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COMPARATIVE PHARMACOLOGICAL AND CLINICAL REVIEW OF SELECTED HERBAL ANTIHYPERTENSIVE AGENTS IN HYPERTENSION MANAGEMENT

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ABSTRACT

Background: Hypertension is a major global health concern and a leading risk factor for cardiovascular morbidity and mortality. Limitations associated with conventional antihypertensive therapy, including poor compliance, adverse effects, and inadequate blood pressure control, have increased interest in herbal agents possessing multitarget pharmacological actions and improved safety profiles. **Methodology:** A comparative literature review was conducted using PubMed, Scopus, Web of Science, Google Scholar, and ScienceDirect databases to identify relevant studies published between 2020 and 2026. Approximately 130 articles were screened, of which 80 relevant experimental studies, clinical trials, and meta-analyses were included for comparative evaluation of the antihypertensive effects, mechanisms, phytochemical profiles, and clinical relevance of selected herbal agents. **Result and Discussion:** Garlic (*Allium sativum*) demonstrated the strongest clinical evidence with consistent reductions in systolic and diastolic blood pressure through ACE inhibition, nitric oxide enhancement, and antioxidant effects. Ginger (*Zingiber officinale*) showed predominantly experimental evidence, with limited clinical evidence, of calcium channel blockade and vascular relaxation. *Rauwolfia serpentina* exhibited potent antihypertensive efficacy but was limited by neuropsychiatric adverse effects, whereas *Terminalia arjuna* provided moderate antihypertensive and cardioprotective benefits. **Conclusion:** Herbal antihypertensive agents exhibit mechanism-specific and stage-dependent therapeutic potential and may serve as supportive interventions in early-stage hypertension and cardiovascular comorbidities. However, the lack of standardization and limited long-term clinical evidence remain major limitations that require further investigation.

INTRODUCTION

Hypertension is a significant international population health issue and a primary risk factor of cardiovascular diseases, such as coronary artery disease, stroke, heart failure, and chronic kidney disease. The World Health Organization estimates that over 1.28 billion adults among the global population are

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impacted by hypertension, with highly disproportionate prevalence witnessed in low- and middle-income nations [1]. Despite the use of a variety of antihypertensive medications, such as angiotensin-converting enzyme inhibitors, calcium channel blockers, beta-blockers, and diuretics, optimal control of blood pressure is not achieved in a considerable number of patients [2]. Among the significant drawbacks linked to the traditional antihypertensive treatment are poor compliance, drug interactions, chronic dependence, and financial constraints [3]. Interest in plant-based and traditional medicines as complementary or alternative therapies for the management of hypertension has increased globally in recent years. The change is motivated by growing knowledge of the side-effect profiles of synthetic drugs, patients' preference for natural medicine, and the revival of integrative medicine models [4]. The natural origin of herbal medicines is often viewed as safer, and most plant-derived compounds have been shown to possess vasodilatory, antioxidant, anti-inflammatory, and cardioprotective properties that are used in blood pressure control [5]. Medicinal plants have a long history of use in herbal medicine systems, including Ayurveda, Traditional Chinese Medicine, Unani, and folk medicine, which have widely documented their use in cardiovascular disorders. The ancient Ayurvedic texts describe several herbs for the treatment of Hridroga (heart diseases) and Raktagata Vata (diseases related to vascular dysfunction), which are currently being examined using a modern pharmacological approach [6]. The fact that traditional remedies remain widely used, particularly in developing nations, underscores the need to demonstrate their safety, effectiveness, and standardization scientifically. Garlic (*Allium sativum*) is one of the many medicinal plants studied for antihypertensive effects, given its common dietary use and established cardiovascular effects. Allicin and ajoene are sulfur-containing compounds found in garlic and have been shown to induce vasodilation, angiotensin-converting enzyme activity, and endothelial function [7].

Clinical trials have shown a positive but modest effect on reducing both systolic and diastolic blood pressure with the use of garlic supplements, especially in patients with mild to moderate hypertension [8]. The other widely used medicinal plant is ginger (*Zingiber officinale*), which was traditionally used to treat circulatory and metabolic diseases. The bioactive compounds in it, such as gingerols and shogaols, have antioxidant, anti-inflammatory, and calcium-channel-blocking properties that may help lower blood pressure [9]. According to experimental studies, ginger may modulate vascular tone and peripheral resistance, whereas epidemiological studies show an inverse association between ginger intake and the prevalence of hypertension [10]. Unlike these dietary herbs, the *Rauwolfia serpentina* is one of the first scientifically confirmed herbal antihypertensive agents. Rauwolfia yielded reserpine, which became the first cardiovascular pharmacological breakthrough, as it demonstrated a strong blood pressure-lowering effect through central sympathetic inhibition [11]. Regardless of its efficacy, *Rauwolfia serpentina* was found to have adverse effects that included depression, sedation, and extrapyramidal symptoms, and hence, safety evaluation must be carried out in addition to its efficacy [12]. *Terminalia arjuna* is a special place among the Ayurvedic cardioprotective medicinal plants. *Terminalia arjuna* is traditionally consumed as a cardiac tonic and contains triterpenoids, flavonoids, and tannins, which are associated with its antioxidant and endothelium-stabilizing properties [13]. Although most of the literature has focused on its application in ischemic heart disease and heart failure, there are also hints that *Terminalia arjuna* may be used to regulate blood pressure due to its vascular and myocardial-protective properties [14]. Although many studies have assessed the antihypertensive effects of these herbs individually, the literature remains fragmented, with most studies focusing on the pharmacological activity of isolated plant compounds. Comparative studies of such agents vis-à-vis standard pharmacodynamic parameters, safety profiles, and clinical relevance are remarkably deficient. A comparative pharmacological assessment is necessary to determine the relative strengths, limitations, and therapeutic appropriateness in different phases of hypertension [15]. Thus, the research should be a comparative assessment of the antihypertensive effects of garlic (*A. sativum*), ginger (*Z. officinale*), *R. serpentina*, and *T. arjuna*. The scope of this paper is to evaluate their phytochemical structures, mechanisms of action, experimental and clinical data, safety concerns, and research prospects. This study would help bring an evidence-based approach to incorporating herbal antihypertensive agents into modern cardiovascular therapeutics by synthesizing the available evidence and integrating it into a single analysis.

