

Role of natural herbs in the treatment of hypertension

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ABSTRACT

Hypertension (HTN) is the medical term for high blood pressure. It is dangerous because it makes the heart work too hard and contributes to atherosclerosis (hardening of arteries), besides increasing the risk of heart disease and stroke. HTN can also lead to other conditions such as congestive heart failure, kidney disease, and blindness. Conventional antihypertensives are usually associated with many side effects. About 75 to 80% of the world population use herbal medicines, mainly in developing countries, for primary health care because of their better acceptability with human body and lesser side effects. In the last three decades, a lot of concerted efforts have been channeled into researching the local plants with hypotensive and antihypertensive therapeutic values. The hypotensive and antihypertensive effects of some of these medicinal plants have been validated and others disproved. However, ayurvedic knowledge needs to be coupled with modern medicine and more scientific research needs to be done to verify the effectiveness, and elucidate the safety profile of such herbal remedies for their antihypertensive potential.

Key words: Antihypertensive, herbs, hypotensive, hypertension, medicinal plants

INTRODUCTION

Hypertension (HTN) or high blood pressure (BP) is a chronic medical condition in which the BP in the arteries is elevated. It is classified as either primary (essential) or secondary. About 90 to 95% of cases are termed *primary* HTN, which refers to high BP for which no medical cause can be found.^[1] The remaining 5 to 10% of cases, called *secondary* HTN, are caused by other conditions that affect the kidneys, arteries, heart, or endocrine system.^[2]

Persistent HTN is one of the risk factors for strokes, heart attacks, heart failure, and arterial aneurysm, and is a leading cause of chronic kidney failure.^[3] Moderate elevation of arterial BP leads to shortened life expectancy. Both dietary and lifestyle changes as well as medicines can improve BP control and decrease the risk of associated health complications.

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CLASSIFICATION

HTN is usually classified based on the systolic and diastolic BPs. Systolic BP is the BP in vessels during a heartbeat. Diastolic BP is the pressure between heartbeats. A systolic or the diastolic BP measurement higher than the accepted normal values for the age of the individual is classified as pre-HTN or HTN.

HTN has several subclassifications including, HTN stage I, HTN stage II, and isolated systolic HTN. Isolated systolic HTN refers to elevated systolic pressure with normal diastolic pressure and is common in the elderly. These classifications are made after averaging a patient's resting BP readings taken on two or more office visits. Individuals older than 50 years are classified as having HTN if their BP is consistently at least 140 mmHg systolic or 90 mmHg diastolic. Patients with BP s higher than 130/80 mmHg with concomitant presence of diabetes or kidney disease require further treatment. HTN is also classified as resistant if medications do not reduce BP to normal levels.^[4] Exercise HTN is an excessively high elevation in BP during exercise.^[5] The range considered normal for systolic values during exercise is between 200 and 230 mmHg.^[6] Exercise HTN may indicate that an individual is at risk for developing HTN at rest.^[7]

CAUSES

Essential Hypertension

Essential HTN is the most prevalent type of HTN, affecting 90

to 95% of hypertensive patients.^[1] Although no direct cause has identified itself, there are many factors such as sedentary lifestyle, stress, visceral obesity, potassium deficiency (hypokalemia),^[8] obesity,^[9] (more than 85% of cases occur in those with a body mass index greater than 25),^[10] salt (sodium) sensitivity,^[11] alcohol intake,^[12] and vitamin D deficiency that increase the risk of developing HTN.^[13] Risk also increases with aging,^[14] some inherited genetic mutations,^[15] and having a family history of HTN.^[16] An elevation of renin, an enzyme secreted by the kidney, is another risk factor,^[17] as is sympathetic nervous system over activity.^[18] Insulin resistance, which is a component of syndrome X, or the metabolic syndrome, is also thought to contribute to HTN. Consuming foods that contain high fructose corn syrup may increase one's risk of developing HTN.^[19]

Secondary hypertension

Secondary HTN by definition results from an identifiable cause. This type is important to recognize since it is treated differently than essential HTN, by treating the underlying cause of the elevated BP. HTN results compromise or imbalance of the pathophysiological mechanisms, such as the hormone-regulating endocrine system, that regulate blood plasma volume and heart function. Many conditions cause HTN. Some are common and well-recognized secondary causes such as Cushing's syndrome, which is a condition where the adrenal glands overproduce the hormone cortisol.^[20] In addition, HTN is caused by other conditions that cause hormone changes such as hyperthyroidism, hypothyroidism, and adrenal gland cancer. Other common causes of secondary HTN include kidney disease, obesity/metabolic disorder, pre-eclampsia during pregnancy, the congenital defect known as coarctation of the aorta, and certain prescription and illegal drugs.

PATHOPHYSIOLOGY

Most of the mechanisms associated with secondary HTN are generally fully understood. However, those associated with essential (primary) HTN are far less understood. What is known is that cardiac output is raised early in the disease course, with normal total peripheral resistance (TPR). Over time, cardiac output drops to normal levels, but TPR is increased. The following three theories have been proposed to explain this:

- Inability of the kidneys to excrete sodium, resulting in natriuretic factors such as atrial natriuretic factor being secreted to promote salt excretion with the side effect of raising TPR.
- An overactive renin-angiotensin system leads to vasoconstriction and retention of sodium and water. The increase in blood volume leads to HTN.^[21]
- An overactive sympathetic nervous system, leading to increased stress responses.^[22]
- It is also known that HTN is highly heritable and polygenic (caused by more than one gene) and a few candidate genes have been postulated in the etiology of this condition.^[23]

Recently, work related to the association between essential HTN and sustained endothelial damage has gained popularity among HTN scientists. It remains unclear however whether endothelial changes precede the development of HTN or whether such changes are mainly due to long-standing elevated BPs.

