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Bioactive Compounds and Antihypertensive Activity of Extracts of *Hibiscus sabdariffa* L

Compuestos bioactivos y actividad antihipertensiva de extractos de *Hibiscus sabdariffa* L.

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Abstract:

Introduction: systemic arterial hypertension (SAH) is the main risk factor for the developing of cardiovascular disease, which the leading cause of death worldwide. One of the best ways to control blood pressure (BP) levels is the combination of lifestyle changes and drug therapy. However, pharmacotherapy is expensive and produces adverse reactions. Thus, it is necessary to find cheap, safe and effective alternative treatments. *Hibiscus sabdariffa* L. (HS) is a plant that is traditionally used in some countries to treat SAH, which has given rise to various investigations to determine their compounds and their antihypertensive activity. **Aim**: the present article aims at reviewing the reports that support the antihypertensive activity of extracts from HS in animal and human models **Conclusions**: the information collected from scientific literature suggests that HS extracts have antihypertensive effects in animals and humans, especially in early stages; however, more studies in advanced stages of hypertension are needed.

Keywords:

systemic arterial hypertension, extracts of Hibiscus sabdariffa, antihypertensive, treatment

Resumen:

Introducción: la hipertensión arterial sistémica (HAS) es el principal factor de riesgo para desarrollar enfermedades cardiovasculares, que a su vez son la principal causa de muerte en el mundo. La mejor forma de controlar los niveles de presión arterial (PA) es la combinación de cambios en el estilo de vida y el tratamiento farmacológico, sin embargo, este último es costoso y en la mayoría de los pacientes ocasiona gastos de bolsillo, además de efectos secundarios adversos. Esto ha generado la necesidad de buscar tratamientos eficaces, seguros y accesibles, tanto económica como físicamente. *Hibiscus sabdariffa* L. (HS) es una planta que se usa tradicionalmente en algunos países para tratar la HAS, lo que ha dado origen a diversas investigaciones para determinar sus compuestos y su actividad antihipertensiva. **Objetivo:** el presente artículo tuvo como finalidad hacer una revisión de la evidencia científica del tratamiento antihipertensivo de extractos de HS en modelos animales y en pacientes humanos, así como revisar los compuestos de la planta. **Conclusiones:** la información recopilada de la literatura científica sugiere que los extractos de HS tienen efectos antihipertensivos en animales y humanos, especialmente en etapas tempranas de HAS, sin embargo, se necesitan más estudios en etapas avanzadas de la enfermedad.

Palabras Clave:

hipertensión arterial sistémica, extractos de Hibiscus sabdariffa, antihipertensiva, tratamiento

INTRODUCTION

Systemic arterial hypertension (SAH) is the main risk factor for the developing of cardiovascular disease, especially ischemic heart disease and cerebrovascular disease. Around the world, cardiovascular diseases are responsible for approximately 17 million deaths per year, representing almost one third of the whole total, only

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complications derived from SAH cause 9.4 million deaths per year. Unfortunately, about 40% of the population over 25 years old has been diagnosed with SAH around the world.[1,2]

According to the National Survey on Health and Nutrition Half Way of Mexico (ENSANUT MC)[3], the current prevalence of SAH is around 25.5%, that is, 1 out of every 4 Mexicans; however, 40.0% of the population do not know they have this disease. Within the patients with a previous diagnosis, only 58.7% had controlled blood pressure (BP) levels and 79.3% were in pharmacological treatment, representing, in most cases, an out-of-pocket expense, since pharmacies of the health care services units do not always have the drugs and the medication must be permanent.[4]

There is also evidence that identifies polypharmacy and the adverse effects of medications as some factors for non-adherence to pharmacological treatment.[5,6]

For these reasons, the antihypertensive effects of natural products such as garlic (*Allium sativum* L.)[7], hawthorn (*Crataegus monogyna* Jacq.)[8], passion fruit (*Passiflora edulis*)[9] and olive (*Olea europea* L.)[10] have been investigated; however, *Hibiscus sabdariffa L.* (HS) is a plant that is usually consumed which makes it culturally more accepted, besides it is affordable and easy to get, becoming a better option for patients with SAH.

HIBISCUS SABDARIFFA L.

HS, known as *jamaica* or *flor de jamaica [flower of jamaica]* in Mexico, belongs to the family Malvace (Table 1). It is a native plant of Africa but is cultivated in different parts of the world in countries of tropical climates such as India, the Philippines, Malaysia, Senegal, Ethiopia and Mexico. HS is a semi-woody shrub plant that can reach up to 3m high. It blooms annually or biennially, and its flowers consist of a purple red calyx and a corolla.[11,12]

Mexico is ranked as the seventh producer worldwide, with 5.14% of the total production, while China, ranked first, produces 27.76%, followed by India with 17.91%, Sudan 9.1%, Uganda 8.40%, Indonesia 6.23% and Malaysia 5.53%.[13]

Table 1. *Taxonomic classification of HS*

Kingdom	Plantae
Subkingdom	Tracheobionta
Division	Anthophyta
Class	Magnoliopsida
Order	Malvales
Family	Malvaceae
Genus	*Hibiscus*
Species	*sabdariffa* L.

