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Review

Medicinal Herbs with Potential Anti-Hypertensive Properties: A Systematic Review of Human and Animal Studies

Maryam Isari[1], Nazli Namazi[2], Mohammad Hossein Ayati[3], Roja Rahimi[4]*

[1]Islamic Azad University of Pharmaceutical Science, Tehran, Iran
[2]Diabetes Research Center, Endocrinology and Metabolism Clinical Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran
[3]Department of Traditional Medicine, School of Persian Medicine, Tehran University of Medical Sciences, Tehran, Iran
[4]Department of Traditional Pharmacy, School of Persian Medicine, Tehran University of Medical Sciences, Tehran, Iran

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Abstract

Blood pressure is one of the vital signs, and is the pressure of circulating blood on the walls of blood vessels. When the large arteries lose their natural elasticity and strength, and the smaller ones are narrowed, blood pressure rises and the pressure is exerted by blood on the walls of blood vessels. High blood pressure is dangerous and very harmful for the heart and blood vessels, and is a major cause of mortality in all nations. Many patients tend to use herbal products for controlling their blood pressure, as they are concerned of the side effects of the chemical drugs. There are huge amount of research work exploring the safety and efficacy of a single herb, or combined herbal products on lowering blood pressure, among which some have shown certain effects, and some are negative in results. Grape seed, Garlic, Saffron, Green and White Mulberry, Quince, and some other herbs have more scientific evidence in lowering blood pressure. In this study, we systematically reviewed the scientific literature of clinical trials and animal studies, in which the safety and effectiveness of herbs on lowering blood pressure were evaluated.

Keywords: Blood pressure; Plant; Herb; Extract

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*Corresponding Author: Roja Rahimi
Department of Traditional Pharmacy, School of Persian Medicine, Tehran University of Medical Sciences, Tehran, Iran
Tel: +982188990837
Email: Rahimi_r@tums.ac.ir

Introduction

Hypertension (HTN) is a global health concern in which BP in the arteries is considerably elevated [1]. The World Health Organization has reported that high BP is the major cause of death among cardiovascular diseases. World HTN League (WHL) also recognized that more than 50% of people with HTN are unaware of their ailment [2]. Long term HTN can enhance the risk for coronary artery disease, stroke, heart failure and chronic kidney disease [1].

Diet, obesity, smoking, alcohol consumption, low physical activity level, stress, and genetic factors are predisposing causes for high BP [3]. Apart from weight management and life style changes, taking biochemical and herbal medicine can be helpful to control HTN and prevent chronic diseases [4]. For available pharmaceutical interventions such as atenolol, amlodipine, diltiazem, losartan, etc., several adverse effects such as tiredness, hypotension, bradycardia, cold extremities, postural hypotension, depression, nausea have been reported [5]. Due to high tendency of people to medicinal herb consumption, studies focus on the efficacy and side effects of herbs with potential anti-hypertensive properties in animal and human studies [6]. There was some systematic review available regarding medicinal herbs with antihypertensive effects. However, they investigated only a number of medicinal herbs and there was no particular investigation about all of the medicinal herbs with antihypertensive properties [7]. In the present study, we aimed to summarize the effect of medicinal herbs on BP considering several factors such as their active agents, therapeutic dosage, side effects, and possible mechanisms in animal and human studies. To best of our knowledge, this is the first systematic review taking into account all of the studies on medicinal herbs with antihypertensive and hypertensive properties.

Methods

PubMed, Scopus, Science Direct, and google scholar electronic data bases were searched for publications about the medicinal plants used for controlling HTN. The articles published till December 2016 with English language were included. Key terms used for systematic search were as follows: “BP” “plants”, “extract”,“extracts”,“herb”,“ herbal”, and “herbs”.

Both animal and human studies were included. Non-English papers, case reports, review articles, theses, abstract in symposium and congress, and In vitro studies were excluded. The articles were evaluated based on the eligibility appraise. The name of medicinal herbs used for lowering BP, their active agents, the part of the plant, form (extract, powder, etc), dosages and the mechanism of action were extracted.

Results and Discussion

Among 1084 publications, 524 papers were duplicated and excluded. After evaluating titles and abstracts, 456 papers were excluded due to the following reasons: irrelevant (n = 167), review articles (n = 12) and articles for being thesis, conference abstracts (n = 216),

non-English language (n = 17), underlying disease (n = 44). Finally, 104 papers (84 animal studies and 20 human studies) were included (Figure 1). After the full texts had been checked, 100 articles were chosen for the review.

