	Ele						
Onyenekwe, 1999, *	P	W	500[a]	60	Dep	Ele						
Onyenekwe, 1999, *	P	W	1000[a]	60	Dep	Ele						
Kuo, 2012, *	F	W	1[b]	35	NS	NS	NS	NS				
Kuo, 2012, *	F	W	2[b]	35	NS	Dep	NS	NS				
Kuo, 2012, *	F	W	5[b]	35	NS	Dep	NS	NS				
Gurrola-Diaz, 2010, **	C	A	100[d]	30	NS	NS	Red	Red				
Gurrola-Diaz, 2010, **	C	A	100[d]	30	NS	NS	NS	NS				
Mohagheghi, 2011, **	C	W	30/4[c]	30	NS	NS				NS	NS	
Ndu, 2011, *	C	A	40[a]	1						NS	NS	NS
Odigie, 2003, *	P	W	250[a]	60	NS				NS	NS	NS	NS
Herrera-Arellano, 2004, **	C	W	9.62[e]	30						Inc	NS	NS
Herrera-Arellano, 2007, **	C	W	250[e]	30						NS	NS	Inc

Notes: Type of study:

* animal studies with rats or mice,

** human studies; Plant part used in extract=F=flower, C=calyx, P=petal L=leaf; Extract mode: W=water, A=alcohol;

Dose: [a]=mg of HS extract/kg weight of animal/day,

[b]%,

[c]mg HS plant part/glasses of water/day,

[d]mg of HS extract/day,

[e]mg anthocyanins/day; End time point: number of days after start of treatment when measurement was taken; Crea=creatinine; Urea: some measurements in this column are Uric acid or Blood Urea Nitrogen; AST=aspartate aminotransferase; ALT=alanine aminotransferase; Mg=Magnesium; Na=Sodium; K=Postassium; Cl=Chlorine; Results: N/A=not available, NS=not significant, Dep=depressed, Ele=elevated, Red=reduced, Inc=increased, depressed or elevated used accordingly when values compared with appropriate control, increased or reduced used when values compared between baseline and end of treatment within the same group

Table 2

Effect of administration of HS extract on rodent systolic and diastolic blood pressure.

Primary author, year	Condition	Sample size	Plant Part	Extract mode	Dose	End time point	Within group SBP	Between group SBP	Within group DBP	Between group DBP
Mojiminiyi, 2007	Normo	6 rats	C	W	1[a]	1	Red		Red	
Mojiminiyi, 2007	Normo	6 rats	C	W	5[a]	1	Red		Red	
Mojiminiyi, 2007	Normo	6 rats	C	W	25[a]	1	Red		Red	
Mojiminiyi, 2007	Normo	6 rats	C	W	125[a]	1	Red		Red	
Onyenekwe, 1999	Normo	5 rats	P	W	500[a]	21	Red	N/A	Red	N/A
Onyenekwe, 1999	Normo	5 rats	P	W	1000[a]	21	Red	N/A	Red	N/A
Mojiminiyi, 2007	Hyper[a]	6 rats	C	W	1[a]	1	NS		NS	
Mojiminiyi, 2007	Hyper[b]	6 rats	C	W	1[a]	1	Red		Red	
Mojiminiyi, 2007	Hyper[a]	6 rats	C	W	5[a]	1	Red		Red	
Mojiminiyi, 2007	Hyper[b]	6 rats	C	W	5[a]	1	Red		Red	
Mojiminiyi, 2007	Hyper[a]	6 rats	C	W	25[a]	1	Red		Red	
Mojiminiyi, 2007	Hyper[b]	6 rats	C	W	25[a]	1	Red		Red	
Mojiminiyi, 2007	Hyper[a]	6 rats	C	W	125[a]	1	Red		Red	
Mojiminiyi, 2007	Hyper[b]	6 rats	C	W	125[a]	1	Red		Red	
Odigie, 2003	Hyper	5 rats	P	W	250[a]	56	Red	Dep	N/A	Dep
Onyenekwe, 1999	Hyper	5 mice	P	W	500[a]	21	Red	Dep	Red	Dep
Onyenekwe, 1999	Hyper	5 mice	P	W	1000[a]	21	N/A	N/A	N/A	N/A
Inuwa, 2012	Hyper	8 rats	C	W	10[b]	70	Red	Dep	Red	Dep
Inuwa, 2012	Hyper	8 rats	C	W	15[b]	70	Red	Dep	Red	Dep
Inuwa, 2012	Hyper	8 rats	C	W	20[b]	70	Red	Dep	Red	Dep
Inuwa, 2012	Hyper	6 rats	F	A	50[a]	5	NS		NS	
Inuwa, 2012	Hyper	6 rats	F	A	100[a]	5	NS		NS	
Inuwa, 2012	Hyper	6 rats	F	A	200[a]	5	NS		NS	

