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Exploring the Anti-Hypertensive Properties of Medicinal Plants and Their Bioactive Metabolites: An Extensive Review

Md. Moaz Ahmed Asif[1*], Susmita Roy Lisa[1*], Nazmul Qais[2#]

[1]Department of Pharmaceutical Chemistry, Faculty of Pharmacy, University of Dhaka, Dhaka, Bangladesh
[2]Department of Clinical Pharmacy and Pharmacology, Faculty of Pharmacy, University of Dhaka, Dhaka, Bangladesh
Email: #nqais@du.ac.bd

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Abstract

Medicinal plants are extensively used in traditional folk medicine. High blood pressure is associated with the risk of cardiovascular diseases (CVDs) and many other serious health complications resulting from it as a major concern of morbidity and mortality in health sector. Use of diuretics, angiotensin converting enzyme (ACE) inhibitors, beta adrenergic receptor antagonists (beta blockers), alpha adrenergic receptor antagonists (alpha blockers), calcium channel blockers (CCBs) etc. are not efficient enough to cure hypertension. Side effects regarding these medications lead to intolerance, impaired control of the disease, and also mismanagement of therapy. So, approach regarding quenching new potent therapeutic compounds from medicinal plants draws attention nowadays. For example, as a first-line therapeutic agent, an alkaloid is highly effective in lowering systolic blood pressure which is isolated from root extract of the plant of *Rauwolfia serpentina* species, namely reserpine. This article comes up with a list of 63 plant species from 37 families, compiling information related to plant parts used for making extracts, types of extract and animals used in these studies, antihypertensive effect of the extracts etc. It also refers to 74 chemically defined molecules, with *in vitro* and *in vivo* anti-hypertensive potential, isolated from these extracts along with their dosage and mechanism of action by using electronic searches of published articles from various databases and reference books. Our present work would be beneficial for researchers to investigate and invent novel anti-hypertensive therapy to treat hypertension.

*Co-first authors.
#Corresponding author.

Keywords

Hypertension, Anti-Hypertensive, Phytoconstituents, Medicinal Plants, Angiotensin Converting Enzyme, Nitric Oxide

1. Introduction

The definition of hypertension (HTN) is when office systolic blood pressure (SBP) and/or diastolic blood pressure (DBP) is equal or greater than 140 mmHg, and 90 mmHg respectively [1]. HTN is often called "the silent killer". If HTN is left untreated, end organ damage may occur [2]. People with elevated blood pressure (BP) may face some major risk of being affected by coronary artery disease with the following complications e.g., blindness in diabetic patients, heart failure, renal diseases, and stroke [3]. 972 million people had HTN in 2000 and this number was predicted to be about 1.56 billion in 2025 [4]. Obesity, unhealthy diet, tobacco use, physical inactivity, and HTN are some factors that increase the risk of CVDs [5]. Reducing SBP by 5 mmHg is shown to lower mortality rate by 9%, 14%, and 7% respectively for coronary heart disease, stroke, and in total [6].

Until now, there are different antihypertensive therapies available, such as: ACE (classified as EC3.4.15.1) inhibitors, angiotensin receptor blocker (ARB), beta blockers, diuretics, and also CCBs [7] [8]. They show their antihypertensive effect by controlling cardiac output (CO) (affecting stroke volume and heart rate), and peripheral or systemic vascular resistance.

Impairment in production of nitric oxide (NO) is a very common reason behind endothelial dysfunction, which leads to HTN [9] [10]. **Figure 1** shows that, endothelial NO synthase (eNOS) produces NO from L-arginine in the blood vessels to control cardiovascular function [11]. High BP was induced due to chronic blocking of NO after administrating Nω-Nitro-l-arginine methyl ester (l-NAME) depending upon dose and time [12]. l-NAME contributes to endothelial dysfunction in resistant vessels by decreasing metabolites of NO present in plasma and downregulating expression of eNOS protein [13].

Oxidative stress also promotes HTN pathogenesis [15]. In a rat model of NO depletion-induced hypertension, excess reactive oxygen species (ROS) and declined amount of endogenous antioxidant enzymes have been found [16]. High amount of vascular superoxide (O_2^-), malondialdehyde (MDA), and plasma protein carbonyl were found in NO deficient hypertensive rats [17] [18]. O_2^- quenches NO to produce peroxynitrite ($ONOO^-$) directly and decreases NO bioavailability [19].

Again, l-NAME causes overproduction of ROS and activates the renin-angiotensin system (RAS) [20] [21]. Angiotensin II (Ang-II) is a potential vasoconstrictor and for that as shown in **Figure 2**, RAS is a compulsory factor in pathogenesis of HTN [22]. Renin is released by renal artery constriction and Ang-II

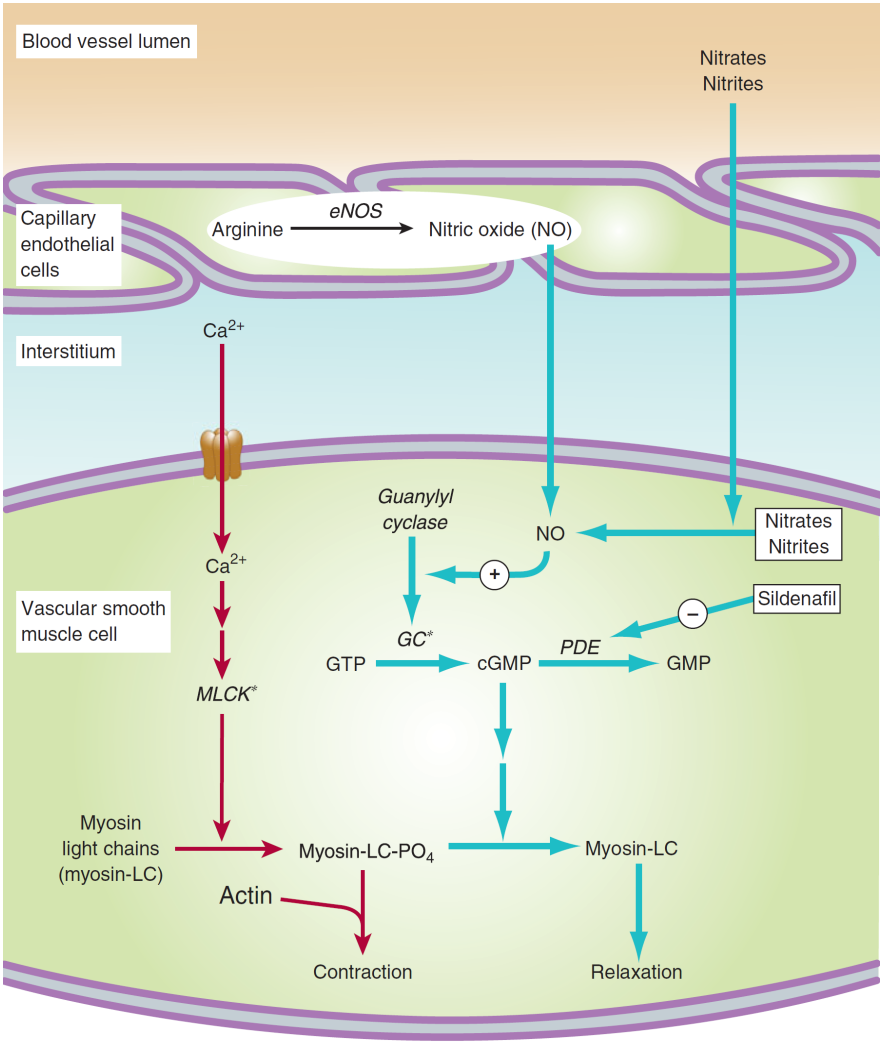

Figure 1. The mechanism of action of Nitrates, and nitrites that increase NO in vascular smooth muscle cells (VSMC). Steps producing vascular contraction are presented with red arrows, and those causing vascular relaxation are displayed with blue arrows [14]. MLCK* = activated myosin light-chain kinase; GC* = activated guanylyl cyclase or guanylate cyclase; PDE = phosphodiesterase.

production is increased by activating RAS in NO deficient hypertensive rats [23] [24]. In l-NAME treated rats, Ang-II stimulates the Ang-II type 1 receptor (AT_1R) which produces O_2^- activated by nicotinamide adenine dinucleotide phosphate (NADPH)-oxidase [13]. Elevated ACE, cardiac and plasma Ang-II, and AT_1R expression also confirmed RAS stimulation in those above-mentioned rats [25].

RAS is also a vital factor because chronic NO inhibition results in arterial remodeling and AT_1R blockers prevent that [26]. Vascular remodeling occurs by Ang-II binding to AT_1R and activating serine/threonine kinase (Akt), one of its own intracellular downstream signaling protein responsible for Ang-II driven proliferation in VSMC [27]. Signal transducers and activators of transcription protein get phosphorylated by Janus kinases induced by AT_1R activation that causes vascular proliferation and remodeling [28].

