Hibiscus

An emerging new botanical medicine

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The Hibiscus genus (family Malvaceae) is comprised of several species, many of which have been used historically for their culinary and medicinal properties. The species Hibiscus sabdariffa is an important medicinal plant grown in Africa, the Middle East, South East Asia and Central America (Ojeda 2010). Traditionally, the aqueous extract of H. sabdariffa, colloquially known as sour tea, has been used to treat hypertension, liver disease and fever (Mozaffari-Khosravi 2009).

More recently, the anti-oxidant, lipid and blood pressure lowering effects of Hibiscus sabdariffa have been investigated. H. sabdariffa extracts have demonstrated anti-oxidant properties, hypolipidemic effects, ACE inhibition and inhibition of vascular smooth muscle cell proliferation and migration secondary to hyperglycemia (Huang 2009, Kao 2009, Ojeda 2010, Yang 2010). Considering its nutritional profile, pharmacological properties and safety, H. sabdariffa shows promise as a cardio-protective agent and potential diabetic therapy (Mozaffari- Khosravi 2009).

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Chemistry

H. sabdariffa contains various phytochemicals, including phenolics, organic acids, sterols, terpenoids, polysaccharides and some minerals (Ojeda 2010). The phenolic content is composed mainly of anthocyanins delphinidin-3-O-sambubioside (85%) and cyanindin-3-O-sambubioside, plant pigments that are isolated from dried calyces (Frank 2005). Anthocyanins, a subgroup of flavonoids, are water-soluble glycosides and acylglycosides of anthocyanidins (Frank 2005). Other phenols include protocatechuic acid, catechin, gallocatechins, caffeic acid and gallocatechin gallates (Yang 2010).

An aqueous extract of H. sabdariffa (HSE) contains varying concentrations of anthocyanins and polyphenols depending on the processing method and storage time (Frank 2005). Regardless, HSEs contain effective antioxidants, radical scavengers and ferric-reducing compounds, the properties which likely impart their therapeutic benefit (Frank 2005).

Preclinical evidence

Anti-oxidant Effects

Oxidation of low-density lipoprotein (oxLDL) occurs in the early stages of atherosclerotic lesion formation. Scavenger receptors have been identified that bind and internalize oxLDL, mediating its uptake into macrophages and leading to the formation of macrophage-derived foam cells. CD36 has been identified as the predominant scavenger receptor for oxidized LDL and its regulation plays an essential role in the formation of macrophage foam cells and atherosclerosis (Kao 2009).

The most recent study investigating the anti-oxidant activity of H. sabdariffa and LDL oxidation was completed by Kao et al (2009). Hibiscus anthocyanin-rich extracts (HAs) prevented lipid accumulation, significantly decreased CD36 mRNA gene and protein expression and significantly decreased PPARγ protein levels, the CD36 upstream transcription factor, in mouse cells treated with oxidized LDL. The study demonstrated that the antioxidant activity of HAs may ultimately inhibit the formation of oxLDL-foam cells.

