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Glen S. Patten [a] , Mahinda Y. Abeywardena [a] & Louise E. Bennett [a b]
[a] CSIRO Preventative Health National Research Flagship, CSIRO Food and Nutritional Sciences , Kintore Avenue , Adelaide South Australia , 5000
[b] 671 Sneydes Road Werribee , Victoria , Australia , 3030
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Glen S. Patten[ac], Mahinda Y. Abeywardena[a], Louise E. Bennett[a,b]

[a]*CSIRO Preventative Health National Research Flagship*

CSIRO Food and Nutritional Sciences, Kintore Avenue, Adelaide South Australia 5000

[b]*671 Sneydes Road Werribee, Victoria, Australia 3030*

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[c]Postal address: PO Box 10041, Adelaide BC 5000, Australia

Telephone (ISD): 61 8 8303 8956

FAX (ISD: 61 8 8303 8899

Email: glen.patten@csiro.au

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ABSTRACT

Hypertension is a major risk factor for coronary heart disease (CHD), kidney disease and stroke. Interest in medicinal or nutraceutical plant bioactives to reduce hypertension has

increased dramatically. The main biological regulation of mammalian blood pressure is via the renin-angiotensin-aldosterone system (RAAS). The key enzyme is angiotensin converting enzyme (ACE) that converts angiotensin I into the powerful vasoconstrictor, angiotensin II. Angiotensin II binds to its receptors (AT_1) on smooth muscle cells of the arteriole vasculature causing vasoconstriction and elevation of blood pressure. This review focuses on the *in vitro* and *in vivo* reports of plant-derived extracts that inhibit ACE activity, block angiotensin II receptor binding and demonstrate hypotensive activity in animal or human studies. We describe 74 families of plants that exhibited significant ACE inhibitory activity and 16 plant families with potential AT_1 receptor blocking activity, according to *in vitro* studies. From 43 plant families including some of those with *in vitro* bioactivity, the extracts from 73 plant species lowered blood pressure in various normotensive or hypertensive models by the oral route. Of these, 19 species from 15 families lowered human BP when administered orally. Some of the active plant extracts, isolated bioactives and BP-lowering mechanisms are discussed.

Key words: hypertension; blood pressure, angiotensin; angiotensin converting enzyme; receptor; inhibition; blocking; plants; extracts

Abbreviations: ACE, angiotensin converting enzyme; AChE, acetylcholine esterase; ARB, angiotensin II receptor blocker; AT_1R, angiotensin 1 receptor; BP, blood pressure; cAMP, cyclic AMP; CHD, coronary heart disease; CRP, C-reactive protein; CVD, cardiovascular disease; DBP, diastolic blood pressure; EDHF, endothelium derived hyperpolarizing factor; EDRF, endothelial derived relaxation factor; ET, endothelin; GABA, gamma-aminobutyric acid; HR, heart rate; HUVEC, human umbilical endothelial cell; mean arterial pressure; IP_3, inositol triphosphate; NHE, sodium hydrogen exchanger; NO, nitric oxide; NOS, nitric oxide synthase;

PAF, plasminogen activating factor; PAI, plasminogen activator inhibitor; PGI_2, prostaglandin I_2; PMN, polymorphonuclear; RAAS, renin-angiotensin-aldosterone-system; ROS, reactive oxygen species; RVLM, rostral ventrolateral medulla; SBP, systolic blood pressure; SD, Sprague-Dawley; TBX_2, thromboxane X_2; TMP, tetramethylpyrazine; TNFα, tumor necrosis factor-alpha; VSM, vascular smooth muscle; WKY, Wistar Kyoto; WR, Wistar rat.

INTRODUCTION

Background

The increasing worldwide use of plants for the treatment of human diseases including high blood pressure (essential hypertension) derived from alternative Indian Ayurvedic, Chinese and other cultural medicine is based on centuries of observation and practice (Cirigliano & Sun 1998; Somanadhan et al, 1999; Wang et al., 1999; Appel, 2000; Martin et al., 2008; Tirapelli et al, 2008). Prevailing economic conditions and poor health services in many developing populations has necessitated the use of alternate, low cost therapies to manage human ailments, including hypertension (Chen et al., 2009). In traditional cultures such as Africa and South America, up to 40% of patients with hypertension may use complimentary and alternate medicine in addition to prescribed pharmaceuticals (Amira and Okubadejo, 2007). Furthermore, nearly 50% of persons in the USA (Eisenberg et al., 1998) and Europe have used dietary or herbal supplements to treat a wide variety of illnesses including hypertension with 60% of these individuals not reporting the use of non-regulated alternate therapies to their healthcare providers (Fisher and Ward, 1994).

Amongst many, herbal products used commonly for medicinal purposes including hypertension are hawthorn, dandelion, yarrow, garlic, tea, soy products, ginkgo biloba, ginger,

bitter leaf, aloe vera and water berry (Ayele et al., 2010). However, because plant extracts contain many compounds, the modern pharmacological approach (Tahraoui et al., 2007) has been to focus on patentable, single bioactive compounds or chemically altered entities that may or may not have undesirable side-effects (Lohith et al., 2006).

By the 1950s there were increasing reports in the scientific literature on the effects of plant extracts such as horse-radish (*Amoracia rusticana*, Brassicaceae) (Malm, 1951) and snakeroot (*Rauwolfia serpentine*, Apocynaceae) (Moyer et al., 1955) for the treatment of human hypertension. From these plants, the anticancer agent sinigrin and the alkaloid yohimbine (α_2-adrenergic receptor antagonist) have been purified and developed for clinical use. Many plants such as *Phytolacca esculens* ("Shoriku", family Phytolaccaceae) indigenous to East Asia have diuretic properties used in Oriental medicine and may explain their hypotensive activity (Funayama and Hilino, 1979). The components of plants likely to contribute to the diuretic properties are flavonoids, saponins, volatile oils, terpenes, polyacetylenes, ascorbic acid and potassium ions (Szentmihalyi et al., 1998; Dimo et al., 2002). Flavonoids, for example, from the leaf of plants including *Bidens pilosa* (burr marigold, family Asteraceae) include chalcones, okanin, butein and quercitrin 3-*O*-glucoside (Dimo et al., 2003) that may operate by several mechanisms including decreased transmembrane Ca^{2+} uptake, inhibitory effect on cAMP- and cGMP-phosphor-diesterase or protein kinase C activity, could account for the vasodilatory and hypotensive effects of these substances (Mpalantinos et al., 1998; Dimo et al., 2002).

Renin-angiotensin-aldosterone system (RAAS) and disease

The main regulation of extracellular fluid volume, arterial vasoconstriction and hence blood pressure is by the renin-angiotensin-aldosterone system (RAAS) (Karalliedde and Viberti,

2006). Briefly, the kidney converts prorenin to renin. Renin is then released from the adrenal cortex of the kidney in response to hypotension or reduced renal blood flow sensed at the juxtaglomerular cells and converts angiotensinogen into the decapeptide angiotensin I. Angiotensin converting enzyme (ACE), a zinc containing nonspecific dipeptidyl carboxypeptidase (EC 3.4.15.1), which is released mainly from endothelial cells of the capillaries of the lungs and kidneys converts angiotensin I to II through the removal of two terminal amino acid residues. ACE also catalyses the degradation of the blood pressure lowering nanopeptide, bradykinin. Bradykinin works on blood vessels through the release of prostacyclin, nitric oxide (NO), and endothelium-derived hyperpolarizing factor (EDHF) (Chen et al., 2009). Pivotal to RAAS is the ACE product, angiotensin II, a potent vasoconstrictor and dispogen which plays a key role in the etiology of hypertension (see Figure 1). Specifically, angiotensin II increases blood pressure by binding to the AT_1 receptor stimulating the G_q protein in vascular smooth muscle cells which in turn activates contraction by an inositol-triphosphate (IP_3)-dependent calcium mechanism. Angiotensin II also stimulates aldosterone release, leading to sodium and water retention in the distal nephron and also has a direct effect on the proximal tubules to increase Na^+ reabsorption. Therefore, dysregulation of RAAS may lead to hypertension and related end-organ diseases (Gradman, 2009).

RAAS is also part of the pathogenic nature of atherosclerosis (Montecuccio et al., 2009). Angiotensin II has prothrombotic potential through adhesion and aggregation of platelets and production of plasminogen activator inhibitor (PAI)-I and PAI-2 which may also stimulate ACE activity (Kawaguchi et al., 1990). Inflammatory molecules such as intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), monocyte chemoattractant

protein-1, tumor necrosis factor-alpha (TNFα), and C-reactive protein (CRP) are modified by ACE inhibitors and angiotensin II receptor blockers (ARB) (Ferrario and Strawn, 2006). So, in addition to being used to treat atherosclerosis, hypertension and reduce mortality following myocardial infarction, ACE inhibitors and ARBs are also used in patients with heart failure, stroke, Type I diabetes and other medical conditions (Mogi et al., 2007; Lu et al., 2009; Takeda et al., 2009; Arozal et al., 2010; Gales et al., 2010; Jing et al., 2010; Webb et al., 2010).

In meta-analysis studies, the evaluation of efficacy of ARBs compared to ACE inhibitors and other BP lowering agents in a wide range of clinical conditions demonstrated that ACE inhibitors and ARBs have similar effects on blood pressure control with comparable risk of myocardial infarction, cardiovascular and all-cause death outcomes (Volpe et al., 2009). However, ACE inhibitors have higher rates of coughing and other side-effects than ARBs and there are fewer withdrawals due to adverse events with ARBs compared to ACE inhibitors (Matchar et al., 2008). It is of note however, that therapeutically ARBs and ACE inhibitors are not recommended to be used together unless monotherapy is ineffective due to increased adverse effects (Kolasinska-Malkowaka et al., 2008; Onuigbo, 2009).

Blood pressure and natural products

Natural products may function to lower blood pressure by many mechanisms. Beside diuretics and the RAAS pathways described above, there are catecholamine (α- and β-adrenergic receptors), muscarinic, calcium channels, and ion channels including Na^+, K^+, and Cl^- mechanisms that may control vascular tone influencing the diameter of arterioles, and hence blood pressure. Importantly, endothelium-derived relaxation factors (EDRF) such as nitric oxide (NO) also play a key role in normal and pathophysiologic processes including hypertension. NO

is synthesized from *L*-arginine by nitric oxide synthase (NOS) isoenzymes including endothelial NOS (eNOS), neuronal NOS (nNOS) and inducible NOS (iNOS) (Sun et al., 2002). NO acts as a vasodilator and potential hypotensive agent when produced by constitutive NOS (cNOS), which is composed of eNOS and nNOS in endothelial cells (O et al 2000). For example, the ethanolic extract of rhizomes from *Kaempferia parviflora* (Thai name "Kra-chai-dahm", family Zingiberaceae) has been shown to increase nitrite concentrations in HUVEC culture media with eNOS mRNA and protein expression enhanced (Wattanapitayakul, 2007).

Screening for potential anti-hypertensive plant extracts

Both *in vitro* and several *in vivo* models of hypertensive disease are well-established for the evaluation of interventions. When screening for potential hypotensive bioactivity from plant sources, *in vitro* assays are commonly employed that probe capacity for inhibition of ACE and/or of angiotensin II binding to the receptor (Hansen K et al 1995; Braga et al 2007; Leifert et al 2009). Further substantiation can be conducted *ex vivo* by measuring relaxation of a vascular tissue systems demonstrated in aortic ring, mesentery bed, or the small arterial conduction vessel preparations. These systems may have the endothelium intact or disrupted to discern whether the relaxation mediators come from the surrounding tissue in an autocrine fashion by EDRFs such as NO or act directly on the vascular smooth muscle tissue (Zonta et al, 1998; Runnie et al, 2004). *In vivo* substantiation is usually conducted using normotensive or genetically, dietary or chemically-induced hypertensive animal models by interperitoneal or intravenous injection and monitored for blood pressure, heart rate and fluid and electrolyte balance. These effects may be transient or short lived. Inhibitors of muscarinic, adrenergic, histaminergic, calcium channels or

handling, or NO generating systems can be employed with plant extract administration to assess the mechanisms of blood pressure modulation.

However, the bioavailability of the potential plant or other food based bioactive agents needs to be assessed. The biological system may need at least an order of magnitude more bioactive to be efficacious by the oral route compared to intravenous administration (Ladeji et al 1996), or not be bioavailable at all (Guerrero et al 2002; Vermeirssen et al 2004). The bioactive may need also to survive intake or be modified to an active or inactive metabolite by, for example, first pass of the liver (Varma et al 2010). This may be assessed by short term experiments using a single dose by gavage of a plant extract and BP monitored by intra-arterial canulation or non-invasive tail cuff procedures (Jabeen et al 2009). Important also is whether the animal is in the developmental stages of hypertension or is already a mature hypertensive animal where vascular remodelling has occurred. This involves feeding young, pre-hypertensive animals with bioactives in the diet or water supply until maturity and monitoring effects on blood pressure (Zeggwagh et al 2008). If the potential bioactive has been anti-hypertensive, it may be withdrawn to reveal if the regulation of hypertension is sustained or attenuated long term. The plant extracts can also be used in animal trials with known pharmaceuticals such as diuretics, adrenergic blockers, ACE inhibitors, ARBs and calcium channel blockers to test for potential synergy. This procedure will also examine potential diet/drug interactions which may alter bioactive pharmacokinetics by limiting uptake, clearance or interfering at site of action (Awang & Fugh-Berman 2002; Izzo & Ernst 2001; Zhou et al 2004; Wang et al 2005; Stump et al 2006).

The aim of this review is to systematically evaluate the *in vitro* and *in vivo* evidence for bioactivity of plant-derived extracts and molecules from their particular family groups which

affect RAAS by ACE inhibitory activity or by acting as an ARB. The correlation between *in vitro* bioactivity and *in vivo* evidence demonstrating efficacy in lowering of blood pressure in animal models or human trials will be explored and discussed. The review addresses the broad question "what is the potential role of plant-derived bioactives in regulating BP via the RAAS biological pathway".

METHODOLOGY

The scientific literature was searched using PubMed and the Cochrane Collaboration data base. Plant taxonomy details were obtained from Google search engine, including Wikipedia and the Merck Index; and updated to October 2010. The key words or phrases entered in searches were: ACE or angiotensin converting enzyme; aldosterone; aldosterone receptor; alternative; angiotensin II; angiotensin II receptor; antihypertensive; arterial blood pressure; ATR; attenuation; blood pressure; bioactive; blocker; blocking; cardiovascular; complimentary; decoction; derived; DBP; diastolic blood pressure; edible; extract; food; herb; herbal; herbal formulation; hypertension; hypertensive; hypotension; hypotensive; inhibition; inhibitor; isolate; isolated; plant; mean arterial pressure; MAP; medicine; metallopeptidase; SBP (or systolic blood pressure). Wherever possible, only publications citing approvals by institutional ethics committee for the use and study of animal or human subjects were used in this review.

The findings in relation to specific plants and effects on BP, were collated under the following topics: plant family name; binomial scientific name; common name in English or local name where no English equivalent found; the main solvent(s) by which the primary extract was prepared; dose administered or % of the diet; highest effective concentration used for *in vitro* and *in vivo* studies with emphasis on IC_{50} (the concentration at which 50 inhibition was achieved) or

EC_{50} (the concentration at which 50% of activity was achieved) values or dose as mg/ml *in vitro* or mg/kg *in vivo*; the route of administration; animal species; strain of normotensive or hypertensive rat; how hypertension was induced; normotensive, untreated or treated hypertensive patients or other conditions as indicated; lowering or attenuating the rise in i) systolic blood pressure (SBP) ii) or mean arterial pressure (MAP) iii) or diastolic blood pressure (DBP) given preferentially as mmHg as notated in text or estimated from figures or as a percentage (%) effect; effect on heart rate; notation of the key bioactive(s) if given. When ACE inhibitory activity or angiotensin receptor binding inhibition was catalogued at a nominal concentration of plant extract in the final assay, only those that inhibited by 50% or more have been included. Other *ex vivo* studies such as effects on aortic ring or mesenteric blood vessel preparations or effects on heart rate or other effects on blood glucose or cholesterol levels were not documented but may be discussed where relevant.

This review focuses on plant-derived bioactives of a non-peptide nature and does not include plant (or animal) derived ACE-inhibitory peptides specifically (see Meisel & Bockelmann, 1999; Severin & Wenshui, 2005; Hartmann & Meisel, 2007; Guang & Phillips 2009). Also excluded are results for mushroom, other fungi (see Tejesvi et al., 2008) and fermentation products (see Pyo & Lee, 2007) with antihypertensive activity. Although there is increasing research in the field, it is also not within the scope of this review to examine effects of plant extracts on the minerocorticoid hormone aldosterone binding and function at its receptor (see Hattori et al., 2006) nor the inhibition of renin and effects on blood pressure (see Takahashi et al., 2008, Gradman 2009).

