Available online at **www.ijmrhs.com**

ISSN No: 2319-5886

International Journal of Medical Research & Health Sciences, 2018, 7(11): 26-48

Surinamese Medicinal Plants for Treating Hypertension with Angiotensin-Converting Enzyme-Inhibitory Activity: A Review of Literature

Dennis R.A. Mans*

Department of Pharmacology, Faculty of Medical Sciences, Anton de Kom University of Suriname, Paramaribo, Suriname

**Corresponding e-mail: dennis_mans@yahoo.com*

ABSTRACT

Plant-based antihypertensive preparations are abundantly used in traditional medicinal practices in many parts of the world including the Republic of Suriname (South America). In some cases, their apparent blood pressure-lowering activity may be related to inhibition of the angiotensin-converting enzyme (ACE). In this literature review, 12 plants that are commonly used in Suriname for treating hypertension have been compiled and assessed for an involvement of ACE inhibition in this condition. The 12 most commonly used 'antihypertensive' plants with ACE-inhibitory properties are Ruellia tuberosa, Mangifera indica, Apium graveolens, Cocos nucifera, Cucumis sativus, Momordica charantia, Punica granatum, Hibiscus sabdariffa, Musa x paradisiaca, Averrhoa bilimbi, Phyllanthus amarus, and Piper betle. All of them inhibited ACE activity in vitro, 3 (M. charantia, P. granatum, and P. betle) inhibited ACE activity in laboratory animals as well, and 2 (P. granatum and M. paradisiaca) were also active against ACE in human subjects. Indications about the identity of the pharmacologically active ingredient(s) were available for R. tuberosa, M. indica, A. graveolens, M. charantia, H. sabdariffa, and P. amarus. In most cases, the active ingredient(s) were associated with phenolic compounds. The results from this study support the involvement of ACE inhibition in the blood pressure-lowering activity of traditionally used Surinamese medicinal plants but also indicate that the scientific evidence for this contention is limited. Further pharmacological studies on these aspects as well as the pharmacologically active constituents of the plants are warranted, since they may help identify novel plant-based ACE inhibitors.

Keywords: Medicinal plants, Suriname, Hypertension, Angiotensin-converting enzyme (ACE), Literature review

INTRODUCTION

Hypertension is defined as systolic and diastolic blood pressures that are persistently above 140 mm Hg and 90 mm Hg, respectively [1]. This condition is one of the most important predisposing factors for potentially fatal coronary artery disease, heart failure, stroke, peripheral vascular disease, vision loss, and chronic kidney disease [1]. Globally, an estimated 1 billion adults (i.e., over 20% of the world population) suffer from hypertension [2]. This comes with enormous medical, economic, and human costs which, in the USA alone, amounted to $ 47 billion to $ 73.4 billion between the years 2009 and 2011 [3].

Hypertension is classified as primary (or essential) hypertension and secondary hypertension [4]. Primary hypertension accounts for more than 90% of cases, does not have a readily identifiable cause, but has been associated with non-specific lifestyle factors such as excess salt intake, obesity, and a sedentary lifestyle, cigarette smoking, high alcohol intake, stress, and a family history [5]. In the remaining 10% of cases categorized as secondary hypertension, the elevated blood pressure is usually related to identifiable conditions such as renal artery stenosis, chronic kidney disease, sleep apnea, hyperthyroidism, pheochromocytoma, the use of oral contraceptives, or pregnancy [4].

In both situations, the elevated blood pressure is associated with an increased total peripheral resistance that is usually attributable to abnormalities in the sympathetic nervous system and/or the renin-angiotensin-aldosterone system [6,7]. In the former case, the increased peripheral resistance is caused by the contraction of arterial smooth muscles and

the constriction of arterioles following overstimulation of β_1- and α_1-adrenoreceptors and the excessive release of adrenaline and noradrenaline [6]. In the latter case, it is caused by the reabsorption of salt and water and enlargement of the vascular volume after excess secretion of renin by juxtaglomerular cells, stimulation of β_1-adrenergic receptors on their surface, and glomerular underperfusion [7]. Defects in the functioning of vasorelaxing factors such as nitric oxide and vasoactive substances such as endothelin and bradykinin may further contribute to and/or maintain hypertension [8].

Lifestyle modifications such as dietary changes, increased physical exercise, weight loss, and stress reduction can lower blood pressure and decrease the risk of health complications [9]. The potential effectiveness of these modifications is similar to, and may even exceed the effects of a single medication [10]. If lifestyle changes are not sufficient to lower the elevated blood pressure, antihypertensive medications are prescribed. These generally include thiazide-diuretics such as hydrochlorothiazide, calcium channel blockers such as amlodipine, β-blockers such as atenolol, angiotensin receptor blockers such as losartan, and angiotensin-converting enzyme (ACE) inhibitors such as captopril [8,11]. These medications are used either alone or at certain combinations [8,11].

ACE and ACE Inhibitors

ACE is a key component of the renin-angiotensin-aldosterone-system which controls blood pressure by helping to regulate the volume of fluids and the sodium-potassium balance in the body [12]. This enzyme is mainly located in the capillaries of the lungs and is also present in endothelial and kidney epithelial cells [12]. ACE converts the inactive decapeptide hormone angiotensin I into the potent vasoconstrictor octapeptide angiotensin II by removing the dipeptide His-Leu from the C-terminus [12]. Angiotensin I is formed by the proteolytic action of renin (formed from prorenin by the action of juxtaglomerular cells in the kidneys when renal blood flow is reduced and is directly released into the circulation) which acts on circulating angiotensinogen (released by the liver) [12]. Angiotensin I is then converted into angiotensin II by ACE which increases blood pressure by narrowing arterioles following binding to type 1 angiotensin II receptor (AT1) on their smooth muscle cells [12], and by stimulating the secretion of aldosterone from the adrenal cortex, increasing salt and water retention [12]. ACE also converts the nine-amino acid vasodilator peptide bradykinin into inactive compounds which further contributes to the increase in blood pressure [12].

ACE inhibitors prevent the formation of angiotensin II and decrease bradykinin degradation which, along with the inhibition of norepinephrine release from sympathetic nerve endings, produces substantial vascular relaxation and vasodilation, reduction of afterload, and improvement in cardiac output [13]. Hence efficacy of these compounds against hypertension [13]. The first ACE inhibitor was captopril, developed in 1977 by Bristol-Myers Squibb from the venom of the Brazilian lancehead viper *Bothrops jararaca* (Wied-Neuwied, 1824) (Viperidae) [13]. This was accomplished by employing QSAR-based modifications following the observation that peptides in the venom inhibited ACE activity from dog lung, and that one of these peptides (bradykinin-potentiating factor) inhibited the conversion of angiotensin I into angiotensin II [13]. Captopril obtained FDA approval in 1981 and became a generic medicine in the USA in 1996 [13]. However, it's relatively short half-life as well as its propensity to cause rash and taste disturbances (which are presumably attributable to the unique thiol moiety), and a dry cough (due to increased bradykinin plasma levels [13]) led to the development of improved analogs such as enalapril, lisinopril, and benazepril [14].

Today, ACE inhibitors have become the first-line treatment of all types of hypertension in many countries [14]. This underlines the importance of targeting ACE as a clinical strategy to fight this condition. At the same time, in many parts of the world including the Republic of Suriname, a variety of herbal preparations with ACE inhibitory properties is used against an elevated blood pressure [15]. These compounds may serve as a model substances for developing potentially novel and/or more cost-effective and more readily accessible ACE inhibitors. The latter considerations are particularly relevant to low-resource countries. However, it is not always clear whether and to which extent ACE inhibition is involved in the blood pressure-lowering actions of the plant preparations. In the current paper, the literature has been consulted to compile the plants that are most commonly used against hypertension in Suriname, after which those that may inhibit ACE activity have been selected and comprehensively discussed.

Suriname

Suriname is located on the northeast coast of South America, bordering the Atlantic Ocean and surrounded by French Guiana, Brazil, and Guyana (Figure 1). Roughly 80% of the approximately 570,000 inhabitants lives in the capital city of Paramaribo and other urbanized areas in the northern coastal zone of the country (Figure 1). The remaining 20%

resides in the rural-coastal areas and the southern-rural interior which comprises approximately 90% of Suriname's land surface and largely consists of sparsely inhabited savanna and undisturbed, dense tropical rainforest with a very high animal and plant biodiversity [16] (Figure 1). Suriname's most important economic means of support are crude oil drilling, bauxite and gold mining, agriculture, fisheries, forestry, and ecotourism [17]. These activities contributed substantially to the gross domestic product in 2017 of USD 3.324 billion, positioning Suriname on the World Bank's list of upper-middle income economies [18].

Figure 1 Map of Suriname depicting the relatively narrow northern coastal zone of the country including the capital city Paramaribo as well as the relatively large rural-coastal areas and the southern-rural interior. The insert depicts the position of Suriname in South America

Suriname's population is among the most varied in the world, comprising Amerindians (the original inhabitants of the country) as well as descendants from enslaved Africans, indentured laborers from Asia, and European settlers, as well as immigrants from various Latin American and Caribbean counties [19]. All ethnic groups have preserved much of their original culture and identity, still practicing the religion they were raised with, speaking the language from their country of origin, maintaining their specific perceptions of health and disease, and adhering to their ethnopharmacological traditions [20,21]. As a result, the use of various forms of traditional medicine is deeply rooted in the country, despite the broad availability of affordable modern health care [21,22]. This inclination, together with the easy access to raw plant material from Suriname's rich biodiversity, probably accounts for the frequent use of traditional herbal medications in the country, either alone or in conjunction with prescription medicines [21,22].

This also holds true for medications for treating hypertension. Together with other lifestyle-related non-communicable diseases [23-27], this condition has, similarly to many low- and middle-income countries, a relatively high prevalence in Suriname [25]. For instance, the comprehensive, nation-wide Suriname Health Study on non-communicable

diseases found an overall prevalence of hypertension in the country of 26.2% [25]. Mean values for systolic and diastolic blood pressure were higher in males than in females, increased with older age, and were highest in urban people from African and Asian descent when compared to individuals living in the rural areas and the interior of the country (including Amerindians) [25]. These findings were consistent with those from two other studies reporting higher prevalence rates of (pre) hypertension in the urban areas than in the rural areas of the country [26,27].

Herbal Medicines for Treating Hypertension with ACE Inhibitory Properties

A broad evaluation of publications addressing the botanical, ethnopharmacological, and phytochemical properties of the Surinamese flora showed that about 800 different plant species are used for medicinal purposes in the country [28]. Around 65 of them (roughly 8%) are used for treating hypertension. These species belong to 38 different families, the most represented of which are the Fabaceae with 7 species, the Solanaceae with 5 species, the Malvaceae and the Piperaceae with 4 species each, and the Asteraceae and the Cucurbitaceae with 3 species each. In 31 cases the leaves are used, in 9 cases the whole plant, in 6 cases the fruits, in 5 cases the bark, and in 1, 2, or 3 cases other plant parts such as roots and flowers. From the 65 'antihypertensive' plants, 12 that are commonly used and may inhibit ACE activity that have selected (Table 1). The involvement of ACE inhibition in their blood pressure-lowering effect is in detail addressed (Table 2) [29,30].

