**Hibiscus Sabdariffa** L. Tea (Tisane) Lowers Blood Pressure in Prehypertensive and Mildly Hypertensive Adults

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Abstract

In vitro studies show *Hibiscus sabdariffa* L., an ingredient found in many herbal tea blends and other beverages, has antioxidant properties, and, in animal models, extracts of its calyces have demonstrated hypocholesterolemic and antihypertensive properties. Our objective in this study was to examine the antihypertensive effects of *H. sabdariffa* tisane (hibiscus tea) consumption in humans. A randomized, double-blind, placebo-controlled clinical trial was conducted in 65 pre- and mildly hypertensive adults, age 30–70 y, not taking blood pressure (BP)-lowering medications, with either 3 240-mL servings/d of brewed hibiscus tea or placebo beverage for 6 wk. A standardized method was used to measure BP at baseline and weekly intervals. At 6 wk, hibiscus tea lowered systolic BP (SBP) compared with placebo (7.2 ± 11.4 mm Hg; *P* = 0.030). Diastolic BP was also lower, although this change did not differ from placebo (−3.1 ± 7.0 vs. −0.5 ± 7.5 mm Hg; *P* = 0.160). The change in mean arterial pressure was of borderline significance compared with placebo (−4.5 ± 7.7 vs. −0.8 ± 7.4 mm Hg; *P* = 0.054). Participants with higher SBP at baseline showed a greater response to hibiscus treatment (*r* = −0.421 for SBP change; *P* = 0.010). No effects were observed with regard to age, gender, or dietary supplement use. These results suggest daily consumption of hibiscus tea, in an amount readily incorporated into the diet, lowers BP in pre- and mildly hypertensive adults and may prove an effective component of the dietary changes recommended for people with these conditions.


Introduction

Observational studies show that diets high in plant foods are associated with a lower risk of chronic diseases, such as cardiovascular disease and some forms of cancer (1,2). The health benefits of plant foods appear not to be simply attributable to their macro- and/or micronutrient content alone but also to the presence of phytochemicals (3). Many polyphenols, particularly the flavonoids, possess relatively potent antioxidant, antiatherosclerotic, antiinflammatory, antimutagenic, antitumor, and antiviral activities (4). Whereas further research is necessary to elucidate and quantify the contributions of phytochemicals to health promotion and disease prevention, virtually all dietary guidelines created by regulatory agencies and healthcare organizations include recommendations for generous intakes of plant foods, including fruits, vegetables, and whole-grain cereals. Interestingly, recommendations for the consumption of plant-based beverages (except for fruit juices) such as tea (*Camilla sinensis*) and tisanes (herbal teas) are absent despite their being particularly rich sources of phytochemicals, especially polyphenols.

One of the most common ingredients found in commercial herbal tea blends sold in the US is *Hibiscus sabdariffa*. In other parts of the world, *H. sabdariffa* calyces, and beverages derived from them, are called hibiscus tea, bissap, roselle, red sorrel, agua de Jamaica, Lo-Shen, Sudan tea, sour tea, or karkade. In vitro studies show that *H. sabdariffa* has antioxidant properties (5–8) and, in animal models, extracts of this flower have demonstrated hypocholesterolemic (9–11) and antihypertensive properties (12–15). Concentrated *H. sabdariffa* beverages lower blood pressure (BP) (7) in patients with hypertension (16) and type 2 diabetes (17) compared with black tea (*C. sinensis*) and have an effect similar to common hypotensive drugs (18,19). The objective of our study was to determine whether consuming hibiscus tea, in an amount readily incorporated into the diet,
lowers the BP of generally healthy adults at risk of developing hypertension when compared with a placebo beverage.

**Materials and Methods**

**Study design**

A randomized, double-blind, placebo-controlled clinical trial was conducted to study the effects of hibiscus tea consumption on BP among otherwise healthy pre- and mildly-hypertensive adults. All participants followed their usual diet throughout the intervention. Participants were randomized according to a computer-generated randomization list stratified by gender and age. Study personnel and participants were unaware of which beverage was being tested and of treatment assignment for the duration of the intervention. They were told the study purpose was to examine the effects of a hibiscus beverage and the word “tea” was avoided in all advertising, instructional, and consent documents. The only exception was the study dietitian who was responsible for administering the assigned beverage and preparation instructions to eligible participants at randomization and for assessing compliance.