METHODOLOGY

Search Strategy

A comprehensive literature review was conducted using electronic scientific databases, including PubMed, Scopus, Web of Science, Google Scholar, and ScienceDirect. Literature published between 2020 and 2026 was systematically searched

using combinations of keywords such as "hypertension," "herbal antihypertensive agents," "*Allium sativum*," "*Zingiber officinale*," "*Rauwolfia serpentina*," "*Terminalia arjuna*," "ACE inhibition," "vascular protection," "phytochemicals," and "cardiovascular herbal therapy."

Inclusion and Exclusion Criteria

Experimental studies, in vivo and in vitro investigations, clinical trials, meta-analyses, and review articles published in English were included if they evaluated antihypertensive mechanisms, cardiovascular effects, phytochemical constituents, or clinical relevance of the selected herbal agents. Studies lacking scientific relevance to hypertension management, duplicate reports, non-English publications, and articles with insufficient methodological clarity were excluded from the analysis.

Data Extraction and Quality Assessment

Relevant information regarding phytochemical composition, pharmacological mechanisms, antihypertensive efficacy, safety profile, dosage range, and therapeutic limitations was extracted and comparatively analyzed from the selected studies. The methodological quality of clinical studies was qualitatively evaluated based on study design, sample size, randomization, blinding procedures, duration of follow-up, consistency of outcome reporting, and potential sources of bias. Greater interpretative importance was given to randomized controlled trials, meta-analyses, and studies with clearly defined clinical endpoints. A structured literature screening approach was used to improve transparency in study selection; however, this review was conducted as a comparative narrative review rather than a formal systematic review or meta-analysis.

Pathophysiology of High Blood Pressure and Herbal Intervention Targets

Hypertension is a multifactorial disease that results from the interaction of genetic and environmental factors and the dysregulation of physiological systems that maintain blood pressure homeostasis. Neural, hormonal, renal, and endothelial mechanisms predominantly control blood pressure by regulating systemic vascular resistance and cardiac output, which are determinants of blood pressure. Impairment of any or all of these regulatory pathways helps cause and also advances sustained hypertension [16].

Overview of Blood Pressure Regulation Mechanisms

In the normal physiological state, arterial blood pressure is regulated by the autonomic nervous system, endocrine signals, the vascular endothelium, and renal sodium-water balance. Baroreceptor reflexes and sympathetic nervous activity mediate short-term regulation, whereas renal mechanisms and the renin-angiotensin-aldosterone system (RAAS) are the main regulators of long-term control [17]. Any sustained disequilibrium in these systems results in increased peripheral resistance, vascular remodeling, and pressure natriuresis dysfunction, which are characteristic of chronic hypertension.

Renin Angiotensin Aldosterone System (RAAS)

The RAAS is important in regulating blood pressure and fluid-electrolyte balance. Angiotensinogen is converted to angiotensin I with the initiation of renin release in the juxtaglomerular apparatus, which is then changed to angiotensin II by angiotensin-converting enzyme (ACE). Angiotensin II is a potent vasoconstrictor that stimulates aldosterone secretion, thereby increasing sodium and water retention, raising blood volume and systemic vascular resistance [18]. Constant excessive activation of the RAAS is also a causative factor of hypertension that causes vascular hypertrophy, endothelial dysfunction, and oxidative stress. Pharmacological inhibition of ACE and angiotensin II receptors remains a cornerstone of traditional antihypertensive therapy [19]. It is worth noting that several plant-based compounds have been shown to possess ACE-inhibitory potential and angiotensin-modulating properties. Thus, the RAAS has become an important therapeutic objective of herbal antihypertensive drugs.

Role of the Sympathetic Nervous System

One of the determinants of short-term blood pressure regulation is the sympathetic nervous system (SNS), which affects heart rate, myocardial contractility, and peripheral vasoconstriction. The improved sympathetic tone leads to increased cardiac output and vascular resistance, which contribute to the development and maintenance of hypertension [20]. The long-term sympathetic stimulation is also linked to sodium retention in the kidney and to stimulation of renin secretion, which further increases RAAS activity. Central and peripheral sympathetic inhibition has thus proven to be a good strategy in the management of hypertension. In the past, *Rauwolfia serpentina* was popular because of its alkaloid reserpine, which depletes catecholamines at sympathetic nerve endings and decreases peripheral resistance and blood pressure [21]. Nevertheless, the role of the SNS in mood and neurological performance highlights the importance of balancing effectiveness and safety when targeting this pathway.

Endothelial Dysfunction

Vascular endothelium is critical in the process of regulating the tone of the vascular system as it releases vasodilatory factors (nitric oxide (NO) and prostacyclin) and vasoconstrictive factors (endothelin-1). Endothelial dysfunction in hypertension is characterized by decreased NO bioavailability, loss of vasodilation, and increased vascular stiffness [22]. This impairment not only increases the blood pressure but also the atherosclerosis and cardiovascular issues. Oxidative degradation of NO and compromised endothelial signaling are the key mechanisms of endothelial dysfunction. Several phytochemicals found in medicinal plants have endothelium-protective properties due to their ability to increase NO production, scavenge reactive oxygen species, and improve vascular compliance [23]. These are especially applicable when the herbal antihypertensive therapy is concerned.

Oxidative Stress and Inflammation

Low-grade, chronic inflammation and oxidative stress are now considered to be important factors in the pathogenesis of hypertension. Overproduction of reactive oxygen species (ROS) causes vascular damage, inflammation, and reduced nitric oxide bioavailability, thereby augmenting peripheral resistance [24]. Inflammatory mediators such as cytokines and adhesion molecules exacerbate endothelial dysfunction and vascular remodeling. Antioxidant and anti-inflammatory interventions have thus received interest as secondary measures in the treatment of high blood pressure. Antioxidants of plant origin, such as flavonoids, phenolics, and organosulfur compounds, have been shown to reduce oxidative stress and inflammatory signaling cascades linked to hypertension [25].