Table 1 Plants with presumed ACE-inhibitory activity used for treating hypertension in Suriname

Family	Plant species (vernacular names in English; Surinamese)	Plant part(s) and mode of preparation	Reference for indications for an antihypertensive activity
Acanthaceae	*Ruellia tuberosa* L. (minnieroot; watrakanu)	Crude aqueous extracts as well as n-butanolic and aqueous fractions from leaves of *Ruellia* species	[31,32]
Anacardiaceae	*Mangifera indica* L. (mango; manya)	Aqueous extract from stem bark; dichloromethane fraction from crude ethanol extract from leaves; mangiferin; Vimang	[33-38]
Apiaceae	*Apium graveolens* L. (celery; selderij)	Aqueous of ethanol extracts from seeds, stalks, or roots; ethanol extract from leaves; powdered ethanol extract from seeds; standardized ethanol extract from seeds	[39-45]
Arecaceae	*Cocos nucifera* L. (coconut; kronto)	Ethanolic extract from endocarp; coconut oil; coconut water; sap from immature inflorescence	[46-52]
Cucurbitaceae	*Cucumis sativus* L. (cucumber; komkommer)	Fruit juice; vine compound tablets	[53,54]
Cucurbitaceae	*Momordica charantia* L. (bitter melon; sopropo)	Fruit juice; aqueous extract from whole plant; extract from fruits	[55-58]
Lythraceae	*Punica granatum* L. (pomegranate; granaatappel)	Fruit juice; extract from peels	[59-68]
Malvaceae	*Hibiscus sabdariffa* L. (roselle; syuru)	Aqueous extract from calyces	[69-79]
Musaceae	*Musa x paradisiaca (banana; banaan)*	Preparations from fruits	[80-85]
Oxalidaceae	*Averrhoa bilimbi* L. (bilimbi; birambi)	Aqueous extract from leaves	[86-88]
Phyllanthaceae	*Phyllanthus amarus* Schumach. and Thonn. (stonebreaker; finibita)	Aqueous and n-butanolic extracts from leaves and seeds; geraniin	[89-96]
Piperaceae	*Piper betle* L. (betle vine; pahnblad)	Aqueous, ethanolic, and acetone extracts from leaves	[97-99]

Table 2 Evidence for the ACE-inhibitory activity of plants used in Suriname for treating hypertension

Plant species	Plant part(s) and mode of preparation [references]	Evidence for ACE inhibition [references]	Key constituent(s) with presumed ACE-inhibitory properties [references]
R. tuberosa	Leaves, ethanolic extract [100]	ACE inhibition *in vitro* [100]	Phenolics, steroids [100]
M. indica	Leaves, dichloromethane fraction from ethanolic extract [35]	ACE inhibition *in vitro* [35]	Mangiferin [34,36]
	Leaves, methanolic extract [101]	ACE inhibition *in vitro* [101]	Urs-12-ene [101]
A. graveolens	Seeds, methanolic extract [102]	ACE inhibition *in vitro* [102]	Junipediol A 8-O-β-d-glucoside [104]
	Leaves, methanolic extract [103].	ACE inhibition *in vitro* [103]	
C. nucifera	Fruits, peptides in globulin hydrolysates [105]	ACE inhibition *in vitro* [105]	Unknown
	Kernel, aqueous extract [106]	ACE inhibition *in vitro* [106]	Unknown
C. sativus	Fruits, methanolic extract [107]	ACE inhibition *in vitro* [107]	Unknown
	Seeds, aqueous extract [108]	ACE inhibition *in vitro* [108]	Unknown
M. charantia	Fruits, aqueous extract [58]	Decreased ACE activity in laboratory animals [58]	Phenolics [109,110]
	Leaves, methanol and aqueous extracts [69]	ACE inhibition *in vitro* [69]	Unknown
	Leaves, ethanolic extract [70]	ACE inhibition *in vitro* [70]	Unknown
P. granatum	Peels, a fraction from methanol extract [62,111]	ACE inhibition *in vitro* [111]; decreased coronary ACE activity in laboratory animals [62]	Unknown
	Fruits, juice extract [59]	Decreased ACE serum levels in angiotensin-II treated laboratory animals [59]	Unknown
	Fruits, fresh juice	Decreased serum ACE activity in hypertensive patients [63]	Unknown
H. sabdariffa	Calyces, aqueous extract [74]	Counteracted cardiomegaly and increased surface area of cardiac capillaries in laboratory animals [74]	Unknown
	Calyces, hydroalcoholic extract [112]	ACE inhibition *in vitro* [112]	Anthocyanins [112]
	Delphinidin-3-O-sambubioside and cyanidin-3-O-sambubioside from an aqueous extract of calyces [113]	ACE inhibition *in vitro* [112]	Anthocyanins [113]
M. paradisiaca	Fruits [84]	Decreased ACE activity in healthy volunteers with elevated blood pressure caused by cold stress [84]	Unknown
	Fruits, ripe *versus* unripened [114]	ACE inhibition *in vitro* [114]	Unknown
A. bilimbi	Leaves, ethanolic extract [115]	ACE inhibition in vitro [115]	Unknown
	Fruits, aqueous extract [116]	ACE inhibition *in vitro* [116]	Unknown
P. amarus	Geraniin [117]	ACE inhibition *in vitro* [117]	Ellagitannins [96,117]
P. betle	Leaves, water, ethanol, and acetone extracts [118]	Inhibition of ACE activity in laboratory animals [118]	Unknown
	Leaves, hydroalcoholic extracts [119]	ACE inhibition *in vitro* [119]	

Acanthaceae-*Ruellia tuberosa L.*

Parts of the minnieroot *R. tuberosa* (Figure 2) are traditionally used in several countries including Suriname for treating, urinary problems, diabetes mellitus, joint pains, muscle strain, gastrointestinal conditions, gonorrhea, and hypertension [29,30]. There is no direct pharmacological evidence for an antihypertensive activity of *R. tuberosa* preparations themselves. However, crude aqueous extract from the leaves of the spreading *Ruellia patula* Jacq. elicited a clear blood pressure-lowering effect in pentothal sodium-anesthetized rats [31]. And crude aqueous extracts

as well as n-butanolic and aqueous fractions from the leaves of *R. patula* and the Mexican petunia *Ruellia brittoniana* Leonard produced (modest) cardiotonic effects in isolated rabbit hearts [32]. These observations may be attributable to the presence of lignan glycosides in these samples [31].

Figure 2 *Ruellia tuberosa* L. (Acanthaceae) (from: https://goo.gl/images/6skTVj)

An involvement of ACE inhibition in the blood pressure-lowering effects of *Ruellia* preparations is suggested by the decreased formation of hippuric acid from hippuryl-L-histidyl-L-leucine by rabbit lung ACE in the presence of an ethanolic *R. tuberosa* leaf extract [100]. This observation has been ascribed to flavonoid, polyphenol, and/or steroid compounds in the extract [100]. It was consistent with the previously reported inhibitory effects of extracts from the leaves of the wild petunia *Ruellia praetermissa* Schweinf. ex. Lindau on rabbit lung ACE activity, and the presence in the extracts of the triterpenoid lupeol, flavonoids such as luteolin and apigenin, as well as a number of sapogenins [120].

Anacardiaceae-*Mangifera indica L.*

Preparations from fruit, stem bark, leaf, seed, and peel of the mango tree *M. indica* are worldwide used in folk medicine against many different conditions including vasculitis, varicose veins, and an elevated blood pressure [29,33,34]. Support for the latter use comes from the inhibitory effect of an aqueous stem bark extract on the contractions of isolated mesenteric arteries from spontaneously hypertensive rats (SHRs) caused by noradrenaline and the thromboxane A2 analogue U46619 [33]. Furthermore, a dichloromethane fraction from a crude ethanol leaf extract induced similar antihypertensive effects as enalapril in SHRs and Wistar rats normalized the baroreflex sensitivity in SHRs and counteracted the hypertension-induced cardiac hypertrophy in the animals to a comparable extent as enalapril [35].

Several lines of evidence suggest that these apparent antihypertensive effects may be attributed to vasodilation and the stimulation of diuresis. Firstly, exposure to the polyphenolic compound mangiferin, the main chemical constituent believed to be responsible for the blood pressure-lowering effects of *M. indica*, led to a relaxation of isolated mesenteric arteries from SHRs precontracted with U46619 [34,36]. Mangiferin also produced notable blood pressure-lowering effects *in vitro* and in laboratory animals as well as diuresis in normotensive laboratory rats [37,38]. Furthermore, Vimang (from 'Vida del mango' meaning 'life of the mango'), a standardized aqueous extract from

M. indica stembark developed in Cuba as an antihypertensive, inhibited the noradrenaline-induced contractions of isolated mesenteric arteries from SHRs [33].

All these observations with *M. indica* preparations are consistent with an involvement of ACE inhibition in their blood pressure-lowering effects. Indeed, comparably to captopril, the above-mentioned dichloromethane fraction from an *M. indica* leaf extract almost completely inhibited the formation of glycine-glycine following hippuryl-glycyl-glycine cleavage by ACE from rabbit lung [35], and a methanol *M. indica* leaf extract inhibited the conversion of hippuryl-L-histidyl-l-leucine by ACE from zebrafish eyes [101]. Interestingly, GC-MS analysis of the extract revealed the presence of 32 compounds, one of which (Urs-12-ene) displayed a very high affinity towards ACE in subsequent docking studies, suggesting its potential usefulness against hypertension [101].

Apiaceae-*Apium graveolens* L.

Preparations from the celery *A. graveolens* (Figure 3) are extensively used in various traditional medicinal systems as a diuretic, laxative, sedative, and for treating, among others, spasms, stomach problems, and joint problems [121]. *A. graveolens* preparations are also used against hypertension as well as the dizziness, headache, and shoulder pain associated with this condition [122,123]. Support for the antihypertensive potential of *A. graveolens* preparations comes from the decreased blood pressure and heart rate in salt-induced hypertensive rats, normotensive rats, and normotensive rabbits which intraperitoneally received aqueous or ethanol extracts from seeds, stalks, or roots of the plant [39-42]. More importantly, patients who had been given the juice or an ethanol extract from the leaves of the plant, or a powdered ethanol extract or a standardized ethanol extract from its seeds experienced a meaningful decrease in their blood pressure [43-45].

Figure 3 *Apium graveolens* L. (Apiaceae) (from: https://goo.gl/images/dvT3x8)

The antihypertensive effects of *A. graveolens* have been attributed to the benzofuran 3-n-butylphthalide that, along with sedanolide, is also primarily responsible for the aroma and taste of the plant [42,124]. These insights and the results from other clinical studies have led to the approval in China of 3-n-butylphthalide for the treatment of cerebral ischemia, and the preparation of clinical studies to assess n-butylphthalide formulated as soft gel capsules for its safety in patients with mild to moderate acute ischemic stroke [125].