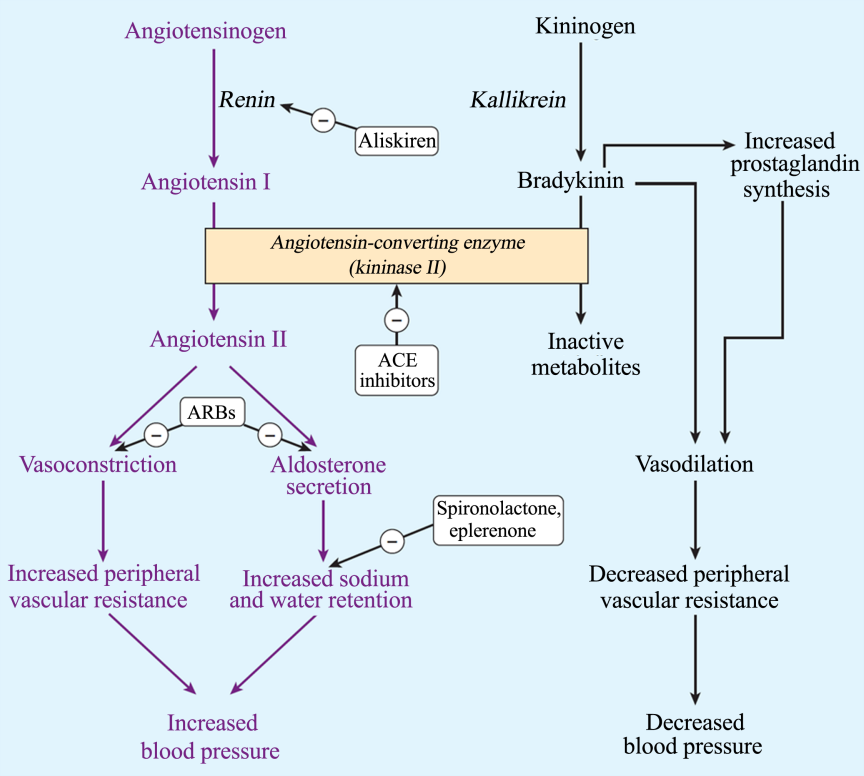

Figure 2. Sites of action of drugs that interfere with the RAS, also known as the renin-angiotensin-aldosterone system (RAAS) [14].

Despite using these agents, many patients cannot control their high BP [29]. HTN cannot be effectively managed in about 30% of the patients who comply with prescription therapies [30]. The available antihypertensive agents are not successful in all the cases along with disease severity [31]. These agents are categorized as combination therapy, costly and their ambiguous regimen of cure decreases drug adherence and may also surge adverse effects as well as drug interactions [32]. Among these, ACE inhibitors cause bronchospasm and cough [33]; ACE inhibitors and CCBs can cause angioedema with upper respiratory tract obstruction [34]; CCBs also increase the risk of cancer by inhibiting the growth of vascular cells and angiogenic growth factors due to increasing apoptosis [35]; beta blockers induce side effects related to central nervous system [36]. Dyspnea, headache, edema, cough, hair loss, and flushes are also reported as side effects of antihypertensive drugs [37]. So, the acceptance of alternative therapy is increasing day by day, as natural herbal products using medicinal plants show fewer side effects [38]. Numerous of them have the potential for therapy of CVDs including, HTN, arrhythmia, and venous insufficiency [39].

The goal of our work is to accumulate various phytoconstituents that exhibit *in vitro* and *in vivo* antihypertensive effects so that they can be used to make safe, patient-adhered, low-cost antihypertensive therapy with preferable minimum side effects. Combination of these natural compounds can also be therapeutic as more than one compound, responsible for antihypertensive effect, are

often found in extracts. Our review includes 63 species of plants from 37 family, plant parts used for making extracts, types of extract and animals used for these experiment, antihypertensive effect of the extracts as well as 74 confirmed anti-hypertensive compounds isolated from these extracts with their dosage and mechanism of action.

2. Discussion about Promising Anti-Hypertensive Plants

Herbal medicine is a tremendous source for seeking out novel therapeutic compounds for numerous diseases. The idea of generating medicine from scratch had originally come out from the traditional uses of herbs and plants by our fellow ancestor to cure many of their ailments. Herbal medicines are quite preferable among people for its significantly low side effects and also the belief regarding nature made.

Traditional use of some plants like *Cocos nucifera* Linn (Arecaceae), *Curcuma domestica* (Zingiberaceae), *Terminalia bellerica* Roxb. (Combretaceae) etc. are well known for treating HTN. Aim of this article is highlighting and compiling the data regarding chemo-profiles, pharmacology of various plant species used to treat HTN. Information regarding plant species is collected from online resources and journals such as PubMed, Google Scholar, SciFinder, ScienceDirect and so on. Table 1 illustrates a comprehensive overview of phytoconstituents, dosage, use, extracts of potential medicinal plants with prominent anti-hypertensive activity.

Among the described compounds, we think four of the compounds were therapeutically efficient. The first one, tilianin which is derived from *Agastache mexicana*, demonstrated dose-dependent anti-hypertensive effects, with an ED_{50} of 53.51 mg/kg which was lower than the LD_{50} of 6624 mg/kg, offers a wide spectrum of pharmacology responses. In addition, this study provides evidence about safety and efficacy of tilianin as antihypertensive agent, as well as, claims of no damage at physiologic, functional and cellular levels in rodent models [41]. The next one is naringenin, isolated from *Cochlospermum vitifolium*, exhibit a statistically significant dose-dependent decay on SBP (control: 184.00 mmHg vs. sample: 154.93 mmHg) after 24 h post-administration at 50 mg/kg, and also, a significant decrease of SBP (control: 184.00 mmHg vs. sample: 142.64 mmHg) and DBP (control: 159.62 mmHg vs. sample: 122.05 mmHg) at 160 mg/kg [55]. Curcumin nanoemulsion is our favorite choice, prepared from *Curcuma domestica* and having a 71.166% inhibition (after corrections) on HMGCR (a liver enzyme that contributes to cholesterol synthesis) to assess antihypercholesterolemic activity when compared to pravastatin. Curcumin:

1) Inhibits hepatic HMG-CoA activity and lowers HMGR gene expression (that produces the HMG-CoA enzyme).

2) Suppresses triglyceride and cholesterol accumulation in the liver due to its antihyperlipidemic properties.

3) Enhances PPARα gene expression that regulates fatty acid oxidation.

Table 1. Anti-hypertensive plant species with isolated phytochemicals and their mechanism of action.

Plant (Family)	Plant Parts, Type of extract	Animal used	Isolated Antihypertensive Phytochemicals	Use and Dosage	Mechanism of action	Citation
Acanthopanax sessiliflorus (Araliaceae)	Fruits, Ethanolic extract	Male Wistar rats	3(a) 22α-hydroxychiisanoside 3(b) 22α-hydroxychiisanogenin 3(c) chiisanoside 3(d) chiisanogenin 3(e) momordin Ib (**Figure 3**)	*In vivo* antithrombotic and antiplatelet activities. 125, 250, 500 and 1000 mg/kg/day.	Ethanolic extracts from *A. sessiliflorus* showed effects by 1) scavenging free radical 2) NO production facilitation 3) inhibition of ACE	[40]
Agastache mexicana (Lamiaceae)	Aerial parts, Methanolic extracts and EtOH: H_2O (7:3) extracts	Male Wistar rats	3(f) tilianin (**Figure 3**)	Vasorelaxant activity. 12.5, 25, 75, 100 mg/kg. 6624 mg/kg is the lethal dose.	Tilianin isolated from methanolic extract of *A. mexicana* exhibited endothelium-dependent vasorelaxant effect by 1) NO production and 2) opening K^+ channel	[41]
Allanblackia floribunda Oliv. (Clusiaceae)	Bark, Aqueous extract.	Sucrose-induced hypertensive rats (SuHR), Alcohol-induced hypertensive rats (AHR)	Not reported	Prevention of HTN in rats induced by alcohol, sugar, and also oxidative stress. Aqueous extract of 200 and 400 mg/kg/day.	Extract of *A. floribunda* Oliv. significantly impeded 1) the upsurge of MDA, superoxide dismutase (SOD), catalase 2) the decrease of glutathione in kidney, liver, aorta, and heart of SuHR and AHR.	[42]
Alstonia scholaris (Apocynaceae)	Bark and leaves, Methanol extract, dichloromethane fraction, ethyl acetate fraction and n-butanol fraction,	Sprague Dawley rats	Not reported	Vasorelaxant activity. 0.5, 1 and 2 mg/mL.	Prepared extracts from *A. scholaris* possess vasodilation by 1) blocking Ca^{2+} channels 2) soluble guanylate cyclase (sGC) direct activation 3) inhibition of inositol 1,4,5-triphosphate formation	[43]
Apium graveolens (Apiaceae)	Plant materials, Hexane, dichloromethane, ethyl acetate and methanol extracts	Male Wistar rats	3(g) apigenin (**Figure 3**)	Vasorelaxant activity. 62, 110 and 200 µg/mL (ethyl acetate extract).	Extracts of *A. graveolens* exerts vasodilation by interfering with 1) voltage-dependent Ca^{2+} channels (VDCC) 2) receptor-operated Ca^{2+} channels (ROCC).	[44]
Areca Catechu L. (Arecaceae)	Seed, Areca II-5-C	Male Spontaneous Hypertensive Rats (SHR)	Not reported	Antihypertensive effects, 100 and 200 mg/kg comparable with 30 and 100 mg/kg of captopril. 10 and 15 mg/kg (IV).	Inhibitory hypertensive effect of *A. catechu* specially Areca II-5-C is mediated by the 1) inhibition of pressor responses to both Angiotensin I and Ang-II.	[45]

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Artemisia campestris L (Asteraceae)	Aerial part, Aqueous extract (AcAE)	Wistar rats and Albino mice	3(h) chlorogenic acid 3(i) 3,4-dicaffeoylquinic acid 3(j) 3,5-dicaffeoylquinic acid 3(k) 4,5-dicaffeoylquinic acid 3(l) vicenin-2 (**Figure 3**)	Antihypertensive, hypotensive and vasorelaxant effect. 40, 150 mg/kg/day.	Aqueous extract (AcAE) of *A. campestris* exerts hypotensive, antihypertensive, and vasorelaxant effect by 1) calmodulin-NO-cGC-PKG pathway 2) Ca^{2+} influx inhibition through volage-operated calcium channels (VOCC) 3) intracellular Ca^{2+} mobilization activation into sarcoplasmic reticulum	[46]
Berberis vulgaris (Berberaceae)	Roots, Ethanolic extract	Not reported	3(m) berberine (**Figure 3**)	*In vitro* antioxidant effect. 0.2 - 1 mg/ml extract decreased production of thiobarbituric acid reactive substances (TBARS) from 9 ± 0.3 to 4 ± 1.1 nmol/g. 0.2 - 1 mg/ml extract and berberine lowered NO, 2,2-diphenyl-1-picrylhydrazyl (DPPH) oxidation in the range of 16% - 25% and 13% - 46% than control respectively ($p < 0.05$); increased liver glutathione peroxidase and SOD activity in the range of 10% - 70% and 55% - 270% respectively.	Not reported	[47]
Calpurnia aurea (Ait.) (Fabaceae)	Seed, 80% methanol extract	Sprague-Dawley rats, Guinea pigs	Not reported	Hypotensive and antihypertensive effects, 5 - 250 mg/L of 80% methanol extract, maximum 92.1% relaxation achieved for 250 mg/L.	Pre-treatment with 80% methanol extract resulted rightward non-parallel shift in Ca^{2+} dose-response curves by 1) blocking Ca^{2+} influx via VDCC which relaxes VSMC.	[48]
Camellia sinensis O. Ktze (Theaceae)	Black tea extract	Male Sprague Dawley rats	4(a) theaflavin-3,3'-digallate (TF3) (**Figure 4**)	1.5 μg/ml extract and 0.1, 0.5 μg/ml TF3 significantly improved ($p < 0.05$) endothelium-dependent relaxations in homocysteine-treated rat aorta.	Black tea extract exerts effects by 1) promoting Homocysteine metabolism 2) inhibition of phosphorylated ATF3, eIF2*α*, and cleaved ATF6 expression which reduces endoplasmic reticulum stress 3) reducing oxidative stress	[49]