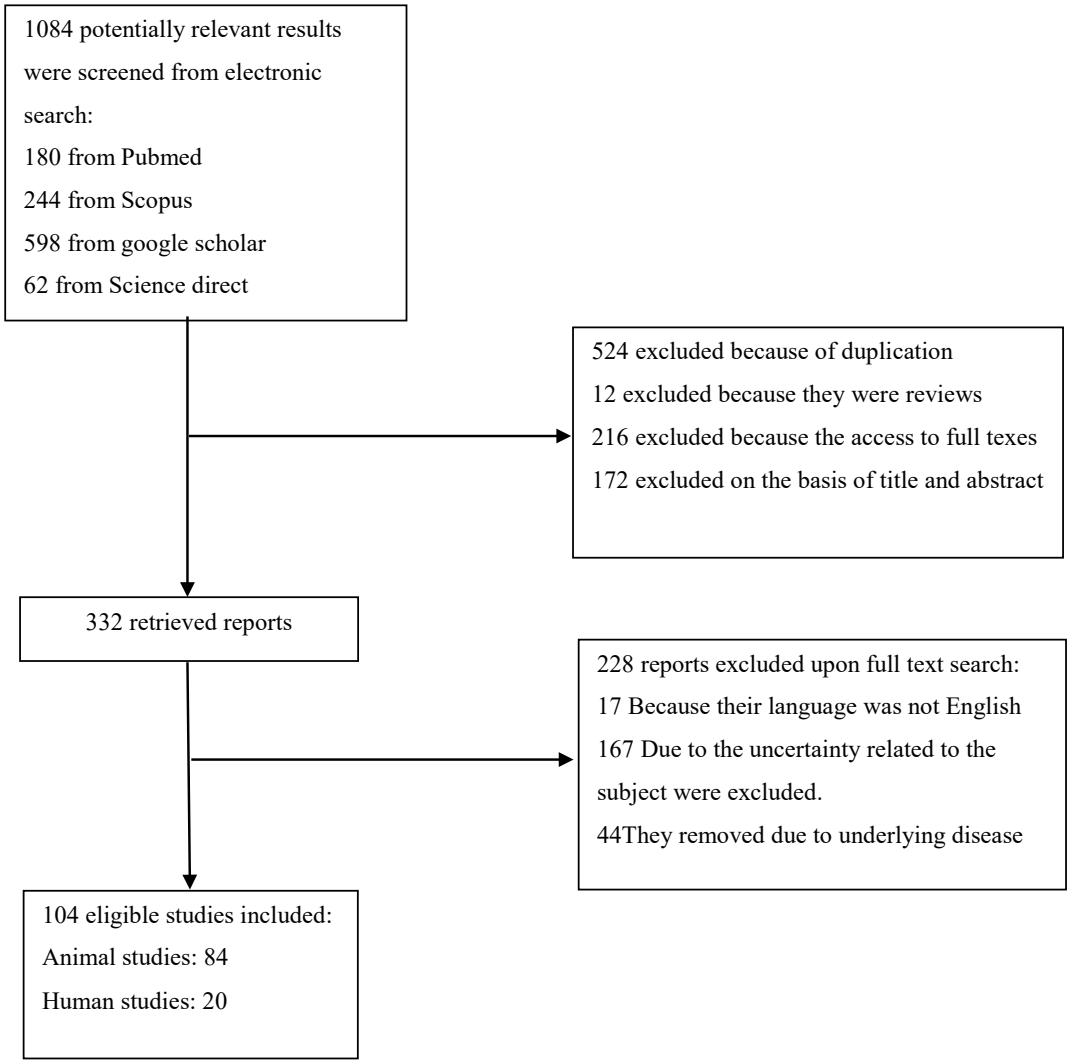

Figure 1. Schematic library diagram of project

Angiotensin converting-enzyme (ACE) inhibitor

Animal studies: *Juglans regia* L. decreased systolic (SYS) and diastolic (DIA) blood pressure (BP) [69]. After using *Rehmannia glutinousa/Aconitum variegatum* L., systolic blood pressure (SBP) decreased through a reduction in atrial natriuretic peptide depressor response [73]. *Olea europaea* L. had a dose dependent prophylactic effect against the rise in BP. Its mechanism of action includes the content of oleuropein acting synergistically with other active principles to exert antioxidant, ACE inhibitor, and possibly calcium channel blocking activities [76]. In another study, *Boletus aestivalis* lowered SBP, DBP and heart rate [91]. *Asystasia gangetica* (L.) lowered SYS, DIA, and mean arterial BP dose-dependently.

However, reduction in heart rate was not dose-dependently (10-400mg/kg from leaf extract) [128].

Human studies: *Hibiscus sabdariffa* L. had also a significant lowering effect on arterial BP (dose: 15mg/kg) [149]. In a human study, a mixture of onion and pumpkin seed oil reduced the SYS pressure by 9.09 mmHg and the DBP by 4.06 mmHg. Its extract seems to aid individuals who would like to monitor their BP by applying lifestyle changes and diet [163].

Ca channel blocker

Animal studies: *Portulaca oleracea* L. increased mean arterial BP while in 40 % of rats BP was reduced. It is suggested to act through the postsynaptic α-adrenoceptors and transmembrane calcium influx interference [98]. *Acorus calamus* L. exhibited a vasoconstrictor effect on the baseline by Ca^{2+} antagonism in addition to a nitric oxide pathway [100]. *Sclerocarya birrea* A. (Rich. Hochst.) caused a dose-dependent fall in mean arterial BP by nitric oxide release or intracellular calcium decrease [108]. Moreover, *Solenostemon monostachyus* (P Beauv.) Briq., containing ESOMO, induced a significant decrease in arterial BP by cardio depression and vasodilation, dose dependently [124].

Human studies: *Olea europaea* L., had a dose-dependent BP lowering effect. However, in order to determine the exact mechanism of action, further studies are required [162]. *Zingiber officinale* lowers SYS and DIA BP and heart rate, although their effects were not statistically significant [150].

Vasodilators

Animal studies: There was a significant reduction in mean arterial BP in response to 50 mg/100gr of aqueous extract of *Crocus sativus* L. (dose-dependent), which was through the reduction of contractile response of vas deferens to epinephrine without any changes in contraction [70]. *Crocus sativus* L. reduced the BP in a dose-dependent manner through relaxation and vasodilatory effect [111]. In another study, *Crocus sativus* L. reduced SYS BP dose dependently (10/20/40 mg/kg for 5 week) with the agents called crocin/safranal. The mechanism of action is through the hypolipidemic effect of crocin in rats, in which crocin inhibits pancreatic lipase [130].

The extract of *Teucrium polium* L., had a positive inotropic effect on heart, reduced the BP, and neutralized by inotropic effects [117]. *Cinnamomum zeylanicum* with its phenolic constituents decreased SYS BP after an hour [121]. *Erythrophleum suaveolens* (Guill and Perr.) Brenan induced relaxation of aortic ring segments through its vasodilating activities [122]. *Crataegus Tourn.* ex L. possessed hypotensive action and it had a greater effect on DIA BP rather than SYS BP. It acted through relaxing isolated aorta and mesenteric arteries. It reduced peripheral vascular resistance (by causing vasodilatation) to lower BP [129].

Human studies: For *Ginkgo biloba* (GBE) L., stiffness index was slightly higher in GBE group compared to placebo group and other outcome variables were unaffected [161]. According to a study, *Ginkgo biloba* L. had a significant BP lowering effect during low

dose experiment (120 mg/day) [165].

Diuretics

Animal studies: *Bredemeyera floribunda* Wild. I. acts as a diuretic; therefore it decreased renal BP and it showed dose-dependent and reversible hypotensive responses with dosage of 76 mg/kg and in high doses, the extract led to bradycardia and death. At dosages of 36 to 70 mg/kg, reversible reduction in BP was observed. At higher doses, irreversible hypotensive responses were also reported [77].

Human studies: *Hibiscus sabdariffa* L. had a significant lowering effect on arterial BP. Its hypotensive effect may occur through the reduction of vascular reactivity during sympathetic nervous system activation [153].