RESULTS AND DISCUSSION

A. Angiotensin converting enzyme (ACE) inhibition by plant bioactives

A comprehensive list of plant derived extracts that inhibit ACE activity published over the preceding few decades is summarised in Table 1. The source of the ACE used to assess inhibitory ability is usually from porcine kidney, rabbit lung or serum. The plants species are listed in family groups showing common names, part of the plant used and the main solvent of primary extraction. The solvents most commonly used to extract ACE inhibitory bioactives in order of usage were water (31%), ethanol (26%), methanol (21%) and acetic acid (11%) which represented about 86% of all solvents employed which besides water, are organic and polar in nature. The non polar solvents ethyl acetate and hexane were used in only 5% of the extractions. The results are given as percentage inhibition at a designated *in vitro* final concentration or as an IC_{50}. Plant extracts that inhibited ACE activity by 50% or more were found in 74 plant families and in more than twice that number of species examined. Many of the samples are from inedible, mostly bitter parts of the plant including roots, bark and leaves with alkaloid concentrations that would make them irritants or even toxic, especially when used long term (Manteiga et al., 1997; Wink, 2008)

Natural classes of compound from plants and other sources that have ACE inhibitory activity include alkaloids, anthocyanins, xanthones, terpenoids, fatty acids, peptides, tannins, and flavonoids (Loizzo et al 2007; Ojeda et al 2010). Many of these classes of compounds are represented in Table 2. Table 2 also shows a brief list of isolated plant bioactives with IC_{50} values demonstrating relative potency to inhibit ACE ranging from about 1-1250 μM. Some examples of relatively high inhibitory activity was demonstrated for the epicatechins (ECG, EGCMG, EGCG) from Chinese herbs and many other plants with inhibitory activity ranging

from 18-37 μM (Lui et al., 2003), for gluco-aurantioobutsin from *Cassia tora* seed (30 μM, Hyun et al 2009), sambacein I-III (30 μM) from *Jasminum azoricud* and *J. grandiflorum* (Somanadhan et al., 1997), oleuropein (20 μM) from *Ligustrum vulgare* (Kiss et al., 2008), ligostoside (25 μM) and geraniin (13 μM) both from *Phylanthus urinaria* (Lin et al., 2008) and myrtillin (~ 20 μM) from *Vaccinium myrtillus* (Persson et al., 2009). The bioactive with the highest activity was guanosine isolated from *Chrysanthemum boareale* (chrysanthemum, family Asteraceae) with an IC_{50} of 1.5 μM. Although the IC_{50} value of the crude extract was not given, the first fraction from a Sephadex G-15 column and subsequent HPLC isolation gave only 45% and 52% inhibition (Kim et al., 2003). Another species of chrysanthemum, *Chrysanthemum indicum* aqueous extract at 20 mg/kg i.v. lowered dog aortic BP with a likely bioactive of chrysanthetriol (Kato et al., 1986). No published effects of these bioactives could be found for oral administration on blood pressure.

B. Interactions of plant bioactives at the angiotensin II receptor (AT_1) Unlike the extent of research that has been undertaken to discover inhibitors of ACE activity, the blocking of binding of angiotensin II or antagonist analogues to the AT_1 receptor has been confined to a smaller selection of plant extracts (Table 3) from a hand full of laboratories. The results indicated that 16 plant families and 16 species exhibited receptor blocking or antagonist activity with IC_{50} values ranging below 1 mg/ml. The range of IC_{50} values were in general, higher than for inhibition of ACE activity (Table 1). Identification of specific phytochemicals that block or antagonise the AT_1 receptor is limited but my include alisol B, benzyl benzoate and derivatives and berberine (Makino et al., 2002a; Callallero-George et al., 2001; Ko et al., 2007).

Angiotensin II is involved in the accumulation of ECM proteins, thereby contributing to the progression of tissue inflammation and kidney damage which can be assisted with ACEi and ARBs (Lee et al., 2009). Plants that affect angiotensin II activity indirectly includes the traditional herb, *Rehmannia glutinosa* (Chinese foxglove, family Scrophulariaceae), which as an aqueous root extract at 500 mg/kg administered for 8 weeks reduced the expression of angiotensin II and kidney AT_{1a} receptor mRNA by 33% in SD rats with renal failure induced by 5/6 nephrectomy. The main constituents are sitosterol and mannitol.

Tetramethylpyrazine (TMP) from *Ligusticum wallichii* Franchat (chuan xiong, Apiaceae) is a cardioprotective agent that inhibited angiotensin II-induced ROS generation, ERK phosphorylation and ET-1 gene expression in vascular endothelial cells (Lee et al., 2005). TMP also has hypotensive effects in rats acting directly on the vasculature as a calcium antagonist via calcium channels and intracellular calcium release (Pang et al., 1996). After gastric gavage of TMP for 8 days at 100 mg/kg per day after portal vein ligation lowered MAP by 12.1 mm Hg with no change in heart rate (Chang et al., 1999).

The herbal agents such as the methanolic extract from the root of *Salacia oblonga* (ekanayaka, family Hippocrateacea) have also been shown to affect RAAS by modulation of the expression of the angiotensin AT_1 receptor. When *S oblonga* extract was given orally at 100 mg/kg for 7 weeks to Zucker diabetic fatty rats there was a suppressed overexpression of AT_1 mRNAs and AT_1 protein with a concomitant reduction in cardiac hypertrophy (Huang et al., 2007).

As described, angiotensin II also plays a profound role in atherosclerosis. Lopez-Martin et al. (2002) have isolated two phenanthrene alkaloids, uvariopsine and stephenanthrine from the

fresh root of *Dennettia tripetala* (pepper fruit, family Annonaceae). When both alkaloids were co-perfused in the submicromolar range with angiotensin II into the rat mesenteric microcirculation they lowered the angiotensin II-induced leukocyte-endothelial cell interaction, reduced endothelial P-selectin upregulation and the generation of reactive oxygen species (ROS) (Estelles et al., 2003). Uvariopsine and stephenanthrine also inhibited plasminogen activating factor (PAF)-induced elevations in intracellular calcium levels in fMLP-stimulated human neutrophils (PMNs) and other PAF effects related to the inflammatory cascade in cardiovascular disease (Estelles et al., 2003). The effect of these alkaloids on blood pressure has yet to be assessed.

Even less information is extended in the scientific literature on plant extracts with potential angiotensin II AT_1 receptor blocking ability affecting blood pressure. Table 4 gives a list from 3 species from 3 families that directly or indirectly affected the angiotensin II induced blood pressure effects in mice and rats. American sweet-gum resin *(Liquidambar styraciflua*, Altingiaceae), seaberry seed total flavone fraction (*Hippophrae rhamnoides*, Elaegnaceae) and areca nutpalm seed extract (*Areca catechu*, Arecaceae) at 2, 150 and 200 mg/kg given orally lowered angiotensin II-induced increase in rodent SBP (Inokuchi et al., 1996; Ohno et al., 2008; Pang et al., 2008).

C. Other mechanisms of action of plant extract and bioactives on blood pressure regulation

Besides RAAS, many other pathways control blood volume, solute concentrations and blood pressure including diuretics such as thiazides which work by inhibiting reabsorption of sodium (Na^+) and chloride (Cl^-) ions from the distal convoluted tubules in the kidneys by

blocking the thiazide-sensitive Na+-Cl^- symporter. Thiazides which are suggested as the first-line low-dose therapy for hypertension reduce all morbidity and mortality outcomes including stroke, coronary heart disease (CHD) and cardiovascular events (Wright and Musini, 2009). Plant extracts contain thousands of molecules with potential bioactivity that may influence the regulation of vascular contractility and water and salt balance which ultimately affect mammalian blood pressure. There are also many ways that vascular tone is maintained in vascular smooth muscle and many central mechanisms of blood pressure control that can be influenced by plant bioactives (Varagic et al., 1991). As emphasised, the vascular endothelium plays a key role in the control of vascular tone by releasing the vasorelaxants nitric oxide (NO), prostaglandin I_2 (PGI_2), endothelium derived hyperpolarizing factor (EDHF) and opposing vasoconstrictors including angiotensin II, endothelins (ET), thromboxane A_2 (TXA_2), PGH_2, superoxide anion, isoprostanes and hydroxyl fatty acids (Abeywardena and Head, 2001; Zhao et al., 2010a,b).

Alpha-1 antagonist

Alpha-1 antagonists such as prazosin block α_1-adrenergic receptors in arteries and smooth muscles and reduce arteriolar resistance and increase venous capacitance causing reflex tachycardia. Depending on plasma concentration they may cause postural hypotension and are usually recommended at bedtime. Dicentrine, a bioactive from *Lindera megaphylla* (a large leafed spice bush, family Lauraceae) is described as an α_1-adrenergic antagonist that at 1 mg/kg i.v. lowered WKY rat MAP by 60 mmHg. By oral administration at 8 mg/kg dicentrine lowered SHR MAP by up to 40% that persisted for 15 h (Yu et al., 1992a). *In vitro* radioligand binding experiments demonstrated that a commercial extract powder of *Serenoa repen* (saw palmetto,

family Arecaceae) that has been used in traditional medicine for lower urinary symptoms showed strong non-competitive α_1-adrenergic antagonism. However, in a follow up study where the α_1-adrenergic antagonism action of saw palmetto extract (as a German prescription drug, Prostagutt uno®) was confirmed, oral administration of 320 mg/kg per day for 8 days did not affect blood pressure in healthy young men (Goepel et al., 2001).

Endothelin antagonists

The endothelins (ET) first isolated in porcine aortic endothelial cells (Yanagisawa et al., 1988) are amongst the most potent vasoconstrictors yet discovered. The three isoforms (ET_1, ET_2 and ET_3) exert their physiological effects through two types of receptors, subtype A and subtype B causing massive vasoconstriction, increased blood pressure and excessive production of ROS (Piechota et al, 2010). Garlic (*Allium sativum*, family Alliaceae) lowered SBP of 2-kidney 1-clip Goldblatt (hypertensive) rats, did not reduce kidney hypertrophy, reduced circulating PGE_2 and TXB_2 levels (Al-Qattan *et al* 2003), and suppressed induction of sodium hydrogen exchanger (NHE)-1 which is responsible for hypertension induced tissue injuries but not that of NHE-3. NHE is responsible for Na^+ uptake from the renal filtrate and pH_i regulation with the sodium pump provides the driving force for the activity of NHE by maintaining the Na^+ gradient.

Gamma amino butyric acid (GABA)

The neurotransmission of amino acids, such as glutamate and gamma-aminobutyric acid (GABA) has been demonstrated to be involved in mediating the effects of centrally antihypertensive drugs in the rostral ventrolateral medulla (RVLM) in the brain. (Peng et al., 2010). A novel fermented milk product containing GABA has been demonstrated to lower BP in mild hypertensives in a randomised, placebo-controlled, single-blind trial (Inoue et al., 2003).

Passion fruit rind (*Passiflora edulis*) contains luteolin (luteolin-6-*C*-chinovoside and luteolin-6-*C*-fucoside) in high concentrations in the leaves with blood pressure lowering effects and also a high concentration of GABA (4.4 mg/g DW) (Ichimura et al., 2006). Flavonoids exhibit diverse biological effects including inhibition of protein kinase C, inhibition of cyclic nucleotide phosphodiesterases, decrease in Ca^{2+} uptake and vasodilatory actions. GABA can lower BP in SHR (Hayakawa et al., 2002) and it was calculated that the amount of GABA in rind may be biologically effective.

Muscarinic system

Several directly acting cholinergic agonists alter the functions of the cardiovascular system when injected directly into the cerebral ventricular system, or directly into various brain regions. The most probable sites of action of acetylcholine esterase (AChE) inhibitors and directly acting cholinergic agonists are the locus coeruleus, the nucleus tractus solitarii and the RVLM (Varagic et al., 1991). The primary activation of the cholinergic synapse is believed to take place in RVLM. Ginger has gingerols, shagaols, zingerone and paradol. Water extract of ginger lowers BP in the rat probably via stimulation of muscarinic receptors and blockade of calcium channels with some effect by 6-gingerol (Ghayur et al., 2005).

Nitric oxide production and release

Although used traditionally for centuries, little clinical evidence for dandelion and Danshen exists although the former may have potassium sparing diuretic properties while Danshen has recently been shown to possess tanshinoate B that selectively activates cNOS modulating NO production in enthothelial cells (O et al., 2000). Hawthorn on the other hand has

blood pressure lowering properties experimentally in L-NAME treated hypertensive rats and lowers human blood pressure of hypertensive and diabetic patients by the oral route.

Aqueous *Artemisia verlotorum* (Chinese mugwort, family Asteraceae) lowered WR MAP 63 mmHg at 0.1 mg/kg i.v. by vasodilation linked to NO release and the NO/cGMP pathway which was blocked by atropine implying muscarinic receptor involvement (Calderone et al., 1999). Essential oils such as carvacrol are monoterpenoid phenols found in high amounts (5-50%) in *Origanum vulgare* (oregano, family Lamiaceae) and in thyme (*Thymus vulgaris*, Lamiaceae). Carvacrol at 100 ug/kg i.v. was found to deceases heart rate, MAP SBP and DBP and inhibit L-NAME induced hypertension (possibly via cardiac L-type calcium channel) (Aydin et al., 2007).

Bulb of *Fritillaria ussuriensis* (family Liliaceae) contains isosteroidal alkaloids: epeiedine, ebeiedinone, isoverticine, verticine, verticinone, hupehenine, ebeienine, imperialine (Kang et al., 2002b, 2004) and the extract inhibited ACE and lowered BP in L-NAME treated rats by vascular release of NO/cGMP which affects cellular calcium handling.

Grape seed extract (GSE) (*Vitis vinifera* L. family Solanaceae) is a rich source of proanthocyanidins made of dimer, trimer and oligomers of monomeric catechins. Administration of GSE has been shown to stop lead-induced (100 ppm) increase in blood pressure via the eNOS system breakdown or NO catabolism; or may affect sympathetic preganglionic neurons that influence SBP by an antioxidant mechanism (Badavi et al., 2008).

The common roselle flower (*Hibiscus sabdariffa*, family Malvaceae) extract affected blood pressure probably via NO inhibition of Ca^{2+} influx through receptor gated channels. (Odigie et al., 2003).

Cudrania tricuspidata (Chinese mulberry), family Moraceae, prevented inactivation of NO/cGMP system and normalized L-NAME increase in BP without further changes in NOS expression in thoracic aorta and improved renal function (Kang et al., 2002c).

Ginkgo biloba (family Ginkgoaceae) administered to SHR stroke prone (SHRSP) lowered BP 48 mmHg while increasing urinary nitrite/nitrate; NO metabolite levels with eNOS mRNA expression were found to be higher (Sasaki et al., 2002). Flavonoids are free radical scavengers of superoxide ions, hydroxyl and peroxyl radicals and inhibit inactivation of EDRF and NO. A pictorial representation of some key plant extracts and how they influence or modulate systems involved with blood pressure regulation is given in Figure 2.

D. Effect of plant extracts on blood pressure in experimental animal experiments and human trials

Table 5 and 6 show the growing list of plant extracts from papers published since the early fifties highlighting species from 58 taxonomic plant families that lowered blood pressure in normotensive and hypertensive animal models (Table 5) and human patients (Table 6). In animal studies, normotensive animals can be used or blood pressure may be elevated by genetic, surgical, chemical or by dietary means. From 43 families, plant extracts were produced from 72 species that could lower blood pressure when ingested orally by gavage, in the diet or in the water supply. Of these, from 15 families, 19 species of plants were of note because an extract, partly purified subfraction or isolated compound lowered human blood pressure by the oral route and are of clinical interest. Lacking are large, long term properly controlled clinical trials that demonstrate tolerability and efficacy of many of the plant extracts highlighted and which are alert to potential drug-herb interactions.

The most active plant extract came from *Viscum album* (European mistletoe, family Loranthaceae) ethanolic stem extract which lowered BP in WR by 23.6 mm Hg at only 0.001 mg/kg (1 μg) i.v. This activity was blocked by the specific muscarinic receptor blocker hexocycline (Radenkovic et al., 2009). This appears about 1000 more potent than any other studies employing mistletoe extract but its activity by the oral route is yet to be confirmed. Most extracts that lowered blood pressure in animal models were administered at a dose of 50-800 mg/kg by the oral route in the diet or via the water supply (Fukunaga et al., 1989; Ojewole & Adewole 2007).