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Cecropia glaziovii Sneth (Cecropiaceae)	Leaves, Aqueous extract and n-butanol fraction	Rats and mice of three-month-old	4(b) procyanidin B5 4(c) procyanidin B3 4(d) catechin 4(e) procyanidin B2 4(f) epicatechin 4(g) procyanidin C1 4(h) orientin 4(i) isoorientin and 4(j) isovitexin (**Figure 4**)	Pronounced hypotension. 0.5 g/kg/bid.	Not reported	[50]
Cistus ladaniferus (Cistaceae)	Aerial parts, Aqueous extract	Adult Wistar rats	4(k) quercetin (**Figure 4**)	Antihypertensive properties. Aqueous extract of 500 mg/kg/day.	The antihypertensive effects of *C. ladaniferus* are mostly 1) due to an endothelium-dependent vasodilatory activity.	[51]
Clitoria ternatea (Fabaceae)	Petals, Aqueous extract, crude lyophilized extracts (CLE)	Not reported	Not reported	6.7 mg/mL CLE induced 61% ACE I inhibitory activity.	1) Reference [52] found flavonoid compounds like quercetin, kaempferol, quercetin-3-rutinoside, and (-) epicatechin presenting more than 42% ACE I inhibition. Flavonoids' number and position of -OH groups in the rings, as well as the existence of double bonds, which form stable chelating complexes with zinc in active site of ACE I [53].	[54]
Cochlospermum vitifolium (Cochlospermaceae)	Bark, Methanolic extract	Wistar rats and Spontaneously hypertensive rats	4(l) naringenin (NG) (**Figure 4**)	120 mg/kg extract, 50 and 160 mg/kg NG exerted acute antihypertensive effects	The NO-cGMP pathway has been identified as the most important signaling mechanism of plant extracts and Naringenin's vasorelaxant activities. Other mechanisms involved also- 1) synthesis of NO 2) PGI_2 production 3) Activation of K^+ channel on endothelial dysfunction.	[55]
Cocos nucifera Linn. (Arecaceae)	Endocarp. Ethanolic extract	Male Wistar rats	5(a) ferulic acid 5(b) vanillic acid (**Figure 5**) 3(h) chlorogenic acid (**Figure 3**)	Vasorelaxant and antihypertensive effects. 300 mg/kg.	The vasorelaxant and antihypertensive effects of *C. nucifera* ethanolic extract is linked to 1) activating NO/GC pathway directly 2) muscarinic receptors stimulation 3) cyclooxygenase pathway	[56]

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Coreopsis tinctoria (Asteraceae)	Dried and powdered flower buds, Ethanol extract	Spontaneously hypertensive rats (SHR), Wistar-Kyoto rats	4(k) quercetin (**Figure 4**) 5(c) quercetagetin-7-O-glucoside 5(d) flavanomarein 5(e) marein 5(f) luteolin 5(g) coreopsis chalcones (**Figure 5**)	Antihypertensive activity. 100 mg/kg ethanol extract.	Flavonoids from *C. tinctoria* ethanolic extracts produce decent effect by 1) downregulating plasma Ang-II and ACE, AT_1R, transforming grown factor-β (TGF-β) expression in left ventricle, but upregulating ACE II	[57]
Cratoxylum formosum (Hypericaceae)	Leaves, Aqueous extract	Sprague-Dawley rats	5(h) phenolic acid (**Figure 5**)	Aqueous extract of 100, 300, and 500 mg/kg lowered SBP (158.2 ± 1.5 mmHg, 137.4 ± 2.1 mmHg, and 139.3 ± 2.5 mmHg) significantly ($p < 0.05$, $n = 8$) in hypertensive rats against control.	*C. formosum* aqueous extract exhibits therapeutic effects by 1) rising plasma NO levels, and decreasing oxidative stress 2) reducing serum ACE, plasma Ang-II and AT_1R upregulating in l-NAME induced hypertensive rats 3) suppressing RAS	[58]
Croton schiedeanus Schlecht (Euphorbiaceae)	Leaves, Aqueous extract	Spontaneously hypertensive rats	Not been elucidated	Antihypertensive, bradycardic, and vasorelaxant effects. Aqueous extract of 5 - 100 mg/kg.	*C. schiedeanus* Aqueous extract exerts antihypertensive, bradycardic, vasorelaxant effects by 1) Ca^{2+} influx blocking through VDCC	[59]
Curcuma domestica (Zingiberaceae)	Curcumin nanoemulsion	Not reported	5(i) curcumin (**Figure 5**)	Antihyperlipidemic, 71.166% inhibition of HMG-CoA reductase (HMGCR) compared to pravastatin after correction, ACE inhibitory activity of curcumin nanoemulsion at 2 mg/mL.	Curcumin inhibits HMGCR production which synthesizes cholesterol in liver [60].	[61]
Echinodorus grandiflorus (Cham. & Schltdl.) Micheli. (Alismataceae)	Leaves, Ethanol soluble fraction (ESEG)	Male Wistar rats	Not reported	Diuretic activity like hydrochlorothiazide of ESEG (30 - 300 mg/kg, p.o.), sparing HCO_3^- and serum nitrite increased. Furthermore, intraduodenal ESEG administration induces antihypertension and hypotension in 2K1C rats significantly.	The hypotensive and antihypertensive action of ethanol soluble fraction of *E. grandiflorus* are mediated by 1) muscarinic and bradykinin B2 receptor activation, with directly involving NO and prostaglandin pathways.	[62]

Continued

Eruca sativa Mill., (Brassicaceae)	Aerial parts, Crude extract of *E. sativa*, n-hexane, chloroform, ethyl acetate, and aqueous extract.	Balb^{C} mice and Sprague-Dawley rats	4(k) quercetin (**Figure 4**) 5(j) erucin (**Figure 5**)	Antihypertensive activity, vasodilatory and partly cardiac effects at 1, 3, 10, 30 and 100 mg/kg	*E. sativa* aqueous and crude extract mediated antihypertensive effect through 1) NO release linked by muscarinic receptors 2) Ca^{+2} influx and release inhibitory effect	[63]
Erythrina senegalensis DC (Fabaceae)	Stem barks, Aqueous extract	Male albinos Wistar rats, Hypertensive diabetic rats (HDR)	Alkaloids, flavonoids, phenols in extract whose antidiabetic and antihypertensive activity have been showed [64].	Antihypertensive, cardiomodulator, antioxidant, hypolipidemic, and hypoglycemic properties. 100 and 200 mg/kg of aqueous extract were tested on two groups of HDR, for 28 days.	Aqueous extract of *E. senegalensis* mainly act by 1) activating AMP-activated protein kinase, expressing Glucose transporter 4 and Glucose transporter 1, and inhibiting protein tyrosine phosphatase 1B by are involved in stimulating basal and insulin responsive glucose uptake [65].	[66]
Eucommia ulmoides Oliv (Eucommiaceae)	Barks, 50% ethanol extract (Lignans) (EuL)	Male Sprague-Dawley rats and male spontaneously hypertensive rats.	Not reported	EuL of 150 and 300 mg/kg bid lowered SBP significantly ($p < 0.05$, $n = 8$) than control.	1) EuL increased plasma NO *in vivo*. This effect is linked with endothelium, that did not follow the result of *in vitro*. *In vivo* EuL metabolizes into compounds which release NO from endothelium. EuL *in vitro* cannot do it.	[67]
Eugenia uniflora L. (Myrtaceae)	Leaves, Aqueous Crude Extracts	Normotensive male Wistar rats	Not reported	For hypotension, ED_{50} was found to be 3 mg dried leaves (d.l.)/kg. For diuresis, 120 mg d.l./kg extract exhibited most potently compared to amiloride.	1) Hypotensive effect of the leave extract of *E. uniflora* is moderated by direct vasodilation 2) Weak diuresis is related to renal blood flow increase.	[68]
Euphorbia cuneata Vahl. (Euphorbiaceae)	Aerial parts, Alcoholic extract	Normotensive albino rats	4(l) naringenin (**Figure 4**) 5(k) isoaromadendrin 5(l) taxifolin 5(m) isosinensin (**Figure 5**)	Naringenin (3.3 mg/kg) decreased BP by 20 mmHg; isoaromadendrin (3.3 mg/kg) decreased BP and heart rate (HR) by 36.5 mmHg and 4% respectfully; taxifolin (3.3 mg/kg) decreased BP by 20 mmHg; isosinensin (3.3 mg/kg) decreased BP and HR by 15 mmHg and 6.2% respectfully; isosinensin (6.6 mg/kg) decreased BP and HR by 16.6 mmHg and 16.6% respectfully	1) Isosinensin found in alcoholic extracts of *E. cuneata* lowers blood pressure due to decrease in HR produced by vasodilatation 2) Isoaromadendrin was most potent having four hydroxyl groups.	[69]