Source: *Cid-Ortega and Guerrero-Beltrán, 2012*[11]

COMMON USES OF HS

Fresh or dried calyces of HS are used in the preparation of beverages based on herbs, hot and cold drinks, fermented beverages, wine, jams, jellies, ice cream, chocolate, puddings, and cakes.[14]

In Egypt, the fleshy calyces are used in the manufacture of tea and fermented beverages[14], while in Sudan and Nigeria, the calyces are boiled with sugar, to produce a known drink as "karkade" or "zoborodo".[15,16]

In Mexico, this beverage is called *jamaica*, *agua de Jamaica* [Hibiscus water] or *té de Jamaica* [Hibiscus tea]. In India, calyces are also used as colorants, flavorings and ingredients in rum. The seeds are eaten toasted or ground, while leaves and shoots are eaten raw or cooked, or as vegetables, known for its sour taste.[14,16]

In Sudan, the leaves are consumed green or dried, cooked with onions and peanuts, while in Malaysia the cooked leaves are eaten as vegetables. In Africa, the seeds are toasted or ground into powder and used in foods, such as soups and oily sauces, another use of the seed is as a coffee substitute.[14-18]

MEDICINAL USES OF HS

HS has also been widely used in traditional medicine. In India, Africa and Mexico, leaves or calyxes infusions are traditionally used for its diuretic, choleretic, febrifuges and antihypertensive effects, besides stimulating peristalsis.[14,18] It is also recommended as a antihypertensive in Senegal.[8] In Egypt, calyces have been used to treat heart and nervous system diseases and as

a diuretic[18]. In Egypt and Sudan a calyces infusion (karkade), is also used to help reducing body temperature.[14]

In Guatemala it is used to treat drunkenness.[18] In North Africa, calyces preparations are used to treat sore throats and cough, as well as genital infections; leaf pulp is used for external wounds and abscesses.[19] In India, decoction seeds are used to relieve pain in urination and indigestion.[20] In Brazil, it is believed that roots have stomach and emollient properties[18]. Traditional Chinese medicine uses it for liver disorders and treat high BP[18]. In Iran, tea is a traditional treatment for SAH[21], while in Nigeria, seeds' decoction is traditionally used to enhance or induce lactation in cases of low milk production.[16]

NUTRITIONAL VALUE

The nutritional composition of HS varies, due to genetic and environmental changes as well as specific characteristics of the cultivation and harvesting of the plant. Table 2 shows the average nutritional content of calyces.[22,23]

***Table 2**. Nutritional content of fresh HS calyces*

Content	Fresh calyces Amount per 100g
Protein	1.9 g
Fat	0.1 g
Carbohydrates	12.3 g
Fiber	2.3 g
Vitamin C	14 mg
β- Carotene	300 µg
Calcium	1.72 mg
Iron	57 mg

***Source** : Padmaja, et al., 2014[18] ; Carvajal-Zarrabal et al., 2012.[24]*

HS BIOACTIVE COMPOUNDS

The main phytochemical constituents of HS, relevant for their pharmacological properties include organic acids, anthocyanins, polysaccharides and flavonoids. Phytochemicals or secondary metabolites refer to non-nutritious bioactive compounds, which are found naturally in almost all parts of the plant, such as flowers, leaves, stems, roots, bark, and seeds. These phytochemicals have antioxidant activity and seem to protect against various degenerative diseases and pathological processes. [13-15,24-29]

Calyces contain anthocyanins in 1.5% (delphinidin-3 sambubioside or hibiscina, cyanidin-3-sambubioside, cyanidin-3-monoglucoside,delphinidin-3-monoglucoside), organic acids by 15% to 30%, which stabilize the anthocyanins (mainly citric, malic, protocatechuic, tartaric and ascorbic acids), 50% of them corresponds to mucilaginous polysaccharides (uronic acids in form of salt and the rest rhamnose, arabinose, and small amounts of glucose, xylose and mannose), flavonoids (primarily quercetin, gossip trina, gosipetina, hibiscitrina and its aglycon hibiscetina), saponins (β-sitosterol-β-Dgalactopiranosido), phytosterols (β-sitosterol, camposterol, ergosterol, stigmasterol), pectin, and fiber.[24,26,29,30]

Nowadays, investigations have been carried out about the potential use of HS in the pharmacological field, due to its benefits as an alternative medicine, demonstrating diuretic[31,] antioxidant[32,33], antiatherosclerotic[34], hypocholesterolemic[35-37], antihypertensive properties (as described below), among others. All these benefits are attributed to compounds present in the plant.