The nitric oxide (NO) secretion

Animal studies: *Cudrania tricuspidata* (Carrière.) Bur. ex Lav. had restored SYS BP to its normal level by decreasing urinary soduim and stimulating nitric oxide release from vascular tissues [78]. *Coffea arabica* L. decreased SYS and DIA BP during ingestion by this mechanism [82]. *Panax ginseng* L. with the active component of Ginsenoside/ Nitric oxide (NO), lowered SYS BP which improved vessel wall thickening and alleviated HTN in SHRs /A maximum decrease of SBP 4-6 h postadministration in SHRs. [84]. *Terminalia superba* Engl. and Diels decreased BP and muscle sensitivity and improved endothelial function through decreased TMSE with a special emphasis on NO pathway and oxidative stress [86]. *Vitis vinifera* L. had a lowering and stabilizing effect on BP because of the concentration of nitric oxide in grape seed [139]. SYS BP was on average 11.5± 2.2 mmHg lower, using *Passiflora edulis* Sims. [136].

Human studies: In the case of *Vitis vinifera* L., BP was modestly affected by GSE, (3.0 mmHg for SBP; 1.4 mmHg for DBP). Therefore, consumption of GSE did not decrease the arterial BP. It showed a relaxing effect on the smooth muscle in the vessel [157]. *Vitis vinifera* L. or grape juice had no effect while the grape wine indicated a significant lowering effect on BP via decreasing the plasma edothelin 1 concentrations [159]. According to a study on *Vitis vinifera* L., it reduced both SBP and DBP significantly compared to the placebo group. The endothelium dependent relaxation evoked by the extract that is mediated by the activation of the PI3K/Akt signaling pathway. Moreover, it led to the phosphorylation of eNOS through a redox-sensitive mechanism [166]. Based on studies, green coffee had positive effects on BP, which seems to be useful in patients with mild HTN [155].

Baroreceptor reflex

Animal studies: In animal studies, *Glycyrrhiza glabra* L. decreased DIA and SYS BP. It acted as Cronotropic (+) and Inotropic (–). It can act through lowering tension in the isolated aorta and increasing heart rate, causing baroreceptor reflex [68]. With *Glycyrrhiza glabra* L., a significant decrease in SYS, DIA and mean BP was shown by the modulatory mechanism of adrenergic system

and synergistic effect with the cholinergic system [93].

Quercetin

Animal studies: *Chromolaena odorata* L. King and H.E. Robins contains kaempferol, quercetin, and sitosterol. It lowered the SYS, DIA, pulse, mean arterial pressures of treated rats, dose dependently [112].

Flavonoids

Human studies: The consumption of these plants may reduce the risk of heart disease and obesity. Anthocyanin in purple corn seems to be useful as an anti-hypertensive agent; however, more long-term studies are needed to making decision about its effect [164].

Cholinomimetics

Animal studies: *Commiphora opobalsamum* (L.) Engl. reduced systemic arterial BP by 20% and decreased heart rate by 14% [80]. Eucommia ulmoides Oliv showed an antihypertensive effect right after drug administration. Doses over 3 mg/kg exhibited tendencies with a plateau effect and decreased SYS BP. Its extract showed an agonistic effect on the nervous system and influenced upon muscarinic acetylcholine receptors [94]. The different fractions of *Ficus exasperate* Vahl decreased BP by aforesaid mechanism [118]. *Tridax procumbens* Linn decreased BP by 72 hours after consuming extract and it increased pulse pressure by altering the SYS and pulse pressures [75]. *Tridax procumbens* L. caused a reduction in mean arterial BP in a dose-related manner. Furthermore, the dosages of 6 and 9 mg/kg caused a reduction in heart rate [127]. With *Parinari curatellifolia* Planch. ex Benth, a great decrease in q D amplitude in cat BP was shown, which was facilitated by the release of vasoactive amines blockade of neurotransmitters such as acetylcholine [142]. *Gongronema latifolium* Benth resulted in BP reduction in the same way as the parasympathomimetic drugs by affecting muscarinic receptors and N-hexane and ethyl acetate fractions [143].

A-blockers

Animal studies: *Cleistanthus collinus* (Roxb.) Benth induced HTN; however, did not influence the effects of adrenergic or dopaminergic agents on BP [135]. With *Camellia sinensis* (L.) Kuntze, contractile responses were greatly inhibited in the presence of GTE in a dose-dependent manner by blocking adrenergic α1-receptors [137]. *Brillantaisia nitens* resulted in a biphasic dose-related hypotensive effect via α1-adrenoceptors blockade and β-adrenergic vasodilation [144].

Beta-blockers

Animal studies: The decrease in BP inhibited by propranolol, phentolamine, atenolol or b2-antagonist was shown with *Tinospora crispa* L. and its extract possesses at least three cardiovascular active components to cause an increase in BP and heart rate [103]. *Persea americana* Mill decreased mean arterial pressure and reduced heart rate and BP [133].

Other mechanisms

The animal studies for medicinal herbs with antihypertensive properties:

Morus alba L. with an active agent of flavenoids (routin and quercetin) lowered the SYS BP [71]. *Dombeya buettneri* K.Schum decreased the BP by muscarinic cholinergic pathway, relaxation of the blood vessels and the mean arterial BP, induced by sodium [72]. Lycoris Radiat (L'Hér.) Herb with an active agent of lycoretine decreased BP in rats and anesthetized dogs and increased BP in conscious dogs through α-adrenergic blocking activities and vasopressin activity [74]. *Bulbus fritillariae* prevented the increase of SBP by stimulation of nitric oxide release from vascular tissues that causes vasodilation [79]. *Cinnamomum camphora* L. decreased DIA BP by an unknown mechanism [81]. *Moringa peregrina* (Forssk) Fiori has active components including lupeol, α- and β-amyrin, β-sitosterol, apigenin, rhamnetin, neochlorogenic acid, and quercetin. It reduced SBP but it was partially hypertensive and had an antioxidant effect [83]. *Cydonia oblonga* Mill. Had a hypotensive effect on rats through an unknown mechanism [85]. With *Schinus molle* L., the mean arterial BP was reduced by inhibiting the effects of noradrenaline on arterial BP. Methanol/dichloromethane is an active component of this herb [87]. *Ageratum conyzoides* L. lowered SYS BP and caused greater fall in DIA pressure compared to that of SYS pressure in anaesthetized rats but the mechanism was not mentioned in this study [88]. *Allium sativum* L. lowered SYS BP by an unknown mechanism. Garlic and Aged Garlic have different mechanisms for their lowering effect on SYS BP [89]. *Ipomoea batatas* (L.) Lam. lowered BP by±4.38 mmHg by increasing the expression of eNOS, increasing the SOD level as an endogenous antioxidant, thus decreasing MDA level in the blood [90].