Continued

Inula viscosa L. (Asteraceae)	Leaves, Petroleum ether extract, dichloromethane extract, ethyl acetate extract and methanol extract.	Hypertensive l-NAME Wistar rats	5(n) 3-O-methylquercetine 5(o) cynarin 5(f) luteolin (**Figure 5**) 3(h) chlorogenic acid (**Figure 3**)	Antihypertensive effect. Methanol extract of 40 mg/kg.	1) Methanol extract exhibited antihypertensive effect predominantly by endothelium-dependent vasodilation. 2) Chlorogenic acid and cynarin isolated from *I. viscosa* Methanol extract, possess strong vasorelaxant activity.	[70]
Ipomoea hederacea Jacq. (Convolvulaceae)	Dried seeds, Aqueous-ethanolic extracts, butanol fraction (Ih.Bn)	Albino rats	Not specified	Antihypertensive activity. Ih.Bn of 0.01 - 100 mg/kg body weight (BW) dose dependently decreased DBP, SBP, HR, mean arterial pressure (MAP), pulse pressure.	1) Potent hypotensive effect was presented by butanol fractions of *I. hederacea* by β blocking, α_1 blocking, and stimulating inducible NO synthase/cyclic guanosine monophosphate (cGMP).	[71]
Kalanchoe pinnata (Crassulaceae)	Leaves, Aqueous extract	Male albinos Wistar rats	Not elucidated	Antihypertensive activity. In salt hypertensive rats, concurrent administration of 25, 50 and 100 mg/kg/day extract prevented SBP increase significantly by 32%, 24%, 47% and also reduced DBP increase by 35%, 33%, 56%.	Antihypertensive extracts of *K. pinnata* act by cardiode-pression, increasing diuresis or through vasorelaxant activity. 1) Conversion from O_2^- to H_2O and H_2O_2 is catalyzed by SOD, thus SOD metabolizes O_2^- and prevents HTN [72].	[73]
Laelia anceps (Orchidaceae)	Roots, crude methanolic extract	Wistar rats	5(p) 2,7-dihydroxy-3,4,9-trimethoxyphenanthrene (**Figure 5**)	Vasorelaxant and antihypertensive effects. L-type (voltage-gated) Ca^{2+} channel (L-VGCC) agonist FPL 64176 (3.16 μM)-induced contraction was significantly diminished by 11.2, 65 μg/mL methanolic extract	1) Root extract of *L. anceps* causes vasorelaxation by blockade of L-VGCC.	[74]
Laelia autumnalis (Orchidaceae)	Plant material, crude methanolic extract (MELa)	Wistar rats	Not reported	Vasorelaxant and antihypertensive activity. MELa (0.15 - 50 μg/mL), 100 mg/kg (orally).	Methanolic extract of *L. autumnalis* produced antihypertensive effect by 1) inhibiting VGCC, receptor-controlled Ca^{2+} channel, cGMP pathway involving blocking of Ca^{2+} channels through endothelium-independent pathway 2) inhibiting Ca^{2+} mobilization from intracellular stores 3) increasing cGMP levels	[75]

Continued

Lepidium sativum L (Brassicaceae)	Seeds, Aqueous extract	WKY and spontaneously hypertensive male rats	Not determined	Decreasing BP and increasing water and electrolytes excretion. 20 mg/kg for 3 weeks.	*L. Sativum* aqueous extract demonstrated antihypertensive effects- 1) by mediated diuretic and natriuretic action.	[76]
Linum usitatissimum (Liliaceae)	Seed	Sprague Dawley normotensive male rats	5(q) secoisolariciresinol diglucoside (SDG) (**Figure 5**)	*In vivo* antihypertensive activity. Decrease in SBP, DBP, and MAP were dose dependent for SDG of 3, 5 mg/kg, 5 - 150 mins after administration. Pretreatment with methylene blue (1 mg/kg) prevented SDG (10 mg/kg) induced reduction in arterial pressures.	SDG exhibited antihypertensive effect by 1) directly stimulating GC (like nitrovasodilator) and not due to NO synthase 2) due to SDG's metabolites (secoisolariciresinol, enterolactone and enterodiol)	[77]
Melothria maderaspatana (Cucurbitaceae)	Leaf, Ethyl acetate extract	Male albino Wistar rats	5(a) ferulic acid (**Figure 5**)	*In vivo* antihypertensive activity. 30, 60, 120 mg/kg BW extract reduced SBP and DBP significantly ($p < 0.05$) after 6 weeks of administration in DOCA-salt hypertensive rats than control.	Ferulic acid found in the extract was reported having antihypertensive effect on spontaneously hypertensive rats [78] by 1) NO-mediated vasodilation 2) improving bioavailability of NO	[79]
Mesona procumbens Hemsl. (Lamiaceae)	Dried full plant, Water extract (WEHT)	Male 6-week-old spontaneously hypertensive rats and Wistar-Kyoto rats	5(r) caffeic acid (CA) (**Figure 5**)	*In vivo* antihypertensive activity. WEHT (1 g/kg of BW) significantly reduced SBP, DBP, HR by 17.7%, 11%, and 7.3%. CA (0.1 g/kg of BW) significantly reduced SBP, DBP, HR by 23.4%, 15%, 11.2%.	1) Water extract of *M. procumbens* had scavenging activity on free radicals and ROS (e.g., hydroxyl or peroxyl/hydroperoxy radicals) 2) plasma metabolites of CA act as antioxidants 3) Both reduced oxidative stresses, or increased antioxidant capacity in cell.	[80]
Moringa oleifera (Moringaceae)	Leaves, Hot water extract	Frog heart, Taenia coli of guinea pig	Not reported	Alkaloidal salts (3 - 48 ng/ml) collected from the extract showed negative inotropic effect on isolated frog heart dose-dependently; inhibited calcium response on frog heart and guinea pig taenia coli.	Alkaloidal salts from *M. oleifera* hot water extract induced 1) negative inotropic effect because of the presence of CCB, or Ca^{2+} antagonist.	[81]

Continued

Mucuna pruriens L. (Fabaceae)	Seeds, Ethyl acetate extract (MPEA)	Wistar rats	6(a) genistein 6(b) ursolic acid (UA) 6(c) L-3,4-dihydroxyphenylalanine (L-DOPA) (**Figure 6**)	*In vitro* antihypertensive activity. IC_{50} of MPEA, Genistein, UA, L-DOPA are 156.45 ± 3.90 μg/mL, 68.59 ± 2.47 μg/mL, 465.83 ± 51.2 μg/mL, and 119.58 ± 4.53 μg/mL (n = 3).	Ethyl acetate extract of *M. pruriens*, Genistein, UA, L-DOPA showed 1) inhibition by non-competitive mode 2) ACE inhibition by protein precipitating (L-DOPA showed very little precipitation).	[82]
Nigella damascene (Ranunculaceae)	Flour of Seeds, Methanol extract	Not reported	Not reported	Highest 43.24% ACE inhibition was shown for bound phenolic-acid extract of seed flour. Highest 84.385% antioxidant activity was shown for glutelin-1 fraction of free phenolic-25˚C extract.	Not reported	[83]
Nigella arvensis (Ranunculaceae)	Flour of Seeds, Methanol extract	Not reported	Not reported	Highest 55.55% ACE inhibition was shown for free phenolic-25˚C extract of seed flour. Highest 69.76% antioxidant activity was shown for albumin fraction of free phenolic-25˚C extract.	Not reported	[83]
Ocimum gratissimum (Lamiaceae)	Fresh whole plant with leaves, stems, and flowers, Water extract	Wistar Kyoto rats, spontaneously hypertensive rats	6(d) rutin (**Figure 6**)	*In vitro* and *in vivo* antihypertensive activity. IC_{50} of the water extract, and Rutin are 56.3 ± 3.12 μg/mL, and 43.08 μg/mL (n = 3).	Rutin found in water extract of *O. gratissimum* 1) inhibited ACE 2) inhibited endothelin-1 (ET-1)	[84]
Olea europea L. variety Picual (Oleaceae)	Fruits, Water-soluble extract of olive oil	Male Spontaneously hypertensive rats	Not reported	*In vitro* and *in vivo* antihypertensive effect. Peptides (0.425 mg/kg of BW) in the extract reduced maximum 20 mmHg BP at 6 h (IC_{50} = 2.5 ± 0 μg protein/mL, n = 3).	Olive oil water-soluble extract from *O. europea* showed antihypertensive effect by 1) inhibiting ACE 2) increasing NO bioavailability 3) acting on ET-1 expression	[85]

Continued

Orthosiphon aristatus (Lamiaceae)	Leaves, Chloroform-soluble portion from the water decoction of the leaves	Stroke prone spontaneously hypertensive rats (SHRSP), Male Wistar rats, male Hartley guinea pigs	6(e) methylripariochromene A (MRC) 6(f) acetovanillochromene (AVC) 6(g) orthochromene A (OC) (**Figure 6**)	100 mg/kg MRC decreased 15 to 30 mmHg mean BP of SHRSP at 3.5 h to 24 h ($p < 0.05$ or $p < 0.01$, $n = 8$); 3.8×10^{-5} M and 1.1×10^{-4} M MRC suppressed contractile force of isolated guinea pig atria by 18.8% ± 2.6% ($p < 0.05$, $n = 4$) and 54.74% ± 2.8% ($p < 0.01$, $n = 4$). IC_{50} of AVC, OC are 1.01×10^{-4} M, 1.32×10^{-4} M.	Methylripariochromene A isolated from the leaves of *O. aristatus* 1) decreased the slow Ca^{2+} inward current 2) decreased CO 3) increased urinary volume and electrolyte excretions 4) have Ca^{2+} antagonism	[86]
Osyris abyssinica var. speciosa (Santalaceae)	Aerial parts, Alcoholic extract	Normotensive Wistar albino rats	4(f) epicatechin (**Figure 4**)	Epicatechin of 3.3 mg/kg decreased BP, and HR by 8.3 mmHg, and 6% respectfully; and 6.6 mg/kg decreased BP, and HR by 8.3 mmHg, and 7.1% respectfully.	Epicatechin found from *O. abyssinica* 1) Lower HR by vasodilatation	[69]
Parkia speciosa (Fabaceae)	Seeds, Hydrolyzed with and without Alcalase	Not reported	Not found	Hydrolyzed samples showed slightly more DPPH scavenging activity of 2.1 - 2.9 mg gallic acid equivalent (GAE)/g seed than non-hydrolyzed ones (1.6 - 2.2 mg GAE/g seed). Hydrolyzed samples inhibited 50.6% - 80.2% of ACE activity.	Hydrolyzed seeds of *P. speciosa* 1) Inhibit ACE	[87]
Passiflora edulis (Passifloraceae)	Fruit Peel, Ethanol extract	Male Spontaneously hypertensive rats	6(h) edulilic acid (EA) 6(i) anthocyanin fraction (AF) (**Figure 6**)	For 2.5, and 50 mg ethanol extract/kg BW, maximum MAP reduced were 8.9 ± 3, and 13 ± 2.5 mmHg; maximum SBP reduced were 10 ± 2.9, and 13.8 ± 2.8 mmHg; maximum DBP reduced were 7.6 ± 2.9, and 10.2 ± 2.2 mmHg. EA and AF significantly decreased ($p < 0.001$) mean variation in HR from baseline over 5 days.	Ethanol extract of *P. edulis* peel extract 1) diminishes sympathetic nervous system activation	[88]

