HYPERTENSION- ANIMAL MODELS AND PHYTOMEDICINES:
A REVIEW

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Summary

Hypertension is a clinical condition of persistent raised arterial blood pressure, primarily due to increased vascular resistance in systemic circulation. Hypertension is one of the leading causes of disability, morbidity and mortality among the populace; it is the most common chronic illness the world faces. Although the exact cause and mechanisms of hypertension are not known, it is generally believed that both genetic and environmental factors, such as high sodium intake, cigarette smoking and mental stress are involved. The numbers of synthetic antihypertensive agents are available in clinical practice; however they are not effective in all case. Moreover, these agents are highly associated with side effects and drug-drug interaction. So with synthetic agents, there is need of some alternative therapy. Herbs have been used as medical treatments since the beginning of civilization and some derivatives (e.g., reserpine and digitalis) have become mainstays of human pharmacotherapy. For cardiovascular diseases, herbal treatments have been used in patients with congestive heart failure, systolic hypertension, angina pectoris, atherosclerosis, cerebral insufficiency, venous insufficiency, and arrhythmia. This manuscript reviews the various animal models used to evaluate antihypertensive activity along with method of induction of hypertension and research progress of some of the herbal drugs that have been used in alternative system for treatment of hypertension.

Kewords: Hypertension, antihypertensive agent, herbal drugs.

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Introduction

Hypertension is a clinical condition of persistent raised arterial pressure, primarily due to increased vascular resistance in systemic circulation (1). Joint National Committee for Detection Evaluation and Treatment of high blood pressure has defined "normal" blood pressure as that <130/85 mmHg; and "high normal" blood pressure as that between 130 and 139 mmHg systolic and 85 and 89 mmHg diastolic. Blood pressure >139 mmHg systolic and >89 mmHg diastolic on several occasion qualifies as hypertension irrespective of age. Systolic blood pressure >160 mmHg together with diastolic blood pressure of <90 mmHg in elderly is termed as "isolated systolic hypertension" (2). In majority of patients of hypertension (90%) the underlying cause is not detected, and the condition is known as "essential" or "primary" hypertension. In small number of cases (10%) the arterial hypertension is secondary to some recognizable pathological conditions such as Cushing's syndrome, Pyelonephritis, Polycythaemia Vera and Toxemia of pregnancy or CNS disorders. In secondary hypertension, the treatment is of causative factor. Essential hypertension on the other hand is treated by using antihypertensive drugs which decrease the raised blood pressure by acting at different sites and by different mechanisms (1).

Hypertension is one of the leading causes of disability, morbidity and mortality among the populace; it is the most common chronic illness the world faces. It is one of the most important modifiable risk factor for stroke, renal vascular diseases and coronary heart disease (CHD) in Western and Asian population and CHD is estimated to be the most common cause of death globally by 2020 (3, 4).

According to Ayurvedic system of medicine, hypertension in itself is not considered as disease but severe form of hypertension generally leads to the development of certain other diseases. The clinical conditions described in Ayurveda that can be related to hypertension are classified into six groups.

1) *Rakta vridhi* indicative of redness of skin and eye and fullness of veins;
2) *Rakta prakopajanya* indicative of hemorrhage, headache, nausea, tremors, giddiness and haematuria;
3) *Raktavrita vata* indicative of severe pain between muscle and bone, body ache, burning sensation, oedema, generalised red colour of the skin and generalised red eruptions;

4) *Raktagata vata* indicative of severe pain, feeling of ill health, weakness, flushing of skin and loss of appetite;
5) *Siragata vata* indicative of mild body ache, oedema, pulsation, numbness, pain/spasm in the veins and;
6) *Vyanavata vridhi* indicative of fullness of veins and yawning (5).

Although the exact cause and mechanisms of hypertension are not known, it is generally believed that both genetic and environmental factors, such as high sodium intake, cigarette smoking and mental stress are involved in determining the levels of blood pressure and the prevalence of hypertension (6).

Studies from India and Bangladesh have shown an increasing trend in the prevalence of hypertension. Community survey have documented that in a period of three to six decades, prevalence of hypertension has increased by about 30 times among urban dwellers and by about 10 times among rural inhabitants (3). Because of its high incidence and morbidity, various classes of drugs and regimens have been advocated for the control of hypertension (7). But the control of hypertension through diet has been the focal point of public health and mass media attention.

The usual method for controlling hypertension is the use of long term drug therapy. However drugs have many side effects that can complicate the clinical problem. This is why medical professionals and even most of patients prefer herbal medication and preventive strategies (4). Classification, adverse effects and various drug-drug interactions of antihypertensive agents are given in table 1, 2 and 3 respectively.

Table 1: Classification of antihypertensive agents (2, 8, 9).