HTN is a major independent risk factor for coronary artery disease, stroke, and kidney failure. Each increase of 20 mmHg in systolic BP and 10 mmHg in diastolic BP, over the range of 115/75

Table 1: Conventional medicines used in the treatment of hypertension

Diuretics:

- Loop diuretics: Bumetanide, Ethacrynic acid, Furosemide, Torsemide
- Thiazide diuretics: Eptizide, Hydrochlorothiazide, Chlorothiazide, Bendroflumethiazide
- Thiazide-like diuretics: Indapamide, Chlorthalidone, Metolazone
- Potassium-sparing diuretics: Amiloride, Triamterene, Spironolactone

Adrenergic receptor antagonists:

- Beta blockers: Atenolol, Metoprolol, Nadolol, Oxprenolol, Pindolol, Propranolol, Timolo
- Alpha blockers: Doxazosin, Phentolamine, Indoramin, Phenoxybenzamine, Prazosin, Terazosin, Tolazoline
- Mixed Alpha + Beta blockers: Bucindolol, Carvedilol, Labetalol

Adrenergic receptor agonists:

- Alpha-2 agonists: Clonidine, Methylodopa, Guanfacine

Calcium channel blockers:

- Dihydropyridines: Amlodipine, Felodipine, Isradipine, Lercanidipine, Nicardipine, Nifedipine, Nimodipine, Nitrendipine
- Non-dihydropyridines: Diltiazem, Verapamil

ACE inhibitors: Captopril, Enalapril, Fosinopril, Lisinopril, Perindopril, Quinapril, Ramipril, Trandolapril, Benazepril.

Angiotensin II receptor antagonists: Valsartan, Candesartan, Eprosartan, Irbesartan, Losartan, Olmesartan, Telmisartan.

Aldosterone antagonists: Eplerenone, Spironolactone.

Vasodilators: Sodium nitroprusside, Hydralazine.

Centrally acting adrenergic drugs: Clonidine, Guanabenz, Methylodopa, Moxonidine.

to 185/115 mmHg, doubles the risk of a fatal coronary event. The American Heart Association and other organizations are now calling for more aggressive BP goals for many people with HTN, in order to reduce these adverse outcomes. The commonly used agents used for the treatment of HTN are mentioned in Table 1.

In the last three decades, a lot of concerted efforts have been channeled into researching into local plants with hypotensive and antihypertensive therapeutic values. The hypotensive and antihypertensive effects of some of these medicinal plants have been validated and others disproved.

Attempts by the low-income group, particularly the rural dwellers in the developing countries, to control HTN and its attendant complications in the face of the scarce socioeconomic resources, have led more people opting for herbal remedy.^[24] However, more scientific research needs to be done to verify the effectiveness and elucidate the safety profile of such herbal remedies. This review provides an introduction of the naturally occurring medicinal plants that have so far been scientifically studied and reported to have hypotensive or antihypertensive effects.

Naturally occurring medicinal plants, herbs having hypotensive/antihypertensive potential

Agathosma betulina

(Family: Rutaceae; Common name: Buchu). It is a South African medicinal plant and has been used by the indigenous people of the area for centuries to treat wider ailments. It is an effective diuretic and anti-inflammatory agent. Early Dutch settlers used buchu to make a brandy tincture, which is still used today to treat many disorders.^[25]

Allium sativum

(Family: Alliaceae or Liliaceae; Common name: Garlic). Garlic has long been used for a variety of cardiovascular conditions, especially hyperlipidemia. It has also been reported to have hypotensive action. It is thought to increase nitric oxide production, resulting in smooth muscle relaxation and vasodilatation. One of the primary active compounds that gives garlic its characteristic odor and many of its healing benefits is called allicin. Meta-analysis of randomly chosen literary data has demonstrated that garlic is related to decrease of BP in patients with increased systolic pressure, but not in patients without increased systolic pressure.^[26] Garlic preparations have been found to be superior to placebo in reducing BP in individuals with HTN.^[27] The antioxidative and antihypertensive effect of garlic has been observed in 20 patients with HTN compared to 20 patients with normal pressure, who have been receiving garlic pearls preparation for a period of two months. The results have revealed decreased BP, significant reduction of 8-hydroxy-2-deoxyguanosin, level of nitric oxide, and lipid peroxidation, and an increased level of antioxidative vitamins (C and E). This study points to the beneficial cardioprotective action of garlic in essential HTN.^[28]

Annona muricata

(Family: Annonaceae; Common name: Prickly Custard apple).

