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, C. nucifera, C. sativus, M. charantia, P. granatum, 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 $\beta_1$- and $\alpha_1$-adrenoceptors 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 $\beta_1$-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, $\beta$-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, ethnomedicochemical, 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

<table>
<thead>
<tr>
<th>Family</th>
<th>Plant species (vernacular names in English; Surinamese)</th>
<th>Plant part(s) and mode of preparation</th>
<th>Reference for indications for an antihypertensive activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acanthaceae</td>
<td><em>Ruellia tuberosa</em> L. (minnieroot; watrakanu)</td>
<td>Crude aqueous extracts as well as n-butanolic and aqueous fractions from leaves of <em>Ruellia</em> species</td>
<td>[31,32]</td>
</tr>
<tr>
<td>Anacardiaceae</td>
<td><em>Mangifera indica</em> L. (mango; manya)</td>
<td>Aqueous extract from stem bark; dichloromethane fraction from crude ethanol extract from leaves; mangiferin; Vimang</td>
<td>[33-38]</td>
</tr>
<tr>
<td>Apiaceae</td>
<td><em>Apium graveolens</em> L. (celery; selderij)</td>
<td>Aqueous of ethanol extracts from seeds, stalks, or roots; ethanol extract from leaves; powdered ethanol extract from seeds; standardized ethanol extract from seeds</td>
<td>[39-45]</td>
</tr>
<tr>
<td>Arecaceae</td>
<td><em>Cocos nucifera</em> L. (coconut; kronto)</td>
<td>Ethanolic extract from endocarp; coconut oil; coconut water; sap from immature inflorescence</td>
<td>[46-52]</td>
</tr>
<tr>
<td>Cucurbitaceae</td>
<td><em>Cucumis sativus</em> L. (cucumber; komkommer)</td>
<td>Fruit juice; vine compound tablets</td>
<td>[53,54]</td>
</tr>
<tr>
<td>Cucurbitaceae</td>
<td><em>Momordica charantia</em> L. (bitter melon; sopropo)</td>
<td>Fruit juice; aqueous extract from whole plant; extract from fruits</td>
<td>[55-58]</td>
</tr>
<tr>
<td>Lythraceae</td>
<td><em>Punica granatum</em> L. (pomegranate; granaatappel)</td>
<td>Fruit juice; extract from peels</td>
<td>[59-68]</td>
</tr>
<tr>
<td>Malvaceae</td>
<td><em>Hibiscus sabdariffa</em> L. (roselle; syuru)</td>
<td>Aqueous extract from calyces</td>
<td>[69-79]</td>
</tr>
<tr>
<td>Musaceae</td>
<td><em>Musa x paradisiaca</em> (banana; banaan)</td>
<td>Preparations from fruits</td>
<td>[80-85]</td>
</tr>
<tr>
<td>Oxalidaceae</td>
<td><em>Averrhoa bilimbi</em> L. (bilimbi; birambi)</td>
<td>Aqueous extract from leaves</td>
<td>[86-88]</td>
</tr>
<tr>
<td>Phyllanthaceae</td>
<td><em>Phyllanthus amarus</em> Schumach. and Thonn. (stonebreaker; finibita)</td>
<td>Aqueous and n-butanolic extracts from leaves and seeds; geraniin</td>
<td>[89-96]</td>
</tr>
<tr>
<td>Piperaceae</td>
<td><em>Piper betle</em> L. (betle vine; pahnblad)</td>
<td>Aqueous, ethanolic, and acetone extracts from leaves</td>
<td>[97-99]</td>
</tr>
</tbody>
</table>
Table 2 Evidence for the ACE-inhibitory activity of plants used in Suriname for treating hypertension

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

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-butanol 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 stem bark 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)acyryloyl]-L-phenylalanil-glycyl-glycine by rabbit lung ACE in the presence of a methanolic seed extract [102], and the decreased conversion of 3-hydroxybutrylglycyl-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-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].
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 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 4 Punica granatum L. (Lythraceae) (from: https://goo.gl/images/H9D6Q)](https://goo.gl/images/H9D6Q)
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 Ca²⁺ 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].
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 \textit{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 \textit{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 \textit{A. bilimbi} preparations [115]. Interestingly, using the same assay, an aqueous extract from fruits of the related species \textit{Averrhoa carambola} inhibited ACE activity to more or less the same extent [116].

\textbf{Phyllanthaceae-Phyllanthus amarus Schumach. and Thonn.}

The leaves, fruits, and whole plant of the bitter-tasting stonebreaker \textit{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 \textit{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 \textit{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 \textit{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)](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*, *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.

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