

Hypertension and Plant Extract as A Solution

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Abstract

Hypertension is a critical health problem and worse other cardiovascular diseases. It is mainly of two types: Primary or essential hypertension and Secondary hypertension. Hypertension is the primary possibility feature for coronary heart disease, stroke and renal vascular disease. Herbal medicines have been used for millions of years for the management and treatment of hypertension with minimum side effects. Over aim to write this review is to collect information on the anti- hypertensive effects of natural herbs in animal studies and human involvement as well as to recapitulate the underlying mechanisms, from the bottom of cell culture and ex-vivo tissue data. According to WHO, natural herbs/shrubs are widely used in increasing order to treat almost all the ailments of the human body. Plants are the regular industrial units for the invention of chemical constituents, they used as immunity booster to enhance the natural capacity of the body to fight against different health problems as well as herbal medicines and food products also. Eighty percent population of the world (around 5.6 billion people) consume medicines from natural plants for major health concerns. This review provides a bird's eye analysis primarily on the traditional utilization, phytochemical constituents and pharmacological values of medicinal herbs used to normalize hypertension; Hibiscus sabdariffa, Allium sativum, Andrographis paniculata, Apium graveolens, Bidens pilosa, Camellia sinensis, Coptis chinensis, Coriandrum sativum, Crataegus spp., Crocus sativus, Cymbopogon citrates, Nigella sativa, Panax ginseng, Salvia emiltiorrhizae, Zingiber officinale, Tribulus terrestris, Carum copticum, Cola lewriifera, Cassia occidentalis, Cyranchum wilfordii.

Keywords: Hypertension, Plant, Extract, Solution, blood pressure

Introduction

A clinical disease known as hypertension (HTN), or high blood pressure, causes the blood vessels' pressure to remain consistently elevated [1]. Blood vessel pressure is increased, making it harder for the coronary heart to pump blood throughout the body [2]. If it is not treated right away, it could lead to serious cardiac issues like a heart attack, a heart growth, and ultimately coronary heart failure [3].

The global preventable risk factor for early death is hypertension [4]. It will raise the risk of peripheral vascular disease, ischemic heart disease strokes, heart failure, aneurysms, and pulmonary embolism [5], as well as other cardiovascular illnesses such hypertension-related headaches like hypertensive

retinopathy and hypertensive nephropathy [6].

Around 17 million deaths worldwide from cardiovascular disease occur each year, accounting for almost one third of all fatalities [3]. Additionally, headaches from high blood pressure cause 9.4 million lives worldwide each year (Lim et al., 2012). At least 45% of fatalities from coronary heart disease and 51% of deaths from stroke are attributable to hypertension [3]. According to a 2008 international survey, approximately 40% of adults aged 25 and older experienced excessive anxiety; the number of people worldwide increased from 600 million in 1980 to at least one billion in 2008. (Global status report on non-communicable diseases 2010 Geneva). High income countries have a modest prevalence of high blood pressure (35%) compared to low-income

countries, where it is significantly higher (40). According to the WHO report "A Global Brief on Hypertension—silent Killer, Global Public Fitness Disaster," the Americas have the lowest prevalence of high blood pressure (35%), while Africa has the greatest prevalence (46%) among persons aged 25 and older [3].

The World Health Organization (WHO), in Geneva, called for more efforts to prevent and treat hypertension, commonly known as high blood pressure, on the occasion of World Health Day on April 7 with a focus on the condition. World Hypertension Day is celebrated on May 17 of each year (WHD). The World Hypertension League (WHL), which was founded to raise awareness of hypertension, created and created World Hypertension Day. According to projections, more than 23 million more individuals will die each year from CVDs by the year 2030 [3].

A few factors that contribute to the etiology of high blood pressure include genetic predisposition, renin-angiotensin-aldosterone system growing activity, kalikerenin in system, sympathetic nervous system, and genetics. Angiotensin converting enzyme (ACE) has a significant role in converting the enzyme angiotensin I into the blood pressure-raising angiotensin II. In order to defeat the renin angiotensin aldosterone system's surge in expression, ACE inhibition should be used as a control [8].

For prehypertensive individuals, lifestyle modifications (diet, weight loss, and exercise) are considered the first line of treatment; nevertheless, pharmacological therapy should be started in cases of partial or nonresponsive response [7]. Diuretics, calcium channel blockers, -blockers, angiotensin-converting enzyme (ACE)inhibitors, angiotensin II

receptor blockers, vasodilators, and centrally acting medications are a few of the pharmacological drug lessons employed [9]. Although those medications help control high blood pressure, they have adverse effects like nausea, dry cough, dizziness, headaches, and fatigue that limit their use, increasing the need for alternative treatments [9].

A variety of antihypertensive medications are now utilized in clinical settings to treat hypertension and combat its symptoms. Although those sellers are frequently used in clinical settings, their effectiveness is the highest. To achieve the best results, it often takes two or more antihypertensive medications from different classes to be combined, which increases the cost of treatment and side effects by 40 to 60%. Dry mouth, drowsiness, mental distress, gastrointestinal disruption, visual issues, headache, and many other adverse effects are typically brought on by using synthetic antihypertensive drugs. The best aspects of traditional living are disturbed by these upsetting aspect effects. There is a need to search for an effective antihypertensive ingredient that is herbal, affordable, and non-toxic [10].

Widespread use of medicinal plants in traditional medical systems and in a wide range of global communities. Around the world, 80% of people rely solely on plant-based medicines for their primary healthcare [11]. Modern medical techniques are therefore essential for the development of drugs, as well as for standardizing extracts and identifying chemical or organic compounds. As a result, emphasis must be put on the conservation of plant populations to ensure the availability of pharmacologically active sources of material for natural remedies [12].

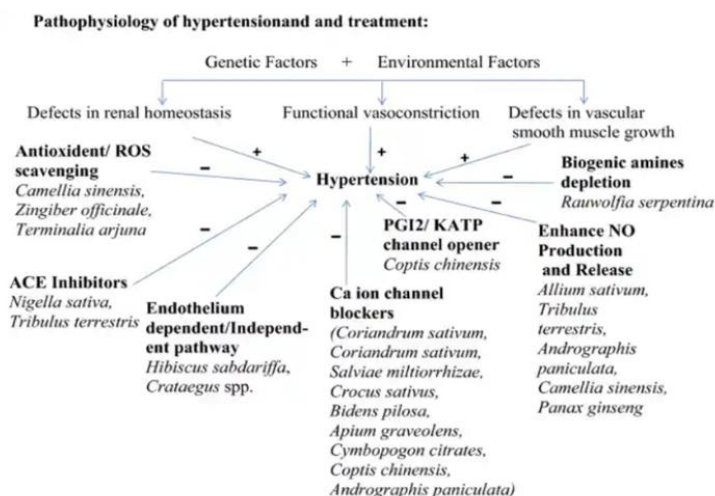


Fig1: Pathophysiology of hypertension and treatment

Hypertension

A persistent medical condition when the blood pressure in the arteries is increased is known as hypertension (HTN) or excessive blood pressure (BP). A main (essential) or secondary assessment is made. About 90–95% of instances are classified as primary HTN, which is high BP for which no identifiable medical reason can be found.¹ Secondary HTN, which accounts for the remaining 5 to 10% of patients, is brought on by additional illnesses that affect the kidneys, arteries, coronary heart, or endocrine system [13].

Persistent hypertension is a major cause of chronic kidney failure and one of the risk factors for stroke, coronary heart attacks, heart failure, and arterial aneurysm [14]. A moderate increase in arterial blood pressure results in a reduced life expectancy. In addition to medications, lifestyle and nutritional adjustments can enhance blood pressure control and lessen the risk of associated health issues [14].

Classification Of Hypertension

Systolic and diastolic blood pressure measurements are frequently used to label HTN. Systolic blood pressure refers to the pressure in vessels throughout a heartbeat. The pressure between heartbeats is known as diastolic BP. Pre-HTN or HTN is defined as systolic or diastolic blood pressure measurements that are higher than the norm for the person's age. There are many subcategories of HTN, including isolated systolic HTN, HTN degree II, and HTN stage I. Elderly people frequently have isolated systolic HTN, which is increased systolic pressure with normal diastolic pressure. These classifications are determined by averaging the resting blood pressure measurements obtained over two or more office visits for the patient. If a person's blood pressure is consistently at least 140 mmHg systolic or 90 mmHg diastolic, they are said to have HTN. Patients with blood pressures better than 130/80mmHg who also have diabetes or renal disease need additional treatment. If treatment fails to lower blood pressure to normal levels, HTN is also classified as resistant [15]. Exercise HTN is defined as an abnormally high increase in BP during exercise [16]. Systolic levels during exercise are typically between 200 and 230 mmHg in range [17]. Exercise-related HTN can also signal a person's risk of developing it during downtime [18].

Hypertension

Primary or Essential Hypertension

90 to 95% of people with hypertension have essential HTN, which is the most common kind of the disease.¹

There are many factors, including sedentary lifestyle, pressure, visceral weight issues, potassium deficiency (hypokalemia), obesity [19] (more than 85% of cases occur in those with a frame mass index more than 25) [20], salt sensitivity (sodium sensitivity), alcohol consumption [21], and vitamin D deficiency that increase the risk of developing the condition [22]. Additionally, risk rises with age [23], some inherited genetic variants [24], and a family history of HTN [25]. Another potential problem is an increase in the kidney's enzyme renin, as well as an overactive sympathetic nervous system [26,27]. It is also believed that syndrome X, or the metabolic syndrome, which includes insulin resistance, contributes to high blood pressure. High-fructose-corn-syrup meals can also raise a person's risk of developing HTN [28].

Secondary Hypertension

Patients' elevated blood pressure is primarily caused by a renal or adrenal disorder (Beevers et al., 2001).

In addition to this, peripheral vascular resistance, cardiac output, and nitric oxide play important roles in high blood pressure [29].

The main goal of writing this evaluation is to compile data on the anti-hypertensive benefits of herbal remedies in human research and animal studies, as well as to recapitulate the underlying mechanisms, starting with the smallest scales of mobile cultures and ex-vivo tissue data. International health organization WHO reports that herbal remedies are increasingly used to treat practically all human illnesses [30]. Any natural plant, depending on the type of phytochemical components it contains, can be used to treat a particular condition or group of illnesses. When compared to allopathic medicine, the use of medicinal herbs and shrubs is essential since it is less expensive and has less negative effects [31,32]. A serious health issue, hypertension makes certain cardiovascular diseases worse. Diuretics are often used to treat high blood pressure by reducing blood volume at the expense of dangerous and unwelcome side effects, either alone or in combination with other antihypertensive medications. Interestingly, the preferred method for treating hypertension and other related ailments is to use medications derived from herbal sources [33]. According to Dubick, plants are employed regularly in manufacturing chemical components, as an immunity booster to enhance the body's inherent ability to combat serious health concerns, as well as in the production of herbal medicines and food items. Natural flora are regarded as curative remedies for practically all diseases in cultural, non-secular, and

traditional traditions [34,35]. Local plant medicinal remedies have been included in World Health Organization regulations since 1970, particularly for developing international locations of the field. The World Health Organization of the United Nations estimates that 5.6 billion people, or 80% of the population, use natural flower-based remedies for their primary health issues [36,37]. This study provides a broad assessment of the traditional uses, phytochemical components, and therapeutic benefits of medicinal plants used to normalize hypertension [38,39].

Pathophysiology

The majority of secondary HTN-related processes are typically well recognized. Those connected to important (main) HTN, however, are far less well characterized. What is known is that early in the course of the illness, cardiac output is increased with normal total peripheral resistance (TPR). Although TPR improves, cardiac output gradually returns to normal levels. Three theories were put out to explain this, and they are as follows:

- The kidneys' inability to eliminate sodium results in the release of natriuretic factors, such as a test natriuretic factor, to encourage salt excretion, which also raises TPR.

Vasoconstriction and the retention of salt and water are caused by an overactive renin-angiotensin system. HTN is brought on by an increase in blood volume [40].

- An excessively responsive sympathetic nervous system, which results in increased pressure responses [41].
- HTN is also thought to be highly heritable and polygenic (caused by multiple genes), and a few potential genes have been proposed as the etiology of this illness [42].

Scientific research on crucial HTN and prolonged endothelium damage has recently acquired recognition among experts in the field. However, it is still questionable whether endothelial adaptations occur before the onset of HTN or whether these alterations are specifically brought on by long-status

enlarged BPs.

HTN is a leading independent risk factor for kidney failure, coronary artery disease, and stroke. The risk of a fatal coronary event doubles for every increase in systolic and diastolic blood pressure of 20mmHg and 10mmHg over the range of 115/75 to 185/115mmHg, respectively. For many people with HTN, more aggressive BP objectives are currently being demanded by the American Heart Association and other organizations in an effort to lessen these negative effects. Many focused attempts have been made over the past three decades to learn more about the local plants that have hypotensive and antihypertensive therapeutic benefits. Some of those medicinal plants' hypotensive and antihypertensive effects have been proven, while others have been found to be false. More people are choosing natural treatment due to low-profit organizations' attempts to control HTN and its complications in the face of limited socioeconomic resources, especially among rural residents in developing nations [43].

Blood Pressure Regulation

Several factors, including cardiac output, blood volume, arterial tone stability, and many others. Blood Pressure of the cardiovascular device can be determined (BP). The maintenance of healthy blood pressure levels involves the interaction of several components of an integrated neurohumoral system, including natriuretic peptides, the renin-angiotensin-aldosterone system (RAAS), endothelial cells, the immune system, and the sympathetic nervous system (SNS). Any imbalance in the neurohumoral device's components can directly or indirectly lead to an increase or drop in the standard blood pressure level.