Ginkgo biloba L. had a strong antithrombotic effect and lowered BP, having an antioxidant activity [92]. *Vernonia polyanthes* less decreased arterial BP dependently. The mechanism has not been elucidated yet [95]. *Azadirachta indica* A. Juss induced bradycardia initially followed by cardiac arrhythmia and dose related fall in BP. It also caused absence of p-wave, bradycardia, and ventricular arrhythmia [96]. *Echium orientale* L. and *Citrus* × *aurantiifolia* increased and decreased BP, respectively. Both of them decreased heart rate, but the mechanism of action was not mentioned in this study [97]. *Clerodendrum trichotomum* Thunb increased urinary flow and Na excretion but had no significant effect on BP after intravenous injection of CTT extract, mechanism of which was not mentioned [99].

Antihypertensive and antioxidant effect of *Ferula foetida* L. was evident and significant reduction in SBP was shown in index-induced rats. It contains ferulic acid. It increased total peripheral resistance andhemodynamic changes, increased vascular pressure responsiveness and increased sympathetic, renin-angiotensin system activities [101]. *Withania somnifera* L. lowered Arterial and DIA BP and it prevented the hypotensive effect of acetylcholine and increased

the hypotensive effect of adrenaline by stimulation of cholinergic receptors and blockage of hypotension actions, having cholinergic agonist effect [102]. Tian Ma Gou Yen (TGY) significantly altered the development and prevented HTN by acting on sympathetic vasomotor activity [105]. *Vitis vinifera* L. (GSPE) increased eNOS expression and NO production in an AMPK/ SIRT1 dependent manner and it-attenuated ouabain induced HTN. The mechanism was through endothelial nitric oxide synthase expression in vessel cells and KLF2 induction [106]. *Farayola* (avocado+garlic) caused no significant change in hematological parameters but had a significant reduction in cholesterol and triglyceride values. It lowered SYS and DIA BP [107]. *Vitex doniana* produced a hypotensive dose-dependent effect and the BP was reduced markedly. It affects the smooth muscle of the vascular system but the exact mechanism is not mentioned [109]. *Salvia miltiorrhiza* Bunge. contains Magnesium Tanshinoate B-enriched (MTB), which caused greater fall in BP compared to SME. It relaxed isolated rat and rabbit coronary arteries and this effect was mimicked by its hydrophilic components, tanshinones [110]. *Pleurotus tuber-regium* (Rumph. ex Fr.) Singer, with its flavonoids content, could moderate all the BP indices and manage HTN [113].

For *Artemisia persia*, the most effective dose was 400 mg/kg and none of the doses affected the DIA BP or heart rate and the oral consumption of AP reduced SYS BP after 20 minutes [114]. *Juniperus oxycedrus* L. induced a significant decrease in SYS basal pressure, at adose of 18 mg/kg and a reduction in DIA basal pressure at 6 and 18 mg/kg, with its methanol dichloromethane content, because of the Presence of sesquiterpenoids [115].

With *Vaccinium corymbosum* L., SBP was reduced by 19% at week 4 and 30% lower, through its antioxidant mechanism [116]. In the case of Adenanthera pavonina L. bilirubin, the protein and globulin fraction was significantly high in AP treated group and the study showed that AP seed has BP lowering potential because of the presence of cardiac glycosides in this plant, which has an antihypertensive effect [119].

The administration of Alibernet Red Wine (AWE) failed to reduce BP and improve endothelial function in the femoral arteries [120]. *Sansevieria liberica* Thunb immediately and dose-dependently lowered SYS BP by altering the SYS and pulse pressure. 250mg/kg dose lowered both SYS and DIA BP and Maintained 192 hr after exertion [123].

The study suggests that using *Persea americana* Mill the extract may produce a lipid profile at 500 mg/kg dose level and reduce the SYS and DIA BP by 45.2% it contains high potassium levels [125]. *Chlorella* sp. showed a full of an average of 63mmHg, 1hour after injection [126]. *Prunus domestica* L. might prevent cardiovascular diseases but It was not mentioned wether the BP decreased or not [131]. When used *Ajuga remota* SYS BP dropped 38mmHg. Treatment with *A. remoata* extract can arrest

and reverse cardiovascular diseases [132]. Dose dependent depression of BP and heart rate was seen with *Viscum album* L. through non-adrenergic and non-cholinergic system [134]. *Elaeis guineensis* Jacq attenuated BP increases in nitric oxide deficient rats significantly [138].

Mean arterial BP was reduced by 32%-55% using *Ferula persica* L., mechanism of which was not mentioned [140]. At 100 and 200 mg doses of *Berberis integerrima* extract significant decrease in JT and TpTe intervals was shown through Blocking fast sodium channels [141].

Oral consumption of *Rhodiola rosea* L. extract decreased SYS BP in a dose dependent manner by β-endorphin secretion [145]

The animal studies for medicinal herbs with hypertensive properties

Catha edulis (Vahl) Endl with the active component of cathinone increased both SYS and DIA BP, time-dependently by QT prolongation [146].

Neurada procumbens L. increased SYS and DIA BP, heart rate, and BP of conscious SHR. It had a significant vasoconstrictive effect on aortic strips and the vasoconstrictive effect caused by *Neurada procumbens* is mediated through α-adrenergic receptors [147]. *Echium orientale* L and *Citrus* × *aurantiifolia* had increased and decreased the BP, respectively. The heart rate for both cases increased [97]. After a 30-day diet with *Ginkgo biloba* L., the SYS BP inreased, according to one study [148].

Human studies for medicinal herbs with antihypertensive effect through other mechanisms

Adenia cissampeloides (Planch. ex Hook.) decreased the BP significantly by reducing the muscular contraction. It had a very little effect on DIA BP [151]. *Ginkgo biloba* L. had a significant antihypertensive effect (both SYS and DIA BP) but the heart rate statistics were similar in placebo and EGB groups. This medicinal plant had an inhibitory effect on cardiovascular neuroendocrine responses during stress [152]. *Allium sativum* L. lowered DIA BP and inhibited the rate of progression of coronary artery calcification [154].

Ephedra sp. had no significant effect on BP, according to the studies [156]. In case of watermelon (*Citrullus lanatus* var. lanatus, family Cucurbitaceae), its extract lowered ankle BP, brachial BP and carotid wave reflection by lowering the wave reflection amplitude, independent of aortic stiffness and brachial BP [158]. *Citrus* × *aurantium* L. had no significant effect on BP [160].