The results from studies with several experimental models have suggested that *A. graveolens* preparations may exert

their antihypertensive effects through vasodilation; the stimulation of muscarinic receptors; and/or the stimulation of diuresis [39,41,126]. Suggestions for an involvement of ACE inhibition in (some of) these effects came from the decreased conversion of N-[3-(2-furyl)acryloyl]-L-phenylalanyl-glycyl-glycine by rabbit lung ACE in the presence of a methanolic seed extract [102], and the decreased conversion of 3-hydroxybutyrylglycyl-glycyl-glycine into Gly-Gly and 3-hydroxybutyric acid by rabbit lung ACE in the presence of a methanolic leaf extract [103]. Subsequent studies led to the identification of junipediol A 8-O-β-d-glucoside as one of the main ACE-inhibiting ingredients of *A. graveolens* [104].

Arecaceae-*Cocos nucifera L.*

The fruits from the coconut palm *C. nucifera* are the source of coconut water, coconut milk, coconut cream, and coconut oil [104]. Coconut oil has a relatively high vitamin E and polyphenol content which would account for its antioxidant properties [127]. *C. nucifera* preparations have long been used in traditional medicine for treating a myriad of disease conditions [127,128]. Pharmacological studies showed actions ranging from anti-inflammatory and antimicrobial effects to antidiabetic and cardioprotective activities [128,129].

Indications for antihypertensive effects of *C. nucifera* preparations come from the relaxation of isolated rat aortic rings pre-contracted with norepinephrine, phenylephrine, or potassium chloride by an ethanolic endocarp extract and the decrease in mean systolic blood pressure in deoxycorticosterone acetate (DOCA) salt-induced uninephrectomized hypertensive Wistar rats by this preparation [46]. These activities might be attributed to the polyphenols in the extract and might be caused by direct activation of the nitric oxide/guanylate cyclase pathway, stimulation of muscarinic receptors, and/or via cyclooxygenase pathway [46]. Furthermore, coconut water given for 14 consecutive days to NaCl-hypertensive Wistar rats led to a decreased heart rate [130], and fresh coconut water elicited a cardiotonic effect in an isolated frog heart that was comparable to that caused by digoxin [131]. Also, oral treatment with 2 mL/day (virgin) coconut oil for 30 days led to a meaningful decrease in mean arterial pressure as well as lipid peroxidation in SHRs [132]. And oral supplementation with coconut oil combined with exercise training improved impaired baroreflex sensitivity and reduced oxidative stress in SHRs [133].

Notably, the regular consumption of coconut water either alone or mixed with mauby, a liquid extracted from the bark of the mauby tree *Colubrina arborescens* (Mill.) Sarg. (Rhamnaceae), reportedly controls hypertension in patients [134]. And fresh coconut neera (a sweet, white-colored translucent sap tapped from the immature inflorescence of the tree) given in the morning at the schedule of 100 mL daily for 5 consecutive weeks led to a decrease of the systolic and diastolic blood pressure in adult women with stage I hypertension [52].

Two pieces of evidence suggest an involvement of ACE inhibition in the blood pressure-lowering effects of *C. nucifera* preparations. Firstly, globulin hydrolysates of coconut cake (the main byproduct of the coconut milk and oil industry) markedly reduced the systolic blood pressure of SHRs with 2 peptides exhibiting, among others, high ACE inhibitory activity [105]. Secondly, an aqueous extract of the kernel (used as an ingredient of an aphrodisiac and fertility-enhancing Nigerian drink called 'kunu aya') inhibited the conversion of hippuryl-L-histidyl-L-leucine into hippuric acid by ACE activity in a rat penile homogenate [106].

Cucurbitaceae-*Cucumis sativus L.*

Preparations from leaves, seeds, flowers, and fruits of the cucumber plant *C. sativus* are traditionally used for treating various diseases such as throat infections, parasite infections, and dysentery in children, but also to stimulate diuresis and to lower an elevated blood pressure [122,135,136]. The former application is supported by the stimulation of diuresis in laboratory rats by an ethanolic extract from *C. sativus* leaves- either alone or incorporated in a polyherbal formulation- at a comparable extent as furosemide [137]. This observation was in line with the increased diuresis caused by an ether seed and an aqueous leaf extract from the muskmelon *Cucumis melo L.* (synonym *Cucumis trigonus* Roxb.) in anesthetized dogs and conscious albino rats, respectively [138,139]. This effect was presumably due to a decreased tubular resorption as suggested by the increased urinary chloride excretion and was comparable to that caused by hydrochlorothiazide [138,139].

Support for a blood pressure lowering effect of *C. sativus* came from the improved myocardial contraction in laboratory animals receiving *C. sativus* vine compound tablets, and the substantial decrease in blood pressure as well as the marked increase in coronary blood flow in hypertensive individuals treated with these tablets [53]. Furthermore,

elderly patients receiving the fruit juice for 7 days experienced a meaningful reduction in mean blood pressure [54]. These effects may be associated with the presence in the plant of bioactive compounds such as cucurbitacins, cucumegastigmanes I and II, cucumerin A and B, vitexin, and orientin [53,140].

An involvement of ACE inhibition in the actions of the *C. sativus* preparations is suggested by the inhibitory effect of a crude fruit extract on the conversion of the ACE substrate dansyltriglycine into dansylglycine and diglycine [107]. Furthermore, an aqueous seed extract inhibited rabbit lung ACE activity by more than 50% as indicated by the inhibition of the formation of hippuric acid from hippuryl-L-histidyl-L-leucine [108]. Also, studying the anti-inflammatory and antioxidant effects of an aqueous cucumber extract in the human dermal microvascular endothelial cell line HMEC-1, some sub-fractions were observed to decrease the production of interleukin 6, the expression of adhesion molecules, and the production of reactive oxygen species induced by angiotensin II while increasing the bioavailability of NO [141].

Cucurbitaceae-*Momordica charantia L.*

The fruits and leaves of the bitter melon *M. charantia* are consumed as vegetables in many countries but all parts of this plant have since long been used in various traditional medicinal practices [142]. Preparations from the dried leaves are particularly renowned for their presumed efficacy against (mild to moderate) type 2 diabetes mellitus [143], but so far there is insufficient evidence to support this assumption [144]. Preparations from various parts of *M. charantia* are also used for treating, among others, asthma, constipation, microbial infections, parasitic diseases, skin problems, as well as liver and spleen ailments [142]. Some of the traditional claims such as potential hypoglycemic, anti-inflammatory, and antimicrobial activity have partially been substantiated by pharmacological studies [142].

Various reports mention that *M. charantia* preparations also lower an elevated blood pressure. Indeed, orally administered fruit juice preparations produced a substantial decrease in blood pressure and conferred partial protection against the hypertension-induced vascular damage in streptozotocin-induced diabetic laboratory rats [55,56]. Furthermore, an intravenously administered aqueous whole plant extract produced a substantial decrease in systemic arterial blood pressure and heart rate of normal as well as hypertensive and salt-sensitive Dahl rats [57]. And a fruit extract given by intubation lowered the elevated systolic pressure (albeit not the diastolic blood pressure) in normal Sprague-Dawley rats [58].

The results from the latter study also showed an appreciable decrease in ACE activity in rats treated with *M. charantia*, suggesting an involvement of this enzyme in the observed antihypertensive effect [87]. Other indications for this assumption are the meaningful inhibition of ACE activity by methanol and aqueous leaf extracts and an 80% ethanolic leaf extract as determined by inhibition of the formation of hippuric acid from hippuryl-L-histidyl-L-leucine by ACE activity in a rat kidney homogenate and that of 3-hydroxybutyrate from 3-hydroxybutyrylglycyl-glycyl-glycine [109,110]. In line with the high ACE inhibitory activity noted in most plants with a high flavonoid content [145], the ACE inhibitory activity of the *M. charantia* preparations has been associated with, among others, a phenolic/flavonoid fraction [109,110].

Lythraceae-*Punica granatum L*.

The fruit and other parts of the pomegranate *P. granatum* (Figure 4) are extensively used as a traditional remedy against infections, gastrointestinal ailments, skin conditions, as well as hypertension [146]. Partial support for these ethnopharmacological uses was provided by, among others, the anti-atherosclerotic, anti-atherogenic, anti-aging, anti-inflammatory, anticancer, and anti-oxidative effects of *P. granatum* preparations noted in pharmacological studies [147]. These potential beneficial effects may be attributable to the considerable amounts of flavonoids (such as anthocyanins, catechins, quercetin, and rutin), other polyphenols, ellagitannins, and antioxidants in parts of this pant [148].

Figure 4 *Punica granatum* L. (Lythraceae) (from: https://goo.gl/images/Hf9D6Q)

Preclinical evidence for an antihypertensive activity of *P. granatum* preparations came from the decrease in mean arterial blood pressure and vascular reactivity changes to various catecholamines caused by fruit juice extracts in angiotensin II-treated normal Wistar rats, angiotensin II-treated streptozotocin-induced diabetic Wistar rats, and DOCA salt-induced hypertensive rats [59-61]. Furthermore, a *P. granatum* peel extract caused a meaningful reduction in systolic blood pressure, vascular damage associated with hypertension, and coronary ACE activity in SHRs [62].

Importantly, *P. granatum* fruit juice or fruit extract caused a decrease in the systolic and/or diastolic blood pressure in hypertensive patients [63-65]; suppressed the postprandial increase in systolic blood pressure following the intake of a high-fat meal [66]; substantially decreased systolic, diastolic, and mean arterial blood pressure in healthy adults [67]; and decreased systolic blood pressure (but not diastolic blood pressure) in individuals with systolic pre-hypertension (albeit not in in normotensive individuals) [68]. Furthermore, these preparations considerably reduced carotid intima media thickness, peak systolic velocity, and end-diastolic velocity in patients with carotid artery stenosis when compared to controls, and improved myocardial perfusion in patients with ischemic coronary heart disease [149,150].

Several lines of evidence suggest that inhibition of ACE activity may play a role in the antihypertensive effects of *P. granatum* preparations. Firstly, a fraction from a methanol extract of the peel displayed meaningful ACE inhibitory properties *in vitro* and caused a significant reduction in coronary ACE activity along with a decrease in systolic blood pressure and vascular damage in SHRs [62,111]. Secondly, a fruit juice extract produced a meaningful decrease in ACE serum levels of angiotensin-II treated Wistar rats [59]. Thirdly, the fruit juice produced a 36% decrease in serum ACE activity of hypertensive patients [63]. However, in one of the above-mentioned studies, the fall in blood pressure (5%) was not paralleled by changes in the concentration of serum ACE (36%) suggesting the involvement of processes additionally to ACE inhibition in the apparent antihypertensive activity of *P. granatum* [67].

Malvaceae-*Hibiscus sabdariffa* L.

The bright red colored calyces as well as the young shoots, leaves, roots, and seeds of the roselle *H. sabdariffa* (Figure 5) are extensively used for preparing food colorings, beverages, certain dishes, cooking oil, as well as soaps and shrubs [151]. Particularly preparations from the calyces are also widely used in various traditional medicinal systems because of their presumed antimicrobial, antioxidant, antidiabetic, diuretic, and antihypertensive properties [122,152]. Phytochemical and pharmacological studies supported some of these uses including those for cardioprotection and lowering an elevated blood pressure [152].