Notes: Condition: Normo=normotension, Hyper=hypertension,

[a] salt loaded induced,

[b] chronic oxide synthase inhibition induced; Plant part used in extract=F=flower, C=calyx, P=petal L=leaf; Extract mode: W=water, A=alcohol;

Dose: [a]=mg of HS extract/kg weight of animal/day,

[b] %; End time point: number of days after start of treatment when measurement was taken; SBP=Systolic blood pressure; DBP=Diastolic blood pressure; Results: N/A=not available, NS=not significant, Dep=depressed, Ele=elevated, Red=reduced, Inc=increased, depressed or elevated used accordingly when values compared with appropriate control, increased or reduced used when values compared between baseline and end of treatment within the same group

Table 3

Hypertension RCT interventions and effects on systolic blood pressure and diastolic blood pressure.

Primary author, year	Condition	Sample size	Substance	Plant part	Extract mode	Dose	# of doses per day	Days dose taken	Mean change in SBP (SD)	Within group p-value	Between group p-value	Mean change in DBP (SD)	Within group p-values	Between group p-values
McKay, 2010	Hyper	31(30)	AHFC		W	1.2/240[a]	3	42	1.3 (10.0)	NS		0.5 (7.5)	NS	
McKay, 2010	Hyper	35(35)	HS	C	W	2.25/240[b]	3	42	7.2 (11.4)	Red	Dep	3.1 (7.0)	Red	Dep
Haji, 1999	Hyper	40(23)	BT	L	W	2/1[c]	1	12	6.3 (7.7)	Red		3.5 (6.0)	Red	
Haji, 1999	Hyper	40(31)	HS	N/A	W	2/1c	1	12	17.6 (6.8)	Red	Dep[a]	10.9 (5.4)	Red	Dep[a]
Mozaffari-Khosravi, 2009	Hyper, Diab	30(26)	BT	L	W	2/240[b]	2	30	8.4 (11.0)	Inc		4.6 (11.8)	NS	
Mozaffari-Khosravi, 2009	Hyper, Diab	30(27)	HS	C	W	2/240[b]	2	30	15.4 (7.5)	Red	Dep	4.3 (12.3)	NS	Dep
Herrera-Arellano, 2004	Hyper	37(32)	Med[a]			25[d]	2	28	16.4 (9.6)	Red		13.1 (7.2)	Red	
Herrera-Arellano, 2004	Hyper	53(38)	HS	C	W	9.62[e]	1	28	14.2 (11.8)	Red	NS	11.2 (6.9)	Red	NS
Herrera-Arellano, 2007	Hyper	93(N/A)	Med[b]			10[d]	1	28	23.3 (7.0)	Red		15.4 (6.0)	Red	
Herrera-Arellano, 2007	Hyper	100(N/A)	HS	C	W	250[e]	1	28	17.1 (10.0)	Red	Dep[b]	12.0 (7.0)	Red	Dep[b]

Notes: Condition: Hyper=hypertension, Diab=diabetes; Sample size= beginning of study (end of study), N/A=not available; Substance: HS=Hibiscus sabdariffa, AHFC=artificial hibiscus flavor concentrate, BT=Black tea, Med=blood pressure medication,

[a]Captopril,

[b]Lispinopril; Plant part used in extract=F=flower, C=calyx, P=petal L=leaf; Extract mode: W=water, A=alcohol;

Dose: [a]=mL substance/mL extraction substance;

[b]g substance/mL extraction substance,

[c]spoonfuls of substance/glass of extraction substance,

[d]mg of substance,

[e]mg total anthocyanins; SBP=Systolic blood pressure, DBP=Diastolic blood pressure, SD=standard deviation; Results: NS=not significant,

Dep=depressed, [a]=more than comparator,

[b]less than comparator, Ele=elevated, Red=reduced, Inc=increased, depressed or elevated used accordingly when values compared with appropriate control, increased or reduced used when values compared between baseline and end of treatment within the same group

Table 4

Effect of administration of HS extract on animal total cholesterol, HDL-C, LDL-C and triglycerides.