Continued

Petroselinum crispum (Mill.) Fuss. (Apiaceae)	Aerial parts, Aqueous extract	Albino adult male Wistar rats	Not reported	*In vivo* and *in vitro* antihypertensive effect. Significant reduction of SBP, MAP and DBP ($p < 0.01$) was observed after 6 h of treating with 160 mg/kg extract. Significant vasorelaxation ($p < 0.0001$) of aortic rings pre-contracted by epinephrine was seen for 0.02 - 2.5 µg/ml extract ($IC_{50} = 0.38 \pm 0.07$ µg/ml).	Aqueous extract of *P. crispum* 1) decreases tension in endothelium-denuded and endothelium-intact aortic rings 2) blocks the entry of extracellular Ca^{2+} via blocking VOCC and ROCC. 3) increases synthesis of NO.	[89]
Phaseolus vulgaris L. varieties plus black (PB), azufrado higuera (AH) and pinto Saltillo (PS) (Fabaceae)	Seeds, Protein extraction by isoelectric precipitation	Male Wistar spontaneously hypertensive rats	Not reported	Total hydrolysates from each variety showed ACE inhibition of $IC_{50} = 4.34 \pm 0.29$, 4.82 ± 1.59, 25.96 ± 0.86 µg/mL respectively. Peptide fraction < 1 kDa showed highest % antioxidant activity among each variety (99.2% ± 0.9%, 87.6% ± 0.7%, and 82.7% ± 2.0% respectively). Peptide fraction 3 - 10 kDa of AH variety lowered SBP up to 27.13 ± 11.17 mmHg at 2 h and up to 23.55 ± 12.44 mmHg at 4 h ($p \leq 0.01$, $n = 3$).	Not reported	[90]
Phragmanthera incana (Schum) Balle (Loranthaceae)	Leaves, Ethanol extract	Wistar male rats	Not found	50, 100, 200 mg ethanol extract/kg p.o. significantly decreased ($p < 0.05$ and $p < 0.001$, $n = 6$) SBP compared to the l-NAME rat group after four weeks' treatment. 100, 200 mg ethanol extract/kg p.o. significantly ($p < 0.05$, $p < 0.01$ respectively, $n = 6$) increased serum nitrite levels compared to the l-NAME rat group.	*P. incana* ethanol extract holds antihypertensive and antioxidant activity by 1) reducing peroxidation of lipid 2) restoring plasma nitrite levels counterbalance the effect of ROS	[91]

Continued

Picrasma quassiodes (D. Don) Benn. (Simaroubaceae)	Dried branches, Dichloromethane extract	Male spontaneously hypertensive rats (SHR), Wistar Kyoto rats	Not found	50, 100, and 200 mg extract/kg significantly lowered ($p < 0.01$, $n = 8$) SBP compared to control group. 100, and 200 mg extract/kg significantly increased NO and SOD than SHR control group ($p < 0.01$, $p < 0.05$ respectively, $n = 6$).	Extract of *P. quassiodes* exerts effects by 1) vascular oxidative stress minimization by increasing SOD activity 2) endothelial function preservation and increase eNOS expression to promote synthesis and release of NO that result in direct vasorelaxation.	[92]
Pistacia atlantica Desf (Anacardiaceae)	Leaves, Dried residue of organic phase redissolved in absolute methanol	Not reported	6(j) glucogallin, 6(k) gallic acid, 6(l) galloylshikimic acid, 6(m) methyl gallate, 6(n) digalloylquinic acid, 6(o) digallic acid, 6(p) trigalloylglucose 6(q) tetragalloylquinic acid (**Figure 6**)	*In vitro* antidiabetic and antihypertension activity. Extracts of 35 - 140 µg/ml produced a dose-dependent ACE I inhibition ranging from 15.1% - 74% (average $IC_{50} = 102 \pm 10.2$ µg/ml).	Phenolic compounds retrieved from leaves of *P. atlantica* show ACE inhibitory activity by 1) forming chelate complex with zinc within the active site of ACE I 2) interactions through hydrogen bonds that is established between -OH groups of compounds close to active site which blocks activity of ACE.	[93]
Prunus serotina Ehrh. (Rosaceae)	Fruits, Lyophilized aqueous and methanolic extracts	Adult male Wistar rats	3(h) chlorogenic acid (CGA) (**Figure 3**) 7(a) cyanidin-3-O-rutinoside 7(b) proanthocyanidins 7(c) quercetine glycosides (**Figure 7**)	The flesh extract showed E_{max} of 27.9% ± 3.6%, EC_{50} of 120 ± 5.7 µg/mL, peel extract showed E_{max} of 54.5% ± 4%, EC_{50} of 34.9 ± 3.4 µg/mL, and whole fruit extract showed E_{max} of 59% ± 5.9%, EC_{50} of 101.8 ± 7.5 µg/mL vasorelaxant response.	1) synergistic effect of the compounds 2) CGA inhibit ROS generating enzymes (NADPH, xanthine oxidase), reduce the formation of $ONOO^-$ and increase bioavailability of NO. It also has protective role in eNOS [94].	[95]
Psidium guineense Sw. (Myrtaceae)	Leaves, Essential oil	Female and male Swiss mice, female Wistar rats	7(d) spathulenol (**Figure 7**)	Antioxidant activity. *P. guineense* essential oil and spathulenol exhibited DPPH free radical activity of $IC_{50} = 60.7$ - 65.92 and 82.43 - 89.38 µg/mL ($n = 3$), respectively; and MDA lipoperoxidation with $IC_{50} = 35.23$ - 40.50 and 24.30 - 28.68 µg/mL ($n = 3$), respectively.	Not reported	[96]

Continued

Salvia elegans Vahl. (Lamiaceae)	Aerial parts (flowers, leaves, and stems), hydroalcoholic extract (SeHA) and n-butanol extract (SeBuOH)	ICR albino mice	Not found	*In vitro* inhibitory effect on ACE. SeHA significantly lowered ($p < 0.05$) SBP from dose as low as 0.75 µg/kg, DBP at 10 mg/kg. SeHA inhibited 50.27% ± 5.09% ACE ($n = 5$) while SeBuOH inhibited 78.40% ± 2.24% ACE ($n = 5$).	SeHA inhibited antihypertensive effect by 1) inhibiting the secretion of ET-1 2) increasing NO production and release 3) activating Ca^{2+}-dependent K^+ conductance that allows hyperpolarization after entry of Ca^{2+}.	[97]
Salvia verbenaca L. (Lamiaceae)	Aerial parts, Alcoholic extract	Normotensive albino rats	7(e) 5-hydroxy-3, 4', 7-trimethoxyflavone (HMF), 7(f) verbenacoside (VBC) (**Figure 7**)	HMF (3.3 mg/kg) decreased BP and HR by 30 mmHg and 28.5% respectfully; VBC (3.3 mg/kg) decreased BP and HR by 13.2 mmHg and 15.4% respectfully; Alcoholic extract 0.5 gm/kg decreased BP and HR by 36.2 mmHg and 18.18%.	1) 5-hydroxy-3, 4', 7-trimethoxyflavone and verbenacoside isolated from alcoholic extract of *S. verbenaca* decreased HR by vasodilatation 2) 5-hydroxy-3, 4', 7-trimethoxyflavone showed potent activity having four -OH groups 3) alcoholic extract lowered BP by synergistic effect of flavonoids present	[69]
Sapium sebiferum (L.) Roxb. (Euphorbiaceae)	Leaves, Aqueous extract	Spontaneously hypertensive rats	7(g) 6-O-galloyl-D-glucose (GDG) (**Figure 7**)	GDG of 1, and 5 mg/kg lowered MAP by 17.3 ± 7.1 and 29.6 ± 10.4 mmHg ($n = 6$) in SHR, and decrease in plasma noradrenaline was parallel to the antihypertensive action.	GDG lowers blood pressure by 1) blocking of noradrenaline release and/or 2) direct vasorelaxation	[98]
Sechium edule (Jacq.) Sw. (Cucurbitaceae)	Roots, Hydroalcoholic extract (SeRHA)	Male Sprague-Dawley albino rats, male ICR albino mice	7(h) cinnamic acid (**Figure 7**)	SeRHA of 200 mg/kg decreases DBP, SBP significantly after Ang-II treatment ($p < 0.05$). SeRHA of 150, 300, 600 µg/ml lowered aorta contraction by 14%, 44%, and 66% of E_{max} after Ang-II treatment (average $EC_{50} = 1.5 \times 10^{-8}$ M).	The hydroalcoholic root extracts of *S. edule* may 1) antagonize AT_1R or by interfering Ca^{2+} fluxes activated by Ang-II 2) obstruct the second messenger system initiated by Ang-II 3) alter Ca^{2+} fluxes in the VSMC and on the RAAS.	[99]

