PharmacologyOnLine August30, 2014

Archives • 2014 • vol.2 • 10-17

Antihypertensive potential of plants used in Cuba

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Abstract

Arterial pressure responds to tissue needs for blood supply. Its chronic elevation (hypertension) is a risk factor for atherothrombotic diseases (myocardial infarction, stroke or lower limb occlusive disease). Therefore, the maintenance of arterial blood pressure levels within low vascular risk levels is essential to prevent these threatened acute events. This review deals with the pharmacological evidence about the anti-hypertensive potential of plants used by Cuban population for alimentary and/or medicinal purposes, in order to provide a scientific basis for the development of natural options for high blood pressure control in Cuba and other countries with environmental and/or cultural similarities. The profiles presented include information about their scientific and common names, botanical family, experimental conditions used, results obtained, mechanisms of action and active compounds. Data from sixteen plant species are described. The 13 botanical families they belong to, mainly Liliaceae, Lamiaceae and Rutaceae, emerge as possible sources for hypotensive drug discovery. Like conventional antihypertensive drugs , the proposed mechanisms of action of these plants´ derivatives include the stimulation of the endothelial formation of nitric oxide, prostacyclin and prostaglandin E2; the activation of vascular muscarinic cholinergic receptors; reduction of endothelin contracting effect; the inhibition of angiotensin-converting enzyme activity, as well as the blockade of Ca^{2+} channels, which confirm the possibility to find new promising agents among these herb products. However, research efforts should be dedicated to the identification of the active compounds still unknown and the manufacture of standardized products with proved clinical efficacy and safety.

Key words: Arterial hypertension, blood pressure, traditional medicine, pharmacology

Introduction

Arterial pressure responds to tissue needs for blood supply. Thus, when the requirement of tissue oxygenation increases, vasoconstrictor events (endothelin I, angiotensin II, norepinephrine) are activated. However, chronic elevation of arterial pressure (hypertension) is a consequence of the vascular endothelium lesion, reduction of vasodilator (nitric oxide, prostacyclin) and predominance of vasoconstrictor (endothelin) endothelial mediators. In turn, chronic hypertension is a determinant of blood vessel walls damage , leading to inflammatory and pro-thrombotic conditions that impair the circulatory system homeostasis and increases the risk for atherothrombosis (myocardial infarction, stroke or lower limb occlusive disease) [2]. These diseases are responsible for high number of deaths and disabilities worldwide[1,2]. Thus, the maintenance of arterial blood pressure levels within low vascular risk levels is essential to prevent these threatened acute events [1].

Besides live styles changes, antihypertensive drugs are usually prescribed for high blood pressure control, including diuretics, ß adrenergic receptor blockers, calcium channel antagonists or angiotensin converting enzyme inhibitors, in single or combined therapeutic schemes[1].

A significant prevalence of arterial hypertension and the fact that cardio- and cerebrovascular diseases are the second and third causes of death among adult Cuban population[3] suggest that discovering new efficacious, safe and low-cost therapeutic options for hypertensive patients is an important research objective.

Folk use of plants to alleviate high blood pressure symptoms has been revealed by Erhnomedical studies[4-9]. The scientific evidence that could support these traditional practices would help developing herb preparations and/or purified drugs with therapeutic efficacy [10, 11]. Since there is a lack of information about the anti-hypertensive potential of medicinal plants used in Cuba, this review deals with the pharmacological evidence about the pharmacological evidence available in this respect in order to provide a scientific basis for the development of natural options in Cuba and other countries with environmental and/or cultural similarities.

The results of pharmacological evaluations of plants used in Cuba[3-19] with validated experimental models[12] and/or controlled clinical trials were searched. Information was withdrawn from Google Scholar and PubMed data bases using the following search parameters or combinations: “the plant scientific name”, “arterial hypertension”, “blood pressure”, “medicinal plant”, without applying restrictions with respect to the publication date, the type of the study or the language.

