POTENTIAL OF NATURAL COMPOUNDS FOR THE MANAGEMENT OF HYPERTENSION: A REVIEW

Vishal Gautam[1], Jyoti Yadav[1], Ritu Dhaiya[1], Laxmi Rani[1], Kanchan Mathur[2], Pooja Mathur[1*]

[1]Department of Pharmacy, School of Medical and Allied Sciences, G.D. Goenka University, Gurugram-122103, Haryana, India

[2]Institute of Pharmaceutical Research, GLA University, Mathura-281406, Uttar Pradesh, India

Email.: poojamathurkuk@gmail.com

ABSTRACT

In cardiovascular diseases, Hypertension is a very critical health issue worldwide. A large number of people are interested in natural constituents as an alternative for the treatment of Hypertension, which has historically been used to treat high blood pressure. A variety of treatments, including diuretic effects, antioxidant activity, blood vessel widening, and angiotensin-converting enzyme (ACE) inhibition are available but these naturally occurring herbs can control blood pressure without any side effects. Ambulatory, home, office, digital, automated blood pressure monitoring are among the analytical methods used in the worldwide research of hypertension. Anti phytoconstituents such as celery, Artemisia campestral L, Calpurnia area, areca catechu, and orographic pediculate, cupids rhizome, allium sativa, coria drum sativa, nigella sativa seeds, salvia miltirrhizae, pan am ginseng, terminally Arjun, hibiscus sabdariffa, basil, chin ease cat claws, ginger, and again can be used to treat hypertension with the aid of reducing factors such as high sodium intake, low potassium, sodium, calcium intake, oxidative stress, genetic factor, overweight, excessive alcohol consumption, RAAS, and obstructive sleep apnea etc. This review is a compilation of global analytics of hypertension its etiology and various phytoconstituents used for the management of hypertension.

Keywords: Hypertension, disease management, phytoconstituents, blood pressure.

1. INTRODUCTION

Hypertension (HTN) is, primary cause of sickness and deaths worldwide affecting above 1.2 billion people worldwide [1]. According to WHO, hypertension usually called raised blood pressure, is a medical condition when the vascular system is under strain? A rise in blood pressure increases the burden of kidney illness and cardiovascular disease (CVD), also leading contributor to several cardiac risks. Because of the prevalence of CVD, it is the leading cause of sickness and mortality [2]. HTN is a dangerous disorder that dramatically raises the risk of numerous cardiovascular diseases, which is why it is also known as the "silent killer"[3]. HTN is roughly characterized as Essential & Secondary hypertension. Essential HTN is multifactorial, with no clearly identifiable etiology. Secondary HTN can be brought on by a variety of particular conditions (comorbid illnesses), including those that affect the endocrine system, the heart, or the arteries, Cushing's syndrome, Coarctation of the aorta, chronic renal disease, sleep apnea with obstruction, Pheochromocytoma, Primary aldosterone's, Reno vascular disease, and thyroid disease [4]. The most of situations —about 95%— considered to be essential hypertension. The other 5% of instances are classified as secondary hypertension, which is brought on by a number of illnesses, such as renal disease [5].

Table 1. Subtypes of Hypertension

Primary Hypertension	Labile Hypertension
Secondary Hypertension	Masked Hypertension
Malignant Hypertension	Nocturnal Hypertension
Isolated systolic Hypertension	White coat Hypertension
Resistant Hypertension	Asthma Hypertension
Pre-eclampsia Hypertension	Paediatric Hypertension
Postpartum Hypertension	Renovascular Hypertension
Gestational Hypertension	Pulmonary Hypertension

2. RECENT UPDATE ON THE GLOBAL STUDY OF HTN

According to a global study of HTN statistics, 317.2 million of Indian males and 321.9 million of Indian women over 1.54 billion population had HTN in 2005. Over 1.26 billion people, 405.7 million men and 399.4 million women, had hypertension in 2008 [6]. In 2010, 6 billion individuals, or 31% of adults worldwide, had hypertension [7]. HTN is acknowledged as the main stroke hazard factor. Stroke, deadly and debilitating cerebrovascular illness. Stroke is responsible for roughly 5.7 million fatalities globally, with 87% of these fatalities taking place in developing countries and medium incomes nations. Recent research conducted in India revealed a prevalence rate of stroke of 471.58/100,000 persons [8]. HTN is accountable for 18.5 billion of all stroke incidences and 70% of stroke fatalities in India (figure 1). Since only 47% of hypertensive women and 38% of hypertensive men got antihypertensive treatment. 23% of the women and 18% of the men attained control blood pressure. Control rates among racial and ethnic minorities are very low [9].