Figure 5 *Hibiscus sabdariffa* L. (Malvaceae) (from: https://goo.gl/images/ppfiih)

Thus, a crude aqueous extract from *H. sabdariffa* calyces dose-dependently decreased the mean arterial pressure in anesthetized rats, possibly through acetylcholine- and histamine-like-dependent mechanisms [69]; lowered systolic and diastolic blood pressures, and stimulated diuresis in SHRs and normotensive Wistar-Kyoto rats [70]; elicited antihypertensive, hypotensive, and negative-chronotropic effects in salt- and N(omega)-L-arginine methyl ester-treated laboratory rats [71]; and attenuated the development of salt-induced hypertension in the animals [72]. Furthermore, chronic treatment with an aqueous calyx extract reversed the cardiac hypertrophy in 2K-1C renovascular hypertensive Sprague-Dawley rats and increased surface capillary area and length density in the myocard of SHRs [73,74].

Notably, a comparison of *H. sabdariffa* calyx tea or a standardized *H. sabdariffa* calyx aqueous extract to black tea, blood pressure medication, or a placebo in pre- and mildly hypertensive patients as well as individuals with stage 1 or 2 hypertension, showed that systolic and diastolic blood pressures decreased in most cases, more in the *H. sabdariffa* groups than the placebo and black tea groups [75-77]. The *H. sabdariffa* preparations were as effective as captopril in one study but less effective than lisinopril in another [78,79]. However, these studies had important flaws in their design such as not being placebo-controlled and not double-blind [153].

The biologically active compounds responsible for the potential cardiovascular benefits of *H. sabdariffa* may include polyphenolic compounds such as chlorogenic acids and flavonoid compounds such as kaempferol, quercetin, and anthocyanins [152,154,155]. Of note, chlorogenic acids (modestly) reduced an elevated blood pressure [154]; kaempferol may have a protective effect in heart diseases [156]; and quercetin caused the release of NO from vascular endothelium, increasing renal vasorelaxation and kidney filtration, stimulating diuresis and decreasing blood pressure [157].

The mechanisms responsible for the blood pressure-lowering effect of *H. sabdariffa* preparations may involve direct vasorelaxation [69,158,159]. This can be inferred from the relaxation of noradrenaline-, KCl-, and/or phenylephrine-precontracted rat aortic ring preparations by aqueous and methanolic calyx extracts [69,158,159]. The antihypertensive and hypotensive effects may also be related to stimulation of diuresis following modulation of aldosterone activity by

the anthocyanins, flavonoids, and chlorogenic acids in the preparations [160].

Similarly to pharmaceutical ACE inhibitors, an *H. sabdariffa* calyx extract counteracted the cardiomegaly and increased the surface area of cardiac capillaries in SHRs, suggesting an involvement of ACE inhibition in its blood pressure-lowering effect [74,161]. More direct evidence for this supposition was provided by the appreciable *in vitro* ACE inhibitory activity of a crude hydroalcoholic extract from *H. sabdariffa* calyces [112], and that of the anthocyanins delphinidin-3-O-sambubioside and cyanidin-3-O-sambubioside from an aqueous extract of the dried calyces [113].

Musaceae-*Musa x paradisiaca* L.

Almost all parts of the banana plant *M. paradisiaca* are used for traditional medicinal purposes [131]. Fruit, peel, leaf, stem, and root preparations are employed against digestive disorders, microbial and parasitic infections, burns and other skin afflictions, diabetes mellitus, and hypertension [162]. Pharmacological evaluations with extracts from several parts of the plant indeed showed, among others, antiulcerogenic, antimicrobial, antioxidant, hypoglycemic, and antihypertensive activities [163].

Indications for blood pressure-lowering activity of *M. paradisiaca* came from the decreased heart rate and mean arterial blood pressure caused by fruit preparations in both normal albino rats and rats previously treated with (DOCA) [80,81]. Furthermore, feeding ripened fruits to laboratory rats prevented the increase in the blood pressure induced by intramuscular injection of deoxycorticosterone enantate [82]. Also, an aqueous *M. paradisiaca* fruit extract relaxed both noradrenaline□and KCl□contracted rat aortic rings, inhibited the contractions of the rings in response to noradrenaline, and completely abolished the spontaneous contractions of isolated rat portal veins [83]. These observations have tentatively been explained by an indirect vasodilatory effect involving vasoactive substances such as serotonin [82], but also by a direct vasodilatory effect caused by the non-specific interference with the availability of Ca^{2+} ions required for vasoconstriction [83].

Of note, the consumption of *M. paradisiaca* fruit countered the increased systolic, diastolic, and mean arterial blood pressure caused by cold stress in healthy volunteers [84,85]. This was accompanied by a meaningful decrease in plasma ACE activity, suggesting that inhibition of this enzyme activity was involved in the observed blood pressure-lowering effects [84]. Interestingly, using hippuryl-L-histidyl-L-leucine as a substrate for rat lung ACE activity, ripened bananas displayed a greater ACE inhibitory activity when compared to unripened bananas [114].

Oxalidaceae-*Averrhoa bilimbi* L.

Parts of *A. bilimbi* (Figure 6) have a long traditional use for treating a variety of conditions such as a cough, cold, syphilis, diabetes mellitus, microbial infections, as well as hypertension [29,164]. Physicochemical and pharmacological studies supported some of these uses including the use as an antihypertensive [164]. For instance, exposure to an aqueous *A. bilimbi* leaf extract led to a decrease in the contractility of isolated guinea pig atria precontracted with norepinephrine [86]. Furthermore, this extract elicited a considerable hypotensive effect in cats [87].

Figure 6 ***Averrhoa bilimbi*** **L. (Oxalidaceae) (from: https://goo.gl/images/qztHBs)**

The results found with the isolated guinea pig atria might be associated with a decrease in cardiac output subsequent to changes in intracellular calcium metabolism and/or phenomena involving the muscarinic receptor [86]. Those with the experimental animals might be accounted for by the stimulation of diuresis by the relatively high levels of oxalate in these preparations [87,165]. Interestingly, an aqueous leaf extract of the related species *Averrhoa carambola* L. caused a dose-dependent decrease in the blood pressure of normotensive laboratory rats and a depression in the maximum response of isolated thoracic rat aortic rings to phenylephrine [88].

An *A. bilimbi* ethanolic leaf extract inhibited the liberation of hippuric acid from hippuryl-L-histidyl-L-leucine by ACE activity from rabbit lung [115]. This effect was comparable to that found for captopril and suggested that ACE inhibition was involved in the blood pressure-lowering effect of *A. bilimbi* preparations [115]. Interestingly, using the same assay, an aqueous extract from fruits of the related species *Averrhoa carambola* inhibited ACE activity to more or less the same extent [116].

Phyllanthaceae-*Phyllanthus amarus* Schumach. and Thonn.

The leaves, fruits, and whole plant of the bitter-tasting stonebreaker *P. amarus* are used in many parts of the world for treating, among others, urinary tract conditions including kidney stones (hence the vernacular name ‘stonebreaker’ [166]), genital affections such as gonorrhea and menorrhagia, as well as hypertension [167]. Phytochemical studies have shown that this plant contains a number of bioactive compounds such as flavonoids, tannins, polyphenols, triterpenes, sterols, and alkaloids [167]. Pharmacological evaluations have indicated among others, antiviral, antimicrobial, antiparasitic, anti-inflammatory, anticancer, antidiabetic, antioxidant, diuretic, and antihypertensive activities [167].

The latter activity was corroborated by the blood pressure-lowering effect of aqueous extracts from *P. amarus* leaves and seeds in laboratory mice [89], and the substantial decrease in mean diastolic, systolic, and arterial pressures in anesthetized normotensive male rabbits by an intravenously administered aqueous leaf extract [90]. Furthermore, n-butanol leaf extracts from the gooseberry tree *Phyllanthus acidus* (L.) Skeels caused dilatation of pre-constricted rat thoracic aortic and a decrease in blood pressure of anesthetized rats [91]. And crude powdered, liquid, and dried extracts from the leaves of the gale of the wind *Phyllanthus niruri* L. - an Andean species that are morphologically

very similar to the Amazonian *P. amarus*- elicited hypotensive and diuretic effects in normal laboratory rats and a substantial decrease in mean arterial blood pressure in diabetic hypertensive rats [92-94].

These effects have been associated with myocardial depression, muscarinic receptor-mediated vascular smooth muscle relaxation, blockade of calcium channels in the vascular smooth muscle cells, and/or stimulation of the release of nitric oxide from the endothelium [117,168,169]. They might be mediated by phyllanthin and hypophyllanthin, two major compounds from *P. amarus* which decreased vascular tone by blocking Ca^{2+} entry into the vascular smooth muscle and inhibited phenylephrine-induced Ca^{2+} release from the endoplasmatic reticulum [170]. In addition, a clinical study with 9 mildly hypertensive patients reported that an aqueous extract of the whole plant given for 10 days lowered the elevated blood pressure, possibly by stimulating diuresis [95].

The support for an involvement of ACE inhibition in the blood pressure-lowering activity of *P. amarus* preparations is mainly indirect, comprising the meaningful *in vitro* ACE inhibitory properties of geraniin, an ellagitannin found in *P. niruri*, and the decrease in systolic and diastolic blood pressure produced by geraniin in SHRs [96,117].

Piperaceae-*Piper betle* L.

The edible leaves of the betel vine *P. betle* (Figure 7) are commonly used as a wrapper for the areca nut from *Areca catechu L.* (Arecaceae), tobacco, lime paste, spices, and condiments in South and Southeast Asia as well as Asian communities in other parts of the world [99]. This is generally done after meals to cleanse the palate and refresh the mouth and has led to the development of *P. betle* leaf preparations to prevent halitosis and body odors [99]. The major antibacterial principles (as well as antioxidant constituents) in *P. betle* leaves are allylpyrocatechol, chavicol, and eugenol [171]. Preparations from leaves, stem, and whole plant are traditionally also used for treating, among others, respiratory ailments, gastrointestinal problems, malaria, microbial and parasitic infections, diabetes mellitus, and hypertension [99]. Pharmacological evaluations have supported some of these uses including that against hypertension [163].

Figure 7 *Piper betle* L. (Piperaceae) (from: https://goo.gl/images/pE2Fmh)

The latter custom was supported by the greater than 50% relaxation of isolated rat aortic rings and isolated perfused

mesenteric arteries exposed to a *P. betle* leaf extract [97]. Furthermore, water and ethanol extracts of the leaves stimulated both the volume of urine and the urinary excretion of sodium, potassium, and chloride in Wister albino rats when compared to control animals [98]. Incidentally, using a rat model of hypertension, a Thai study found that traditional recipes containing plants in the families of Piperaceae exhibited potent antihypertensive activity [166].

Water, ethanol, and acetone extracts of *P. betle* leaves inhibited ACE activity by about 50% and lowered blood pressure in laboratory animals [118], suggesting that these preparations contained ACE-inhibitory substances with antihypertensive activity. This assumption is supported by the (relatively modest) ACE inhibitory properties of crude hydroalcoholic extracts and fractions of *P. betle* leaves as determined by measuring the release of hippuric acid from hippuryl-l-histidyl-l-leucine [119].