From Tables 5 and 6 it can be deduced that hypotensive plants with both high edibility and medicinal rating can be recognised from at least twelve plant families. These would include the plant family Alliaceae including the common plant names as onions, garlic, chives and challots; Apocynaceae as dogbane; Asteraceae as sweetleaf and yarrow; Brassicaceae as horseradish; Lythraceae as pomegranate juice; Malvaceae as hibiscus flowers; Oleaceae of olive oil or olive leaf; Pedaliaceae as sesame; Roseaeceae as hawthorn varieties; Rubiaceae including green coffee; Rutaceae as grapefruit; and Solanaceae as tomato. Many of these plants are described in traditional medicine and as part of a Western or Mediterranean diet which from epidemiological studies are linked to positive cardiovascular outcomes (Kokkinos et al., 2005; Covas 2007).

E. Isolated bioactives that lower blood pressure and possible mechanisms

Flavanoids are a class of plant compounds containing over 6400 polyphenolics sharing a common skeleton of phenylchromate which allows for a multitude of substitution patterns leading to the subclasses flavonols, flavones, flaverones, catechins, anthocyanidins, isoflavones,

dihydroflavonols and chalcones (Middleton et al., 2000). The isoflavones found in soy (*Glycine max*, family Fabeaceae) such as genistein, daidzen and equol can relax VSM both *in vitro* and *in vivo* by a combination of mechanisms including potentiation of endothelial-dependent and endothelial-independent vasodilator systems and inhibition of constrictor mechanisms (McCue et al., 2005). Isoflavone bioactivity is mediated in part via interaction with oestrogen receptors including the signalling pathways for ERK1/2, IP_3-kinase/Akt and cAMP via inhibition of phosphodiesterase (Peluso 2006) leading to activating of eNOS in the vasculature involved with blood pressure modulation (Martin et al., 2008). Soy isoflavones also increase renal blood flow, sodium excretion and the RAAS system in animal systems with the findings for humans remaining controversial (Xiao 2008). On the other hand a recent study has shown that supplementation with isoflavones and anthocyanins reduce lifespan in SHRSP potentially via cholesterol lowering effects that alter membrane fluidity and function (Gilani 2009).

The flavonol triglycoside quercetin has been shown to induce a progressive, dose-dependent and sustained reduction in blood pressure when given chronically in several rat models of hypertension, including SHR, L-NAME-treated rats, DOCA-salt hypertensive rats, two-kidney one-clip Goldblatt rats, rats with aortic constriction and Dahl salt-sensitive hypertensive rats (Duarte et al., 2001; Jalili et al., 2006). Quercetin was also effective in reducing blood pressure in rat models of metabolic syndrome, including the obese Zucker rats as well as rats treated with a high-sucrose, high-fat diet (Perez-Vizcaino et al., 2009). A high dose of quercetin also reduced blood pressure in stage 1 hypertensive patients in a randomized, double-blind, placebo-controlled, crossover study with no quercetin-evoked reduction in systemic markers of oxidative stress (Edwards et al., 2007). Quercetin lowered BP in salt-sensitive rat

model high BP (Mackraj et al., 2008a) by modulation of renal function with increased Na^+ and urinary output, decreased aldosterone and AT_{1a} mRNA. Quercetin is bioavailable and has been detected intact in the serum of WR 15 minutes after gavage with 80 mg/kg and up to 6 hours but no breakdown products as deglycosylated products rutin and hirsutin were detected (Guo et al., 2006). Red onion peel (*Allium cepa*, Solanaceae) lowered fructose-induced elevated WR BP by 21 mmHg by a possible antioxidant mechanism and potentially by inhibiting vascular smooth muscle cell Ca^{2+} influx (Naseri et al., 2008).

F. Role of dietary and herbal plants in regulation of BP – epidemiological studies

Garlic (Alliciaea) has been used for centuries as a foodstuff and medicine due to its strong aromatic and spicy flavour and to treat inflammatory conditions and hypertension. When crushed garlic produces sulphur containing compounds including allicin, ajoene, S-allylsysteine along with saponins, polyphenols, flavonoids, flavanols, anthocyanins, tannins and ascorbic acid which may work in synergistic combinations to lower blood pressure (Chen et al., 2009). Animal and human trials have shown that garlic extracts or powder time-release preparations lowered BP in people with elevated BP (Sobenin et al., 2009) but not necessarily in normotensives (Reinhart et al., 2008) with epidemiological studies supporting these claims (Ried et al., 2008). Raw garlic and aged garlic both lowered SHR SBP but raw garlic may cause anaemia and the generation of papilloma in the forestomach (Harauma & Moriguchi 2006).

Coffee is consumed daily by millions of people worldwide and caffeinated coffee may influence blood pressure and heart disease. Chlorogenic acids (CGA) from green coffee bean (*Coffea arabica*, Rubiaceae) extract reduce BP in SHR and humans. Mild hypertensive patients receiving CGA at 140 mg/d had significantly lower SBP of 9.7 mmHg and DBP 2.3 mmHg

respectively after 12 weeks with no effect on pulse rate (Watanabe et al., 2006) and with no apparent side effects. However, coffee is a rich source of antioxidative polyphenols but meta-analysis produced from epidemiological studies demonstrated a significant rise in SBP of 2.04 mmHg and DBP of 0.73 mmHg respectively after pooling coffee and caffeine trials. In coffee studies alone the rise in SBP and DBP were small at 1.22 and 0.49 mmHg respectively (Noordzij et al., 2005). CGAs are a family of esters formed by quinic acid and several hydroxycinnamic acids, such as caffeic, ferulic and ρ-coumaric acids. The major CGAs in coffee are caffeoylquinic (CQA), feruloyquinic, and dicaffeoylquinic acids. Water-soluble green coffee bean extract (GCE) reduces SHR BP (Suzuki et al., 2002) as does a single oral dose of 5-CQA. ROS involved in hypertension with SHR exhibit increased generation of NADPH driven superoxide anions O_2^- in resistance (mesenteric) and conductance (aortic) vessels that may react with NO and EDRF to form peroxynitrite ($ONOO^-$) a vasoconstrictor which is toxic to endothelial cells (Beckman 1996). Coffee also has benzenetriols such as 1,2,4-trihydroxybenzene (hydroxyhydroquinone, HHQ) that generate ROS. Based on the ratio of HHQ and chlorogenic acids in coffee, higher levels of HHQ interfered with CQA-induced improvement in BP and endothelial function in SHR (Suzuki et al., 2008).

Tomato extract when added to patients treated with low doses of ACE inhibitor, CCB or combinations with low dose diuretics reduced SBP by 10 mm Hg and DBP by 5 mm Hg respectively with no side effects. There has also been a correlation between plasma lycopene and SBP (Paran et al., 2009). Tomato has α-tocopherol, carotenoids: beta carotene, phytoene, phytofluene and lycopene most potent.

Tea flavanols and catechins abundant in green tea such as quercetin and kaempferol have many biological effects. They can specifically delay the progression of diabetes, associated oxidative stress and elevation of blood pressure in rats (Igarashi et al., 2007). Our studies have found green tea and black tea inhibited ACE activity with IC_{50} values of 0.19 mg/mL and 0.41 mg/mL respectively (Patten et al., 2011 in press). Both green and black tea inhibited human umbilical endothelial cells (HUVEC) ACE activity (Persson et al., 2006). Of the tea components, only procyanidins and epigallocatechin generated ACE inhibition with IC_{50} values in the micromolar range. Red wine was more effective than white wine and green tea more efficacious than black tea which is in agreement with other findings (Actis-Goretta et al., 2006). On the other-hand, the tea-leaf saponin reduced a time-dependent increase in blood pressure of young SHR when administered orally after only 5 days p.o. at 100 mg/kg with little *in vitro* ACE inhibitory activity (Sagesaka-Mitane et al., 1996). From a systematic review of blood pressure lowering bioactives in human hypertensives, Wahabi et al., (2009) concluded that roselle (*Hibiscus sabdariffa*, Malvaceae) needed more evidence but may be better than tea (Theaceae).

G. Role of dietary and herbal plants in regulation of BP

Lifestyle factors that lower risk of hypertension include smoking cessation, weight reduction, physical exercise, reduction of excessive alcohol intake, and dietary measures such as reduction in sodium, an increase in potassium, fruit and vegetables with suitable levels of dietary fibre and resistant starch and a decrease in saturated and total fat intake (Mancia et al., 2007). There is also growing evidence for a substitution of saturated fat with polyunsaturated fat, especially the long chain polyunsaturated fatty acids found at high levels in oily fish as eicosapentaenoic acid and docosahexaenoic acid (de Leiris et al., 2009; Chen et al., 2009). There

is a need for plant extracts with hypotensive properties that do not induce reflex tachycardia or arrhythmia and depression of myocardial contractility as do the majority of antihypertensive drugs (Botta et al., 2003).

From traditional Chinese medicine, mixtures containing up to 11 herbs such as hachimi-jio-gan, shichimotsu-koka-to, and tian ma gou teng yen lowered or attenuated increases in BP of hypertensive rat models (Hiwara et al., 1994, 1996; Zhang et al., 1989). Shichimotsu-koka-to, a kampo formula of plants, reduced SBP in Dahl salt sensitive rats in 6 weeks with attenuation of glomerular sclerotic lesions in the kidney (Hiwara et al., 1994). Oral administration of Tian Ma Gou Teng Yen, a mixture of 11 plants (Zhang et al., 1989), at 0.5 mL/kg orally twice daily to 5 wk old SHR until 16 wk altered development of and prevented hypertension in these rats probably through action on sympathetic vasomotor activity.

The ethanolic extract of the laiju herbal mixture of *Semen raphani* (radish seed, Ranunculaceae) and *Flos chrysanthemi* (wild chrysanthemum, Asteraceae) at 300 mg/kg per day lowered blood pressure in the renal hypertensive rats and SHR (Chen et al., 2007). Kangen-Karyu (KGK), containing peony root, cnkidium rhizome, safflower, cyperus rhizome, saussurea root and *Salvia miltiorrhiza* root, is a Chinese traditional medicine formula to invigorate the 'blood' and dispel 'blood stasis', arising from poor blood circulation (Makino et al., 2003). This extract improved high – fructose induced metabolic syndrome including lowered BP (Yokozawa et al., 2003). KGK lowered SHRSP BP by 24 mmHg at 3.3% of diet and increased NO_2/NO_3 in urine (Gao et al., 2001).

H. Known interactions of dietary and herbal plants with drugs

The prevalence of herb-drug interactions may have been exaggerated (Awang & Fugh-Berman 2002) and the documentation is sparse (Izzo & Ernst 2001). However some herbs, including garlic, ginkgo, ginseng that are listed herein with BP lowering potential may have a significant influence on concurrently administered drugs. Herbal medicines may mimic, decrease, or increase the action of prescribed drugs. This can be especially important for drugs with narrow therapeutic windows and in sensitive patient populations such as older adults, the chronically ill, and those with compromised immune systems. It is well known that some vegetable protein sources and grains contain phytates, which act to bind trace elements and minerals in the digestive tract, preventing their absorption (Hurrell 2003) and may interfere with hypertensive drug uptake.

Ginkgo biloba (family Ginkgoaceae) may raise BP when combined with a thiazide diuretic and can attenuate the therapeutic potency of nicardipine in rats (Kubota et al., 2003) and may have adverse effects in long term SHR studies (Tada et al., 2008). Garlic (*Allium sativum*, Alliaceae) changes pharmacokinetics of paracetamol and saquinavar (Hu et al., 2005) while both gingko and garlic can lower the blood concentration of warfarin (Izzo & Ernst 2001). On the other hand, a herbal mixture used to dispel blood status or hypertension, KGK, suppressed the metabolism of warfarin and increased bleeding (Makino et al., 2002b). Also, the hypolipidemic effects of garlic were attenuated by the blood pressure lowering medications propranolol (β-receptor blocker) and hydrochlorothiazine (diuretic) and was augmented by captopril (ACE inhibitor) in the rat (Syed et al., 2009). Polyphenolic compounds such as resveratrol (*trans*-3,5,4'-trihydroxystilbene) found in abundance in grape skin (Stewart et al., 2003) and grape seed extracts (Shi et al., 2003) can block the uptake of nutrients including cholesterol and iron (Leifert

& Abeywardena 2008; Kim et al., 2008). Finally, it has been shown that a combination of ginkgo and onion (*Allium cepa*, family Alliaceae) that contain the flavonoid, quercetin, decreased the oral availability of cyclosporine (immunosuppressant drug) (Yang et al., 2006).

Herbal supplements can either potentiate or counteract warfarin such as Ginseng and St John's wort (Izzo & Ernst 2001) which both induce the metabolism of warfarin. Garlic and *Ginkgo biloba* both inhibit platelet aggregation via the ADP pathway (Hiyasat et al., 2009). With regard to hypertensive medication, the flavanoid and nonflavanoid components of grapefruit juice may affect the bioavailability of some calcium channel blockers by inhibition of enterocyte CYP3A4 isozyme activity which is involved in the metabolism of over 50% of commonly prescribed drugs (Sica, 2006; Pillai et al., 2009).

Recent cellular and animal studies have demonstrated that Devil's claw, *Harpagophytum procumbens* (Pelaliaceae) and stem bark extract of *Mangifera indica* (mango, family Anacardiaceae) contain polyphenols used traditionally for a range of conditions including inflammation and hypertension may interact with the multidrug transporter ABCB1/P-gp (Chieli et al., 2009; Romiti et al., 2009) and St John's wort, *Hypericum perforatum* (Clusiaceae), used in depression can affect indivar uptake from the small intestine into the plasma (Ho et al., 2009). A recent study has demonstrated that the bioactive dipeptide, Val-Tyr, derived from sardine is a potent ACE inhibitor *in vitro* (IC_{50} of 10 μM) with significant antihypertensive activity in SHR and human mild hypertensives (Kawasaki et al., 2000; Vercruysse et al., 2005) blocks the uptake of captopril and attenuates its antihypertensive effects in SHR (Matsui et al., 2006).

I. Metabolism and bioavailability

With regard to potential anti-hypertensive effects of plant extracts, there is discrepancy between *in vitro* and *in vivo* results. There is no doubt that further investigation into the *in vivo* and clinical hypertensive effect of animal or plant derived ACE inhibitory activity is essential. However, based on biological mechanisms, *in vitro* studies are a good starting point for initial screening (Guang 2009).

A well known example of a bioactive that has not attained promised pharmaceutical potential for blood pressure control is the diterpene forskolin. Forskolin is extracted from the root of *Coleus forskohlii* (Indian coleus, family Lamiaceae) by organic solvent and acts directly on the membrane bound catalytic subunit of adenylate cyclase and a cytoplasmic cAMP protein kinase (Metzger & Lindner 1981). Forskolin has been shown to lower rat MAP by 48 mmHg when given at 0.1 mg/kg i.v. while increasing heart rate as a compensating mechanism (Lindner et al., 1978). In patients with idiopathic congestive cardiomyopathy it was demonstrated that thermodilution catheter infusion of forskolin altered hemodynamic properties including lowering of SBP, DBP and MAP (Baumann et al., 1990). However, when obese men were given oral forskolin (dose not cited) for 12 weeks their SBP and DBP was lowered by 6.3 and 4.7 mm Hg respectively which was not significant (Godard et al., 2005).

Oral stevioside, a natural sweetener and bioactive in *Stevia rebaudiana* (sweetleaf, Asteraceae) at 200 mg/kg i.p. lowered BP in DOCA-salt and SHR and at 0.1% in water lowered and prevented hypertension in mature and immature SHR respectively (Hsu et al., 2002). Further, in a human hypertensive trial using 750 mg stevioside orally per day, after 3 months SBP and DBP were lower by 13.4-14.4 mmHg that persisted for a further 9 months (Hsieh et al., 2003). A following study at levels of 1500 mg per day for 2 years lowered human hypertensives

SBP and DBP 10 and 6 mmHg respectively with no change in HR (Chan et al., 2000). However later studies could not confirm these findings. Ferri et al (2006) demonstrated that graded 3.75-15 mg/kg per day of crude stevioside (up to 1200 mg for an 80 kg person) for 24 weeks lowered human hypertensive SBP and DBP 17 and 10 mmHg respectively, but with similar outcomes in the placebo group. Normotensives and diabetic patients receiving 250-1000 mg oral stevioside or rebaudioside-A had no changes to their blood pressure in the short term (3 days) (Geuns et al., 2007) and longer term treatments (4 months) (Barriocanal et al., 2008; Maki et al., 2008).