Hypolidemic Effects

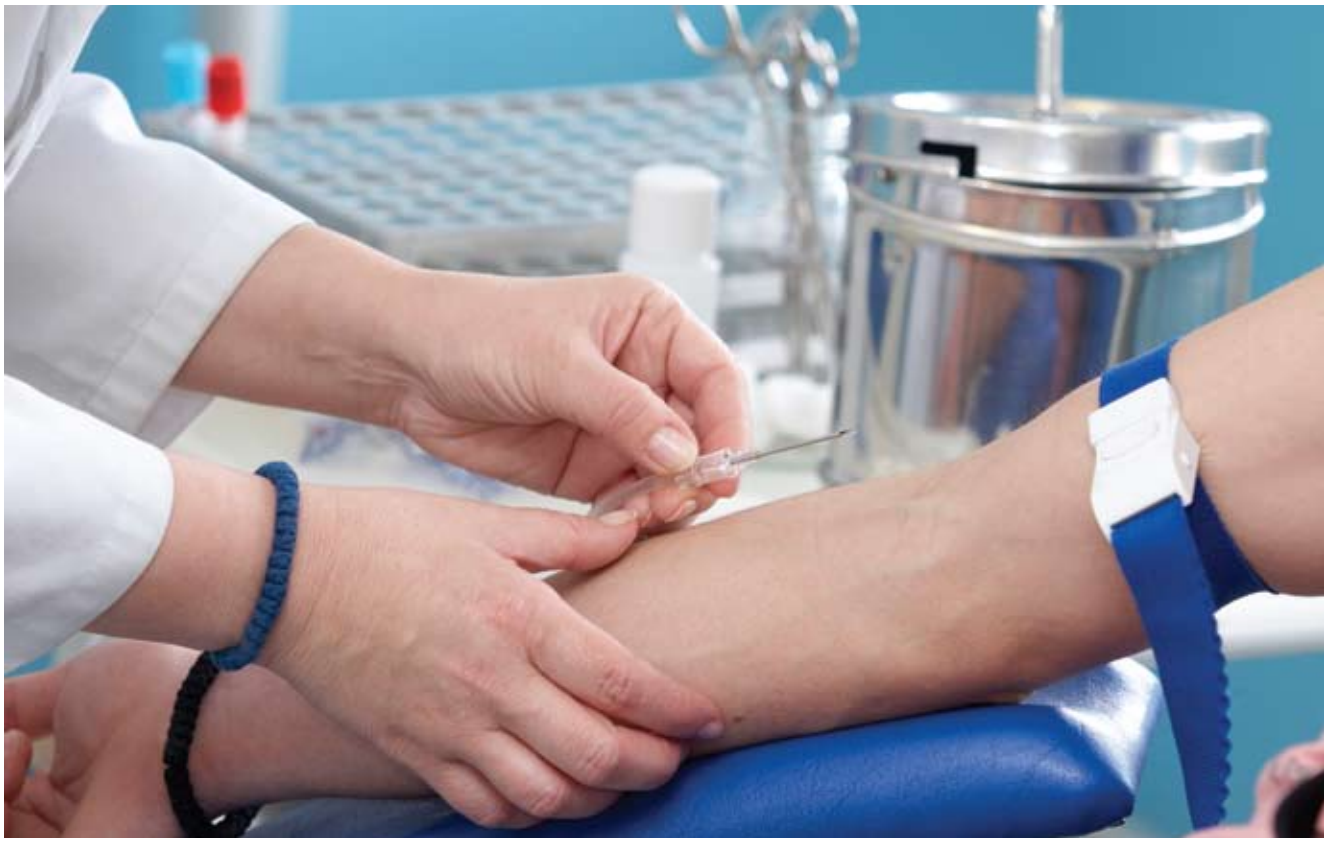
The hypolipidemic effect of a Hibiscus sabdariffa 74% polyphenol extract (HPE), composed mostly of protocatechuic acid (PCA), caffeic acid and gallocatechin gallate (GCG) were investigated in an animal model (Yang 2010). Hamsters were fed a high fat diet for 10 weeks with or without HSE or HPE; both HSE and HPE fed hamsters experienced a decrease in serum triglycerides and total cholesterol in a dose-dependent manner. However, the HPE had a greater effect on decreasing plasma and LDL cholesterol and increasing HDL than a crude extract (HSE) containing only 2% polyphenols.

At 0.5 mg/mL, HPE decreased fatty acid synthase and HMG-CoA reductase 75% and 69% respectively. The HSE did not alter the protein expression of fatty acid synthase, but rather altered the phosphorylation of AMP-activated protein kinase (AMPK). Previous reports have outlined the importance of AMPK in regulating lipid metabolism; activation (phosphorylation) of AMPK simultaneously inhibits fatty acid and cholesterol synthesis in rat hepatocytes by inactivating the acetyl CoA carboxylase and HMG CoA reductase, respectively (Yang 2010).