Primary author, year	Condition	Sample size	Plant Part	Extract mode	Dose	End time point	Within group TC	Between group TC	Within group HDL-C	Between group HDL-C	Within group LDL-C	Between group LDL-C	Within group TG	Between group TG
Olatunji, 2005	None	6 rats	P[a]	W	1[a]	28		NS		NS		Dep		NS
Olatunji, 2005	None	6 rats	P[b]	W	1[a]	28		NS		NS		Dep		NS
Olatunji, 2005	None	6 rats	P[a]	W	1.5[a]	28		Dep		NS		Dep		NS
Olatunji, 2005	None	6 rats	P[b]	W	1.5[a]	28		Dep		NS		Dep		NS
Farombi, 2007	None	5 rats	F	A	100[a]	28		NS		NS		N/A		NS
Farombi, 2007	None	5 rats	F	A	200[a]	28		Dep		NS		N/A		Dep
Peng, 2011	None	8 rats	C	A	200[a]	63		NS		N/A		N/A		NS
Chen, 2003	Hyper	6 rabbits	N/A	W	0.5[b]	70		Dep		NS		Dep		Dep
Chen, 2003	Hyper	6 rabbits	N/A	W	1[b]	70		Dep		NS		Dep		Dep
El-Saadany, 1991	Hyper	6 rats	C	N/A	5[b]	63		Dep		N/A		N/A		Dep
El-Saadany, 1991	Hyper	6 rats	C	N/A	10[b]	63		Dep		N/A		N/A		Dep
Hirunpanich, 2006	Hyper	6 rats	C	W	250[a]	42	NS	Dep	NS	NS	NS	Dep	NS	NS
Hirunpanich, 2006	Hyper	6 rats	C	W	500[a]	42	Red	Dep	NS	NS	Red	NS	Red	Dep
Hirunpanich, 2006	Hyper	6 rats	C	W	1000[a]	42	Red	Dep	NS	NS	Red	Dep	Red	NS
Chen, 2004	Hyper	6 rats	F	W	10000[a]	84		Dep		NS		Dep		NS
Chen, 2004	Hyper	6 rats	F	W	20000[a]	84		Dep		NS		Dep		NS
Carvajal-Zarrabal, 2005	Hyper	N/A rats	C	A	5[c]	28		Dep		NS		Dep		Dep
Carvajal-Zarrabal, 2005	Hyper	N/A rats	C	A	10[c]	28		NS		NS		Dep		Dep
Carvajal-Zarrabal, 2005	Hyper	N/A rats	C	A	15[c]	28		NS		NS		Dep		Dep
Peng, 2011	Hyper	8 rats	C	A	100[a]	63		NS		N/A		N/A		Dep
Peng, 2011	Hyper	8 rats	C	A	200[a]	63		Dep		N/A		N/A		Dep
Ochani, 2009	Hyper	6 rats	C	A	500[a]	30		Dep		Ele		Dep		Dep
Gosain, 2010	Hyper	6 rats	L	A	100[a]	28	NS	NS	NS	NS	NS	NS	NS	NS

Primary author, year	Condition	Sample size	Plant Part	Extract mode	Dose	End time point	Within group TC	Between group TC	Within group HDL-C	Between group HDL-C	Within group LDL-C	Between group LDL-C	Within group TG	Between group TG
Gosain, 2010	Hyper	6 rats	L	A	200[a]	28	Red	Dep	NS	NS	Red	Dep	Red	Dep
Gosain, 2010	Hyper	6 rats	L	A	300[a]	28	Red	Dep	NS	NS	Red	Dep	Red	Dep
Ochani, 2009	Hyper	6 rats	L	A	500[a]	30		Dep		Ele		Dep		Dep
Farombi, 2007	Diab	5 rats	F	A	100[a]	28		Dep		NS		N/A		NS
Farombi, 2007	Diab	5 rats	F	A	200[a]	28		Dep		NS		N/A		NS
Lee, 2009	Diab	5 rats	F	A	100[a]	56		Dep		NS		Dep		Dep
Lee, 2009	Diab	5 rats	F	A	200[a]	56		Dep		NS		Dep		Dep
Peng, 2011	Hyper, diab	8 rats	C	A	100[a]	63		NS		N/A		N/A		Dep
Peng, 2011	Hyper, diab	8 rats	C	A	200[a]	63		Dep		N/A		N/A		Dep

Notes: Condition: Hyper=hyperlipidemia, Diab=diabetes; Plant part used in extract=F=flower, C=calyx, P=petal, L=leaf, a=red, b=green; Extract mode: W=water, A=alcohol;

