

Plant-Derived Therapeutics in Hypertension: A Comprehensive Review of Phytochemical Mechanisms, Clinical Evidence and Translational Perspectives

Muhammad Zubair¹; Pankaj Kishor Mishra^{1*}; Saurabh Singhal²

¹Subharti College of Allied and Healthcare, Swami Vivekanand Subharti University, Meerut, Uttar Pradesh, India.

²Netaji Subhash Chandra Bose, Subharti Medical College, Swami Vivekanand Subharti University, Meerut, Uttar Pradesh, India

Corresponding Author: Pankaj Kishor Mishra^{1*}

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Abstract: Despite the many adverse effects of conventional pharmacology, the poor therapeutic response of these drugs and poor adherence to therapy by patients, hypertension still continues to be a major cause of cardiovascular morbidity and mortality worldwide. There is increasing evidence that many plant-derived compounds have potent antihypertensive properties through a variety of mechanisms including ACE inhibition, vasodilation, reduction in oxidative stress, restoration of endothelial function and autonomic nervous system modulation. It is a comprehensive assessment of the phytochemical composition, pharmacological mechanisms, preclinical and clinical investigations and translatability of some of the major medicinal plants with antihypertensive activity. We discuss research on garlic (*Allium sativum*), hibiscus (*Hibiscus sabdariffa*), hawthorn (*Crataegus* species), green tea (*Camellia sinensis*), olive leaf (*Olea europaea*), arjuna (*Terminalia arjuna*), ginseng (*Panax ginseng*), ashwagandha (*Withania somnifera*), curcumin (*Curcuma longa*), and other botanicals with potential cardiovascular benefits. It is important to address the standardization problems, bioavailabilities concerns, drug interaction and regulatory issues that constitute the major impediments to clinical translation. The future possibilities of precision phytomedicine, systems pharmacology and the integration of plant-derived therapeutics into evidence-based cardiovascular treatments are discussed, along with new technology developments based on nanotechnology to deliver phytochemicals. From this study, it can be concluded that plant medicines have great potential as complementary medicines for the treatment of hypertension, but more multicenter clinical trials and chemistry standardisation procedures and mechanistic validation are needed for their general clinical application. Combination of old remedies of the plant kingdom with the newest developments of molecular pharmacology offers plenty of scope for developing novel multi-target anti-hypertensive agents with improved safety and tolerability.

Keywords: Hypertension, Phytotherapy, Medicinal Plants, Antihypertensive Mechanisms, Phytochemicals, Cardiovascular Pharmacology, Natural Products, Standardization, Clinical Translation, Nanotechnology.

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I. INTRODUCTION

The most prevalent modifiable risk factor for cardiovascular diseases is hypertension, which is defined as hypertension (sustained systemic arterial blood pressure >140/90 mmHg) and affects more than 1.3 billion people around the world, is the leading cause of myocardial infarction, stroke, heart failure and chronic kidney disease (1,2,3). While hypertension is a condition that can be treated

with a variety of drugs including angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), calcium channel blockers, thiazide diuretics and beta-adrenergic antagonists, only half of people who have hypertension achieve good blood pressure control (3,4). This therapeutic gap is due to several inter-dependent factors: a progressive tolerance to antihypertensive drugs, drug interactions, inability to access combination drugs because of cost, and poor patient adherence to long-term drug therapy

(5). As these deficits have been increasingly recognized, there has been a revival of scientific interest in traditional botanical remedies, as epidemiological studies have consistently been correlated with reduced prevalence of cardiovascular disease and better control of blood pressure among people eating more plant-rich diets (6,7). In-depth study of phytochemicals in medicinal herbs has shown that some of these herbal plants have bioactive constituents that have pharmacological properties similar to or, in certain instances, superior to the conventional antihypertensive drugs in vitro and animal models (8,9). These phytochemicals work through various molecular mechanisms, such as renin-angiotensin-aldosterone system (RAAS) inhibition, nitric oxide (NO) mediated vasodilation, decrease in the production of reactive oxygen species (ROS), inhibition of pro-inflammatory signaling pathways, modulation of the intracellular calcium handling, and restoration of endothelial function. Furthermore, medicines derived from plants tend to be polypharmacological, meaning that a single plant-based medicine may be made up of various bioactive substances that have a number of different targets that act on several different pathogenic mechanisms, some of which may be advantageous over mono-specific synthetic medicines. Although there is significant preclinical evidence and interest in these plant-based antihypertensive agents in the clinic, they are underutilized in the conventional medical setting (10). There are a number of valid concerns for this gap: Absence of well-designed, well powered randomized placebo controlled trials; Absence of standardized botanical preparations with a defined and consistent content of phytochemicals; limited bioavailability and systemic exposure of active phytochemicals and constituents; poor understanding of herb-drug interactions and potential adverse effects; regulatory uncertainty of botanical medicines; and Absent mechanistic understanding of how active phytochemicals and constituents translate into in vivo efficacy from animal models to human cardiovascular physiology. This extensive review summarizes the knowledge on the use of therapeutics derived from plants for treating hypertension. We discuss pathophysiological mechanisms that play a role in the development of hypertension, review important medicinal plants that demonstrate antihypertensive effects, discuss the evidence for their mechanisms in both preclinical and clinical studies, critically review technological advances that have enhanced the bioavailability of phytochemicals, consider standardization and safety issues, and propose future translation strategies for the incorporation of these medicinal plants into evidence-based cardiovascular care (1,2,3,4,5).

II. PATHOPHYSIOLOGY OF HYPERTENSION

The dys-regulation of several physiologic systems that regulate the maintenance of blood pressure (11) is responsible for the genesis of hypertension. These pathogenic mechanisms give reasons to identify and optimise plant-derived interventions acting on certain pathways.

➤ Renin-Angiotensin-Aldosterone System Dysregulation

One of the important pathways of hormones controlling vascular tone, sodium-water reabsorption, and cardiac

remodeling is the renin-angiotensin-aldosterone system (12). In about 60% of the population who suffer from hypertension, there is dysregulation of this system which leads to the excessive production of angiotensin II, and sodium retention via aldosterone. Angiotensin converting enzyme (ACE) is responsible for converting angiotensin 1 to the potent vasoconstriction and pro-inflammatory peptide angiotensin 2, which acts on the angiotensin receptor type 1 (AT1) on vascular smooth muscle, endothelial and myocardial cells, leading to vasoconstriction, aldosterone release, sympathetic nervous system activation, vascular remodeling, and myocardial hypertrophy (13). Numerous plant-based compounds are effective in biochemical assays and animal models in inhibiting ACE (9), whereas this pathway is inhibited by ACE inhibitors, which are the major components of conventional antihypertensive drugs.

➤ A significant Portion of Cardiovascular Disease is Attributable to Endothelial Dysfunction and Decreased Nitric Oxide Bioavailability

In addition, nitric oxide is a potent vasodilator and anti-inflammatory signaling molecule that is produced and secreted by the vascular endothelium and is important to maintaining vascular homeostasis (14,15). The endothelial dysfunction in hypertension is caused by a reduction in NO production, increase of phosphodiesterase-mediated NO degradation, and increase in superoxide anions which kill NO and generate peroxynitrite, and additional decrease in NO bioavailability (16). Elevated systemic vascular resistance is maintained by a decrease in nitric oxide-mediated vasodilation and an increased sympathetic tone and angiotensin II-induced vasoconstriction. Endothelial dysfunction occurs prior to the development of hypertension, and is an independent risk factor for cardiovascular events, regardless of BP (17). Therefore, re-establishing endothelial function and enhancing the bioavailability of NO could be a rational therapeutic strategy and plant-based antioxidants and NO donors have been shown to be promising in experimental models (9).

➤ The Production of Reactive Oxygen Species (ROS) is Related to Oxidative Stress

Oxidative stress, which is the excessive production of reactive oxygen species (superoxide, hydrogen peroxide, hydroxyl radicals) in relation to the endogenous antioxidant defense, is a key player in the pathogenesis of hypertension (18). In hypertension, several enzymes produce ROS: NADPH oxidase complexes, uncoupled NOS, MEC, and XO (19). Reactive oxygen species are known to cause hypertension by several mechanisms: they can interact with NO to generate peroxynitrite; they can stimulate pro-inflammatory signaling cascades; they can stimulate vascular smooth muscle cell proliferation and migration; they can stimulate the sympathetic nervous system; and they can increase AT1 receptor expression, augmenting angiotensin II signal pathways (20). On the other hand, blood pressure is lowered by increasing the endogenous antioxidants such as superoxide dismutase, catalase and glutathione peroxidase in experimental animals (21). Phytochemicals derived from plants that contain polyphenolic and phenolic antioxidants, and other antioxidants, may have a beneficial effect on blood

pressure by direct scavenging of the ROS and by increasing the expression of the endogenous antioxidant enzymes (9).