Lindner et al (1976) using the purified alkaloid, 13-hyroxylupanine-2-pyrrolcarbonic acid ester (Hoe933) isolated from an extract of *Cadia ellisiana* (black boy plant or dikana, family Fabaceae) lowered heart rate and decreased canine SBP and DBP by i.v. injection of 0.2 mg/kg by 59 and 57 mmHg respectively and rhesus monkey MAP by 63 mmHg (59 mmHg in cats) and 0.5 mg intraduodenal to the dog lowered MAP by 36 mmHg. Hoe 933 also lowered renal hypertensive rats at 10 and 200 ug/kg i.v. by 34 and 87 mmHg respectively. In unconscious SHR 100 ug/kg HOE 933 lowered MAP by 25 mmHg. However, in conscious SHR and 8 renally hypertensive rats there were no effects on blood pressure after repeated oral administration of 50 mg/kg (Lindner et al., 1976).

The extract of *Croton schiedeanus* (in Columbia called “almizclillo”, family Euphorbaceae) lowered SHR MAP by 45.6% (~ 77 mmHg) at 20 mg/mL i.v. but at 200 mg/mL p.o. had no affect on blood pressure at 3 hours (Guerrero et al., 2002). Acute intravenous administration of a bioactive plant extract, eg from *Cepropia obstusifolia* (family Cecropiaceae) or trumpet tree aqueous leaf extract, lowered normotensive rat (Vidrio et al., 1982) and SHR (Salas et al., 1987a) blood pressure but had no chronic effects on MAP when fed for 4 weeks to

SHR (Salas et al., 1987b). The extract from *Uncaria callophylla* (cat's claw, family Rubiacea) contains two active dihydro-corynantheines that when given i.v. to a conscious SD rat at 5 mg/kg lowered arterial BP by 32.8 mmHg (Chang et al., 1989) and gambirine at 10 mg/kg i.v. lowered both SBP and DBP and induced bradycardia (Mok et al., 1992). *U Callophylla* also has alkaloid from the leaves called gambirine which given i.v. to SD rats lowered SBP and DBP 30 and 51 mmHg respectively (Mok et al., 1992) but there does not appear to be evidence for oral activity of these potential bioactives in the literature.

CONCLUSIONS

The pleiotropic action of plant extracts in BP regulation are manifest to a large extent in modulation of the RAAS and muscarinic atropine-sensitive systems, endothelial NO synthesis pathway, and the adrenergic, endothelin and GABA systems that involve calcium homeostasis and vascular contractility, along with water and salt balance that ultimately effect the regulation of blood pressure. Of the 57 families with plant extracts found to lower blood pressure *in vivo* including normotensive or hypertensive animal models or human subjects; the extracts of 43 plant families representing 73 plant species were demonstrated to effectively control BP by the oral route. Of these, 16 species from 13 families exerted a significant effect in lowering BP in human subjects. Plant families with demonstrated capacity for lowering BP in human subjects listed in sequence of taxonomic family, scientific and finally common names are as follows: Alliciacea, *Allium sativum* (garlic); Apocynaceae, *Apocynum venetum* (dogbane), *Raufolfia serpentine* (snakeroot); Asteraceae, Achillea wilhelmsii (yarrow), *Stevia rebaudiana* (sweetleaf); Burseracea, *Balsamodendron mukul* (Indian bedellium); Chlorellaceae, *Chlorella pyrenoidosa* (chlorella green algae); Lythraceae, *Punica granatum* (pomegranate); Malvaceae, *Hibiscus*

sabdariffa (roselle); Oleaceae, *Olea europaea* (olive); Pedaliaceae, *Sesamum indicum* (sesame); Rosaceae, *Crataegus curvisepala* and *C. laevigata* (hawthorn); Rubiaceae, *Coffea Arabica* (green coffee) and *Uncaria rhynchophylla* (cat's claw); Solanaceae, *Lycopersicon esculentum* (tomato). Many of these common names although found in Ayurveda and Chinese traditional medicine are also familiar to the Western world and are recognised as ingredients found in the "Mediterranean" diet and also may be attributed to the dietary "French paradox" (Iijima et al., 2002). Notwithstanding the potential for BP regulation by use of plant bioactives, there are significant gaps in understanding of efficacy and in particular, the 'Required Daily Intake' (RDI) of specific plants for effective regulation of BP. There appears to be significant potential for plant bioactives, particularly dietary plants, to control BP and to maintain BP in the normal range before the necessity for drug intervention. Clinical trials may be required for checking interactions of specific plant bioactive preparations with anti-hypertensive drugs. Ongoing research is required for the development of dietary plants as functional food ingredients for BP management in the future.

In summary, we have produced a comprehensive analysis of plant derived anti-hypertensive extracts tabulated in their family groups that may function via RAAS or other mechanisms for potential human therapeutic use. These bioactives should ideally be bioavailable via the oral route and be non-toxic without interacting with prescribed medication under advice of health professionals.

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Table 1. Summary of plant taxonomic families and individual species associated with *in vitro* ACE inhibitory activity, including medium of extraction and specific activity of extractable solids.

Family	**Species**	**Common name[1] (part)[2] [main solvent][3] {fraction}**	**IC_{50} (units??) or % inhibition (mg/ml)[4]**	**Reference**
Acanthaceae	*Andrographis echioides*	False waterwillow (aerial) [A]	55% at 0.33	Somanadhan et al 1999
	Asystasia gangetica	Chinese violet (leaf) [M]	51% at 1	Ramesar et al 2008
	Hygrophila auriculata	Ikshura (seed) [E]	0.77	Khan & Gilani 2001
	Justica flava	Worm-bark (leaf) [W]	53% at 1	Ramesar et al 2008
	Trichocalyx obovatus	(aerial part) [M]	0.42	Oleski et al 2006
Agavaceae	*Agave americana*	Century plant (leaf) [E]	82% at 0.33	Duncan et al 1999
Alliaceae	*Agapanthus africanus*	African lily (leaf, root) [W]	63% at 0.33	"
	Allium sativum	Wild garlic (bulb) [W]	58% at 0.3	Sendl et al 1992
	Tulbaghia violacea	Society garlic (leaf) [W]	72% at 0.33	Duncan et al 1999
	Tulbaghia violacea	Society garlic (leaf) [M]	71% at 1	Ramesar et al 2008
Amaranthaceae	*Amaranthus dubius*	Red spinach (leaf) [M]	67% at 1	"
	Amaranthus hybridus	Smooth pigweed (leaf) [W]	52% at 1	"
Anacardiaceae	*Mangifera indica*	Mango tree (bark) [A]	61% at 0.33	Somanadhan et al 1999
	Poupartia borbonica	Bois blanc rouge (bark) [E]	98% at 0.33	Adsersen & Adsersen 1997
	Schinus latifolius	Pepper tree (not defined) [E]	74% at 0.33	Hansen et al 1995
	Semecarpus anacardium	Marking nuts (nuts) [E]	0.17	Khan et al 2001
Annonaceae	*Polyalthea longifolia*	Indian mast tree (stem bark) [E]	0.17	"
Apiaceae	*Centalla asiatica*	Pennywort (stem) [W]	73% at 0.33	Hansen et al 1995
	Oenanthe javanica	Water dropwort (aerial part) [W]	53% (ND)	Noh & Song 2001
Apocynaceae	*Ceropegia rupicola*	Bukira (aerial part) [M]	0.11	Alasbahi & Melzig 2008
	Wrightia tintoria	Dyer's oleander (seed) [W]	52% at 0.33	Nyman et al 1998
Aracaceae	*Areca catechu*	Arecu nut palm (seed) [M]	96% at 0.2	Inokuchi et al 1986
Araliaceae	*Panax ginseng*	Asian ginseng (root) [W]	5.0	Persson et al 2006
Araranthaceae	*Salsola oppositifolia*	Tumbleweed (aerial part) [EA]	0.18	Loizzo et al 2007
Asteraceae	*Artemisia pallens*	Davana (aerial part) [E]	51% at 0.33	Somanadhan et al 1999
	Aspilia helianthoides	NF (aerial part) [M]	0.13	Alasbahi & Melzig 2008

	Galinsoga parviflora	Gallant soldier (leaf) [M]	56% at 1	Ramesar et al 2008
	Gynura procumbens	Duan (leaf) [E (FA-1)]	0.8	Hoe et al 2007
	Pulicaria stefanocarpa	ND (aerial part) [M]	0.33	Oleski et al 2006
Berberidaceae	*Epimedium brevicornum*	Epimedium (branch, leaf) [M]	84% at 0.2	Inokuchi et al 1986
Bignoniaceae	*Mansoa hirusta*	ND (leaf) [DC, M]	54% at 0.33	Braga et al 2000
Burseraceae	*Boswellia elongata*	Frankincense tree (bark) [M]	0.29	Oleski et al 2006
	Canarium euphyllum	Indian white mahogany (bark) [AA]	100% at 0.33	Somanadhan et al 1999
Caesalpiniaceae	*Cassia fistula*	Golden shower tree (bark) [AA]	90% at 0.33	"
	Cassia tora	Foetid cassia (root) [AA]	97% at 0.33	"
	Humboldtia vahliana	Tamil (bark) [E]	93% at 0.33	"
Caricaceae	*Carica papaya*	Papaya (leaf) [W]	86% at 0.33	Adsersen & Adsersen 1997
Casuarinacea	*Casuarina equisetifolia*	She-oak (fruit) [W]	94% at 0.33	"
Celastraceae	*Celastrus paniculatus*	Black-oil tree (seed) [W]	50% at 0.33	Somanadhan et al 1999
Chenopodiaceae	*Salsola soda*	Saltwort (aerial) [W]	0.28	Loizzo et al 2007b
Clusiaceae	*Calophyllum brasiliense*	Guanandi (stem) [E]	55% at 0.1	Braga et al 2007
	Calophyllum tacamahaca	Takamaka (leaf) [E]	100% at 0.33	Adsersen & Adsersen 1997
Combretaceae	*Combretum fruticosum*	Chameleon vine (leaf)[E]	54% at 0.1	Braga et al 2007
	Terminalia bialata	Indian silver greywood (bark) [E]	86% at 0.33	Somanadhan et al 1999
	Terminalia bentzoe	Benjoin (leaf) [W]	53% at 0.33	Adsersen & Adsersen 1997
	Terminalia catappa	Indian almond tree (leaf) [W]	80% at 0.33	"
	Terminalia catappa	Indian almond tree (leaf) [E]	54% at 0.1	Braga et al 2007
	Terminalia chebula	Black myrobalan (fruit) [AA]	68% at 0.33	Somanadhan et al 1999
Convolvulaceae	*Cuscta japonica*	Japanese dodder (seed) [EA]	89% at 0.4	Oh et al 2002
Crassulaceae	*Kalanchoe farinaceae*	ND (aerial part) [M]	0.09	Oleski et al 2006
	Sedum sarmentosum	Stingy stonecrop (aerial) [EA]	80% at 0.4	Oh et al 2004
Cucurbitaceae	*Benincasa hispida*	Wax gourd (seed) [W]	69% at 0.25	Huang et al 2004
Cupressaceae	*Crytomeria japonica*	Japanese cedar (outer bark) [E]	0.016	Tsutsumi et al 1998
Cunoniaceae	*Weinmannia tinctoria*	Tan rouge (leaf) [E]	79% at 0.33	Adsersen & Adsersen 1997
Dipterocarpaceae	*Shorea rubasta*	Sal tree (stem bark) [W]	0.26	Khan et al 2001
Ephedraceae	*Ephadra sinica*	Ephadra, "ma huang" (stem) [M]	98% at 0.2	Inokuchi et al 1984
Ericaceae	*Philippia montana*	Branle vert (leaf) [E]	96% at 0.33	Adsersen & Adsersen 1997
	Vaccinium ashei reade	Blueberry (leaf) [W]	0.05	Sakaida et al 2007
	Vaccinium myrtillus	Bilberry (leaf) [W]	0.0025*	Persson et al 2009
	Vacciniun oxycoccos	Cranberry (fruit) [W]	66% at 2.6	Apostolidis et al 2006
Erythroxylaceae	*Erythroxylum laurifolium*	Bois de rongue (leaf)[E]	84% at 0.33	Adsersen & Adsersen 1997
Euphorbiaceae	*Cordemoya integrifolia*	Boutonia (bark) [AA]	59% at 0.33	"
	Jatropha curcus	Ratanjyot (leaf) [W]	65% at 0.33	"
	Jatropha unicostata	ND (leaf and fruit) [M]	0.18	Oleski et al 2006
Fabaceae	*Abrus precatorius*	Crab's eye (aerial) [W]	51% at 0.33	Nyman et al 1998
	Adenopodia spicata	Spiny splinter bean (leaf) [W]	97% at 0.33	Duncan et al 1999
	Antidesma madagascariense	Bigaignon sauvage (leaf) [AA]	53% at 0.33	Adsersen & Adsersen 1997
	Glycine max	Soy bean (seed) [W]	95% dng	McCue et al 2005
	Lespedeza capitata	Roundhead (leaf) [E]	89.1% at	Wagner & Elbl 1992

			0.33[5]	
	Pseudarthria hookeri	Velvet bean (ND) [E]	90% at 0.33	Hansen et al 1995
	Pseudarthria viscida	Viscid pseudarthria (ND) [E]	71% at 0.33	"
Flacourtiacae	*Aphloia theiformis*	Albino-berry (leaf) [AA]	67% at 0.33	Adsersen & Adsersen 1997
Gentianaceae	*Exacum affine*	Persian violet (aerial) [M]	0.31	Oleski et al 2006
Gunneraceae	*Gunnera tinctoria*	Chilean rhubarb (ND) [E]	57% at 0.33	Hansen et al 1995
Iridaceae	*Dietes iridioides*	African iris (leaf, root) [W]	80% at 0.33	Duncan et al 1999
Labiatae	*Hyssopus officinalis*	Lyssop (aerial part) [H]	0.052	Loizzo et al 2008
Lamiaceae	*Calamintha origanifolia*	None found (aerial) [C]	0.11	"
	Marrubium radiatum	Horehound (aerial) [M]	0.07	"
	Melissa officinalis	Lemon balm (leaf) [W]	81.9% at 4	Kwon et al 2006b
	Rabdosia coetsa	Mint type (whole plant) [E]	71% at 10	Li et al 2008
	Rosmarinus officinalis	Rosemary (leaf) [W]	90.5% at 4	Kwon et al 2006b
	Salvia acetabulosa	Sage (aerial) [M]	0.053	Loizzo et al 2008
	Salvia elegans	Mirto (aerial) [E]	50.3% at 100	Jimenez-Ferrer et al 2010
	Salvia militorrhiza	Danshen (aerial) [W]	0.17	Kang et al 2002a
	Satureja thymbra	Thyme-leaved savory (aerial) [C]	0.29	Loizzo *et al* 2008
Lauraceae	*Cassytha filiformis*	Love vine (herb) [AA]	73% at 0.33	Adsersen & Adsersen 1997
	Cinnamomum zeylanicum	Ceylon cinnamon (bark) [M]	87% at 0.2	Inokuchi et al 1984
Leeaceae	*Leea rubra*	Red Leea (aerial) [E]	57.0% at 0.1	Braga et al 2007
Liliaceae	*Fritillaria ussuriensis*	Paemo (bulb) [EA]	0.29	Kang et al 2002b
Lythraceae	*Cuphea cartagenesis*	Cattail (leaf) [DC,M]	50% at 0.33	Braga et al 2007
Malvaceae	*Hibiscus sabdariffa* L.	Roselle (flower) [E]	1.9	Jonadet et al 1990
	Pavonia odorata	Hribera (whole plant) [E]	51% at 0.3	Somanadhan et al 1999
Monimiaceae	*Monimia ovalifolia*	Mapou (leaf) [E]	88% at 0.33	Adsersen & Adsersen 1997
	Monimia rotundifolia	Mapou blanc (leaf) [E]	55% at 0.33	"
Moraceae	*Musanga cecropioides*	Umbrella tree (leaf) [M]	100% at 0.33	Lacaille-Dubois et al 2001
Moringaceae	*Moringa oleifera*	Horseradish tree (fruit shell) [W]	72% at 0.33	Somanadhan et al 1999
	Moringa oleifera	Horseradish tree (leaf) [W]	59% at 0.33	Adsersen & Adsersen 1997
Myrcinaceae	*Badula barthesia*	Bois de savon (leaf) [AA]	100% at 0.33	"
	Embelia angustifolia	Liane savon (leaf) [AA]	92% at 0.33	"
	Embelia basaal	Vavding (stem) [E]	87% at 0.33	Somanadhan et al 1999
	Embelia basaal	Vavding (fruit) [E]	100% at 0.33	"
Mytaceae	*Hexachlamys edulis*	Pêssego-do-mato (ND) [AA]	91% at 0.33	Hansen et al 1995
Oenotheraceae	*Oenothera paradoxa*	Evening primrose (seed) [W]	0.055	Kiss et al 2008a
Oleaceae	*Abeliophyllum distichum*	White forsythia (leaf) [M]	50% at 0.4	Oh et al 2003
	Jasminum azoricum	Azores jasmine (aerial) [W]	86% at 0.33	Somanadhan et al 1999
	Jasminum grandiflorum	Spanish jasmine(aerial) [AA]	78% at 0.33	"
	Jasminum multiflorum	Downy jasmine (flower) [AA]	92% at 0.33	"
	Ligustrum vulgare	Common privet (leaf) [W]	0.1	Kiss et al 2008b
	Olea lancea	Bois d'olive blanc (leaf) [E]	89% at 0.33	Adsersen & Adsersen 1997
Onagraceae	*Epilobium angustifolium*	Willowherb (aerial) [EA]	0.15	Kiss et al 2004
	Ouratea semiserrata	(NF) stem [DC, M]	68% at 0.33	Braga et al 2007