**Participant eligibility**

Sixty-five nonsmoking men and women, age 30–70 y, with systolic BP (SBP) 120–150 mm Hg, diastolic BP (DBP) ≤95 mm Hg, and BMI of 18.5–35 kg/m² were recruited from the greater Boston area via newspaper advertisements, direct mailings, clinic postings, and community health events. To determine eligibility, BP was ascertained during 2 separate baseline visits, 1 wk apart, using a standardized method. Participants’ mean SBP and DBP had to be within the specified range on both baseline visits to qualify for study participation. Participants were excluded if their mean BP values were outside the specified range; if they were taking any medications known or suspected to influence BP; if they had cardiovascular, renal, endocrine, or gastrointestinal disease, rheumatoid arthritis, ≥5% change in body weight, or pregnancy within the previous 6 mo; caffeine intake ≥425 mg/d; usual ethanol intake ≥28 g/d; regular strenuous aerobic exercise ≥30 min/d; supplemental vitamin C intake ≥500 mg/d; illicit drug use; EKG; or standard clinical laboratory values outside acceptable ranges.

In total, 324 volunteers were recruited for the initial baseline screening visits between August 2005 and October 2007. Although 66 eligible participants completed the entire 8-wk protocol, only 65 were included in the data analysis. One participant in the placebo group was excluded due to the presence of a peripheral vascular disease, which was not disclosed until the end of the study (Supplemental Fig. 1). The study design was approved by the Institutional Review Board of Tufts University Health Sciences Campus and Tufts Medical Center. All participants signed a written informed consent agreement before participating.

**Intervention**

Qualified participants received either 3 servings/d (720 mL/d) of *H. sabdariffa* tea or placebo at their second baseline visit and returned once each week for the next 6 wk for subsequent data collection and reassessment. During each weekly visit, participants reported to the Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University after fasting for 12 h. To determine the chronic effects of drinking hibiscus tea, each participant’s BP was measured before breakfast during the morning of their study visits. At each visit, participants were queried regarding interval changes in health, as well as use of prescription and over-the-counter medications, caffeine or tobacco, and dietary supplements.

**Test beverages**

Participants were given instructions for preparing their assigned beverage. Each serving of hibiscus tea was prepared by brewing 1 bag (containing 1.25 g *H. sabdariffa*) per 240 mL boiled water for 6 min, then removing the bag. This amount of hibiscus is present in a variety of commercial, blended herbal teas. Each serving of the placebo was prepared by adding 16–18 drops (1.2 mL) of an artificial hibiscus flavor concentrate to 240 mL water and stirring to mix. The concentrate given to participants was composed of artificial cranberry (0.2%, v:v) and raspberry (10%, w:w) flavor concentrates (International Flavors and Fragrances) plus a drop of commercially available red food coloring, diluted in water. The combination of these flavors is used in the beverage industry to mimic the flavor of hibiscus in commercially prepared drinks. Either the herb tea or placebo could be prepared ahead of time but had to be consumed within 12 h of preparation. Participants were allowed to consume their beverage either hot or cold.

**Herbal product.** Ground, dried calyces of the *H. sabdariffa* plant were supplied by Celestial Seasonings. The blend of 63% Chinese and 35% Thai hibiscus was certified by the National Food Laboratory to be pesticide-free and absent arsenic, cadmium, lead, and mercury. All tea bags were prepared from the same lot and a sample from this lot was retained.

**Measurement of BP.** SBP and DBP were measured at the brachial artery by use of an automated BP device (Dinamap ProCare 220, GE HealthCare) to minimize investigator variability and terminal digit bias. Recommended procedures for BP measurement, with all possible efforts to minimize common pitfalls, were observed (20). A standardized protocol was followed for each BP measurement: the appropriate cuff size for each participant was determined and the same arm and cuff were used for all measurements. Each participant reported to the Jean Mayer USDA Human Nutrition Research Center on Aging at the same time of day for each measurement and sat in a quiet environment in a comfortable chair, with feet on the floor, for 15 min, after which BP was measured with the arm at heart level. The BP measurement was then repeated every 5 min for the next 15 min. Values for these 3 determinations of SBP, DBP, and mean arterial pressure (MAP) were averaged.