Furthermore, if this imbalance persists for an extended period of time, it results in both CVD and damage to the target organ (such as CKD and left ventricular hypertrophy). Different physiological effectors that regulate vascular tone include potassium channels, nitric oxide (NO), the renin-angiotensin system, reactive oxygen species, and calcium ions. Any imbalance in these components may cause hypertension [44].

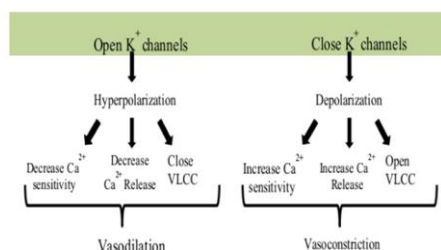


Fig 2: Effect of potassium channels blood vascular system [156]

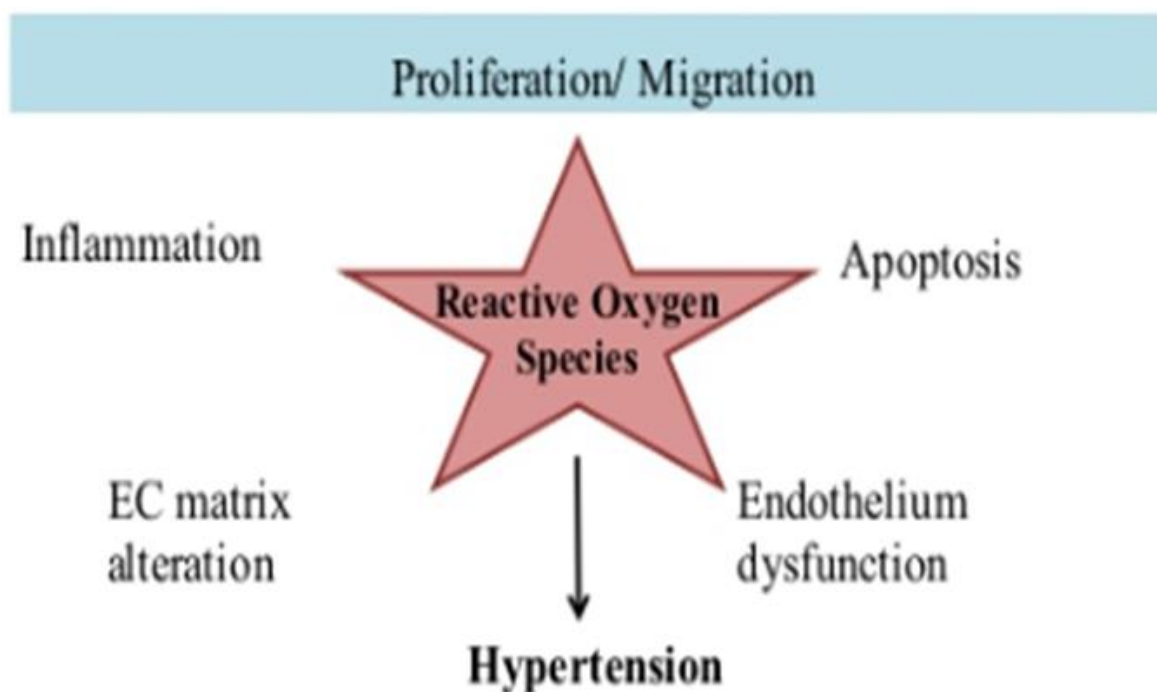


Fig 3: Effect of reactive oxygen species on blood vascular system [156]

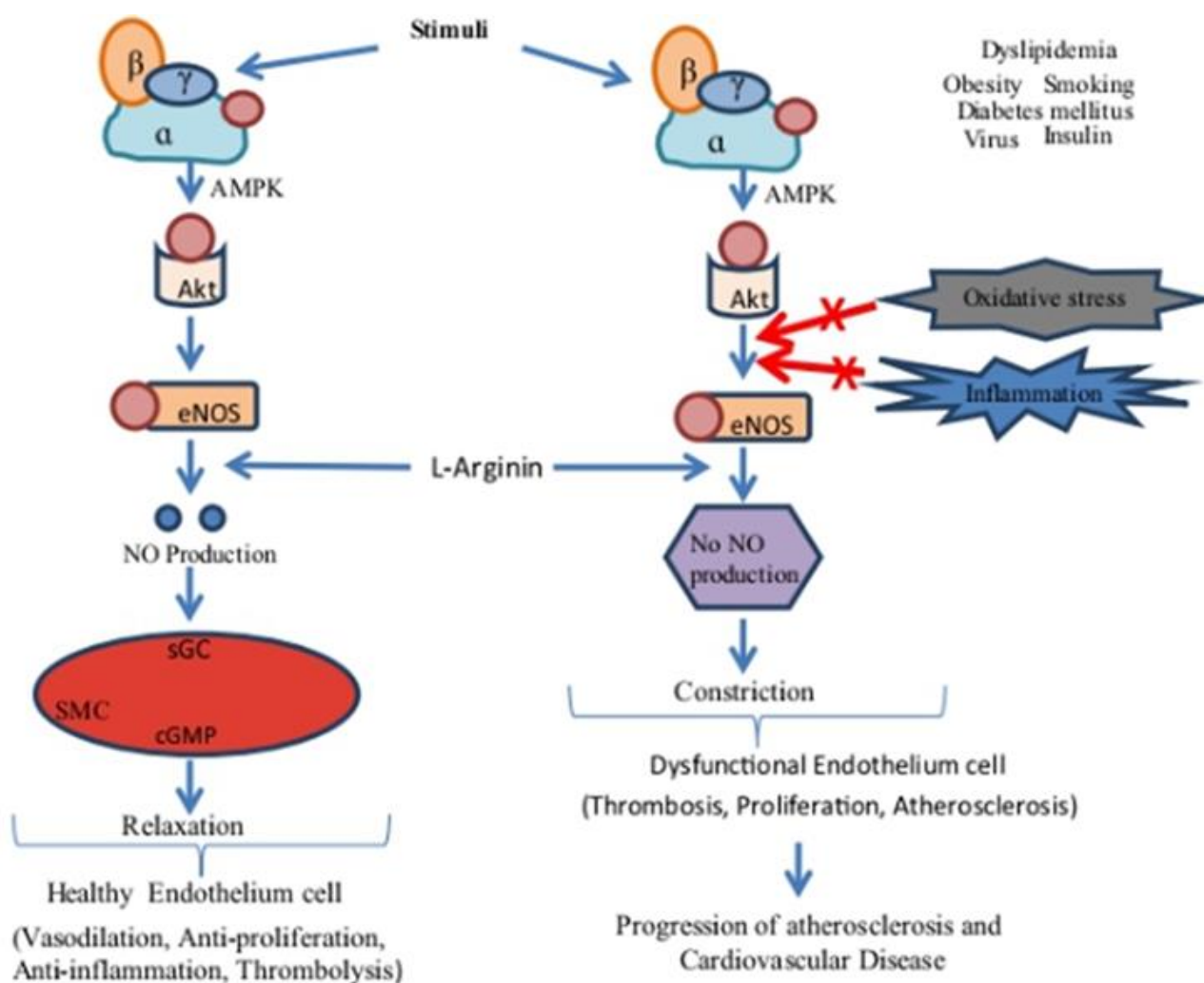


Fig 4: Oxidative stress and role of NOS on blood vascular system [156]

Plant Derived Antihypertensive Phytochemicals

Drugs made from plants have been used to treat hypertension and the difficulties that it causes. Digitoxin, for instance, has been produced from *Digitalis purpurea* (foxglove). Like aspirin, reserpine is derived from *Rauwolfia serpentina*, tetramethylpyrazine from *Jatropha podagrica*, and tetrandrine from *Stephania tetrandra* [45]. These plant-derived antihypertensive agents were demonstrated scientifically using unique processes [46].

In the past two decades, medicinal flowers have continued to be crucial resources for the discovery of new chemicals. They can be used to create antihypertensive medications that are secure, effective, and economical [47]. Secondary plant metabolites that are generated from plants have a long history of being utilized as medicines. Depending on the species, topography, and weather of the initial country, they can contain various types of dynamic principles and have a wide spectrum of activity [48].

Alkaloids

Most heterocyclic nitrogen-containing substances known as alkaloids have antihypertensive properties. Reserpine comes from the plant *Rauwolfia serpentina*. Reserpine is an indole *Rauwolfia serpentina* that has been used for a long time in India to treat fever, snakebites, and insanity [49]. An antihypertensive medication called reserpine has been used to treat chronic hypertension [50]. Every other alkaloid, veratrine, discovered from *Sabadilla* seeds, was declared demonstrate antihypertensive activity. Von Bezold came to believe that this activity is likely the result of reflex action coming from the heart [51,52]. Tubers of the *Papaveraceae* plant *Corydalis racemosa* (Thunb.) Pers. are the source of the chemical dl-tetrahydropalmatine hydrochloride. Experimental hypertensive rats were used to assess its antihypertensive impact. It was hypothesized that dl-tetrahydropalmatine hydrochloride's ability to diminish sympathetic tone in spontaneously hypertensive rats' central nervous system was a key factor in the drug's ability to lower blood pressure [53].

A natural aporphinoid alkaloid called (+)-nantenine was tested for its potential in vivo effects on the rat circulatory system. This was the initial in vivo observation. *Uncaria rhynchophylla* is another often used medicinal plant. Acute intravenous (i.v.) treatment of (+)-nantenine in anesthetized normotensive rats resulted in a dose-dependent fall in mean arterial pressure, as well as a significant decrease in heart rate [54]. This plant is the source of the indole alkaloid hirsutin. Fura-2-Ca²⁺ fluorescence

was used to examine its impact on the cytosolic Ca²⁺ level ([Ca²⁺] cyt) in the smooth muscle of the isolated rat aorta.

After the increase in [Ca²⁺] cyt brought on by nor adrenaline and high K⁺, hirsutine administration significantly decreased [Ca²⁺] cyt, proving that hirsutine blocks Ca²⁺ influx naturally via a voltage-dependent Ca²⁺ channel. Additionally, the effect of hirsutine on intracellular Ca²⁺ storage was investigated utilizing caffeine-induced aortic contractions in rats. Hirsutine mildly but significantly reduced the constriction brought on by coffee. Based on the analysis, it can be said that hirsutine lowers intracellular Ca²⁺ levels by acting on both the Ca²⁺ shop and the voltage-dependent Ca²⁺ channel [62]. Since ancient times, China has utilized the plant *Stephania tetrandra* as an analgesic, antipyretic, antirheumatic, and antihypertensive medication. The main chemical present in *Stephania tetrandra* is tetrandrine. Tetrandrine was studied for its potential modes of action and effects on rats with spontaneous hypertension. At a dose of 100 mg/kg in the test subject, tetrandrine significantly lowered the blood pressure of spontaneously hypertensive rats. Tetrandrine increased overall sleep time, which in turn improved sleep efficiency [55].

Flavonoids

They are secondary metabolites, flavonoids. They have been used for many years as an effective ACE inhibitor to treat high blood pressure. Captopril, Enalapril, and Ramipril are few examples. However, using them for an extended period of time can have negative side effects. There is a desire to seek for fresh options without side effects as a result. The majority of scientists conducted research to look for bioactive substances in naturally occurring resources. The bioactive compounds peptides, anthocyanins, flavonols, and triterpenes have been demonstrated to exhibit ACE inhibitor action [8].

Commonly found in fruit, greens, nuts, seeds, stems, flowers, tea, wine, propolis, and honey, flavonoids have phenolic structures. The 2-phenyl- benzopyrane or flavane nucleus, which consists of two benzene rings connected by a heterocyclic pyrane ring, is the fundamental structural feature of flavonoid molecules [56]. Consuming flavonoids lowers the risk of developing a number of diseases, such as cancer, cardiovascular disease, and neurological disorders. For instance, human neuroblastoma cells (SH-SY5Y) are protected by the flavonoid molecule quercetin-three-O-glucoside, which is typically found in fruits [58].

The water-soluble plant pigments called

anthocyanins give fruits and vegetables their red, blue, and purple hues [59]. Anthocyanins have ACE inhibitory properties. Cyanidin-3-O-sambubiosides and delphinidin-3-O-sambubiosides, which were isolated from extracts of *Hibiscus sabdariffa*, inhibited ACE in a dose-dependent manner [60]. In a similar manner, cyanidin-3-O-glucoside isolated from *Rosa damascena* demonstrated in vitro ACE inhibition [61]. Cyanidin, delphinidin, and malvidin are three of the main anthocyanins found in *Vaccinium myrtillus* preparations. In a model using human umbilical vein endothelial cellular subcultures, their efficacy as ACE inhibitors have been assessed. After cells were pre-incubated with bilberry extracts, the ACE activity was significantly lowered [62]. Because of their antioxidant action, maintenance of endothelial nitric oxide, and inhibition of serum lipid oxidation, anthocyanins have been linked to a reduction in blood pressure [63]. Compounds known as flavanols (Flavan-3-ols) can exist as monomers (catechins) or polymers (procyanidins) [59]. According to research, those showed ACE inhibitory activity [64].