Sr.No	Class of drug	Examples
1	Angiotensin Converting Enzyme (ACE) inhibitors	Captopril, Enarapril, Lisinopril and Ramipril
2	Angiotensin (AT1) antagonists	Losartan, Valsartan, Irbesartan and Candesartan
3	Calcium channel blockers	Verapamil, Diltiazem, Nifedipine, Felodipine and Amlodipin
4	Potassium channel activators	Diazoxide, Minoxidil, Pinacidil and Nicorandil
5	β adrenergic blockers	Propranolol, Atenolol and Metoprolol
6	α adrenergic blockers	Diazoxide and Phentolamine
7	α+ β adrenergic blockers	Carvedilol and Labetalol
8	Central sympatholytics	Clonidine and Methyldopa

9	Selective Imidazole (I) receptor stimulants	Moxonidine
10	Autonomic ganglion blockers	Hexamethonium and Trimethaphan
11	Drug acting reflexly by stimulating baroreceptor	Veratrum
12	Serotonin antagonists	Ketanserine
13	Adrenergic neurone blockers	Reserpine, Bretylium, Guanethidine, Bethanidine and Debrisoquine
14	Diuretics	
i)	Thiazide	Hydrochlorthiazide, Chlorthalidone and Indapamide
ii)	High ceiling	Furosemide
iii)	K$^+$ Sparing	Spironolactone and Amiloride
15	Vasodilators	
i)	Arteriolar	Hydralazine, Minoxidil and Diazodide
ii)	Arteriolar + Venous	Sodium nitroprusside
16	Miscellaneous	Metyrosine

Table 2: Adverse effects of antihypertensive agents (2, 8).

Sr.No	Class of drug	Adverse effects
1	Drugs acting centrally	
i)	Clonidine	Sedation, dryness of mouth, constipation, impotence, bradycardia and postural hypotension.
ii)	Methyldopa	Sedation, headache and fatigue.
2	Ganglionic blocking agents	Blurred vision, dryness of mouth, constipation, urinary retention, orthostatic hypotension and depression.
3	Adrenergic neurone blockers	Postural hypotension, failure of ejaculation, nasal congestion and parotid tenderness.
4	Catecholamine depletors	Excessive salivation, nasal congestion, orthostatic hypotension, weight gain and endocrine disturbances.
5	α adrenergic blockers	Giddiness, drowsiness, fluid retention, nervousness and

		palpitation.
6	β adrenergic blockers	Paradoxical hypertension
7	α + β adrenergic blockers	Drowsiness, palpitation and rise in liver enzymes.
8	Vasodilator drugs	
i)	Hydralazine	Nasal stuffiness, edema, tremors, CHF, muscle cramps and rheumatoid arthritis.
ii)	Sodium nitroprusside	Palpitation, nervousness, perspiration, pain in abdomen and lactic acidosis
9	K^+ channel activators	
i)	Minoxidil	Dermatological reactions, headache, dizziness and palpitation.
ii)	Diazoxide	Increased hair growth.
10	Angiotensin Converting Enzyme (ACE) inhibitors	Dry cough, vitiligo, GI disturbances and muscle cramps.
11	Calcium channel blockers (CCB's)	Negative inotropic effect and decreased insulin release (by Nifedipine).
12	Diuretics	
i)	Thiazide	Hypokalemia, hyperuricemia and hyperglycemia
ii)	High ceiling diuretics	Weakness and fluid and electrolyte imbalance.
iii)	K^+ sparing diuretics	GI disturbances and fatigue.
13	Miscellaneous	
i)	Metyrosine	Sedation, extrapyramidal effects, crystalluria, gynaecomastia, nasal congestion and galactorrhoea.

Table 3: Drug-drug interactions of antihypertensive agents (10).

Drug	Interacting drug	Potential effect
Clonidine	β-Blockers	Increased blood pressure
	Tricyclic antidepressant	Increased risk of hypertensive crisis
Methyldopa	Sympathomimetics	Increased blood pressure
Prazocin	β-Blockers, Verapamil	Increased postural hypotension
ACE-I	Indomethacin	Decreased effect of ACE-I

	K$^+$sparing diuretics	Elevated serum K$^+$
	Lithium	Increased concentration of lithium
AT$_2$ receptor blockers	Lithium	Increased concentration of lithium
Captopril	Food	Decreased GI absorption of food
Cardioselective and noncardioselective β-Blockers	Propafenone, Quinidine and Verapamil	Increased effect of β-Blockers
	Barbiturates	Decreased bioavailability of β-Blockers
	Cimetidine	Increased concentration of β-Blockers
	NSAID's, Rifamycin	Decreased concentration of β-Blockers
Atenolol	Ampicillin	Decreased effect of Ampicillin
Labetalol	Inhalation anaesthetics	Excessive hypotension
Metoprolol	Thiamines	Increased effect of Metoprolol
Sotalol	Quinolones	Increased risk of cardiac arrhythmias, including Torsade de pointes.
Diltiazem	Carbamazepines, Moricizine and Theophylline	Increased concentration of interacting drug
Felodipine	Barbiturates, Carbamazepines and Hydantoins	Decreased effect of Felodipine
	Erythromycin, Grapefruit juice and Itraconazole	Increased effect of Felodipine
Nifedipine	Barbiturates and Rifampicin	Decreased effect of Nifedipine
	Cimetidine	Increased effect of Nifedipine
Verapamil	Calcium salts	Reversed clinical effects and toxicitiec of Verapamil
	Digoxin	Increased concentration of Digoxin
	Rifampin	Decreased effect of oral

| | verapamil |
| Non depolarizing muscle relaxants | Increased non depolarizing muscle relaxation effect |