The scientific and vernacular names, botanical families and uses in Cuba of plants with hantihypertensive potentials are summarized in the Table 1. Details of their pharmacological effects, proposed mechanisms of action and active principles are described as follows:

***Allium sativum* L.** *(A. sativum)*

The use of traditional preparations from this species as hypotensive or diuretic remedies have been reported in Morocco[4, 5], Togo[6], Nigeria[7], Spain [20], India and Thailand[21]. The evaluation of the effects of oral administrations of A. sativum minced bulbs, as well as water and organic bulb extracts have suggested an antihypertensive potential in dogs and rats[22-24] that seems to be mediated by the induction of vascular smooth muscle relaxation and decrease of vascular resistance through nitric oxide formation and inhibition of endothelin contracting effect[24]. Moreover, allicin and gamma glutamyl cysteine derivative contained in A. sativum bulbs inhibited angiotensin I-converting enzyme activity25. However, clinical evidence available on its hypotensive effect is still insufficient2[6-28].

***Anacardium occidentale* L.** *(A. occidentale)*

This species is used for renal problems in Nigeria[29]. A patent covering a process for obtaining an anti-hypertensive principle from A. occidentale bark has been registered[30]. On the other hand, aqueous extracts from its leaves demonstrated relaxing effects on rat aortas and mesentery vessels, apparently due to nitric oxide release from the vascular endothelium[31].

Artocarpus altilis (Parkinson) Forberg *(A. altilis)*

It is used for high blood pressure control in Trinidad and Tobago[8]. In vitro experiments demonstrated the relaxation of potassium chloride (KCl) - and phenylephrine- contracted rat aortas and competitive inhibition of KCl - induced vascular smooth muscle contraction after incubation with an aqueous extract of *A. altilis* leaves in addition

hypotensive and bradycardiac responses were shown on anaesthetized normotensive rats intravenously treated with this extract32.
Furthermore, ethanol and methanol leaf extracts, exhibited potent ACE-inhibitory activities, while hot aqueous extracts showed poor effects [33,34].

***Cassia occidentalis* Linn.** (*C. occidentale)*
It is appreciated as a diuretic herb in India [35] and Cuba (see Table 1). A *C. occidentale* aqueous leaf extract showed a relaxant effect on rat's aortic rings *in vitro* that could b*e* the consequence of unspecific inhibition of Ca^{2+} influx channels [36].

Citrus paradisi L. (*C. paradisi)*
Its traditional use to treat hypertension has been reported in Trinidad and Tobago[8] and Cuba (see Table 1). Reduced coronary resistance and mean arterial tension were demonstrated with the Langendorff´s perfused- isolated- heart model and with dog heart/ lung preparations after incubation with a *C. paradisi* peel aqueous extract. On the other hand, decreased diastolic and systolic arterial blood pressures were shown in normotensive and hypertensive voluntary subjects that consumed *C. paradisi juice* [37]. Phenolic compounds seem to be involved in this effect [38].

***Citrus sinensis* L** (*C. sinensis)*
It is among plants used to treat hypertension in Brazil [39]. A single-blind randomized crossover study with healthy subjects showed a significant fall of diastolic and systolic blood pressures after daily intake of commercial but not natural *C. sinensis* juice [40].

Cymbopogon citratus* (DC.) Stapf. (C. citratus*)
It is considered a hypotensive and diuretic plant in Thailand [21] Brazil [41], and Cuba (see Table 1). The relaxation of rat mesenteric arteries was induced by C. *citratus* aqueous leaf extracts *in vitro,* an effect that could be mediated by nitric oxide and prostacyclin released from the vascular endothelial cells [31,42]. Moreover, C. *citratus* aqueous and hydro alcoholic leaf extracts as well as its essential oils, provoked hypotension and bradycardia in rats. These effects have been attributed to the stimulation of muscarinic cholinergic receptors on vascular smooth muscle [43, 44]. Flavonoids from the leaves could be responsible for these biological responses [45].

Daucus carota Mil. (*D. carota)*
It is among plants used for the treatment of kidney diseases in Pakistan [46]. Arterial tension of rats fed a high-carbohydrate high-fat diet decreased to normality after treatment with *D. carota* juice [47]. On the other hand, an increase in urine flow was observed in dogs treated with *D. carota* fruit ethanol extract [48]. Coumarin glycosides of aerial parts of *D. carota c*aused inhibited K^+ -induced contractions of rabbit aortas. Furthermore, the intravenous administration of these products to anesthetized rats led to arterial blood pressure fall [49].