In addition the activation of AMPK by HPE decreased the expression of sterol regulatory element binding protein (SREBP), a membrane bound transcription factor which regulates lipid metabolism, and the transcription of its target genes, HMG CoA reductase and fatty acid synthase. Further investigation revealed that HPE also enhances the expression of the LDL-receptor, increasing LDL uptake and hepatic clearance (Yang 2010).

ACE-Inhibition Effects

The inhibition of angiotensin I converting enzyme (ACE) by H. sabdariffa has been demonstrated in vitro with a crude hydroethanol extract from the plant calyces (Ojeda 2010). Using an aqueous extract of H. sabdariffa, delphinidin-3-O-sambubioside and cyanidin-3-O-sambuioside were identified as the two most abundant anthocyanins. Evaluation of in vitro ACE inhibition was completed by quantifying the hydrolysis of N-[3-(2-furyl)



acryloyl]-L-phenylalanylglycylglycine (FAPGG) by ACE, both of which were isolated from rabbit lung. A combined anthocyanin-rich fraction, as well as isolated extracts of each anthocyanin were used to inhibit ACE activity in a dose-dependent manner. Both anthocyanins were more effective on their own than the combined extract, and delphinidin-3-O-sambubioside was more effective than cyanidin-3-O-sambubioside, likely owing to the fact that it has more hydroxyl groups. Kinetic analysis suggested ACE was inhibited by the anthocyanins via competition for the enzyme's active site, most likely due to the rigid planar structure of the anthocyanins and the presence of ortho-dihydroxylation on the aromatic ring.

Inhibition of Vascular Smooth Muscle Cell Proliferation

In hyperglycemia of metabolic syndrome or diabetes mellitus, high-glucose conditions mediate the growth and extracellular matrix (ECM) gene expression of vascular smooth muscle cells (VSMC) to promote anti-apoptotic signalling, chemotaxis and migration. Hyperglycemia also promotes the formation of advanced glycation end (AGE) products, which is believed to play a role in atherosclerotic plaque formation when they interact with their specific receptor (Receptor for Advanced Glycation End Products-RAGE) (Huang 2009).

A polyphenolic extract of H. sabdariffa was examined for its protective activity against high-glucose-treated VSMC. The extract reduced the high-glucose-stimulated cell proliferation and migration in a dose and time dependent manner (Huang 2009). Proliferating cell nuclear antigen (PCNA), a marker of proliferation, and activation of matrix metalloproteinase (MMMP)-2, the ECM-degrading enzyme during the process of migration, were suppressed by treatment with the H. sabdariffa extract. Furthermore, expression of connective tissue growth factor (CTGF) and RAGE, usually enhanced by hyperglycemia, were also suppressed by treatment with the extract.

Pharmacology

In a study examining the pharmacokinetics of monomeric anthocyanins after consumption of H. sabdariffa extracts, the anthocyanins were incorporated and excreted in urine in their intact glycosidic forms. 147.4 mg of total anthocyanins were administered to six healthy subjects and maximum excretion rates occurred at 1.5-2.0 hours after ingestion. While oral absorption of H. sabdariffa anthocyanins was fast, maximum plasma concentrations were low, between 1.3-3.4 ng/ml. Peak plasma concentrations occurred almost simultaneously as urinary excretion rates, with maximum excretion rates occurring at 1.5-2.0 hours after ingestion (Frank 2005).

Some evidence suggests that deglycosylation is the rate-limiting step for the absorption of dietary flavonoid glycosides in the small intestine. β-glucosidases, lactase-phlorizin hydrolase (LPH), and the cytosolic β-glucosidase (CBG) are found in the epithelial cells of the small intestine and normally function to deglycosylate flavonoid glycosides during passage across the gut wall (Nemeth 2003). Anthocyanins are not substrates for these β-glucosidases and this may explain the low bioavailability of these compounds,