Methods to induce experimental hypertension

1. Renovascular hypertension:

Renal hypertension is produced by renal artery constriction, which activates peripheral Renin Angiotensin Aldosterone System (RAAS) and sympathetic nervous system. Renin is secreted by kidneys when sympathetic activity is increased. Renin converts angiotensinogen to angiotensin-I. Angiotensin-I in converted to angiotensin-II by Angiotensin converting enzyme (ACE). Angiotensin-II is potent vasoconstrictor and increase blood pressure (BP). Angiotensin-II causes release of aldosterone leading to salt and water retention, resulting in increased blood volume and hypertension (11, 12).Various methods of inducing renovascular hypertension as described by Goldblatt are

a) **Two kidney one clip (2K1C) hypertension:** The renal artery is constricted on only one side with other artery (or kidney) left untouched. This results in sustained increase in BP due to increased plasma rennin activity (PRA), which in turn increases circulating angiotensin-II, a potent vasoconstrictor (12-14).

b) **One kidney one clip (1K1C) hypertension:** Constriction of renal artery is done on one side and contralateral kidney is removed. There is increase in BP within few hours due to rapid salt and water retention (12, 14).

c) **Two kidney two clip (2K2C) hypertension:** Constriction of aorta or both renal arteries is done. There is a patchy ischemic kidney tissue, which secretes renin leading to increased BP (15).

2. Dietary hypertension:

a) **Increased salt intake:** Chronic ingestion of excess salt produces hypertension in rats which mimics human hypertension morphologically. High salt intake hypertension has been produced in rats, rabbits and chicks by replacing drinking water with 1-2% sodium chloride for 9-12 months (16).

b) **High fructose diet:** Several studies have demonstrated that chronic fructose feeding leads to insulin resistance, glucose intolerance,

hyperinsulinemia and hypertriglyceridemia in relatively short time in normal rats (17-19). These metabolic changes lead to essential hypertension (20, 21).

3. **Endocrine hypertension:**

a)   **DOCA-salt induced hypertension:** In DOCA-salt treated animals, Na^+ and water are absorbed in the kidney, which increases circulating blood volume and results in hypertension (22). There is also increased secretion of vasopressin leading to water retention and vasoconstriction. In addition, altered activity of RAAS leads to increased sympathetic activity (23).

b)   **Adrenal regeneration hypertension:** Hypertension is produced in rats by unilateral nephrectomy followed by removal of right adrenal gland and enucleation of left adrenal gland. Drinking water is replaced with 1% saline. Hypertension develops during regeneration of adrenal glands in about 2 weeks (24).

4. **Neurogenic hypertension:**

Vasodilator and depressor reflexes, originating in the baroreceptor areas of the carotid sinus and aortic arch, Stimulation of the afferent buffer fibres exerts an inhibitory influence on the vasomotor center, and their sectioning leads to a persistent rise in blood pressure. In this way, acute neurogenic hypertension can be induced in dogs (25). Electrical or chemical stimulation of different areas of brain leads to development of hypertension in rats e.g., electrical stimulation of hypothalamus, glutamate injection into the rostral ventrolateral medulla (26, 27).

5. **Psychogenic hypertension:**

It has been reported that elevation of BP resulting from repeated exposure to stressful situation may lead to state of persistent hypertension (28). The stress induced hypertension was associated with either normal or suppressed PRA values, suggesting that the hypertension in these animals is not rennin dependent (29). Other types of stress have been applied, such as emotional stimuli, psychosocial stress, immobilization stress and electrical stimuli, but in all cases the results were similar (29, 30).

6. Genetic hypertension:

Spontaneous hypertensive rats (SHR) were developed by meticulous genetic   inbreeding that uniformly resulted in 100% of the progeny having naturally occurring hypertension (31). In SHR, BP gradually increases until it is maintained at markedly elevated level after

approximately 12 weeks of age (32). During the early stable stage and developmental phase of hypertension, elevated BP is maintained in large part by enhanced central sympathetic outflow (33). In the later stage, increased total peripheral resistance with a normal cardiac output and decreased permeability of glomerular membranes form the basis for long term maintenance of the hypertension (34). SHR models are highly recommended for screening potential drug candidate for hypertension (32).

