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REVIEWS

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A review and update on the use of *Hibiscus sabdariffa* (karkadeh) in the treatment of essential hypertension

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A – Study Design, **B** – Data Collection, **C** – Statistical Analysis, **D** – Data Interpretation, **E** – Manuscript Preparation, **F** – Literature Search, **G** – Funds Collection

Summary **Background.** Essential hypertension is a common, significant worldwide disease whose adequate treatment requires a multidrug regime in 70% of patients, where adherence to treatment ranges from low to very low (72.7% to 19.7%), and where each additional medication used causes a decrease in adherence by up to 85%. *Hibiscus sabdariffa* L. (HS) is a widely used herb which has been used for its antihypertensive effect, which may offer to play a useful synergistic role to pharmacotherapy.
Objectives. This review sought to identify relevant basic laboratory studies, human randomised controlled studies (RCTs), meta-analysis and reviews studying the safety, mechanism and/or effect of HS on blood pressure.
Material and methods. A search was done, ending on the 1st of October 2019, of the following databases: Medline, COCHRANE and EMBASE. RCTs were assessed for quality using the Jadad scale.
Results. Basic laboratory studies have shown that HS is rich in bioactive anthocyanins, which inhibit angiotensin-converting enzyme (ACE) in a dose-dependent manner, and HS extracts also have a direct vasodilator effect. 13 safety studies have found HS to be safe at normal doses with minimal clinically important drug-herb interaction. Very high doses (> 300 mg/kg/day) are associated with liver enzyme abnormalities and raised uric acid in rat studies. 14 RCTs show that HS causes a significant reduction in systolic blood pressure (-6.3 to -31.9 mm Hg) and diastolic blood pressure (-1.1 to -19.7 mm Hg).
Conclusions. HS is a widely available, acceptable, cheap and effective synergistic agent in the management of essential hypertension.
Key words: essential hypertension, hibiscus, therapeutics.

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Background

Hypertension is one of the most common diseases in the world, with a global prevalence estimated to be 31% [1] and a similar prevalence in Arab countries at 29.5% [2], with an annual incidence of 8.6% in men and 8.2% in women [3]. With a mortality rate of 13%, it is one of the leading causes of death [2]. Many patients (almost 70%) fail to reach therapeutic targets (< 140/90 mm Hg) with monotherapy, and polytherapy is required for effective control [4].

The challenge of adherence

Adherence to treatment is poor. Medication event monitors show that half of patients stop treatment within a year, and 48% have a drug holiday – a cessation of medication for three or more days, especially on weekends [5]. A study conducted in Poland showed that while most patients (72.7%) are adherent with their anti-hypertensives, it is halved if they are on polytherapy compared to those on monotherapy [6]. Studies looking at urinary and serum metabolites of medication as a markers of adherence have shown adherence rates to antihypertensive medication to be 58.4% in the UK and 68.5% in the Czech Republic, with nonadherence increasing by 85% (UK) and 77% (Czech) for each additional antihypertensive medication [7]. Data from the Middle East area is similarly low: Jordan and Lebanon 55.9% [8], while in Saudi Arabia, the rate of adherence in females is 59%, but is significantly lower in males at 19.7% [9].

Attitude of patients and doctors to herbal treatments

Over 25% of patients with hypertension reported the use of herbal medication based on recommendations from family and friends with little information from doctors [10]. Compliance for non-pharmacological therapy for hypertension is relatively higher [6]. Hypertensive patients have a higher likelihood of using herbal treatments [11]. Usage of herbal treatments is widespread, especially in low-income countries [12], and they are widely available over the counter, through the web and even in popular markets [13]. Herbs are considered "natural products", and patient adherence to herbal treatments is higher, and they report a better quality of life [14].

The majority of family physicians have a negative view of the effectiveness of herbal medicine [15], and they are apprehensive of their safety due to poor regulation by authorities [13]. Case reports of hepatotoxicity and occasional deaths associated with some herbs, such as *Polygonum multiflorum* Thunb. (tuber fleeceflower), support a blanket 'do no harm' approach [16].