CONCLUSION

Suriname has a rich tradition of medicinal plant use for treating a large variety of disease conditions including hypertension. This literature review on Surinamese antihypertensive herbal preparations with ACE inhibitory properties suggests that this may hold true for those from *R. tuberosa*, *M. indica*, *A. graveolens*, *C. sativus*, *C. nucifera*, *M. charantia*, *G. barbadense*, *M. paradisiaca*, *A. bilimbi*, *P. amarus*, and *P. betle*. These plants are among the most widely used plants for treating hypertension in Suriname and belong to 10 distinct plant families [28]. This indicates that ACE-inhibitory activity is not uncommon in the plant kingdom [15,169].

All plants inhibited ACE activity *in vitro* and 3 of them also inhibited ACE activity in animal models (*M. charantia, P. granatum*, and *P. betle*), but there were only indications for ACE-inhibitory activity in human subjects for *P. granatum* and *M. paradisiaca*. Suggestions about the identity of the pharmacologically active ingredient(s)- which mostly seemed to be associated with phenolic compounds- were available for *R. tuberosa*, *A. graveolens, M. indica, M. charantia, H. sabdariffa*, and *P. amarus*. Thus, the scientific information to support the involvement of ACE inhibition in the blood pressure-lowering activity of these plants is limited.

Notably, in many cases, the evidence for the use of preparations from these plants against hypertension is also insufficient [170,171]. This indicates a need of carrying out more high-quality animal and human studies, not only to demonstrate their benefit in this condition but also to corroborate the involvement of ACE inhibition in their apparent blood pressure-lowering activity [170,171]. Hopefully, these investigations may help identify novel plant-based ACE inhibitors for treating hypertension. Important considerations in these efforts should involve measures dealing with the fair and equitable sharing of arising benefits. In this way, the unfairness towards the holders of the traditional knowledge could be avoided, as happened with the development of captopril which was directly based on the traditional knowledge from the indigenous Brazilian tribe who, however, did not profit from their knowledge [13,14].

DECLARATIONS

Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

REFERENCES

[1] Beevers, Gareth, Gregory YH Lip, and Eoin O'Brien. "ABC of hypertension: the pathophysiology of hypertension." *BMJ: British Medical Journal,* Vol. 322, No. 7295, 2001, pp. 912-16.

[2] Mills, Katherine T., et al. "Global disparities of hypertension prevalence and control clinical perspective: a systematic analysis of population-based studies from 90 countries." *Circulation,* Vol. 134, No. 6, 2016, pp. 441-50.

[3] Cohen, Jerome D. "Hypertension epidemiology and economic burden: refining risk assessment to lower costs." *Managed Care,* Vol. 18, No. 10, 2009, pp. 51-58.

[4] Weber, Michael A., et al. "Clinical practice guidelines for the management of hypertension in the community: a statement by the American Society of Hypertension and the International Society of Hypertension." *The Journal of Clinical Hypertension,* Vol. 16, No. 1, 2014, pp. 14-26.

[5] Pinto, Isabel C., and Débora Martins. "Prevalence and risk factors of arterial hypertension: A literature review." *Journal of Cardiovascular Medicine and Therapeutics,* Vol. 1, No. 2, 2017, pp. 1-7.

[6] Esler, Murray, Elisabeth Lambert, and Markus Schlaich. "Point: Chronic activation of the sympathetic nervous

system is the dominant contributor to systemic hypertension." *Journal of Applied Physiology,* Vol. 109, No. 6, 2010, pp. 1996-98.

[7] Navar, L. Gabriel. "Counterpoint: Activation of the intrarenal renin-angiotensin system is the dominant contributor to systemic hypertension." *Journal of Applied Physiology,* Vol. 109, No. 6, 2010, pp. 1998-2000.

[8] Delacroix, Sinny, R. C. Chokka, and S. G. Worthley. "Hypertension: pathophysiology and treatment." *Journal of Neurology and Neurophysiology,* Vol. 5, No. 6, 2014.

[9] Brook, Robert D., et al. "Beyond medications and diet: alternative approaches to lowering blood pressure: a scientific statement from the American Heart Association." *Hypertension,* Vol. 61, No. 6, 2013.

[10] Mancia, Giuseppe, et al. "2013 ESH/ESC Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC)." *European Heart Journal,* Vol. 34, No. 28, 2013, pp. 2159-99.

[11] James, Paul A., et al. "2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8)." *JAMA,* Vol. 311, No. 5, 2014, pp. 507-20.

[12] Montani, J.P., and B. N. Van Vliet. "General physiology and pathophysiology of the renin-angiotensin system." *Angiotensin Vol. I*. Springer, Berlin, Heidelberg, 2004, pp. 3-29.

[13] Arora, Pradeep Kumar, and Ashish Chauhan. "ACE inhibitors: a comprehensive review." *International Journal of Pharmaceutical Sciences and Research,* Vol. 4, No. 2, 2013, pp. 532-48.

[14] Williams, Bryan. "Drug discovery in renin-angiotensin system intervention: past and future." *Therapeutic Advances in Cardiovascular Disease,* Vol. 10, No. 3, 2016, pp. 118-25.

[15] Sharifi, Niusha, et al. "Discovery of new angiotensin-converting enzyme (ACE) inhibitors from medicinal plants to treat hypertension using an in vitro assay." *DARU Journal of Pharmaceutical Sciences,* Vol. 21, No. 1, 2013, p. 74.

[16] Hammond, David S. "Forest conservation and management in the Guiana Shield." *Tropical forests of the Guiana Shield. CABI Publishing, Wallingford, UK*, 2005, pp. 481-520.

[17] voor de Statistiek, Algemeen Bureau. "Suriname in cijfers 303-2014-04 (General Bureau of Statistics. Suriname in numbers 303-2014-04)." *Basis indicatoren (Basic indicators). Paramaribo: Algemeen Bureau voor de Statistiek*, 2014.

[18] The World Bank Group. "The World Bank: Suriname." World Bank Publications, 2014.

[19] voor de Statistiek, Algemeen Bureau. "Demographic and Social Characteristics and Migration." Algemeen Bureau voor de Statistiek, Paramaribo, 2013.

[20] Helman, Albert. "Cultural mosaic of Suriname." *A contribution to mutual understanding. De Walburg Pers, Zutphen,* 1977.

[21] Mans, Dennis RA, Deeksha Ganga, and Joëlle Kartopawiro. "Meeting of the minds: traditional herbal medicine in multiethnic Suriname." *Aromatic and Medicinal Plants-Back to Nature*. InTech, 2017, pp. 111-32.

[22] Mans, Dennis RA. "Nature, green in leaf and stem". Research on plants with medicinal properties in Suriname." *Clinical and Medical Investigations*, Vol. 2, No. 1, 2016, pp. 1-10.

[23] Krishnadath, Ingrid SK, et al. "Ethnic differences in prediabetes and diabetes in the Suriname Health Study." *BMJ Open Diabetes Research and Care,* Vol. 4, 2016.

[24] Krishnadath, Ingrid SK, et al. "Ethnic differences in prediabetes and diabetes in the Suriname Health Study." *BMJ Open Diabetes Research and Care,* Vol. 6, No. 12, 2016.

[25] Krishnadath, Ingrid SK, et al. "Ethnic differences in prevalence and risk factors for hypertension in the Suriname Health Study: a cross-sectional population study." *Population Health Metrics,* Vol. 14, 2016, p. 33.

[26] Diemer, F., et al. "Prehypertension and hypertension in urban Suriname." *Journal of Hypertension,* Vol. 34, 2016.

[27] Karamat, Fares, et al. "Lbos 03-02 prehypertension and hypertension in urban Suriname: the HELISUR study." *Journal of Hypertension,* Vol. 34, 2016, p. e551.

[28] Mans, Dennis RA, Angela Grant, and Nicholaas Pinas. "Plant-based ethnopharmacological remedies for hypertension in Suriname." 2017.

[29] Raghoenandan, U. P. D. "An ethnobotanical investigation among Hindustanis in Suriname." *Anton de Kom Universiteit van Suriname, Paramaribo*, 1994.

[30] Chothani, Daya L., et al. "Review on *Ruellia tuberosa* (cracker plant)." *Pharmacognosy Journal* Vol. 2, No. 12, 2010, pp. 506-52.

[31] Ahmad, Mansoor, et al. "Studies on the medicinal herb *Ruellia patula*." *International Journal of Pharmacognosy,* Vol. 31, No. 2, 1993, pp. 121-29.

[32] Akhtar, M. Farid, et al. "Cardiovascular evaluation of *Ruellia patula* and *Ruellia brittoniana*." *Medical Journal of Islamic World Academy of Sciences,* Vol. 5, No.1, 1992, pp. 67-71.

[33] Beltrán, Amada E., et al. "Vascular effects of the *Mangifera indica L.* extract (Vimang)." *European Journal of Pharmacology,* Vol. 499, No. 3, 2004, pp. 297-305.

[34] Ronchi, Silas Nascimento, et al. "Phytochemical and *in vitro* and *in vivo* biological investigation on the antihypertensive activity of mango leaves (*Mangifera indica L.*)." *Therapeutic Advances in Cardiovascular Disease,* Vol. 9, No. 5, 2015, pp. 244-56.

[35] Matkowski, Adam, et al. "Mangiferin-a bioactive xanthonoid, not only from mango and not just antioxidant." *Mini Reviews in Medicinal Chemistry,* Vol. 13, No. 3, 2013, pp. 439-55.

[36] Devi, MS Shree. "Acute toxicity and diuretic activity of *Mangifera indica* L. bark extracts." *International Journal of Pharmacy and Biological Sciences,* Vol. 2, No. 3, 2011, pp. 141-46.

[37] Raj, R.R., Kumari, A., Guruprasad, R. "*In vitro* and *in vivo* screening of angiotensin-converting enzyme inhibitor using *Mangifera indica*; a solution for hypertension". World *Journal of Pharmacy and Pharmaceutical Sciences*, Vol. 6, No. 1, 2017, pp. 1063-71.

[38] Al-Asmari, Abdulrahman Khazim, Md Tanwir Athar, and Saeed G. Kadasah. "An updated phytopharmacological review on medicinal plant of Arab region: *Apium graveolens* Linn." *Pharmacognosy Reviews*, Vol. 11, No. 21, 2017, pp. 13-8.

[39] Chai, L. M., et al. "Antihypertensive effects of roots of *Apium graveolens* extract in renal hypertensive rats". *Chinese Journal of Experimental Traditional Medical Formulae*, Vol. 16, No. 11, 2010, pp. 101-03.

[40] Moghadam, Maryam Hassanpour, Mohsen Imenshahidi, and Seyed Ahmad Mohajeri. "Antihypertensive effect of celery seed on rat blood pressure in chronic administration". *Journal of Medicinal Food,* Vol. 16, No. 6, 2013, pp. 558-63.

[41] Sarkarati, A. R., and M. Gharooni. "Application of *Apium graveolens* in treatment of hypertension". *Tehran University Medical Journal,* Vol. 58, No. 3, 2000, pp. 67-69.

[42] Dewi, Kartika, Diana Krisanti Jasaputra, and Oddy Litanto. "The effect of celery ethanol extract (*Apium graveolens* L.) on male adult's blood pressure". *Planta Medical Journal,* Vol. 1, No. 2, 2010, pp. 27-34.