The BP is frequently represented as a ratio of systolic to diastolic pressure, HTN expressed as either a (SBP) more than 140 mmHg or (DBP) more than 90 mmHg. [10]. In 2019, Hypertension was responsible for over 20% of all deaths [11]. Stroke (6 million deaths) and ischemic heart disease (9 million deaths) , In 2021, 20.5 million individuals died as a result of a CVD[12] .

According to current Indian research, uncontrolled hypertension accounts for 52% of mortality. Currently, 31% of the country's population is HTN-positive, 37% of Indians are aware of their hypertension condition, 30% of Indians are getting treated for hypertension. yet only 15% hypertensive Indians have their BP under control [13]. Studies conducted in 2022–2023 indicate that 119.6 million people worldwide have hypertension. There are still about 30% of Indians who are affected by it.

	Rural %	Urban%
North India	14.5%	28.8%
East India	31.7%	34.5%.
West Indian	18.1%	35.8%
South Indian	21.1%	31.8%

	Awareness of HTN	Treated / Under Treatment	Achieved / Under control
18-49 Years	44.7%	13.3%	7.9%
15-54 Years	21.5 %	12.6 %	6.1 %
18-69 Years	27.9%	14.5%	12.6%

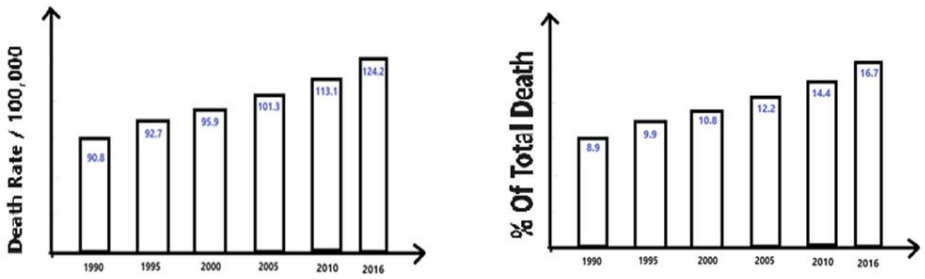

Figure 1. The Global Burden of Diseases, the death rate/ 100,000 people and % of total deaths.

3. ANALYTICAL TECHNIQUES

Normal blood pressure regulation depends on the harmony between peripheral resistance (PR) and outflow from the heart. BP = PR x Output [14]. Blood pressure is always checked when you are at rest and on various days. You are deemed to have high blood pressure if several of the readings are too high either Systolic or Diastolic. In medicine, high blood pressure is referred to as "hypertension"[15].

A sphygmomanometer is a blood pressure measuring instrument. To avoid errors, verify your arm position and always start your reading meters at the zero mark of the lower meniscus. Otherwise, mercury sphygmomanometers were seen as being inaccurate [16].

3.1 AMBULATORY BPM

ABPM is a method of assessing & controlling hypertension, comparing and contrasting readings etc. ABPM readings provide more information about cardiovascular and cerebrovascular risk than standard blood pressure measurements. All patients with elevated blood pressure, especially those suspected of having white-coat or concealed hypertension, should undergo ABPM [17]. Blood pressure measurements can be gathered numerous times per hour across a 24-hour period utilizing ABPM. when the patient is engaging in regular activities [18].

3.2 HOME BPM

HBPM is a self-analysis approach. It gives patients a better grasp of HTN management. Additionally, it capable of doing a number of readings throughout time. Emptying the bladder, not drinking anything with caffeine for 30 minutes prior to taking the measurement, and using an upper-arm cuff that fits properly on a bare arm, take a five-minute break before collecting the measurement, recommended practices for HBPM include not chatting while the reading is being taken. [19]. According to worldwide blood pressure recommendations, it is recommended to gather a minimum of two readings at minimum one-minute intervals. [20].

3.3 OFFICE BPM

OBPM is a method employed in the office with a digital sphygmomanometer that, due to its ease of use, has replaced the mercury sphygmomanometer, ABPM, on the other hand, is a technology that monitors blood pressure 24 hours a day.

3.4 AUTOMATED OFFICE BPM

The patient's blood pressure is taken using the AOBP test after a five-minute snooze, Then, while the patient is laying happily alone, a completely automated series of five measures is performed during a five-minute period [21].