➤ *Inflammation of the Blood Vessels and Activation of the Immune System*

Chronic low-grade vascular inflammation is associated with higher levels of circulating and vascular tissue pro-inflammatory cytokines such as tumor necrosis factor alpha (TNF α), interleukin-6 (IL-6) and interleukin-1 beta (IL-1 β) and is a direct contributor to the development of hypertension (22,23). Inflammatory mediators stimulate the recruitment of leukocytes, vascular remodeling, smooth muscle proliferation, and endothelial dysfunction and SNS hyperactivity. In addition, there is some evidence that a pro-inflammatory activation is associated with an oxidative stress, as pro-inflammatory cytokines activate enzymes that produce reactive oxygen species and the reactive oxygen species in turn activate pro-inflammatory transcription factors like nuclear factor-kappa B (NF-kB) (24). Anti-inflammatory compounds in plants such as polyphenols and terpenoids inhibit the production of inflammatory cytokines by many mechanisms such as antagonism of toll-like receptors, inhibition of nuclear factor-kappa B and suppression of mitogen-activated protein kinase pathway (25).

➤ *Sympathetic Nervous System Hyperactivity*

Excessive release of norepinephrine and heightened sensitivity of vascular and cardiac α - and β -adrenergic receptors lead to the development of hypertension via increased vasoconstriction, augmentation of cardiac contractility, renin release and sodium reabsorption (26,27). Prolonged sympathetic hyperactivity results in upregulation of α 1 receptors, increased vascular responses to the catecholamines and the progressive blunting of the parasympathetic counterregulatory mechanisms. The hypothalamic brainstem nuclei and afferent baroreceptor information, as well as the stress-responsive systems, are involved in complex interactions that regulate central sympathetic outflow (28). This dysregulation of these regulatory networks, which can be caused by chronic stress, salt excess or inflammation, maintains pathological sympathetic activation. The hypotensive effects of phytochemical compounds with GABAergic, serotonergic or dopaminergic activity may involve reduction of sympathetic tone at the central level.

➤ *Vascular Smooth Muscle Dysfunction and Altered Calcium Signaling*

In the absence of other factors, an increase in the intracellular calcium concentration leads to activation of calmodulin-dependent myosin light chain kinase that in turn phosphorylates the regulatory light chain, allowing the crossbridges to cycle (29). Increased mobilisation of calcium into cells and increased sensitivity of the contract proteins to calcium is linked to hypertension which results in a longer vasospasm and vascular remodelling. Main pathway of calcium entry is the voltage-gated L-type calcium channels and main pathway of calcium release from sarcoplasmic reticulum stores is through inositol-1,4,5-trisphosphate and ryanodine receptors (30). Calcium handling defect is a

common feature in several mechanisms of hypertension, including the effect of angiotensin II on calcium channel expression and activity, the effect of sympathetic stimulation on calcium influx, the effect of oxidative stress on sarcoplasmic reticulum calcium handling and the effect of inflammatory mediators on calcium signaling (31). Some drugs, including calcium channel antagonists and those that regulate the action of calcium in the body, can help to prevent contractions of the blood vessels and help reduce blood pressure.

III. MECHANISM OF ACTION AND EVIDENCE OF THE ANTIHYPERTENSIVE EFFECTS OF MAJOR PLANT-DERIVED THERAPEUTICS

Mechanisms and Phytochemistry” The antihypertensive effects have been demonstrated in several medicinal plants with a variety of phytochemical constituents and mechanisms involved (32, 33). This is followed by a review of the most common botanicals studied, their phytochemical composition, known mechanisms of action, pre-clinical findings and clinical trial data (including safety and therapeutic limitations).

➤ *Allium Sativum (Garlic)*

One of the best studied of the plant-based antihypertensive remedies is garlic, a traditional health remedy used for thousands of years (34). When fresh cloves are cut, crushed or chewed, they release alliinase that breaks a large number of the sulfur-containing compounds in the bulb such as alliin, ajoene and s-allylcysteine which compromise the compartmentalization of the cells. These volatile thiosulfuric compounds are able to cross cell membranes easily and are distributed throughout the body, explaining garlic's characteristic pungent odour and wide pharmacological activities. The in vitro biochemical assays as well as the animal studies indicate that the sulfur compounds extracted from garlic produce the same effects as the widely used ACE inhibitor, captopril (12,34). The inhibitory mechanism is direct competition with the enzyme, which will reduce the production of angiotensin II and increase vasodilation. In addition, garlic compounds activate endothelial nitric oxide synthase (eNOS) expression and activity, which will improve NO-mediated vasodilation (36). In animal studies, garlic has shown to reduce the SBP and DBP by 10-25 mmHg, comparable to moderate dose antihypertensive drugs (34). The results of clinical studies on the antihypertensive activity of garlic are inconsistent and depend on how the garlic is prepared, the dosage, the length of the study and the severity of baseline hypertension (37). Higher dose and aged garlic extracts had the greatest lowering effect on both SBP and DBP, decreasing SBP by approximately 5-8 mmHg and DBP by 3-5 mmHg in hypertensive individuals in a meta-analysis of RCTs (12). Mechanistic actions that might contribute to these clinical effects include vascular and systemic mechanisms: ACE inhibition blocks angiotensin II; nitric oxide augmentation increases vascular nitric oxide; platelet aggregation inhibition lowers the vascular thrombotic burden; and oxidative stress reduction upregulates cellular antioxidant systems (9,38).

Garlic is safe to use at dietary doses and in moderate doses of supplements, which is indicated by its low toxicity (39). Side effects sometimes mentioned are gastrointestinal upset, flatulence and a characteristic garlic odor which decreases the social acceptability. Importantly, garlic has been demonstrated to inhibit several cytochrome P450 enzymes that metabolize drugs, which could lead to an increase in the plasma levels of drugs metabolized by these pathways, including warfarin, certain protease inhibitors and certain antihypertensive agents (10). So, people taking garlic supplements at the same time as blood thinners or drugs that can affect how your blood clot, should be monitored for higher than usual side effects.

➤ *Hibiscus Sabdariffa (Roselle)*

Hibiscus sabdariffa commonly known as roselle/sorrel is a tropical plant which produce calyces rich in polyphenolic compounds (40,41), organic acids (citric and malic acid) and anthocyanin pigments. In African and Asian cultures, the calyces are traditionally used as a tart beverage, and have been shown to have potent antihypertensive activity in various clinical trials. Several mechanisms of antihypertensive activity of hibiscus have been identified, all of which involve its beneficial action on the renin-angiotensin system: direct ACE inhibition, like that of captopril, in biochemical assays; an ability to enhance endothelial NO production; to exert mild diuretic activity with consequent sodium and water excretion; and to modulate sympathetic tone. (12,41,42). Based on this landmark systematic review and meta-analysis, the administration of hibiscus was shown to consistently lower blood pressure, by 7.5 to 13.3 mmHg for the systolic blood pressure and 3.1 to 6.0 mmHg for the diastolic blood pressure depending on the baseline severity of hypertension and the method of preparation of hibiscus (43). Interestingly, the magnitude of antihypertensive effect was near to the conventional antihypertensive drug treatments in mild to moderate hypertension. The 3-5 g/d for 4-12 weeks appears to be the most optimum consumption of hibiscus, with longer duration studies needed to determine its continued effects. The anthocyanin content and total antioxidant activity were correlated to antihypertensive potency of hibiscus preparations, indicating that it might be beneficial to standardise the preparations to a specific concentration of anthocyanins for better therapeutic consistency (41). Most populations tolerate *Hibiscus* well, and will suffer little side effects (44). Uncommon side effects are gastrointestinal discomfort and hepatotoxicity (unknown cause). In particular, the compounds in the hibiscus calyces that inhibit estrogen metabolism may be of interest to certain groups because these compounds could help to reduce the amount of estrogen in the plasma of women using contraceptive drugs or hormone replacement therapy. In addition, extracts of hibiscus have mild diuretic properties that could combine with other blood pressure-lowering medications, or speed the depletion of potassium, making their use with potassium-losing medications a concern.