Pharmacological Targets Relating to Herbal Agents

Due to the multifactoriality of hypertension, herbal antihypertensive agents tend to cause their effects on more than one pharmacological target. The key ones involve ACE inhibition, calcium channel blockade, sympathetic inhibition, augmentation of endothelial nitric oxide generation, and inhibition of oxidative stress [26]. The multitargeted method can potentially provide therapeutic benefits, especially in mild hypertension or in its early stages, where synthetic drugs may not be required as a single treatment.

Hypothesis Relating Phytochemicals to Antihypertensive Effect

The antihypertensive effects of medicinal plants can be conceptually explained by the association between phytochemicals and the main regulatory pathways of blood pressure. Garlic compounds containing sulfur affect RAAS and endothelial activity; gingerols and shogaols regulate calcium channels and oxidative signaling; alkaloids of *Rauwolfia serpentina* have a central effect on sympathetic neurotransmission; and polyphenols of *Terminalia arjuna* promote vascular protection and myocardial activity [27]. This unified structure demonstrates the importance of phytotherapy as a complementary approach in the management of high blood pressure and warrants systematic comparative analysis.

Pharmacognosy and Phytochemical Profile of Selected Herbal Antihypertensive Agents

Phytochemical characterization and pharmacognostic analysis are necessary in the perception of the therapeutic potential of herbal antihypertensive agents. The efficacy, safety, and reproducibility of plant-based interventions are directly associated with botanical identity, plant part used, phytochemical composition, and extraction methods. The pharmacognosy and key bioactive constituents of garlic (*Allium sativum*), ginger (*Zingiber officinale*), *Rauwolfia serpentina*, and *T. arjuna* are also discussed in this section, with a focus on constituents relevant to the antihypertensive process.

Garlic (*Allium sativum*)

Garlic is a bulbous perennial plant of the family Amaryllidaceae and is popularly grown both as food and medicine. The main medicinal part is the bulb, which consists of several cloves and is covered by a papery coating. Garlic has a strong odor and is white to off-white in color with oil cells filled with sulfur compounds, which are pharmacognostically characteristic of it [28]. Garlic organosulfur compounds are considered the main contributors to garlic's antihypertensive effect. The intact garlic contains alliin (S-allyl-L-cysteine sulfoxide), which is enzymatically converted to allicin by the enzyme alliinase after crushing or chopping. Allicin is volatile and quickly converts to other sulfur-containing metabolites like ajoene, diallyl sulfide, diallyl disulfide, and S-allylcysteine [29].

It has been demonstrated that these compounds exert vasodilatory effects through increased nitric oxide bioavailability, inhibition of angiotensin-converting enzyme, and regulation of vascular smooth muscle tone. Pharmacognostically, the garlic cultivar, processing method (raw, aged, or powdered), and extraction method significantly affect phytochemical yield and biological activity. Specifically,

aged garlic extract has been reported to contain stable, water-soluble sulfur compounds that are more tolerable and exhibit uniform antihypertensive activity [30].

Ginger (*Zingiber officinale*)

Ginger is a perennial herb belonging to the family Zingiberaceae, and the rhizome is the part that is active medically. The rhizome is aromatic, with an inner color of pale yellow and abundant oleoresin, which imparts its pungent taste and pharmacological action. Ginger has an extensive history of application in traditional medicine systems to circulatory, digestive, and inflammatory disorders [31]. Ginger rhizomes contain high levels of phenolic compounds; the main ones are gingerols, shogaols, paradols, and zingerone. The most common of them is 6-gingerol, the most abundant and pharmacologically active constituent, and shogaols are formed during drying or thermal treatment [32]. These are antioxidants, anti-inflammatories, and calcium channel blockers, all of which apply to blood pressure control. Experimental research shows that ginger extracts can cause vasorelaxation by blocking voltage-dependent calcium channels in vascular smooth muscle and by inhibiting oxidative stress-induced endothelial dysfunction [33]. The geographical origin, time of harvesting, and post-harvest processing determine the pharmacognostic quality of ginger and the concentration of phenolic bioactives.

Rauwolfia serpentina

Rauwolfia serpentina is an Ayurvedic and Unani Medicine, a perennial shrub in the Apocynaceae family, traditionally used to treat hypertension, insomnia, and mental disorders. The official medicinal part is the dried roots, which are bitter in taste, tortuous in shape, and grayish-brown in color [34]. *Rauwolfia serpentina* is known to have pharmacological effects mainly attributed to its indole alkaloids, chiefly reserpine, with others such as ajmaline, ajmalicine, and serpentine. The antihypertensive effect of reserpine is due to its irreversible inhibition of vesicular monoamine transporters, resulting in the loss of catecholamines from sympathetic nerve terminals [35]. This causes decreased peripheral vascular resistance and low blood pressure. Although pharmacognostic standardization of *R. serpentina* emphasizes a content of alkaloids, its modern clinical application is restricted due to the adverse effects of the drug, depending on the dose (depression, extrapyramidal symptoms). However, its historical significance underscores the role of plant-derived alkaloids in the development of contemporary antihypertensive treatments [36].

Terminalia arjuna

Terminalia arjuna is a giant tree that belongs to the family of Combretaceae and is native to the Indian subcontinent. The medicinally significant part is the bark, which is traditionally used as a cardiotonic. The outer layer looks thick, externally smooth and gray, and internally pinkish [37]. The *Terminalia arjuna* bark was analyzed using phytochemicals; it contains triterpenoids (arjunolic acid, arjunic acid), flavonoids, tannin, and glycosides. These are powerful antioxidants, anti-inflammatory compounds, and endothelium-protective compounds [38], unlike agents that primarily lower blood pressure. Cardioprotective effects on myocardial function and vascular integrity are characteristic of *Terminalia arjuna*. Even though the antihypertensive action of *Terminalia arjuna* is not particularly strong, its endothelial effect and oxidative stress-lowering effect render it a useful adjunct in cardiovascular management, especially in patients with comorbid cardiac conditions [39].