Paeoniaceae	*Paeonia suffruticosa*	Tree poeny (root bark) [M]	61% at 0.2	Inokuchi et al 1984
Palmae	*Pheonix roebelenii*	Pigmy date palm (leaf) [E]	79.7% at 0.1	Braga et al 2007
Passifloraceae	*Passiflora edulis*	Passionfruit (leaf) [W]	80% at 0.33	Adsersen & Adsersen 1997
Piperaceae	*Piper betle*	Betel leaf (leaf) [W]	56% at 0.33	Somanadhan et al 1999
	Polygonum aviculare	Common knotgrass (aerial) [M]	94% at 0.2	Inokuchi et al 1984
	Rheum officinale	Chinese rhubarb (root) [M]	95% at 0.2	"
Phyllanthaceae	*Phyllanthus phillyreifolius*	Bois de négresse (leaf) [E]	93% at 0.33	Adsersen & Adsersen 1997
Polygonaceae	*Oxygonum sinuatum*	Kindri (leaf) [W]	59% at 1.0	Ramesar et al 2008
Rosaceae	*Potentilla chinensis*	Chinese cinquefoil (aerial) [M]	54% at 0.2	Inokuchi et al 1984
Rubiaceae	*Antirrhea borbonica*	Bois d'osto (leaf) [AA]	50% at 0.33	Adsersen & Adsersen 1997
	Coffea mauritanica	Coffee tree (leaf) [AA]	65% at 0.33	"
	Psathura borbonica	Bois cassant (leaf) [E]	77% at 0.33	"
	Uncaria rhynchophylla	Cat's claw herb (ND) [E]	58% at 0.33	Hansen et al 1995
Rutaceae	*Aegle marmelos*	Bengal quince (stem bark) [EA]	0.27	Khan et al 2001
	Citrus limon	Lemon (leaf) [W]	71% at 0.33	Adsersen & Adsersen 1997
	Euodia simplex	None found (leaf) [E]	82% at 0.33	"
	Clausena anistata	Horsewood (leaf) [W]	54% at 0.33	Duncan et al 1999
Salvadoraceae	*Salvadora persica*	Toothbrush tree (seed) [W]	55% at 0.33	Nyman et al 1998
Santalaceae	*Scleropyrum pentandrum*	Benduga (nut shell) [W]	61% at 0.33	Duncan et al 1999
Sapindaceae	*Cardiospernum halicacabum*	Balloon vine (stem) [W]	50% at 0.33	Somanadhan et al 1999
	Dodonea viscosa	Sticky hopbush (leaf) [AA]	63% at 0.33	Adsersen & Adsersen 1997
	Molinaea alternifolia	Tan Georges (leaf) [E]	65% at 0.33	"
Simaroubaceae	*Ailanthus excelsa*	Tree of heavan (leaf) [M]	54% at 0.33	Loizzo et al 2007a
Solanaceae	*Physalis viscosa*	Tomato weed (leaf) [M]	60% at 1.0	Ramesar et al 2008
Stangeriaceae	*Stangeria eriopus*	Stanger's cycad (leaf) [H]	55% at 0.33	Duncan et al 1999
Theaceae	*Camellia sinensis*	Green tea black tea (leaf) [W]	1.0	Persson et al 2006
Tiliceae	*Triumfetta rhoboidea*	Triumfetta burr (ND) [E]	61% at 0.33	Hansen et al 1995
Urticaceae	*Cecropia glaziovii*	Pumpwood (stipules) [M]	91% at 0.33	Lacaille-Dubois et al 2001
Verbenaceae	*Clerodendron trichotomum*	Harlequin glorybower (stems) [M]	0.37[5]	Kang et al 2003a
Viscacaea	*Viscum triflo rum*	African mistletoe (leaf) [W]	75% at 0.33	Adsersen & Adsersen 1997
Vitaceae	*Cissus hamaderohensis*	ND (leaf) [M]	0.39	Oleski et al 2006
	Leea guinenis	ND (leaf) [E]	100% at 0.33	Adsersen & Adsersen 1997
	Vitis vinifera	Wine grape vine (fruit) [W]	0.08[6]	Meunier et al 1987
Zygophyllaceae	*Tribulus terrestris*	Puncture vine (aerial) [W]	50% at 0.33	Somanadhan et al 1999
74	*Tribulus terrestris*	Puncture vine (fruit) [W]	56% at 0.33	"

[1]The common name is in English or as described from a country of origin.

[2]Part of the plant as described in the methods.

[3]The solvent denoted is the dominant used for plant extraction and the one listed giving highest ACE inhibition. Note that other solvents may have also been used.

[4]Inhibitory ACE activity as IC_{50} (mg/ml) or as % inhibition at designated mg/ml.

[5]Identified as active agent from plant species.

[6]Oligomeric proanthocyanidinins

*ACE activity measured in HUVEC tissue.

Abbreviations: A, acetone; AA, acetic acid; C, chloroform; DC, dichloromethane; dng, dose not given; E, ethanol; EA, ethyl acetate; ET, ether; FA-1, see extraction by author; H, n-hexane; M, methanol; ND, not defined; PA, plasma ACE W, water.

Table 2. Isolated bioactives from plant sources with *in vitro* ACE inhibitory activity*

Bioactive	**IC_{50} (μM)**	**Plant source (common name[1], family) ***	**Reference**
Aceteoside	368	*Abeliophyllum distichum* (white forsythia, Oleaceae)	Oh et al 2003
Isoaceteoside	465		
Rutin	421		
Apigenin	280	*Ailanthus excelsa* (tree of heaven, Simaroubaceae)	Loizzo et al 2007a
Luteolin	290		
Kaempferol-3-*O*-*α*-arabinopyranoside	320		
Kaempferol-3-O-*β*-galactopyranoside	260		
Quercetin-3-*O*-*α*-arabinopyranoside	310		
Luteolin-7-*O*-*β*-glucopyranoside	280		
Gluco-aurantioobtusin	30	*Cassia tora* seed (foetid cassia, Caesalpinacea)	Hyun et al 2009
Guanosine	1.5	*Chrysanthemum boreale* Makino (chrysanthemum, Asteraceae)	Kim et al 2003
Epicatechin-3-*O*-gallate	18	Chinese herbs	Lui et al 2003
Epigallocatechin-3-O-methylgallate	27		
Epigallocatechin-3-O-gallate	37		
3,5,-Di-*O*-caffeoyquinic acid	596	*Cuscuta japonica* (Japanese dodder, Convolvulaceae)	Oh et al 2002
Methyl 3,5-Di-*O*-caffeoylquinate	483		
3,4,-Di-*O*-caffeoylquinic acid	534		

Methyl 3,4-Di-O-caffeoylquinate	460		
Catechin	55	*Crytomeria japonica* (Japanese cedar (Cupressaceae)	Tsutsumi et al 1998
Epicatechin	53		
Epigallocatechin	123		
3,7-Dihydroxyflavone	39		
Fisetin	73		
Morin	81		
Quercetin	88		
Kaempferol-3-*O*-(2”-*O*-galloyl)-glucoside	421	*Diospyros kaki* (persimmon, Ebanaceae)	Kameda et al 1987
Puqienine E	68	*Fritillaria puqiensis* (Liliaceae)	An et al 2010
Verticinone	360	*Fritillaria ussuriensis* (ping bei mu, Liliaceae)	Oh et al 2003
Verticine	721		
Peimisine	1238		
Astragalin	400		
Isoquercitrin	401		
Kaemferol	100	Green vegetables	Olszanecki et al 2008
Delphinindin-3-*O*-sambubioside	85	*Hibiscus sabdariffa* (Roselle, Malveraceae)	Ojeda et al 2010
Cyanidin-3-*O*-sambubioside	68		
Sambacein I-III	30	*Jasminum azoricud, J. grandiflorum* (Azores jasmine, French perfume jasmine, Oleaceae)	Somanadhan et al 1997
Oleuropein	20	*Ligustrum vulgare* (common privet, Oleaceae)	Kiss et al 2008b
Epicatechin-3-*O*-gallate	165	*Oenothera paradoxa* (evening primrose, Oenotheraceae)	Kiss et al 2008a
Ellagic acid	400		
Caffeic acid	220		
Oenothein B	250		
Quercetin glucuronide	300		
Pentagalloyl glucose	35		
Methyl gallate	500		
Procyanidin B3	135		
Ligstroside	25	*Phyllanthus urinaria* (chamber bitter, Euphorbiaceae)	Lin et al 2008
Geraniin	13		
Lithospermic acid B	120	*Salvia militorrhiza* Bunge (Danshen, Lamiaceae)	Kang et al 2003b
Myrtillin chloride	~20	*Vaccinium myrtillus* (bilberry, Ericaceae)	Persson et al 2009

[1]Common name is usually in English or the name from the original country if known.

*Listed alphabetically as to scientific binominal or general name.

Table 3. Summary of plant taxonomic families and individual species associated with *in vitro* angiotensin type 1A receptor blocking activity, including medium of extraction and specific activity of extractable solids.

Family	Species	Common name[1] (part)[2] [Solvent][3]	IC_{50} or % inhibition (mg/ml)[4] [bioactive]	Reference
Alismataceae	*Alisma orientale*	Water plantain, Ze Xie (root) [W]	59.6% at 0.025 0.008 [alisol B]	Makino et al 2002a
Altingiaceae	*Liquidambar styraciflua*	American sweetgum (resin) [E]	50% at 0.1[5]	Ohno et al 2008
Anacardiaceae	*Anacardium occidentale*	Cashew tree (bark) [DC, M]	85% at 0.1 [benzyl benzoate]	Caballero-George et al 2001
Begoniaceae	*Begonia urophylla*	Begonia (leaf) [DC, M]	82% at 0.1	"
Cecropiaceae	*Cecropia cf. obtusifolia*	Trumpet tree (stem) [DC, M]	59% at 0.1	"
Clusiaceae	*Clusia coclensis*	Sambo gum (branch) [W]	67% at 0.1	"
Cochlospermaceae	*Cochlospermum vitifolium*	Buttercup tree (bark) [EA]	68% at 0.1	"
Cucurbitaceae	*Momordica charantia*	Bitter melon (aerial) [C]	68% at 0.1	"
Fabaceae	*Astragalus complanatus*	Milkvetch (seed, total flavonoids) [ND]	0.31 mg/L in portal vein of SHR	Xue et al 2008
Lauraceae	*Persea americana*	Avocado (leaf) [DC, M]	55% at 0.1	Caballero-George et al 2001
Papervaraceae	*Bocconia frutescens*	Tree poppy (root) [DC, M]	100% at 0.1	"
Ranunculaceae	*Coptis chinensis* Franch	Goldthread (Zoa Gum Hwan - Korean herbal remedy) [W]	47% at 0.01[6] [berberine]	Ko et al 2007
Solanaceae	*Witheringia solanacea*	Diguima goi (branch) [C]	80% at 0.1	Caballero-George et al 2001
Sterculiaceae	*Guazuma ulmifolia*	Bay cedar (bark) [W]	75% at 0.1	"
	"	Bay cedar (bark) [C, EA, B]	0.025	"
Rubiaceae	*Psychotria poeppigiana*	Sore-mouth bush (stem) [C]	66% at 0.1	"
Zingiberaceae	*Dimerocostus strobilaceae*	Pinuue Barbat (root) [DC, M]	92% at 0.1	"

[1]Common English name or name from the country of origin is used and the part of the tree where usually most activity is described.

[2]Part of the plant used.

[3]The solvent denoted is the one that gave the highest inhibition. Note that other solvents may have also been used.

[4]Blocking of angiotensin receptor binding assay is given as IC_{50} (K_i) (μM) or % inhibition at a known concentration (mg/ml). In a membrane or *in vitr*o tissue preparation.

[5]Inhibition of angiotensin II generated increase in $[Ca^{2+}]_i$ of mAT_{1a}(HA)/293T cells.

[6]Inhibition of angiotensin II induced MCP-1 secretion in HUVECs.

Abbreviations: B, butanol; C, chloroform; EA, ethyl acetate; M, methanol; DC, dichloromethane; ND, not defined; RHR, renovascular hypertensive Wistar rat; W, water.

Table 4. Summary of plant taxonomic families and individual species associated with angiotensin type 1A receptor blocking activity, producing *in vivo* blood pressure lowering effects in experimental animals and humans.

Family	**Species**	**Common name[1] (part)[2][solvent][3]**	**Dose (mg/kg rat weight)**	**Effect**	**Reference**
Altingiaceae	*Liquidambar styraciflua*	American sweetgum (resin) [E]	2 mg/kg p.o.	Lowered mice SBP Ang-II induced increase in BP	Ohno et al 2008
Arecaceae	*Areca catechu*	Areca nut palm (seed) [M]	15 mg/kg i.v. and 200 mg/kg p.o.	Lowered SHR SBP and inhibited pressor response of Ang-I and Ang-II	Inokuchi et al 1986
Elaeagnaceae	*Hippophae rhamnoides*	Seaberry (seed, total flavones) [PE]	150 mg/kg/d p.o.	Lowered sucrose fed SD rat SBP by 23 mmHg is this ATRi pathway specific??	Pang et al 2008

[1]Common English name or name from the country of origin.

[2]Part of the plant used in study.

[3]The solvent used to make plant extract.

Abbreviations: AT_1, angiotensin type 1 receptor; E, ethanol; ip, intraperitoneal; M, methanol; PE, petroleum ether; SD, Sprague Dawley; SHR, spontaneous hypertensive rat; SBP, systolic BP; N.D., not determined.

Table 5. Summary of plant taxonomic families and individual species producing *in vivo* blood pressure lowering effects in experimental animals.