Table 1. Human trials of hibiscus

Methods	Outcome	References
A double-blind, placebo controlled trial (n=57) enrolled subjects with LDL-c levels of 130-190 mg/dl divided into groups receiving either HSE capsules (500 mg bid) or placebo for 90 days. Overweight patients were advised to achieve weight loss of 5%.	Body weight and serum LDL significantly decreased in both groups from baseline with no difference between groups. LDL decreased 18% in the hibiscus group and 12% in the control group. The difference between groups was not significant. Serum triglycerides were reduced a significant 10% in the hibiscus group and not significantly impacted in the control group.	Kuriyan 2010
A double-blind, randomized, placebo controlled trial (n=65) recruited pre- and mildly hypertensive adults (SBP 120-150 mmHg, DBP < 95 mmHg, BMI 18.5-35) and divided them into two groups. Participants received 3 x 240 ml servings/day of brewed Hibiscus tea steeped for 6 minutes (1.25 g dried H. sabdariffa per tea bag) or placebo for six weeks.	In the treatment group, SBP, DBP and MAP significantly decreased by 5.5%, 4.0% and 4.7% respectively. The magnitude of effect was higher in individuals with higher baseline SBP. There was no significant difference in these measurements in the placebo group. Between group differences were only significant for SBP.	McKay 2010
A follow-up study carried out in a factorial, randomized design (n=124) divided participants into two groups, those with and without metabolic syndrome (MeSy). Subjects in both groups were randomly allocated into three treatment groups: preventative diet, HSE capsules (100 mg qd) or diet combined with HSE capsules for 31 days.	Among patients without metabolic syndrome hibiscus achieved significant reductions in fasting glucose (6.7%) and triglyceride (23%), and increased HDL-C (10%). Among patients with metabolic syndrome hibiscus significantly reduced fasting glucose (8.4%), total cholesterol (10%), and LDL-C (20%), and increased HDL-C (39%).	Gurrola-Diaz 2010
A sequential randomized controlled clinical trial (n=53) enrolled subjects with type II diabetes mellitus. Subjects were divided into two groups and received either Hibiscus tea (sour tea) or black tea as treatment (2 g bid) for 30 days. The tea was prepared by adding 240 ml of water, steeping for 20-30 minutes and adding one cube (5g) of sugar. Fasting cholesterol levels were assessed on day zero and day 30. Blood pressure was assessed on day zero, day 15, and day 30.	- In the treatment group, total cholesterol, LDL-c, triglycerides and Apo-B100 decreased by 7.6%, 8.0%, 14.9% and 3.4%, respectively, and HDL-c increased 16.7% (p=0.002). Only the changes in triglycerides, Apo-B100 and HDL-c were significant. - In the treatment group, mean SBP significantly decreased from 134.4 + 11.8 mmHg at day 0 to 112.7 + 5.7 mmHg at day 30 (p < 0.001), while it significantly increased in the black tea group (from 118.6 + 14.9 mmHg to 127.3 + 8.7 mmHg). Similarly, the mean PP decreased in the HSE group (p < 0.001) and increased in the black tea group (p = 0.01). No significant changes were observed in DBP in either group.	Mozaffari-Khosravi 2009a Mozaffari-Khosravi 2009b
A randomized controlled, double-blind clinical trial (n=171) comparing Hibiscus sabdariffa dried extract (standardized to 250 mg of total anthocyanins qd) and lisinopril (10 mg qd) in patients with stage I or II hypertension for four weeks.	In the group treated with Hibiscus, systolic and diastolic blood pressure was reduced 11.58% and 12.21% (p < 0.05). Although BP reductions and therapeutic effectiveness were significantly less than the lisinopril group (15.79% reduction to systole and 15.68% reduction to diastole), patients treated with HSE showed decreased plasma ACE activity (p = 0.0001) and reduced serum sodium levels without changes in serum potassium levels. The authors concluded that HSE seems to exert an antihypertensive action through dieresis and ACE inhibition.	Herrera-Arellano 2007
A randomized controlled clinical trial (n=75) compared the antihypertensive effectiveness and tolerability of HSE (10g of dry calyx prepared in 500 mL water and steeped for 10 minutes, 9.6 mg anthocyanins qd) and 25 mg of captopril bid for 4 weeks.	Significant reductions in blood pressure values were observed in both groups; hibiscus group -10.2% SBP, -12.3% DBP, captopril group -11.4% SBP, -14.3% DBP. The differences between the hibiscus group and the captopril group were not significant.	Herrera-Arellano 2004
A randomized controlled clinical trial (n=54) evaluated the effect of HSE on essential hypertension (SBP 160-180 mmHg, DBP 100-114 mmHg) compared with regular tea. Patients were instructed to consume one glass of decoction (two spoonfuls of tea boiled in one glass of water for 20-30 minutes) at least one hour before measuring blood pressure. Blood pressure was measured at days four, eight, 12 and three days after stopping treatment. Patients were also advised to exercise, abstain from excessive salt intake, saturated fats and smoking.	Blood pressure was lowest on the 12th day in the treatment group, with an 11.2% decrease in SBP and 10.7% decrease in DBP. Three days after cessation of drinking tea, SBP increased and DBP increased to pre- treatment levels.	Faraji 1999