Comparative Pharmacognostic Perspective: Comparatively, the chosen herbal agents are quite diverse in their phytochemical classes and predominant pharmacological targets. Garlic and ginger contain high levels of sulfur and phenolics, respectively, which have peripheral vascular and endothelial effects. *Rauwolfia serpentina* acts centrally as an alkaloid-mediated sympathetic suppressant, whereas *Terminalia arjuna* provides vascular and myocardial protection through its polyphenolic compounds. These differences also underscore the role of phytochemical diversity in determining antihypertensive effects and clinical utility [40]. A comparative pharmacognostic and phytochemical overview of the selected herbal antihypertensive agents is presented in Table 1.

Mechanisms of Antihypertensive Action: Evidence from Experimental and Clinical Studies

Hypertension is a multifactorial disease that entails neurohormonal stimulation, vascular dysfunction, oxidative stress, and inflammatory pathways. In contrast to traditional antihypertensive medications, which tend to engage only one pathway, herbal antihypertensive medications are multitarget pharmacological and, as such, are specifically applicable in multifactorial and early-stage hypertension. In this section, the synthesis of experimental and clinical findings on the antihypertensive effects of garlic (*Allium sativum*), ginger (*Zingiber officinale*), Rauwolfia serpentina, and *Terminalia arjuna* is presented.

Table 1: Comparative Pharmacognostic and Phytochemical Profile of Selected Herbal Antihypertensive Agents

Herbal Agent	Family	Medicinal Part Used	Major Phytochemical Constituents	Primary Pharmacological Targets	Relevance to Hypertension	Reported Therapeutic Dosage Ranges
***Allium sativum* (Garlic)**	Amaryllidaceae	Bulb (cloves)	Allicin, ajoene, diallyl sulfide, diallyl disulfide, S-allylcysteine	ACE inhibition, nitric oxide enhancement, antioxidant pathways	Reduces peripheral vascular resistance; improves endothelial function; effective in mild–moderate hypertension	600–2400 mg/day garlic preparations or aged garlic extract
***Zingiber officinale* (Ginger)**	Zingiberaceae	Rhizome	Gingerols, shogaols, paradols, zingerone	Calcium channel blockade, antioxidant, and anti-inflammatory pathways	Induces vasorelaxation; reduces oxidative stress–mediated vascular dysfunction	1–3 g/day ginger powder or extract
Rauwolfia serpentina	Apocynaceae	Root	Reserpine, ajmaline, ajmalicine, serpentine (indole alkaloids)	Central sympathetic inhibition via monoamine depletion	Potent blood pressure reduction; limited by neuropsychiatric adverse effects	0.05–0.25 mg/day reserpine equivalent
Terminalia arjuna	Combretaceae	Bark	Arjunolic acid, arjunic acid, flavonoids, tannins	Endothelial protection, antioxidant, and cardiotonic mechanisms	Supports vascular integrity; adjunct role in hypertension with cardiac comorbidities	500 mg–3 g/day bark extract

***Dosage ranges represent commonly reported values from experimental and clinical studies and may vary depending on formulation, extraction method, and study design.*

Modulation of the Renin–Angiotensin–Aldosterone System (RAAS): The renin-angiotensin-aldosterone system is one of the main regulators of blood pressure and fluid homeostasis. The continuous effect of the RAAS on vascular constriction, sodium retention, vascular remodeling, and oxidative stress continues to cause persistent hypertension [41]. Endothelial dysfunction from Angiotensin II and vascular fibrosis from aldosterone also increase cardiovascular risk. Garlic has been the most stable RAAS-modulating agent among the chosen herbal agents. Organosulfur compounds such as allicin and S-allylcysteine have been reported to suppress angiotensin-converting enzyme activity, thereby inhibiting angiotensin II production and inducing vasodilation [42]. According to clinical trials and meta-analyses, there were significant decreases in systolic & diastolic blood pressure in hypertensive patients who took garlic supplements, making it functionally similar to mild ACE inhibitors [43]. *T. arjuna* has no direct effect on ACE but indirectly affects RAAS activity by stabilizing the endothelium & inhibiting oxidative stress, thus preventing angiotensin II-induced vascular injury [44].

Calcium Channel Blockade and Vascular Smooth Muscle Relaxation: Calcium influx into vascular smooth muscle cells via voltage-dependent calcium channels is a major determinant of peripheral vascular resistance. Excessive calcium influx increases vasoconstriction, leading to high blood pressure [45]. Calcium channel blockers are thus one of the mainstays of antihypertensive treatment. Experimental studies have shown that ginger has a calcium channel-blocking effect, leading to dose-dependent relaxation of isolated arterial preparations [46]. Gingerols and shogaols prevent calcium-induced contractions of vascular smooth muscle, thereby decreasing peripheral resistance. These are similar to the effects of conventional calcium channel blockers in preclinical models, but clinical data remain scarce [47]. Garlic has also been found to have a slight calcium-antagonistic effect, which is yet another factor contributing to vasodilation [48].

Sympathetic Nervous System Suppression: The sympathetic nervous system is a critical factor in the development and sustenance of hypertension. Chronic sympathetic hyperactivity causes elevated heart rate, peripheral vasoconstriction, renin release, and sodium retention [49]. *Rauwolfia serpentina*, a representative of herbal antihypertensive agents, is unique in its central mechanism of action. Reserpine permanently blocks vesicular monoamine transporters, which cause norepinephrine, dopamine, and serotonin in sympathetic nerve endings [50]. This decreases cardiac output and systemic vascular resistance,

resulting in strong antihypertensive effects. Although effective, the central nervous system effects of reserpine, such as depression and sedation, have been the major limiting factors to long-term clinical use [51]. However, *Rauwolfia serpentina* has remained a historic example of the use of plants as sources of antihypertensive pharmacology. Endothelial Function and Nitric Oxide Bioavailability: These include endothelial dysfunction, characterized by defects in nitric oxide production and elevated endothelin activity, both of which are present in hypertension and vascular disease [52]. One of the main therapeutic goals is thus restoration of endothelial functioning. Garlic increases the bioavailability of nitric oxide by stimulating the enzyme and inhibiting its oxidative decomposition [53]. Human trials have shown enhanced flow-mediated dilation with garlic supplementation, indicating that the endothelium is safeguarded beyond blood pressure lowering [54]. *Terminalia arjuna* has endothelial-protective effects that stabilize the vascular endothelium through flavonoids and triterpenoids, thereby enhancing arterial compliance [55]. These effects are specifically useful in hypertensive patients who have ischemic heart disease concomitants.