➤ *Crataegus Species (Hawthorn)*

Hawthorn is a collective name used to describe a group of plants called *Crataegus* species that have been used in European traditional medicine for centuries to treat

cardiovascular diseases such as hypertension, congestive heart failure and cardiac arrhythmias (45,46). Polyphenols, such as proanthocyanidins, flavonoids and phenolic acids, found in the berries, leaves and flowers, have several cardiovascular properties. Hawthorn preparations appear to have a positive inotropic effect, increase myocardial contractility and cause peripheral vasodilation and a reduction in systemic vascular resistance, beneficial effects in the management of hypertension and heart failure (46,47). The direct mechanisms of action of hawthorn for vasodilation and blood pressure reduction are direct relaxation of vascular smooth muscle, an increase in nitric oxide mediated vasodilation, inhibition of phosphodiesterase (which leads to an increase in cyclic guanosine monophosphate in the vascular tissue) and modulation of calcium signaling in the vascular tissue. Furthermore, the antioxidant flavonoids in hawthorn help to limit the production of reactive oxygen species and anti-inflammatory polyphenols help to inhibit pro-inflammatory pathways (45,46). The extracts from hawthorn have been shown to lower blood pressure in various models of hypertension in animal studies, and lowers systolic blood pressure by around 15-20 mmHg at effective doses. There have been fewer and less well-designed human clinical trials of hawthorn's antihypertensive effects than have been found in the garlic and hibiscus studies. There are a few small RCTs that have reported that hawthorn preparations reduce SBP by 7-11 mmHg and DBP by 4-8 mmHg in individuals with hypertension; the evidence from larger, well designed trials has yet to come. The therapeutic effects of the hawthorn formulations employed in clinical studies are consistent only if they are phytochemically standardized, and the formulations are generally standardized according to the level of proanthocyanidins or flavonoids. In clinical populations, hawthorn is remarkably safe with adverse effects rare and usually mild (48). Hawthorn compounds do inhibit phosphodiesterase enzymes that regulate cardiac function, however, and could enhance the effect of phosphodiesterase inhibitors such as milrinone. In addition, hawthorn has a slight negative chronotropic effect that could have a potentially significant negative chronotropic effect when combined with beta-adrenergic antagonists, but this effect is not considered clinically significant.

➤ *Camellia Sinensis (Green Tea)*

Green tea leaves are a rich source of natural catechins such as epigallocatechin gallate, epigallocatechin, epicatechin gallate and epicatechin (49,50). The catechins are found in green tea and account for 30% of the dry matter of the tea, and the bulk of the pharmacological activity of green tea comes from these catechins. The epidemiological evidence that links the consumption of green tea with reduced risk of cardiovascular disease (CVD) and hypertension has spurred a myriad of studies on the mechanisms underlying these associations (51, 52). The Green tea catechins' antihypertensive effects have a few complementary mechanisms of action: direct inhibition of VEG-F receptors with increased angiogenesis and improved vascular remodeling; eNOS expression and activity upregulation, direct scavenging of pro-oxidative ROS, and upregulation of intracellular antioxidant enzymes, which reduces oxidation stress; nuclear factor-kappa B inhibition, and production of

pro-inflammatory cytokines; direct anti-Angiotensin II receptor (AT1) activity inhibiting Ang-II signaling; modulation of activity of central catecholaminergic systems (49,50,52). Animal studies have consistently demonstrated a positive effect of green tea extracts on blood pressure in different models of hypertension, at doses of 5 to 10 mmHg reduction in blood pressure to 15 to 20 mmHg reduction in the systolic pressure, depending on models, concentration of catechins and the duration of treatment (49). Mechanistic studies show that the antihypertensive effects of green tea are associated with increased bioavailability of endothelial nitric oxide, increased endothelial vasodilatory function (as measured by flow-mediated dilation), and decreased levels of markers of oxidative stress (uric acid, urinary isoprostane excretion) (50,52). The human randomized controlled trials of the effects of green tea on hypertension have shown that green tea has modest but consistent antihypertensive effects (49,51,52). Multiple clinical trials were subsequently combined together and a meta-analysis showed an average drop in systolic blood pressure of about 2 mmHg and in diastolic blood pressure of about 1 mmHg after 12-24 weeks of regular green tea drinking. The small effects, however, seen in the populations are clinical, but less pronounced than the effects of garlic or hibiscus in similar trials. The results of all these trials indicate that green tea is safe to consume and that it can be included in the diet, which is especially attractive at the population level for the long term management of hypertension and cardiovascular disease. In most populations (53), green tea has a remarkably safe profile, with few adverse effects. Tolerability issues are primarily related to caffeine content and may include nervousness, insomnia or palpitations in people sensitive to caffeine, which can be prevented by using the decaffeinated versions. Another effect of the green tea catechins is that they are CYP3A4 inhibitors, and at high concentrations, may affect the metabolism of various drugs, such as immunosuppressants and some benzodiazepines, but not necessarily the metabolism of other drugs at typical amounts.

➤ *Olea Europaea (Olive Leaf)*

The polyphenolic compounds in olive leaf extracts are abundant and include 54,55 up to 1.4 percent oleuropein by weight of fresh leaves, derived from the *Olea europaea* tree's leaves. Oleuropein, on drying and extraction, converts to hydroxytyrosol, which is one of the strongest antioxidants. Pharmacological activity of olive leaf is linked to other polyphenols (caffeic acid derivatives and verbascoside). In traditional Mediterranean medicine, olive leaf infusions have been used for centuries for cardiovascular diseases; recent studies demonstrated the antihypertensive effects of olive leaf (54). The mechanisms responsible for the BP-lowering properties of olive leaf extract are its high antioxidant activity, as a result of the presence of oleuropein and hydroxytyrosol, which both neutralize ROS; its ability to promote the expression and activity of endothelial nitric oxide (eNOS) leading to vasodilation; its ACE inhibitory activity (like mild-to-moderate intensity conventional antihypertensive drugs); its calcium channel antagonism activity, which results in vascular smooth muscle relaxation; and its modulation of sympathetic nervous system activity (55,56). In animal studies, olive leaf administration has

shown a considerable reduction in blood pressure in several different models of hypertension, achieving systolic pressure reductions of 10–18 mmHg. Encouraging results have been obtained from clinical trials that have studied the effects of olive leaf extract on hypertension (54,55,56). The results of the randomized, double-blind, placebo-controlled trial showed a 11.4 mmHg decrease in SBP and 4.8 mmHg decrease in DBP in stage-1 hypertensive individuals after 8 weeks of daily use of standardized olive leaf extract containing 40 mg of oleuropein, a decrease greater than that seen with green tea. Interestingly, this effect size was approaching the level of efficacy of antihypertensive drugs as monotherapy. These were subsequently confirmed in clinical trials and the hypotensive activity of the standardized preparations of olive leaves has been obtained comparable in intensity and in all kinds of hypertensives. In clinical populations, olive leaf extracts are very well tolerated and have very few side effects (57). Often there are gastrointestinal symptoms, usually mild constipation or diarrhoea. A few cytochrome P450 enzymes are inhibited by the compounds in olive leaves, but interactions with these enzymes are unlikely at the usual dose. However, due to the reported mild antiplatelet effect of olive polyphenols, people who are already on anticoagulant medications might need monitoring.

➤ *Terminalia Arjuna (Arjuna)*

The bark of *T. arjuna* or arjuna is used in Ayurvedic medicine and has been used in traditional Indian medicine for over three millennia for cardiovascular diseases including hypertension, congestive heart failure (58,59), and myocardial infarction. In the bark, various bioactive compounds, such as triterpenoids, tannins, glycosides and polyphenols, including arjunic acid and arjunolic acid, are found. Arjuna bark is traditionally used as a cardiovascular tonic and more recent phytochemical studies have been able to provide scientific backing for its antihypertensive and cardioprotective activity (58). Thanks to its direct vasodilatory effect through vascular smooth muscle relaxation, its effect in enhancing endothelial nitric oxide synthase expression and nitric oxide mediated vasodilation, its significant antioxidant activity because of polyphenolic and phenolic compounds, its action in reducing the oxidative stress in the organism by the upregulation of its antioxidant enzymes such as superoxide dismutase and catalase, its anti-inflammatory effect through inhibition of the NF-kappa B pathway, its positive inotropic effect and its ACE inhibitory activity, which is similar to the action of conventional antihypertensive agents, Arjuna demonstrates several actions that benefit the health of the cardiovascular system (59,60). Animal studies have shown that extracts of Arjuna bark can help reduce blood pressure by 15-20 mmHg in animal models of hypertension. There has been very limited clinical human trials of the use of arjuna in hypertension; these trials have supported its use (58,59). A randomized double blind controlled study showed that the effect of arjuna bark extract on systolic blood pressure was 9.8 mmHg and for diastolic blood pressure was 5.3 mmHg in stage 1 hypertensive patients after 12 weeks treatment which was comparable with mild antihypertensive drug used alone. Further studies indicate that administration of arjuna can also have a

beneficial effect for patients with congestive heart failure with decreased ejection fraction, which may be through combined haemodynamic and direct myocardial protection (60). However, bigger and wider clinical trials proving the antihypertensive effect of arjuna in different hypertensive patients are needed. There are no significant adverse effects reported from traditional use and clinical trials of Arjuna bark (61). Occasionally reported adverse effects are mild gastrointestinal upset and allergic reactions in susceptible individuals. The iron content of arjuna preparations could potentially cause interference in iron absorption and warrant monitoring in people with iron deficiency anaemia. Furthermore, arjuna compounds can inhibit some cytochrome P450 enzymes, which could cause drug interactions; this should be assessed in people who are on medications that have narrow therapeutic windows.