Conclusion

In this review, *Hibiscus sabdariffa, Crocus sativus, Ginkgo Biloba, Vitis vinifera, Glycyrrhiza glabra and Tridax procumbens* showed anti-hypertentive properties. However, Ephedra sp. and *Citrus* × *aurantium* L. had no significant effect on HTN. It seems like even though pharmacological approach may come with adverse effects for some patients, the medicinal herbs presented in this review article cannot replace them. The fact that they contain antihypertensive

Table 1. animal studies for the efficacy and mechanism of action of different medicinal plants for HTN

Scientific name	Part and extract/ active constituent	Animal model	Dose	Duration	Result	Mechanism of action	Ref.
Glycyrrhiza glabra L.	Hydroalcoholic extract of root	Acetylcholine-induced HTN in rat	90 mg/kg	1 w	↓SBP & DBP Chronotropic+ Inotropic –	↓Tension in isolated aortic ↑HR Baroreceptor reflex	68
Juglans regia L.	Hydroalcoholic extract of blade	NaCl-induced HTN in dog	5,15,45 mg/kg	20 min	↓SBP & DBP of 15 minutes of administration Short time impression	Artery muscle relaxant Renin- angiotensin system	69
Crocus sativus L.	Petals	KCl-induced HTN in rat, Guinea pig	50 mg/ 100 g	3-4 w	↓MAP	Reduced the contractile responses of vas deferens to epinephrine without any changes in contraction	70
Morus alba L.	Leaf/ rutin & quercetin	Rat	1 mg/ml	1 w	↓SBP	ND	71
Dombeya buettneri K.Schum.	Aqueous extract of leaf	NaCl (8%)-induced HTN in rat	6 mg/kg	6 w	↓BP	relaxation of the blood vessels, muscarinic cholinergic receptor pathway	72
Rehmannia glutinousa (Gaertn.) DC./ *Aconitum variegatum* L.	Aqueous extract	SHR	600gr/ 1500ml water & 75 g/ 1500 ml water	120 min	↓SBP	↓Atrial natrioretic peptide depressor response Renin-angiotensin-aldosterone	73
Lycoris radiate (L'Hér.) Herb.	Bulb/ lycorenine	Surgical femoral HTN in rat & dog	10-40 mg/kg	4 h	↓BP in rats ↑BP in conscious dogs ↓BP in anesthetized dogs	α-adrenergic blocking activities Vasodepressor action of licorenine	74
Tridax procumbens (L.) L.	Leaf	Salt-loaded diet in rat	150-200 mg/kg	192 h	↓BP by 72 h after extract ↑pulse pressure	Alteration of SBP & pulse pressure	75
Olea europaea L.	Leaf	L-NAME-induced HTN in rat	50 mg/kg	4 w	Dose-dependent prophylactic effect against the rise in BP	Oleuropein acting synergistically with other active principles to exert antioxidant, ACE inhibitory and possibly Ca^{2+} channel blocking activities	76
Bredemeyera floribunda Willd.	Crude extract of roots	NaCl-induced HTN in rat	20-80 mg/kg	50 min	↓renal BP with doses 76 & higher the effect was irreversible/ bradycardia & death in high doses At dose of 36-70 mg/kg reversible decrease in BP	Diuretic effects	77

Cudrania tricuspidata (Carrière.)Bur. ex Lav.	Aqueous extract	L-NAME-induced HTN in rat	60 mg/kg	4-6 w	Restored SBP to normal level	↓urinary blood Na^+ stimulation of NO release from vascular tissues	78
Fritillaria ussuriensis MAXIM.	Bulb/water extract	L-NAME-induced HTN in rat	60 mg/kg	4 w	Prevents the increase of SBP	stimulation of nitric oxide release from vascular tissues that causes vasodilation	79
Commiphora opobalsamum (L.) Engl.	Branch extract/fresh leaf & flowers	NaCl-induced HTN in rat	4 mg/kg	ND	Systemic ABP by 20%, ↓HR by 14%	Activation of muscarinic cholinergic receptors	80
Cinnamomum camphora L.	Aqueous extract	Orthostatic hypotension in rat	20 mg/kg	1-3 w	↓DBP	ND	81
Coffea arabica L.	Bean extract	Spontaneous hypertensive rats	140 mg/kg	4 w	↓SBP & DBP	NO-mediated vasodilation	82
Moringa peregrina (Forssk.) Fiori.	Hydroalcoholic leaf extract/ lupeol, α- and β-amyrin, β-sitosterol, apigenin, rhamnetin, neochlorogenic acid, quercetin	Dexamethasone (30 µg/kg) & saline (1ml/kg)- induced HTN in rat	100, 200, 400 mg	14 d	↓SBP	Antioxidant effect	83
Panax ginseng L.	Root/ ginsenoside, NO	NaCl-induced HTN in rat	500 mg/kg	4 w	↓SBP improved vessel wall thickening, A maximum decrease of SBP 4-6 h post-administration	Affecting the Akt-dependent phosphorylation of eNOS/ Increased NO	84
Cydonia oblonga Mill.	Leaf extract	NaCl 0.9%-induced HTN in rat	25 mg/kg	2 w	↓HTN	ND	85
Terminalia superba Engl.& Diels	Extract	SHR	150 mg/kg	5 w	↓BP & sensitivity of muscles, improves endothelial function	TMSE decrease special emphasis to NO pathway and oxidative stress	86
Schinus molle L.	Methanolic extract of leaf	Saline-induced HTN in rat	32-38 mg/kg	30 min	↓MAP & SBP	Inhibition of the effects of noradrenaline on ABP	87
Ageratum conyzoides L.	ND	Nerve-diaphragm hypertensive rat & rabbit	2-6 mg/kg	2 min	↓SBP & DBP Better effect on DBP than SBP in anaesthetized rats	ND	88
Allium sativum L.	Bulb	SHR	ND	10 w	↓SBP Garlic & aged garlic have different mechanisms for their lowering effect on SBP	ND	89
Ipomoea batatas (L.) Lam.	Aqueous extract of tubers	NaCl-induced HTN in rat	ND	4 w	↓±4.38 mmHg BP	Increased expression of eNOS & SOD, decreasing MDA level	90