Antioxidant and Anti-inflammatory mechanisms: Oxidative stress and chronic low-grade inflammation are essential in the pathogenesis of hypertension, as they impair endothelial function, increase vascular rigidity, and activate the RAAS [56]. The four herbal agents have different antioxidant activities. Garlic and ginger eliminate reactive oxygen species and inhibit the production of pro-inflammatory cytokines, thereby indirectly lowering vascular resistance [57]. *Terminalia arjuna* is a powerful antioxidant with high polyphenolic content, which helps protect the vascular system over the long term [58]. These antioxidant processes argue the notion that herbal antihypertensives could be especially helpful in averting hypertension-related target-organ injury. The major pathophysiological pathways targeted by selected herbal antihypertensive agents are illustrated in Figure 1. Illustration depicting key pathophysiological pathways involved in hypertension—RAAS activation, sympathetic nervous system overactivity, endothelial dysfunction, and oxidative stress—and the corresponding sites of action of garlic, ginger, *R. serpentina*, and *T. arjuna*. The comparative antihypertensive mechanisms of the selected herbal agents are summarised in Figure 2.

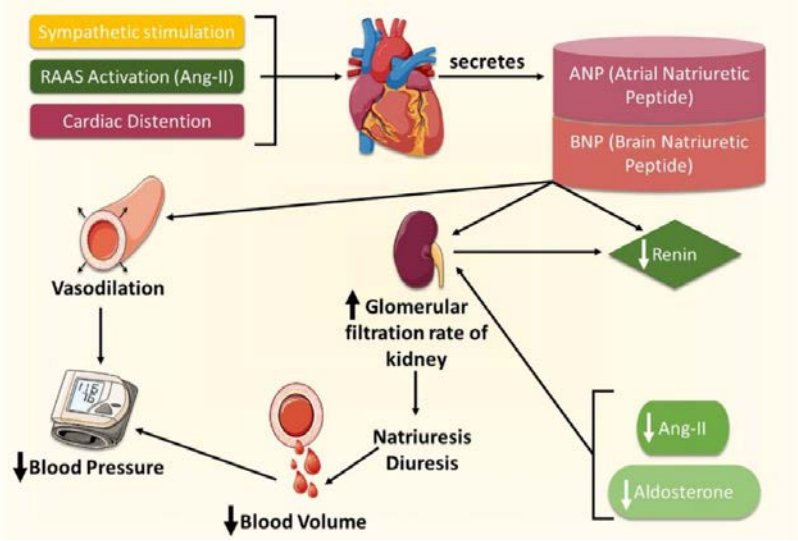

Figure 1: Pathophysiological Targets of Herbal Antihypertensive Agents

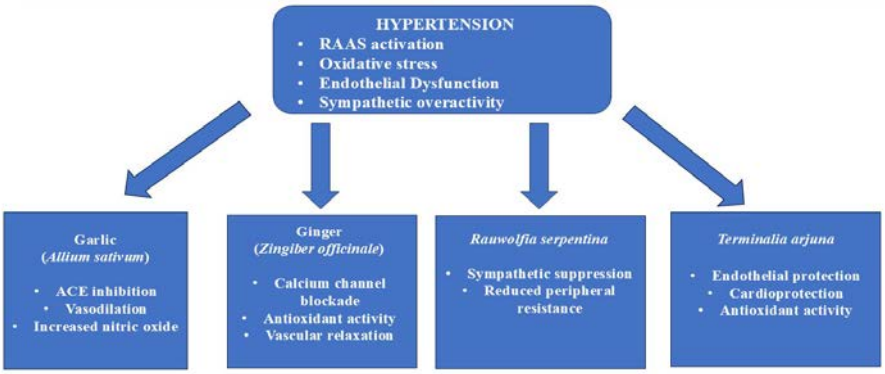

Figure 2: Major Antihypertensive Mechanisms of Selected Herbal Agents

Comparative overview of the major antihypertensive mechanisms of selected herbal agents, including ACE inhibition, calcium channel blockade, sympathetic suppression, endothelial protection, and antioxidant activity. A comparative summary of the major antihypertensive mechanisms and evidence levels of the selected herbal agents is presented in Table 2.

Table 2: Mechanisms of Antihypertensive Action of Selected Herbal Agents

Herbal Agent	Primary Mechanism	Secondary Mechanisms	Level of Evidence
A. sativum	ACE inhibition, NO enhancement	Antioxidant activity, calcium antagonism	Human clinical trials, meta-analyses
Z. officinale	Calcium channel blockade	Antioxidant, anti-inflammatory effects	Animal and in-vitro studies
R. serpentina	Central sympathetic inhibition	Reduced renin release	Clinical use (historical), safety-limited
T. arjuna	Endothelial protection	Antioxidant, cardiotonic effects	Clinical and experimental studies

Comparative Efficacy, Safety, and Therapeutic Limitations

Although several herbal agents show antihypertensive potential through different pharmacological mechanisms, their clinical applicability is limited not only by efficacy but also by safety, tolerability, standardization, and long-term use. This section presents a critical comparison of garlic (*Allium sativum*), ginger (*Zingiber officinale*), Rauwolfia serpentina, and *Terminalia arjuna* in terms of blood pressure-lowering efficacy, safety profile, therapeutic limitations, and clinical relevance.