A combined approach

In recognition of the World Health Organisation's Traditional Medicine strategy [17] to "strengthen the role traditional medicine plays in keeping populations healthy", this article aims to provide an update and review of the latest research on *Hibiscus sabdariffa* L. (HS), a traditional herb thought to have originated in India or Africa [18]; its common names are roselle and

karkadeh in Arabic. HS offers a potentially synergistic effect with traditional pharmacotherapy, which family doctors may be able to draw upon when offering lifestyle and dietary advice to patients, especially for those that are reluctant to climb the ladder of pharmacological treatments.

Methods

The need for approval was ascertained from the Primary Health Care Corporation Research subcommittee, who advised that ethical approval was not required. The following databases were searched for relevant publications prior to October 2019 by the first two authors: Medline via PubMed, EMBASE, Cochrane Central Register of Controlled Trials. The search strategy used is given by the following nested Boolean string: ((*hypertens*[Title]) OR (essential hypertension[Title]) OR (blood pressure[Title]) OR (Essential Hypertension[MeSH Terms]) OR (Hypertension[MeSH Terms]) OR) AND ((hibiscus*[Title]) OR (sabdariffa*[Title]) OR (roselle*[Title]) OR (karkad*[Title])).

Studies included in this review were human RCTs, meta-analyses, reviews and interventional trials. Studies over 10 years old, case reports and non-English publications were excluded.

Results

Biological mechanism of action

HS contains bioactive anthocyanins, responsible for the red, purple and blue colours in the plants. Anthocyanins inhibit platelet aggregation, cause vasorelaxation, have antioxidant activity, reduce cellular lipid peroxidation and improve lipid profiles [19]. HS calyces are rich in anthocyanins (622.91 mg/100 g) [20], with good antioxidant capacity [21].

Two anthocyanins extracted from HS delphinidin-3-O-sambubioside and cyanidin-3-O-sambubioside inhibit angiotensin-converting enzyme (ACE) activity by competing with the active site in a dose-dependent manner, with an average 50% inhibitory concentration on ACE function (IC_{50}) of 132.55 μM [22]. Compared to the IC_{50} for captopril 23 nM [23], they are weak inhibitors of ACE function.

Other mechanisms include a direct vasodilator effect mediated by an endothelium-derived nitric oxide-cGMP-relaxant pathway and inhibition of calcium (Ca(2+))-influx into vascular smooth muscle cells [24] and activation of endothelial nitric oxide synthase [25]. Acute consumption of HS also increases flow mediated dilatation of the brachial artery [26].

Safety and drug interaction

Data from 13 studies shows that HS has little effect on liver enzymes, electrolytes and trace elements, except at very high doses of greater than 300 mg/kg/day over 3 months, which had an adverse impact of liver enzymes and increased uric acid levels in rat studies [27]. The LD50 for HS ranges from 2,000 to 5,000 mg/kg/day [27] as compared to the LD50 for caffeine at 367 mg/kg [28]. Typical daily doses used in HS RCTs have been 9 mg/kg [29], 14 mg/kg [30] up to 17 mg/kg [31]. HS infusion and powdered extracts are very likely to be safe when used in the dosages studied, though caution may be needed in patients with hepatic pathology and gout.

HS-drug interaction

HS increases the diuretic effect and slows elimination of hydrochlorothiazide in a dose-dependent manner [32]. Human volunteer studies show that it slows the elimination of acetaminophen by 11.69% [33]. In vitro studies show a minimal impact on cytochrome P450 isoenzymes and the pharmacodynamics of caffeine [34]. Current data shows no clinically relevant HS-drug interactions.