➤ *Panax Ginseng (Asian Ginseng)*

Panax ginseng is one of the most important traditional medicinal plants, and widely researched for more than four thousand years used in the treatment of disease in East Asian medicine (62,63). It contains approximately 30 per cent of bioactive substances known as ginsenosides in its root. The ginsenosides are triterpenoid saponins that have different pharmacological effects, depending on a variety of aglycone skeletons (protopanaxadiol and protopanaxatriol) and different attachments of the glucose moiety. Moreover, ginseng is abundant in polyphenolic compounds, polysaccharide and volatile oils, which are responsible for therapeutic effect of ginseng (62). Ginseng has several anti-hypertensive effects, including sympathomimetic and sympatholytic activities with complex, dose-dependent and time-dependent relationships: Ginseng can initially cause a rise in blood pressure due to its sympathomimetic activity, but as time goes on, it can show vasodilatory and parasympathomimetic activity; Ginseng can promote nitric oxide (NO) production and vasodilation in the vascular endothelium; Ginseng acts as an antioxidant, reducing production of reactive oxygen species; Ginseng inhibits nuclear factor-kappa B which is thought to be an anti-inflammatory property; Ginseng increases endothelial functioning and vascular compliance; Ginseng modulates calcium signaling in vascular smooth muscle (63, 64). Ginseng has been demonstrated to have hypotensive effects in animal models with hypertension, which may be attributed to different ginseng preparation standardization and ginsenoside content. There have been inconsistent findings from human clinical trials of the antihypertensive effects of ginseng (62,63,64). Small decreases in systolic blood pressure (5-8 mmHg) have been reported in some randomized controlled trials with ginseng supplementation, but others report little to no antihypertensive effects. This heterogeneity may be due to the different species of ginseng used (*Panax ginseng* and *Panax quinquefolius*) as well as differing ginseng preparation which alters the composition and bioavailability of ginsenosides, dosing protocols, and the severity of baseline hypertension. The available data indicated that ginseng has greatest antihypertensive effects in people with existing endothelial dysfunction, and least effects in people with uncomplicated hypertension (64). Overall, ginseng seems to be safe to take, although these side effects may be more

common when taken in high doses (65). Side effects are nervousness, insomnia and palpitations, secondary to sympathomimetic effects, particularly when administered in high doses or over extended periods. In addition, ginseng has been demonstrated to inhibit several cytochrome P450 enzymes, including 3A4, 2D6 and 2C9, which could further increase the levels of certain drugs in the blood, such as warfarin, which may lead to poorer control of anticoagulation, statins, which may lead to poorer efficacy in lowering lipids, and immunosuppressants, which may lead to increased risk of infection (10). In addition, ginseng is a sympathomimetic and can increase the hypertensive effects of individuals with uncontrolled hypertension and/or sympathomimetic amines.

➤ *Withania Somnifera (Ashwagandha)*

Ashwagandha, also known as *Withania somnifera*, is an Ayurvedic herb, which belongs to a family of adaptogenic herbs. Withanolides, steroidal lactones, make up up to 5% of dried extract of the roots and leaves, and they are bioactive (66,67). Besides withanolides, ashwagandha also possesses other pharmacological properties like saponins, polyphenols and alkaloids. Ashwagandha has been traditionally prescribed to increase energy, stress, anxiety and cardiovascular health benefits, and some of the recent studies have supported their traditional uses (67). There are multiple ways that Ashwagandha can help lower blood pressure; it is an adaptogen, which means that it affects multiple systems that are part of the stress response. The major mechanisms are through the ability to reduce circulating levels of cortisol and catecholamines, due to the ability of the withanolides to suppress the hypothalamic-pituitary-adrenal axis; through antioxidant and anti-inflammatory effects, which lowers levels of oxidative stress and inflammatory markers; through an improvement in the tone of the parasympathetic nervous system and a decrease in sympathetic overactivity; through the improvement in endothelial function and vascular reactivity; through vasodilating activity, which includes enhancing nitric oxide availability; and through anxiolytic activity, which decreases psychogenic blood pressure elevations (66,67,68). In animal models, Ashwagandha administration results in more consistent reduction in blood pressure in models of stress-induced hypertension as compared to genetic hypertension models, suggesting a preference for stress-related hypertension. In particular, a few studies have investigated the effect of ashwagandha on hypertension in human clinical trials in the context of stress and mild hypertension (67,68). Ashwagandha root extract has been shown to lower systolic blood pressure by 8-12 mmHg and diastolic blood pressure by 4-7 mmHg in 8-12 weeks in people with high baseline stress and moderate or mild hypertension in several randomized controlled trials. In particular, the administration of ashwagandha simultaneously lowered anxiety scores and diminished the perception of stress indicating that the reduction of blood pressure might be partly because of the stress-related mechanisms (68). But efficacy seems to be less pronounced in those with uncomplicated hypertension not related to psychological stress. Individuals who take ashwagandha at typical dosages generally tolerate it quite well, and there are few side effects (69). Occasionally noted effects include gastrointestinal

upset, somnolence (typically used as a mild sedative) and rare allergic reactions. Theoretically, withanolides could interfere with some cytochrome P450 enzymes, which may lead to a change in the metabolism of certain drugs, such as benzodiazepines and some immunosuppressants, but interactions at standard supplemental doses do not seem to be clinically relevant.

➤ *Curcuma Longa (Turmeric) and Curcumin*

Curcuma longa is a rhizomatous plant with curcuminoids as the predominant constituents of which curcumin is the most active and dominant (about 3 per cent of dried rhizome) (70,71). Turmeric also contains other compounds with biological activity similar to curcumin, including demethoxycurcumin, bisdemethoxycurcumin and volatile oils such as turmerone, which is responsible for the aroma of turmeric. Turmeric has been used for more than 4,000 years in traditional and Ayurvedic medicine for a variety of health issues such as inflammation, pain and cardiovascular diseases (70). The antihypertensive activity of curcumin can be attributed to several complementary mechanisms indicating the multi-faceted nature of its pharmacological properties: direct relaxation of vascular smooth muscle cells via calcium channel antagonism and opening of potassium channels; increased expression of endothelial nitric oxide synthase and nitric oxide production; strong antioxidant activity through direct scavenging of reactive oxygen species and induction of antioxidant enzymes such as superoxide dismutase and catalase; potent anti-inflammatory activity, which includes inhibition of nuclear factor-kappaB and suppression of pro-inflammatory cytokine production; inhibition of angiotensin II signaling by direct antagonism of the AT1 receptor; reduced sympathetic nervous system activity and improved insulin sensitivity that may contribute to an antihypertensive effect via metabolic mechanisms (70,71,72). Antihypertensive effect of curcumin is well documented in animal models and reduce blood pressure in various animal models by 15-25 mmHg. A few human clinical studies have demonstrated somewhat divergent effects of curcumin in the treatment of hypertension (70,71). A few studies have been done in which individuals with prehypertension or stage-1 hypertension were given curcumin for 8-12 weeks, and found that curcumin reduced the systolic blood pressure by 5-8 mmHg and the diastolic blood pressure by 3-5 mmHg. Of particular significance, administration of curcumin resulted in improvement of endothelial function markers, such as flow-mediated dilation, and decreased oxidative stress markers (72) at the same time. Minimal effects were, however, reported in some studies, with the noted heterogeneity being due to differences in curcumin bioavailability, which is still significantly hindered by low bioavailability (inability to get the compound absorbed into the blood stream, rapidly metabolized and eliminated). The use of curcumin in doses of several grams per day is well tolerated and has few side effects (73). The most common side effects are gastrointestinal upset and very infrequent allergies. The great challenge for the therapeutic use of curcumin is, however, its intrinsic bioavailability. Curcumin is rapidly glucuronidated and sulfated in the liver, which leads to systemic bioavailability of less than 1% of the doses that were administered without absorption enhancers

(71). The bioavailability limitation has led to the development of formulations of curcumin, which increase its bioavailability (including liposomes, curcumin-phytosome complexes bound to phospholipids, and nanoparticles) that have marked higher systemic exposure and antihypertensive efficacy than unformulated curcumin.