Comparative Antihypertensive Efficacy: There is clinical and experimental evidence indicating that the antihypertensive effects of herbal agents vary significantly with the prevailing mechanism of action, dosage form, and the population under study. *Rauwolfia serpentina*, one of the agents chosen, has the strongest blood pressure-lowering effect. The initial clinical trials have shown significant decreases in systolic and diastolic blood pressure, especially in patients with moderate to severe hypertension [59]. Nevertheless, its highly effective action is strictly linked to central monoamine depletion, a process associated with serious adverse outcomes. Garlic has been shown to produce consistent, statistically significant decreases in systolic and diastolic blood pressure, especially in patients with untreated or mild hypertension. Meta-analyses of randomized controlled trials indicate a mean reduction in systolic blood pressure of 5 to 10 mmHg and a mean reduction in diastolic blood pressure of 3 to 6 mmHg [60]. Though minor compared to the effects of the traditional antihypertensive medications, they are clinically significant at the population level. Ginger (*Zingiber officinale*) exhibits antihypertensive activity, primarily supported by experimental and observational evidence. Experimental studies have shown dose-dependent blood pressure-lowering effects in animal models through calcium channel blockade, antioxidant activity, and vascular smooth muscle relaxation [61]. In addition to preclinical evidence, a limited number of human studies have reported modest reductions in systolic and diastolic blood pressure following ginger supplementation at doses of 1–3 g/day. Some clinical observations have also suggested improvements in endothelial function and reduction of inflammatory biomarkers in individuals with cardiovascular risk factors. However, currently available human studies remain limited by small sample sizes, variability in study designs, and insufficient long-term follow-up, preventing definitive conclusions about its standalone therapeutic efficacy in the management of hypertension. *Terminalia arjuna* exhibits an indirect antihypertensive effect, as evidenced by a slight decrease in blood pressure in patients with cardiovascular comorbidities. Its main advantage is its cardioprotective, endothelium-stabilizing, and myocardial-enhancing effects rather than forceful lowering of blood pressure [62].

Adverse Effects and Safety Profile: Safety is a significant factor in the long-term use of antihypertensive treatment. Garlic is generally well tolerated, and the most frequently reported adverse effects are gastrointestinal intolerance, heartburn, and odor problems. Garlic can increase the risk of bleeding, particularly when used in combination with anticoagulants, at high doses, and due to its antiplatelet activity [63]. The safety profile of ginger is also favorable, provided that it is taken in therapeutic or dietary amounts. The most commonly reported adverse effects are mild gastrointestinal irritation and reflux. Notably, ginger has not been linked to a high level of cardiovascular or neuropsychiatric toxicity and hence may be used as a complementary agent [64]. Conversely, *Rauwolfia serpentina* is linked with severe dose-related side effects, such as depression, sedation, nasal congestion, extrapyramidal, and gastrointestinal disturbances. The potential of depressive illness associated with the use of reserpine has been adequately reported, and this has resulted in a reduced clinical acceptability

of the drug even though it has been proven to be effective [65]. *Terminalia arjuna* is regarded as relatively safe, with few adverse effects reported in clinical trials. Gastrointestinal upsets are occasional, and severe toxicity is uncommon. It has a good safety profile, allowing long-term use, especially in patients with chronic cardiovascular disease [66].

Herb Drug Interactions and Clinical Limitations: The problem of herb–drug interaction is a serious issue in the integrative management of hypertension. Garlic has the potential to augment the action of antihypertensive medications, resulting in an additive effect on blood pressure, and may also augment the effect of anticoagulants [67]. Ginger has been documented to interact with antiplatelet and hypoglycaemic agents, but the clinical significance is rare [68]. *Rauwolfia serpentina* is extremely dangerous in terms of interaction because it affects the central nervous system and may interfere with antidepressants, antipsychotics, and sympathomimetic medications [69]. Such interactions also limit its application in contemporary clinical practice. The biggest limitation of all herbal antihypertensive agents is that their formulations are not standardized. The inconsistency in phytochemical content due to variation in plant source, processing, and extraction procedures makes it difficult to optimize dosage and replicate therapeutic effects [70]. Also, large-scale, long-term randomized controlled trials are few, making it difficult to draw conclusive judgments about comparative effectiveness. Potential CYP-mediated herb–drug interactions associated with selected herbal antihypertensive agents are summarised in Table 3.

Therapeutic Positioning in the management of hypertension: According to the existing evidence, herbal antihypertensive agents seem to be the most appropriate for use in early aortic hypertension, prehypertension, and as a supplement to existing medications. Garlic and ginger are particularly well-suited to lifestyle-based and preventive approaches because they are safe and offer additional metabolic benefits. *Terminalia arjuna* is potentially of particular importance in patients with hypertension and co-morbid ischemic heart disease or heart failure. Conversely, *Rauwolfia serpentina* demonstrates strong antihypertensive efficacy but has limited modern applicability because of significant neuropsychiatric adverse effects associated with reserpine. Nevertheless, low-dose reserpine combinations continue to be used in certain low-resource settings and resistant hypertension management strategies because of their cost-effectiveness and potent blood pressure-lowering activity. Recent clinical observations suggest that ultra-low-dose reserpine formulations may provide antihypertensive benefits with comparatively reduced central nervous system adverse effects when carefully monitored. However, further large-scale safety evaluations remain necessary before broader clinical reintroduction can be recommended. [71]. Comparative antihypertensive efficacy and therapeutic strength of the selected herbal agents are presented in Table 4. Major adverse effects and therapeutic limitations of the selected herbal antihypertensive agents are summarised in Table 5.

Table 3: Cytochrome P450 (CYP)-Mediated Herb–Drug Interactions of Selected Herbal Antihypertensive Agents

Herbal Agent	CYP Enzyme Interaction	Potential Clinical Implication
***Allium sativum* (Garlic)**	Possible modulation of CYP3A4 and CYP2E1	May alter the metabolism of antihypertensive agents, anticoagulants, and statins
***Zingiber officinale* (Ginger)**	Mild interaction with the CYP2C9 and CYP3A4 pathways	Possible enhancement of anticoagulant or antiplatelet drug effects
Rauwolfia serpentina	Limited direct CYP data; significant pharmacodynamic CNS interactions	May interact with antidepressants, antipsychotics, and sympathomimetic drugs
Terminalia arjuna	Possible CYP3A4 modulation (limited evidence)	Potential interaction with cardiovascular medications; further studies required