Catechins, including (-)-epicatechin, (-)-epigallocatechin, (-)-epicatechingallate, and (-)-epigallocatechingallate, are the primary phytoconstituents of tea. Additionally, these compounds have their own, dose-dependent ACE inhibition [65]. The maritime pine Pycnogenol comes from French maritime pine. It is an oligomer of procyanidin. It is an effective mediator for controlling blood pressure, probably through ACE inhibition [66]. Flavonols make up a large portion of the flavonoid sub-composition in food. Quercetin, kaempferol, and myricetin are the most prevalent flavonols. They frequently appear in our diet [59]. Numerous flavonols have ACE inhibitory properties. Traditional medicinal plant *Sedum sarmentosum* is the source of five flavonols that have been found to have ACE inhibitory action [67]. Usually referred to as cluster figs, *Ficus racemosa* Rich in kaempferol Plant. In one of the studies, the stem bark demonstrated a dose-dependent ACE inhibitory property in vitro [68]. In an ex vivo test using the aorta tissues of male Wistar-Kyoto rats, kaempferol was found to be a potent ACE inhibitor [69]. Quercetin supplementation at 73 mg/d for 28 days was found to be effective in lowering blood pressure in hypertension patients in a randomized, double-blind, placebo-controlled, crossover research [70]. In another investigation, angiotensin I and bradikinin injections-induced hypertension in male Wistar rats was dramatically reduced by captopril and quercetin therapies [71].

Flavonoids called isoflavones have structural

similarities to the hormone mammalian estrogen. They are frequently referred to as phytoestrogens and can connect to estrogen receptors [72]. Plants often contain three isoflavones: genistein, daidzein, and glycitein. Genistein is frequently used for medicinal purposes [73]. Genistein has a reputation for reducing elevated blood pressure in test animals. In stroke-prone spontaneously hypertensive rats, genistein lowered NaCl-sensitive hypertension. It also decreased ACE gene expression and enzyme activity in rat aortic endothelial cells, serum, and aorta tissue in a dose-dependent manner [74]. Genistein, administered as a single intravenous injection at a dose of 25 mg/kg, had demonstrated antihypertensive effects in hypertensive Wistar rats. The anti-hypertensive impact changed as a result of the plasma of rats having significantly less ACE activity [75].

Two major flavones, apigenin and luteolin, were isolated from *Ailanthus excelsa* Roxb and exhibit dose-dependent ACE enzyme inhibition [76]. In vitro, the ethanol extracts of *Japanescedar's* outer bark shown ACEinhibitor action. It is discovered that the extract contains flavan-3-ols and flavones [77]. Chalcones are precursor chemicals in the flavonoids' biosynthesis processes Rupasinghe HPV [78]. It has a variety of useful dwellings. In vitro, the inhibition of ACE by chalcones and their pyrazole derivatives was concentration-dependent [79]. It has been discovered that the chalcone butein can lower arterial blood pressure in normotensive rats under general anesthesia.⁸⁰ The effects of quercetin (10 mg/kg) on blood pressure, vascular structure, endothelial function, and oxidative state in spontaneously hypertensive rats and normotensive Wistar Kyoto rats were assessed in one study [81]. Quercetin caused a significant reduction.

In spontaneously hypertensive Wistar Kyotorats, but no longer in normotensive Wistar Kyotorats, in systolic, diastolic, and suggest arterial blood stress and coronary cardiac charge [81].

In a different study, the ACE inhibitory properties of an apple peel extract rich in flavonoids, its components, a few flavonoids, and quercetin metabolites were examined using a biochemical assay of ACE inhibition and a human umbilical vein endothelial cell model. All of the studied flavonoids, with the exception of genistein, including the quercetin metabolites quercetin-3-O-glucuronic acid and quercetin-3-O-sulfate strongly reduced ACE in the study's flavonoid-rich apple peel extract [8]. Propolis is a honeybee product that is consumed and used as a complementary medicine. Its ingredients

have anti-inflammatory, anti-microbial, and anti-cancer properties. Brazilian unseasoned propolis considerably lowers blood pressure when tested for antihypertensive effects on rats that develop hypertension on their own. Flavonoids, such as dihydrokaempferide, isosakuranetinbetuletol, and kaempferide, which were isolated and identified by column chromatography, were the active components. These flavonoids significantly decrease blood pressure in hypertensive rats after oral treatment. Additionally, these ingredients reduced isolated spontaneously hypertensive rats' blood pressure in an attention-focused manner [82].

Tannins

The angiotensin converting enzyme is inhibited by the tannins, which are organic polyphenols (ACE). From Chinese herbs, the researchers identified 18 polyphenolic substances (tannins) [83]. They looked at how these polyphenols affected the action of ACE inhibitors in vitro. Additionally, they examined the tannins' in vivo inhibitory effects on rats with spontaneously hypertensive conditions whose blood pressure was enhanced by the production of angiotensin I. Nine tannins, including caffeoylquinates, flavan-3-ols, and gallotannins, were identified. They discovered that caffeineylquinates chelate the ACE zinc cofactor in vitro. There were two non-specific inhibitors of flavan-3-ols—epigallocatechin-3-O-gallate and epigallocatechin-3-O-methylgallate—and one of gallotannin—1, 2, 3, 4, 6-penta-O-galloyl-beta-D-glucose. After the addition of bovine serum albumin, the ACE inhibition of 1, 2, 3, 4, 6-penta-O-galloyl-beta-D-glucose was likewise decreased, indicating a nonspecific method of action. In the presence of angiotensin, I infusion, 1, 2, 3, 6-tetra-O-galloyl-beta-D-glucose and epigallocatechin-3-O-methylgallate showed a robust dose-dependent hypotensive effect, dramatically lowering blood pressure in spontaneously hypertensive rats. These results imply that some of the tannins extracted from herbs block ACE activity in an untargeted manner [83].

Diterpenoids

Traditional uses of *andrographis paniculata* include the treatment of diarrhea, hypertension, and the common cold. It contains andrographolide (AP1), 14-deoxy-11, 12-didehydroandrographolide (AP3), and neoandrographolide as its three main active diterpenoids (AP4). Yoopan et al. (2007) used Conscious rats and their isolated aortas and right atria were used as the test models to examine the effects of these diterpenoids, AP1, AP3, and AP4, isolated from *A. paniculata*, and different aqueous plant

extracts on blood pressure, vascular, and chronotropic responses. He discovered that AP3 was the most effective molecule for causing vasorelaxation and lowering heart rate among the three main diterpenoids. As a result, some individuals taking this herbal medication may have hypotension as a result of using *A. paniculata* preparations that contain more AP3 [84].

Another study used anesthetized rats to investigate the impact of *salvia* diterpenoids cinnabarina, 3, 4-seicosopimar-4(18), 7, 15-triene-3-oic acid on arterial blood pressure. Chlorisondamine (2.5 mg/kg.i.p.), a ganglion-blocking medication, was administered to various rat groups. An infusion of the nitric oxide synthase inhibitor (0.3 mg/kg/min i.v.) was given before and after the effects of 3, 4-seicosopimar-4(18), 7, 15-triene-3-oic acid (3 mg/kg i.v.) were assessed. The mean arterial blood pressure decreased after receiving dosages of 3, 10, and 30 mg/kg of 3,4-seicosopimar-4(18),7,15-triene-3-oic acid intravenously. This effect was unaffected by chlorisondamine or nitric oxide synthase inhibitor therapy of the rat. The findings imply that 3,4-seicosopimar-4(18),7,15-triene-3-oic acid has a hypotensive impact through a peripheral mechanism that is distinct from endothelial nitric oxide release [85].

Glycoside

A natural glycoside called stevioside was purified from the *Stevia rebaudiana* Bertoni plant. In Brazil and Japan, it has long been utilized as a commercial sweetening agent. Stevioside has an antihypertensive impact, according to studies conducted on both humans and animals. One study involved 174 patients who had their effects on stevioside assessed. The study had 87 participants—87 men and 87 women—and 168 people finished it. When compared to the placebo group, the stevioside group experienced significant drops in mean arterial blood pressure after two years. Body mass index and blood biochemistry did not significantly alter during the course of the trial, and both groups' lab test findings were comparable. There was no discernible difference between groups in the frequency of negative effects [86].

Plants used for the treatment of hypertension/Bioactive mechanism

There are certain negative effects from many antihypertensive medications used to treat HTN. Therefore, research-based recommendations for its therapy include a variety of lifestyle changes and the use of appropriate medicinal herbs [87]. Some herbs and spices' secondary metabolites have

antihypertensive characteristics. The majority of herbal remedies have the ability to inhibit endothelial permeability, increase angiogenesis, and exert antioxidant, anti-inflammatory, and anti-apoptotic effects on HTN [88].

Garlic (*Allium sativum*)

As with conventional blood pressure medications, garlic supplements have shown promise in the treatment of HTN by lowering blood pressure by roughly 10 mmHg systolic and 8 mmHg diastolic. The antibacterial, antioxidant, anti-inflammatory, anti-cancer, and hypocholesteremic properties of this herb are well known [89]. One study showed that the efficiency of garlic in treating HTN was around 80%.

Compared to other forms of garlic, aged garlic extract (AGE) causes a consistent reduction in blood pressure. Additionally, taking garlic supplements significantly lowers SBP and DBP by 3.75 and 3.39 mmHg, respectively (Wanget al., 2015). In a different trial, HTN patients who took garlic tablets (300–1500 mg/d) for 24 weeks reported significant drops in SBP of 9.2 mm Hg and DBP of 6.27 mm Hg [90]. A daily dose of 150 or 400 mg/kg of garlic extract caused an increase in eNOS activity and a decrease in nicotinamide adenine dinucleotide phosphate (NADPH)-oxidase in the aortas of fructose-fed rats. Additionally, AGE possesses superoxide scavenging activities in human neutrophils [91]

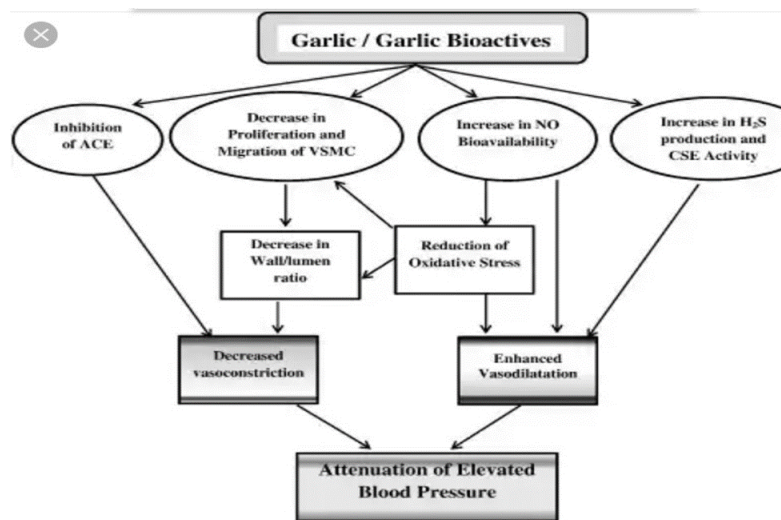


Fig 5: Mechanism of action Source: flipper.diff.org

Turmeric (*Curcuma longa*)

Turmeric, also known as curcuma longa, is a tropical plant native to Southeast India that is widely grown throughout South Asia. Curcumin, another name for turmeric, has anti-inflammatory and anti-cancer

qualities [92]. Curcumin has positive benefits on CVDs such HTN. By interfering with SP1/AT1R DNA binding, curcumin inhibits the progression of HTN by reducing AT1R expression in arteries and AT1R-mediated vasoconstriction [93].

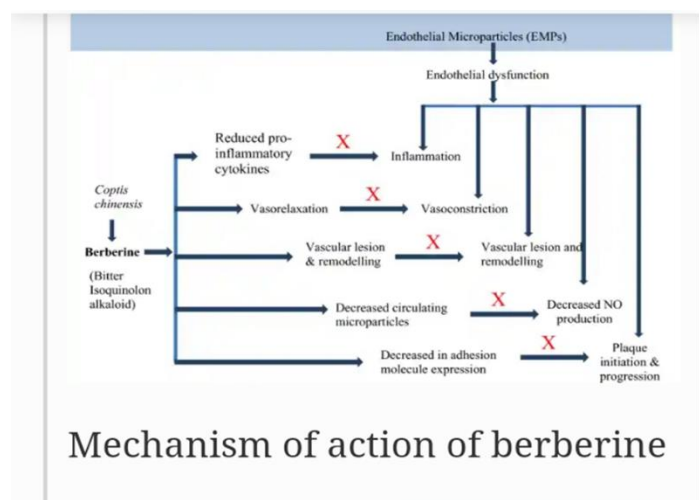


Fig 6A: Mechanism of action of curcumin (Source: flipper.diff.org)

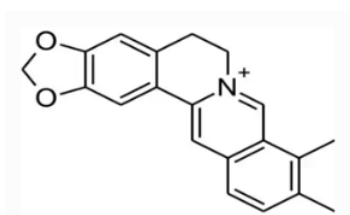


Fig 6B: Structure of curcumin

Bindii (*Tribulus terrestris*)

A medicinal herb called *Tribulus terrestris* is used to treat HTN. In rats with spontaneously hypertensive (SHR) conditions, Bindii lowers blood pressure. It has been demonstrated that its methanolic and aqueous extracts (0.3–15 mg/mL) exhibit vasodilatory effects [94]. This plant's diuretic properties are used. Additionally, all of the plant's saponins (furostanol and spirostanol saponins, as well as sulphakopted tigogenin and diosgenin saponins) inhibit H₂O₂ generation and VSMC proliferation [95].