➤ *Additional Plant-Derived Antihypertensive Agents with Supporting Evidence*

Apart from the above-mentioned botanicals that have been studied in detail, there are some other medicinal plants which have antihypertensive activity and are briefly discussed here (74,75,76). Cinnamon (*Cinnamomum* species) has been found to contain ACE inhibitory and antioxidant compounds like cinnamaldehyde and polyphenols, and while there are not many clinical trials, cinnamon supplementation was seen to lower blood pressure by 4-7 mmHg (74). *Nigella sativa* (black seed) contains thymoquinone and polyphenols which has antioxidant and anti-inflammatory properties, and a few animal studies and small clinical trials demonstrated that it can reduce blood pressure by 5 to 10 mmHg (75). The endothelial function and vasodilation benefits of *Moringa oleifera* (drumstick) are provided through isothiocyanates and polyphenols, however, there is limited clinical evidence (76). *Coptis chinensis* and *Berberis* species are plants that contain berberine alkaloids that have strong antihypertensive, anti-inflammatory and lipid-lowering properties (77). Mechanistically, berberine acts to inhibit the production of reactive oxygen species from the mitochondria, increase the signaling of the AMP-activated protein kinase, improve endothelial function, lower inflammatory markers and the metabolic parameters such as glucose control and lipid profiles. Based on human trials, administration of berberine has been shown to lower systolic blood pressure by 8-12 mmHg and improve several cardiovascular risk factors at once (77). Cocoa (*Theobroma cacao*) contains high levels of epicatechin polyphenols related to the polyphenols in green tea, and mechanistic studies indicate that these polyphenols promote the expression of endothelial nitric oxide synthase (eNOS) and nitric oxide (NO) bioavailability (78). In studies looking at the effect of cocoa consumption on hypertension, researchers have seen reductions of 3 to 6 mmHg, which is less than the effects of green tea, but is consistent with the low number of catechins in cocoa compared to green tea. Pomegranate (*Punica granatum*) has high levels of polyphenol antioxidants like ellagic acid and punicalagins, which are anti-inflammatory (79). Limited clinical trial evidence indicates that pomegranate juice could reduce systolic blood pressure by 5-7 mmHg which may be attributed to the antioxidant properties and angiotensin-converting enzyme inhibitory effect of pomegranate juice (79). There is evidence that some polyphenols, carotenoids and marine microalgae like *Chlorella* and *Spirulina* have positive effects on vascular health and endothelial function; but there are inconsistent clinical data concerning their antihypertensive effects. The observations described here indicate that rational mixtures of botanicals that could target complementary, but different, pathways can result in superior therapeutic efficacy than can single botanicals, and represent a possible strategy for future clinical trials. (32,33).

A. Improved Understanding of the Mechanisms of Antihypertensive Activity of Plant Origin.

The antihypertensive activity of plant-derived substances is mediated through several complementary and overlapping mechanisms that act on the different pathophysiological derangements related to hypertension (80, 81). This section gathers mechanistic insights based on the studied botanicals and centers on the integrated multi-target approach of phytotherapeutics.

➤ *Angiotensin Converting Enzyme (ACE) Inhibition and RAAS Modulation*

A variety of phytochemicals, however, have been found to competitively and directly inhibit ACE binding to the enzyme's active site to prevent angiotensin II formation and promote vasodilation, like ACEIs (12,34,41). In biochemical assays, garlic extract, hibiscus extract and olive leaf extract exhibited high potent ACE inhibitory properties, which were close to the properties of the ACE inhibitors which are used in the traditional medicine. Also, certain plant constituents such as flavonoids and tannins indirectly regulate RAAS through their action on endothelial cell signaling by the upregulation of ACE2 expression and activity which is an alternative enzyme that breaks down angiotensin II into inactive metabolites, favouring angiotensin II degradation and decreasing hypertensive signalling (82). This multi-level RAAS modulation via both pathways (ACE inhibition and ACE2 upregulation) is an integrated approach to the conventional antihypertensive mechanisms, which are based on the inhibition of a single pathway.

➤ *Vasodilation and Endothelial Nitric Oxide Production*

The endothelial nitric oxide production is the mechanism responsible for vasodilation in the setting of Nitric oxide, produced by the endothelial cells, is the main regulator of basal vascular tone and a deficiency in the bioavailability of nitric oxide is a direct contributing factor to hypertension (14,15). There are several phytochemicals that work through various mechanisms to increase the bioavailability of NO. These compounds in green tea (catechins), in hibiscus (anthocyanins), and in olive leaf (phenols) are able to up-regulate endothelial nitric oxide (NO) synthase expression in a mitogen activated protein kinase pathway (MAPK) and in an estrogen receptor dependent manner directly, leading to nitric oxide production (49,50,52,55). Meanwhile, antioxidants in plants like curcumin and garlic antioxidants help to reduce ROS production and directly scavenge superoxide anions, which may reduce the production of peroxynitrite, which can destroy nitric oxide (NO) (20,34,70). This is because polyphenols increase the production of nitric oxide and decrease its breakdown, bringing about a tremendous vasodilatory effect. Plants also have some compounds that activate silent information regulator proteins (sirtuins) to protect the endothelial function of mitochondria and reduce oxidative stress to ensure a constant production of nitric oxide, as well as vascular health (83).

➤ *Antioxidant Activity and Reactive Oxygen Species Reduction*

Oxidative stress is a crossroads at which several pathogenic mechanisms of hypertension converge, such as activation of the RAAS, inflammation and endothelial dysfunction (18,19,20). The polyphenols and other plant compounds have two complementary activities in combating oxidative stress. First, they act as direct free radical scavengers, the polyphenolic structures having several hydroxyl groups which can donate electrons to ROS, thus making them more stable and unreactive. Other natural free radical scavengers, such as epigallocatechin gallate from green tea, curcumin from turmeric and anthocyanins from hibiscus, have been identified as the most potent (49,50,70,71). Second, polyphenolic compounds activate the nuclear factor erythroid 2-related factor-2, a master transcription factor controlling antioxidant response element-driven gene expression, to increase antioxidant enzyme systems, such as superoxide dismutase, catalase and glutathione peroxidase, which are endogenous antioxidant enzymes (84). This is a dual mechanism and the antioxidant effect is more than just a direct scavenging effect. In animal models, polyphenol extracts from plants are shown to decrease several markers of oxidative stress such as urinary isoprostanes, plasma malondialdehyde and aortic superoxide production, in parallel with blood pressure (85). The chronic vascular inflammation caused by the elevated levels of pro-inflammatory cytokines, increased number of circulating leukocytes, activated endothelial cells and vascular remodeling has been reported to be of significant role in the development and maintenance of hypertension (22,23). There are several ways in which plant compounds can help to reduce inflammation. Curcumin, resveratrol and flavonoids are some polyphenols which are known to suppress the activity of a master transcription factor called NF- κ B, which is important in regulating the expression of pro-inflammatory genes (24,70,71). They suppress the phosphorylation and proteasomal degradation of inhibitor of κ B, thus blocking the nuclear translocation of p65 and p50 subunits of nuclear factor- κ B, which leads to decreased expression of interleukin-6, tumor necrosis factor α and interleukin-1 β . Further, compounds isolated from plants have been found to block the activation of mitogen-activated protein kinase pathways, such as extracellular regulated kinases 1/2, c-jun N-terminal kinase and p38 kinase that regulate inflammatory transcription (25). Phenols activate peroxisome proliferator-activated receptors; ligand-activated nuclear receptors that have anti-inflammatory effects by transrepressing nuclear factor- κ B and activator protein-1 transcription factors (86). Plant-derived compounds have anti-inflammatory activity believed to be strong because of the multiple points of inflammatory signalling pathway suppression.

➤ *Clinical Evidence Summary: Systematic Analysis of Human Trials*

The results of clinical trials which have assessed the effectiveness of plant-based medicines in hypertension treatment are summarised in the following section (table 1). In this analysis, the quality of the evidence, methodological rigor, effect size, and the consistency of trials across evidence are considered (87,88).

Table 1 Clinical Evidence Summary Showing Plant-Derived Antihypertensive Therapeutics with Documented Human Trial Data. BP, Blood Pressure; HTN, Hypertension; RCT, Randomized Controlled Trial.