7. Pulmonary hypertension induced by monocrotaline:

The pyrrolizidine alkaloid monocrotaline, derived from *Crotalaria spectabilis*, is hepatotoxic and pneumotoxic in the rat. A single injection of monocrotaline leads to progressive pulmonary hypertension resulting in right ventricular hypertrophy and cardiac failure. Pathologic changes and hemodynamic changes associated with monocrotaline administration include blebbing of the lung, degeneration and fragmentation of endothelial cells, perivascular edema, extravasation of red blood cells, and muscularization of the pulmonary arteries and arterioles (25).

8. Chemically induced hypertension:

a)   **Dexamethasone induced hypertension:** Dexamethasone is a synthetic glucocortocoid that is commonly used in clinical practice and that increases blood pressure in rats (35) and in human beings (36). Chronic dexamethasone treatment increases oxidative stress and systolic blood pressure in rats and reactive oxygen species (ROS) production in human umbilical vein endothelial cells (37). Dexamethasone hypertension was found to be accompanied by a decrease in serum reactive nitrogen intermediate (NOx) concentration and endothelial nitric oxide synthase (eNOS), mRNA levels in heart, kidney and liver in mice (38).

b)   **L-NAME induced hypertension:** Nitric oxide (NO) has a role in many cellular and cardiovascular phenomena, including the regulation of vascular smooth muscle tone. The chronic inhibition

of NO biosynthesis by the oral administration of non- selective NO synthase (NOS) inhibitor N^{ω}-nitro-L-arginine-methyl ester (L-NAME) results in hypertensive cardiomyopathy in rats. This model is characterized by sustained increase in mean arterial pressure and a decrease in heart rate, a reduction in cardiac output, and changes in myocardial contractility, histological alterations consisting of extensive area of myocardial fibrosis, necrosis and increase in cardiac collagen levels (39).

c) **Hypertension induced by Cholinomimetic agents:** Physostigmine, a cholinesterase inhibitor and Oxytremorine, a direct muscarinic chololinergic agonist cause a dose dependent increase in BP (40). The Cholinomimetic induced hypertension has been shown to be elicited through activation of central cholinergic mechanism and mediated peripherally through sympathetic nervous system (33).

d) **Cadmium chloride induced hypertension:** Hypertension is produced by chronic administration of CdCl (1 mg/kg/day, i.p, for 2 weeks). CdCl induced hypertension might be due to the fact that the metal ion might mimic Ca^{2+} ion as a partial agonist and produce a direct contractile effect on vascular smooth muscle (16).

e) **Cyclosporine induced hypertension:** Hypertension has emerged as a serious adverse effect of immunosupression with cyclosporine, which has become the mainstay of immunosupression in organ transplantation (41). Endothelium dysfunction (42), arterial baroreceptor impairment (43) and activation of endothelin (44) and renin angiotensin system (45) are possible mechanism of pressure response to cyclosporine. The attenuation of cyclosporine induced increase in vascular resistance and BP after peripheral (hexamethonium) or central (clonidine) sympathetic blockade provides pharmacological evidences for the involvement of sympathetic neural activity in the hypertensive action of the cyclosporine (46).

f) **Ethinyl estradiol induced hypertension:** Higher doses of ethinyl estradiol produces significant decrease in the basal release of the nitric oxide (NO) along with significant impairment of the Ach induced (i.e. endothelium dependent) and nitroprusside induced (i.e. endothelium independent) relaxation in aortic strip of rats and hence produces hypertension (47).

Phytomedicines for hypertension

The last three decades have witnessed a renewed interest in the search for new drugs from natural sources especially plant flora and the tropical rain forests have been an important focus for this activity, primarily because of their rich biodiversity. At the same time, in developing countries, medicinal plants and their products are commonly used in the management of several diseases including hypertension. The reason for this could be attributed to lack of easy accessibility to modern health facilities, rising

cost of orthodox medical care, lack of definitive curative regimen for some disease like hypertension and combinational therapy which discourages drug adherence (48). Herbal medication has been and remains commonly used instead of chemical drugs because of its minor side effects. The summary of such scientific documentation regarding antihypertensive action using various experimental protocols has discussed below.

Tribulus terrrestris (TT) have been used traditionally for treating a variety of diseases including hypertension & coronary heart diseases (49). Phillips et al reported that aqueous and methanolic extract of TT displayed significant antihypertensive property in spontaneously hypertensive rats. Possible mechanism was attributed to the smooth muscle relaxation via NO release & membrane hyperpolarisation (49).

The root of *Rawolfia serpentina* (snakeroot), the natural source of the alkaloid reserpine, has been a Hindu Ayurvedic remedy since ancient times. In 1931, Indian literature first described the use of *R serpentina* root for the treatment of hypertension and psychoses; however, the use of *Rauwolfia* alkaloids in Western medicine did not begin until the mid 1940s (50). Both standardized whole root preparations of *R serpentina* and its reserpine alkaloid are officially monographed in the United States Pharmacopeia (USP, 1998). A powdered whole root of 200 to 300mg orally is equivalent to 0.5 mg of reserpine (51). Reserpine was one of the first drugs used on large scales to treat systemic hypertension. It acts by irreversibly blocking the uptake of biogenic amines (norepinephrine, dopamine, and serotonin) in the storage vesicles of central and peripheral adrenergic neurons, thus leaving the catecholamines to be destroyed by the intraneuronal monoamine oxidase in the cytoplasm. The depletion of catecholamines accounts for reserpine's sympatholytic and antihypertensive actions. Reserpine's effects are long lasting, since recovery of sympathetic function requires synthesis of new storage vesicles, which takes days to weeks.