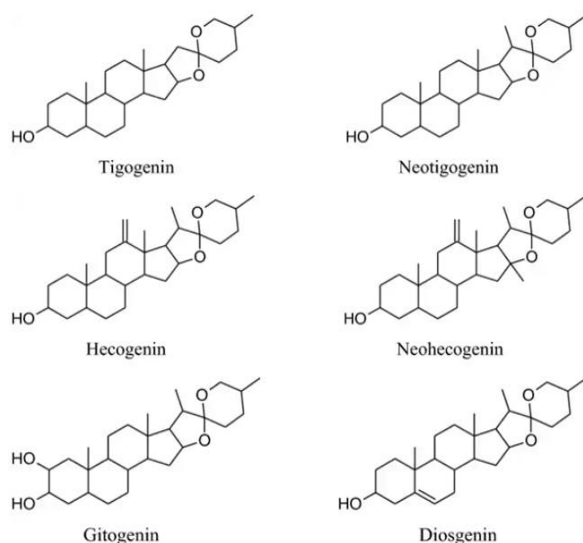


Fig 7: Bindii (*Tribulus terrestris*) Source: pubs.rsc.org

Black Cumin (*Nigella sativa*)

For many years, people in the Middle East, Europe, and Africa have used the *Nigella sativa* plant, sometimes known as the "seed of blessing." The components of this plant and their effects on BP [96]. In mildly hypertensive male patients, oral treatment of *N. sativa* seed oil extract (100 or 200 mg) for eight weeks causes a decrease in SBP and DBP of 10.6 and 9.6 mmHg, respectively [97]. Additionally, black cumin reduces blood pressure by relaxing the veins due to its capacity to block Ca²⁺ channels. Other potential explanations for *N. sativa*'s hypotensive impact include its diuretic, antioxidant, and anti-inflammatory characteristics [98].

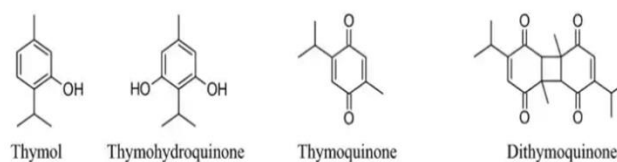


Fig 8: Black Cumin (*Nigella sativa*) Source: pubs.rsc.org

Black-Jack (*Bidens pilosa* L.)

An annual plant belonging to the Asteraceae family called Black Jack grows in South America and can also be found in tropical and subtropical areas of the world. Different rat models of HTN were able to be inhibited and reduced by Black Jack leaf extract. Six hours after receiving 75 and 150 mg/kg of methanolic leaf extract from rats fed fructose, SBP fell by 17% and 21%, respectively [37]. Additionally, *B. pilosa* has the potential to scavenge free radicals and possesses anti-cancer and anti-obesity properties [37].

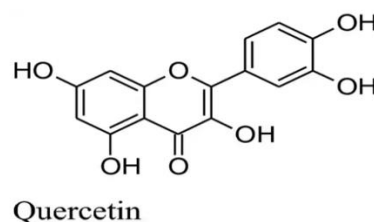


Fig 9: Black-Jack (*Bidens pilosa* L.) Source: researchgate.net

Coriander (*Coriandrum sativum*)

Traditional medicine employs coriander in the treatment of digestive and cardiovascular conditions. It has been demonstrated to have anti-oxidant properties. SBP, DBP, and MABP are decreased when the aqueous methanolic extract of the seeds is administered intravenously (1-30 mg/mL), presumably because of the Ca²⁺ antagonist. Furthermore, this extract has diuretic effects [100].

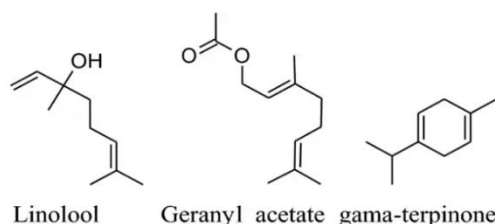


Fig 10: Coriander (*Coriandrum sativum*) Source: pubs.rsc.org

Ginger (*Zingiber officinale*)

Ginger, also known as *Zingiber Officinale*, is frequently used in daily meals and for a variety of medical conditions. Potassium, which contributes to the control of blood pressure and heart rate, is abundant in ginger. Two ginger bioactive substances, (6)-gingerol and (6)-shogaol, when administered intravenously (1.75–3.5 mg/kg) or orally (70–140

mg/kg), respectively, produce tri-phasic blood pressure profiles: first, a rapid drop in blood pressure, then an intermediate rise, and finally, a delayed decline in blood pressure. (6)-Gingerol is now thought to be a novel Ang II type 1 receptor antagonist [101]. Researchers recently discovered that ginger lowers blood levels of triglycerides, low-density lipoprotein (LDL), and very low-density lipoproteins (VLDL). It also reduces the activity of ACE-1 [102].

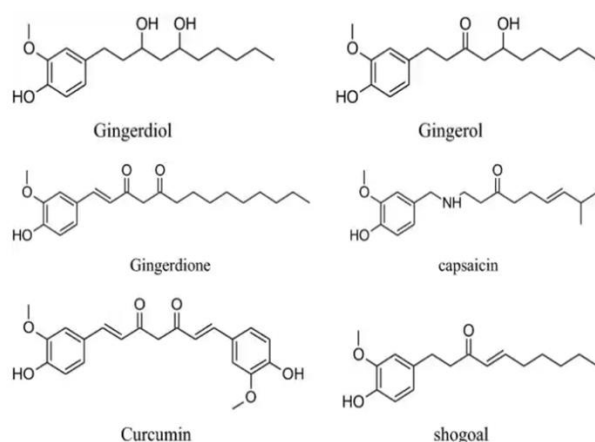


Fig 11: Ginger (*Zingiber officinale*) Source: researchgate.net

Ginseng (*Panax spp.*)

Ginseng is utilized in a variety of ways, including as tea, extracts, dried roots, capsules, tablets, and oils. It also possesses hypotensive properties [103]. Smaller ginseng doses raise blood pressure; however larger amounts cause hypotension. Therefore, ginseng presumably alters vascular function, modulates the autonomic nervous system, or modifies the arterial baroreflex to lower blood pressure in hypotensive patients [104].

In mildly hypertensive patients, the panax ginseng extract significantly lowers SBP by 3.1 mm Hg and DBP by 2.3 mm Hg. 59 Red ginseng's ginsenoside Rg3 increases eNOS, raises levels of NO and cGMP, and activates Ca²⁺-gated K⁺ channels. Additionally, ginseng exerts antihypertensive, anti-atherosclerotic, and anti-proliferative effects on VSMCs [105].

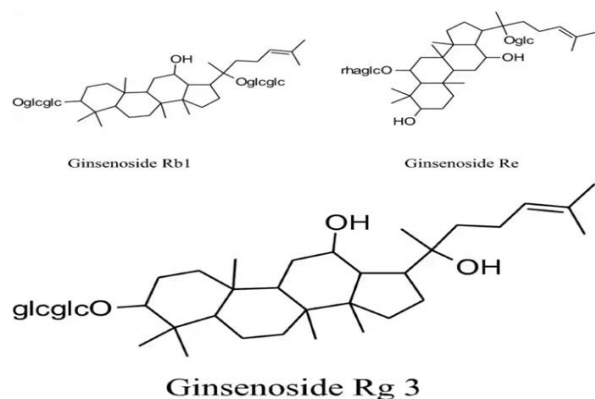


Fig 12: Ginseng (*Panax spp.*) Source: researchgate.net

Ajwain (*Carum copticum* L.)

The Apiaceae family includes *Carum copticum*, which grows in a number of locations throughout Central Europe, Iran (especially in the eastern Baluchistan), India, Afghanistan, and Pakistan.106 Because of its ability to inhibit calcium channels, *C. copticum* plays a significant part in controlling blood pressure and heart rate. In normotensive (NMT) rats, the aqueous-methanolic extract of *C. copticum* Benth. Seeds (CSE) (1-30 mg/kg) results in a reduction in blood pressure and heart rate (HR). There have been reports of bradycardia at higher doses (10–30 mg/kg) [106].

Black plum (*Vitex doniana*)

In 45 minutes following oral delivery of the fresh black plum fruit, both SBP and DBP had significantly decreased. After 2 hours, BP started to recover to normal [107].

Greater burdock

Commonly known as *Arctium lappa*, is used to treat HTN. This plant can decrease vascular inflammation, scavenge reactive oxygen species (ROS), and promote vasorelaxation [108]. One bioactive substance in burdock's dry seeds, arctigenin (a dietary phytoestrogen), raises NO generation while lowering superoxide anion levels [109].

Burhead (*Echinodorus grandiflorus*)

Brazilian folk medicine employs *Echinodorus grandiflorus* as a diuretic. This plant's aqueous extracts have the ability to lower SHR's mean arterial pressure (MAP), cardiac output, and vascular resistance. By activating muscarinic and bradykinin receptors with effects on the prostaglandins and nitric oxide pathways, burhead also causes sustained diuresis and lower blood pressure [110].

Cardamom (*Elettaria cardamomum*)

Elettaria cardamomum fruit powder has been evaluated for its capacity to lower blood pressure. When taken in powder form (3g), it has been demonstrated to improve overall antioxidant status in pre-hypertensive patients, resulting in mean MAP, SBP, and DBP reductions of 19 and 12 mmHg, respectively [111].

Carrot (*Daucus carota* L.)

Traditional medicine has included carrot as a mediator for treating hypertension. Improves endothelial function and controls fluid balance is *Daucus carota* L. Antioxidants included in carrot juice reduce oxidative stress and regulate blood vessel structure and function. Due to the presence of potassium, carrots control blood pressure. Intravenous dosing of DC-2 and DC-3, two of the

bioactive elements found in the aerial portions of *D. carota*, caused NMT rats' arterial blood pressure to drop. DC-2 and DC-3 can block calcium channels to have an effect [112].

Cat's Claw herb (*Uncaria rhynchophylla*)

Traditional Chinese medicine uses the herb cat's claw to treat HTN. This plant lowers blood pressure and eases several neurological disorders. *Uncaria rhynchophylla*'s hypotensive action is brought on by the anindole alkaloid hirsutine, which lowers intracellular Ca^{2+} levels by acting on the Ca^{2+} storage and the voltage-dependent Ca^{2+} channel [113].

Celery (*Apium graveolens*)

In rats with hypertension brought on by the hormone deoxycorticosterone acetate (DOCA), celery seed extract has been found to lower blood pressure. The hexane extract significantly lowers blood pressure, most likely via lowering circulating catecholamine levels and reducing vascular resistance. It has extraordinary antioxidant properties as a result of the flavonoid content in it [114].

Chakshushya (*Cassia absus L.*)

Ayurvedic ethnomedical records exist for the herb *Cassia absus*, which belongs to the Fabaceae family. This plant can be found all over India and in tropical climates. Rats' blood pressure is lowered by intravenous administration of the alkaloid (1–30 mg/kg) that was extracted from the seeds of *Cassia absus* Linn. The HR declines at higher doses (10 and 30 mg/kg). A same dose repeatedly injected causes tachyphylaxis [115].

Chinese Sage (*Salvia miltiorrhiza*)

Salvia miltiorrhiza, a traditional Chinese herb, has been found to protect the heart in both people and animals. In addition to its ability to dilate blood vessels, Chinese sage also has anti-hypertensive properties. These include antioxidative effects through increased antioxidative enzymes and decreased ROS production, anti-proliferative activities by preventing platelet-derived growth factor (PDGF)-induced proliferation of VSMCs, and anti-inflammatory properties by inhibiting the production of TNF- and NF-B [116].

Cinnamon (*Cinnamomum zeylanicum*)

Cinnamomum zeylanicum is another herb that is utilized in the treatment of HTN. Several animal models and patients with prediabetes and type 2 diabetes have shown that cinnamon lowers blood pressure (T2D). Its stem bark extract, which is aqueous, lowers SBP and inhibits contractions brought on by potassium chloride (KCl), which is

linked to the endothelium, NO, and ATP-sensitive K^{+} channel (K ATP channel). Levels of NO are raised by the bark's methanolic extract [117].

Coco Beans (*Theobrom acacao*)

By encouraging the production of NO, boosting vasodilatation, and reducing endothelial dysfunction, cocoa powder enhanced with flavonoid components is utilized to prevent CVDs. Dark or milk chocolate (40 to 105 g) can reduce SBP by around 5 mm Hg and DBP by about 3 mm Hg when consumed daily [118].

Coffee Weed (*Cassia occidentalis*)

Coffee weed also lowers blood pressure. This plant's leaf is used as an antihypertensive medication. Coffee weed has been found to lower blood pressure, most likely via inhibiting external Ca^{2+} influx. Along with having diuretic effects, coffee weed leaves also contain anti-inflammatory and antioxidant qualities. They reduce the amount of lipid peroxide and stop phospholipase A2 from working (Ali et al., 2019).

Dogbane (*Apocynum venetum*)

The dogbane plant's leaves appear to be abundant in flavonoids and quercetin derivatives, which have been discovered to aid in the treatment of HTN. Dogbane leaf extracts (10 g/mL) cause vasorelaxation via increasing NO, which scavenges ROS. The extracts from this plant have an antihypertensive impact through enhancing kidney function [119].

Dog-strangling Vine (*Cynanchum wilfordii*)

Traditional Chinese medicine makes use of the plant *Cynanchum wilfordii*, and almost all of its parts are thought to be beneficial for treating various vascular illnesses. In high fat/cholesterol-fed rats, ethanol extracts of *C. wilfordii* (100 and 200 mg/kg/d) decreased blood pressure via stimulating Akt, increasing eNOS activity, increasing NO generation, and decreasing the expression of VCAM-1 and endothelin-1 (ET-1) [120].

Harmel (*Peganum harmala*)

Persian names for the plant known as Syrian rue in the wild include "Espand," and its seeds, bark, and root have all been utilized in traditional medicine [121]. The drug espond is used to treat HTN. *Peganum harmala* induces relaxation via both VSMCs and endothelial cells. The active ingredients in espond are three harmala alkaloids, harmine, harmaline, and harmalol, which have demonstrated vasodilatory activities through boosting NO generation [122].

Fang Ji (*Stephania tetrandra*)

By decreasing the expression of inducible nitric oxide synthase (iNOS) and inhibiting Ca^{2+}

channels, *Stephania tetrandra* can control excessive blood pressure. The bioactive component of this plant, tetrandrine, has antioxidant and anti-inflammatory properties, both of which are likely implicated in the plant's antihypertensive effects [123].