Continued

Solanum capsicoides All. (Solanaceae)	Aerial parts, Methanol extract	Normotensive Wistar-Kyoto (WKY) rats, Spontaneously hypertensive rats (SHR)	Not reported	*In vitro*, *in vivo* antihypertensive activity. Significant increase in the vasorelaxation of endothelium denuded mesenteric rings from SHR (E_{max} = 102.1% ± 5.7%, EC_{50} = 29.6 - 55.8 µg/ml, $p < 0.05$). 40 mg/kg methanol extract significantly ($p < 0.05$) reduced MAP greater in SHR (25.4% ± 1.4%) when compared WKY rats (17.7% ± 2.6%).	Methanol extract induced antihypertensive effect by 1) reducing peripheral vascular resistance 2) reducing sensitivity to the adrenergic agonist 3) increasing NO sensitivity	[100]
Solanum melongena (Solanaceae)	Fruits, Lyophilized powders	Male 14-week-old spontaneously hypertensive rats	7(i) acetylcholine (ACh) (**Figure 7**)	10^{-3} - $10^{-0.5}$ µM ACh which is identified from eggplant powder, exerted concentration-dependent vasorelaxation (EC_{50} = 0.0372 ± 0.008 µM). And SBP decreased significantly ($p < 0.05$) after 3 h and 9 h by 4.81 and 10 mmHg.	ACh showed antihypertensive activity by 1) activating the M3 muscarinic ACh receptor on blood vessels 2) suppressing the secretion of hypertensive catecholamines 3) suppressing sympathetic nervous activity	[101]
Solanum sisymbriifolium Lam. (Solanaceae)	Root, Hydro ethanolic crude root extract (CRE), Butanol fraction (F_{BtOH}), B3 subfraction	Swiss adult albino male mice	7(j) nuatigenin-3-O-*β*-chacotriose ($B_{3\text{-}1}$) (**Figure 7**)	CRE of 50 mg/kg, F_{BtOH} of 5 mg/kg, and B3 subfraction of 1 mg/kg significantly decreased DBP and SBP ($p < 0.001$ and $p < 0.01$, $n = 6$). 1, 2.5, 5 mg/kg $B_{3\text{-}1}$ significantly decreased ($p < 0.001$; $n = 6$) DBP and SBP.	$B_{3\text{-}1}$ induced vasorelaxation by 1) inhibiting cyclic adenosine monophosphate (cAMP) phosphodiesterase, cAMP increases indirectly in VSMC [102].	[103]
Tagetes lucida Cav. (Asteraceae)	Aerial parts, Ethanolic extract	Normotensive male Wistar rats, male spontaneously hypertensive rats	7(k) 6,7,8-trimethoxycoumarin, 7(l) 6,7-dimethoxycoumarin (**Figure 7**)	Ethanolic extract of 3.03 - 1000 µg/ml showed E_{max} of 99%, EC_{50} of 40.5 µg/ml (endothelium intact) and E_{max} of 100%, EC_{50} of 148.2 µg/ml (endothelium denuded). The extract relaxed KCl-induced contraction with EC_{50} of 100 µg/ml and E_{max} of 100%. Both compounds displayed significant activity ($p < 0.05$) in concentration and partly endothelium dependent manner.	Ethanol extract showed endothelium derived relaxant effect by 1) Producing NO that outspreads to VSMC to activate sGC which produces cGMP, and induces relaxes smooth muscle as the main second messenger. 2) Blocking the L-VGCC	[104]

Continued

Terminalia bellerica Roxb. (Combretaceae)	Fruits, Aqueous-methanolic extract, crude extract (Tb.Cr)	Sprague-Dawley rats, guinea-pigs, rabbits	Not reported	Tb.Cr of 100, 30, and 10 mg/kg showed a dose-dependent decrease of 44.7% ± 3.1%, 25.1% ± 2.3%, and 15.6% ± 2.0% in MAP of rats; 0.1 - 10 mg/ml inhibited guinea-pig atrial force and contraction rate (EC_{50} = 4.5 ± 1.2 and 5.9 ± 1.3 mg/mL respectively, n = 4) and also relaxed K^+ and phenylephrine (PE) induced contraction in isolated rabbit aorta (EC_{50} = 6.4 ± 1.3, 7.5 ± 1.3 mg/mL respectively, n = 4 - 5).	Crude extract of *T. bellerica* fruit induced antihypertension by 1) negative inotropic and chronotropic effect due to the Ca^{2+} antagonism effect decreasing CO and so reducing BP 2) equipotently blocking Ca^{2+} influx through VDCC and ROCC 3) suppressing the PE agonist, and thus inhibiting internal store release of Ca^{2+} 4) endothelium-independent vasodilation	[105]
Thymus serpyllum L. (Lamiaceae)	Whole plant, Aqueous and freeze-dried extract	Normotensive Wistar rats, Male spontaneously hypertensive rats (SHR)	7(m) rosmarinic acid (**Figure 7**)	Freeze dried extract (100 mg/kg BW dissolved into saline of 0.2 ml) decreased SBP, DBP, and total peripheral vascular resistance significantly ($p < 0.001$, n = 7) in SHR. *In vitro* NO-scavenging ability of 1 mg/ml extract led to 63.43% reduced nitrite production (IC_{50} = 122.36 µg/ml).	Rosmarinic acid found in this extract had *in vitro* antioxidant effect against low density lipoprotein (LDL) oxidation [106] by 1) inhibiting conjugated diene and TBARS formation.	[107]
Tropaeolum majus L. (Tropaeolaceae)	Leaves, semi-purified fraction (TMLR) and hydroethanolic extract (HETM)	Wistar-Kyoto rats, Spontaneously hypertensive rats	7(n) isoquercitrin (ISQ) (**Figure 7**)	50, 100 mg/kg TMLR, 100, 300 mg/kg HETM, and 2, 4 mg/kg ISQ significantly ($p < 0.001$, n = 6) decreased MAP in a dose-dependent manner in normotensive rats; 300 mg/kg HETM, 50, 100 mg/kg TMLR ($p < 0.01$) and 10 mg/kg ISQ ($p < 0.001$) significantly inhibited ACE activity in conscious rats compared to control.	Isoquercitrin inhibited ACE activity but single administration of hydroethanolic extract, semi-purified fraction, Isoquercitrin did not change HR because results of ACE inhibition take several months to bring to light. ACE inhibition by Isoquercitrin may also be occurring in central nervous system.	[108]

Continued

Vitex pubescens (Lamiaceae)	Leaves, Petroleum ether extract (VPPE)	Spontaneously hypertensive rats	7(d) Spathulenol (Figure 7)	VPPE of 500 mg/kg significantly decreased ($p < 0.001$, $n = 6$) SBP, DBP from 3 days, and 0.25 - 4 mg/ml significantly relaxed ($p < 0.001$, $n = 6$) pre-contracted endothelium intact aortic ring. Fraction F2-VPPE of 0.5, 1, 2 mg/mL significantly ($p < 0.001$) attenuated $CaCl_2$-induced of endothelium-denuded aortic ring vasoconstriction.	Fraction F2-VPPE of *V. pubescens* induced relaxation by 1) Activating K_{ATP} channel which causes hyperpolarization and Ca^{2+} inflow inhibition through VDCC 2) intracellular Ca^{2+} release inhibition from Ca^{2+} storage 3) extracellular Ca^{2+} inflow inhibition through ROCC. Spathulenol show vasorelaxant activity [109] by Ca^{2+} inflow inhibition through VDCC.	[110]

4) Elevates the transcription of the LXR*α* gene, which controls the CYP7A1 enzyme (encoding cholesterol-7a-hydroxlylase, an enzyme that participates in converting cholesterol to bile acids before excretion).

5) Prevents atherosclerotic lesion formation in the atherogenic diet-fed mice, as evidenced by a decrease in the atherogenic indicator and an increase in the % ratio of HDL and total cholesterol [60].

In comparison to pure curcumin, curcumin nanoemulsion demonstrated a higher rate of ACE inhibition, which suggests that higher inhibition activity of curcumin exerted by the nanoemulsion carrier system was caused by improving its solubility [61]. The last one 2,7-dihydroxy-3,4,9-trimethoxyphenanthrene, obtained from *Laelia anceps*, caused relaxant activity on norepinephrine precontracted aortic rings with E_{max} of 90% ± 1.35% (with endothelium) and 96.45% ± 1.2% (without endothelium) [74].