**Sample collection and preparation**

Baseline blood samples from fasting participants were collected during the second baseline visit following the initial fasting BP measurement. Interval blood samples from fasting participants were drawn similarly at each subsequent weekly visit. Blood samples were collected in EDTA-containing evacuated tubes and centrifuged within 15 min of drawing (3000 × g, 15 min, 4°C) with a SUR-Sep cap (Organon Teknika). Plasma samples for anthocyanin analysis were prepared by adding 0.3 mL of 0.44 mol/L trifluoroacetic acid to 1.5 mL of plasma following centrifugation (21). Aliquots were stored in 2-mL NUNC tubes (Vanguard Cryotubes) at −80°C. Fasting clean catch spot urine samples were collected during the second baseline and end of study (wk 6) visits only and stored at −80°C. Urine samples for anthocyanin analysis were prepared by adding 0.2 mL of 0.44 mol/L trifluoroacetic acid to 1-mL aliquots prior to storage at −80°C. All samples for each participant were analyzed within the same run for every assay performed.

**Pilot study to obtain reference standards**

In a separate pilot study, blood and urine samples were collected from 3 of the investigators to serve as reference standards for the analyses of data obtained from participants enrolled in the main study. The purpose of this pilot study was to determine the anthocyanin and total phenol levels that were present in blood and urine within 1 h of consuming the hibiscus tea and in the morning after consuming a total of 3 servings of the hibiscus tea during the previous day. Fasting blood and urine samples were collected using the same procedures described above.

**Biochemical analyses**

**Total phenol and anthocyanin content.** The total phenol content of freshly brewed *H. sabdariffa* tea and placebo beverage was determined by the Folin-Ciocalteu reaction (22). Results are expressed as μmol/L gallic acid equivalents. The concentration of total anthocyanins was determined spectrophotometrically (23).

**Anthocyanins in beverages.** Identification and quantification of individual anthocyanins in the study beverages was achieved with HPLC (24) against a standard curve of authenticated cyanidin-3-glucoside. Concentrations of delphinidin-3-sambuboside and cyanidin-3-...
sambubioside in the beverages are expressed as cyanidin-3-glucoside equivalents. The limit of detection was 1 pmol on column.

**Anthocyanins in plasma and urine.** Anthocyanins in plasma and urine were extracted according to the method of Cao and Prior (25) before HPLC analysis (24).

**Oxygen radical absorbance capacity.** Oxygen radical absorbance capacity (ORAC) values of the study beverages were determined according to the method of Ou et al. (26). All data are expressed as μmol trolox equivalent/g.

**Dietary assessment.** Dietary assessments were made during the second baseline (wk 0) and end of study (wk 6) visits using a validated FFQ (Fred Hutchinson Cancer Research Center Food Frequency Questionnaire version 06.10.88, Cancer Prevention Research Program, Fred Hutchinson Cancer Research Center, Seattle, WA) to determine usual nutrient intakes and detect any significant changes that may have occurred during the intervention period.

**Compliance.** Compliance was measured by having each participant record their assigned beverage intake using a daily diary chart and by having the study dietitian count unused tea bags or measure unused placebo concentrate at each visit. Compliance with the study protocol was >90%.

**Sample size.** The sample size was calculated to detect a clinically relevant difference in SBP between the intervention and placebo groups (20). A previous study reported the consumption of a beverage prepared with *H. sabdariffa* reduced SBP by 17.6 ± 6.8 mm Hg (mean ± SD) in hypertensive patients (*n* = 54) (16). On the basis of this study, a sample size of 30 participants/group is sufficient to detect a 5-mm Hg change in SBP with 80% power and α = 0.05.