Dose: [a]=mg of HS extract/kg weight of animal/day,

[b]%,

[c]g extract/100 g basal diet; End time point: number of days after start of treatment when measurement was taken; TC=total cholesterol, HDL-C=high-density lipoprotein cholesterol, LDL-C=low-density lipoprotein cholesterol, TG=triglycerides; Results: N/A=not available, NS=not significant, Dep=depressed, Ele=elevated, Red=reduced, Inc=increased, Depressed or elevated used accordingly when values compared with appropriate control, increased or reduced used when values compared between baseline and end of treatment within the same group

Table 5

Cholesterol RCT interventions and effects of cholesterol RCT interventions on total cholesterol, HDL-C, LDL-C, and triglycerides.

Primary author, year	Condition	Sample size	Substance	Plant part	Extract mode	Dose	# of doses per day	Days dose taken	TC (SD)	p-value	HDL-C (SD)	p-value	LDL-C (SD)	p-value	TG (SD)	p-value
								0	206 (39)		44.3 (8.3)		130.8 (29)		153.5 (59)	
Mohagheghi, 2011	Hyperten	45(42)	HS	C	W	.015/2[a]	2	15	212 (37)	Inc	46 (7.2)	Inc	133.2 (26)	NS	157.5 (58)	NS
								0	202.6 (41.6)		41.6 (10.3)		124.1 (41.7)		148.0 (61.3)	
Gurrola-Diaz, 2010	None	26 (26)	HS	C	A	100[b]	1	30	197.5 (37.0)	NS	45.8 (9.3)	Inc	124.5 (35.5)	NS	113.8 (54.1)	Red
								0	199.8 (40.5)		32.0 (5.8)		130.1 (34.8)		172.3 (107.4)	
Gurrola-Diaz, 2010	MeSy	18 (18)	HS	C	A	100[b]	1	30	179.7 (21.2)	Red	44.5 (8.3)	Inc	104.1 (20.4)	Red	137.6 (62.1)	NS
								0	207.1 (32.5)		42.0 (9.4)		155.3 (13.9)		159.9 (90.6)	
Kuriyan, 2010	Hyperlip	30 (28)	HS	L	A	500[b]	2	90	198.5 (33.2)	NS	42.6 (8.9)	NS	127.6 (24.1)	Red	143.3 (73.9)	Red
								0	236.2 (58.1)		48.2 (10.6)		137.5 (53.4)		246.1 (84.9)	
Mozaffari-Khosravi, 2009	Diab	30 (27)	HS	C	W	2/240[c]	2	30	218.6 (38.4)	Red	56.1 (11.3)	Inc	128.5 (41.2)	Red	209.2 (57.2)	Red
Lin, 2007	Hyperlip	14 (N/A)	HS	F	W	500[b]	3	0	201.9 (27.2)							
								28	194.6 (24.2)	Red						
							6	0	223.4 (36.8)							
Lin, 2007	Hyperlip	14 (N/A)	HS	F	W	500[b]		28	213.9 (37.0)	Red						
							9	0	207.5 (26.5)							
Lin, 2007	Hyperlip	14 (N/A)	HS	F	W	500[b]		28	212.6 (40.0)	NS						

Notes: Condition: Hyperten=hypertension, MeSy=metabolic syndrome, Hyperlip=hyperlipidemia, Diab=diabetes; Sample size= beginning of study (end of study), N/A=not available; Substance: HS=Hibiscus sabdariffa; Plant part used in extract=F=flower, C=calyx, L=leaf; Extract mode: W=water, A=alcohol;

Dose: [a]=g substance/glass of extraction substance,

[b]mg of HS extract,

[c]g of substance/mL of extraction substance; TC=total cholesterol, HDL-C= high-density lipoprotein cholesterol, LDL-C=low-density lipoprotein cholesterol, TG=triglycerides, SD=standard deviation; Results: NS=not significant, Reduced=Red, Increased=Inc

Table 6

Quality of RCT reporting.

Primary author, year	CONSORT 2001	CONSORT Herbal Interventions Elaboration
McKay, 2010	95.45	66.67
Haji, 1999	81.82	27.78
Mozaffari-Khosravi, 2009	81.82	50.00
Herrera-Arellano, 2004	81.82	60.00
Herrera-Arellano, 2007	68.18	55.00
Mohagheghi, 2011	63.64	33.33
Gurrola-Diaz, 2010	63.64	65.00
Kuriyan, 2010	72.73	50.00
Mozaffari-Khosravi, 2009	81.82	38.89
Lin, 2007	59.09	65.00