Table 1. Data obtained from studies

Author	Study design	No. of patients	Administration method	HS Daily Dose	Baseline SBP/DBP (mm Hg)	Mean change (mm Hg) SBP/DBP	Health status	Herb source and ID	Jadad score
Herranz-Lopez 2019 [43]	R, C (placebo), DB	55	pill	325 mg HS, 175 mg LC (dose 4.3 mg/kg)	129.2 ± 14.84/ /79.60 ± 11.89	-20.65 ± 2.8*/ /-11.07 ±1.97**	NMT	MetabolAid® *Hibiscus sabdariffa* and *Lippia citriodora* (Spain)	4
Boix-Castejon 2018 [42]	R, C (placebo), DB	54	pill	325 mg HS, 175 mg LC (dose 4.3 mg/kg)	117.4 ± 12.13/ /73.40 ± 5.00	-3.5**/-3.92**	NMT	MetabolAid® *Hibiscus sabdariffa* and *Lippia citriodora* (Spain)	3
Nwachukwu 2017 [44]	R, C (placebo, Lisinopril), DB	78	infusion	20 g/L (dose 150 mg/kg)	148-152/ /99–101	-17.08 ± 2.01*/ /-12.12 ± 1.04*	Mild-Mod HTN	sourced locally (Nigeria)	3
Seck 2016 [29]	R, C (Kinkeliba, Enalapril), DB	125	pill (micronized powder, max 500 mcm = 1.78 cm diameter)	640 mg (dose ~ 9 mg/kg)*	155.5/95.4	-11.2±3.3*/ /-6.0 ± 4.7*	Mil-Mod HTN, no CBM	sourced locally by Dixa AG® (Senegal)	5

CBM – co-morbidities; HTN – hypertension; NMT – normotensive; R – randomised; C – controlled; DB – double blind; SB – single blinded; * $p < 0.001$; ** $p < 0.0001$.

Antihypertensive effect

Studies on rats show a reduction in both systolic blood pressure (SBP) and diastolic blood pressure (DBP) (SBP 139.6 ± 1.6 mm Hg vs 174 ± 2.4 mm Hg, $n = 5$; $p < 0.001$ Intervention vs Control) [35]. The first human trial in 1999 showed a reduction in SBP/DBP (SBP -11.2%; DBP -10.7%) after 12 days of treatment [36].

A 2009 Cochrane review of literature did not identify any RCTs that met their inclusion criteria requiring a placebo controlled trial [37]. Three other systematic reviews and one meta-analysis have reviewed literature on the treatment of hypertension with HS [27, 38, 39]; the number of unique RCTs was five, all with positive outcomes for the effect of HS on SBP and DBP. A previous review of literature done in 2016 identified ten RCTs and included those previously identified by the last three reviews [40]. Six of the ten papers scored 3 on the Jadad scale for RCTs, implying a reasonable quality. Two of these were placebo controlled RCTs. All ten studies showed a significant decrease in SBP (-6.3 to -31.9 mm Hg), and nine studies showed a decrease in DBP (-1.1 to -19.7 mm Hg). Both placebo controlled studies also showed a decrease in SBP/DBP (-7.2/-3.1 mm Hg [31], -17/-11.2 mm Hg [41]).

Since 2010, there have been four further RCTs, whose findings are summarised in Table 1. Three of the four studies had a placebo arm, and all four showed a significant and positive effect on lowering SBP/DBP (-3.5 to -20.5/-3.92 to -12.12 mm Hg). The lowest decrease was seen in subjects who had baseline normotensive blood pressures [42]. There was significant heterogeneity in the form of HS used: powder versus infusions. The most methodologically robust trial, with a Jadad score of 5 with allocation blinding and the largest number of participants, showed a significant decrease in SBP/DBP (-11.2 ± 3.3 ($p < 0.001$) -6.0 ± 4.7 ($p < 0.001$) mm Hg) compared to the placebo [29].

Discussion

Although 14 RCTs have now been conducted to-date there is significant variation in trial design and quality, dosage preparation and form of HS used, method used to determine the dosage and patient type enrolled in the studies. The degree of heterogeneity prevents a valid meta-analysis. Based on published data and an expected magnitude of effect of 10 mm Hg reduction in SBP, an adequately powered RCT will at least require 102 patients [45]. To date, only two trials have crossed this threshold of enrolment with 193 patients: Herrera et al., who used an extract of HS [46], and Seck et al., who used micronized HS in pill form [28] with 125 patients. The current data is encouraging and suggests that HS is a biologically plausible and beneficial dietary option that can act synergistically in the treatment of essential hypertension. Further adequately powered and aligned trials are required to strengthen the evidence base.

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Tables: 1
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References: 46

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