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HERBAL INTERVENTIONS FOR HYPERTENSION: A REVIEW OF TRADITIONAL PLANTS, BIOACTIVE COMPOUNDS, AND NANOTECHNOLOGICAL ADVANCES

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ABSTRACT: Hypertension (HTN), a major global health concern and the primary cause of cardiovascular disease (CVD) death is expected to impact 29% of all adults by 2025. Hypertension (HTN) is a multifactorial condition, arising from the complex interaction of hereditary, environmental, and physiological variables that contribute to elevated systolic and diastolic blood pressure. It is frequently caused by dysregulation of blood pressure control mechanisms, such as over activity of the renin-angiotensin system and increased sympathetic nervous system activity. Traditional hypertension therapies, such as ACE inhibitors and beta-blockers, have drawbacks, including low solubility and absorption. As a result, researchers are increasingly focusing on novel treatment approaches, such as medicinal plants and nanotechnology. Herbal plants such as Ashwagandha, Cat's Claw, Ginger, Ginseng, Murungai, and Touch-Me-Not belonging to different families are renowned for pharmacological activities and have shown potential medicines antihypertensive properties, which are often attributed to their bioactive constituents. Recent breakthroughs in nanotechnology have permitted the manufacture of nanoparticles derived from these plants, improving their stability, bioavailability, and potency. These plant-mediated nanoparticles show potential in controlling hypertension by lowering oxidative stress, increasing endothelial function, and regulating nitric oxide levels. As research progresses, combining nanomedicine with traditional herbal therapy may provide novel and effective methods for hypertension management. Future clinical trials and thorough patient education on herbal medicines will be required to realize their promise while maintaining safety and efficacy fully.

INTRODUCTION: Hypertension (HTN) is the leading risk factor for acute myocardial infarction, accounting for around 16.5% of deaths worldwide each year. The disordered regulation of blood pressure (BP), often known as the silent killer, can result from a combination of hereditary and environmental variables ¹⁻².

It is also the primary cause of morbidity and mortality in cardiovascular disease (CVDs) ³. It is anticipated that by 2025, 29% of the world's adults, a total of 1.56 billion individuals, will suffer from HTN ⁴. The threshold for eligibility is systolic blood pressure (SBP) ≥ 140 mm Hg and diastolic blood pressure (DBP) ≥ 90 mm Hg, based on the average of two consecutive BP readings ².

In nations like India, the prevalence of hypertension among adults stands at 11%, with a notable increase observed particularly in urban areas compared to rural regions ⁵. In a study encompassing 8000 subjects in India hypertension

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emerged as the primary risk factor for CAD in over 50% of both young and elderly participants followed by smoking and diabetes^{6, 7}. The estimated annual cardiovascular deaths in India amount to 2.5 millions with projections indicating it may become the leading cause of mortality by 2020⁸. Hypertension has three subcategories: stage I, stage II, and isolated systolic hypertension (ISH) which is defined by elevated systolic pressure alongside normal diastolic pressure and often occurs in the elderly. Additionally, hypertension is deemed resistant if medications fail to lower blood pressure to normal levels. This condition typically lacks early symptoms but constitutes a significant cardiovascular risk in the long term⁹. The precise mechanisms underlying hypertension (HTN) particularly essential hypertension, remain incompletely understood¹⁰.

HTN is distinguished by dysregulation of blood pressure control mechanisms, in which inadequate sodium secretion by the kidneys causes increased excretion of natriuretic factors such as atrial natriuretic factor. An overactive renin-angiotensin system also causes vasoconstriction, which aids in the retention of salt and water¹¹. The accumulation of blood volume is a significant contributor to the development of HTN. Furthermore, heightened activity of the sympathetic nervous system exacerbates stress, further complicating the condition¹¹⁻¹².