A. muricata is a member of the family of custard apple trees called Annonaceae and a species of the genus *Annona*, known mostly for its edible fruits Annona. The tree grows natively in the Caribbean and Central America. The leaf extract of the plant has been reported to lower an elevated BP by decreasing the peripheral vascular resistance.^[29]

Apium graveolens

(Family: Apiaceae; Common name: Celery). According to Chinese theory, Celery is effective for HTN because it acts upon the liver; one type of HTN is associated with liver. In Mainland China, celery was useful in reducing HTN in 14 of 16 patients. The juice was mixed with equal amount of honey and about 8 ounces were taken orally three times each day for up to one week.^[30] It has also been reported to reduce systolic and diastolic BP. The difference of BP in human beings before and after treatment has been found to be significant ($P < 0.05$), indicating that seeds of *A. graveolens* can be used as a safe and effective treatment of high BP.^[31] Fresh celery juice can be mixed with vinegar to relieve dizziness and headache and shoulder pain associated with HTN. It is also administered in HTN associated with pregnancy and climacteric.^[25]

Aristolochia manshuriensis

(Family: Aristolochiaceae; Common name: Guan Mu Tong). This Chinese plant is being used as a diuretic and antiphlogistic for the treatment of edema and rheumatic pain. The extract of this plant has been reported to contain aristolochic acid, aristolosite, magnoflorine, oleanolic acid, hederagenin, and tannins. Magnoflorine has been found to possess hypotensive properties.^[32]

Artocarpus altilis

(Family: Moraceae; Common name: Breadfruit). The plant is native to the Malay Peninsula and western Pacific islands. A study has shown that the leaf extract of the plant decreased the tension of phenylephrine-stimulated isolated guinea pig aorta rings by 15 to 35%.^[29]

Avena sativa

(Family: Poaceae/Gramineae; Common names: Dietary Fiber, Green Oat). A diet containing soluble fiber-rich whole oats can significantly reduce the need for antihypertensive medication and improve BP control. Considering the lipid and glucose improvements as well, increased consumption of whole oats may significantly reduce cardiovascular disease risk.^[33] The addition of oat cereals to the normal diet of patients with HTN has been found to significantly reduce both systolic and diastolic BP. Soluble fiber-rich whole oats may be an effective dietary therapy in the prevention and adjunct treatment of HTN.^[34]

Blond psyllium

(Family: Plantaginaceae; Common name: Indian plantago). Preliminary clinical research shows that taking a *B. psyllium* (*Plantago* species) supplement 15 g daily can modestly lower BP; systolic by about 8 mmHg and diastolic by 2 mmHg.^[33]

Camellia sinensis

(Family: Theaceae; Common name: Tea). There are many potential health benefits from drinking tea. There is lots of interest among researchers on the effect of tea on cardiovascular disease. Research on tea and HTN is contradictory. Research on black tea (fermented tea) (*Camellia sinensis*) shows no effect on BP in people with HTN. Population research links consumption of green tea (unfermented) (*Camellia sinensis*) and oolong tea (partially fermented) (*Camellia sinensis*) with a decreased risk of developing HTN.^[35]

Capparis cartilaginea

(Family: Capparaceae; Common name: Lasaf). It is a prostrate or scrambling shrub found in rocky ground, sometimes hanging from cliffs. It has been reported that crude extract of *C. cartilaginea* produces a dose-dependent decrease in BP and slight bradycardia in anesthetized rats.^[36]

Carum copticum

(Family: Umbelliferae; Common name: Ajwain). The crude extract of *C. copticum* (1-30 mg/kg) produces a fall in BP and heart rate (HR) of anesthetized normotensive (NMT) rats. Hypotension produced is very brief and returns to normal within a minute. At the low dose (up to 1 mg/kg), the crude extract produces negligible change in the HR. However, bradycardia has been reported at the higher doses (10-30 mg/kg).^[37]

Cassia absus

(Family: Caesalpinaceae; Common name: Chaksu). This plant is found in the tropical region and is found everywhere in India. It has been reported that an intravenous administration of a crude extract of *C. absus* produces a dose-related (1-30 mg/kg) decrease in BP, accompanied with a decrease in HR at the higher doses (10 and 30 mg/kg). Repeated injections of the same dose of the crude extract have been seen to produce tachyphylaxis. A sustained fall in BP of anesthetized animals and weak antiacetylcholine effect has been reported.^[38]

Cassia occidentalis

(Family: Caesalpinaceae; Common name: Coffee weed). It is a small tree growing 5 to 8 m in height. The leaf of this plant is used in local folk medicine as an antihypertensive agent. *In vitro* studies of the leaf extract have shown a relaxant effect on the aortic rings. The studies revealed that cassia extract may be relaxing smooth muscle and reducing BP by inhibiting Ca²⁺ influx through receptor-operated channel and voltage-sensitive channel, showing its nonselectivity on these Ca²⁺ channels.^[39]

Castanospermum australe

(Family: Fabaceae; Common name: Black bean). Crude extract of *C. australe* has been reported to cause a fall in systolic as well as diastolic BP in a dose-dependent manner (1-100 mg/kg). This fall in BP has been attributed to the saponin fraction and medicogenic acid glucoside present in the crude extract.^[40]