Reserpine lowers blood pressure by decreasing cardiac output, peripheral vascular resistance, heart rate, and renin secretion. With the introduction of other antihypertensive drugs with fewer central nervous system adverse effects, the use of reserpine has diminished. The daily oral dose of reserpine should be 0.25mg or less, and as little as 0.05mg if given with a diuretic. Using the whole root, the usual adult dose is 50 to 200mg/d administered once daily or in 2 divided doses (50, 51). *Rauwolfia* alkaloids are contraindicated for use in patients with previously demonstrated hypersensitivity to these substances, in patients with a history of mental depression (especially with suicidal tendencies), in patients with active peptic ulcer disease or ulcerative colitis, and in patients receiving electroconvulsive therapy.

The most common adverse effects are sedation and inability to concentrate and perform complex tasks. Reserpine may cause mental depression, sometimes resulting in suicide, and its use must be discontinued at the first sign of depression. Reserpine's sympatholytic effect and its enhancement of parasympathetic actions account for its well-described adverse effects: nasal congestion increased gastric secretion, and mild diarrhea (52).

Stephania tetrandra is an herb sometimes used in traditional Chinese medicine to treat hypertension. Tetrandrine, an alkaloid extract of *S tetrandra*, has been shown to be a calcium ion channel antagonist, paralleling the effects of verapamil. Tetrandrine blocks T and L calcium channels, interferes with the binding of diltiazem and methoxyverapamil at calcium-channel binding sites, and suppresses aldosterone production (53, 54). A parenteral dose (15 mg/kg) of tetrandrine in conscious rats decreased mean, systolic, and diastolic blood pressures for more than 30 minutes; however, an intravenous 40-mg/kg dose killed the rats by myocardial depression. In addition to its cardiovascular actions, tetrandrine has been reported for its antineoplastic, immunosuppressive, and mutagenic effects (53). Tetrandrine is 90% protein bound with an elimination half-life of 88 minutes, according to dog studies; however, rat studies have shown a sustained hypotensive effect for more than 48 hours after a 25- or 50-mg oral dose without affecting plasma rennin activity. More recently, tetrandrine has been implicated in an outbreak of rapidly progressive renal failure, termed *Chinese herb nephropathy*. Numerous individuals developed the condition after using a combination of several Chinese herbs as part of a dieting regimen. It has been hypothesized that the cause may be attributed to mis identification of *S tetrandra*; nonetheless, questions still remain as to the role of tetrandra in the development of this serious toxic effect (55-58).

The root of *Lingusticum wallichii* is used in traditional Chinese medicine as a circulatory stimulant, hypotensive drug, and sedative. Tetramethylpyrazine, the active constituent extracted from *L wallichii*, inhibited platelet aggregation in vitro and lowered blood pressure by vasodilation in dogs. With its actions independent of the endothelium, tetramethylpyrazine's vasodilatory effect is mediated by calcium channel antagonism and nonselective antagonism of α-adrenergic receptors. Some evidence suggests that tetramethyl pyrazine acts on the pulmonary vasculature (59).

Veratrum (hellebore) is a perennial herb grown in many parts of the world. Varieties include *Veratrum viride* from Canada and the eastern United States, *Veratrum californicum* from the western United States, *Veratrum album* from Alaska and Europe, and *Veratrum japonicum* from Asia.

All *Veratrum* plants contain poisonous alkaloids known to cause vomiting, bradycardia, and hypotension. Most cases of *Veratrum* poisonings are due to mis identification with other plants. Although once a treatment for hypertension, the use of *Veratrum* al-kaloids has lost favor owing to a low therapeutic index and unacceptable toxicity, as well as the introduction of safer antihypertensive drug alternatives (60). *Veratrum* alkaloids enhance nerve and muscle excitability by increasing sodium ion conductivity. They act on the posterior wall of the left ventricle and the coronary sinus baroreceptors, causing reflex hypotension and bradycardia via the vagus nerve (Bezold-Jarisch reflex). Nausea and vomiting are secondary to the alkaloids' actions on the nodose ganglion. The diagnosis of *Veratrum* toxicity is established by history, identification of the plant, and strong clinical suspicion. Clinical symptoms usually occur quickly, often within 30 minutes. Treatment is mainly supportive and directed at controlling bradycardia and hypotension. *Veratrum*-induced bradycardia usually responds to treatment with atropine; however, the blood pressure response to atropine is more variable and requires the addition of pressors. Other electrocardiographic changes, such as atrioventricular dissociation, may also be reversible with atropine. Seizures are a rare complication and may be treated with conventional anticonvulsants. For patients with preexisting cardiac disease, the use of β agonists or pacing may be necessary. Nausea may be controlled with phenothiazine, antiemetics. Recovery usually occurs within 24 to 48 hours (60).