Mechanisms of Hypertension / Hypertensive Mechanisms: Hypertension results from complex interactions between multiple physiological systems and factors. Key mechanisms underlying high blood pressure include: Genetic predispositions, autonomic nervous system dysregulation, renin-angiotensin-aldosterone system (RAAS) activation, vascular structure and function alterations, stimulation of the sympathetic nervous system, vasopressin regulation, disrupted G protein-coupled receptor signaling, inflammatory responses, T-cell mediated immune mechanism, and a wide range of vasoactive peptides secreted by other endothelial and smooth muscle cells¹³⁻¹⁴. Enhanced vasoconstriction may be attributed to a combination of factors, including vascular smooth muscle cell (VSMC) hyperplasia and hypertrophy, leading to increased muscle mass and contractility, elevated basal and activated calcium levels

facilitated by altered calcium channel activity, and augmented arterial reactivity resulting from dysregulation of pro-oxidant enzymes and impaired endothelial nitric oxide synthase (eNOS) function¹⁵. These mechanisms collectively contribute to exaggerated vasoconstriction, potentially exacerbating hypertension¹⁶. Angiotensin II (Ang II) can promote the advancement of the cell cycle¹⁷.

Antihypertensive medications used to treat HTN include angiotensin-converting enzyme inhibitors, renin blockers, diuretics, sympatholytic drugs, calcium channel blockers, β -adrenergic and $\alpha 1/\beta$ -adrenergic antagonists, and vasodilators¹⁰. The majority of standard antihypertensive medicines are poorly water-soluble and undergo first-pass metabolism, which contributes to their very low bioavailability, short half-life, and high dosage frequency¹. To circumvent these limitations, designing new-generation alternative antihypertensive therapeutics and proper delivery systems is the primary focus of research in this field¹⁸.

Plants with medicinal properties and their bioactive compounds are used around the world to treat and prevent a wide range of illnesses. According to Pant (2014), around 80% of the world's population relies on herbal medicines to cure, prevent, and manage a variety of medical issues¹⁹.

The potential of the active components of herbal medicine to function as natural therapeutic agents, as well as its availability, accessibility, affordability, and reported reduced or non-toxic effects, may explain why herbal medicines are becoming more popular than conventional treatments²⁰⁻¹⁹. In recent decades, various researchers found and classified medicinal plants and their bioactive components for use in the treatment and prevention of life-threatening and chronic illnesses such as cerebrovascular accidents, diabetes, stroke, arthritis, and psychiatric diseases, among others²¹. The initial identification of reserpine approximately five decades prior, derived from the roots of the Indian plant *Rauwolfia serpentina*, demonstrated considerable cardioselectivity²². First introduced reserpine for hypertension treatment, with subsequent advancements including its structural elucidation

and total synthesis achieved between 1952 and 1958²³⁻²⁴. Polyphenols, naturally occurring plant compounds found in various plant-based foods such as vegetables, fruits, dark chocolate, tea, spices, wine, and herbs, play an important role in neutralizing harmful free radicals that can damage cells and increase the risk of conditions like diabetes, cancer, and cardiovascular disease²⁵⁻²⁶. Regular intake of flavonoids, a type of polyphenol has been shown to mitigate the onset or progression of numerous cardiovascular diseases, particularly hypertension²⁷. Carotenoids, which contribute to the red, yellow, and orange hues of fruits and vegetables, are present in smaller quantities but are still vital. They are thought to be responsible for the foods' therapeutic effects in reducing cardiovascular disease and other human disorders²⁸.

Nanoparticles are sub-ionized colloidal structures made of synthetic or semi-synthetic polymers with sizes ranging from 10 to 100 nanometers (nm). These compounds are commonly employed in the pharmaceutical industry because they play an important role in drug delivery by dissolving, entrapping, encapsulating, or adhering to the matrix. Nanomaterials' unique features, such as their nanoscale size, high surface area to volume ratio, and variable surface chemistry, make them interesting candidates for use in therapeutic applications²⁹.

Nanoparticle synthesis mediated by "Green chemistry" is currently a major dominant holder. This method is preferred for biomedical and pharmaceutical applications. This approach is not only eco-friendly but also financially affordable. As a result, we can say that green chemistry is an affordable and environmentally benign strategy for plant extract-assisted biogenesis of metal nanoparticles³⁰.