Boletus aestivalis (Paulet) Fr.	Hot water extract of mushrooms	SHR	77 mg/kg	2-18 w	↓SBP & DBP ↓HR	Converts inactive angiotensin I to vasopressor angiotensin II	91
Ginkgo biloba L.	Extract	Stroke prone/ electric field stimulation in rat	60, 120 mg/kg	3 w	↓BP, antioxidant activity	Strong antithrombotic effect	92
Glycyrrhiza glabra L.	Hydroalcoholic extract	Normotensive rat	0.01 mg/kg	45 min	↓SBP, DBP, mean BP	Modulation of adrenergic system and synergistic effect with cholinergic system	93
Eucommia ulmoides Oliv.	Leaf extract	Pre-hypertensive & SHR	3, 10, 30 mg/kg	3 w	↓SBP -Doses over 3mg/kg exhibited tendencies with a plateu effect	Agonistic effect on nervous system & acted on muscarinic acetylcholine receptors	94
Vernonia polyanthes Less.	Leaf extract	LiCl (60 mmol/ 100 g body weight)-induced HTN in rat	0.5, 1 mg/kg	7 d	↓ABP, ↑Creatinine clearance ↑Glomerular filtration rate	The precise mechanism underlying the arterial pressure falls induced by CHE-treatment has not yet been identified	95
Azadirachta indica A.Juss.	Leaf extract	Rat	100, 300, 1000 mg/kg	ND	Initial bradycardia Cardiac arrhythmia ↓BP dose-dependently	Caused absence of p-wave, bradycardia & ventricular arrhythmia	96
Echium oriental e L.	Petals, fruit / Aqueous extract	Phenylephrine-induced HTN in rat	30, 180, 250 mg/kg	6 d	↓BP & HR	ND	97
Portulaca oleracea L.	Aqueous extract of leaf	Rat	1.4, 56 mg/kg	1-2 min	↑MAP In 40 % of rats BP was decreased	Acted on postsynaptic α-adrenoceptors and by interference with trans-membrane Ca^{2+} influx	98
Clerodendrum trichotomum Thunb.	Leaf	Saline-induced HTN in rat & dog	0.24 gcTT equivalent per kg	1 w	↑Urine flow & Na excretion No significant change in BP	ND	99
Acorus calamus L.	Extract of rhizome	Saline-induced HTN in rat & rabbit	10, 50 mg/kg	1 h	Exhibited a vasoconstrictor effect on baseline	Ca^{2+} antagonism in addition to NO pathway	100
Ferula foetida (Bunge) Regel.	Stem extract/ ferulic acid	Dexamethasone-induced HTN in rat	200/400 /800 mg/kg	18 d	↓SBP, Antioxidant activity	Increased total peripheral resistance & hemodynamic changes ↑Vascular pressure responsiveness ↑Sympathetic, renin-angiotensin system activities	101
Withania somnifera L.	Roots	Adrenaline/ saline-induced HTN in dog	120, 240 mg/kg	32 min	↓DBP & ABP Prevention of the hypotensive effect of acetylcholine & increased the hypotensive effect of adrenaline	Stimulation of cholinergic receptors	102
Tinospora crispa L.	Stem	Saline-induced HTN in rat	1-100 mg/kg	40 min	↓BP inhibited by propranolol,	β_2-antagonists	103

					phentolamine, & atenolol		
Hibiscus sabdariffa L.	Calices	Saline-induced HTN in rat	60, 125 mg/kg/d	1 w	↓BP ↑Metabolism Anti-inflammatory & antioxidant activities	Diuresis & inhibition of the angiotensin 1 converting enzyme	104
Tian Ma Gou Yen containing *Rhizoma Gastrodiae* and *Fructus Gardeniae* as chief ingredients	-	SHR	5 mg/kg	15 w	Significantly altered the development & prevented HTN	Action on sympathetic vasomotor activity	105
Vitis vinifera L. (GSPE)	Seed	Saline-induced HTN in rat	250 mg/kg/ d	5 w	↑eNOS expression and NO production in an AMPK/SIRT1 dependent manner ↓BP	Increase in eNOS expression in vessel cells KLF2 induction	106
Farayola (*Persea americana* +*Allium sativum*)	ND	Adrenaline-induced HTN in rat	1000, 2500, 5000 mg/kg	14 d	↓Cholesterol & triglyceride, ↓SBP & DBP	ND	107
Sclerocarya birrea A. Rich. Hochst.	Leaf extract	Saline-induced HTN in rat	10^{-7} to 10^{-5} mg/ml	ND	↓MAP dose-dependently	NO release or intracellular Ca^{2+} decrease	108
Vitex doniana Sweet	Stem bark	Saline-induced HTN in rat	200-800 mg/kg	5	↓BP dose-dependently	Affects the smooth muscle of the vascular system	109
Salvia miltiorrhiza Bunge.	Root/ Magnesium Tanshinoate B-enriched	Saline-induced HTN in rat	0.7-175 mg/kg	3 min	The enriched extract caused greater fall in BP compared to the whole plant extract	Relaxed isolated rat and rabbit coronary arteries by tanshinones	110
Crocus sativus L.	Petals	Electrical field stimulation in rat, Guinea pig	50 mg/ 100 g b.w.	3-4 w	↓BP dose-dependently, Reduced contractile responses of vas deferens to epinephrine	Relaxatory and vasodilation	111
Chromolaena odorata (L.) King & H.E. Robins.	Leaf/ kaempferol, quercetin, β-sitosterol	Salt loaded diet in rat	100, 200 mg/kg	8 d	↓SBP, DBP, MAP dose-dependently	Antihypertensive effect and improvement of functional vascular changes	112
Pleurotus tuber-regium (Rumph. ex Fr.) Singer	Sclerotia/ flavonoids	Salt loaded diet in rat	100-200 mg/kg	10 d	Can moderate all the BP indices & manage HTN	- Presence of flavonoid & phytosterol (β-sitosterol)	113
Artemisia persia	Leaf	Ephedrine-induced HTN in rat	300, 400, 500 mg/kg	40 min	Most effective dose was 400mg/kg None of the doses affected BP or HR ↓SBP after 20 min	ND	114
Juniperus oxycedrus L.	Leaf & stem	Saline-induced HTN in rat	2-48 mg/kg	ND	↓Systolic basal pressure at dose of 18 mg/kg & diastolic basal	Presence of sesquiterpenoids	115