Garden Cress (*Lepidium sativum* L.)

Garden cress has a hypotensive action and increases sodium, potassium, and chloride excretion through the urine. It has been discovered that *Lepidium sativum* possesses anti-inflammatory properties. *Lepidium sativum* has potent antioxidant properties and promotes diuresis, which may explain why it has antihypertensive benefits [124].

Garden Nasturtium (*Tropaeolum majus* L.)

A member of the Tropaeolaceae family is the garden nasturtium. *Tropaeolum majus* has a beneficial effect on the circulatory system, according to studies. Garden nasturtium hydroethanolic extracts have been shown to lower MAP in SHR rats. Diuretic properties can be found in the ethanolic extract of T. majus (300 mg/kg), cure element (100 mg/kg), or isoquercitrin (10 mg/kg). Each of the aforementioned components has the ability to lower plasma ACE levels. An active flavonoid called isoquercitrin increases the generation of NO [125].

Giant dodder (*Cuscuta reflexa*)

The genus *Cuscuta*, also referred to as dodder, belongs to the convolvulaceaceae family. Rats under anesthesia experienced a drop in SBP and DBP in response to the ethanolic extract of *C. reflexa*. Antihypertensive action and bradycardia observed in a dose-dependent manner [126].

Pointed Phoenix Tail (*Gynura procumbens*)

Gynura procumbens is referred to as "longevity spinach" in Thai and "pointed phoenix tail" in Chinese. In SHRs, the aqueous phoenix tail extract lowers blood pressure. It inhibited ACE activity and Ang I and Ang II-induced contractions in rat aortic rings through a NO-dependent mechanism. Additionally, the crude extract of this plant (0.003 and 0.009 g/mL) suppressed phenylephrine- and KCl-induced contractions, which are linked to the opening of K channels, blocking the Ca²⁺ channels and releasing prostacyclin. As a result, it had a vasod [127].

Pomegranate (*Punica granatum*)

The pomegranate is a deciduous shrub that bears fruit and is a member of the Lythraceae family. It is native to the area between Iran and northern India. Pomegranate reduces ACE activity by around 36%. One study found that consuming 50 cc of its juice each day for a year resulted in a slight reduction in

SBP [128].

Prickly Custard Apple (*Annona muricata*)

The custard apple tree family includes *Annona muricata* as a species. Fruit from the Annonaceae family is edible. *A. muricata* is a native of the Caribbean and Central America. *A. muricata* leaf ethanolic extract has been reported to lower high blood pressure by lowering peripheral vascular resistance [129].

Qingxue Dan (*Chunghyul-dan*)

An herbal mixture called *Chunghyul-dan* lowers blood pressure in stroke patients with stage 1 HTN. SBP and DBP in stroke patients were significantly lower than baseline after receiving 1200 mg of Chunghyul-dan [130].

Radish (*Raphanus sativus*)

Radish is a root vegetable that can be eaten and is cultivated all over the world. It belongs to the Brassicaceae family. The seeds (0.1-3 mg/kg) reduced BP along with HR, whereas the leaf ethyl acetate extract (30 and 90 mg/kg) decreased SBP in SHRs. Radish extracts boost antioxidant levels and NO generation. The antihypertensive impact of the radish may be partially attributed to its anti-proliferative and anti-inflammatory properties [131].

Roselle (*Hibiscus sabdariffa*)

Tea made from *Hibiscus sabdariffa* L. (HS) is consumed and used as a therapy for hyperlipidemia and HTN. Treatment with the dried extract of the calyx (250 mg) for 4 weeks has demonstrated notable antihypertensive effects in patients with HTN.132 The SBP and DBP of hypertension individuals were considerably reduced by 15.32 and 11.29 mmHg after four weeks of consuming 10g/d of hibiscus calyx. Hibiscus tea (240ml) taken three times per day for six weeks significantly reduced SBP, DBP, and MAP in mild and pre-hypertensive patients by 7.2, 3.1, and 4.5mmHg, respectively [7]. The increased NO generation, Ca²⁺ channel blockade, and KATP channel opening contributed to its effects. Roselle has diuretic properties, demonstrates strong antioxidant activity, and inhibits LDL oxidation. Additionally, it exhibits anti-inflammatory properties via inhibiting ACE activity and VSMC growth [133].

Safflower (*Carthamus tinctorius* L.)

Traditional Chinese medicine makes considerable use of *Carthamus tinctorius* L., also known as Kafesheh (Persian), for a variety of ailments, including cerebrovascular and CVDs. Safflower yellow (SY) decreased rennin activity and Ang II levels in SHRs in addition to lowering BP by opening KATP channels. The seed extract (2.1 g daily) lowers

blood pressure in healthy humans as well as VCAM-1 and LDL levels, suppresses PDGF-induced VSMC proliferation, and lessens arterial stiffness [66].

Saffron (*Crocus sativus*)

Saffron, also known as *Crocus sativus* L., is an aromatic plant in the Iridaceae family. This plant is indigenous to Iran, India, Greece, Spain, Morocco, Pakistan, and Iran [134]. Healthy people who received 400 mg of saffron tablets daily for seven days saw their SBP and MAP drop by 11 and 5 mmHg, respectively. Crocin therapy (200 mg/kg for 7 days) significantly reduced oxidative stress and elevated antioxidant enzymes in male Wistar rats [135]. Additionally, the inflammatory pathways NF- κ B and TNF- α were inhibited by saffron and its constituents [136].

Sesame (*Sesamum indicum*)

A flowering plant in the genus *Sesamum* is the sesame. A good preventative therapy for HTN is sesame oil. In rats under anesthesia, the alcoholic extract of the seeds (1–30 mg/kg) was found to cause a drop in blood pressure [137].

Shell Ginger (*Alpinia zerumbet*)

Shell Ginger, commonly referred to as bright ginger, is a kind of perennial ginger from the Zingiberaceae family. A plant from west Asia called *alpinia zerumbet* has only mild hypotensive effects. The methanolic component of shell ginger's essential oil causes vasorelaxant reactions through influencing endothelial cells, or VSMCs [138]. The methanolic extract of the leaves of this plant (100 and 300 g/mL) caused vasodilation in DOCA-salt-treated rats through increasing NO or cGMP production. *Alpinia zerumbet* essential oil inhibits Ca²⁺ channels at concentrations of 1 to 20 mg/kg, and at 0.1 mg/L, it lowers plasma levels of oxidized LDL [139].

Tianma (*Gastrodia elata* Blume)

Traditional Chinese medicine makes use of the saprophytic perennial herb *Gastrodia elata*, which belongs to the Orchidaceae family. The rhizome of *Gastrodia* is antihypertensive. The rhizome's acidic polysaccharides are removed, and they significantly lower blood pressure. By lowering iNOS expression and NO levels, the methanolic extracts (0.02 ml/g) of *Tianma* demonstrated anti-inflammatory effects. The main bioactive component of *Tianma*, gastrodin, caused an increase in NO levels, a decrease in endothelin levels, and a decrease in SBP and pulse pressures in elderly patients with refractory HTN. By

interacting with the RAAS and lowering serum levels of Ang II as well as the expression of both ACE and AT1R, Gastrodin (aphenolic glycoside) lowered SBP [140].

Tomato (*Lycopersicon esculentum*)

The *Solanum lycopersicum* plant's edible portion is the tomato. Carotenoids, which are considered as effective antioxidants, are present in tomato extract. Tomato extract (Lyc-O-Mato), which has a clinically significant capacity to lower SBP by more than 10 mm Hg and DBP by more than 5 mm Hg, moderately reduced blood pressure in individuals with HTN [141]. In rats with hypertension, tomato root extract decreased BP levels. In hypertension individuals, the antioxidant-rich tomato extract has been shown to lower both SBP and DBP [142].

Umbrella tree (*Musanga cecropioides*)

The African corkwood or umbrella tree, *Musanga cecropioides*, is widespread in tropical rain forests, primarily in West Africa. This plant's latex and leaf extract are employed as a vasorelaxant and a hypotensive mediator, respectively. At doses of 10 mg/kg and 40 mg/kg, respectively, the aqueous extract of the stem bark results in a dose-dependent reduction in MABP (4.51 $\pm$ 0.5 mmHg and 65.23 $\pm$ 6.28 mmHg) [143].

Vidanga (*Embelia ribes*)

False black pepper or *Embelia ribes* is a species of plant in the Primulaceae family. It is spread quite far across India. Effects of *Embelia ribes* are hypotensive. SBP and HR can both be decreased by the aqueous extract of *E. ribes* (100mg/kg), which can also increase endogenous antioxidants like SOD, CAT, and GSH [144].

White Horehound (*Marrubium vulgare*)

The flowering plant *Marrubium vulgare*, sometimes known as common horehound, is indigenous to Europe, northern Africa, and southwestern and central Asia. SBP significantly drops as a result of white horehound. Due to its anti-hypertrophic and vasorelaxant qualities, this substance may have a hypotensive impact. The diterpene marrubenol extracted from this plant has the ability to significantly inhibit L-type Ca²⁺ channels, hence preventing VSMC contraction. Additionally, white horehound phenylpropanoids can stop endothelin-1 from secreting when lipoproteins are present [145].

Table 1: Some effective medicinal plants used on hypertension

Plants	Mechanism of Action	Part used	Dose
Ajwain (<i>Carumcopticum</i>)	1. Blocks calcium channel 2. Cholinomimetic effects 3. Causes to vasodilation of coronary arteries 4. Decreases systemic blood pressure	1. Leaves 2. Seed-like fruit	1-30 mg/kg
Bindii (<i>Tribulusterrestris</i>)	1. Increases NO 2. Reduces ACE 3. Inhibits Ang II-induced proliferation	1. Leaves 2. Aqueous extract of Tribulus fruit	0.3–15 mg/mL
BlackCumin (<i>Nigellasativa</i>)	1. Increases in cardiac heme oxygenase-1 activity 2. Prevents of plasma nitric oxide loss	1. Seeds oil	100 mg/kg and 200 mg/kg
ChineseSage (<i>Salviaemiltiorrhizae</i>)	1. Increases NO 2. Opens KATP channels	1. Dried root	0–10 mg/mL

Scientific Evidence of Medicinal Plants Having Antihypertensive Activity

Centella asiatica

Intharachatorn *et al.*, 2013 determined the effects of *Centella asiatica* extract on blood pressure and heart rate of N-nitro-L-arginine methyl ester (L-NAME) induced hypertensive rats. *Centella asiatica* extract (16g/20ml/kg) and quercetin significantly lowered the elevated [146].

Citrus aurantifolia

Citrus aurantifolia is used in African folk medicine for the treatment of hypertension. The effects of aqueous extract of *Citrus aurantifolia* (Ecita) on arterial blood pressure and on isolated heart and aorta activities has been studied. Extract produced a dose-dependent significant decrease in rabbit blood pressure ($p < 0.05$)

Allium sativum

Allium sativum belongs to Liliaceae family, commonly known as garlic, used in variety of cardiovascular conditions, especially hyperlipidemia. Its hypotensive action has also been reported. Meta-analysis of randomly chosen literary data has demonstrated that garlic is involved in decreasing BP in patients with increased systolic pressure, but not in patients without increased systolic pressure [148].

Apium graveolens

Apium graveolens (Family: Apiaceae) commonly known as celery used in several disorders. According to Chinese theory, Celery is effective for HTN that is associated with liver (Han *et al.*, 1999). In a study conducted on human beings, it has been reported that it is involved in decreasing systolic and diastolic BP [149].

Artocarpusaltilis

Artocarpusaltilis belongs to family Moraceae commonly known as breadfruit, widely distributed in western Pacific islands. Its leaf extract of exhibited anti-hypertension effect in phenylephrine-stimulated isolated guinea pig aorta rings [150].

Cuscuta reflexa

C. reflexa crude extract decreases systolic and diastolic BP as well as HR in anesthetized rats. Extract produces dose dependent antihypertensive activity and bradycardia, accompanied with decrease in HR. Study reported that pretreatment with atropine (1mg/kg) did not close down the cardiovascular responses to *C. reflexa* [151].

Daucuscarota

Traditionally, *Daucuscarota* has been used to treat HTN. Aerial part of *Daucuscarota* contains two coumarin glycosides coded as DC-2 and DC-3. Intravenous administration of both compounds caused a concentration-dependent (1-10mg/kg) fall in arterial BP in anesthetized rats. Furthermore, both compounds caused a dose-dependent (10-200µg/ml) inhibitory effect on spontaneously beating guinea pig atria as well as on the K^+ -induced contractions of rabbit aorta at similar concentrations. The findings 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 [152].

Lavandula stoechas

L. stoechas crude extract produce a fall in BP and HR in anesthetized NMT rats. Pretreatment of atropine eliminate the cardiovascular responses, demonstrating that the antihypertensive and bradycardia effects of the crude extract of *L. stoechas*

may be arbitrated through mechanism (s) similar to that of acetylcholine [152].

Moringa oleifera

The crude extract of the leaves of *M. oleifera* caused a decrease in systolic, diastolic and mean BP in a dose dependent manner in anesthetized rats. The antihypertensive effect was recurring to normal within two minutes. HR was affected significantly, at high doses (3 and 10mg/kg). It was also reported that thiocarbamate and isothiocyanate fractions of the crude extract were responsible for the antihypertensive activity [153].

Peganum harmala

Crude extract fraction of *P. harmala* and all pure compounds such as harmine, harmaline, tetrahydroharmine, harmol, and harmaloi exhibited antihypertensive effects in anesthetized rats in a dose dependent manner [151].

Punicagranatum

Research has been reported that pomegranate reduces the activity of angiotensin converting enzymes (ACE) by about 36% [154].