3. Observed Compounds Having BP Lowering Properties

The discussed antihypertensive compounds, structure demonstrated in Figures 3-7, are 31 types of compounds, such as 1) anthocyanidin (cyanidin-3-O-rutinoside), 2) anthocyanin (anthocyanin fraction), 3) biogenic amine (acetylcholine), 4) catecholamines (L-3,4-dihydroxyphenylalanine), 5) chalcones (marein, coreopsis chalcones), 6) chromenes (methylripariochromene A, acetovanillochromene, orthochromene A), 7) cinnamates (cynarin, caffeic acid, cinnamic acid), 8) coumarins (6,7,8-trimethoxycoumarin, 6,7-dimethoxycoumarin), 9) cyclic acid glucoside (edulilic acid), 10) diarylheptanoid (curcumin), 11) dihydrophenanthrene (2,7-dihydroxy-3,4,9-trimethoxyphenanthrene), 12) flavones (apigenin, vicenin-2, orientin, isoorientin, isovitexin, luteolin), 13) flavonols (quercetin, taxifolin, 3-O-methylquercetine, rutin, quercetine glycosides, 5-hydroxy-3,4',7-tri- methoxyflavone, verbenacoside, isoquercitrin), 14) flavonoid glucosides (tilianin,

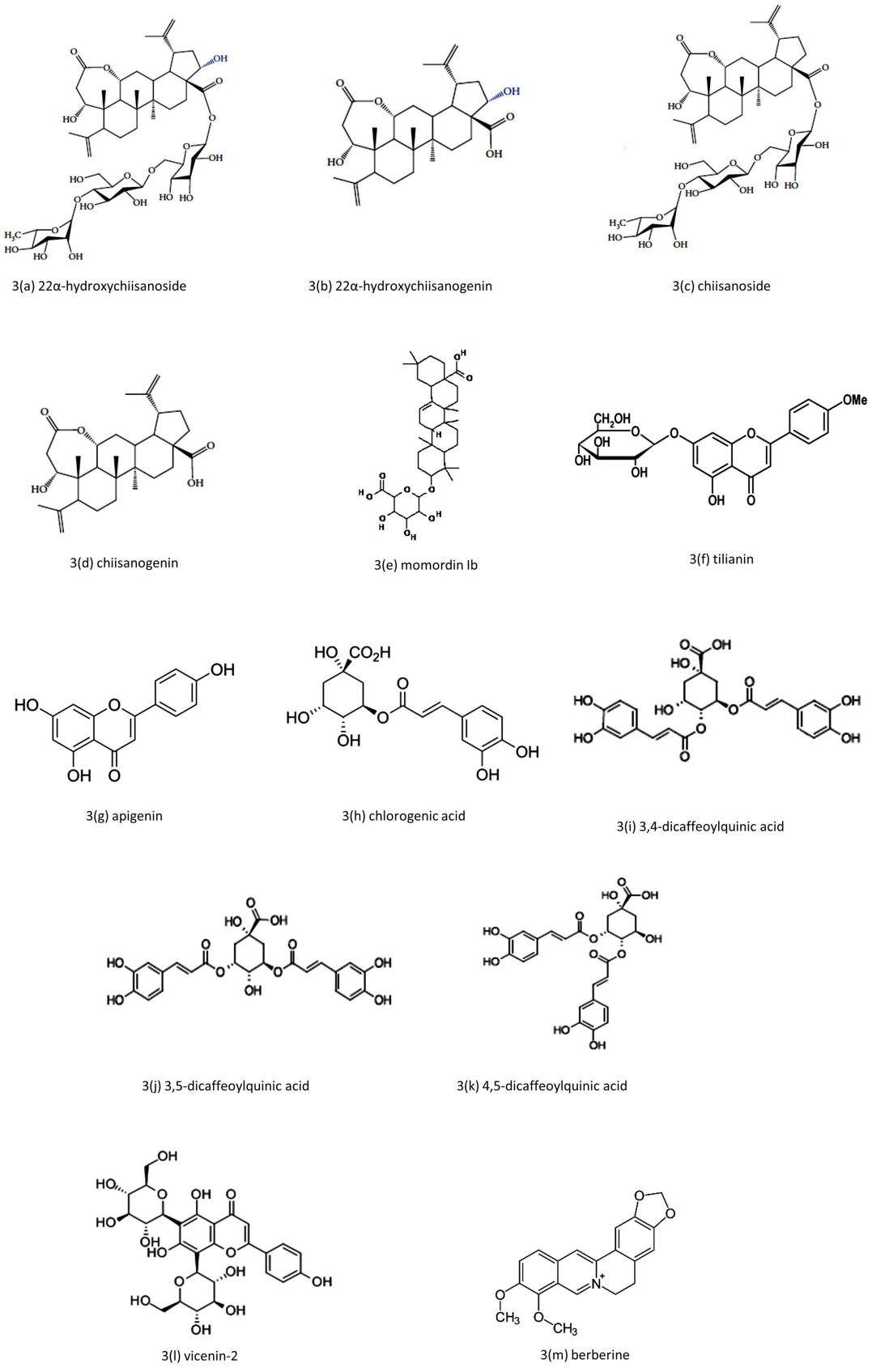
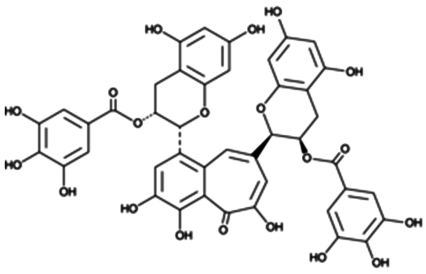
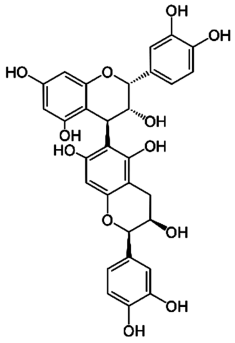


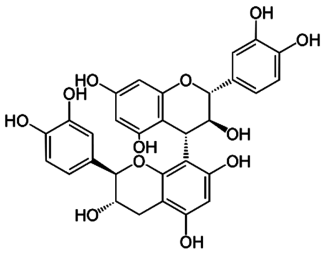
Figure 3. Reported compounds from medicinal plants manifest anti-hypertensive activity.



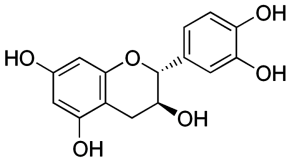
4(a) theaflavin-3,3'-digallate



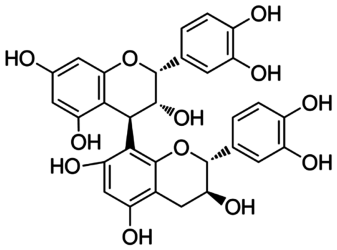
4(b) procyanidin B5



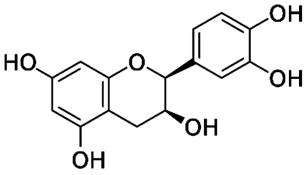
4(c) procyanidin B3



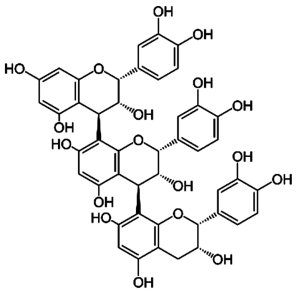
4(d) catechin



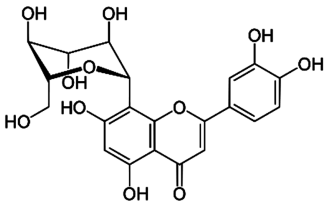
4(e) procyanidin B2



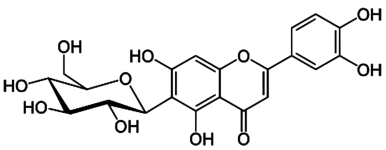
4(f) epicatechin



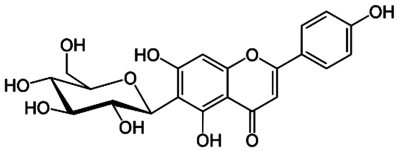
4(g) procyanidin C1



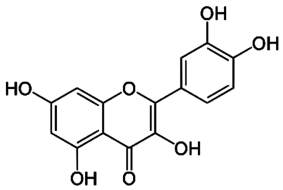
4(h) orientin



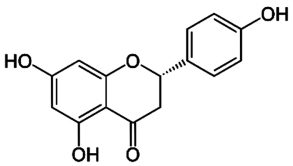
4(i) isoorientin



4(j) isovitexin

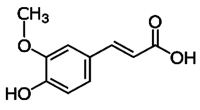


4(k) quercetin

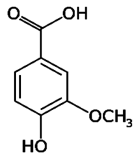


4(l) naringenin

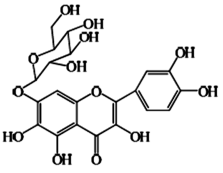
Figure 4. Reported compounds from medicinal plants manifest anti-hypertensive activity.



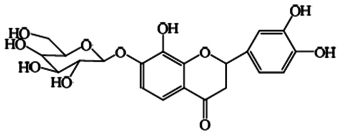
5(a) ferulic acid



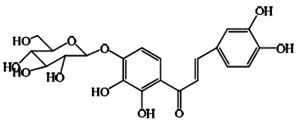
5(b) vanillic acid



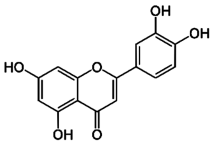
5(c) quercetagetin-7-O-glucoside



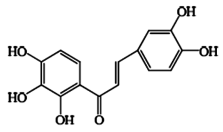
5(d) flavanomarein



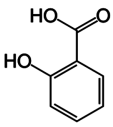
5(e) marein



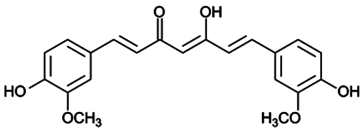
5(f) luteolin



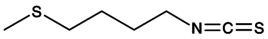
5(g) coreopsis chalcones



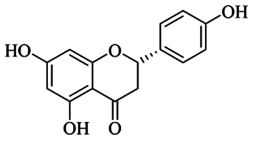
5(h) phenolic acid



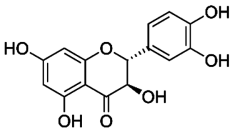
5(i) curcumin



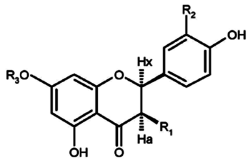
5(j) erucin



5(k) isoaromadendrin

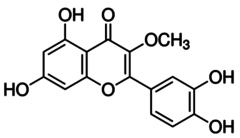


5(l) taxifolin

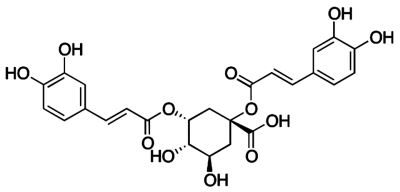


R_1= OH, R_2= H, R_3= β-D-glucoside

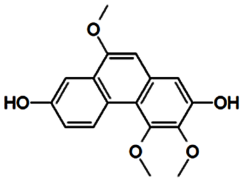
5(m) isosinensin



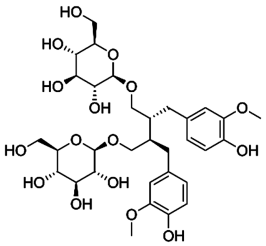
5(n) 3-O-methylquercetine



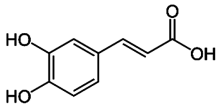
5(o) cynarin



5(p) 2,7-dihydroxy-3,4,9-trimethoxyphenantrene

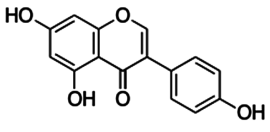


5(q) secoisolariciresinol diglucoside

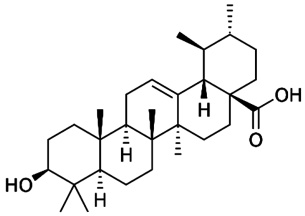


5(r) caffeic acid

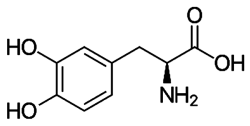
Figure 5. Reported compounds from medicinal plants manifest anti-hypertensive activity.