Family	Species	Common name(s) (part)[1] [solvent][2] {Tradename, fraction}[3]	Dose and route of administration	Effect (mechanism) {bioactive}	Reference
Acanthaceae	*Andrographis paniculata*	Creat (aerial part) [W]	2.8 g/kg i.p. chronic	Lowered SBP in SHR by 35 mm Hg	Zhang & Tan 1996
	Andrographis paniculata	Creat (aerial part) [W]	60 mg/kg p.o. 8 d	Lowered WR SBP by 24.2% {14-deoxy-11,12-didehydroandrographolide}	Yoopan et al 2007
Alismataceae	*Echinodorus grandiflorus*	Leather hat, burhead (leaf) [E]	1000 mg/kg i.p., 100 mg/kg i.v. or 100 mg/kg p.o.	Lowered SHR MAP by 23% and 51% for 3 min i.v. and 35 mmHg at 4 wk p.o. (NO pathway and muscarinic and PAF receptors)	Lessa et al 2008
Alliaceae	*Allium cepa*	Onion (bulb, powder) [W]	5% in diet for 4 wk	Lowered L-NAME SD rat and SHR SBP by 20 mmHg	Sakai et al 2003
	Allium cepa	Welsh onion, green type (bulb) [W]	5% in diet for 4 wk	Lowered high fat/sucrose SD rat SBP by 24 mmHg	Yamamoto et al 2005
	Allium cepa	Red onion (peel) [E]	800 mg/kg p.o. for 3 wk	Lowered 10% fructose in DW-induced elevated WR SBP by 21 mmHg	Naseri et al 2008
	Allium sativum	Garlic (clove) [W]	0.5 ml/kg p.o.	Lowered SHR SBP by 65.7 mmHg at 30 min	Foushee et al 1982
	Allium sativum	Garlic (clove) [W] {Kwai}	0.1 & 1% of diet for 26 and 45 d	Lowered SHR SBP by 15 and 14 mmHg	Preuss et al 2001
	Allium sativum	Garlic (clove) [W]	50 mg/kg p.o. for 7 d	Lowered SD 2K1C rat SBP by 26 mmHg, (reduced induction of NHE-1, and increased Na^+ pump activity in kidneys)	Al-Qattan et al 2003
	Allium sativum	Garlic (clove) [W]	1.5% of diet for 10 wk	Lowered SHR SBP by 19.4 mm Hg	Harauma & Moriguchi 2006
	Allium ursinum	Wild garlic (leaf powder) [W]	0.1% & 1% of diet for 26 and 45 d	Lowered SHR SBP by 28 and 16 mmHg	Preuss et al 2001
Anacardiaceae	*Harpephyllum caffrum*	Wild plum (stem bark) [W]	400 mg/kg i.v.	Lowered DSS rat SBP MAP and DBP by 81.9, 58.1 and 49 mmHg	Ojewole 2006
	Pistacia lentiscus	Mastic (aerial parts) [W]	25 mg/kg i.v.	Lowered WR SBP and DBP by 32 and 30 mm Hg	Sanz et al 1992
	Sclerocarya birrea	Marula (stem bark) [E]	240 mg/kg i.v. 4 h or 120 mg/kg p.o. 5 wk	Lowered MAP in WR and STZ-diabetic WR by 11.4 and 9.8 i.v. at 2 h and 9.8 and 8.1 mmHg p.o. at 5 wk	Gondwe et al 2008
Annonaceae	*Polyalthia longifolia* var. *pendula*	Indian mast tree (root bark) [W,M]	30 mg/kg i.v.	Lowered SD and egg-feed hypertensive SD MAP by 47.5% and 29%	Saleem et al 2005

Apocynaceae	*Amsonia elliptica*	Japanese bluestar (whole plant) [W]	1 mg/kg i.v. indole alkaloid	Lowered MAP by 30% {β-yohimbine} (increased HR)	Ozaki 1989
	Apocynum venetum	Dogbane, luobuma (leaf) [W]	70 mg/kg p.o. for 40-100 d	Lowered SHR SBP, 2K1C and NaCl-fed WR by 10.8, 19.7 and 14.7 mmHg	Kim et al 2000
	Apocynum venetum	Dogbane (leaf) [W]	5% in diet	Lowered SHR SBP by 30.7 mmHg (no WKY)	Kagawa et al 2004
Apiaceae	*Angelica keiskei*	Ashitaba (leaf) [E]	G fraction, 21.8 mg/kg/d p.o.	Lowered SHR SBP by 11 mm Hg at 11 wk	Shimizu et al 1999
	Corindrum sativum	Coriander (fruit) [M]	30 mg/ml i.v.	Lowered SD SBP and DBP up to 40.8%	Jabeen et al 2009
	Foeniculum vulgare	Fennell (aerial parts) [W]	190 mg/kg/d p.o.	Lowered SHR SBP by 12% at 5 d (increased water, Na^+ and K^+ excretion via diuresis)	El Bardai 2001
Arecaceae	*Areca catechu*	Areca nut palm (seed) [W] {Areca II-5-C}	15 mg/kg i.v. and 200 mg/kg p.o.	Lowered SHR and WKY SBP 58 and 21 mmHg i.v. and 34 mmHg SHR p.o.	Inokuchi et al 1986
Asteraceae	*Artemisia herba-alba*	White wormwood (aerial) [W]	150 mg/kg p.o. for 20 d	Lowered SHR SBP by 32.3 mmHg at 8 d (increased urinary output, no change in HR)	Zeggwagh et al 2008
	Artemisia verlotorum	Chinese mugwort (leaf) [W]	0.1 mg/kg i.v.	Lowered WR MAP by 63 mmHg	Calderone et al 1999
	Bibens pilosa	Burr marigold (leaf) [M,DCM]	150 mg/kg p.o for 24 h and 350 mg/kg for 3 wk	Lowered WR SBP by 21% at 6 h and prevented WR fructose-induced elevated SBP by 14 mmHg at 3 wk and lowered by 34 mmHg	Dimo et al 2002
	Bibens pilosa	Burr marigold (leaf) [M, DCM]	20 mg/kg i.v.	Lowered NT, SHR and salt-loaded rat SBP by 42.5%, 39.0% and 34.1% (altered cardiac pump efficiency)	Dimo et al 2003
	Chrysanthemum indicum	Chrysanthemum (flower) [W]	20 mg/kg i.v.	Lowered dog aortic BP and MAP by 16.4% and 31.9%	Kato et al 1986, 1987
	Gynura procumbens	Sambung nyawa (leaf) [E, H, B]	0-10 mg/kg i.v.	Lowered SHR MAP with ED_{50} 1.1 mg/kg	Hoe et al 2007
	Gynura procumbens	Sambung nyawa (leaf) [W]	500 mg/kg p.o. for 4 wk	Lowered SHR SBP by 19 mmHg (increased blood vessel NO)	Kim et al 2006
	Helichrysum ceres S Moore	Strawflower (leaf) [E]	120 mg/d p.o.	Prevented DSS rat elevation in MAP by 53.5 mm Hg	Musabayane et al 2008
	Stevia rebaudiana	Sweetleaf (leaf) [W]	~ 8 g/kg p.o. for 30 d	Lowered NTl and 2K1C rat MAP by 44 and 47 mmHg	Melis 1996
	Verbesina caracasana	Crownbeard (whole plant) [M]	1.6 mg/kg i.v.	Lowered WR SBP and DBP by 36 and 40 mm Hg {G2, caracasandiamide}	Botta et al 2003
Berberidaceae	*Berberis vulgaris*	Barberry (fruit) [W]	10 mg/kg i.v.	Lowered SD and DOCA-treated rat SBP and DBP by 73 and 51 and 132 and 119 mmHg	Fatehi et al 2005
Brassicaceae	*Lepidium sativum*	Garden cress (seed) [W]	20 mg/kg/d p.o. for 3 wk	Lowered SHR SBP from 7 d by 23 mmHg at 21 d (increased Na^+, K^+ and Cl^- excretion in WKY and SHR and increased water excretion and GFR in WKY)	Maghrani et al 2005

Buddlejaceae	*Buddleja crispa*	Himalayan butterfly bush (whole plant) [M]	10 mg/kg i.v.	Lowered WR SBP 30%	Gilani et al 2009
Caricaceae	*Carica papaya*	Paw paw tree (unripe fruit) [E]	20 mg/kg i.v.	Lowered NT, 2K1C and DOCA-salt WR MAP by 18.2, 87.5 and 106.1 mmHg (ED_{50} 34.6 mg/kg)	Eno et al 2000
Carvophyllaceae	*Herniaria glabra*	Rupturewort (saponins)	200 mg/kg p.o. for 30 d	Lowered SHR SBP and DBP by 46 and 29 mmHg (increased urinary flow)	Rhiouani et al 1999
	Spergularia purpurea Pers.	Purple sandspurry [M, B]	5 mg/kg/d p.o. for 7 d	Flavanoids lowered SHR SBP and DBP by 34.1 and 29.8 and WR 14.5 and 10.7 mmHg (increased GFR, water excretion and Na^+, K^+ and Cl^- loss)	Jouod et al 2001
Cecropiaceae	*Cecropia glaziovii* Sneth	Pumpwood (leaf) [W, B]	0.5 g/kg/d p.o.	Lowered WR SBP 22 mmHg 30-60 d and SHR 13 mmHg at 15 d and 2K-1C 21 at 50 d (by Ca^{2+} handling)	Lima-Landman et al 2007
	Cecropia obtusifolia	Trumpet tree (leaf) [W]	50 mg/kg i.v.	Lowered SHR MAP by 23.5% or 38 mmHg	Salis et al 1987
	Cecropia obtusifolia	Trumpet tree (leaf) [W]	20 mg/kg p.o. for 4 wk	No effect on SHR MAP	Salis et al 1987
Clusiaceae	*Mammea africana*	African mammee tree (stem bark) [M,DCM]	200 mg/kg/d p.o. for 4 wk	Prevented L-NAME induced increase in SBP by ~ 102 mmHg	Nguelefack-Mbuyo et al 2008
Combretaceae	*Combretum molle*	Velvet bush willow (leaf) [W]	40 mg/kg i.v.	Lowered WR and DSS SBP, MAP and DBP by 81, 70, and 75 and 79, 72 and 78 mmHg (lowered HR) {1α-hydroxy-cycloartenoid saponin}	Ojewole 2008
Crassulaceae	*Rhodiola sacra*	Plateau gingeng (aerial parts) [M]	50 mg/kg i.v.	Lowered SD SBP, MAP and DBP by 55, 51 and 52 mmHg (HR up 13%)	Shih et al 2008
Cucurbitaceae	*Momordica charantia*	African cucumber (whole plant) [W]	800 mg/kg i.v.	Lowered NT SBP, MAP and DBP and DSS rat by 26.4, 45.3 and 44, and 77, 57.4 and 55.9 mmHg	Ojewole et al 2006
Dicksoniaceae	*Dicksonia swllowiana*	Xaxim (leaf) [E]	40 mg/kg i.v.	Lowered WR MAP by 47.3% (blocked by atropine)	Rattmann et al 2009
Dilleniaceae	*Curatella americana*	Sandpaper tree (aerial) [E]	20 mg/kg i.v. and 200 mg/kg p.o for 3 h	Lowered SHR MAP by 77.4 mmHg (no effect p.o.)	Guerrero et al 2002
Ericaceae	*Arbutus unedo*	Stawberry tree (leaf, root) [W]	250 mg/kg/d p.o. for 4 wk	Reduced the L-NAME induced SBP increase by leaf and root by 19 and 33 mmHg	Afkir et al 2008
	Vaccinium cyanococcus	Blueberry (fruit) [W]	3% in diet for 8 wk	Lowered SHR SBP up to 30% (38 mmHg)	Shaughnessy et al 2009
Eucommiaceae	*Eucommia ulmoides*	Chinese rubber plant (bark) [M]	1200 mg/kg/d p.o. for 22 d	Lowered SHR SBP by 38 mm Hg at 22 d	Lang et al 2005
Euphorbiaceae	*Croton schiedeanus*	Almizelillo (aerial) [E]	20 mg/kg i.v.	Lowered SHR MAP by 19.2 mmHg	Guerrero et al 2002
	Croton zehntneri	Cunha (leaf) [EO]	20 mg/kg i.v.	Lowered WR MAP and HR by 43.2% and 82.8% (followed by	De Siqueira et al 2006

				pressor response) {estragole and E-anethole}	
	Phyllanthus amarus	Black catnip (leaf) [W]	80 mg/kg i.v.	Lowered rabbit DBP, SBP and MAP by 49.7, 45.5 and 48 mmHg (blocked by atropine and Ca channel blockade)	Amaechina & Omogbai 2007
	Phynathus urinaria	Wrinle-fruited leaf flower (whole plant) [A]	5 mg/kg geraniin p.o.	Lowered SHR SBP and DBP by 23.5 and 21mmHg from 2 to 24 d (geraniin)	Lin et al 2008
Fabaceae	*Cadia ellisiana*	Black boy plant or dikana (root) {Hoe 933}	0.5 mg i.d. and 50 mg/kg p.o.	Lowered dog MAP by 36 mmHg i.d. (no effect p.o.) (13-hydroxylupanine-2-pyrrolcarbonic acid)	Lindner et al 1976
	Caesalpinia ferrea	Brazilain ironwood (stem bark) [W]	80 mg/kg i.v.	Lowered WR MAP by 51%	Menezes et al 2007
	Glycyrrhiza uralensis	Chinese licorice (root) [E,EA,A]	300 mg/kg/d p.o. for 4 wk	Lowered SHR SBP by 31.7 mmHg at 3 wk	Mae et al 2003
	Lupinus amandus	ND (aerial) [E]	20 mg/kg i.v.	Lowered SHR MAP by 24.4 mmHg	Guerrero et al 2002
	Moldenhawera nutans	Caingai (stem) [M] {Labd-8}	10 mg/kg i.v.	Lowered conscious and unconscious WR MAP by 17%	Lahlou et al 2007
	Pueraria lobata	Kudzu (vine root) [W]	100 mg/kg i.p.	Lowered conscious SHR SBP by 28 mmHg (HR down 19%) {puerarin}	Song et al 1988
	Retana raetam Forssk.	White weeping broom (leaf) [W]	20 mg/kg/d p.o. for 3 wk	Lowered SBP SHR by 26.5 mmHg from 7 d (increased Na^+, K^+ and Cl^- excretion, and enhanced GFR and diuresis in WKY)	Eddouks et al 2007
	Vigna angularis	Azuki bean (bean) [W]	0.8% in diet for 8 wk	Lowered WKY and SHR SBP by 9 and 28 mm Hg	Sato et al 2008
	Vigna angularis	Azuki bean (bean) [W]	0.9% in diet for 20 wk	Lowered SHR SBP and DBP by 21.1 and 25 mmHg	Mukai & Sato 2009
Ginkgoaceae	*Ginkgo biloba*	Ginkgo biloba (leaf) [W]	2% in diet 3 wk	Attenuated increase in DOCA-salt rats SBP by 40.2 and 19.1 mmHg at 12 and 19 d (no effect on NT)	Umegaki et al 2000
	Ginkgo biloba	Ginkgo biloba (leaf) [W] {EGB 761}	120 mg/kg p.o. for 3 wk	Lowered SHRSP SBP by 48 mmHg	Sasaki et al 2002
	Ginkgo biloba	Ginkgo biloba (leaf) [W]	0.5% of diet 24 d	Lowered rise in DSS rat by 20.8 mm Hg	Kubota et al 2006
Hypoxidaceae	*Hypoxis hemerocallidea*	African potato (corm) [W]	400 mg/kg i.v.	Lowered DSS SBP, MAP and DBP by 79.8, 58.5 and 49.1 mmHg for 45 min (depressed heart rate 61.6%)	Ojewole et al 2006
Lamiaceae	*Ajuga remota*	Blue bugle (leaf) [M]	10 mg/L p.o. for 9 wk	Lowered 1% saline-induced SBP in albino rat by 52.8 mmHg at 6 wk	Odek-Ogunde et al 1993
	Clerodendron colebrookianum	Gloryblower (leaf) [W]	8 mg/kg i.v. alkaloid extract	Lowered WR BP by 30.2 mmHg for 108 s (blocked by atropine)	Gupta et al 1994
	Coleus forskohlii	Coleus herb	0.1-10 mg/kg	Lowered SHR SBP 48-61 mmHg	Lindner et al