HSE = Hibiscus sabdariffa extract (unless otherwise stated), SBP = systolic blood pressure, DBP = diastolic blood pressure, LDL-c = low density lipoprotein cholesterol, HDL-c = high density lipoprotein cholesterol, PP = pulse pressure

as they were not hydrolyzed to their aglycones and were absorbed only as intact glycosides in small amounts (Frank 2005). However, it is known that most polyphenols ingested from flavonoid-rich beverages are metabolised in the colon (Rechner 2002).

The half-life of total anthocyanins from the H. sabdariffa extract was derived from urinary excretion and was determined to be 2.63 hours (Frank 2005). In a separate study, H. sabdariffa calyx extracts demonstrated a very low degree of toxicity, with an LD50 above 5000 mg/kg in rats (Onyenekwe 1999). Further studies are needed on human plasma and urinary intact glycosides and their in vivo metabolites and/or conjugates in order to fully characterize the pharmacokinetics of H. sabdariffa (Frank 2005).

Human evidence

We identified seven controlled human clinical trials evaluating hibiscus preparations. See Table 1. Five of the trials evaluated impact on blood pressure, three trials evaluated impact on serum lipid profiles, and one trial evaluated impact on plasma glucose levels. Only one trial failed to demonstrate a positive outcome; the trial evaluated impact to cholesterol levels and was compounded by recommendations to achieve reductions in body weight. Therefore both the hibiscus group and the control group experienced significant improvement in cholesterol profiles, with no significant difference between the two groups (Kuriyan 2010).

All five trials evaluating blood pressure demonstrated significant benefit, with a magnitude of effect ranging from 5-15% for reductions to systole and diastole (Faraji 1999, Herrera-Arellano 2007, Herrera-Arellano 2004, Mozaffari-Khosravi 2009b, McKay 2010). The two trials demonstrating positive impact to cholesterol levels revealed reductions in total cholesterol, LDL- cholesterol and triglyceride, as well as increased HDL-C levels (Gurrola-Diaz 2010, Mozaffari-Khosravi 2009a). The only trial to evaluate glucose levels likewise demonstrated significant improvement to glucose control (Gurrola- Diaz 2010).

Discussion

Hibiscus, delivered in an array of dosage forms (standardized extracts, teas, decoctions), has demonstrated an impressive magnitude of benefit to key metabolic abnormalities, notably the constellation of abnormalities comprising the diagnostic criteria of the metabolic syndrome; glucose control, blood pressure, and plasma cholesterol levels, specifically triglyceride and HDL-cholesterol (as defined by Grundy 2004). The ease of delivery, the marginal cost of the medicine (especially in tea or decoction dosage forms), and an impressive safety profile make hibiscus a promising medicine for an array of very common clinical presentations. Longer- term trials are needed to determine if the effects of hibiscus are sustained beyond 30 days. Also, impact to blood glucose control deserves more research attention. •

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