[43] Madhavi, Doddabele, Daniel Kagan, and Venkatesh Rao. "A pilot study to evaluate the antihypertensive effect of a celery extract in mild to moderate hypertensive patients". *Natural Medicine Journal,* Vol. 5, No. 4, 2013, pp. 1-5.

[44] Zhu, J., Zhang, Y., Yang, C. "Protective effect of 3-n-butylphthalide against hypertensive nephropathy in spontaneously hypertensive rats". *Molecular Medicine Reports*, Vol. 11, No. 2, 2015, pp. 1448-54.

[45] Abdoulaye, Idriss Ali, and Yi Jing Guo. "A review of recent advances in neuroprotective potential of 3-n-butylphthalide and its derivatives". *BioMed Research International*, 2016.

[46] Pattigadapa, Hemanth Sairam, et al. "Cardiotonic activity of coconut water (*Cocos nucifera*)". *Recent Research in Science and Technology,* Vol. 3, No. 4, 2011, pp. 155-57.

[47] Alves, Naiane Ferraz Bandeira, et al. "Coconut oil supplementation reduces blood pressure and oxidative stress in spontaneously hypertensive rats". *BMC Proceedings,* Vol. 8, 2014.

[48] Alves, Naiane FB, et al. "Coconut oil supplementation and physical exercise improves baroreflex sensitivity and oxidative stress in hypertensive rats". *Applied Physiology Nutrition and Metabolism*, Vol. 40, No. 4, 2015, pp. 393-400.

[49] Alleyne, Trevnmar, et al. "The control of hypertension by use of coconut water and mauby: two tropical food drinks". *West Indian Medical Journal*, Vol. 54, No. 1, 2005, pp. 3-8.

[50] Bhagya, D., and Soumya Gopan. "Effects of coconut neera (*Cocos nucifera* L.) on blood pressure among hypertensive adult women". *International Journal of Applied and Pure Science and Agriculture*, Vol. 2, No. 9, 2016, pp. 1-7.

[51] Li, Yan, et al. "Purification, characterization, synthesis, *in vivo* and *in vitro* antihypertensive activity of bioactive peptides derived from coconut (*Cocos nucifera* L.) cake globulin hydrolysates". *RSC Advances*, Vol. 6, 2016, pp. 92688-98.

[52] Adejoh, I.P., et al. "Aphrodisiac and fertility-enhancing actions of 'kunu aya' (a beverage blend developed from *Cyperus esculentus*, *Phoenix dactylifera* and *Cocos nucifera*) via testosterone-boosting, anxiolysis and inhibition of key enzymes associated with erectile process". *World Journal of Pharmaceutical Research*, Vol. 7, No. 1, 2018, pp. 139-64.

[53] Mukherjee, Pulok K., et al. "Phytochemical and therapeutic potential of cucumber". Fitoterapia Vol. 84, 2013, pp. 227-36.

[54] Hansen, Klaus, et al. "*In vitro* screening of traditional medicines for anti-hypertensive effect based on inhibition of the angiotensin-converting enzyme (ACE)". *Journal of Ethnopharmacology*, Vol. 48, No. 1, 1995, pp. 43-51.

[55] Ojewole, John AO, Stephen O. Adewole, and Gbola Olayiwola. "Hypoglycaemic and hypotensive effects of *Momordica charantia* Linn (Cucurbitaceae) whole-plant aqueous extract in rats." *Cardiovascular journal of Southern Africa*, Vol. 17, No. 5, 2006, pp. 227-32.

[56] Clouatre, Dallas L., Sadanand N. Rao, and Harry G. Preuss. "Bitter melon extracts in diabetic and normal rats favorably influence blood glucose and blood pressure regulation." *Journal of Medicinal Food*, Vol. 14, No. 12, 2011, pp. 1496-1504.

[57] Shodehinde, Sidiqat A., et al. "Phenolic composition and evaluation of methanol and aqueous extracts of bitter gourd (*Momordica charantia* L) leaves on angiotensin-I-converting enzyme and some pro-oxidant-induced lipid peroxidation *in vitro.*" *Journal of Evidence-Based Complementary and Alternative Medicine*, Vol. 21, No. 4, 2016, pp. 67-76.

[58] Lestari, Putri, and Putu Gita Maya Widyaswari Mahayasih. "Inhibition activity of angiotensin converting enzyme (ACE) and determination of total phenolic and flavonoid compound from bitter melon leaves (*Momordica charantia* L.)." *Pharmacognosy Journal*, Vol. 9, No. 2, 2017, pp. 252-56.

[59] Chaudhari, P.M., et al. "Antihypertensive effect of the *Punica granatum* juice in deoxycorticosterone acetate-salt model of hypertension in rats." *Asian Journal of Pharmaceutical and Clinical Research,* Vol. 11, No. 6, 2018, pp. 498-504.

[60] dos Santos, Roger L., et al. "Pomegranate peel extract attenuates oxidative stress by decreasing coronary angiotensin-converting enzyme (ACE) activity in hypertensive female rats." *Journal of Toxicology and Environmental Health*, Vol. 79, No. 21, 2016, pp. 998-1007.

[61] Aviram, Michael, and Leslie Dornfeld. "Pomegranate juice consumption inhibits serum angiotensin converting enzyme activity and reduces systolic blood pressure." *Atherosclerosis*, Vol. 158, No. 1, 2001, pp. 195-98.

[62] Asgary, Sedigheh, et al. "Clinical investigation of the acute effects of pomegranate juice on blood pressure and endothelial function in hypertensive individuals." *ARYA Atherosclerosis*, Vol. 9, No. 6, 2013, pp. 326-31.

[63] Asgary, Sedigheh, et al. "Clinical evaluation of blood pressure lowering, endothelial function improving, hypolipidemic and anti-inflammatory effects of pomegranate juice in hypertensive subjects." *Phytotherapy Research*, Vol. 28, No. 2, 2014, pp. 193-99.

[64] Mathew, Aarati Susan, et al. "Acute effects of pomegranate extract on postprandial lipaemia, vascular function and blood pressure." *Plant Foods for Human Nutrition*, Vol. 67, No. 4, 2012, pp. 351-57.

[65] Lynn, Anthony, et al. "Effects of pomegranate juice supplementation on pulse wave velocity and blood pressure in healthy young and middle-aged men and women." *Plant Foods for Human Nutrition*, Vol. 67, No. 3, 2012, pp. 309-14.

[66] Carpenter, L. A., C. J. Conway, and F. Broughton Pipkin. "Pomegranates (*Punica granatum*) and their effect on blood pressure: a randomized double-blind placebo-controlled trial". *Proceedings of the Nutrition Society*, Vol. 69, 2010.

[67] Aviram, Michael, et al. "Pomegranate juice consumption for 3 years by patients with carotid artery stenosis

reduces common carotid intima-media thickness, blood pressure and LDL oxidation." *Clinical Nutrition,* Vol. 23, No. 3, 2004, pp. 423-33.

[68] Sumner, Michael D., et al. "Effects of pomegranate juice consumption on myocardial perfusion in patients with coronary heart disease." *American Journal of Cardiology*, Vol. 96, No. 6, 2005, pp. 810-14.

[69] Mojiminiyi, F. B. O., et al. "Antihypertensive effect of an aqueous extract of the calyx of *Hibiscus sabdariffa.*" *Fitoterapia*, Vol. 78, No. 4, 2007, pp. 292-97.

[70] Mojiminiyi, F. B. O., et al. "Attenuation of salt-induced hypertension by aqueous calyx extract of *Hibiscus sabdariffa.*" *Nigerian Journal of Physiological Sciences*, Vol. 27, No. 2, 2012, pp. 195-200.

[71] Odigie, I. P., R. R. Ettarh, and S. A. Adigun. "Chronic administration of aqueous extract of *Hibiscus sabdariffa* attenuates hypertension and reverses cardiac hypertrophy in 2K-1C hypertensive rats." *Journal of Ethnopharmacology*, Vol. 86, No. 2-3, 2003, pp. 181-85.

[72] Inuwa, Ibrahim, et al. "Long-term ingestion of *Hibiscus sabdariffa* calyx extract enhances myocardial capillarization in the spontaneously hypertensive rat." *Experimental Biology and Medicine*, Vol. 237, No. 5, 2012, pp. 563-69.

[73] McKay, Diane L., et al. "*Hibiscus sabdariffa* L. tea (Tisane) lowers blood pressure in prehypertensive and mildly hypertensive adults." *Journal of Nutrition*, Vol. 140, No. 2, 2010, pp. 298-303.

[74] Mozaffari-Khosravi, H., et al. "The effects of sour tea (*Hibiscus sabdariffa*) on hypertension in patients with type II diabetes." *Journal of Human Hypertension*, Vol. 23, No. 1, 2009, pp. 48-54.

[75] Faraji, M. Haji, and AH Haji Tarkhani. "The effect of sour tea (*Hibiscus sabdariffa*) on essential hypertension." *Journal of Ethnopharmacology,* Vol. 65, No. 3, 1999, Vol. 231-36.

[76] Herrera-Arellano, A., et al. "Effectiveness and tolerability of a standardized extract from *Hibiscus sabdariffa* in patients with mild to moderate hypertension: a controlled and randomized clinical trial." *Phytomedicine*, Vol. 11, No. 5, 2004, pp. 375-82.

[77] Herrera-Arellano, Armando, et al. "Clinical effects produced by a standardized herbal medicinal product of *Hibiscus sabdariffa* on patients with hypertension. A randomized, double-blind, lisinopril-controlled clinical trial." *Planta Medica*, Vol. 73, No. 1, 2007, pp. 6-12.

[78] Wahabi, H. A., et al. "The effectiveness of *Hibiscus sabdariffa* in the treatment of hypertension: a systematic review." *Phytomedicine*, Vol. 17, No. 2, 2010, pp. 83-86.

[79] Zhao, Youyou, et al. "Antihypertensive effects and mechanisms of chlorogenic acids." *Hypertension Research*, Vol. 35, No. 4, 2012, 370-74.

[80] Perfumi, Marina, Maurizio Massi, and Giuseppe de Caro. "Effects of banana feeding on deoxycorticosterone-induced hypertension and salt consumption in rats". *International Journal of Pharmacognosy*, Vol. 32, No. 2, 1994, pp. 115-25.

[81] Orie, N.N. "Direct vascular effects of plantain extract in rats". *Experimental Physiology,* Vol. 82, No. 3, 1997, pp. 501-06.

[82] Sarkar, Chayna, et al. "Effect of banana on cold stress test and peak expiratory flow rate in healthy volunteers". *Indian Journal of Medicinal Research*, Vol. 110, 1999, pp. 27-29.

[83] Suherman, Jo, and Megawati Rusli. "Effect of Pisang ambon (*Musa accumenta* Colla) on adult female blood pressure on cold stress test." *Jurnal Medika Planta,* Vol. 1, No. 2, 2010, pp. 21-25.

[84] Rao, N. Mallikarjuna, K. V. S. R. G. Prasad, and K. S. R. Pai. "Angiotensin-converting enzyme inhibitors from ripened and unripened bananas." *Current Science,* Vol. 76, No. 1, 1999, 86-88.