		(root) [DCM]	i.v.	{forskolin}(increased HR)	1978
	Marrubium vulgare	White horehound (aerial parts) [W]	80 mg/kg/d p.o. for 5 d	Lowered SHR SBP by 16% (via vascular reactivity)	El Bardai et al 2001
	Marrubium vulgare	White horehound (aerial parts) [W]	80 mg/kg/d p.o. for 14 wk	Lowered SHR SBP by 33 mm Hg	El Bardai et al 2004
	Menthan x villosa	Apple mint (aerial parts) [essential oil, W]	20 mg/kg i.v.	Lowered WR and DOCA-salt rat MAP by 31.4% and 46.2 %	Lahlou et al 2002
	Menthan x villosa	Apple mint (aerial parts) [essential oil by steam]	30 mg/kg i.v.	Lowered WR MAP by 58% (82% lower HR) (blocked by atropine) {piperitenone oxide}	Guedes et al 2004
	Ocimum gratissimum	African (wild) bazil (leaf) [EO]	20 mg/kg i.v. (or eugenol 10 mg/kg)	Lowered NT DOCA-salt rat MAP by 41 % and 59% (slowed HR) (VSM relaxation) {eugenol}	Interminense et al 2005
	Origanum minutiflorum	Oregano (leaf) [W]	100 µl/kg essential oil i.p. {carvacrol}	Lowered L-NAME WR and SHR SBP and DBP by 32 and 64 and 44 and 55 mmHg (decreased HR) {carvacrol}	Aydin et al 2007[4]
	Orthosiphon aristatus	Cat's whiskers (leaf)	100 mg/kg s.c. {as methylripariochromene A}	Lowered SHRSP SBP by 22.4 mmHg at 24 h (reduction in HR, increase in urinary volume and Na^+, K^+ and Cl^- excretion)	Matsubara et al 1999
	Orthosiphon aristatus	Cat's whiskers (leaf) [W,C]	100 mg/kg s.c.	Lowered SHRSP SBP by 28.5 mmHg (reduction in HR) {methylripariochromene A}	Ohashi et al 2000
	Salvia elegans	Mirto (aerial) [E]	10 mg/kg p.o.	Lowered mice angiotensin-induced BP increase (s.c.) by 34.7 mmHg for SBP and 8.8 mmHg for DBP	Jimenez-Ferrer et al 2010
	Salvia miltiorrhiza	Dashen (aerial part) [W]	1 mg/kg/d p.o. for 12 wk	Lowered SHR SBP by 18 mm Hg (ns) at 12 wk	Han et al 2002
	Salvia militorrhiza	Danshen (aerial part) [W]	135 mg/kg p.o. for 3 wk	Lowered SBP in 2K1C rat by 15 mmHg (PAC lower, increased ANP)	Kang et al 2002a
	Salvia militorrhiza	Danshen (root) [E]	381 mg/kg i.v.	Lowered SD rat MAP by 15%	Lam et al 2006
	Salvia militorrhiza	Danshen (root) [E]	10 mg/kg i.p. and tanshinone IIA 60 mg/kg p.o.	Lowered SHR SBP by 58 mmHg and {tanshinone IIA} lowered SBP 26 mmHg (via vasodilation with no effect in WKY)	Chan et al 2009
Lauraceae	*Aniba canelilla*	Rosewood (bark) [essential oil, W]	20 mg/kg i.v.	Lowered WR MAP by 46.2% (HR 63.5% lower)	Lahlou et al 2005
	Cinnamomum burmannii	Indonesian cinnamon (bark) [AA]	8% in diet 4 wk	Lowered SBP of sucrose-induced BP elevation SHR and SHR by 13 mm Hg	Preuss et al 2006
	Ocotea duckei	Louro de cheiro (leaf) [EO]	15 mg/kg i.v.	Lowered WR MAP by 40 mmHg (HR lower 53%)	Barbosa-Filho et al 2008
	Persia Americana Mill	Avacado (leaf) [W]	400 mg/kg i.v.	Lowered WR and DSS rat SBP, MAP and DBP by 82, 73, and 87, and 70, 70, and 63 mmHg	Ojewole et al 2007

Liliaceae	*Aloe barbadensis*	Aloe vera (leaf) [M]	100 mg/kg i.v.	Lowered NT rat MAP by 55.1%	Saleem et al 2001
	Fritillaria ussuriensis	Ping bei mu (bulb) [W]	0.1 mg/kg i.v.	Lowered SD SBP by 40 mmHg	Kang et al 2002b
	Fritillaria ussuriensis	Paemo (bulb) [M]	650 mg/kg/d p.o. for 4 wk	Lowered L-NAME rat SBP to control by ~25 mmHg	Kang et al 2004
	Tulbhagia violacea	Wild garlic (leaf) [W]	50 mg/kg/d i.p.	Lowered DSS rat SBP by 9.1% (decreased renal AT_{1a} gene expression 5 fold)	Mackraj et al 2008b
Loranthaceae	*Globimetula cupulata*	Mistletoe (leaf) [W]	800 mg/kg i.v.	Lowered WR and DSS rat SBP, MAP and DBP by 48.1, 45.2, and 44.2 and 78.1, 65 and 62 mmHg (lowered HR ~ 55% and 54%)	Ojewole, Adewole 2007
	Viscum album L. var. *coloratum* Ohwi	Japanese mistletoe (leaf) [M]	40 mg/kg i.v. and 100 mg/kg p.o.	Lowered cat MAP by 45 mmHg i.v. and SHR by 21.8 mmHg p.o.	Fukunaga et al 1989a
	Viscum album L.	European mistletoe (leaf) [M]	40 mg/kg i.v. and 100 mg/kg p.o.	Lowered cat MAP by 55 mmHg i.v. and SHR by 18.2 mmHg p.o. at 24 hr	Fukunaga et al 1989b
	Viscum album	European mistletoe (stem) [E]	0.001 mg/kg i.v.	Lowered WR MAP by 23.6 mmHg	Radenkovic et al 2009
Lythraceae	*Punica granatum*	Pomegranate (fruit) [W]	50 ml/d p.o. for 2 wk	Lowered HHT SBP by 8 mmHg	Aviram, Dornfield 2001
Malvaceae	*Hibiscus sabdariffa*	Roselle (flower) [W]	20 mg/kg i.v.	Lowered SD rat MAP by 30.9 mmHg	Adegunloye et al 1996
	Hibiscus sabdariffa	Roselle (petal) [W]	250 mg/kg p.o. for 8 wk	Attenuated SD 2K1C increase in SBP by 34.4 mmHg	Odigie et al 2003
	Hibiscus sabdariffa	Roselle (calyx) [W]	125 mg/kg i.v.	Lowered 8% salt, L-NAME and control WR MAP by 94.4, 136.5, and 10.3 mmHg	Mojiminiyi et al 2007
	Gossypium barbadense	Pima cotton (leaf) [W]	~ 2 mg/kg i.v.	Lowered WR BP by 36 mmHg	Hasrat et al 2004
Meliaceae	*Azadirachta indica*	Neem tree (leaf) [W]	20 mg/kg p.o.	Prevented development of increase in MAP in DOCA-salt rats by 28 mmHg	Obeifuna, Young 2005
	Ekebergia capensis Sparrm	Cape ash (leaf) [E]	18 mg/kg i.v. and 120 mg/kg p.o. 4 wk	Lowered MAP acutely in NT rat by 9 mmHg and chronically at 2-4 wk in DSS rat by 14.2-18.7 mmHg	Kamadyaapa et al 2009
Menispermaceae	*Stehania tetrandrae*	Stephania root (root) [W]	150 mg/kg/d p.o.	Lowered DOCA-salt rat BP from 2 d to 9 wk	Wong et al 2000
	Stehania tetrandrae	Stephania root (root) [DMSO,W]	150 mg/kg/d p.o. 9 wk	Lowered DOCA-salt rat SBP by 63 mmHg at 9 wk (similar for tetrandine)	Yu et al 2004
Moraceae	*Cudrania tricuspidata*	Chinese mulberry (stem) [M]	720 mg/kg p.o. for 2 wk	Lowered SD L-NAME SBP by 17 mmHg	Kang et al 2002c
	Dorstenia psilurus	Common dorsteria (root) [M,DCM]	200 mg/kg p.o. for 3 wk	Lowered WR fructose-fed BP by 23 mmHg	Dimo et al 2001
	Ficus exasperate	Sandpaper leaf	30 mg/kg i.v.	Lowered WR MAP by 38.3	Ayinde et al

		tree (leaf) [W]		mmHg	2007
	Morus bombycis Koidzumi	Silkworm mulberry (root bark) [W,E,M]	100 mg/kg po. 42 days	Lowered SHR SBP by ~ 20 mmHg	Oh et al 2007
	Musanga cecropioides	Umbrella tree (stem bark) [W]	5 ug/kg i.v.	Lowered SD SBP by 54%	Adeneye et al 2006
Moringaceae	*Moringa oleifera*	Drumstick tree (leaf) [E]	10 mg/kg i.v. extract (or 3 mg/kg fraction)	Lowered WR MAP by 56.9% (niaziminin A and B, lowered MAP 37.5% and 40.3%)	Faizi et al 1994
	Moringa oleifera	Drumstick tree (pod) [E]	30 mg/kg i.v. and 10 mg/kg PBA	Lowered WR MAP by 41% and 75% {p-hydroxybenzoate}	Faizi et al 1998
Myrtaceae	*Eugenia uniflora* L	Surinam cherry (leaf) [W]	6 mg/kg i.p.	Lowered WR BP by 47%	Consolini et al 1999
	Pigmentua diocia	Allspice (fruit) [W]	100 mg/kg i.v.	Lowered BP in SHR ED_{50} 45 mg/kg (diminished with hexamethonium)	Suarez et al 2000
	Psidium guajava Linn.	Apple guava (leaf) [W]	800 mg/kg i.v.	Lowered DSS rat SBP, MAP and DBP by 66.8, 56.9, and 56.2 mmHg	Ojewole 2005
Oleaceae	*Fraxinus excelsior*	European ash (seed) [W]	20 mg/kg/d p.o. for 3 wk	Lowered SHR SBP by 38 mmHg from 7 d to 21 d (increased urination and Na^+, K^+ and Cl^- excretion in WKY and SHR)	Eddouks et al 2005
	Olea africana	African olive (root, stem bark) [W]	70 mg/kg i.v. and 100 mg/kg/d p.o.	Lowered WR MAP by 22% i.v. and DOCA-salt 23 mmHg p.o.	Osim et al 1999
	Olea eurpaea L	Olive (leaf) [E] {EFLA®943}	100 mg/kg/d p.o for 6 wk	Lowered L-NAME (50 mg/kg for 12 wk) induced rise in BP in WR at 4 wk 100%	Khayyal et al 2002
	Syringa vulgaris	Lilac (flower) [W]	10 mg/kg i.v.	Lowered WR MAP for 2-3 min (lowered HR) {acetoside}	Ahmad et al 1995
Orchidaceae	*Laelia autumnalis*	Autumn flowering laelia (whole plant) [W]	100 mg/kg p.o.	Lowered WR DBP, SBP and MAP by ~ 20% (lowered HR by ~14%) (blocking Ca^{2+} channels)	Vergara-Garcia et al 2008
Passifloraceae	*Passiflora edulis*	Passion fruit (rind) [M]	50 mg/kg p.o.	Lowered SHR SBP by 28 mm Hg at 1 h for 6 h (not WKY) (luteolin)	Ichimura et al 2006
Pedaliaceae	*Sesamum indicum*	Sesame (sesamin, 1%) [na]	1% sesamin in diet 5 wk	Lowerred DOCA-salt rat SBP by 46 mmHg (lower O_2^-)	Nakano et al 2003
Pinaceae	*Pinus maritime* Lam	French maritime pine (bark) [E] {Flavagenol, Pyenogenol}	0.1% Flavagenol in diet	Lowered SBP in DOCA-salt rat by 26 mmHg at 5 wk	Kwak et al 2009
Poaceae	*Andropogon muricatus* Retz.	Cuscus grass (aerial parts) [W]	50 mg/kg i.v.	Lowered SD MAP by 56% (Ca^{2+} channel blocking?)	Gilani et al 2007
Polygalaceae	*Bredemeyera floribunda*	ND (root) [E]	76 mg/kg i.v.	Lowered rat SBP and DBP by 75 and 58 mmHg	Bevevino et al 1994
Rosaceae	*Crataegus tanacetifolia*	Hawthorn (leaf) [W]	100 mg/kg/d p.o. 4 wk	Lowered L-NAME WR MAP by 12 mm Hg (hyperoside by 42 mmHg)	Kocyildiz et al 2006
	Geum japonicum	Large leaf Avens	2.5 mg/kg i.v.	Lowered SHR SBP and DBP by	Xie et al 2007

		(whole plant) [A]		38% and 51% for 30 min (NO mechanism)	
Rubiaceae	*Coffea arabica*	Green coffee (bean) [W]	750 mg/kg p.o. or 1% diet 6 wk	Lowered SHR SBP by 12% at 12h and 32 mmHg at 6 wk (no effects in WKY)	Suzuki et al 2002
	Pavetta crassipes	Vikuyu (leaf) [E]	1-32 mg/kg i.v.	4 mg/kg lowered WR and cat MAP by 36.7 and 32.5 mmHg (blocked by propanolol)	Amos et al 2003
	Uncaria macrophylla	Cat's claw, Gouteng (leaf) [W] {total alkaloid}	20 mg/kg i.v.	Lowered unconscious dog MAP by 32 mmHg (lowered HR)	Lui et al 1983
	Uncaria rhynchophylla	Cat's claw, Gouteng (leaf) [W]	6 mg/kg i.v. indole alkaloids	Lowered WR MAP by 21%, 16%, 15% and 18% {as hirsitune, hirsuteine, ryhnchophuline, and isorhynchophylline} (decrease in HR)	Ozaki 1989
	Uncaria rhynchophylla	Cat's claw, Gouteng (leaf) [W] {total alkaloid}	50 mg/kg p.o. for 20 d.	Lowered SHR MAP by 24 mmHg at 15 d {total alkaloid}	Lui et al 1990
Rutaceae	*Casimiroa edulis*	Custard apple (seed) [M]	1 g/kg of fractions containing histamine deriv and aa i.v.	Lowered WR MAP by > 50 mmHg	Magos et al 1999
	Citrus paradisi	Grapefruit (peel) [E]	8 μg/kg canine heart-lung preparation and N.D. p.o. NT HT humans	Lowered control and L-NAME dog MAP by 6.2 and 17.1 mmHg and NT and HHT SBP and DBP by 25 and 30 and 25 and 10 mmHg	Diaz-Juarez et al 2009
Sapotaceae	*Mimusops elengi*	Bullett wood (leaf) [M]	16 mg/kg iv	Lowered NT rat MAP by 38%	Dar et al 1999
Saururaceae	*Saururus chinensis*	Chinese lizard's tail [H,E,W]	100 mg/kg p.o. 14 d	Lowered SHR SBP by ~ 20 mmHg	Ryu et al 2008
Solanaceae	*Solanum indicum*	African nightshade (fruit) [E]	300 mg/kg/d po	Lowered L-NAME rat increase in SBP pre and post by 80%	Bahgat et al 2008
	Solanum sisymbriifolium	Sticky nightshade (root) [E, W]	100 mg/kg i.v. and p.o	Lowered ARH+DOCA HT WR SBP and DBP by 70% and 80% in i.v. and to 83% BP p.o. at 4 h	Ibarola et al 1996
	Vitis labrusca	Fox (red) grape (skin) [W, E]	100 mg/kg/d p.o. for 4 wk	Lowered L-NAME and DOCA-salt WR SBP, MAP and DBP by 28, 35 and 28 and 11, 9 and 7 mmHg at 4 wk	Soares de Moura et al 2002
	Vitis vinifera	French red wine (wine) [W]	50 mg/kg p.o. polyphenols	Stopped progression of fructose-fed rat rise in BP by 22 mmHg	Al-Awwadi et al 2005
	Vitis vinifera	Red grape (seed) [E]	100 mg/kg GSE p.o. 45 d	Suppressed 100 ppm Pb-induced increase in WR SBP by ~ 18.8 mmHg	Badavi et al 2008
	Vitis vinifera	Red grape (seed)	100 mg/kg/d p.o. 45 d	Attenuated WR lead-induced increase of SBP by ~ 21 mmHg	"

Sterculiaceae	*Guazuma ulmifolia*	West Indian elm (bark) [A]	50 mg/kg i.v. or 10 mg/kg p.o.	Lowered sugar-fed WR MAP 71 mmHg i.v. and fed procyanidin fraction decreased L-NAME SBP by 78 mmHg p.o.	Magos et al 2008
Ulmaceae	*Ulmus macrocarpa*	Large-fruited Elm (root bark) [E]	100 mg/kg/d p.o. for 42 d	Decreased SHR SBP by ~ 20 mmHg (or 39 mmHg c.f. SHR)	Oh et al 2008
Verbanaceae	*Clerodendron clebrookianum*	Gloryblower (leaf) [alkaloidal extract,W]	8 mg/kg i.v.	Lowered WR MAP by 30.2 mmHg	Gupta et al 1994
	Clerodendron trichotomum	Gloryblower (leaf) [W,E]	0.5 g/kg/d p.o. for 6 wk	Lowered SHR SBP by 14 mmHg	Lu et al 1994
	Vitex doniana	Black plum (stem bark) [W]	0.8 mg/kg i.v. or 200 mg/kg p.o.	Lowered WR and SHR MAP i.v. by 9 and 17 mmHg i.v. after 5 min and by 16 and 21 mmHg p.o. after 30 min	Ladeji et al 1996
Zingiberaceae	*Alpinea zerumbet*	Glooryblower (leaf) [W]	20 mg/kg and terpinen-4-ol 10 mg/ml i.v.	Extract {and Trp-4-ol} lowered NT and DOCA-salt rat MAP by 37.7% and 53.6% and 32.9% and 50.8%	Lahlou et al 2003
	Alpinea zerumbet	Colonia (leaf) [E,W]	50 mg/kg/d p.o. in water 28 d	Lowered DOCA-salt rat SBP, MAP and DBP by 32, 26 and 23 mm Hg at 28 d	Soares de Moura et al 2005
	Curcuma longa	Tumeric (rhizome) [M]	30 mg/kg i.v.	Lowered WR MAP by 31.5%	Adaramoye et al 2009
	Elettaria cardamomum	Ceylon cardamom	100 mg/kg i.v.	Lowered WR MAP of 52.6% (partial block with atropine)	Gilani et al 2008
	Zingiber officinale Roscoe	Ginger (rhizome) [M]	10 mg/kg i.v.	Lowered SD arterial BP by 46.9%	Ghayar, Gilani 2005
	Zingiber officinale Roscoe	Ginger (rhizome) [W]	10 mg/kg i.v.	Lowered SD MAP by 46.9% (blocked by atropine)	Ghayur et al 2005
Zygophyllaceae	*Tribulus terrestris*	Puncturevine (fruit) [W]	10 mg/kg/d p.o. for 4 wk	Lowered 2K1C rat SBP to control by 67.5 mmHg	Sharifi et al 2003
	Zygophyllum coccineum	Kammun (whole plant) [C, M,W]	5 mg/kg i.v.	Lowered WR MAP 113 mmHg (reduced HR by 39 bpm) (via membrane hyperpolarization)	Gibbons & Oriowo 2001

[1]Common English name or name from the country of origin is used and the part of the plant where most activity was described.