ANTIHYPERTENSIVE PROPERTIES

STUDIES IN ANIMALS

HS extracts have been tested to determine its hypotensive effect. Chronic administration of an extract of dried petals (250 mg / kg / day) significantly decreased BP ($p < 0.001$) in a group of hypertensive rats, even at normal values, without finding significant difference with the BP of rats in the control group.[38] Also, diuretic effect of different calyces of HS extracts was tested. Likewise, the administration of HS extract (20 mg/kg) demonstrated a diuretic effect higher than the hydrochlorothiazide and furosemide in rats.[38] This effect was significantly ($p<0.05$) higher (9.25 mL) even when compared to controls treated with hydrochlorothiazide (8.94 mL) and furosemide (4.8 mL). The extract did not induce macromorphological or histopathological alterations.[38]

Joven et al.[39] reported that the daily administration of HS extract (60 mg/kg) in rats during one week, significantly reduced BP at day 7, and it was observed a decrease on the diastolic blood pressure (DBP) in 25% (22-23 mm Hg).

STUDIES IN HUMANS

In human patients with SAH, researches have also been conducted demonstrating the antihypertensive properties of HS extracts. Herrera-Arellano et al.[40] administered a standardized extract of dried HS calyces (9.6 mg of anthocyanins) to a control group, while the experimental group received 25 mg of captopril. Systolic blood pressure (SBP), DBP and heart rate significantly decreased in both groups.[40] It is important to mention that the HS extract was similar in effectiveness to captopril. In addition, patients treated with the HS extract showed a significant increase in urinary sodium excretion ($p<0.001$), without substantially modifying other urinary electrolytes, including potassium.[40]

In the same way, the clinical effect of a standardized extract of HS calyxes (250 mg total anthocyanins) was evaluated in patients with SAH, using 10 g of lisinopril as control.[41] The HS extract induced a significant reduction of BP ($p<0.05$), with an effectiveness of 65.12%. Both treatments were safe; while there was 100% of tolerability in the experimental group, there was 98.81% in the control group.[41]

Mozaffari-Khosravi et al.[21] investigated the effect of administering HS tea on blood pressure, compared to black tea, in patients with SAH and diabetes type II. Both groups drank 250 mL of the corresponding tea twice a day, morning and evening, between main courses for a month. The HS group showed statistically significant differences throughout the study, SBP decreased from 134±11.8 mm Hg to 112.7±5.79 ($p<0.001$) at the end of the study. Likewise, the pulse fell from 52±12.2 to 34.5±9.3 ($p<0.001$). In the black tea group, the mean SBP and pulse did not show significant differences.

Another study was conducted in patients with SAH in its early stages, in order to evaluate the consumption of HS tea (1.25 g) or a placebo, three times a day (720 mL/day), for six consecutive weeks, over the BP. At the end of the treatment, the HS tea significantly decreased SBP by 27.2±11.4 mm Hg versus placebo 21.3±10.0 mm Hg ($p=0.030$). DBP was also lower, although this change did not differ from the placebo (23.1±7.0 mm Hg versus 20.5±7.5 mm Hg respectively, $p=0.160$).[19]

Chukwu et al.,[20] divided their population in three groups, Group A: they received a placebo, prepared from blackcurrant, is doses equivalent in volume to 150 mg/kg of the HS extract, administered orally, once a day before breakfast, for four weeks. Group B: patients were given 10 mg of lisinopril, by oral route, once a day for four weeks. Group C: patients took orally 150 mg/kg of HS infusion once a day, before breakfast during four weeks. It was observed that in the group C, the BP was reduced to normal levels in 76% of the cases, while lisinopril reached 65%. Compared to the placebo, HS significantly decreased the SBP in week 2 ($p<0,01$), and in weeks 3 and 4 ($p<0.001$), while lisinopril significantly decreased the levels of SBP only until last week ($p<0.001$). The effects of lisinopril and HS on the DBP were significant ($p<0.001$) in weeks 3 and four as opposed to the placebo. The HS produced a significant reduction in the mean BP as of week 2, whereas lisinopril did it as of week 3. At the end of the study, lisinopril and HS significantly reduced BP by 30.1% and 32.1%, respectively ($p<0.001$), compared to the placebo. However, there was no difference between both active treatments ($p>0.05$). In addition, there were no side effects in groups A and C.[20]

TOXICITY

In general, HS extracts have demonstrated to be safe. The lethal dose (LD_{50}) varies from 2000 to more than 5000 mg/kg/day.[27,42]

Also, there is evidence of a possible liver damage after a chronic consumption of doses higher than 3000 mg/kg/day.[43] Severe weight loss and diarrhea have been observed with a dose of 2000 mg/kg/day for 90 days in laboratory animals.[44]

CONCLUSIONS

The studies in animal models and in human patients with SAH, demonstrated the potential use that can be given to HS, and it can be recommended as treatment for the early

stages of this disease. However, studies that evaluate the potential of the plant in more advanced stages are needed, because most cases of SAH are diagnosed thanks to characteristic symptoms, which occur when the disease has progressed. In Mexico, HS represents an option to treat SAH because it is traditionally consumed, which favors its acceptance by the population, at the same time, it is a product economically affordable and physically easy to get, which favors even more its therapeutic use, especially in environments where medicines or money are very limited.

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