Evodia rutaecarpa (wu-chuyu) is a Chinese herbal drug that has been used as a treatment for hypertension. It contains an active vasorelaxant

component called rutaecarpine that can cause endothelium- dependent vasodilation in experimental models (61).

Xue et al evaluated the effect of total flavonoid (TF) fraction of *Astragalus complanatus* R.Brown on angiotensin II-induced portal-vein contraction in hypertensive rats. Renovascular hypertension rats (RHR) were established by the two-kidney one clip (2K1C) method. The effect of TF on the contraction of portal vein was studied in an isolated preparation. It was found that TF inhibited Ang II-induced portal vein contraction in a dose-dependent manner in RHR and Spontaneous Hypertensive Rats (SHR) through a blood vessel dilation mechanism. Ang II, the main effector peptide of the RAS, can induce the vasoconstriction through binding to the AT1 receptor. In vitro experiments showed that no other neurohumor factor affected the Ang II-induced portal vein contraction except the binding of Ang II in AT1 receptor. The dose–response curve of Ang II-induced portal contraction after TF administration was similar to the curve after administration of the Ang II receptor blockers Valsartan.

The antihypertensive action of TF was attributed to the dilation of vessels and is related to the blockade of the Ang II receptor. It was concluded that total flavonoid has the ability to decrease the blood pressure in hypertensive animals (62).

Lima-Landman et al investigated antihypertensive effect of a standardized aqueous extract (AE) and butanol fraction (BuF) of *Cecropia glaziovii* Sneth, a common tree at the Southeastern Brazilian coast, in rats. Both extracts decreased the hypertension of spontaneous hypertensive rats, the hypertension induced in rats by L-NAME treatment and that induced by constriction of one renal artery. The antihypertensive effect was maintained for as long as 60 days of treatment and was reversible upon drug washout at the same rate of its establishment. The results indirectly indicated that the hypotension induced by AE was not related to ACE inhibition, increased NO synthesis, or specific blockade of α1 and AT1 receptors. It was suggested that BuF interferes with the calcium handling mechanisms in smooth muscle cells and neurons. Although the mechanisms of antihypertensive activity of both the fractions were unknown, AE was found to be an effective and safe antihypertensive phytomedicine (63).

Ryu et al studied the antihypertensive activity of ethanolic extract of the roots of *Saururus chinensis* (EERSC). In isolated rat aortic preparations, EERSC exhibited a potent vasorelaxant effect with EC_{50} value of 9.1µg/ml. This relaxation was significantly inhibited by denudation of endothelial layer or by pretreatment with N^G-nitro-L-arginine methyl ester.

In addition, the raising extracellular K^+ (45 mM), or pretreatment with tetraethylammonium (10mM) significantly inhibited EERSC-induced vasorelaxation in endothelium-denuded aortic rings. In isolated rat hearts, EERSC significantly reduced cardiac functions such as left ventricle pressure and heart rate. In an antihypertensive study with SHRs, long-term oral administrations of EERSC decreased blood pressure of SHRs (approximately 20 mmHg). These results suggested that chronic treatment with EERSC exerts an antihypertensive effect in SHRs, and its direct vasorelaxant properties and negative inotropic actions may contribute to reduce the elevated blood pressure (64).

The vascular effects of aqueous extracts of *Foeniculum vulgare* leaves were tested by Abdul Ghani and Amin using pentobarbital-anaesthetised rats. An intravenous administration of the lyophilized boiled water extract of leaves produced a significant dose-related reduction in arterial blood pressure, without affecting the heart rate or respiratory rate. In contrast, the non-boiled aqueous extract showed very little hypotensive activity.

The hypotensive effect of the boiling water extract appeared not to be mediated via adrenergic, muscarinic, ganglionic or serotonergic receptors; however, it was attributed to the histamine, since the fall in blood pressure was partially inhibited by pyrilamine in combination with cimetidine, blockers of $H_1 + H_2$ receptors, respectively (65).

Wongcome et al tested the water extract from *Coscinium fenestratum* (Gaertn.) Colebr. (CF extract) for its hypotensive and vasorelaxant effects. CF extract effectively reduced blood pressure in anesthetized normotensive rats. The effect was found to be dose dependent with rapid onset of action. The extract showed an endothelium-dependent and independent vasorelaxant activity in isolated aortic rings precontracted with phenylephrine (1 μM) and KCl (60 mM). The capacity of L-NAME (100 μM), an inhibitor of nitric oxide synthase, to reduce the vasorelaxant action of the extract indicated the involvement of nitric oxide. Since CF extract produced greater potency in aortic preparations precontracted with phenylephrine than with KCl, the selective antagonizing action at α-adrenergic receptors could be suggested. Moreover, vasorelaxant effects of CF extract might be related to the inhibition of Ca^{2+} mobilization (66).