Table 4: Comparative Antihypertensive Efficacy of Selected Herbal Agents

Herbal Agent	Magnitude of BP Reduction	Clinical Evidence	Therapeutic Strength
Allium sativum	Mild–moderate (↓ SBP 5–10 mmHg)	RCTs, meta-analyses	Adjunct / early hypertension
Zingiber officinale	Mild (experimental)	Animal, limited human studies	Preventive/supportive
Rauwolfia serpentina	High	Historical clinical trials	Potent but safety-limited
Terminalia arjuna	Mild–moderate (indirect)	Clinical and experimental	Cardioprotective adjunct

SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure

Table 5: Safety Profile and Key Limitations

Agent	Common Adverse Effects	Major Limitations
Allium sativum	GI irritation, bleeding risk at high doses	Drug interactions, odor issues
Zingiber officinale	Mild GI discomfort	Limited clinical trials
Rauwolfia serpentina	Depression, sedation, extrapyramidal effects	Poor tolerability, CNS toxicity
Terminalia arjuna	Rare GI upset	Modest BP-lowering efficacy

Clinical Relevance and Future Research Directions: The clinical significance of herbal antihypertensive agents is that they can be used as preventive, adjunct, or even alternative treatments for hypertension in stratified management. Since hypertension has a multifactorial pathophysiology and its treatment is chronic, agents with acceptable efficacy & have good safety profiles might be especially useful in the initial stages of the disease and in populations where access to traditional pharmacotherapy is limited.

Clinical Applicability at the Stages of Hypertension: Synthesized evidence in this review indicates that garlic (*Allium sativum*) and ginger (*Zingiber officinale*) are best suited to those with prehypertension or mild essential hypertension, where small drops in blood pressure can mean a lot for cardiovascular risk in the long run [72]. Their other metabolic and anti-inflammatory effects further support their use in lifestyle-based interventions. *Terminalia arjuna* has been found to have the highest clinical applicability among patients who are hypertensive with co-morbid cardiovascular diseases, including ischemic heart disease or early heart failure. Its cardiotonic and endothelial-protective effects can be used in addition to conventional antihypertensive therapies, especially in patients with high vascular stiffness and myocardial stress [73]. Conversely, *Rauwolfia serpentina* demonstrates a high level of antihypertensive effect, but the adverse neuropsychiatric safety of this plant restricts its clinical use. It is now mostly historical or confined to well-supervised environments where other forms of therapy are not available [74]. Collectively, the selected herbal antihypertensive agents act through multiple complementary mechanisms, including modulation of the renin–angiotensin–aldosterone system, calcium channel blockade, suppression of the sympathetic nervous system, enhancement of endothelial nitric oxide bioavailability, and reduction of oxidative stress and inflammation. Garlic predominantly targets the RAAS and endothelial pathways; ginger mainly influences calcium-mediated vascular relaxation and oxidative stress; *Rauwolfia serpentina* acts through central sympathetic inhibition; whereas *Terminalia arjuna* primarily provides endothelial and cardioprotective support. Mechanistic and translational clinical insights associated with the selected herbal antihypertensive agents are summarised in Table 6.

Interaction with Traditional Antihypertensive Treatment

Herbal antihypertensive therapies are best incorporated as supplements rather than alternatives to conventional agents. Garlic (*A. sativum*) and ginger (*Z. officinale*) may complement conventional antihypertensive therapies by exerting additive vasodilatory, antioxidant, and endothelium-protective effects. Experimental studies and limited clinical evidence suggest that garlic supplementation may enhance blood pressure reduction when used alongside ACE inhibitors or calcium channel blockers. Similarly, ginger may provide supportive vascular and anti-inflammatory benefits when combined with standard antihypertensive treatment. However, current evidence remains limited, and further controlled clinical studies are necessary to establish the safety, efficacy, and clinical significance of these combination approaches [75]. Nonetheless, such a combination should be carefully observed due to the potential for additive hypotension & pharmacodynamic interactions. Clinical integration also requires that physicians be aware of, and that patients disclose, their use of herbs. The unaccounted herbal supplementation can be a contributor to the variation in the blood pressure regulation that cannot be explained, as well as a negative drug interaction, especially in the polypharmacy context [76].

Problems with Standardization and Formulation

The lack of standardized formulations is also a major impediment to the clinical translation of herbal antihypertensive agents. Changes in plant species, cultivation practices, harvest timing, and extraction methods result in inconsistent phytochemical profiles and unpredictable therapeutic effects [77]. Most herbal preparations lack consistent dosing instructions, unlike synthetic drugs, which limits the reproducibility of clinical studies. Standardization of herbal antihypertensive formulations should rely on quantifiable phytochemical markers to ensure consistency, reproducibility, and therapeutic reliability. In garlic (*A. sativum*), allicin and S-allylcysteine may serve as important markers for standardization

due to their established cardiovascular and antihypertensive activities. Similarly, 6-gingerol & shogaols are considered major bioactive markers for ginger (*Z. officinale*) preparations. Reserpine content remains the principal marker for *R. serpentina*, whereas arjunolic acid & total flavonoid content may be useful indicators for standardization of *T. arjuna* formulations. Marker-based quality control may significantly improve formulation consistency and translational clinical applicability. Improvements in the standardization of phytochemicals, marker-based quality control, and formulation science, such as sustained-release and bioavailability-enhanced preparations, are necessary to bridge the gap between traditional usage & evidence-based medicine [78].

Table 6: Mechanistic and Translational Insights into the Clinical Applicability of Selected Herbal Antihypertensive Agents