					pressure at 6 &18 mg/kg		
Vaccinium corymbosum L.	Fruit	NaCl 1% in stroke-prone rat	3% freezed BB extract	8 w	↓SBP	Antioxidant effects	116
Teucrium polium L.	Stem bark & leaf extract	Normal saline in rabbit	20, 40, 80 mg/kg	ND	Positive inotropic effect on heart ↓BP	Relaxant and vasodilator on smooth muscles	117
Ficus exasperata Vahl.	Leaf extract	Rabbit	0.25-40 mg/kg	ND	↓BP with different fractions	Cholinomimetic effect	118
Adenanthera pavonina L.	Seed	Saline-induced HTN in rat	200 mg/kg	4 w	↓BP, Bilirubin, protein & globulin fraction were significantly high in extract treated group	The presence of cardiac glycosides in this plant has antihypertensive effect	119
Vitis sp. (as Alibernet Red Wine, AWE)	Fruit/ wine	Normotensive & hypertensive rat	24.2 mg/kg/day	3 w	No significant change in BP & endothelial function	ND	120
Cinnamomum zeylanicum Blume	Stem bark/ phenolic compounds	NaCl 9%-induced HTN in rat	5, 10, 20 mg/kg	60 min	↓SBP	Vasorelaxant & vasodialtory activity Reducing cardiac activity	121
Erythrophleum suaveolens (Guill. & Perr.) Brenan	Stem bark	Rat/ guinea pig	0.1-100 µg/ml	ND	Induced relaxation of aortic ring segments	Vasodilatory activity	122
Sansevieria liberica Thunb.	Leaf	Salt loaded diet in rat	200, 250 mg/kg	7 w	↓SBP dose-dependently ↓SBP & DBP 250 mg/kg	Alteration of the systolic & pulse pressure	123
Solenostemon monostachyus (P Beauv.) Briq.	Leaf	Rat/ guinea pig	0.6-17.6 mg/kg	ND	↓ABP dose-dependently	Ca^{2+} channel blocking Cardiodepression & vasodilation	124
Persea Americana Mill.	Seed extract	Pre-hypertensive rat	200, 500, 700 mg/kg	4 w	↓SBP & DBP by 45.2% Improvement of lipid profile parameters	High content of potassium	125
Chlorella sp.	Algae leaf	Rat	15-30 mg/rat	5 h	↓BP of an average of 63 mmHg	ND	126
Tridax procumbens L.	Leaf extract	Saline-induced HTN in rat	3-6-9 mg/kg	ND	↓ABP dose-dependently ↓HR with 6 & 9 mg/kg doses	Activation of muscarinic cholinergic receptors	127
Asystasia gangetica (L.) T.Anderson	Leaf extract	SHR	10-400 mg/kg	3 h	↓SBP, DBP, MAP dose, ↓HR dose-independently	Modulation of ACE, ANG 2 receptor, & HR	128

Crataegus sp.	Leaf & flower	Saline-induced HTN in rat	3.125,6.25,12.5,25 mg/kg	50 min	↓Both SBP & DBP with a better effect on DBP	Relaxing isolated aorta and mesenteric arteries/ reduces peripheral vascular resistance	129
Crocus sativus L.	Stigma/ crocin, safranal	DOCA salt-induced HTN in rat	10/20/40 mg/kg	5 w	↓SBP dose-dependently	ND	130
Prunus domestica L.	Fruit	SHR	ND	5 w	↓BP	Antioxidant properties	131
Ajuga remota Benth.	Leaf	Saline-induced HTN in rat	5-60 mg/lit	16 w	↓SBP 38 mmHg	ND	132
Persea americana Mill.	Seed extract	Rat	260 mg/kg	10 d	↓BP, MAP, HR	β-adrenoceptor blocker	133
Viscum album L.	Leaf extract	Pre-hypertensive rat	5-160 mg/kg	6 w	↓BP dose-dependently	Non-adrenergic, Non-cholinergic	134
Cleistanthus collinus (Roxb.) Benth.	Leaf extract	Saline-induced HTN in rat			↓BP	Exerts α-receptor blocking activity	135
Passiflora edulis Sims	Peel	SHR	10-50 mg/kg	4 w	↓SBP 11.5± 2.2 mmHg	NO modulation	136
Camellia sinensis (L.) Kuntze	Leaf	Phenylephrine-induced HTN in rat	0.3-1.2 mg/ml	4 w	Inhibition of contractile responses dose-dependently	Blockage of α_1-adrenergic receptors	137
Elaeis guineensis Jacq.	Frond	L-NAME-induced HTN in rat	ND	ND	↓BP	ND	138
Vitis vinifera L.	Seed	Pre-hypertensive rat	4 mg/kg/day	6 month	↓BP	NO-dependent vasodilation	139
Ferula persica L.	Stem, leaf, petal	Rat	30 mg/kg/d	1 month	↓MAP by 32%-55%	ND	140
Berberis integerrima Bunge	Fruit extract	Rat	50, 100, 200 mg/kg	2 w	↓JT&TpTe intervals with 100 & 200 mg/kg	Blocking fast Na^+ channels	141
Parinari curatellifolia Planch. ex Benth.	Bark, leaf, root	Snake venom-induced HTN in cat & rabbit	1 mg/ml	ND	↓q.Dcm amplitude in cat ↓BP	Release of vasoactive amines/ blockade of neurotransmitters such as acetylcholine	142
Gongronema latifolium Benth.	Leaf	Atropine & adrenaline-induced HTN in cat	1-5 mg of crude	ND	↓BP	Affecting muscarinic receptors	143
Brillantaisia nitens Lindau	Leaf	L-NAME-induced HTN in rat	10-40 mg/kg	4 w	Biphasic dose-related hypotensive effect	α_1-adrenoceptors blockade/ β-adrenergic vasodilation	144
Rhodiola rosea L.	Whole plant	Pre-hypertensive rat	30-35-75 mg/kg	2 w	↓SBP dose-dependently	β-endorphin secretion	145

MAP=mean arterial pressure, SBP=systolic blood pressure, DBP=diastolic blood pressure, L-NAME= nitro-l-arginine methylester, eNOS= endothelial nitric oxide synthase, ABP=arterial blood pressure, HTN= hypertension, HR= heart rate, NO= nitric oxide, DOCA= desoxycorticosterone acetate, KLF2= Krüpple like factor 2, AMPK= 5′-AMP activated protein kinase, MTB=magnesium tanshinoate B, SHR= spontaneously hypertensive rat, D= day, W= week, ND= not determined

Table 2. animal studies for the efficacy and mechanism of action of different medicinal plants which increases the blood pressure.

Scientific name	Part	Model	Does	Duration	Result	Mechanism of action	Ref.
Catha edulis (Vahl) Endl.	Shrub/ cathinone	NaCl 9%-induced HTN in rat	3 g/kg	60 min	↑SBP & DBP time-dependently	↑QT interval	146
Neurada procumbens L.	Aqueous extract	SHR & saline injection in rat	1-2 g/kg	60-180 min	↑SBP, DBP, HR	Vasoconstrictive effect on aortic strips via α-adrenergic receptors	147
Citrus × aurantiifolia	Petals & fruit aqueous extract	Phenylephrine (1.672 mg)-induced HTN in rat	30, 180, 250 mg/kg	6 d	↑BP	ND	97
Ginkgo biloba L.	Leaf	Pre-hypertensive rat	0.05% -0.5%	30 d	↑SBP	ND	148

HTN= hypertension, MAP= mean arterial pressure, HR= heart rate, SBP= systolic blood pressure, DBP= diastolic blood pressure

Table 3. The list of medicinal plants used for treatment of HTN in human subjects.