***Hibiscus sabdariffa* L** (*H. sabdariffa)*
Traditional medicines of Trinidad and Tobago [8] and Cuba (see Table 1) recommend include this species among those with anti-hypertensive and diuretic effects respectively. *H. sabdariffa* water leaf extract induced isolated rat aorta relaxation [50]. Besides, a reduction of systolic blood pressure has been demonstrated in patients with mild to moderate hypertension who consumed *H sabdariffa leaf* infusions while taking part of controlled and uncontrolled clinical trials [51, 52]. However, this evidence is considered not definitive due to weaknesses of the experimental designs used, like non placebo- controlled and non-double-blind studies [53].

***Lycopersicon esculentum* L.** (*L. esculentum)*
L. esculentum is used in the treatment of high blood pressure in Cameroon [9.] A modest blood pressure decrease was seen in patients with mild untreated arterial hypertension after *L. esculentum* fruit extract intake [54]. Moreover this extract significantly increased the effects of low doses of conventional antihypertensive therapies [55]. A virtual screening allowed knowing that Stigmasterol from *L. esculentum* has a high binding affinity with Angiotensin 1-converting enzyme, renin and extracellular regulated kinase 2 proteins that play key roles in regulation of arterial blood pressure [56].

***Manguifera indica* L.** (*M. indica*)
Cuban traditional medicine includes this species among those considered useful to improve diuresis (see table 1). Noradrenaline- and U46619 (thromboxane A2 analogue), but not KCl - induced contractions of mesenteric arteries isolated from spontaneously hypertensive rats were inhibited by a *M. indicia* stem bark extract.

On the other hand, mangiferin (C-glucosyl xanthone), its main chemical constituent, was effective against U46619- and KCl- but not noradrenaline-induced vascular smooth muscle contraction in similar experimental conditions, suggesting that it could be partially responsible of the extract pharmacologic effect [57].

***Ocimum basilicum* L.** (*O. basilicum)*
The use of *O. basilicum* is part of Asian [58] and Cuban (see table 1) traditions for hypertension control. Renal artery clamping-induced high systolic and diastolic blood pressures and cardiac hypertrophy in rats were reduced by pretreatment with an *O. basilicum* whole plant water extract. Concomitant decays of angiotensin converting enzyme activity and endothelin concentration were also observed and could be involved in this extract mechanism of action [58].

***Orthosiphon aristatus* (Blume) Miq.** (*O. aristatus)*
The traditional use as a diuretic plant has been reported in Thailand and Vietnam[21] , Indonesisa[59] and Cuba (see Table 1).The chloroform fraction of an O. *aristatus* leaf decoction inhibited KCl-induced contractions of isolated rat thoracic aortas. Diterpenes, chromones and flavones isolated from the leaves of this species exhibited similar effects[59, 60].

***Persea americana* Mill.** (*P. Americana)*
People from Togo [6], Nigeria [7] and Trinidad and Tobago [8] use *P. Americana* preparations for hypertension treatment, while it is considered a diuretic plant by Cuban traditional medicine (see Table 1). Acute and repeated intravenous injections of an aqueous seed extract of *P. americana* reduced high blood pressure and heart rate in normotensive rats. These effects were comparable to those of acetylcholine [61]. A hypotensive effect was displayed by *P. americana* water and methanol leaf extracts given to normotensive rats through the intravenous or oral routes. On the other hand, *in vitro* experiments demonstrated that a *P. americana* leaf aqueous extract induced vasorelaxation responses in rat aortas precontracted with noradrenaline and produced a rightward shift of the concentration-response curves to noradrenaline and KCl in a manner dependent on the stimulation of the synthesis and release of endothelium-derived relaxing factors, PGI2 and PGE2, besides the. inhibition of Ca^{2+} mobilization channels [62]

***Psidium guajava* L.** (*P. guajava)*
It is a plant species traditionally used for high blood pressure control in Togo [6] and Nigeria [7]. Acute intravenous administrations of *P. guajava* leaf aqueous extract produced dose-dependent, atropine resistant reductions of systemic arterial blood pressures and heart rates of hypertensive Dahl salt-sensitive rats [63]. Clinical trials showed mean blood pressure fall in hypertensive patients after daily intake of guava fruits [64,].