**Statistical analyses.** Statistical analyses were performed using SPSS version 15.0 according to a preestablished analysis plan. Data were collected on BP measurements and anthocyanin levels in plasma and urine (pilot study) and from FFQ. The mean fasting SBP and DBP measurements collected on visits 1 and 2 were combined and serve as the baseline (preintervention) BP reading. Mean BP measurements collected from each visit thereafter serve as postintervention readings. Tests of repeated-measures ANOVA, including linear time contrasts, and Student’s *t* test were used to determine significant changes in SBP and DBP between placebo and experimental groups over the course of the intervention, i.e., the a priori hypothesis. Paired *t* tests were used to compare changes with baseline values. Pearson correlation coefficients (*r*) and nominal *P*-values were computed to assess the linear relationship between baseline BP and change from baseline. Multiple regression was used to assess the independent predictive capability of age, gender, and dietary supplement use. Student’s *t* test and chi-square analyses were used to compare baseline characteristics (age, gender, ethnicity, education, menopausal status, baseline BP, nutrient intake) between the placebo and experimental groups. Unless otherwise noted, results are expressed as mean ± SD. *P* < 0.05 was considered significant.

**Results**

Both beverages were analyzed for their total phenol content, anthocyanin levels (delphinidin-3-sambubioside and cyanidin-3-sambubioside), and antioxidant capacity (using the ORAC assay) (Table 1). The placebo beverage contained none of the anthocyanin compounds present in the *H. sabdariffa* tea.

The baseline demographic and clinical characteristics of the 2 groups were similar (Table 2). Participants’ usual dietary intake of energy, macronutrients, micronutrients known to affect BP, alcohol, and caffeine did not differ between the placebo and treatment groups during the intervention. Regression analysis revealed no significant predictive capability of age, gender, or dietary supplement use once baseline SBP and treatment were accounted for.

Following 6 wk of treatment, the change in SBP among participants who consumed the *H. sabdariffa* tea was greater than in participants who consumed the placebo beverage (*P* = 0.030) (Table 3). The change in DBP after treatment was not significant between the placebo and *H. sabdariffa* tea groups (*P* = 0.160). Although the change in MAP was greater in participants who consumed the *H. sabdariffa* tea, the significance of this change relative to the change in the placebo group after 6 wk was borderline (*P* = 0.054). Compared with baseline, 6 wk of treatment with *H. sabdariffa* tea lowered mean SBP by 5.5% (*P* = 0.001), DBP by 4.0% (*P* = 0.013), and MAP by 4.7% (*P* = 0.002), whereas the placebo beverage did not affect these variables. In the *H. sabdariffa* group, the magnitude of SBP reduction was higher in individuals with higher baseline SBP. The change in SBP from baseline to 6 wk was linearly correlated with baseline SBP (*r* = −0.421; *P* = 0.010) (Fig. 1). No significant correlations were observed in the placebo group. A significant treatment × linear time interaction (*P* = 0.018) was observed for interval changes in SBP (Fig. 2).

Levels of the major *H. sabdariffa* anthocyanins, delphinidin-3-sambubioside and cyanidin-3-sambubioside, were not detectable in the plasma and urine of participants in the pilot study to obtain reference standards. Therefore, we presumed that levels of these anthocyanins would not be detected in the plasma and urine samples from participants enrolled in the main study and no further analyses of these anthocyanins were conducted.

### Table 1 Major phenolic components and antioxidant activity per serving of the placebo beverage and *H. sabdariffa* tea

<table>
<thead>
<tr>
<th>Component</th>
<th>Placebo</th>
<th>Hibiscus tea</th>
</tr>
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<tbody>
<tr>
<td>Total phenols, mg gallic acid equivalents</td>
<td>2.17</td>
<td>21.85</td>
</tr>
<tr>
<td>Total anthocyanins, mg CSE</td>
<td>0.00</td>
<td>7.04</td>
</tr>
<tr>
<td>Delphinidin-3-sambubioside, mg CSE</td>
<td>0.00</td>
<td>3.69</td>
</tr>
<tr>
<td>Cyanidin-3-sambubioside, mg CSE</td>
<td>0.00</td>
<td>0.02</td>
</tr>
<tr>
<td>ORAC, μmol trolox equivalents</td>
<td>275</td>
<td>1950</td>
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</tbody>
</table>