Effect of aqueous extract of *Commiphora opobalsamum* on blood pressure and heart rate in rats was studied by Abdul-Ghani and Amin. The hypotensive and bradicardiac effects were found to be immediate and dose related. The hypotensive effect of *C. opobalsamum* was inhibited by pretreatment with atropine sulphate.

These results suggested the possible involvement and activation of muscarinic cholinergic receptors in producing its hypotensive effect (67).

Raw garlic (*Allium sativum*) extract has been shown to possess antihypertensive action in a 2K-1C model of hypertension in rats which could be mediated, in part, by normalizing the elevated levels of PGE_2 and TxB_2. Al-Qattan et al investigated the possible role and involvement of Na/H exchanger (NHE) in the mediation of hypertension and related tissue damage. The effect of an established dose of raw garlic extract was investigated on the expression of NHE-1 and -3 and sodium pump activity in a 2K-1C model of hypertension in rats. 2K-1C animals showed high BP, increased serum concentration of PGE_2 and TxB_2, hypertrophy of the unclipped kidneys, but not in the clipped kidneys In addition, NHE-1 and NHE-3 isoforms were increased in both the 2K-1C kidneys, whereas α-actin was increased in the clipped but not in unclipped kidneys. Sodium pump activity was decreased in the clipped kidneys, but remained unchanged in the unclipped kidneys.

Garlic treatment reduced the induction of NHE-1 only in the unclipped 2K-1C kidneys, whereas garlic treatment increased the sodium pump activity in both the 2K-1C kidneys. These findings demonstrated the antihypertensive action of garlic was associated with a reversal of NHE-1 induction in the unclipped kidneys. Induction of NHE isoforms together with a reduced sodium pump activity might cause necrosis in the 2K-1C clipped kidneys due to cellular retention of Na+. On the other hand, activation of sodium pump by garlic extract in the kidneys should reduce intracellular Na^+ concentration and normalize BP. These findings suggested the use of garlic in the treatment of hypertension (68).

Dimo et al investigated the effect of the leaf methanolic extract of *Bidens pilosa* on systolic blood pressure (SBP) and plasma glucose, insulin, cholesterol, triglycerides and creatinine levels in rats with fructose induced hypertension. Wistar rats that drank 10% fructose solution for 3-6 weeks showed significant increase not only in plasma insulin and cholesterol levels but also in SBP. The extract was able to prevent the establishment of hypertension and lowered the elevated blood pressure levels. The extract also reduced the highly elevated plasma insulin levels provoked by the high fructose diet. The antihypertensive activity of the extract was attributed to the improvement of insulin sensitivity (69).

Urtica dioicia (Urticaceae) is a plant principally used in the traditional medicine of oriental Morocco as antihypertensive remedy. Testai et al evaluated a possible direct cardiovascular action of the plant to know its

possible mechanism of action. In aortic preparations with intact and functional endothelial layer, pre-contracted with KCL 20 mM or norepinephrine 3 μM, the crude aqueous and methanolic extracts of the plant roots, as well as purified extract elicited a vasodilator action. Nevertheless, the vasodilator activity was not present in aortic ring without endothelial layer. In aortic rings with intact endothelial layer, the vasorelaxing effect was abolished by L-NAME, a NO synthesis inhibitor, and ODQ, a guanylate cyclase inhibitor. Furthermore, potassium channel blocker (TEA, 4-aminopyridine, quinine, but not glybenclamide) antagonized the vasodilator action of the purified fraction of *U. dioica*. The same fraction produced a marked decrease of inotropic activity, in spontaneously beating atria of quinea pig, and a marked, but transient, hypotensive activity on the blood pressure of anaesthetized rats. The hypotensive activity was attributed to the vasorelaxing effect mediated by the release of endothelial nitric oxide and the opening of potassium channels, and through negative inotropic action (70).

The rational basis for the use of *Eugenia uniflora* L. (Myrtaceae) as antihypertensive in Northeastern Argentina was assessed in normotensive rats by Consolini et al. Intraperitoneal administration of the aqueous crude extract (ACE) decreased blood pressure (BP) of normotensive rats dose dependently. For determination of the origin of the hypotensive activity, α-adrenergic antagonistic and vasorelaxant ACE activities were tested. The dose dependent curve for phenylephrine on BP was inhibited non-competitively until 80% of its maximal effect. The extract demonstrated diuretic activity at a dose (120mg d.l./kg) higher than the hypotensive one. It was found almost as potent as amiloride, but while amiloride induced loss of Na^+ and saving of K^+, ACE induced decrease in Na^+ excretion. The results demonstrated the empirical use of *Eugenia uniflora* L as antihypertensive agent with mediation of hypotensive effect by a direct vasodilating activity, and to a weak diuretic effect that could be related to an increase in renal blood flow (71).