[85] Alhassan, Alhassan Muhammad, and Qamar Uddin Ahmed. "*Averrhoa bilimbi* Linn: a review of its ethnomedicinal uses, phytochemistry, and pharmacology." *Journal of Pharmacy and Bioallied Sciences*, Vol. 8, No. 4, 2016, pp. 265-71.

[86] Lima, Vera Lúcia Arroxelas Galvão De, Enayde De Almeida Mélo, and Santos Lima. "Physicochemical characteristics of bilimbi (*Averrhoa bilimbi*)." *Revista Brasileira de Fruticultura*, Vol. 23, No. 2, 2011, pp. 421-23.

[87] Soncini, Roseli, et al. "Hypotensive effect of aqueous extract of *Averrhoa carambola* L. (Oxalidaceae) in rats: an *in vivo* and *in vitro* approach." *Journal of Ethnopharmacology,* Vol. 133, No. 2, 2011, pp. 353-57.

[88] Das, Susmita, and Bratati De. "Evaluation of angiotensin I-converting enzyme (ACE) inhibitory potential of some underutilized indigenous fruits of West Bengal using an *in vitro* model." *Fruits*, Vol. 68, No. 6, 2013, pp. 499-506.

[89] Leeya, Yuttapong, et al. "Hypotensive activity of an n-butanol extract and their purified compounds from leaves of *Phyllanthus acidus* (L.) Skeels in rats." *European Journal of Pharmacology*, Vol. 649, No. 1-3, 2010, pp. 301-13.

[90] Devi, M. Vimala, S. Satyanarayana, and A. Sambasiva Rao. "Effect of *Phyllanthus niruri* on the diuretic activity of Punarnava tablets." *Journal of Research and Education in Indian Medicine*, Vol. 5, No. 1, 1986, pp. 11-12.

[91] Ramakrishnan, P. N., et al. "Oral hypoglycemic effect of *Phyllanthus niruri* leaves." *Indian Journal of Pharmaceutical Sciences,* Vol. 44, No. 1, 1982, pp. 10-12.

[92] Bharati, D., S. Rawat, and P. Sharma. "Evaluation of *in vivo* efficacy of aqueous leaf extract of *Phyllanthus niruri* in diabetic hypertensive rats." *Annals of Clinical and Experimental Hypertension*, Vol. 3, No. 3, 2015, p. 1031.

[93] Amonkan, Augustin K., et al. "Comparative effects of two fractions of *Phyllanthus amarus* (Euphorbiaceae) on the blood pressure in rabbit." *Greener Journal of Medical Sciences*, Vol. 3, No. 4, 2013, pp. 129-34.

[94] Chongsa, Watchara, Kanyanatt Kanokwiroon, and Chaweewan Jansakul. "Effects of 6 weeks oral administration of *Phyllanthus acidus* leaf water extract on the vascular functions of middle-aged male rats." *Journal of Ethnopharmacology,* Vol. 176, 2015, pp.79-89.

[95] Lin, Shyr-Yi, et al. "Antioxidant, anti-semicarbazide-sensitive amine oxidase, and anti-hypertensive activities of geraniin isolated from *Phyllanthus urinaria*." *Food and Chemical Toxicology*, Vol. 46, No. 7, 2008, pp. 2485-92.

[96] Ramji, Niranjan, et al. "Phenolic antibacterials from *Piper betle* in the prevention of halitosis." *Journal of Ethnopharmacology,* Vol. 83, No. 1-2, 2002, pp. 149-52.

[97] Manosroi, Aranya, et al. "Potent antihypertensive activity of Thai-Lanna medicinal plants and recipes from "MANOSROI III" database." *Pharmaceutical Biology,* Vol. 51, No. 11, 2013, pp. 1426-34.

[98] Somanadhan, Brinda, et al. "An ethnopharmacological survey for potential angiotensin converting enzyme inhibitors from Indian medicinal plants." *Journal of Ethnopharmacology,* Vol. 65, No. 2, 1999, 103-12.

[99] Barbosa-Filho, José M., et al. "Natural products inhibitors of the angiotensin converting enzyme (ACE). A review between 1980-2000." *Brazilian Journal of Pharmacognosy,* Vol. 16, No. 3, 2006, pp. 421-46.

[100] Desmiaty, Yesi, Deni Rahmat, and Angelina Noeryanti Rainoer. "*In vitro* ACE, inhibitory activity and total flavonoids quantification of ethanolic extract of pletekan (*Ruellia tuberosa L.*) leaves." *Indonesian Traditional Medicine for Human Welfare*, 2014, pp. 527-32.

[101] Van Andel, T.R., and S. Ruysschaert. "Medicinal and Ritual Plants of Suriname." KIT Publishers, 2011.

[102] Obidoa, Onyechi, Parker Elijah Joshua, and Nkechi J. Eze. "Phytochemical analysis of *Cocos nucifera* L." *Journal of Pharmacy Research,* Vol. 3, No. 2, 2010, pp. 280-86.

[103] Kappally, Shijna, Arun Shirwaikar, and Annie Shirwaikar. "Coconut oil-a review of potential applications". *Hygeia Journal of Drugs and Medicines*, Vol. 7, No. 2, 2015, pp. 34-41.

[104] Lima, E. B. C., et al. "*Cocos nucifera* (L.) (Arecaceae): a phytochemical and pharmacological review". *Brazilian Journal of Medical and Biological Research*, Vol. 48, No. 11, 2015, pp. 953-64.

[105] Sahu, Tripti, and Jyoti Sahu. "*Cucumis sativus* (cucumber): a review on its pharmacological activity". *Journal of Applied Pharmaceutical Research*, Vol. 3, No. 1, 2015, pp. 4-9.

[106] Saboo, Shweta S., et al. "Ancient and recent medicinal uses of Cucurbitaceae family". *International Journal of Therapeutic Applications,* Vol. 9, 2013, pp. 11-19.

[107] Trejo-Moreno, Celeste, et al. "*Cucumis sativus* aqueous fraction inhibits angiotensin II-induced inflammation and oxidative stress *in vitro*". *Nutrients*, Vol. 10, No. 3, 2018.

[108] Ahmad, Nesar, et al. "*Momordica charantia*: for traditional uses and pharmacological actions". *Journal of Drug Delivery and Therapeutics*, Vol. 6, No. 2, 2016.

[109] Balasuriya, Nileeka, and HP Vasantha Rupasinghe. "Antihypertensive properties of flavonoids-rich apple peel extract." *Food Chemistry,* Vol. 135, No. 4, 2012, pp. 2320-25.

[110] Bhowmik, Debjit, et al. "Medicinal uses of *Punica granatum* and its health benefits." *Journal of Pharmacognosy and Phytochemistry,* Vol. 1, No. 5, 2013, pp. 28-35.

[111] Nkumah, Okereke CHUKWU. "Phytochemical analysis and medicinal uses of *Hibiscus sabdariffa.*" *International Journal of Herbal Medicine*, Vol. 2, No. 6, 2015, pp. 16-19.

[112] Jyothirmayi, N., and N. Mallikarjuna Rao. "Banana medicinal uses." *Journal of Medical Science and Technology*, Vol. 4, No. 2, 2015, pp. 152-60.

[113] Swathi, D., B. Jyothi, and C. Sravanthi. "A review: pharmacognostic studies and pharmacological actions of *Musa paradisiaca*." *International Journal of Innovative Pharmaceutical Research*, Vol. 2, No. 2, 2011, pp. 122-25.

[114] Bipat, Robbert, et al. "Effects of plants popularly used against hypertension on norepinephrine-stimulated guinea pig atria". *Pharmacognosy Magazine*, Vol. 4, No. 13, 2008, pp. 12-19.

[115] Boim, Mirian A., Ita P. Heilberg, and Nestor Schor. "*Phyllanthus niruri* as a promising alternative treatment for nephrolithiasis." *International Brazilian Journal of Urology*, Vol. 36, No. 6, 2010, pp. 657-64.

[116] Patel, Jay Ram, et al. "*Phyllanthus amarus*: ethnomedicinal uses, phytochemistry and pharmacology: a review." *Journal of Ethnopharmacology*, Vol. 138, No. 2, 2011, pp. 286-313.

[117] Rekha, V. P. B., et al. "A review on *Piper betle* L.: nature's promising medicinal reservoir." *American Journal of Ethnomedicine,* Vol. 1, No. 5, 2014, 276-89.

[118] Barbosa-Filho, José M., et al. "Natural products inhibitors of the angiotensin converting enzyme (ACE). A review between 1980-2000." *Brazilian Journal of Pharmacognosy,* Vol. 16, No. 3, 2006, pp. 421-46.

[119] Stowe, Caroline Bell. "The effects of pomegranate juice consumption on blood pressure and cardiovascular health." *Complementary Therapies in Clinical Practice,* Vol. 17, No. 2, 2011, pp. 113-15.

[120] Salah, A. M., et al. "Angiotensin-converting enzyme-inhibitory effect by *Ruellia praetermissa*." *Pharmaceutical Biology,* Vol. 39, No. 1, 2001, pp. 16-19.

[121] Sarkarati, A. R., and M. Gharooni. "Application of *Apium graveolens* in treatment of hypertension". *Journal of Dentistry of Tehran University of Medical Sciences,* Vol. 58, No. 3, 2000, pp. 67-69.

[122] Tang, Fen-fang, et al. "Study on hypotensive and vasodilatory effects of celery juice." *Food Science*, Vol. 28, No. 1, 2007, pp. 322-25.

[123] Brankovic, S., D. Kitic, and M. Radenkovic. "Hypotensive and cardioinhibitory effects of the aqueous and ethanol extracts of celery (*Apium graveolens*, Apiaceae)". *Acta Medica Medianae*, Vol. 49, No. 1, 2010, pp. 13-16.

[124] ur Rehman, Ata, et al. "Comparative study of ethanolic and aqueous extracts of *Apium graveolens* L. root with furosemide for its diuretic activity and excretion of urinary metabolites in Wistar rats". *Science International*, Vol. 28, No. 3, 2016, 2503-37.

[125] Umamaheswari, Muthuswamy, et al. "*In vitro* angiotensin converting enzyme inhibitory and antioxidant activities of seed extract of *Apium graveolens* Linn". *Annals of Biological Research,* Vol. 3, No. 3, 2012, pp. 1274-82.

[126] Simaratanamongkol, Arunee, et al. "Identification of a new angiotensin-converting enzyme (ACE) inhibitor from Thai edible plants". *Food Chemistry,* Vol. 165, 2014, pp. 92-97.

[127] DebMandal, Manisha, and Shyamapada Mandal. "Coconut (*Cocos nucifera* L.: Arecaceae): in health promotion and disease prevention". *Asian Pacific Journal of Tropical Medicine*, Vol. 4, No. 3, 2011, pp. 241-47.

[128] Bankar, Girish R., et al. "Vasorelaxant and antihypertensive effect of *Cocos nucifera* Linn. endocarp on isolated rat thoracic aorta and DOCA salt-induced hypertensive rats". *Journal of Ethnopharmacology*, Vol. 134, No. 1, 2011, pp. 50-54.