Herbal Plants used in Treatment of Hypertension:

Ashwagandha (*Withania somnifera*):

Ashwagandha has been revered for its extensive benefits, being recognized as a potent rejuvenator, a versatile health tonic, and a remedy for various health issues. Its properties encompass sedative, diuretic, and anti-inflammatory qualities, while also being esteemed for its ability to enhance energy,

endurance, and act as an adaptogen, bolstering immune response and mitigating stress. *Withania somnifera*, often referred to as Indian ginseng or Indian Winter Cherry plays a vital role in ancient medical disciplines like Ayurveda and Unani³¹. Its roots are key components of various formulations treating respiratory and reproductive diseases³²⁻³³. It is rich in alkaloids such as withanine and withasomnin, as well as steroidal lactones and glycosides known as withanoloids and sitoindosides³⁴⁻³⁵. Extracts derived from *Withania somnifera* exhibit analgesic mildly sedative anti-inflammatory, and anabolic properties proving beneficial in managing conditions like stress, fatigue, pain, skin disorders, diabetes, gastrointestinal issues, rheumatoid arthritis, epilepsy, chronic fatigue syndrome, and even during pregnancy without adverse effects³⁶.

Research has demonstrated influence of this plant on neurological, endocrine, and cardiovascular functions. It is commonly utilized as a general tonic to promote vitality and enhance overall health and longevity. Human studies suggest its potential to faster growth in children, elevate hemoglobin levels, increase red blood cell count, and enhance physical performance in adults³⁷. Furthermore, animal studies have corroborated its impact on sex hormone production, demonstrated by its effects on luteinizing hormone, follicle-stimulating hormone, testosterone, and progesterone levels³⁸.

In recent years, *Withania somnifera* has been investigated for its involvement in the production of nanoparticles, which are gaining importance in medical studies, particularly for the treatment of hypertension. The green synthesis of nanoparticles using plant extracts is a rapidly growing field due to its eco-friendly and sustainable approach. Ashwagandha includes a variety of bioactive chemicals, including alkaloids and flavonoids, that can act as reducing and capping agents in the creation of metal nanoparticles such as silver (AgNPs) and gold (AuNPs).

These biosynthesized nanoparticles have demonstrated significant potential in biomedical applications due to their enhanced stability, biocompatibility, and targeted drug delivery capabilities. Specifically, in the context of hypertension, the antioxidant properties of

Ashwagandha-derived nanoparticles have been studied for their ability to reduce oxidative stress, a major contributor to high blood pressure. These nanoparticles can modulate the levels of nitric oxide (NO), a critical molecule in regulating vascular tone and blood pressure, thereby providing a novel therapeutic avenue for hypertension management³⁹⁻⁴⁰. Furthermore, Ashwagandha-mediated nanoparticles have shown promise in improving endothelial function and reducing vascular Inflammation, both of which are crucial factors in the pathogenesis of hypertension. These nanoparticles also exhibit minimal side effects, making them a viable option for long-term use in managing chronic conditions such as hypertension⁴¹ **Table 1** and **Fig. 1**.

Cat's Claw (*Uncaria rhynchophylla*): *Uncaria* species are primarily utilized to treat ulcers and wounds, asthma, hyperpyrexia, hypertension, gastrointestinal disease, headaches, fever, rheumatism, and bacterial/fungal infections⁴². It is prepared from the dried stem of the plant, along with a segment featuring five curled, hook-shaped structures. The medicinal components of this remedy come from *U. rhynchophylla* and *U. sinensis*. In recent years, extensive studies on *Uncaria* species have led to the successful identification of several metabolites, including alkaloids, triterpenes, and flavonoids. Notably, monoterpenoid indole alkaloids such as hirsutanine, rhynchophylline units, and uncariolins have been recognized as key components of this herb. These compounds exhibit a range of pharmacological effects, including antidepressant, anticancer, and antihypertensive properties⁴³. *U. rhynchophylla*, native to tropical regions, contains phenolic compounds (such as hyperin, caffeic acid, procyanidin B2, epicatechin, chlorogenic acid, rutin, and hyperoside), pentacyclic triterpene esters, and indole alkaloids (including rhynchophylline and isorhynchophylline). Passive targeting is a significant advantage since it allows nanoparticles to enter and aggregate in tumors, which contain blood arteries with greater fenestrations due to angiogenesis and inefficient lymphatic drainage⁴⁴ **Table 1** and **Fig. 1**.