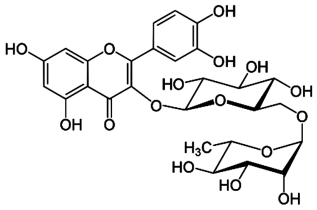
6(a) genistein



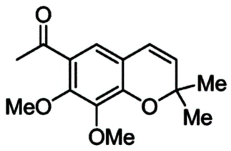
6(b) ursolic acid



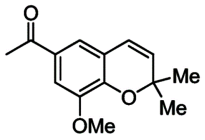
6(c) L-DOPA



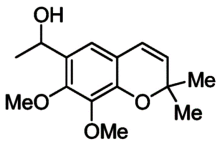
6(d) rutin



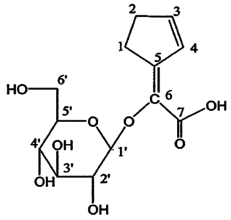
6(e) methylripariochromene A (MRC)



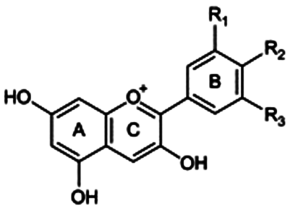
6(f) acetovanillochromene



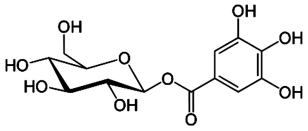
6(g) orthochromene A



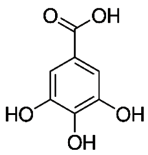
6(h) edulilic acid



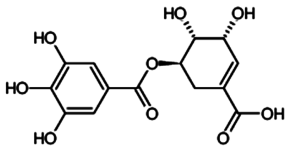
6(i) anthocyanin fraction



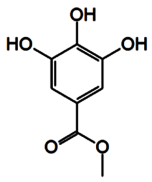
6(j) glucogallin



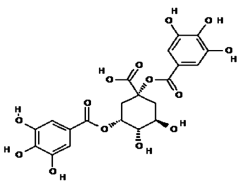
6(k) gallic acid



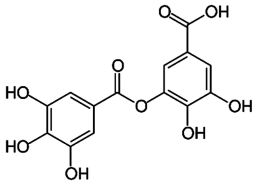
6(l) galloylshikimic acid



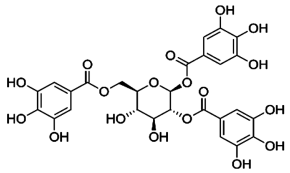
6(m) methyl gallate



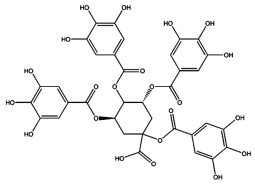
6(n) digalloylquinic acid



6(o) digallic acid

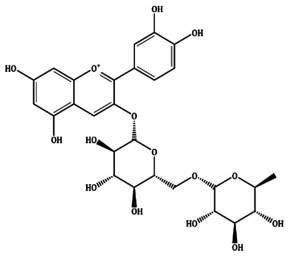


6(p) trigalloylglucose

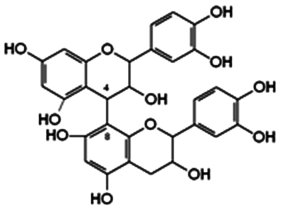


6(q) tetragalloylquinic acid

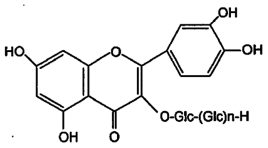
Figure 6. Reported compounds from medicinal plants manifest anti-hypertensive activity.



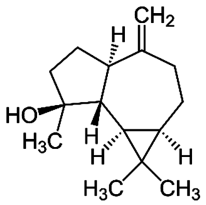
7(a) cyanidin-3-O-rutinoside



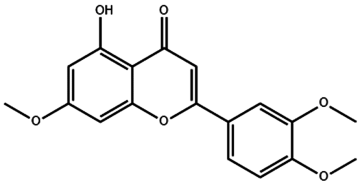
7(b) proanthocyanidins



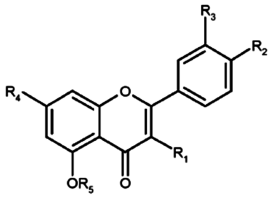
7(c) quercetine glycosides



7(d) spathulenol

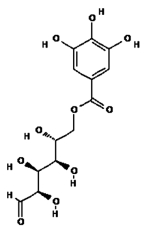


7(e) 5-hydroxy-3,4',7-trimethoxyflavone

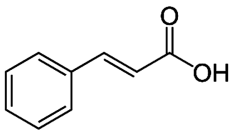


$R_1 = R_3 = R_4 = H$, $R_2 = OH$, $R_5 = \beta$-D-glucoside

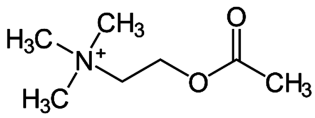
7(f) verbenacoside



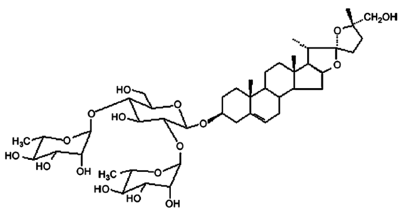
7(g) 6-O-galloyl-D-glucose



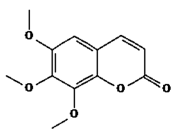
7(h) cinnamic acid



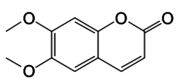
7(i) acetylcholine



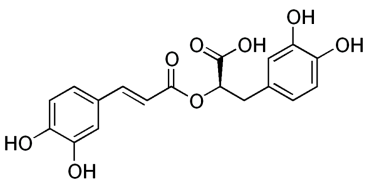
7(j) nuatigenin-3-O-β-chacotriose



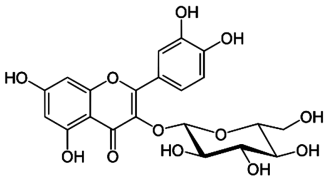
7(k) 6,7,8-trimethoxycoumarin



7(l) 6,7-dimethoxycoumarin



7(m) rosmarinic acid



7(n) isoquercitrin

Figure 7. Reported compounds from medicinal plants manifest anti-hypertensive activity.

quercetagetin-7-O-glucoside, flavanomarein, isosinensin), 15) flavan 3-ols (catechin, epicatechin), 16) flavanones (naringenin, isoaromadendrin), 17) hydroxybenzoate ether (vanillic acid), 18) isoflavone (genistein), 19) isoquinoline alkaloid (berberine), 20) lignan glucoside (secoisolariciresinol diglucoside), 21) phenolic acid, 22) phenylpropanoids (3,4 Dicaffeoylquinic acid, 3,5-Dicaffeoylquinic acid, 4,5-Dicaffeoylquinic acid, chlorogenic acid, ferulic acid, rosmarinic acid), 23) polyphenolic flavonoid (theaflavin-3,3'-digallate), 24) proanthocyanidins (procyanidin B5, procyanidin B3, procyanidin B2, procyanidin C1), 25) sesquiterpenes (spathulenol), 26) steroidal trisaccharide (Nuatigenin-3-O-β-chacotriose), 27) tannins and galloyl derivatives (glucogallin, gallic acid, galloylshikimic acid, methyl gallate, digalloylquinic acid, digallic acid, trigalloylglucose, tetragalloylquinic acid, 6-O-galloyl-D-glucose), 28) thiocyanate (erucin), 29) triterpene (momordin Ib), 30) triterpenoids (22α-hydroxychiisanogenin, chiisanogenin, ursolic acid), and 31) triterpenoid saponins (22α-hydroxychiisanoside, chiisanoside). Highest number of compounds are tannins and galloyl derivatives, flavonols, flavones, phenylpropanoids, proanthocyanidins and flavonoid glucosides.

Structure of the compounds reveals that most of the compounds possess heterocyclic oxygen atom which is thought to exert the desired antihypertensive or antioxidative activities. The possible way would be chelating with the zinc atom present in the center of the ACE I.

4. Conclusion

The goal of our research is to let everyone know that there are an ample number of natural compounds that can be made into antihypertensive therapies. We noticed that the majority of the researches focused on the effect of the extracts on antihypertensive therapy along with the mechanism of action and more than half of them elucidated structures of compounds responsible for the activity. As a result, expanding studies into mechanisms and structure elucidation can contribute to the development of new drugs. 63 plant species from 37 families and 74 isolated compounds are reviewed here. Among them, tilianin, naringenin, curcumin nanoemulsion, 2,7-dihydroxy-3,4,9-trimethoxyphenanthrene are the topmost candidate for producing antihypertensive therapy from natural products in a safe, efficient, and patient adhering way. On the other hand, relaxation of blood vessels, formation of NO, blockage of calcium channels, increase in potassium, suppression of the renin-angiotensin pathway, activation of intracellular cGMP, and inactivation of the sympathetic system are mostly the mechanisms discovered in these medicinal plants for antihypertensive activity. Depending upon the side effects of the ongoing therapies, we think it is high time that the pharmaceuticals took the appropriate steps to synthesize effective drug candidate from these phytochemicals that can reach every human being's doorway. Further studies of the rest of the compounds could also lead to promising antihypertensive therapies.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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