Coleus forskohlii

(Family: Lamiaceae; Common name: Karpurvali). The

pharmacological properties of coleonol, a diterpene, isolated from *C. forskohlii*, have been investigated. Its predominant effect has been to lower the BP of anesthetized cat and rat as well as of the spontaneously hypertensive rat due to relaxation of the vascular smooth muscle. In small doses, it has a positive inotropic effect on isolated rabbit heart as well as on cat heart *in vivo*. Coleonol also exhibits nonspecific spasmolytic activity on smooth muscle of the gastrointestinal tract in various species, but not on bronchial musculature of guinea pig. Large doses of coleonol have a depressant action on the central nervous system.^[41]

Commelina virginica

(Family: Commelinaceae; Common name: Virginia dayflower). It is a perennial herbaceous plant in the dayflower family. It is native to the mideastern and southeastern United States. Whole plant extract has been reported to decrease the tension of phenylephrine-stimulated isolated guinea pig aorta rings by 15 to 35%.^[29]

Crataegus pinnatifida

(Family: Rosaceae; Common name: Chinese Hawthorn). It has been used in China as a decoction for treatment of HTN for thousands of years. Pharmacological and clinical trials have shown that it lowers BP. The two main substances that contribute to hawthorn's beneficial effects on heart are flavonoids and oligomeric procyanidins, which are potent antioxidant agents. Rhynchophylline, an alkaloid in cat's claw, has demonstrated an ability to inhibit platelet aggregation and thrombosis, which suggests that it may be useful in preventing strokes and reducing the risk of heart attack by lowering BP, increasing circulation, and inhibiting both the formation of plaque on arterial walls and formation of blood clots in the brain, heart, and arteries.^[42] In experiments with anesthetized rabbits, intravenous administration of the extract preparation lowered the BP for up to 3 hours.^[43] Grataegic acid was identified as the hypotensive principle. Mechanisms of action of *Crataegus* postulated to date reveal a remedy with potentially broad-based influence on the cardiovascular system. These effects include a hypotensive activity through vasorelaxation resulting from nitrous oxide stimulation,^[44] significant antioxidant activity, and a tonic action on cardiac myocytes.^[45]

Crinum glaucum

(Family: Amaryllidaceae; Common name: River Lily, Swamp Lily). *C. glaucum* used traditionally in Western Nigeria for treatment of asthma was investigated for its effects on respiratory and cardiovascular functions. Increasing doses of the aqueous extract caused an increase in tidal volume (increase in ventilatory rate and depth) and a corresponding decrease in both systolic and diastolic pressures.^[46]

Cuscuta reflexa

(Family: Cuscutaceae; Common name: Giant dodder). Crude extract of *C. reflexa* has been reported to cause a decrease in systolic and diastolic BP as well as HR in anesthetized rats. The antihypertensive activity and bradycardia produced were found

to be dose-dependent, but the decrease in HR was observed at slightly higher doses. Pretreatment with atropine (1 mg/kg) did not abolish the cardiovascular responses to *C. reflexa*.^[47]

Daucus carota

(Family: Umbelliferae; Common name: Carrot). It has been used in traditional medicine to treat HTN. Activity-directed fractionation of aerial parts of *D. carota* resulted in the isolation of two coumarin glycosides coded as DC-2 and DC-3. Intravenous administration of these compounds caused a dose-dependent (1–10 mg/kg) fall in arterial BP in NMT anesthetized rats. In the *in vitro* studies, both compounds caused a dose-dependent (10–200 µg/ml) inhibitory effect on spontaneously beating guinea pig atria as well as on the K⁺-induced contractions of rabbit aorta at similar concentrations. These results indicate that DC-2 and DC-3 may be acting through blockade of calcium channels, and this effect may be responsible for the BP-lowering effect of the compounds observed in the *in vivo* studies.^[48] Two new guaiane-type sesquiterpene terpenoids containing an interesting epoxy unit, daucoside and daucosol, have been isolated from fruits of *D. carota*.^[49]

Desmodium styracifolium

(Family: Leguminosae; Common name: Osbeck). Preparations from the dry leaves and stem of the plant injected intravenously into anesthetized dogs increased coronary circulation, lowered arterial BP, slowed HR, and decreased the oxygen consumption of the heart.^[43] The cardiovascular pharmacology of aqueous extracts of *D. styracifolium* (DSE) and *Clematis chinensis* (CCE) was studied in rats both *in vivo* and *in vitro* by Ho *et al.* in 1982. DSE produced two successive hypotensive actions: the first one mediated through cholinergic receptor stimulation, whereas the second was potentiated by blockades of autonomic ganglion and alpha-adrenoceptor. In contrast to DSE, CCE produced only one hypotensive response, which was mediated through histaminergic activity. Furthermore, both extracts relaxed isolated methoxamine-precontracted helical tail artery strips. CCE also produced both negative chronotropic and inotropic effects on isolated atria, whereas DSE showed positive chronotropic effect, without apparent effect on the contractile force.^[50]

Fuchsia magellanica

(Family: Onagraceae; Common name: Hardy Fuchsia, Chiko, Tilco). This plant is native to Southern Argentina and Chile. Infusion of the leaf extract reduces body temperature, acts as a diuretic, and lowers BP.^[51] Schmeda-Hirschmann *et al.* investigated the ethanol/aqueous extracts of this species in NMT rats and found a moderate to strong reduction in the mean arterial pressure.^[52]