Ginger (*Zingiber officinale*): *Zingiber officinale* commonly known as ginger has been widely incorporated into everyday diets and utilized for

various therapeutic intentions. It is comprised of potassium, which helps regulate the heart rate and blood pressure activities⁴⁵. It contains a variety of cations and anions, including calcium, magnesium, and phosphorus, which are essential for bone growth, muscular contraction, and nerve conduction⁴⁵. The root nodules assists by inhibiting the electrical current of calcium channels. These channels typically stimulate the contraction of smooth muscle tissue found in organs and arterial walls thus facilitating smoother blood flow and consequently lowering blood pressure. It also aids in reducing hypertension by decreasing the body's requirement for dietary salt⁴⁶. *Z. officinale* is considered as one of the interests for the treatment of many cardiovascular diseases. The studies suggest that *Z. officinale* has anti-inflammatory, antioxidant, anti-platelet, hypotensive and hypolipidemic effects in *in-vitro* and animal studies⁴⁷. Studies on silver nanoparticles produced using ginger extract have shown that these particles are quite persistent in solution. The use of biologically generated nanoparticles, which reduce aspects like toxicity and cost and are observed to be highly stable, could be an effective way to use silver nanoparticles in biomedical applications⁴⁸ **Table 1** and **Fig. 1**.

Ginseng (*Panax spp.*): Ginseng stands out as one of the most popular medicinal herbs⁴⁹, often purported to have efficacy across a wide array of conditions, including cancer⁵⁰, erectile dysfunction⁵¹ and postmenopausal symptoms⁵². Extensive research has delved into the cardiovascular effects of ginseng or its individual ginsenosides. While a particular study indicated that ginseng is unlikely to effectively reduce blood pressure, other researchers have proposed its potential in addressing hypertension⁵³. Several *in-vivo* studies have suggested that ginseng might lower blood pressure in a manner not dependent on dosage. Ginseng is available in many forms such as capsules, tablets, extracts, dried roots, oil, or tea, and it has hypotensive properties. Minimal dosages of ginseng can raise blood pressure, whereas increased doses have a hypotensive impact. Ginseng is likely to regulate blood pressure levels in hypotensive patients by altering vascular function, influencing the autonomic nervous system, or adjusting the arterial baroreflex⁵⁴.

In recent decades, there has been an increasing interest in using nanotechnology to improve the medicinal potential of ginseng, particularly in the treatment of hypertension. The bioactive compounds in ginseng, especially ginsenosides, have been used in the green synthesis of nanoparticles, which are recognized for their potential to treat hypertension effectively. The phytochemicals in ginseng act as reducing and stabilizing agents during the nanoparticle synthesis process, resulting in nanoparticles that are biocompatible and effective for medical applications. These ginseng-mediated nanoparticles, particularly gold (AuNPs) and silver nanoparticles (AgNPs), have shown promising results in preclinical studies.

The nanoparticles exhibit strong antioxidant properties, which are crucial in managing oxidative stress, a key factor contributing to hypertension. By scavenging reactive oxygen species (ROS), these nanoparticles help protect the cardiovascular system from oxidative damage, thereby supporting the maintenance of normal blood pressure levels⁵⁵. Moreover, these nanoparticles have been found to enhance the bioavailability and efficacy of ginsenosides, allowing for more efficient modulation of vascular function and blood pressure. The nanoparticles also improve endothelial function and nitric oxide (NO) production, both of which are critical in the regulation of blood pressure. These findings suggest that ginseng-based nanoparticles could offer a novel and more effective approach to hypertension treatment, combining traditional herbal medicine with cutting-edge nanotechnology⁵⁶ **Table 1 and Fig. 1.**

Murungai (*Moringa oleifera*): Murungai, which is part of the Moringaceae family is a herbal plant that has been researched for its effects on blood pressure in sedated rats. Moringa leaf phytochemicals, including flavonoids, quercetin, and phenolic acid, are thought to ameliorate non-alcoholic fatty liver disease (NAFLD)⁵⁷. The crude leaf extract of *M. oleifera* caused a dose-dependent decrease in systolic, diastolic, and mean blood pressure. However, this antihypertensive effect was short-lived, with blood pressure returning to normal within two minutes. Heart rate was not significantly impacted, except at higher doses, which caused a

slight bradycardia. The crude extract's thiocarbamate and isothiocyanate fractions were also revealed to be responsible for its antihypertensive effect⁵⁸. In addition to the conventional antihypertensive properties of *Moringa oleifera*, recent research has delved into its potential in the synthesis of nanoparticles for therapeutic applications, including the treatment of hypertension.