Scientific name	Part	Study design	Does	Jadad score	Groups	Duration	Result	Mechanism of action	Ref.
Hibiscus sabdariffa L.	Aqueous calyx extract	Uncontrolled trial using cold pressor test	15 mg/kg	0	20 healthy subjects	ND	Elevation of MAP & HR were significantly lower with the extract	Reduction of vascular reactivity during sympathetic nervous system activation	149
Zingiber officinale Roscoe	Rhizome	Double-blind randomized trial	50, 100 mg/kg	2	Group A: distilled water Group B:100 mg/kg of plant Group C: 50 mg/kg of plant	2-4 h	↓SBP, DBP, HR	Blockade of voltage dependent Ca^{2+} channels	150
Adenia cissampeloides (Planch. ex Hook.) Harms	Extract	Single-blind trial	150 mg/kg	0	14 patients Group A: Test group Group B: Control group	1 year	↓BP with little effect on SBP	Reduction in muscular contraction	151
Ginkgo biloba L.	Leaf	Double-blind, placebo-controlled trial	120 mg	1	70 patients	Single-dose administration	↓SBP & DBP No significant effect on HR	Inhibition of cardiovascular neuroendocrine responses during stress	152
Hibiscus sabdariffa L.	Calyx	Randomized uncontrolled trial	15 mg/kg	1	20 healthy subjects	ND	↓MAP	Reduction of vascular reactivity during sympathetic nervous system activation	153

Allium sativum L.	Bulb	Placebo-controlled, double-blind, randomized trial	1000 mg	2	210 patients: 106 test 106 placebo	1 year	↓DBP	Inhibition of artery calcification rate	154
Coffea arabica L.	Been	Placebo-controlled, randomized, double-blind trial	140 mg/kg	2	28 patients: 14 placebo 14 test	14 w	↑BP Useful for mild hypertensive patients	NO-mediated vasodilation	155
Ephedra sp.	Sprout	Double-blind, randomized, placebo-controlled	15 mg extract 60 mg caffeine	2	13 healthy subjects	7 d	No significant change in any cardiovascular parameter	ND	156
Vitis vinifera L.	Seed	Double blind placebo-controlled randomized	300 mg/d	2	70 patients: 35 placebo 35 test	8 w	↓3.0 mmHg for SBP & 1.4 mmHg for DBP No significant change in ABP	NO synthesis dependent pathway Relaxes the smooth muscles on vessels	157
Citrullus lanatus var. l anatus	Whole fruit	Randomized, placebo-controlled trial	6 g/d	2	14 patients	6 w	↓Ankle BP, brachial BP, & carotid wave reflection	Reduction of wave reflection amplitude independent of aortic stiffness & brachial blood pressure	158
Vitis vinifera L.	Juice/ wine	Double-blind, placebo-controlled trial	800 mg	1	60 patients: 30 test 30 placebo	4 w	Wine: ↓BP, Juice: No significant change in BP	↓Plasma endothelin-1 concentrations	159
Citrus × *aurantium* L.	Fruit	Uncontrolled trial	80 mg/d	-	30 healthy adults	6 w	No significant change in BP & HR	ND	160
Ginkgo biloba L.	Leaf	Single-blind, randomized, placebo-controlled trial	6 capsules of 360 mg of the extract	1	14 young healthy male	6 h	↑Stiffness index (slightly higher)	ND	161
Olea europaea L.	Leaf	Randomized, open, controlled-parallel-group co-twin trial	500, 1000 mg/d	2	40 borderline monozygotic twins divided into treatment & placebo groups	8 w	↓Mean BP in high dose group	Cholesterol lowering action in humans	162
Allium cepa L. + *Cucurbita* sp.	*A. cepa* bulb, *Cucurbita* seed oil	Open-label, placebo-controlled pilot-study	ND	5	12 subjects	12 w	↓SBP 9.09 mmHg & DBP 4:06 mmHg	Antioxidant effects, Inhibition of angiotensin-converting enzyme activity	163
Zea mays L.	Grain	Double-blinded, placebo-controlled,	300 mg/d	3	30 healthy subjects	3 w	↓SBP & DBP	Anthocyanin seems to be useful in anti-	164

		randomized, crossover trial						hypertensive effect of purple corn	
Ginkgo biloba L.	Leaf & fruit	Double-blind, placebo-controlled, randomized trial	120 mg/d	3	54 patients	3 month	↓DBP	Vasodilatory properties in selected cerebral regions	165
Vitis vinifera L.	Seed	Single center, double-blind, placebo-controlled, randomized trial	300 mg/d	2	66 subjects	2 w	↓SBP & DBP	Endothelium dependent relaxation through activation of PI3K/Akt signaling	166

LDH=Lactate dehydrogenase, CK=creatine kinase, DBP=diastolic blood pressure, SBP=systolic blood pressure, ABP=arterial blood pressure, eNOS= endothelial nitric oxide synthase, MAP= mean arterial pressure, D= day

compounds does not indicate that patients can use it instead of drugs. So with these raw data available, patients should be advised against medicinal herb consumption, since they may cause several complications. Even though the desired effect for the medicinal herbs mentioned here has been proved by several human and animal studies, the safety of these compounds are not elucidated nor could it be a therapeutic course for patients with HTN.

Conflicts of Interest

None.

Acknowledgment

None.

List of abbreviations

Systolic= SYS
Diastolic= DIA
LDH=Lactate dehydrogenase
CK=creatine kinase
EGB=extract of ginkgo biloba
DBP=diastolic blood pressure
SBP=systolic blood pressure
BP=blood pressure
ABP=arterial blood pressure
eNOS= endothelial nitric oxide synthase
MAP= mean arterial pressure
SBP=systolic blood pressure
L-NAME= nitro-l-arginine methylester
Enos= endothelial nitric oxide synthase
ABP=arterial blood pressure
EL=eucommia leaf
GSPE= Grape seed proanthocyanidin extracts
KLF2= Krüpple like factor 2
AMPK= 5′-AMP activated protein kinase
MTB=magnesium tanshinoate B
AP=Artemisia Persia
SHR= spontaneously hypertensive rats
GTE= green tea extract

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