Glycine max

(Family: Fabaceae Common name: Soybean). Soybean has been found to be effective as a hypotensive agent. One study has shown a very modest reduction in BP, whereas other study shows no benefit.^[53]

Gossypium barbadense

(Family: Malvaceae; Common name: Pima cotton). It is a tropical perennial plant that produces yellow flowers and has black seeds. A study has shown that the leaf extract of the plant decreased the tension of phenylephrine-stimulated isolated guinea pig aorta rings by 15 to 35%. In Suriname's traditional medicine, the leaves of the plant are used to treat HTN and delayed/irregular menstruation.^[29]

Hibiscus sabdariffa

(Family: Malvaceae; Common name: Roselle). This happens to be one of the most extensively studied plants for antihypertensive properties. The leaves, calyx, and corolla of this plant are used traditionally in many West African countries for various medicinal purposes and as edibles. The antihypertensive effect of this plant extract has been variously studied. One study reported the antihypertensive effect of calyx of HS.^[54] A similar result was independently produced in Lagos, Nigeria by Adegunloye *et al.*^[55] An intravenous administration of 20 mg/kg of a water extract of dry HS calyx produced a fall in the BP of experimentally induced hypertensive rats. The antihypertensive effects of the crude extract of the HS have been attributed to mediation through acetylcholine and histamine like dependent mechanism through direct vasorelaxant effects.^[55] Earlier report showed that the petal crude extract of same plant had a direct relaxant effect on the aortic smooth muscle of rats.^[56] The chronic administration of aqueous extract of HS has been reported to reverse cardiac hypertrophy in renovascular hypertensive rats.^[57]

Clinical trials of the plant extract in human being have shown reliable evidence of antihypertensive effects. A standardized dose of HS (9.6 mg per day) given to 39 patients and captopril, 50 mg per day, given to the same number of patients did not show significant difference relative to hypotensive effects, antihypertensive effectiveness and tolerability.^[58]

Lavandula stoechas

(Family: Lamiaceae; Common name: French Lavender). Crude extract of *L. stoechas* has been reported to produce a fall in BP and HR in anesthetized NMT rats. Pretreatment of atropine abolished the cardiovascular responses, suggesting that the antihypertensive and bradycardia effects of the crude extract may be mediated through mechanism(s) similar to that of acetylcholine.^[59]

Lepidium latifolium

(Family: Cruciferae; Common name: Rompepiedra or Stone breaker). This plant has been used as a folk medicine in the Canary Islands for renal lithiasis. It has been found to have hypotensive effect due to its diuretic action in rat. The aqueous leaf extract given in doses of 50 and 100 mg/kg through intraperitoneal and oral routes, respectively, produced significant and dose-dependent diuretic and hypotensive activities. The study went further to extrapolate the diuretic action of the extract from rats to man, using the activity of furosemide in both cases as guideline. The standard daily dose for *L. latifolium* in man was 3 to

5 g/day in the form of tea, which is equivalent to 43 to 71 mg/kg body weight in a 70 kg subject.^[60]

Linum usitatissimum

(Family: Linaceae; Common name: Linseed, Flaxseed). It is an annual herb believed to have originated in Egypt. Linseed and its oil are rich in α -linolenic acid, an essential fatty acid that appears to be beneficial for the heart diseases, inflammatory bowel disease, arthritis, and other health problems. α -linolenic acid belongs to a group of substances called omega-3 fatty acids. Several studies suggest that diets rich in omega-3 fatty acids lower BP significantly in people with HTN. Flaxseed may protect against atherosclerotic cardiovascular disease through a number of mechanisms, including reducing serum cholesterol, platelet aggregation, and inflammatory markers; improving glucose tolerance; and acting as an antioxidant. Daily consumption of 15 to 50 g/day of ground flaxseed can modestly reduce total cholesterol and low-density lipoprotein concentrations without altering triglycerides or high-density lipoprotein cholesterol. However, the exact mechanism is unclear.^[61]

Lumnitzera racemosa

(Family: Combretaceae; Common name: Black Mangrove). It is a handsome shrub or a small tree found on the coast of India and on the Andaman and Nicobar Island. According to folk medicine, the fruits of this plant are curative in skin disorders and useful for treating snake and insect bites. Antihypertensive action has been reported for the aqueous acetone extract of the plant. The antihypertensive activity of eleven hydrolysable tannins contained in the leaves of *L. racemosa* has been investigated. From the screening in spontaneously hypertensive rats, corilagin, castalagin, and chebulinic acid were identified as the major active substances.^[62]

Lycopersicon esculentum

(Family: Solanaceae; Common name: Tomato). Tomato extract contains carotenoids, such as lycopene, beta carotene, and vitamin E, which are known as effective antioxidants, to inactivate free radicals and to slow the progress of atherosclerosis. A study showed that extract of tomato (Lyc-O-Mato) modestly reduces BP in patients with mild, untreated HTN.^[63] A significant correlation has been observed between systolic BP and lycopene levels. Tomato extract when added to patients treated with low doses of ACE inhibition, calcium channel blockers, or their combination with low-dose diuretics had a clinically significant effect-reduction of BP by more than 10 mmHg systolic and more than 5 mmHg diastolic pressure. No side effects to treatment were recorded and the compliance with treatment was high.^[64]