Zingiber officinale

Cooks frequently utilize ginger root. It is well recognized to increase blood flow and to relax the muscles around blood vessels. In rats under anesthesia, the crude extract of ginger reduced arterial blood pressure in a dose-dependent manner (0.3–3 mg/kg) [155].

Carum copticum

The crude extracts of *C. copticum* at a dose of 1–30mg/kg decreases BP and heart rate of anesthetized normotensive rats. Conversely, at the low dose (up to 1mg/kg), the extract exhibited insignificant change in the heart rate. However, the extract causes Bradycardia at the higher doses (10–30 mg/kg) [152].

Conclusion

One of the most significant risk factors for several cardiovascular disorders, including atherosclerosis, heart failure, coronary artery disease, and stroke, is high blood pressure. Hypertension is treated with a variety of synthetic medications. The majority of these medications are more effective but have several adverse effects. Because they are readily available, have fewer side effects, and are affordable, herbal remedies have recently received attention as an alternative treatment for cardiovascular issues.

It's an intriguing method for finding bioactive items to use natural substances with plant origin as cardioprotective and antihypertensive medicines.

Flavonoids, alkaloids, tannins, and terpenoids are only a few of the diverse secondary metabolites that are abundant in plants. These were discovered to have antihypertensive effects in vivo. Therefore, the current review is a good place to start when picking specific molecules from the list of categories that will be valuable therapeutic instruments in the future.

Recommendation

Traditional botanical research on therapeutic plants offers fresh research directions on how medicinal plants lower blood pressure. Although medicinal plants can be treated to create natural medicines, their safety and efficacy should be shown through pharmacological research and clinical trials.

Future research focusing on extended randomized trials may help to elucidate the long-lasting benefits of therapeutic herbs. Additionally, research on several herbs with hypotensive effects has been encouraging thus far and will soon result in the development of novel herbal antihypertensive medications.

Conflict of Interest

The authors declare no conflict of interest.

References

1. Carretero, O. A., Oparil, S. (2000). Essential hypertension. Part I: Definition and etiology. *Circulation*, 101:329-335.
2. Sundström, J., Arima, H., Jackson, R., Turnbull, F., Rahimi, K., Chalmers, J., Woodward, Mark Neal, B. (2015). Effects of Blood Pressure Reduction in Mild Hypertension. *Annals of Internal Medicine*, 162: 184-191.
3. World Health Organization (WHO) (2008). Global Health Observatory Data Repository. Geneva, World Health Organization, 2008 11th February 2013
4. Burt, V. L., Cutler, J. A., Higgins, M. et al. (1995). Trends in the prevalence, awareness, treatment, and control of hypertension in the adult US population. Data from the health examination surveys, 1960 to 1991. *Hypertension*, 26: 60-69.
5. O'Brien, E., Beevers, D.G., Lip, Gregory, Y. H. (2007). ABC of hypertension. *BMJ Books*, London
6. Franklin, S. S., Wilkinson, I. B., & McEniery, C. M. (2012). Unusual hypertensive phenotypes: what is their significance?. *Hypertension*, 59(2), 173-178.
7. McKay, D. L., Chen, C. Y., Saltzman, E., and Blumberg, J. B. (2010). *Hibiscus sabdariffa* L. tea (Tisane) Lowers Blood Pressure in

- Prehypertensive and Mildly Hypertensive Adults. *J. Nutr.* 140, 298–303.
8. Balasuriya, B. N., & Rupasinghe, H. V. (2011). Plant flavonoids as angiotensin converting enzyme inhibitors in regulation of hypertension. *Functional foods in health and disease*, 1(5), 172-188.
9. Jackson, R., Bellamy, M. (2015). Antihypertensive Drugs. *BJA Education*, 15: 280–285.
10. Vasant, O. K., Vijay, B. G., Virbhadrappa, S. R., Dilip, N. T., Ramahari, M. V., & Laxamanrao, B. S. (2012). Antihypertensive and diuretic effects of the aqueous extract of *Colocasia esculenta* Linn. leaves in experimental paradigms. *Iranian journal of pharmaceutical research: IJPR*, 11(2), 621.
11. Tagboto, S., Townson, S. (2001). Antiparasitic properties of medicinal plants and other naturally occurring products. *Adv. Parasitol.*, 50: 199-295.
12. Dianella, S. (2012). Plant-derived antimicrobial compounds: Alternatives to antibiotics. *Future Microbiol.*, 7: 979-990.
13. Beevers, G., Lip, G. Y., O'Brien, E. (2001). ABC of hypertension: The pathophysiology of hypertension. *BMJ.*, 322:912-916.
14. Pierdomenico, S. D., Di Nicola, M., Esposito, A.L., Di Mascio, R., Ballone, E., Lapenna, D., et al. (2009). Prognostic value of different indices of blood pressure variability in hypertensive patients. *Am. J. Hypertension*, 22:842-847.
15. Chobanian, A. V., Bakris, G. L., Black, H.R., Cushman, W.C., Green, L.A., Izzo, J.L. Jr., et al. (2003). Seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure. *Hypertension*, 42:1206-1252.
16. Jette, M., Landry, F., & Blümchen, G. (1987). Exercise hypertension in healthy normotensive subjects. Implications, evaluation and interpretation. *Herz*, 12(2), 110-118.
17. Pickering, T. G. (1987). Pathophysiology of exercise hypertension. *Herz*, 12(2), 119-124.
18. Rost, R., & Heck, H. (1987). Exercise hypertension--significance from the viewpoint of sports. *Herz*, 12(2), 125-133.
19. Wofford, M. R., & Hall, J. E. (2004). Pathophysiology and treatment of obesity hypertension. *Current pharmaceutical design*, 10(29), 3621-3637.
20. Haslam D.W., James, W. P. (2005). Obesity. *Lancet*. 366:1197-1209.
21. Djoussé, L., & Mukamal, K. J. (2009). Alcohol consumption and risk of hypertension: does the type of beverage or drinking pattern matter?. *Revista Española de Cardiología (English Edition)*, 62(6), 603-605.
22. Lee, J. H., O'Keefe, J. H., Bell, D., Hensrud, D. D., & Holick, M. F. (2008). Vitamin D deficiency: an important, common, and easily treatable cardiovascular risk factor?. *Journal of the American college of cardiology*, 52(24), 1949-1956.
23. Tuohimaa, P. (2009). Vitamin D and aging. *J. Steroid Biochem. Mole. Biol.*, 114:78-84
24. Dickson, M. E., & Sigmund, C. D. (2006). Genetic basis of hypertension: revisiting angiotensinogen. *Hypertension*, 48(1), 14-20.
25. Luma, G. B., & Spiotta, R. T. (2006). Hypertension in children and adolescents. *American family physician*, 73(9), 1558-1566.
26. Segura, J., & Ruilope, L. M. (2007). Obesity, essential hypertension and renin–angiotensin system. *Public health nutrition*, 10(10A), 1151-1155.
27. Sorof, J., & Daniels, S. (2002). Obesity hypertension in children: a problem of epidemic proportions. *Hypertension*, 40(4), 441-447.
28. Hwang, I. S., Ho, H., Hoffman, B. B., & Reaven, G. M. (1987). Fructose-induced insulin resistance and hypertension in rats. *Hypertension*, 10(5), 512-516.
29. Bilanda, D.C., Dzeufiet, P. D. D., Kouakep, L., Aboubakar, B.F.O., Tedong, L. P., Kamtchouing, Dimo, T. (2017). B.M.C. Complement.Altern. Med., 17: 479–486.
30. Ghaffari, S., & Roshanravan, N. (2019). Saffron; An updated review on biological properties with special focus on cardiovascular effects. *Biomedicine & Pharmacotherapy*, 109, 21-27.
31. Kapoor, D., Vijayvergiya, R., & Dhawan, V. (2014). Terminalia arjuna in coronary artery disease: ethnopharmacology, pre-clinical, clinical & safety evaluation. *Journal of ethnopharmacology*, 155(2), 1029-1045.
32. Laurent, S. (2017). Antihypertensive drugs. *Pharmacological research*, 124, 116-125.
33. Vaz, N.P., Oliveira, D.R.D., Abouelella, G.A., Abouelella, N.A., Khater, H.F. (2019). Recent Prog. Med. Plants, 48: 219–244.

34. Ghazanfer, S.A. (1994). Handbook of Arabian Medicinal Plants (CRC Press, Boca Raton, FL, 1994), p. 180.
35. Manvitha, K., & Bidya, B. (2014). Review on pharmacological activity of *Cymbopogon citratus*. *Int J Herb Med*, 6, 7.
36. Bodeker, G., Ong, C-K., Grundy, C., Burford, G., Shein, K. (2005). WHO Centre for Health Development, <https://www.who.int/iris/handle/10665/43108>. Accessed 4 Jan 2020
37. Bartolome, A. P., Villaseñor, I. M., & Yang, W. C. (2013). *Bidens pilosa* L.(Asteraceae): botanical properties, traditional uses, phytochemistry, and pharmacology. *Evidence-based complementary and alternative medicine*, 2013
38. Potawale, S.E., Shinde, V.M., Harle, U.N., Borade, S.B., Libi, S.B., Anandi, L., Dhalawat, H.J., Deshmukh, R.S. (2008). *Pharmacol. Online* 2: 185–196.
39. Talaei, B., Mozaffari-Khosravi, H., Bahreini, S. (2018). *J. Nutr. Food Secur.* 3(2): 70–78.
40. Pimenta, E., & Oparil, S. (2009). Role of aliskiren in cardio-renal protection and use in hypertensives with multiple risk factors. *Vascular Health and Risk Management*, 453-463.
41. Takahashi, H. (2008). Sympathetic hyperactivity in hypertension. *Nihon rinsho. Japanese Journal of Clinical Medicine*, 66(8), 1495-1502.
42. Sagnella, G. A., & Swift, P. A. (2006). The renal epithelial sodium channel: genetic heterogeneity and implications for the treatment of high blood pressure. *Current pharmaceutical design*, 12(18), 2221-2234.
43. Farnworth, N.R., Akerele, O., Bingel, A.S., Soejarto, D.D., Guo, Z.G. (1985). Medicinal plants in therapy. *Bull WHO.* 3:965-981.
44. Nelson, M.T., Quayle, J.M. (1995). *Am. J. Physiol.*, 268: 799–822.
45. Ojewole, J. A. O., & Odebiyi, O. O. (1980). Neuromuscular and cardiovascular actions of tetramethylpyrazine from the stem of *Jatropha podagrica*. *Planta Medica*, 38(04), 332-338.
46. Nie, S. Q., Xie, Z. C., & Lin, K. C. (1985). Effects of tetrapyrazine on membrane fluidity and electrophoretic mobility of platelets and the relation to its antiaggregation effect. *Yao xue xue bao= Acta Pharmaceutica Sinica*, 20(9), 689-692.
47. Amira, O. C., & Okubadejo, N. U. (2007). Frequency of complementary and alternative medicine utilization in hypertensive patients attending an urban tertiary care centre in Nigeria. *BMC complementary and alternative medicine*, 7, 1-5.
48. Assob, J.C., Kamga, H.L., Nsagha, D.S. et al (2011). Antimicrobial and toxicological activities of five medicinal plant species from Cameroon Traditional Medicine. *BMC Complement. Altern. Med.*, 11: 70-81.
49. Gawade, B.V., Fegade, S.A. (2012). Rauwolfia (Reserpine) As a Potential Antihypertensive Agent: A Review. *Int. J. Pharm. Phytopharmacol. Res.*, 2: 46-49.
50. Baumeister, A. A., Hawkins, M. F., & Uzelac, S. M. (2003). The myth of reserpine-induced depression: role in the historical development of the monoamine hypothesis. *Journal of the History of the Neurosciences*, 12(2), 207-220.
51. Von-Bezold, A.A., Hirt, A.L. (1867). Über die physiologischenwirkungen des Essigsäurenveratrine. *Under physiol lab wurtzburg*, 1: 75-156.
52. Kraye, O., & Meilman, E. (1977). Veratrum alkaloids with antihypertensive activity. *Antihypertensive agents*, 547-570.
53. Chu, L. H., Hsu, F. L., Chueh, F. Y., Niu, C. S., & Cheng, J. T. (1996). Antihypertensive Activity of dl-Tetrahydropalmatine, an Active Alkaloid Isolated from the Tubers of *Corydalis racemosa*. *Journal of the Chinese Chemical Society*, 43(6), 489-492.
54. Orallo, F. (2004). Acute cardiovascular effects of (+)-nantenine, an alkaloid isolated from *Platycapnos spicata*, in anaesthetised normotensive rats. *Planta medica*, 70(02), 117-126.
55. Zhang, J., Yu, B., Zhang, X. Q., Sheng, Z. F., Li, S. J., Wang, Z. J., ... & Zhang, Y. H. (2014). Tetrandrine, an antihypertensive alkaloid, improves the sleep state of spontaneously hypertensive rats (SHRs). *Journal of ethnopharmacology*, 151(1), 729-732
56. Fowler, Z. L., Baron, C. M., Panepinto, J. C., & Koffas, M. A. (2011). Melanization of flavonoids by fungal and bacterial laccases. *Yeast*, 28(3), 181-188.
57. Tlili, N., Elfalleh, W., Saadaoui, E., Khaldi, A., Triki, S., & Nasri, N. (2011). The caper (*Capparis* L.): Ethnopharmacology, phytochemical and pharmacological properties. *Fitoterapia*, 82(2), 93-101.
58. Reichling, J. (1999). Plant-microbe interactions and secondary metabolites with antiviral,