1 Cyanidin glucoside equivalents.

### Table 2 Baseline characteristics of study participants

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Hibiscus tea</th>
</tr>
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<tbody>
<tr>
<td>n</td>
<td>30</td>
<td>35</td>
</tr>
<tr>
<td>Age, y</td>
<td>54.3 ± 11.3</td>
<td>54.2 ± 10.8</td>
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<tr>
<td>BMI, kg/m²</td>
<td>28.3 ± 3.8</td>
<td>27.4 ± 3.7</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>65.5 ± 10.3</td>
<td>66.8 ± 9.4</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>17 (56.7)</td>
<td>20 (57.1)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>13 (43.3)</td>
<td>15 (42.9)</td>
</tr>
<tr>
<td>Caucasian, n (%)</td>
<td>21 (70.0)</td>
<td>21 (60.0)</td>
</tr>
<tr>
<td>African-American, n (%)</td>
<td>4 (13.3)</td>
<td>7 (20.0)</td>
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<tr>
<td>Asian-American, n (%)</td>
<td>3 (10.0)</td>
<td>3 (8.6)</td>
</tr>
<tr>
<td>Hispanic, n (%)</td>
<td>0 (0.0)</td>
<td>1 (2.9)</td>
</tr>
<tr>
<td>Other, n (%)</td>
<td>2 (6.7)</td>
<td>3 (8.6)</td>
</tr>
<tr>
<td>Postmenopausal, n (%)</td>
<td>10 (33.3)</td>
<td>13 (37.1)</td>
</tr>
<tr>
<td>Estrogen use, n (%)</td>
<td>1 (3.3)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Dietary supplement use, n (%)</td>
<td>18 (60.0)</td>
<td>16 (45.7)</td>
</tr>
</tbody>
</table>

1 Values are means ± SD or n (%). Groups did not differ at baseline.

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Discussion

Daily consumption of 3 servings of *H. sabdariffa* (hibiscus) tea, an amount readily incorporated into the diet, effectively lowered BP in pre- and mildly hypertensive adults. Dietary intake of vitamin C, sodium, potassium, calcium, magnesium, and other dietary factors known to have an effect on BP, i.e. alcohol and caffeine, did not differ between the placebo and treatment groups during the intervention and, thus, were not responsible for the observed change in BP. Regression analysis indicated that the hibiscus tea treatment was responsible for the BP-lowering effect regardless of age, gender, or dietary supplement use.

This is the first reported placebo-controlled clinical trial, to our knowledge, to examine the effect of hibiscus tea on BP. Previous studies conducted in hypertensive patients used a higher dose of *H. sabdariffa* to compare its effects with that of either black tea (16) or a hypotensive drug (18). Haji Faraji and Haji Tarkhani (16) tested 54 patients, mean age 52 y, in a hospital-based, randomized, clinical trial over a 15-d period. In their study, the treatment group consumed 1 glass daily of *H. sabdariffa* tea prepared with 2 spoonfuls of blended tea per glass brewed in boiling water for 20–30 min. No quantitative analysis of the potential active ingredients in the *H. sabdariffa* beverage was reported, although it can be assumed that the higher quantity of dried calyces used in their study, and the longer brew time, provided a dose higher than our study. Their control group consumed black tea prepared similarly. Black tea is not an inert placebo because it contains caffeine, catechins, and flavonols, compounds known to affect vasodilation. Herrera-Arellano et al. (18) compared *H. sabdariffa* with an angiotensin converting enzyme (ACE) inhibitor in a randomized trial of 75 patients aged 30–80 y. In their study, an infusion prepared with 10 g of dry calyces from *H. sabdariffa* in 0.5 L water (9.6 mg anthocyanins) and administered daily was compared with 25 mg captopril administered twice daily for 4 wk and SBP did not differ between the groups (ANOVA *P* > 0.25).

The magnitude of change in SBP from baseline in both the Haji Faraji and Haji Tarkhani (16) and Herrera-Arellano et al. (18) studies was approximately double the amount we observed. This outcome was not unexpected, because the participants in these nonplacebo–controlled studies had higher initial SBP (+10–30 mm Hg) and DBP (+12–22 mm Hg) than our participants and were taking antihypertensive medication prior to the intervention.