Plant Species	Preparation/Dose	Study Duration	Systolic BP Change	Diastolic BP Change	Study Type	Population	References
Garlic	3-5g daily extract	4-12 weeks	-5 to -8 mmHg	-3 to -5 mmHg	RCT/Meta-analysis	Hypertensive	(12,34,37)
Hibiscus	3-5g daily calyces	4-12 weeks	-7.5 to -13.3 mmHg	-3.1 to -6.0 mmHg	RCT/Meta-analysis	Stage 1 HTN	(41,43)
Hawthorn	500-1200mg standardized extract	8-12 weeks	-7 to -11 mmHg	-4 to -8 mmHg	RCT	Mild HTN	(45,46,47)
Green Tea	Daily 240-320 mg catechins	12-24 weeks	-2 to -3 mmHg	-1 to -2 mmHg	RCT/Meta-analysis	General population	(49,50,51,52)
Olive Leaf	40mg oleuropein daily	8 weeks	-11.4 mmHg	-4.8 mmHg	RCT	Stage 1 HTN	(54,55,56)
Arjuna	Bark extract 500-1000mg	12 weeks	-9.8 mmHg	-5.3 mmHg	RCT	Stage 1 HTN	(58,59,60)
Ginseng	Root extract 2-3g daily	8-12 weeks	-5 to -8 mmHg	-2 to -4 mmHg	RCT	Mild HTN	(62,63,64)
Ashwagandha	Root extract 300-500mg	8-12 weeks	-8 to -12 mmHg	-4 to -7 mmHg	RCT	Stress-related HTN	(67,68)
Curcumin	500-1000mg daily	8-12 weeks	-5 to -8 mmHg	-3 to -5 mmHg	RCT	Prehypertension/Stage 1 HTN	(70,71,72)

IV. CHALLENGES AND LIMITATIONS: BARRIERS TO CLINICAL TRANSLATION

Although there are significant preclinical data and several prospective trials demonstrating the efficacy of plant-based antihypertensive treatments on humans, several obstacles hinder the clinical use of these treatments on a large scale (89,90). In order to promote the translation of science and clinical implementation of these limitations must be understood and addressed.

➤ *Phytochemical Standardization and Quality Control*

There is significant standardization issues associated with plant-derived therapeutics, due to botanical complexity (91,92). Depending on the species of the plant, location of the plant, type of soil, planting season, time of harvest, storing and processing, medicinal plants can contain hundreds to thousands of different chemical constituents. For instance, garlic allicin is found in low amounts in aged garlic preparations, and up to 3-fold higher in fresh garlic cloves, and Hibiscus anthocyanin content varies 3-fold depending on the cultivar and season. This difference in composition creates great challenges for therapeutic preparations of a uniform composition (93). Current regulations and quality control do not always provide for these issues of standardisation. Many of the commercially available botanical supplements contain significantly different amounts of active ingredient(s) in each product, some do not contain any documented evidence of standardisation in the extraction of the botanicals, and some products do not do anything to confirm the true botanical identity through pharmacognostic methods. No standardization requirement resulting in variable clinical trial results, and varying levels of phytochemical content in the preparation have varying

clinical outcome. For standardization, the use of high-performance liquid chromatography, gas chromatography-mass spectrometry and other related analytical methods for the quantification of the main bioactive compounds is necessary, as is the establishment of minimum concentrations of the main bioactive compounds in pharmacopeial standards, the application of rigorous quality control testing of each batch, and traceability of the plant material by documented chains of supply, and the harmonization of international standards for a consistent manufacture of botanical preparations by the producers (94).

➤ *Bioavailability and Absorption Limitations*

Other components of plants have low bioavailability which is a significant factor that limits systemic exposure and antihypertensive activity (71,95). Challenges include the bioavailability, as, for instance, curcumin's bioavailability is under 1 percent, and has very rapid hepatic metabolism, quick gastrointestinal transit and low intestinal absorption (71). The polyphenolic compounds are typically highly metabolised in the liver after first passage to mainly glucuronidated and sulfated metabolites. In addition, these compounds may be poorly soluble in water, thus limiting dissolution and absorption at gastrointestinal epithelium. Furthermore, many of the compounds found in plants can be metabolized in the gut to compounds with different pharmacological activities from the parent compound, and this makes it difficult to draw structure-activity relationships (95). One of the strategies has been to use water-soluble derivatives of the prodrugs, which improve the intestinal absorption; other strategies include the use of excipients that are known to increase the intestinal permeability; nanoparticles or polymeric systems that protect the compounds from degradation and increase the lipophilicity and cellular absorption; and the preparation of

the nanoparticles in the form of a liposomal or phytosomal formulation to improve the intestinal permeability (96,97). The technology of nanotechnology has recently gained a lot of interest; studies have demonstrated that the bioavailability of plant compounds formulated using nanoparticles can be 5 to 10 times higher than that of unformulated compounds.

➤ *Herb-Drug Interactions and Pharmacokinetic Considerations*

The active components present in plants often have several mechanisms of interaction with conventional drugs, which can result in both beneficial and adverse effects (10,98). There are a number of botanicals that are known inhibitors of cytochrome P450 enzymes including 3A4 (which metabolizes about 75 percent of all therapeutic drugs), 2D6, 2C9 and 2C19. By reducing the clearance of the substrate drugs, inhibitors increase the plasma levels of the drugs resulting in a larger effect or toxicity. Some notable examples include the induction of cytochrome P450 2C9 that leads to reduced warfarin anticoagulation control with ginseng use, and the inhibition of cytochrome P450 3A4 which may lead to an increase in statin concentrations and toxicity with garlic use (10,99). Epilepsy medications like phenobarbital, phenytoin, and phenytoin-like drugs (Fosphenytoin) as well as other drugs such as oral contraceptives and immunosuppressants are also metabolized by cytochrome P450 enzymes. Other botanicals, rather than some botanicals, actually increase the metabolism of these medications in the plasma (increase = promote), which decreases the amount of the medication in the plasma. In addition to CYP interactions, botanicals interact with other metabolic enzymes, such as UDPGT, which is involved in the metabolism of acetaminophen, morphine and related drugs. Furthermore, some phytochemicals have a direct effect on the pharmacokinetics of some drugs, e.g. by interfering with drug transporters like P-glycoprotein and organic anion transporters (98,100). So, interactions between herbs and drugs must be documented comprehensively to manage them and evidence-based guidance for safe concurrent use of both conventional drugs and botanicals is needed, as is patient counselling about the risk of interactions, plasma drug level monitoring, and monitoring of patients' response to both conventional drugs and botanicals with narrow therapeutic indices (99,100).

➤ *Inadequate Clinical Trial Design and Evidence Limitations*

In many instances, there is a lack of rigorous clinical trial evidence of antihypertensive efficacy of plant-derived compounds (87,88). These are the limitations of the current evidence: small sample sizes, no statistical power to test meaningful differences between groups; short study duration, not long enough to evaluate long-term efficacy and tolerability; a heterogeneous study population, which makes generalizations difficult; variable plant preparations, making the meta-analysis and comparison of different trials difficult; suboptimal blinding and randomization, resulting in methodological weaknesses; no active comparator controls to determine the magnitude of the effects compared to conventional antihypertensive agents; under-represented assessment of potential adverse effects and safety signals; and

limited evaluation in vulnerable populations such as paediatrics, geriatrics, pregnant and renal-compromised patients (89,90,101). To advance botanical research, it is recommended to perform a rigorously designed, well-powered, well-funded multicenter randomized controlled trial with long-term follow-up for safety and efficacy, compare results with an active antihypertensive control, conduct mechanistic biomarker studies, use diverse populations, and report results according to the Consolidated Standards of Reporting Trials guidelines (101,102). There is a need for more extensive clinical trials to enhance the evidence supporting clinical implementation.

A. Two Major Areas Explored were Nanotechnology and Advanced Delivery Systems for Improving the Bioavailability of Phytochemicals.

The two main areas that were studied were nanotechnology and advanced delivery systems for increased bioavailability of phytochemicals. Recently, innovation, known as nanotechnology, was developed to address the limitation of bioavailability of phytochemicals and significantly improve the systemic delivery and effect of those compounds that are poorly absorbed by the body (103,104). Nanotechnology delivery systems include specially engineered nanostructures that transport ingredients from the plant without their degradation and ensure they reach the cells and tissues. Currently, the use of SMEAPs in the form of liposomes and phytosomes is being carried out.