- antibacterial and antifungal properties. *Functions of Plant Secondary Metabolites and Their Exploitation in Biotechnology*, Vol. 3, 187-273.
59. Archivio, M., Files, C., Benedetto, R.D., Gargiulo, R., Giovannini, C., Masella, R. (2007). Polyphenols, dietary sources and bioavailability. *Ann 1st Super Sanita.*, 43: 348-361.
 60. Ojeda, D., Jiménez-Ferrer, E., Zamilpa, A., Herrera-Arellano, A., Tortoriello, J., Alvarez, L. (2010). Inhibition of angiotensin converting enzyme (ACE) activity by the anthocyanins delphinidin- and cyanidin- 3-O-sambubiosides from *Hibiscus sabdariffa*. *J Ethnopharmacol.* 127:7-10.
 61. Kwon, E.K., Lee, D.Y., Lee, H., Kim, D.O., Baek, N.I., Kim, Y.E., Kim, H.Y. (2010). Flavonoids from the buds of *Rosa damascena* inhibit the activity of 3-hydroxy-3-methylglutaryl-coenzyme a reductase and angiotensin I-converting enzyme. *J Agric Food Chem.*, 58: 882-886.
 62. Horie, S., Yano, S., Aimi, N., Sakai, S., Watanabe, K. (1992). Effects of hirsutine, an antihypertensive indole alkaloid from *Uncaria hynchophylla*, on intracellular calcium in rat thoracic aorta. *Life Sci.*, 50(7): 491-498.
 63. Shindo, M., Kasai, T., Abe, A., Konido, Y. (2004). Effects of dietary administration of plant-derived anthocyanin-rich colours to spontaneously hypertensive rats. *J. Nutr. Sci. Vitaminol.*, 53(1): 90-93.
 64. Actis-Goretti, L., Ottaviani, J.I., Fraga, C.G. (2006). Inhibition of angiotensin converting enzyme activity by flavanol-rich foods. *J. Agric Food Chem.*, 54(1): 229-234.
 65. Persson, I.A.L., Persson, K Andersson RGG (2009). Effect of *Vaccinium myrtillus* and its polyphenols on angiotensin-converting enzyme activity in human endothelial cells. *J. Agric Food Chem.*, 57(11): 4626-4629.
 66. Zhou, D., Liu, B., Xiao X, Dai P, Ma S, Huang, W. (2013). The effect of safflower yellow on spinal cord ischemia reperfusion injury in rabbits. *Oxid Med Cell Longev.*, 2013:692302.
 67. Oh, H., Kang, D.G., Kwon, J.W., Kwon TO, Lee SY, Lee DB. Lee, H.B. (2004). Isolation of angiotensin converting enzyme (ACE) inhibitory flavonoids from *Sedum sarmentosum*. *Biol Pharm Bull.*, 27:2035-2037.
 68. Ahmed, F., Siddesha, J.M., Urooj, A., Vishwanath, B.S. (2010). Radical scavenging and angiotensin converting enzyme inhibitory activities of standardized extracts of *Ficus racemosa* stem bark. *Phytother Res.*, 24(12): 1839-1843.
 69. Olszanecki, R., Bujak-Gizycka, B., Madej, J., Suski, M., Wolkow, P.P., Jawien, J., Korbut R. (2008). Kaempferol, but not resveratrol inhibits angiotensin converting enzyme. *J Physiol Pharmacol.*, 59 :2)387-392.
 70. Edward, R.L., Lyon, T., Litwin, S.E., Rabovsky, A., Symons, J.D. Jalili, T. (2007). Quercetin reduces blood pressure in hypertensive subjects. *J. Nutr.*, 137: 2405-2411.
 71. Hackl, L.P.N., Cuttle, G., Dovichi, S.S., Lima-Landman, M.T., Nicolau, M. (2002). Inhibition of angiotensin converting enzyme by quercetin alters the vascular response to bradykinin and angiotensin I. *Pharmacol.*, 65: 182-186.
 72. Jackson, C.J.C., Rupasinghe, H.P.V. (2002). Food sources and composition of phytoestrogens. In: *Phytoestrogens and Health* (Ed.) Messina M, AOCS Press, Champaign, IL, USA. 95-123.
 73. Wu, J., Muir, A.D. (2008). Isoflavone content and its potential contribution to the antihypertensive activity in soybean angiotensin I converting enzyme inhibitory peptides. *J. Agric. Food Chem.*, 56: 9899-9904.
 74. Xu, Y.Y., Yang, C., Li, S.N. (2006). Effects of genistein on angiotensin-converting enzyme in rats. *Life Sci.*, 79: 828-837.
 75. Montenegro, M.F., Pessa, L.R., Tanus-Santos, J.E. (2009). Isoflavone genistein inhibits the angiotensin converting enzyme and alters the vascular responses to angiotensin I and bradykinin. *Eur. J. Pharmacol.*, 607: 173-177.
 76. Loizzo, M.R., Said, A., Tundis, R., Rashed, K., Statti, G.A., Hufner, A., Menichini, F. (2007). Inhibition of angiotensin converting enzyme (ACE) by flavonoids isolated from *Ailanthus excels* (Roxb) (Simaroubaceae). *Phytother Res.*, 21: 32-36.
 77. Tsutsumi, Y., Shimada, A., Miyano, A., Nishida, T., Mitsunaga, T. (1997). In vitro screening of angiotensin I- converting enzyme inhibitors from Japanese cedar (*Crptomera japonica*). *J. Wood Sci.*, 44: 463-468.
 78. Paliyath, G., Lurie, S., Murr, D., Handa, A. (2008). *Postharvest Biology and Technology of Fruits, Vegetables, and Flowers*. The role of polyphenols in quality, postharvest handling and processing of fruits. Ed: Wiley-Blackwell Publishers, pp.260-281.

79. Bonsei, M., Loizzo, M.R., Statti, G.A., Michel, S., Tillequin, F. (2010). The synthesis and angiotensin converting enzyme (ACE) inhibitory activity of chalcones and their pyrazole derivatives. *Bioorg. Medicinal Chem. Lett.*, 20: 1990-1993.
80. Kang, D.G., Kim, Y.C., Sohn, E.J., Lee, Y.M., Lee, A.S., Yin, M.H., Lee, H.S. (2003). Hypotensive effect of butein via inhibition of angiotensin converting enzyme. *Biol. Pharm. Bull.*, 26(9): 1345.
81. Duarte, J., Pérez-Palencia, R., Vargas, F., Ocete, M.A., Francisco, P-V., Antonio, Z., Juan, T. (2001). Antihypertensive effects of the flavonoid's quercetin in spontaneously hypertensive rats. *Br. J. Pharmacol.*, 133(1): 117-124.
82. Maruyama, H., Sumitou, Y., Sakamoto, T., Araki, Y., Hara, H. (2009). Antihypertensive effects of flavonoids isolated from brazilian green propolis in spontaneously hypertensive rats. *Biol Pharm Bull.*, 32: 1244-1250.
83. Liu, J.C., Hsu, F.L., Tsai, J.C., Chan, P., Liu, J.Y., Thomas, G.N., Tomlinson, B., Lo, M.Y., Lin, J.Y. (2003). Antihypertensive effects of tannins isolated from traditional Chinese herbs as non-specific inhibitors of angiotensin converting enzyme. *Life Sci.*, 73: 1543-1555.
84. Yoopan, N., Thisoda, P., Rangkadilok, N., Sahasitawat, S., Pholphana, N., Ruchirawat, S., Satayavivad, J. (2007). Cardiovascular effects of 14-deoxy-11,12 didehydroandrographolide and Andrographispaniculata extracts. *Planta Med.*, 73(6): 503-511.
85. Alfieri, A., Maione, F., Bisio, A., Romussi, G., Mascolo, N., Cicala, C. (2007). Effect of a diterpenoid from *Salvia cinnabarina* on arterial blood pressure in rats. *Phytother Res.*, 21: 690-692.
86. Hsieh, M. H., Chan, P., Sue, Y. M., Liu, J. C., Liang, T. H., Huang, T. Y., ... & Chen, Y. J. (2003). Efficacy and tolerability of oral stevioside in patients with mild essential hypertension: a two-year, randomized, placebo-controlled study. *Clinical therapeutics*, 25(11), 2797-2808.
87. Pourjabali, M., Mohammadrezaei-Khorramabadi, R., Abbaszadeh, S., Naghdi, N., Naji-Haddadi, S., Bahmani, F. (2017). Medicinal plants used for hypertension. *J Pharm Sci. Res.*, 9(5):537-541.
88. Liu, C., Huang, Y. (2016). Chinese herbal medicine on cardiovascular diseases and the mechanisms of action. *Front Pharmacol.* 7:469.
89. Shouk, R., Abdou, A., Shetty, K., Sarkar, D., & Eid, A. H. (2014). Mechanisms underlying the antihypertensive effects of garlic bioactives. *Nutrition research*, 34(2), 106-115
90. Ashraf, R., Khan, R.A., Ashraf, I., Qureshi, A.A. (2013). Effects of *Allium sativum* (garlic) on systolic and diastolic blood pressure in patients with essential hypertension. *Pak J Pharm Sci.*, 26(5):859-63.
91. Vazquez-Prieto, M.A., Rodriguez, L.C., Lembo, C., Galmarini, C.R., Miatello, R.M. (2011). Garlic and onion attenuate vascular inflammation and oxidative stress in fructose-fed rats. *J Nutr Metab.*, 2011:475216.
92. Dolati S, Ahmadi M, Rikhtegar R, Babaloo Z, Ayromlou H, Aghebati-Maleki L, et al. Changes in Th17 cells function after nanocurcumin use to treat multiple sclerosis. *Int Immunopharmacol.*, 61:74-81.
93. Leong, X.F. (2018). The spice for hypertension: protective role of *Curcuma longa*. *Biomed Pharmacol J.*, 11(4):1829-1840.
94. Kumar, K., Sharma, Y.P., Manhas, R.K., Bhatia, H. (2015). Ethnomedicinal plants of Shankaracharya Hill, Srinagar, J. K, India. *J Ethnopharmacol*, 170: 255-274.
95. Sharifi, A.M., Darabi, R., Akbarloo, N. (2003). Study of antihypertensive mechanism of *Tribulus terrestris* in 2K1C hypertensive rats: role of tissue ACE activity. *Life Sci.*, 73(23):2963-2971.
96. Leong, X.F., Rais, M.M., Jaarin, K. (2013). *Nigella sativa* and its protective role in oxidative stress and hypertension. *Evid Based Complement Alternat Med.*, 201:120732.
97. Jaarin, K., Foong, W.D., Yeoh, M.H., Kamarul, Z.Y., Qodriyah, H.M., Azman, A., et al.(2015). Mechanisms of the antihypertensive effects of *Nigella sativa* oil in L-NAME-induced hypertensive rats. *Clinics (Sao Paulo)*, 70(11):751-7.
98. Kundu, J.K., Liu, L., Shin, J.W., Surh, Y.J. (2013). Thymoquinone inhibits phorbol ester-induced activation of NF- κ B and expression of COX-2, and induces expression of cytoprotective enzymes in mouse skin in vivo. *Biochem Biophys Res Commun.*, 438(4):721-727.
99. Ramkissoon, J.S., Mahomoodally, M.F., Ahmed, N., Subratty, A.H. (2013). Antioxidant and anti-glycation activities correlates with phenolic