***Zingiber officinale* Rosc.** (*Z. officinale)*
Ayurvedic medicine recommends *Z. officinale* for diuretic treatment[65]. A crude extract of its rhizomes produced a dose-dependent fall in the arterial blood pressure of anesthetized rats. In addition it provoked a decrease on guinea pig atria spontaneous contractions rate and force. Furthermore, it showed vasodilator effect on KCl- contracted rabbit thoracic aorta and a verapamil –like shift of Ca^{2+} dose-response curves to the right, suggesting a calcium channel blocking mechanism of relaxant action [66]. However, clinical trials aimed to assess the hypotensive effect of *Z. officinale* preparations are scarce and not concluding [67].

Discussion

This study has presented a list of 16 plant species with antihypertensive potential with alimentary and/or medicinal uses in Cuba. These plants and the nine botanical families they belong to, mainly Lamiaceae, Liliaceae, and Rutaceae, emerge as possible sources to develop new therapeutic options for the treatment of arterial hypertension. Ethnomidical studies have described their traditional uses for hypotensive or diuretic treatments, being the last indication one of the antihypertensive drugs´ mechanisms of action [1]. Some coincidences of Cuban with Latin-American, Caribbean and Asian traditions may be appreciated in correspondence to the history of Cuban culture formation and its geographical situation. This observation supports the utility that this work may have for researchers from other countries with cultural and geographical similarities to Cuba. Pharmacological evidence have been obtained mainly from the assessment of plant extracts with *in vitro* and *in vivo* experiments, while clinical trials are scarce and with insufficient results to demonstrate the efficacy of these preparations

in humans, thus suggesting the need for more investigation in this respect. Like conventional antihypertensive drugs [1], the proposed mechanisms of action of plant derivatives include the stimulation of endothelial formation of nitric oxide, prostacyclin and prostaglandin E2; the activation of vascular muscarinic cholinergic receptors; the reduction of endothelin contracting effect, inhibition of angiotensin-converting enzyme activity, as well as the blockade of Ca^{2+} channels, which confirm the possibility to find new promising agents among these herb products. However, research efforts should be dedicated to the identification of the active compounds still unknown and the manufacture of standardized products with proved clinical efficacy and safety.

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Scientific name (Family)	Common Name	Oral uses in Cuba [14- 19]
Allium sativum L. (Liliaceae)	Ajo	Spice, cold, pain, circulatory disorders.
Anacardium occidentale L. (Anacardiaceae)	Marañón	Fruit, diabetes, hypercholesterolemia, cold, hemoptysis, dysentery, stomach ulcer.
*Artocarpus altilis (*Parkinson*)* Forberg (Moraceae)	Arbol del pan	Food
Cassia occidentalis Linn. (Cesalpinaceae)	Yerba hedionda, Platanillo	Diuretic, hepatic and gastric disorders.
Citrus paradisi L. (Rutaceae)	Toronja	Fruit, cold, hypertension.
Citrus sinensis L. (Rutaceae)	Naranja dulce	Fruit, cold, circulatory diseases, carminative
Cymbopogon citratus (DC.) Stapf (Poaceae)	Caña santa, Yerba de calentura	Hypotensive, antipyretic, cold, antitussive, diuretic, sedative.
Daucus carota Mill. (Apiaceae)	Zanahoria	Food, gastric tonic.
Hibiascus sabdariffa L. (Malvaceae)	Flor de Jamaica, Serení	Diuretic, hypolipidemic.
Lycopersicon esculentum (Solanaceae)	Tomate	Food, gastric tonic, to improve hematopoiesis.
Manguifera indica L. (Anacardiaceae)	Mango	Fruit, bronchitis, bronchial asthma, fever, diuretic.
Ocimum basilicum L. (Lamiaceae)	Albahaca blanca	Spice, spasmolytic, emetic, diuretic, cold, diarrhea, cancer, high blood pressure, sedative, somniferous.
*Orthosiphon aristatus (*Blume) Miq. (Lamiaceae)	Te de riñon	Diuretic.
Persea americana Mill. (Lauraceae)	Aguacate	Food, antitussive, emmenagogue, abortive, diuretic.
Psidium guajava L. (Myrtaceae)	Guayaba	Fruit, diarrhea, stomachache, anemia, cold, bronchial asthma.
Zingiber officinale Roscoe (Zingiberaceae)	Jengibre, ajengibre	Spice, anti-vomiting, anti-rheumatic, aphrodisiac, immune-stimulant, tonic, anti-diarrheic, cough reliever.

Table 1. Plants with antihypertensive potentials used in Cuba