[129] Syafriani, Rini, et al. "The effect of coconut water (*Cocos nucifera* L.) and an isotonic drink on the change of heart rate frequency in the rat's induced hypertension". *Procedia Chemistry*, Vol. 13, 2014, pp. 177-80.

[130] Alves, Naiane Ferraz Bandeira, et al. "Coconut oil supplementation reduces blood pressure and oxidative stress in spontaneously hypertensive rats". *BMC Proceedings,* Vol. 8, 2014.

[131] Alves, Naiane FB, et al. "Coconut oil supplementation and physical exercise improves baroreflex sensitivity and oxidative stress in hypertensive rats". *Applied Physiology Nutrition and Metabolism*, Vol. 40, No. 4, 2015, pp. 393-400.

[132] Alleyne, Trevnmar, et al. "The control of hypertension by use of coconut water and mauby: two tropical food drinks". *West Indian Medical Journal*, Vol. 54, No. 1, 2005, pp. 3-8.

[133] Bhagya, D., and Soumya Gopan. "Effects of coconut neera (*Cocos nucifera* L.) on blood pressure among hypertensive adult women". *International Journal of Applied and Pure Science and Agriculture*, Vol. 2, No. 9, 2016, pp. 1-7.

[134] Li, Yan, et al. "Purification, characterization, synthesis, *in vivo* and *in vitro* antihypertensive activity of bioactive peptides derived from coconut (*Cocos nucifera* L.) cake globulin hydrolysates". *RSC Advances*, Vol. 6, 2016, pp. 92688-98.

[135] Palanisamy, V., et al. "Evaluation of diuretic activity of polyherbal formulation". *International Journal of Pharmaceutics*, Vol. 5, No. 1, 2015, pp. 244-47.

[136] Singh, R. C., and C. S. Sisodia. "Pharmacodynamic investigations into the diuretic activity of *Cucumis melo* seed (ether extract)". *Indian Journal of Medical Research*, Vol. 58, No. 4, 1970, pp. 505-12.

[137] Naik, V. R., N. V. Agshikar, and G. J. S. Abraham. "*Cucumis trigonus* Roxb. II. Diuretic activity". *Journal of Ethnopharmacology*, Vol. 3, No. 1, 1981, pp. 15-19.

[138] Lu, G. L., W. X. Yuan, and Y. J. Fan. "Clinical and experimental study of tablet cucumber vine compound in treating essential hypertension". *Chinese Journal of Modern Developments in Traditional Medicine*, Vol. 11, No. 5, 1991, pp. 274-76.

[139] Pertami, Sumirah Budi, and Dian Yuniar Syanti Rahayu. "Effect of cucumber (*Cucumis sativus*) juice on lowering blood pressure in elderly." Public Health of Indonesia Vol. 3, No. 1, 2017, pp. 30-36.

[140] Kouchmeshky, Azita, et al. "Investigation of angiotensin-converting enzyme inhibitory effects of medicinal plants used in traditional Persian medicine for treatment of hypertension: screening study". *Thrita Student Journal of Medical Sciences*, Vol. 1, No. 1, 2012, pp. 13-23.

[141] Governa, Paolo, et al. "Phytotherapy in the management of diabetes: a review." *Molecules*, Vol. 23, 2018, p. 105.

[142] Ooi, Cheow Peng, Zaitun Yassin, and Tengku□Aizan Hamid. "*Momordica charantia* for type 2 diabetes mellitus." *Cochrane Database of Systematic Reviews*, Vol. 8, 2012.

[143] Sharma, A. K., et al. "The beneficial effects of *Momordica charantia* fruit juice on streptozotocin-induced diabetes and hypertension in rats." *International Journal of Diabetes*, Vol. 4, 1996, pp. 29-38.

[144] Abas, Razif, Faizah Othman, and Zar Chi Thent. "Effect of *Momordica charantia* fruit extract on vascular complication in type 1 diabetic rats." *EXCLI Journal*, Vol. 14, 2015, pp. 179-89.

[145] Rahimi, Hamid Reza, Mohammad Arastoo, and Seyed Nasser Ostad. "A comprehensive review of *Punica granatum* (pomegranate) properties in toxicological, pharmacological, cellular and molecular biology researches". *Iranian Journal of Pharmaceutical Research,* Vol. 11, No. 2, 2012, pp. 385-400.

[146] Afaq, Farrukh, et al. "Anthocyanin- and hydrolyzable tannin-rich pomegranate fruit extract modulates MAPK and NF-kappa B pathways and inhibits skin tumorigenesis in CD-1 mice." *International Journal of Cancer*, Vol. 113, No. 3, 2005, pp. 423-33.

[147] Harshal, Waghulde, et al. "*Punica granatum* attenuates angiotensin-II-induced hypertension in Wistar rats". *International Journal of PharmTech Research*, Vol. 2, No. 1, 2010, pp. 60-67.

[148] Mohan, Mahalaxmi, Harshal Waghulde, and Sanjay Kasture. "Effect of pomegranate juice on angiotensin II-induced hypertension in diabetic Wistar rats". *Phytotherapy Research*, Vol. 24, 2010, pp. 196-203.

[149] Arun, K. B., et al. "Studies on activity-guided fractionation of pomegranate peel extracts and its effect on antidiabetic and cardiovascular protection properties." *Journal of Food Processing and Preservation*, Vol. 41, 2016.

[150] Ismail, Amin, Emmy Hainida Khairul Ikram, and Halimatul Saadiah Mohd Nazri. "Roselle (*Hibiscus sabdariffa* L.) seeds - nutritional composition protein quality and health benefits." *Food*, Vol. 2, No. 1, 2008, pp. 1-16.

[151] Adegunloye, B. J., et al. "Mechanisms of the blood pressure lowering effect of the calyx extract of *Hibiscus sabdariffa* in rats." *African Journal of Medicine and Medical Sciences,* Vol. 25, No. 3, 1996, pp. 235-38.

[152] Onyenekwe, P. C., et al. "Antihypertensive effect of roselle (*Hibiscus sabdariffa*) calyx infusion in spontaneously hypertensive rats and a comparison of its toxicity with that in Wistar rats." *Cell Biochemistry and Function*, Vol. 17, No. 3, 1999, pp. 199-206.

[153] Grajeda-Iglesias, Claudia, et al. "Isolation and characterization of anthocyanins from *Hibiscus sabdariffa* flowers." *Journal of Natural Products*, Vol. 79, No, 7, 2016, pp. 1709-18.

[154] M Calderon-Montano, J., et al. "A review on the dietary flavonoid kaempferol". *Mini Reviews in Medicinal Chemistry*, Vol. 11, No. 4, 2011, pp. 298-344.

[155] Alarcón-Alonso, Javier, et al. "Pharmacological characterization of the diuretic effect of *Hibiscus sabdariffa* Linn (Malvaceae) extract." *Journal of Ethnopharmacology,* Vol. 139, No. 3, 2012, pp. 751-56.

[156] Ajay, Machha, et al. "Mechanisms of the anti-hypertensive effect of *Hibiscus sabdariffa* L. calyces". *Journal of Ethnopharmacology*, Vol. 109, No. 3, 2007, 388-93.

[157] Sarr, Mamadou, et al. "*In vitro* vasorelaxation mechanisms of bioactive compounds extracted from *Hibiscus sabdariffa* on rat thoracic aorta." *Nutrition and Metabolism,* Vol. 6, No. 45, 2009.

[158] Jiménez-Ferrer, Enrique, et al. "Diuretic effect of compounds from *Hibiscus sabdariffa* by modulation of the aldosterone activity." *Planta Medica,* Vol. 78, No. 18, 2012, pp. 1893-98.

[159] Ziada, Amal M., et al. "Long-term exercise training and angiotensin-converting enzyme inhibition differentially enhance myocardial capillarization in the spontaneously hypertensive rat." *Journal of Hypertension,* Vol. 23, No. 6, 2005, pp.1233-40.

[160] Jonadet, M., et al. "*In vitro* enzyme inhibitory and *in vivo* cardioprotective activities of hibiscus (*Hibiscus sabdariffa* L.)." *Journal de Pharmacie de Belgique*, Vol. 45, No. 2, 1990, pp. 120-24.

[161] Ojeda, Deyanira, et al. "Inhibition of angiotensin convertin enzyme (ACE) activity by the anthocyanins delphinidin-and cyanidin-3-O-sambubiosides from *Hibiscus sabdariffa.*" *Journal of Ethnopharmacology,* Vol. 127, No. 1, 2010, pp. 7-10.

[162] Osim, E. E., et al. "The effect of plantain and banana extracts on blood pressure and heart rate in albino rats." *Nigerian Journal of Physiological Sciences*, Vol. 6, No. 2, 1990, pp. 114-19.

[163] Osim, E. E., and J. O. Ibu. "The effect of plantains (*Musa paradisiaca*) on DOCA-induced hypertension in rats". *Pharmaceutical Biology,* Vol. 29, No. 1, 1991, pp. 9-13.

[164] Winarti, C, and Marwati, T. "Effect of bilimbi leaf extracts on decrease blood pressure." *Jurnal Pascapanen Pertanian*, Vol. 6, No. 1, 2009, pp. 54-61.

[165] Muthia, Rahmi, Asep Gana Suganda, and Elin Yulinah Sukandar. "Angiotensin-I converting enzyme (ACE) inhibitory activity of several Indonesian medicinal plants." *Research Journal of Pharmaceutical, Biological and Chemical Sciences*, Vol. 8, 2017, pp. 192-99.

[166] Muthia, Rahmi, Asep Gana Suganda, and Elin Yulinah Sukandar. "Angiotensin-I converting enzyme (ACE) inhibitory activity of several Indonesian medicinal plants." *Research Journal of Pharmaceutical, Biological and Chemical Sciences*, Vol. 8, 2017, pp. 192-99.

[167] Amaechina, Fabian C., and Eric K. Omogbai. "Hypotensive effect of aqueous extract of the leaves of *Phyllanthus amarus* Schum and Thonn (Euphorbiaceae)." Acta Poloniae Pharmaceutica Vol. 64, No. 6, 2007, pp. 547-52.

[168] Inchoo, Marisa, et al. "Endothelium-independent effects of phyllanthin and hypophyllanthin on vascular tension." *Fitoterapia*, Vol. 82, No. 8, 2011, pp.1231-36.

[169] Srividya, Nct al, and S. Periwal. "Diuretic, hypotensive and hypoglycemia effect of *Phyllanthus amarus*." *Indian Journal of Experimental Biology*, Vol. 33, No. 11, 1995, pp. 861-64.

[170] Ueno, Hajime, et al. "Chemical and pharmaceutical studies on medicinal plants in Paraguay. Geraniin, an angiotensin-converting enzyme inhibitor from 'paraparai mi', *Phyllanthus niruri*." *Journal of Natural Products*, Vol. 51, No. 2, 1988, pp. 357-59.

[171] Runnie, I., et al. "Vasorelaxation induced by common edible tropical plant extracts in isolated rat aorta and mesenteric vascular beds." *Journal of Ethnopharmacology,* Vol. 92, No. 2-3, 2004, pp. 311-16.