➤ *Liposomal and Phytosomal Formulations*

Vesicles containing lipids similar to the lipids of bio-membranes containing bioactive compounds are called liposomal formulations and they are much enhanced for cellular uptake by endocytosis mechanisms (105). Polyphenolic compounds are protected against degradation by enzymes, first-pass liver metabolism and microbial metabolism in the gastrointestinal tract by liposomal encapsulation. Unformulated curcumin levels are 10 to 100 times lower in plasma with 10 times more after taking liposomal curcumin, and there's a 71-fold increase in antioxidant and anti-inflammatory activities (71,103). The phytosomes are a particular class of liposomes in which polyphenolic compounds are linked with the phospholipids, through hydrogen-bonds and van der Waals interactions and are more easily absorbed than liposomes, but also exert a protecting effect. Green tea polyphenol-phospholipid complexes are more readily delivered and retained within the liver, and enhance the antioxidant activity (104). This is because it is known that the bioavailability of a botanical medicine is difficult to achieve, which renders both liposomal and phytosomal methods effective in significantly increasing the therapeutic utility of the medicines.

➤ *Polymeric and Inorganic Nanoparticles*

To achieve controlled release properties and to avoid enzymatic degradation of the compounds, the compounds are encapsulated in polymeric nanoparticles consisting of a biodegradable polymer matrix like polylactide, polycaprolactone or chitosan (104,106). The smaller the particle size, the greater its ability to penetrate from the gastrointestinal lumen to the epithelium (transcellular and

paracellular pathways) and particles within the 50-500 nm size range are better absorbed with the presence of mucous layers. PEG coating results in a half-life extension by lowering the recognition/reticuloendothelial system clearance. Inorganic nanoparticles, such as gold nanoparticles, silver nanoparticles and silica nanoparticles, can be used as transporters and can also possess independent anti-inflammatory and antioxidant activity (106,107). Animal studies have yielded preliminary data that show that nanoparticle formulations of curcumin, resveratrol, and polyphenol-rich plant extracts are 5-15-fold more bioavailable than the bulk drugs, and have been demonstrated to be more effective in antihypertensive trials (103,104); however, these are not yet translatable to the clinic.

➤ *Nanoemulsions and Solid Lipid Nanoparticles*

Oil-in-water or water-in-oil emulsions with droplet size less than 200 nm are called nanoemulsions and have been reported to greatly enhance the solubility of lipophilic botanical compounds in the water-based material, thereby improving the intestinal absorption (105,107). The smaller droplets are able to reach the intestinal epithelial cells at the surface area without hepatic first pass metabolism and enter the lymphatics. SLN (solid lipid nanoparticles) are nanoparticles that are made of biodegradable lipids, which form crystals that contain botanical compounds with a slow release effect. Lipophilic phytochemicals can be formulated as lipids which would have many applications for curcumins, resveratrol, flavonoids, and other compounds which are metabolized by enzymes that result in their degradation and inactivation. Lipid formulation strategies have been found to enhance the tissue distribution and reduce the metabolism-induced degradation of these compounds (104,106). Recent clinical trials evaluating the efficacy of nanoemulsion formulations of botanical extracts have demonstrated that they have a more powerful effect on hypertension than extracts without the use of a formulation (103,107).

B. Future Perspectives: Advancing Plant-Derived Therapeutics in Hypertension Management

Traditional botanical medicine's historic association with contemporary molecular pharmacology, computational chemistry, systems biology and nanotechnology offers unparalleled opportunities for novel, evidence-based phytotherapeutics (108,109). In this section, novel strategies have been explored toward the development of plant antihypertensive drugs.

➤ *Precision Phytomedicine and Pharmacogenomics*

Precision medicine has the potential to maximize antihypertensive effect of plant-based medicines while minimizing side effects by targeting the action at genetic, metabolic and phenotypic aspects of the individual patient is a great promise (109,110). The genetic variations in the enzymes, transporters and pharmacological targets that alter the activity of the botanicals can be analyzed to understand how individuals might respond to some of the botanicals; this is called pharmacogenomic analysis. For instance, individuals who are slow metabolizers of cytochrome P450 2C19 could need lower doses of plants that are metabolized by this enzyme; and people who are fast metabolizers could

need higher doses of the plants. Specific pathotypes of hypertension (oxidative stress predom, inflammation predom and sympathetic predom) could be metabolically characterized to select a targeted botanical according to the predominant pathogenic mechanisms (110,111). Precision phytomedicine represents a paradigm shift as compared to population level botanical recommendations to an individual level therapeutic selection, aiming at maximising the effects taking into account the genetic and phenotypic heterogeneity.

➤ *Systems Pharmacology and Multi-Target Polypharmacology*

Systems pharmacology is a method that is based on network biology, which explains how multi-component molecular and/or cellular networks associated with a disease are modulated by the phytochemical constituents (109,111,112). Systems approaches focus on entire networks of interactions and the combined activities of several plant compounds on several pathogenic mechanisms, instead of on the single plant compound acting on a single target. Subsets of phytochemicals are found within the same plant that have complementary pathways and could provide a greater therapeutic benefit than individual compounds is identified using a computational network analysis. The application of systems approaches can be used to rationally design the combination of botanical treatments that cover the highest number of pathogenic mechanisms of hypertension in the lowest number of redundant drugs (111, 112). Furthermore, systems pharmacology can be used to predict the risk of adverse effects through identification of off-target interactions, and could be used as a guide for the development of better botanical formulations with more favourable properties and adverse interactions.

➤ *Artificial Intelligence-Guided Phytochemical Screening and Discovery*

By using artificial intelligence and machine learning algorithms on the phytochemical and botanical databases, high-throughput virtual screening can be performed to discover new botanical active compounds having predicted antihypertensive activity (113,114). Known structure–activity relationships can help to predict the pharmacological activity of plant constituents like ACE inhibitory activity, antioxidant activity, or vasodilatory activity using machine learning models. Important plants used historically as traditional medicine which are recognized to have cardiovascular benefits can be prioritized for experimental validation from ethnobotanical databases, traditional medicine texts and scientific literature using NLP (113,114). Deep learning algorithms can process high dimensional biological data, including genomics, proteomics and metabolomics data, to identify botanical compounds that are likely to inhibit specific disease pathways using this information. Combination of AI-assisted discovery of botanicals and their experimental proof-of-concept opens up possibilities for quick identification of effective phytochemicals and rational optimization of botanical preparations (114,115).

➤ Integration into Conventional Cardiovascular Care

Multiple supportive efforts are needed to integrate the use of plant-based therapeutics into mainstream cardiovascular treatments based on evidence (115,116). Firstly, healthcare systems should make investments in well-designed and well-funded, multicenter clinical studies to verify botanical antihypertensive efficacy, safety, and comparative effectiveness in comparison with conventional antihypertensive medicines. Secondly, there is a need to incorporate phytopharmacology into the medical curriculum to equip the clinicians with the knowledge to counsel their patients on the use of herbs, the possible interactions between herbs and their prescribed drugs, and give good prescription of botanicals in the treatment of hypertension. Thirdly, the regulatory authorities should establish standards for botanical preparation manufacture and quality control to ensure that they meet pharmaceutical grade standards. Fourth, there is a need to develop uniform preparation of precisely defined phytochemical composition and bioavailability properties before the wide-spread clinical use of the botanicals. Fifth, establishment of registries of healthcare professionals which record concentrations of botanical constituents and interactions allows for the identification of adverse events and signal detection in a timely manner. Finally, at the population level, evidence-based dietary approaches, like the plant-based Mediterranean diet and DASH diet, and alarm against herbals being used as a substitute for antihypertensive therapy, provide an opportunity to optimize direct BP control (116,117).

➤ Future Directions: Research and Translational Priorities

The conversion of plant-based therapeutics from lab to drug-scale mechanistic to move large-scale clinical implementation, research needs to be systematic and prioritized. of research goals consonant with present scientific and clinical needs. While a number of botanical compounds show promise of antihypertensive activity, there are still a number of gaps in the support for standardization, clinical pathways to integration, trial design and formulation optimization [109,110,111,115,116,117,]. These opportunities and challenges are important areas of future studies that will help to define the potential of botanical therapeutics. Treatment of hypertension in clinical practice: Evidence-based approach (Table 3). The following research priorities are essential areas of research priorities to be targeted. This will need to be investigated in the next 5-10 years to improve precision in the field through phytochemistry integration (Table 3). These priorities address multiple areas. Including botanical standardization, clinical trial methodology, mechanistic studies and statistical analysis. Optimize delivery system, investigation, pharmacogenomic characterization, understand mechanism of action of therapeutic and adverse effects, elucidate the regulatory pathway, select doses effectively and in cost-conscious manner for drug development. The essential analysis of effectiveness, adverse effect documentation and clinical guideline development [109,110,111,115,116,117]. Converting botanical information to evidence-based clinical guidelines that fit into hypertension management guidelines: Strategic attention to ten priority areas. clinical practice integration [115,116,117].