Moringa oleifera

(Family: Moringaceae; Common name: Murungai). In anesthetized rats, the crude extract of the leaves of *M. oleifera* caused a fall in systolic, diastolic, and mean BP in a dose-dependent manner. The antihypertensive effect was brief, returning to normal within two minutes. HR was not affected significantly, except at high doses (3 and 10 mg/kg), which produced a small degree

of bradycardia. It was also established that thiocarbamate and isothiocyanate fractions of the crude extract were responsible for the antihypertensive activity.^[65]

Musanga cecropiodes

(Family: Cecropiaceae; Common name: Umbrella tree, Cork Wood). It is a rapidly growing plant ubiquitous to the tropical rain forests, particularly of West Africa. The ethanol extract of the plant stem bark has been reported to have antidiarrheal activity.^[66] Several workers have demonstrated the scientific efficacy of the latex and the leaf extract as a vasorelaxant, and therefore a hypotensive agent.^[67] The water extract of the stem bark has been reported to produce a dose-dependent reduction in mean arterial BP, which fell by 4.51 ± 0.5 mmHg at the dose of 10 mg/kg and 65.23 ± 6.28 mmHg at 40 mg/kg dose.^[68]

Ocimum basilicum

(Family: Lamiaceae; Common name: Basil). It has been reported that a crude extract of *O. basilicum* causes a fall in systolic, diastolic, and mean BP in a dose-dependent manner with median effective dose of 30 mg/kg. The antihypertensive effect is brief and returns to normal within two minutes. This cardiovascular effect of the extract has been attributed to eugenol, which exerts its effect by blocking the calcium channels.^[69]

Peganum harmala

(Family: Nitrariaceae; Common name: Harmal). The crude extract fraction and all pure compounds: harmine, harmaline, tetrahydroharmine, harmol, and harmaloi from *P. harmala* produced antihypertensive effects in anesthetized rats in a dose-dependent manner.^[70]

Phyllanthus amarus

(Family: Euphorbiaceae; Common name: Nela nelli). This plant is used as a diuretic and to lower BP in traditional medicine practice. Amaechina and Omogbai reported that intravenous administration of the aqueous extract of the leaves of this plant (5-80 mg/kg) to anesthetized NMT male rabbits produced a significant fall in mean diastolic, systolic, and mean arterial pressures in a graded dose-response manner. The dose of 5 mg/kg produced the least hypotensive effect, causing a fall in mean diastolic, systolic, and mean arterial pressure of 13.3 ± 3.1 , 19.7 ± 5.4 , and 14.3 ± 3.4 mmHg, respectively, whereas the dose of 80 mg/kg produced the greatest fall in mean diastolic, systolic, and mean arterial pressure of 49.7 ± 7.9 , 45.5 ± 9.5 , and 48.00 ± 6.5 mmHg, respectively. The extract produced greater depressant effect on the diastolic BP than the systolic BP.^[71]

Pinus pinaster

(Family: Pinaceae; Common name: Maritime Pine). *Pycnogenol* is an extract from French maritime pine bark. It is most commonly known as a treatment for venous insufficiency and other vascular conditions. But it is being studied for a long list of other conditions, including HTN. Preliminary clinical research shows that pycnogenol 200 mg/day can modestly lower BP in people with mild HTN. It has been reported to act by inhibiting angiotensin-converting enzymes.^[72]

Pueraria lobata

(Family: Fabaceae; Common name: Kudzu). The dry root of this plant is officially listed and used in China as a muscle relaxant, antipyretic, and for the treatment of dysentery and HTN.^[73] The total isoflavones, from the ethanol extract of roots, have shown hypotensive effect on anesthetized dogs and unanesthetized hypertensive dogs.^[74] The isoflavone-puerarin, when administered intravenously at a dose range of 100 to 200 mg, in clinical trials to patients suffering from HTN or angina pectoris, showed a decrease in blood catecholamine levels, BP, and HR.^[75]

Punica granatum

(Family: Lythraceae; Common name: Pomegranate). Pomegranate juice is becoming a more popular fruit drink. Research shows that pomegranate reduces the activity of angiotensin converting enzymes (ACE) by about 36%. Clinical research reveals contradictory results. One study shows modest reduction in systolic BP after drinking 50 ml/day of pomegranate juice for a year. Another study shows no benefit after drinking 240 ml/day of the juice for 3 months.^[76]

Raphanus sativus

(Family: Cruciferae; Common name: Radish): The plant has been found to have antihypertensive activity. Isolated tissue preparations were suspended in tissue baths containing Krebs solution, while acute toxicity study was performed in mice for 24 hours. The extract caused a dose-dependent (0.1-3 mg/kg) fall in BP and HR of rats that was mediated through an atropine-sensitive pathway. In isolated guinea-pig atria, it showed dose-dependent (0.03-3.0 mg/ml) inhibition of force and rate of contractions. In the atropine-treated tissues, the inhibitory effect was abolished and a cardiac stimulant effect was unmasked, which was resistant to adrenergic and serotonergic receptor blockade. In the endothelium-intact rat aorta, it inhibited phenylephrine-induced contractions, which was blocked by atropine. The extract was safe in mice up to the dose of 10 g/kg. The study showed that the cardiovascular inhibitory effects of the plant are mediated through activation of muscarinic receptors, thus possibly justifying its use in HTN.^[77]