Herbal Agent	Experimental Evidence (*In vitro* / *In vivo* / Clinical)	Molecular & Cellular Targets	Core Mechanistic Pathways	Key Mechanistic & Functional Findings	Translational Clinical Insight
***Allium sativum* (Garlic)**	*In vitro* (ACE inhibition, endothelial NO assays); *In vivo* (hypertensive rodent models); Clinical RCTs	ACE, eNOS, ROS-generating enzymes	ACE inhibition → ↓ Ang II; ↑ NO bioavailability; oxidative stress attenuation	Produces consistent SBP/DBP reductions (~5–10 mmHg); improves endothelial function and arterial compliance; reduces inflammatory and oxidative biomarkers	Optimal for prehypertension and mild essential hypertension, where endothelial dysfunction is dominant; long-term modest BP reduction confers substantial cardiovascular risk reduction [72]
***Zingiber officinale* (Ginger)**	*In vitro* (vascular smooth muscle Ca^{2+} flux assays); *In vivo* (vasorelaxation models); Limited clinical studies	L-type Ca^{2+} channels, prostaglandin synthesis enzymes, antioxidant pathways	Calcium channel antagonism; inhibition of vasoconstrictor prostanoids; ROS scavenging	Demonstrates dose-dependent vasorelaxation and reduced peripheral vascular resistance; attenuates oxidative & inflammatory signaling	Best suited for prehypertension and early hypertension as part of lifestyle and preventive strategies; complements metabolic & anti-inflammatory interventions [72]
***Terminalia arjuna* (Arjuna)**	*In vivo* (ischemia and cardiac stress models); Clinical studies in IHD and heart failure	Myocardial Ca^{2+} handling proteins, endothelial NO pathways, lipid peroxidation markers	Cardiomyocyte protection; endothelial stabilization; reduced myocardial oxidative injury	Improves left ventricular function, reduces myocardial oxygen demand, and decreases vascular stiffness; supports endothelial repair	Highly applicable in hypertensive patients with ischemic heart disease or early heart failure; effective as an adjunct to conventional antihypertensive therapy [73]
***Rauwolfia serpentina* (Rauwolfia)**	*In vivo* and historical clinical trials	VMAT2, central monoamine storage vesicles	Depletion of norepinephrine, dopamine, and serotonin → ↓ sympathetic tone	Produces profound and sustained BP reduction but causes CNS monoamine depletion, leading to depression, sedation	Strong antihypertensive efficacy but limited modern clinical use due to neuro-psychiatric adverse effects; restricted to supervised or historical contexts [74]

Requirement of Strict Clinical Trials

Although the current evidence is encouraging, existing studies remain limited by small sample sizes, short study durations, and heterogeneity in outcome measures. To establish dose–response relationships, long-term safety & comparative therapeutic effectiveness, large-scale randomized controlled trials using standardized herbal extracts and well-defined clinical endpoints are required [79]. Future research should additionally focus on:

- Pharmacodynamic and pharmacokinetic evaluation of active phytochemicals.
- Assessment of herb–drug interactions in real-world clinical practice.
- Identification of patient populations most likely to benefit from herbal antihypertensive interventions.
- Development of bioavailability-enhanced nanoformulations and targeted delivery systems for phytochemicals such as allicin, gingerols, and arjunolic acid.
- Investigation of sustained-release and nanoparticle-based herbal formulations to improve pharmacokinetic stability, tissue targeting, and therapeutic consistency.

- Molecular and translational studies evaluating synergistic interactions between herbal phytochemicals and conventional antihypertensive agents.
- Advanced phytochemical standardization and marker-based quality control approaches to improve reproducibility and clinical reliability of herbal formulations.
- Long-term randomized clinical studies assessing safety, efficacy, dose optimization, and pharmacokinetic behavior of standardized herbal preparations.

Regulatory and Translational Perspectives

Herbal medicines are subject to a broad spectrum of regulatory frameworks, including those that classify them as dietary supplements and those that regulate them as prescription drugs. Standardization of regulatory requirements, as well as robust post-marketing surveillance, is essential to ensure safety and quality and to make them accessible across a broader clinical setting [80].

Translationally, to incorporate validated herbal antihypertensive agents into the national hypertension guidelines, clinical evidence is needed, along with clinician education and patient-centered communication interventions. Clinical positioning and future research priorities of selected herbal antihypertensive agents are presented in Table 7.

Table 7: Clinical Positioning and Research Priorities for Selected Herbal Antihypertensive Agents

Herbal Agent	Optimal Clinical Use	Key Advantages	Priority Research Needs
Allium sativum	Prehypertension, mild HTN, adjunct therapy	Good safety, clinical evidence	Does standardization, long-term RCTs
Zingiber officinale	Preventive and supportive use	Multisystem benefits, safety	Controlled human trials
Rauwolfia serpentina	Limited, monitored use	Potent BP reduction	Safer derivatives, CNS risk mitigation
Terminalia arjuna	HTN with cardiac comorbidity	Cardioprotection	BP-focused trials, formulation studies

CONCLUSION

This comparative evaluation demonstrates that herbal antihypertensive agents exhibit mechanism-specific and stage-dependent therapeutic potential in the management of hypertension. Garlic and ginger provide modest but clinically meaningful reductions in blood pressure and appear most suitable for early-stage hypertension, preventive strategies & vascular protection. *T. arjuna* offers additional cardioprotective and endothelial protective benefits, particularly in patients with cardiovascular comorbidities. In contrast, *R. serpentina* exhibits potent antihypertensive efficacy but remains limited by significant neuropsychiatric adverse effects associated with reserpine. From a translational clinical perspective, selected herbal antihypertensive agents may be integrated as supportive interventions within lifestyle-oriented hypertension management strategies recommended by contemporary JNC and ESC/ESH guidelines. Garlic (*Allium sativum*) and ginger (*Zingiber officinale*) may be particularly valuable in prehypertension and mild essential hypertension because of their favorable safety profiles and multitarget vascular effects. *Terminalia arjuna* may provide additional cardiovascular support in patients with cardiac comorbidities, whereas *Rauwolfia serpentina* may retain limited relevance in resistant hypertension under careful clinical supervision. However, these herbal agents should complement rather than replace evidence-based pharmacotherapy in moderate-to-severe hypertension until stronger long-term clinical evidence becomes available.

Nevertheless, the present analysis is limited by variability in study designs, insufficient standardization of herbal formulations, and the lack of large-scale, long-term randomized clinical trials. Despite these limitations, herbal antihypertensive agents demonstrate promising translational potential, particularly in integrative and resource-limited healthcare settings. Further well-designed clinical studies focusing on safety, efficacy, pharmacokinetic standardization, and bioavailability-enhanced formulations are necessary to support their evidence-based clinical application.

FINANCIAL ASSISTANCE

NIL

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTION

Hemanga Mazumdar conducted the literature review and drafted the manuscript. Mrinmoy Basak supervised the work and critically revised the manuscript. Both authors approved the final version of the manuscript.

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