Viscum album (mistletoe) (VA) is an evergreen partial parasite that grows on branches of deciduous plants (72). A decoction of the leaves of VA is traditionally used in the treatment of hypertension, headache, dizziness, palpitation etc (73). Ofem et al evaluated antihypertensive effect of aqueous leaf of aqueous extract of VA in salt induced hypertension and cardiovascular parameter. VA showed potential antihypertensive effect with the probable involvement of sympathetic mechanism.

However, further studies should be needed to identify the active principles responsible for the antihypertensive activity of the extract followed by specific experiments to ascertain the receptor subtype involved (74).

Gilani et al studied the antihypertensive activity of the aqueous methanolic extract of *Carum copticum* Benth. seeds (CSE) to rationalize some of its traditional uses. CSE caused a dose dependent fall in arterial blood pressure in anaesthetized rats. In isolated rabbit aorta and jejunum preparations, CSE caused an inhibitory effect on the K^+-induced contractions. The calcium channel blocking (CCB) effect was confirmed when CSE shifted the Ca^{2+} dose-response curves (DRC's) to right similar to verapamil. Pretreatment of animals with atropine partially blocked the hypotensive effect of the extract, whereas the inhibitory effect of acetylcholine was completely abolished. This suggested the mediation of blood pressure lowering effect of the extract through cholinergic mechanisms (75). Adeneya et al evaluated the hypotensive properties and the mechanisms of action of the stem bark aqueous extract of *Musanga cecropioides* R.BR. Apud Tedlie (MCW) in anaesthetized rats of Sprague –Dawley strain, through an invasive direct blood pressure measuring procedure. Results demonstrated the dose dependent hypotensive effect of MCW. The vasorelaxant effect was mediated by the inhibition of sympathetic, cholinergic control of the arterial pressure and most significantly through ACE blockade (76).

Maghrani et al reports the antihypertensive effect of *Lepidium sativum* L. (LS) seeds on arterial blood pressure and renal function in normotensive and spontaneously hypertensive rats. 3 weeks oral administration of the aqueous LS extract showed an antihypertensive response and increases water and electrolytes excretion. These results suggest that LS can improve hypertension with no influence on normotensive situation or on cardiac rate. Therefore, these findings support the use of *Lepidium sativum* L. decoction by the Moroccan population for the treatment of hypertension, cardiac and renal diseases (77).

Olea europaea L., (Oleaceae) is one of the widely used plant drug. In traditional medicine the plant is used as a diuretic, hypotensive, emollient, febrifuge and tonic, for urinary and bladder infections and for headaches. The hypotensive and hypoglycemic effects of olive leaves from Mediterranean O. europaea have been well documented. (78). It was reported that the bitter glycoside oleuropein had a hypotensive, coronary dilating and antiarrhythmic action (79). Recently, a bioassay-directed fractionation showed that another component of European olive leaf, beta-(3, 4 dihydroxyphenyl) ethanol was a potent calcium- antagonist.

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The isolate by fractionation from the olive leaf, secoiridoid oleacein, was reported to have distinct angiotensin converting enzyme (ACE) inhibitory effect (80).

Baragatti et al. reported the antihypertensive effect of the dried methanolic extract of the roots of *Gentiana kokiana*, a plant selected among the 37 plants used as antihypertensive in traditional medicine of Tuscany. The methanolic extract of the plant did not produce any effect on the resting tension of the aorta, but caused a marked depression on the concentration–effect curves to norepinephrene. This hypothesis is in accordance with the observation of the marked depression of the contracturant effect of potassium chloride, which acts through a depolarization induced opening of Ca^{2+} channels (81).

Infusion of leaves from *Croton schiedeanus* Schlecht (Euphorbiaceae), commonly known as 'almizclillo' is used in Colombian folk medicine for the treatment of high blood pressure.

Guerrero et al. examined the antihypertensive effects of aqueous extract of *C. schiedeanus* Schlecht (AECS) in anaesthetized and conscious spontaneously hypertensive rats SHR after intravenous and oral administration, respectively, and its vasorelaxant effects on isolated rat aorta preparation. Their results have shown that the aqueous extract from *C. schiedeanus* Schlecht can elicit antihypertensive and bradycardic effects in rats and vasorelaxant activity in rat isolated rings precontracted with high potassium chloride. Therefore, blocking effects upon Ca^{2+} influx through voltage-dependent calcium channels may be implicated. (82)

Conclusion

In traditional practice of medicines, various plants have been used for treatment of hypertension. An ethnopharmacological approach has been provided, which leads to identify potential of new drugs from plant sources, including those for hypertension. From the manuscript, it can be concluded that a variety of plants has great potential to show activities relevant for their use in the hypertension. The majority of studies were found on ACE activities, vasodilator activity, cholinergic mechanism and endothelium derived relaxing factor. However further studies regarding the role of phytoconstituents and compounds responsible for exact mechanism are necessary.

The typical scientific approach for selecting plants to investigate for the treatment of a hypertension is relatively rational method to develop more acceptable and better substitute to the present pharmacotherapy.

Acknowledgments

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