Rauwolfia serpentina

(Family: Apocynaceae; Common name: Rauwolfia). It is a tropical woody plant indigenous to Asia, South America, and Africa. Extracts of its different parts and of plants resembling to rauwolfia were used in Hindu medicine for snakebite, insomnia, insanity, and many other diseases and complaints. This is considered to be the most powerful hypotensive plant. Reserpine, the purified alkaloid of *R. serpentina*, was the first potent drug widely used in the long-term treatment of HTN. Only a small dose is required to achieve results and to avoid side effects. Nasal congestion is the most common side effect. In 1952, reserpine was introduced under the name Serpasil in the treatment of HTN, tachycardia, and thyrotoxicosis. The combination of reserpine, dihydroergocristine, and a diuretic is still on the market (Brinerdin, Crystepin).^[78]

Rhaptopetalum coriaceum oliver

(Family: Scytopetalaceae). A decoction of the plant stem bark is traditionally prepared or soaked in locally distilled gin and taken as a remedy for HTN. Preliminary studies carried out on the plant stem bark extract showed its BP-lowering effects on NMT rats. *In vitro* studies of its vasodilatory mechanism revealed its action to be through calcium channel blockade, at a concentration of 0.2 mg/ml of *R. coriaceum* extract. This was done through inhibition of Ca²⁺ release and blockade of potential sensitive channels and receptor-operated channels by inhibiting noradrenaline and KCl-induced Ca²⁺ influx. Results from the *in vitro* studies suggest that ethanol extract of *R. coriaceum* may be more potent as calcium channel blocker than nifedipine.^[79]

Sesamum indicum

(Family: Pedaliaceae; Common name: Sesame). Alcoholic extract of seeds (1–30 mg/kg) caused hypotension in anesthetized rats. A fall in systolic as well as diastolic BP in dose-dependent manner was observed. HR was found to decrease at slightly higher doses (10-30 mg/kg). Atropine (2 mg/kg) was reported to abolish the cardiovascular responses, indicating the presence of acetylcholine-like substance in the seeds. Sesamin and sesaminol are the major phenolic constituents of sesame oil. A study in hypertensive patients indicated that sesame oil consumption remarkably reduced oxidative stress and simultaneously increased glutathione peroxidase, superoxidase dismutase, and catalase activities. These results support the hypothesis that sesame oil consumption may help to enhance antioxidant defense system in human beings. The investigators suggested that sesamin is a useful prophylactic treatment in HTN and cardiovascular hypertrophy.^[80]

Solanum sisymbriifolium

(Family: Solanaceae; Common Name: Sticky Nightshade, Wild Tomato). The root of *S. sisymbriifolium* Lam., a perennial herb, has been used as a traditional medicine possessing diuretic and antihypertensive properties in Paraguay. The hypotensive effect of the crude hydroalcoholic extract from root was investigated both in NMT and hypertensive rats. The intravenous administration of the extract (50 and 100 mg/kg) produced a significant decrease in BP in anesthetized hypertensive (adrenal regeneration HTN + deoxycorticosterone acetate) rats. Oral administration of the extract (10, 50, 100, and 250 mg/kg) also produced a dose-dependent hypotensive effect in conscious hypertensive animals. In anesthetized NMT rats, the extract (50 and 100 mg/kg, i.v) also induced hypotension in a dose-dependent manner. Lastly, no significant effect on BP was produced by the extract when administered orally (10, 50, 100, 250, 500, and 1000 mg/kg) to conscious NMT rats.^[81] In another study, nuatigenosido was isolated from the extract as one of the prospective active compounds. Nuatigenosido at 100 µg/kg and 1 mg/kg i.v lowered BP in rats and at 10⁻⁶ and 10⁻⁵ M augmented the contractile force in the right atrium of a bullfrog, and at 10⁻⁷ M increased the overshoot amplitude in frog atrial myocytes, action potential durations were shortened, the calcium current was increased, and the delayed outward potassium current was

increased. The results suggested that nuatigenosido may play an important role in the therapeutic effects of this herb.^[82]

Theobroma cacao

(Family: Malvaceae; Common names: Chocolate, Cocoa Bean, Cocoa Butter). Cocoa powder, enriched with flavonoid constituents, is used for preventing cardiovascular disease. Flavonoids, contained in chocolate, stimulate formation of nitric oxide, increase vasodilatation, and reduce endothelial dysfunction. A growing body of clinical research also shows that daily consumption of dark or milk chocolate (*T. cacao*), 46 to 105 g daily, providing 213 to 500 mg of cocoa polyphenols, can lower systolic BP by about 5 mmHg and diastolic by about 3 mmHg.^[83]

Triticum aestivum

(Family: Poaceae/Gramineae; Common names: Bran, Wheat bran). It has been reported that increasing dietary wheat bran intake by 3 to 6 g/day modestly reduces systolic and diastolic BP.^[84]