- composition of tropical medicinal herbs. *Asian Pac J Trop Med.*, 6(7):561-569.
100. Wu, T.T., Tsai, C.W., Yao, H.T., Lii, C.K., Chen, H.W., Wu, Y.L., et al. (2010). Suppressive effects of extracts from the aerial part of *Coriandrum sativum* L. on LPS-induced inflammatory responses in murine RAW 264.7 macrophages. *J Sci Food Agric*, 90(11):1846-1854.
 101. Akinyemi, A.J., Ademiluyi, A.O., Oboh, G. (2013). Aqueous extracts of two varieties of ginger (*Zingiber officinale*) inhibit angiotensin I-converting enzyme, iron (II), and sodium nitroprusside-induced lipid peroxidation in the rat heart in vitro. *J Med Food*, 16(7):641-646.
 102. Akinyemi, A.J., Ademiluyi, A.O., Oboh, G. (2014). Inhibition of angiotensin-1-converting enzyme activity by two varieties of ginger (*Zingiber officinale*) in rats fed a high cholesterol diet. *J Med Food*, 17(3):317-323.
 103. Kim, J.H. (2012). Cardiovascular diseases and *Panax ginseng*: a review on molecular mechanisms and medical applications. *J Ginseng Res.*, 36(1):16-26.
 104. Rhee, M.Y., Cho, B., Kim, K.I., Kim, J., Kim, M.K., Lee, E.K., et al. (2014). Blood pressure lowering effect of Korea ginseng derived ginseol K-g1. *Am J Chin Med.*, 42(3):605-618
 105. Jovanovski, E., Bateman, E.A., Bhardwaj, J., Fairgrieve, C., Mucalo, I., Jenkins, AL, et al. (2014). Effect of Rg3-enriched Korean red ginseng (*Panax ginseng*) on arterial stiffness and blood pressure in healthy individuals: a randomized controlled trial. *J Am Soc Hypertens*, 8(8):537-541.
 106. Boskabady, M.H., Alitaneh, S., Alavinezhad, A. (2014). *Carum copticum* L.: A herbal medicine with various pharmacological effects. *Biomed Res Int.*, 2014:569087
 107. Ladeji, O., Udoh, F.V., Okoye, Z.S. (2005). Activity of aqueous extract of the bark of *Vitex doniana* on uterine muscle response to drugs. *Phytother Res.*, 19(9):804-806.
 108. Lee, Y.J., Choi, D.H., Cho, G.H., Kim, J.S., Kang, D.G., Lee, H.S. (2012). *Arctium lappa* ameliorates endothelial dysfunction in rats fed with high fat/cholesterol diets. *BMC Complement Altern Med.*, 12:116.
 109. Cheng, Y., Zhou, M., Wang, Y. (2016). Arctigenin antagonizes mineralocorticoid receptor to inhibit the transcription of Na/K-ATPase. *J Recept Signal Transduct Res.*, 36(2):181-188.
 110. Prando, T.B., Barboza, L.N., Araújo, Vde O., Gasparotto, F.M., de Souza, L.M., Lourenço, E.L., et al. (2016). Involvement of bradykinin B2 and muscarinic receptors in the prolonged diuretic and antihypertensive properties of *Echinodorus grandiflorus* (Cham. & Schltdl.) Micheli. *Phytomedicine*, 23(11):1249-1258.
 111. Verma, S.K., Jain, V., Katewa, S.S. (2009). Blood pressure lowering, fibrinolysis enhancing and antioxidant activities of cardamom (*Elettaria cardamomum*). *Indian J Biochem Biophys.*, 46(6):503-506.
 112. Kaur, R., Khanna, N. (2012). Pathophysiology and risk factors related to hypertension and its cure using herbal drugs. *Spatula DD.*, 2(4):245-56.
 113. Lamba, A., Oakes, A.K., Roberts, L., Deprele, S. (2018). The Effects of Crude and Purified Cat's Claw Extracts on Viability and Toxicity of HeLa Cells. Southern California Conference for Undergraduate Research (SCCUR).
 114. Siska, S., Mun, I.A., Bahtiar, A., Suyatna, F.D. (2009). Effect of *Apium graveolens* extract administration on the pharmacokinetics of captopril in the plasma of rats. *Sci Pharm.*, 86(1):6.
 115. Ahmad, S., Hassan, A., Abbasi, W.M., Rehman, T. (2018). Phytochemistry and pharmacological potential of *Cassia absus* - a review. *J Pharm Pharmacol.*, 70(1):27-41.
 116. Jiang, B., Li, D., Deng Y, Teng F, Chen J, Xue S, et al. (2013). Salvianolic acid A, a novel matrix metalloproteinase-9 inhibitor, prevents cardiac remodeling in spontaneously hypertensive rats. *PLoS One*, 8(3): e59621.
 117. Nyadjieu, P., Nguелеfack-Mbuyo, E.P., Atsamo, A.D., Nguелеfack TB, Dongmo AB, Kamanyi, A. (2013). Acute and chronic antihypertensive effects of *Cinnamomum zeylanicum* stem bark methanol extract in L-NAME-induced hypertensive rats. *BMC Complement Altern Med.*, 13:27.
 118. Irondi, A.E., Olawuyi, A.D., Lawal, B.S., Boligon, A.A., Olasupo, F., Olalekan, S.I. (2019). Comparative inhibitory effects of cocoa bean and cocoa pod husk extracts on enzymes associated with hyperuricemia and hypertension in vitro. *Int Food Res J.*, 26(2):557-564.
 119. Ali, M., Ansari, S.H., Ahmad, S., Sanobar, S., Hussain, A., Khan, S.A., et al. (2019).

- Phytochemical and pharmacological approaches of traditional alternate *Cassia occidentalis* L. In: Ozturk M, Hakeem KR, eds. *Plant and Human Health, Volume 3: Pharmacology and Therapeutic Uses*. Cham: Springer; p. 321-341.
120. Choi, D.H., Lee, Y.J., Kim, J.S., Kang, D.G., Lee, H.S. (2012). *Cynanchum wilfordii* ameliorates hypertension and endothelial dysfunction in rats fed with high fat/cholesterol diets. *Immunopharmacol Immunotoxicol.*, 34(1):4-11.
 121. Moloudizargari, M., Mikaili, P., Aghajanshakeri, S., Asghari, M.H., Shayegh, J. (2013). Pharmacological and therapeutic effects of *Peganum harmala* and its main alkaloids. *Pharmacogn Rev.*, 7(14):199-212.
 122. Cheraghi, N.M., Farzaei, M.H., Amin, G. (2015). Medicinal properties of *Peganum harmala* L. in traditional Iranian medicine and modern phytotherapy: a review. *J Tradit Chin Med.*, 35(1):104-109.
 123. Dang, Y., Xu, Y., Wu, W., Li, W., Sun, Y., Yang, J., et al. (2014). Tetrandrine suppresses lipopolysaccharide-induced microglial activation by inhibiting NF- κ B and ERK signaling pathways in BV2 cells. *PLoS One*, 9(8):102522.
 124. Fan, Q.L., Zhu, Y.D., Huang, W.H., Qi, Y., Guo, B.L. (2014). Two new acylated flavonol glycosides from the seeds of *Lepidium sativum*. *Molecules*, 19(8):11341-11349.
 125. Junior, A.G., Prando, T.B., Leme, T.S., Gasparotto, F.M., Lourenço, E.L., Rattmann, Y.D., et al. (2014). Mechanisms underlying the diuretic effects of *Tropaeolum majus* L. extracts and its main component isoquercitrin. *J Ethnopharmacol.* 141(1):501-509.
 126. Ravichandra, V.D., Ramesh, C., Swamy, M.K., Purushotham, B., Rudramurthy, G.R. (2018). Anticancer plants: chemistry, pharmacology, and potential applications. In: Akhtar MS, Swamy MK, eds. *Anticancer Plants: Properties and Application*. Singapore: Springer; p. 485-515.
 127. Ng, H.K., Poh, T.F., Lam, S.K., Hoe, S.Z. (2013). Potassium channel openers and prostacyclin play a crucial role in mediating the vasorelaxant activity of *Gynura procumbens*. *BMC Complement Altern Med.*, 13:188.
 128. Asgary, S., Hashemi, M., Goli-Malekabadi, N., Keshvari, M. (2015). The effects of acute consumption of pomegranate juice (*Punica granatum* L.) on decrease of blood pressure, inflammation, and improvement of vascular function in patients with hypertension: a clinical trial. *J Shahrekord Univ Med Sci.*, 16(6):84-91.
 129. De, C.C., Pinto, N., Campos, L.M., Evangelista, A.C.S., Lemos, A.S.O., Silva, T.P., Melo, R.C.N., et al. (2017). Antimicrobial *Annona muricata* L. (soursop) extract targets the cell membranes of gram-positive and gram-negative bacteria. *Ind Crops Prod.*, 107:332-340.
 130. Moon, S.K., Kim, S.B., Kwon, S., Cho, S.Y., Park, S.U., Jung, W.S., et al. (2018). Anti-hypertensive effect by single administration of *Chunghyul-dan*: a case series. *J Korean Med.*, 39(1): 95-103
 131. Kook, S.H., Choi, K.C., Lee, Y.H., Cho, H.K., Lee, J.C. (2014). *Raphanus sativus* L. seeds prevent LPS-stimulated inflammatory response through negative regulation of the p38 MAPK/NF- κ B pathway. *Int Immunopharmacol.*, 23(2):726-734.
 132. Herrera-Arellano, A., Miranda-Sánchez, J., Avila-Castro, P., Herrera-Alvarez, S., Jiménez-Ferrer, J.E., Zamilpa, A., et al. (2007). Clinical effects produced by a standardized herbal medicinal product of *Hibiscus sabdariffa* on patients with hypertension. A randomized, double-blind, lisinopril controlled clinical trial. *Planta Med.*, 73(1):6-12.
 133. Hopkins, A.L., Lamm, M.G., Funk, J.L., Ritenbaugh, C. (2013). *Hibiscus sabdariffa* L. in the treatment of hypertension and hyperlipidemia: a comprehensive review of animal and human studies. *Fitoterapia.*, 85:84-94.
 134. Mokhtari-Zaer, A., Khazdair, M.R., Boskabady, M.H. (2015). Smooth muscle relaxant activity of *Crocus sativus* (saffron) and its constituents: possible mechanisms. *Avicenna J Phytomed.*, 5(5):365-375.
 135. El-Beshbishy, H.A., Hassan, M.H., Aly, H.A., Doghish, A.S., Alghaithy, A.A. (2012). Crocin "saffron" protects against beryllium chloride toxicity in rats through diminution of oxidative stress and enhancing gene expression of antioxidant enzymes. *Ecotoxicol Environ Saf.*, 83:47-54.
 136. Nam, K.N., Park, Y.M., Jung, H.J., Lee, J.Y., Min, B.D., Park, S.U., et al. (2010). Anti-inflammatory effects of crocin and crocetin in rat brain microglial cells. *Eur J Pharmacol.*, 648(1-3):110-116.
 137. Mirmiran, P., Bahadoran, Z., Golzarand, M.,

- Rajab, A., Azizi, F. (2013). Ardeh (*Sesamum indicum*) could improve serum triglycerides and atherogenic lipid parameters in type 2 diabetic patients: a randomized clinical trial. *Arch Iran Med.*, 16(11):651-656.
138. da Cunha, G.H., de Moraes, M.O., Fachine, F.V., Frota Bezerra FA, Silveira ER, Canuto, K.M., et al. (2013). Vasorelaxant and antihypertensive effects of methanolic fraction of the essential oil of *Alpinia zerumbet*. *Vascul Pharmacol.*, 58(5-6):337-345.
 139. Shen, X.C., Tao, L., Li, WK, Zhang, YY, Luo H, Xia, Y.Y. (2012). Evidencebased antioxidant activity of the essential oil from *Fructus A. zerumbet* on cultured human umbilical vein endothelial cells' injury induced by ox-LDL. *BMC Complement Altern Med.*, 12:174.
 140. Liu, Y., Wang, G., Yang, M., Chen, H., Zhao, Y., Yang, S., et al. (2015). Arctigenin reduces blood pressure by modulation of nitric oxide synthase and NADPH oxidase expression in spontaneously hypertensive rats. *Biochem Biophys Res Commun*, 468(4):837-842.
 141. Paran, E., Novack, V., Engelhard, Y.N., Hazan-Halevy, I. (2009). The effects of natural antioxidants from tomato extract in treated but uncontrolled hypertensive patients. *Cardiovasc Drugs Ther.*, 23(2):145-151.
 142. Monteiro, F.S., Silva, A.C., Martins, I.R., Correia, A.C., Basilio, I.J., Agra, M.F., et al. (2012). Vasorelaxant action of the total alkaloid fraction obtained from *Solanum paludosum* Moric. (Solanaceae) involves NO/cGMP/PKG pathway and potassium channels. *J Ethnopharmacol.* 141(3):895-900.
 143. Owolabi, O.J., Ayinde, B.A., Nworgu, Z.A., Ogbonna, O.O. (2010). Antidiarrheal evaluation of the ethanol extract of *Musanga cecropioides* stem bark. *Methods Find Exp Clin Pharmacol.*, 32(6):407-411.
 144. Chaudhari, H.S., Bhandari, U., Khanna, G. (2012). Preventive effect of embelin from *Embelia ribes* on lipid metabolism and oxidative stress in high-fat diet-induced obesity in rats. *Planta Med.*, 78(7):651-657.
 145. Yousefi, K., Fathiazad, F., Soraya, H., Rameshrad, M., Maleki-Dizaji, N., Garjani, A. (2014). *Marrubium vulgare* L. methanolic extract inhibits inflammatory response and prevents cardiomyocyte fibrosis in isoproterenol-induced acute myocardial infarction in rats. *Bioimpacts* 4(1):21-27.
 146. Intharachatorn, T., Srisawat, R. (2013). Antihypertensive Effects of *Centella asiatica* extract 2013 International Conference on Food and Agricultural Sciences IPCBEE vol.55 (2013) © (2013) IACSIT Press, Singapore
 147. Souza, A., Lamidi, M., Ibrahim, I., Aworet, R.R.R., Samseny, B.M., M'Batchi, I.B. (2011). Antihypertensive effect of an aqueous extract of *Citrus aurantifolia* (Rutaceae) (Christm.) Swingle, on the arterial blood pressure of mammal. *International Research of Pharmacy and Pharmacology*, 1: 142-148.
 148. Bayan L, Koulivand, P. H., Gorji, A. (2014). Garlic: a review of potential therapeutic effects. *Avicenna J. Phytomed*, 4(1):1-14.
 149. Gharooni, M., Sarkarati, A.R. (2000). Application of *Apium graveolens* in treatment of hypertension. *Tehran Univ. Med.*, 58: 67-69.
 150. Hasrat, J.A., Pieters, L., Vlietinck, A.J. (2004). Medicinal plants in Suriname. *J.Pharm. Pharmacol.*, 56: 381-387
 151. Gilani, A.H. Aftab, K. (1992). Pharmacological Actions of *Cuscuta reflexa*. *Informa Healthcare*, 4: 296-302.
 152. Hansawasdi, C.C., Kawabata, J., Kasai, T. (2000). Alphaamylase inhibitors from Roselle (*Hibiscus sabdariffa* Linn.) tea. *Bio Sci. Bio. Technol. Biochem.*, 64: 1041-1043.
 153. Siddiqui, B.S., Saleem, R., Aftab, K., Shaheen, F., Gilani, A.H. (1998). Hypotensive constituents from the pods of *Moringa oleifera*. *Planta Med.*, 64: 225-228.
 154. Dornfeld, M.L. (2001). Pomegranate juice consumption inhibits serum angiotensin converting enzyme activity and reduces systolic blood pressure. *Atherosclerosis*, 158: 195-198.
 155. Fugh-Berman, A. (2000). Herbs and dietary supplements in the prevention and treatment of cardiovascular disease. *Prev. Cardiol.*, 3: 24-32.
 156. Verma, T., Manish, S., Nitin, B., Shyam, Raj Y., Kamal, S., Nagendra, S. C. (2021). Plants Used as Antihypertensive. *Natural Products and Bioprospecting*, 11:155–184.