Table 2 Priorities for Future Research to Advance Antihypertensive Medicines Generated from Plants. Research Gaps and Opportunities that Need Funding are Indicated by the Current State and Related References.

Research Priority	Current Status	References
Standardized, pharmaceutical-grade botanical preparations	Limited commercial availability	(91,92,94)
Adequately-powered, multicenter clinical trials	Sparse funding, limited initiation	(87,88,101,102)
Pharmacogenomic-guided precision phytochemistry	Preclinical/early development	(109,110,111)
Nanotechnology bioavailability enhancement	Animal models, early clinical trials	(103,104,105,106,107)
Integration protocols for herb-drug combinations	Preliminary guidelines	(10,98,99,100)
Adverse effect surveillance systems	Minimal existing infrastructure	(89,90,101)
AI-guided phytochemical discovery platforms	Computational validation phase	(113,114,115)
Systems pharmacology mapping plant-disease networks	Early implementation	(109,111,112)
Medical education curriculum development	Minimal existing content	(115,116)
Regulatory standardization across jurisdictions	Highly heterogeneous current frameworks	(91,92,93,94)

V. COMPARATIVE MECHANISTIC SUMMARY TABLE

The molecular understanding of the main plant-derived antihypertensive medications is summarised in Table 3, which shows different but complementary pathways that botanical chemicals target (80,81).

Table 3 Comparative Mechanistic Summary Showing Plant-Derived Antihypertensive Compounds and their Effects on Major Hypertension Pathways. ACE, Angiotensin-Converting Enzyme; NO, Nitric Oxide; (+) = Modest, (++) = Moderate, (+++) = Strong Effect. EGCG, Epigallocatechin Gallate.

Plant Species	Primary Compounds	ACE Inhibition	Vasodilation/NO	Antioxidant	Anti-inflammatory	Sympatholytic
Garlic	Allicin, S-allylcysteine	+++	+++	+++	++	+
Hibiscus	Anthocyanins, Polyphenols	+++	+++	+++	++	+

Hawthorn	Proanthocyanidins, Flavonoids	++	+++	++	++	+
Green Tea	EGCG, Catechins	+	+++	+++	++	+
Olive Leaf	Oleuropein, Hydroxytyrosol	+++	++	+++	++	+
Arjuna	Triterpenoids, Tannins	++	+++	+++	+	+
Ginseng	Ginsenosides	+	++	++	+	++
Ashwagandha	Withanolides	+	++	++	++	+++
Curcumin	Curcuminoids	++	+++	+++	+++	++

VI. CONCLUSION

The usage of plant-based drugs for treating hypertension is an interesting and promising strategy as it has the element of traditional medicine for thousands of years and the modern molecular pharmacology (1,2,3,4). The antihypertensive properties of a number of medicinal plants such as garlic, hibiscus, hawthorn, green tea, olive leaf, arjuna and others have also been well established in both preclinical and clinical studies, and are achieved by a variety of complementary mechanisms acting on different pathophysiological derangements that underlie hypertension (9,12,34,41,45,49,54,58,70). Botanicals may be advantageous over single component synthetic drugs in terms of the polypharmacological action of plants, which implies a plant can have more than one active component that has a slightly different mechanism and/or target for the pathogen, particularly for multi-factorial and complex diseases like hypertension (32,33,80,81). Despite this, there are significant challenges at present to the clinical use of plant based antihypertensive agents (89,90,91,92,93,94). The challenges of phytochemical standardization are related to the natural variation in plants, and strict analytical chemistry standards and pharmaceutical-grade production methods must be used (91,92,93,94). However, many plant compounds suffer from bioavailability problems and need new technologies of nanotechnology and formulations for therapeutic optimization (71,95,96,97,103,104,105,106,107). Herb-Drug interactions constitute a serious safety issue that needs to be thoroughly characterized by detailed PK characterization and clinical monitoring (10,98,99,100). Most importantly, there is limited evidence in clinical trials, due to poor funding of clinical trials and methodological flaws in the translation of promising preclinical models and model systems to definitive clinical evidence of efficacy (87,88,89,90,101,102). But opportunities are present in the near future in the therapeutics of plant origin to treat hypertension; however, the challenges are faced. Advanced nanotechnology methods are promising to greatly enhance the bioavailability of the phytochemicals, while artificial intelligence screening will help identify possible novel phytochemicals that may have antihypertensive properties (103,104,105,106,107,113,114,115). With the ability to rationalize the selection of botanical compounds based on patient-specific characteristics, precision phytomedicine strategies can benefit the therapeutic impact while minimizing the side effects of treatment (109, 110, 111). Systems pharmacology techniques can be applied to characterize the modulation of the molecular networks of diseases by plant constituents, and to identify potential side

effects (109,111,112), which are suitable for rational design of combinations of plants according to the desired polypharmacological coverage. To ensure that plant-based antihypertensive drugs are part of evidence-based cardiovascular therapy, there are some complementary activities that need to be maintained: (115,116,117) Investments for well-designed, multicenter, adequately powered, randomized controlled trials with standardized preparations of the plants to establish comparative efficacy, optimal dosing, duration of efficacy, and comprehensive safety profiles (87,88,101,102). Second, the ability to develop processed botanicals (botanical preparations) with well-defined phytochemical composition, standard manufacturing processes and proven bioavailability properties is required (91,92,93,94). Third, through in-depth characterization of herb-drug interactions in the major class of drugs, safe clinical implementation and adverse effect prevention is possible (10,98,99,100). Fourth, adverse effect surveillance systems and clinical monitoring protocols enable quick detection of adverse effects (89,90,101). Fifth, the introduction of the field of phytopharmacology into medicine education programmes equips physicians to provide competent and useful counselling to their patients and to include phytochemicals as an additional component in their anti-hypertensive treatment (115,116). This extensive review has demonstrated that the potential of plant-based therapies as complementary and possibly even primary antihypertensive drug in certain patients is very promising (1,2,3,32,33). How the traditional concept of botanical medicine meets the modern molecular pharmacology, systems biology and nanotechnology presents unparalleled possibilities of developing multi-target therapies with potentially more favorable safety and tolerability profile than conventional pharmaceutical drugs (103,104,105,106,107,109,110,111,112,113,114,115). But, this potential needs to be balanced by rigorous scientific validation, standardisation and safety assessment prior to a wide-scale implementation. The integration of botanical-pharmaceutical approaches in a thoughtful manner, with the use of botanical wisdom and yet obtaining scientific rigor and safety of the patient as paramount principles, may well represent the future of hypertension management (115,116,117).

➤ Conflict of Interest Statement

The authors declare no conflicts of interest, financial relationships, or affiliations with pharmaceutical, botanical supplement, or related commercial entities that could bias this review. This manuscript was prepared without commercial sponsorship or funding that could influence scientific

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- Author P.K.M: Conceptualization, Methodology, Literature Review, Writing (Original Draft), Data Analysis, Validation
- Author S.S: Literature Review, Writing (Review and Editing), Resources, Critical Discussion of Evidence Quality

All authors have reviewed the final manuscript, approved submission, and agree to be accountable for all aspects of the work.

➤ *Data Availability Statement*

This review synthesizes information from published scientific literature without accessing restricted datasets. All cited references are publicly available through PubMed, Web of Science, Scopus, and related databases. The authors commit to providing any additional information upon reasonable request.

➤ *Ethical Statement*

This manuscript represents a literature review synthesizing previously published data and requires no institutional review board approval. The authors affirm adherence to ethical principles including scientific accuracy, transparency, objectivity in evidence evaluation, and responsible communication without exaggerated claims or misrepresentation of evidence quality. All cited references are appropriately attributed.

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Tables Abbreviations

Abbreviation	Definition
ACE	Angiotensin-Converting Enzyme
AT1	Angiotensin II Type 1 Receptor
BP	Blood Pressure
DASH	Dietary Approaches to Stop Hypertension
EGCG	Epigallocatechin Gallate
GABAergic	Gamma-Aminobutyric Acid-related
HTN	Hypertension
NO	Nitric Oxide
NOS	Nitric Oxide Synthase
RAAS	Renin-Angiotensin-Aldosterone System

RCT	Randomized Controlled Trial
ROS	Reactive Oxygen Species
VSM	Vascular Smooth Muscle
cGMP	Cyclic Guanosine Monophosphate
eNOS	Endothelial Nitric Oxide Synthase