Uncaria rhynchophylla

(Family: Rubiaceae; Common name: Cat's Claw herb). In traditional oriental medicine, *U. rhynchophylla* has been used to lower BP and to relieve various neurological symptoms. The hypotensive activity has been attributed to an indole alkaloid called *hirsutine*, which has been found to act at the Ca²⁺ channels.^[71] The effects of hirsutine on cytosolic Ca²⁺ level ([Ca²⁺]cyt) were studied by using fura-2- Ca²⁺ fluorescence in smooth muscle of the isolated rat aorta. Noradrenaline and high K⁺ solution produced a sustained increase in [Ca²⁺]cyt. Application of hirsutine after the increases in [Ca²⁺]cyt induced by noradrenaline and high K⁺ notably decreased [Ca²⁺]cyt, suggesting that hirsutine inhibits Ca²⁺ influx mainly through a voltage-dependent Ca²⁺ channel. Furthermore, the effect of hirsutine on intracellular Ca²⁺ store was studied by using contractile responses to caffeine under the Ca²⁺-free nutrient condition in the rat aorta. When hirsutine was added at 30 μM before caffeine treatment, the agent slightly but significantly reduced the caffeine-induced contraction. When added during Ca²⁺ loading, hirsutine definitely augmented the contractile response to caffeine. These results suggest that hirsutine inhibits Ca²⁺ release from the Ca²⁺ store and increases Ca²⁺ uptake into the Ca²⁺ store, leading to a reduction of intracellular Ca²⁺ level. It is concluded that hirsutine reduces intracellular Ca²⁺ level through its effect on the Ca²⁺ store as well as through its effect on the voltage-dependent Ca²⁺ channel.^[85]

A methanol extract of the hooks of an *Uncaria* species was found to have a potent and long-lasting hypotensive effect in rats and the activity was different from that of *U. rhynchophylla* and its analogue. Further studies of the extract resulted in the isolation of 3-indole alkaloid, glycoside, cadambine, dihydrocadambine, and isodihydrocadambine. The latter two were found to be the hypotensive principles, whereas cadambine was inactive.^[86]

Viscum album

(Family: Santalaceae; Common name: Mistletoe). The aqueous

extracts of *V. album* leaves have shown significant coronary vasodilator activity on the Langendorff's isolated and perfused heart model. The data obtained suggest that the aqueous extract of *V. album* contains some biologically active principles that may act as inducer of the nitric oxide/soluble guanylate cyclase pathway.^[87] The effect of the crude aqueous extract from mistletoe leaves was studied on arterial BP and HR in albino Wistar rats under pentobarbitone anesthesia. The crude extract produced a significant decrease in BP, that is, 11.28, 23.98, and 18.80% in the NMT, renal artery occluded hypertensive (ROH), and sham-induced hypertensive (SIH) treated subgroups. The depression produced by the extract on the corresponding HR was not significant in the NMT, ROH, or SIH subgroups. Propranolol blocked the action of the extract on BP. However, atropine did not prevent the extract-induced depression of BP. The extract-blocked noradrenaline induced increase in BP in the NMT. The results suggested that the mistletoe extract produces antihypertensive effect without alteration in HR, possibly involving sympathetic mechanism.^[88]

Vitex doniana

(Family: Verbenaceae; Common name: Black plum). Ladeji *et al.* investigated the effect of oral administration of the extract of this plant on BP of rats. The extract was found to exert hypotensive effect. Both the systolic and diastolic BPs were significantly reduced within 45 min after oral administration of the extract. The BP began to return to normal after 2 hours.^[89]

Zingiber officinale

(Family: Zingiberaceae; Common name: Ginger). Ginger root is commonly used in Asian cooking. It acts to improve blood circulation and relaxes muscles surrounding blood vessels. The crude extract of ginger (Zo.Cr) induced a dose-dependent (0.3-3 mg/kg) fall in the arterial BP of anesthetized rats. In guinea pig paired atria, Zo.Cr exhibited a cardiodepressant activity on the rate and force of spontaneous contractions. In rabbit thoracic aorta preparation, Zo.Cr relaxed the phenyl ephrine-induced vascular contraction at a dose ten times higher than that required against K⁺ (80 mM)-induced contraction. Ca²⁺ channel-blocking activity was confirmed when Zo.Cr shifted the Ca²⁺ dose-response curves to the right, similar to the effect of verapamil. These data indicate that the BP-lowering effect of ginger is mediated through blockade of voltage-dependent calcium channels.^[90] Chronic administration of Pet ether extract (PE) (50 mg/kg/day; po), toluene fraction (10 mg/kg/day; po) of ginger rhizome, and Korean ginseng extract (KGE) (30 mg/kg/day; po) significantly reduced the BP in deoxycorticosterone acetate salt-induced hypertensive rats, whereas PE (50 mg/kg/day; po) and KGE (30 mg/kg/day; po) reduced the BP in fructose-induced hypertensive rats. The mechanism of action may partly involve the serotonergic antagonistic property.^[91] Human trials for hypotensive effect of ginger have been few and generally used a low dose with inconclusive results.^[92]

The renewed interest in the search for new drugs from natural sources, especially from plant sources, has gained global attention

during the last two decades. The tropical rain forests have become an important point of this activity, primarily due to the rich biodiversity they harbor, which promises a high diversity of chemicals with the potential novel structures. However, of this rich biodiversity, only a small portion has been studied for its medicinal potential. Thus, natural plants and herbs can be our source of drugs, with fewer side effects and better bioavailability for treatment of HTN in future.

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