[2]The solvent denoted is the one that gave the highest inhibition.

[3]Tradename of extract or product, or particular fraction of plant.

[4]Carvacrol is up to 92% of the essential oil from *Origanum minutiflorum*.

Abbreviations: 2K1C, two kidney one clip Goldblatt renovascular hypertensive; A, acetone; aa, amino acid; AA, acetic acid; ANP, plasma atrial natriuetic peptide; ARH+DOCA, adreanal

regeneration hypertension plus deoxycorticosterone acetate treated; AT_{1a}, angiotensin type 1a receptor; B, butanol; CAS, coronary artery stenosis; CGA, chlorogenic acid fraction; derive, derivative; DW, drinking water; DSS, Dahl salt sensitive; E, ethanol; EO, essential oil; GABA, γ-amino butryric acid; GFR, glomerular filtration rate; H, hexane; HHT, human hypertensive patients; i.d., intraduodenal; i.p., intraperitoneal; L-NAME, L-N^G-nitroarginine methyl ester; M, methanol; ND, not determined; NHE-1, sodium hydrogen exchanger-1 isoform; NT, normotensive rat; PAC, plasma aldosterone concentration; PBA, *p*-hydroxybenzylaldehyde; SHR, spontaneous hypertensive rat; SBP, systolic BP; STZ, streptotozotocin; SD, Sprague-Dawley; W, water; WKY, Wistar Kyoto rat; WR, Wistar rat; ns, not significant.

Table 6. Summary of plant taxonomic families and individual species producing blood pressure lowering effects in humans.

Family	**Species**	**Common name(s) (part)[1] [solvent][2] {Tradename, fraction}[3]**	**Dose and route of administration**	**Effect (mechanism) {bioactive}**	**Reference**
Acanthaceae	*Strobilanthes cusia*	"D aching yeh" (leaf) [W]	ND	Lowers human SBP ND {4(3H)-quinazoline}	Li et al 1993
Alliaceae	*Allium satvium*	Garlic (clove powder) [W] {Allicor, Kwai}	600 or 900 mg/d p.o. Allicor or Kwai	Allicor lowered HHT SBP and DBP by 7 and 3.8 mmHg; Kwai lowered SBP 5.4 mmHg	Sobenin et al 2009
Apocynaceae	*Apocynum venetum*	Dogbane (leaf) [W]	0.75 g/d of extract as decoction for 8-12 wk	Lowered HHT SBP and DBP by 23 and 7 mmHg	Ma & Chen 1989
	Rauwolfia serpentina	Snakeroot (root) [W]	40 mg/d p.o. for 2 mo (Roxinil)	In responsive HHT (67%) lowered SBP and DBP both by 15 mmHg	Moyer et al 1955
Asteraceae	*Achillea wilhelmsii*	Yarrow (aerial parts) [E]	~ 250 mg/d day p.o.	Lowered HHT SBP and DBP by 14.1% and 14.7%	Asgary et al 2000
	Stevia rebaudiana	Sweetleaf (leaf) [W]	500 mg/d p.o for 2 yr	Lowered HHT SBP and DBP by 10 and 6 mmHg (no effect on HR) {stevioside}	Hsieh et al 2003
Brassicaceae	*Armoracia rusticana*	Horseradish (root) [W,E]	~ 3.0 g/d p.o. for 6-8 wk	Lowered 7 HHT SBP by > 30 mmHg	Malm 1951

Chlorellaceae	*Balsamodendron mukul*	Indian bedellium (gum) [W]	1.5 g/d p.o. ± 10 mg/d nifedipine	Lowered HHT SBP and DBP ± nifedipine after 42 d by 20.2 and 8.9 and 26.8 and 15.7 mm Hg	Panneerselvam et al 2005
Fabaceae	*Astragalus adsurgens*	Standing milkvetch	10 mg/kg i.v.	Hypotensive in WR {GABA at 0.1%}	Hikino et al 1976
	Hedysarum polybotrys	Sweetvetch (root) [M]	10 mg/kg i.v.	Hypotensive in WR {GABA at 0.1%}	Hikino et al 1976
Lamiaceae	*Coleus forskohlii*	Coleus herb (root) {DCM}	0.5-3 μg/kg/min i.v. over 2 h	Lowered human idiopathic congestive cardiomyopathy patient SBP, DBP and MAP by 50% {forskolin} (increased cardiac output)	Baumann et al 1990
Lythraceae	*Punica granatum*	Pomegranate (fruit) [W]	Juice p.o. for 12 mo	Lowered CAS patients SBP by 21 mmHg	Aviram et al 2004
Malvaceae	*Hibiscus sabdariffa*	Roselle (flower) [W]	Two teaspoons blended tea (sour tea) p.o. for 15 d	Lowered HHT SBP and DBP by 17.6 (11.2%) and 10.9 mmHg (10.7%) at 12 d	Faraji, Tarkhani 1999
	Hibiscus sabdariffa	Roselle (calyx) [W]	10 g/d p.o. (anthocyanins 9.6 mg) 4 wk	Lowered HHT SBP and DBP by 15.3 and 11.3 mmHg	Herrera-Arellano et al 2004
	Hibiscus sabdariffa	Roselle (calyx) [W]	250 mg/d (of total anthocyanidin) p.o. for 4 wk	Lowered HHT SBP and DBP by 17.1 and 12.0 mmHg	Herrera-Arellano et al 2007
Oleaceae	*Olea europaea*	Olive (virgin oil) [none]	60 g/d p.o. for 4 wk	Lowered treated elderly HHT SBP by 14 mmHg	Perona et al 2004
	Olea eurpaea L	Olive (leaf) [E] {EFLA®943}	1 g/day p.o.	Lowered borderline HHT SBP and DBP by 5 and 13 mmHg at 8 wk	Perrinjaquet-Mocceei et al 2008
Orchidaceae	*Rhizoma gastrodiae*	"Tian ma" (tuber) [W]	1000 mg i.v.	Lowered refractory HHT SBP 12 mmHg {gastrodin}	Zhang et al 2008
Ranunculaceae	*Nigella sativa*	Fennel flower (seed) [W]	200 mg twice per day p.o.	Lowered human SBP and DBP 2.2 and 1.8 mmHg at 8 wk	Degkordi, Kamkhah 2008
Rosaceae	*Crataegus curvisepala* Lind	English hawthorn (leaf and flower) [E]	60 drops per d (~ 3 mg flavanoids) p.o. for 4 mo	Lowered HHT SBP and DBP by 9 and 5 mmHg	Asgary et al 2004
	Crataegus laevigata	Hawthorn (flower top) [W] {Faros® 600}	1200 mg/d p.o.	Lowered treated diabetic human DBP by 2.6 mmHg	Walker 2006
Rubiaceae	*Coffea arabica*	Green coffee (bean) [W}	185 mg/d p.o. for 28 d	Lowered mild HHT SBP and DBP by 5.6 and 3.9 mmHg	Kozuma et al 2005
	Coffea arabica	Green coffee (bean) [W, CGA]	140 mg/d CGA p.o. for 12 wk	Lowered mild HHT SBP and DBP by 9.7 and 2.3 mmHg {chlorogenic acid}	Watanabe et al 2006
Solanaceae	*Lycopersicon esculentum*	Tomato extract (fruit) [encapsulated]	Paste capsules 250 mg/day p.o.	Lowered HHT SBP and DBP by 10 and 4 mmHg	Engelhard et al 2006
	Lycopersicon esculentum	Tomato extract (fruit)	One 250 mg capsule (15 mg	Lowered treated HHT SBP and DBP (capsule–placebo) 13.6 and	Paran et al 2009

		{Encapsulated, Lyc-O-Mato®}	lycopene)/d p.o.	4.2 mmHg or (placebo-capsule) 11.7 and 5.9 mmHg	

[1]Common English name or name from the country of origin is used and the part of the plant where most activity was described.

[2]The solvent denoted is the one that gave the highest inhibition.

[3]Tradename of extract or product, or particular fraction of plant.

Abbreviations: CAS, corony artery senosis; CGA, chlorogenic acid; DBP, E, ethanol; diastolic blood pressure; p.o., HHT, human hypertensive; M, methanol; ND, not determine; per oral; SBP, systolic blood pressure; W, water.

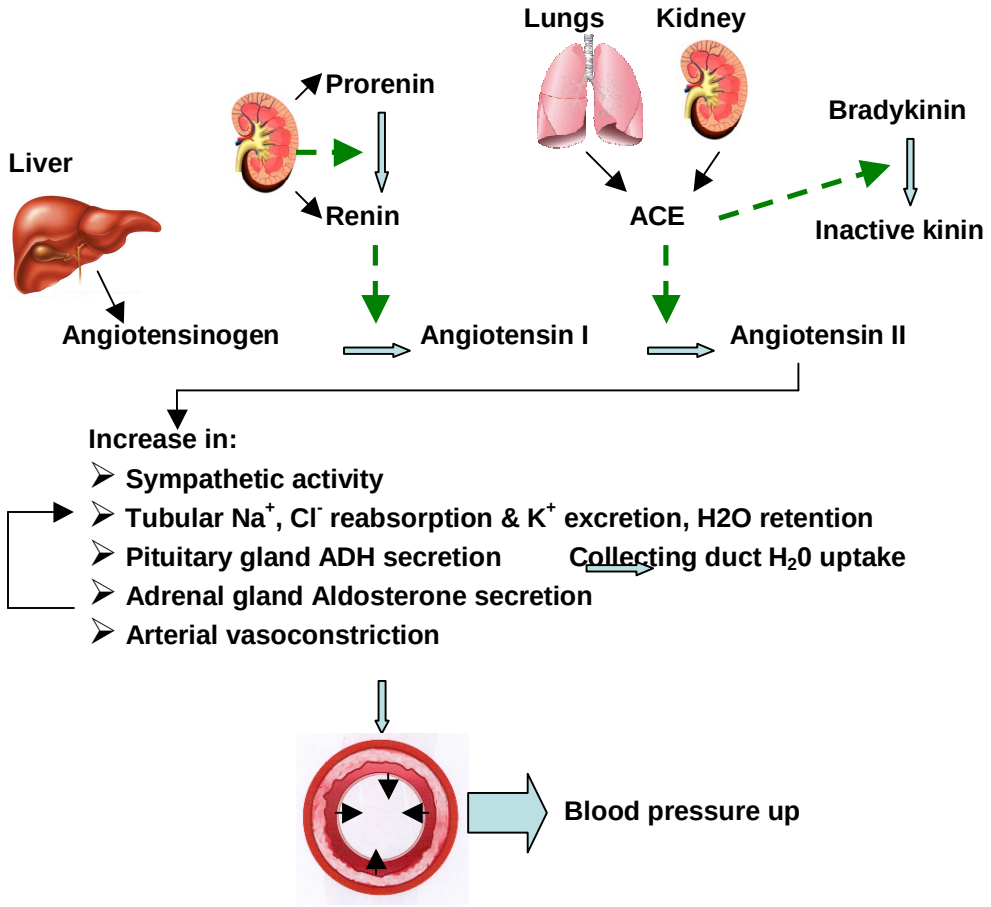

Figure 1. Diagramatic representation of the renin-angiotensin-aldosterone system (RAAS). The key enzymes are renin which converts angiotensinogen from the liver to angiotensin I and ACE from the endothelial tissue of lungs and kidneys which converts angiotensin I to angiotensin II and deactivates the hypotensive agent bradykinin. Angiotensin II has pleotropic effects on mammalian physiology leading to feed back mechanisms with antidiuretic hormone (ADH, or vasopressin) and aldosterone which lead to increased water and salt retention, arterial vasoconstriction and an increase in arterial blood pressure. Plant extracts and isolated bioactives

can inhibit at many stages of the RAAS system, and interact at the sympathetic, neuroendocrine and autocrine levels to effect changes in blood pressure.

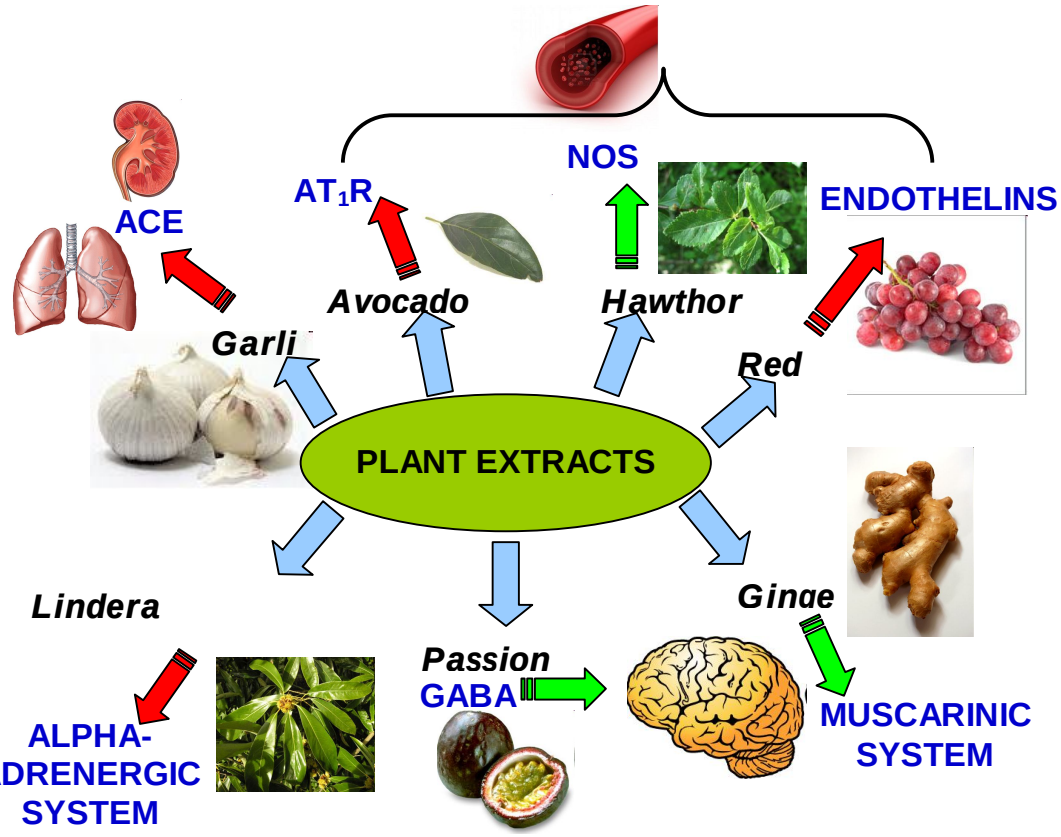

Figure 2. Schematic of plant extracts that may influence various biological systems and lower blood pressure. The red non-continuous arrows leading from a specific plant extract (in italics) indicate inhibition or blockade of a system (in blue) involved with blood pressure regulation whereas the green non-continuous arrows indicate addition or stimulation of a particular system. The extracts may work via the central nervous system or at endothelial or muscular tissue receptors of vascular vessels causing vasorelaxation and a lowering of blood pressure. Some plant extracts may also work at various sites to influence blood pressure, even with opposing effects, such as red grape seed or skin extracts rich in polyphenols which can also

inhibit ACE activity thus limiting the production or circulating angiotensin II. Abbreviations: ACE, angiotensin converting enzyme; AT_1R, angiotensin receptor type-1; GABA, gamma aminobutyric acid; NOS, the nitric oxide synthase system.