The bioactive compounds present in *M. oleifera*, such as flavonoids, phenolics, and glucosinolates, have been effectively utilized in the green synthesis of nanoparticles, particularly silver nanoparticles (AgNPs). These *Moringa oleifera*-mediated nanoparticles exhibit remarkable antioxidant properties, which are crucial in counteracting oxidative stress, a major factor in the development of hypertension. The nanoparticles enhance the bioavailability of nitric oxide (NO), a vasodilator that plays a vital role in regulating blood pressure by relaxing blood vessels. The increase in NO availability facilitated by these nanoparticles helps in reducing vascular resistance, thereby lowering blood pressure⁵⁹. Furthermore, studies have shown that these biosynthesized nanoparticles can improve endothelial function, reduce inflammation, and prevent the progression of hypertension-related vascular damage. Their biocompatibility and minimal side effects make them promising candidates for long-term use in managing hypertension⁶⁰ **Table 1 and Fig. 1.**

Touch-Me-Not (*Mimosa pudica*): *Mimosa pudica* L. is a perennial herb from the Mimosaceae family. Phytochemical studies have identified several compounds in *M. pudica*, including terpenoids, tannins, alkaloids, sterols, and fatty acids. The medicinal properties of *Mimosa pudica* reported to date primarily encompass antidepressant, anticonvulsant, hyperglycemic, and anti-implantation effects⁶¹. Among the plant groups with potential biological effects, the genus *Mimosa* stands out, as several of its species have been scientifically investigated for their impact on the cardiovascular and renal systems. Notably, *M. pigra* has been shown to mitigate the progression of experimental pulmonary hypertension⁶². Green silver nanoparticles derived from *M. pudica* flower extract had strong antibacterial and antibiofilm properties against *E. coli*⁶³.

Recent research has expanded the exploration of *M. pudica* to include its potential in the green synthesis of nanoparticles, particularly in the context of hypertension treatment. Nanoparticles synthesized from plant extracts have gained attention for their biocompatibility and eco-friendly production processes. *Mimosa pudica*'s phytochemicals, such as flavonoids and tannins, play a significant part in the reduction and stability of metal ions during nanoparticle synthesis, which leads to stable and effective nanoparticles. Specifically, *Mimosa pudica* has been used in the biosynthesis of silver nanoparticles (AgNPs), which have indicated potential in a variety of biological applications. These nanoparticles have significant antioxidant activities, which are important in the control of oxidative stress, a major contributor in the development and progression of hypertension. The antioxidant activity of *Mimosa pudica*-mediated AgNPs can help reduce oxidative damage in the

vascular system, thereby potentially lowering blood pressure and preventing further cardiovascular complications⁶⁴. Moreover, studies have suggested that these nanoparticles can enhance nitric oxide (NO) availability, leading to vasodilation and improved endothelial function, both of which are important in the management of hypertension. The use of *Mimosa pudica* in nanoparticle synthesis thus represents a novel and promising approach to the treatment of hypertension, combining the traditional medicinal properties of the plant with innovative nanotechnology⁶⁵. The exploration of *Mimosa pudica* in the field of nanomedicine underscores the potential of this plant not only in antibacterial and antiparasitic treatments but also in addressing complex conditions such as hypertension, offering a natural and sustainable alternative to conventional therapies **Table 1** and **Fig. 1**.