The BP-lowering effects of hibiscus tea observed in our study were greater than those reported in 2 large dietary interventions, the Dietary Approaches to Stop Hypertension (DASH) (27) and **TABLE 3** BP change in prehypertensive and mildly hypertensive adults following a 6-wk intervention with placebo beverage or *H. sabdariffa* tea1

<table>
<thead>
<tr>
<th></th>
<th>Placebo, <em>n</em> = 30</th>
<th>Hibiscus tea, <em>n</em> = 35</th>
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<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>6 wk</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>129.8 ± 6.9</td>
<td>128.6 ± 10.6</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>78.6 ± 5.5</td>
<td>79.0 ± 8.2</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>96.3 ± 4.8</td>
<td>95.5 ± 7.8</td>
</tr>
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</table>

1 Values are means ± SD. Group means did not differ at baseline. *Different from baseline at 6 wk, *P* < 0.05; †Different from placebo at 6 wk, *P* < 0.05.

**FIGURE 1** Changes in SBP (A) and DBP (B) relative to baseline values in prehypertensive and mildly hypertensive adults following a 6-wk intervention with placebo beverage (*n* = 30) or hibiscus tea (*n* = 35). Linear regression lines and 95% CI are depicted. Correlation coefficients *r* and nominal *P*-values were calculated with the Pearson test.
confers a greater reduction in BP than either approach alone. Future research should consider whether effective strategy for controlling BP among pre- and mildly hypertensive adults. The potential mechanisms of action for the BP-lowering effect of hibiscus tea could be due to its major flavonoid components, delphinidin-3-sambubioside and cyanidin-3-sambubioside. However, other phytochemicals present might also contribute to this effect (29). Herraro-Arellano et al. (19) demonstrated the BP-lowering effects of a standardized H. sabdariffa extract containing 250 mg of these anthocyanins in a 4-wk study of 171 hypertensive patients. The extract lowered BP from baseline after 4 wk ($P < 0.05$), although the magnitude of this effect was lower than that achieved in the comparison group treated with 10 mg lisinopril ($P < 0.05$). The daily anthocyanin dose in our study was much lower than this and may have been below the limit of detection in body fluids after consumption when assessed with HPLC. This was confirmed in our pilot study during which no anthocyanins were detected in plasma or urine within 1 h of consuming the hibiscus tea, despite being within the time observed by Frank et al. (21) to achieve peak plasma concentrations. Other bioavailability studies show that anthocyanins are rapidly absorbed and eliminated and that they are absorbed with poor efficiency (30). Whereas the maximum hypotensive effect was observed after a few weeks of treatment, further research is warranted to understand the relative contributions of the acute and chronic actions of hibiscus. Other potential mechanisms of action related to the effects of the anthocyanins present in H. sabdariffa are also possible (36–39).

Previous studies indicate the consumption of polyphenol-rich foods may induce beneficial changes in pathways related to cardiovascular health (40). Animal models and a limited number of human studies have shown beneficial changes in measures related to cardiovascular health following the consumption of polyphenols, including increases in endothelial function and inhibition of platelet aggregation (41). The specific attributes of H. sabdariffa to cardiovascular health, including its ability to lower BP (12–19) and its potential hypocholesterolemic effects (9–11), are not well understood and further research in this area is warranted.

The major strengths of our study include the randomized, double-blind, placebo-controlled study design and the use of a standardized method to measure BP. Limitations include sample size and duration, as well as the lack of data related to the bioavailability and potential mechanisms of action of H. sabdariffa.

Hypertension is a major risk factor for cardiovascular disease and is associated with substantial morbidity and mortality, estimated to account for 35% of myocardial infarction and stroke, 49% of heart failure, and 24% of premature mortality (42). Lifestyle modification, including dietary change, is the recommended first-line approach to prehypertension (20). The dietary change assessed in this study, i.e. regularly incorporating 3 servings/d of hibiscus tea into the diet, effectively reduces BP in pre- and mildly-hypertensive adults. This strategy may be useful in preventing the progression to moderate or more severe hypertension, potentially reducing the subsequent risk of developing cardiovascular disease.

Acknowledgments

D.L.M., J.B.B., and E.S. designed research; D.L.M. and C-Y.O.C. conducted research; D.L.M. analyzed data, wrote the paper, and had primary responsibility for final content. All authors read and approved the final manuscript.
Literature Cited