TABLE 1: HERBAL PLANTS AND ITS SECONDARY METABOLITES IN THE MANAGEMENT OF HYPERTENSION

Sl. no.	Common Name	Botanical Name	Family	Secondary Metabolites	Reference
1	Ashwagandha	<i>Withania somnifera</i>	Solanaceae	Withanolides, Withanosides, Alkaloids (e.g., somniferine, anaferine), Flavonoids and Sитоindosides.	66
2	Cat’s Claw	<i>Uncaria rhynchophylla</i>	Rubiaceae	Isorhynchophylline, Rhynchophylline, Hirsutine, Corynoxene and Corynantheine.	67
3	Ginger	<i>Zingiber officinale</i>	Zingiberaceae	Gingerol, Shogaol, Zingerone, Paradols and Flavonoids.	68
4	Ginseng	<i>Panax spp.</i>	Araliaceae	Ginsenosides, Polyacetylenes, Polysaccharides and Flavonoids.	69
5	Moringa	<i>Moringa oleifera</i>	Moringaceae	Glucosinolates, Quercetin, Chlorogenic Acid and β-Sitosterol.	70
6	Touch-me-not	<i>Mimosa pudica</i>	Fabaceae	Flavonoids, Tannins, Saponins and Alkaloids.	71

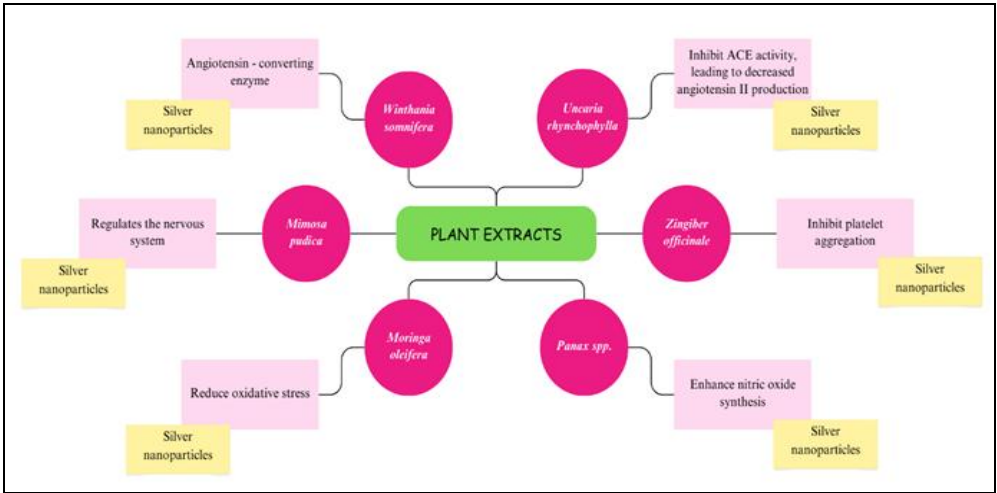


FIG. 1: SCHEMATIC REPRESENTATION OF PLANT EXTRACTS AND IT’S ON THE MANAGEMENT OF HYPERTENSION

CONCLUSION: In recent years, developing more effective treatments for hypertension and cardiovascular disease (CVD), the leading cause of death worldwide, has become critical. Nature has historically served as an inspiration for the development of new small-molecule drugs, which may explain why many patients prefer herbal therapy to allopathic treatments for CVD management. This article examines the most often used plants for treating hypertension, as well as their modes of action. These natural plants and their compounds have pharmacological effects on the pathogenesis of hypertension by modulating endothelial function, reactive oxygen species (ROS) production, pro-inflammatory signaling, platelet activation, ion channel regulation, ACE inhibition, and gene expression.

Nano-formulations are a new tool in biology and medicine that provide distinct physicochemical and biological features due to their size, shape, and surface characteristics. These characteristics make them an attractive platform for creating novel, non-conventional medicines. To effectively convert research findings into clinical practice, it is critical to take use of all advances in nanomedicine to gain a more precise grasp of the subject. This necessitates collecting precise data on existing nanotherapeutics and thoroughly examining their intrinsic features and biological impacts. Such an approach will make it possible to create smart nano-formulations that are suited to specific diseases and personalize nano-therapies. Herbal medicines are anticipated to receive more attention in the future due to their broad range of efficacy, assuming that relevant clinical and experimental research are done. It is also critical to educate patients on the safe use of herbs such as black cumin, coriander, garlic, Chinese sage, ginger, and ginseng, particularly because some ingredients can elevate blood pressure and be hazardous if not chosen appropriately.

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