3.5 DIGITAL BPM

If you move when using DBP, it won’t be as exact. Although they may also be worn on the finger or upper arm, DBP monitors are most frequently worn on the wrist and are activated by pushing a button. Inaccurate readings can occasionally be produced by digital meters, which is always a possibility, especially in people who have specific heart rhythm difficulties or arteries that have hardened due to arteriosclerosis. [15].

4. ETIOLOGY

4.1 HIGH SODIUM IONS INTAKE

Our diet's major source of sodium is salt. Consuming too much sodium has been linked to high blood pressure as indicated in Figure 2. Edible salt is made up of sodium ($Na^{+)}$ and chloride (Cl^{-}). Water follows sodium into the stream as it enters, this raises the pressure by increasing the flow of fluid into the vessels.

Contrarily, consuming less salt lowers mortality and morbidity from cardiovascular disease as well as blood pressure and the likelihood of developing hypertension. In India, additional salt intake accounts for greater than 75 % of total sodium consumption [22]. The average Indian eats roughly 10 gram of salt per day, which is greater than WHO recommended intake of 5g (2000 mg of Na^{+}/ day) [23]. Flow through the membrane is determined by the Conc. Gradient, and intercellular to extracellular diffusion is promoted.

Among participants in the National &Nutrition Examination Survey I, throughout the course of an average 19 years of follow-up, heart failure (HF) has been strongly associated with greater dietary salt consumption [24]. Ambulatory Heart Failure, coronary artery disease, HTN, and heart attacks. More importantly, a 23% higher risk of stroke is linked to higher salt intake, as is a 17% higher risk of all cardiovascular disease. Heart failure (HF) accounts for around 90% of cases.

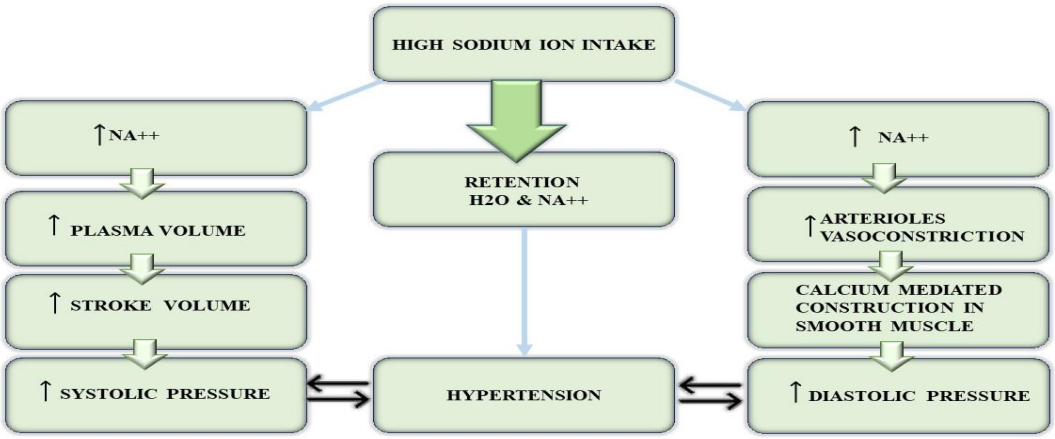

Figure 2. Salt consumption and hypertension's relationship

4.2 GENETIC FACTOR

The genetics of hypertension is complicated; there isn't a single gene that is understood to be significantly influential. Instead, numerous genes, each with little effect, respond to different environmental stimuli that might impact blood pressure. The hereditary component of blood pressure variance, or heritability estimates, ranges from 30 to 50% [25]. For decades, people have argued about whether hypertension is an inherited condition, there is a hereditary predisposition to hypertension. Hypertensive people are more prone to develop it themselves, especially if both of their parents have it. However, the inheritance pattern is unknown.

4.3 SLEEP APNEA SYNDROME

The development of hypertension is attributable in part to obstructive sleep apnea (OSA). Because of recurring nocturnal hypoxia, hypoxemia, hypercapnia, and elevated sympathetic activity, sleep apnea syndrome, a set of potentially hazardous sleep-related breathing disorders, is recognized as one of the most important secondary hypertensions [26]. 35% of patients with basic HTN and up to 80% of those with drug-resistant HTN have OSA.

In particular, neuroinflammation is a defining feature of OSA-induced hypertension [27]. if experiencing recurring or irregular bouts, pause breathing for 10 seconds and complete a polysomnography test. Occupying the airways during sleep causes OSA. imbalance in the brain's respiratory centre is known as CSA. CPAP, behavioural adjustment, lifestyle modifications, mandibular advancement devices, and surgical procedures are some of the current forms of therapy. Despite the fact that the clinical manifestation of OSA appears to be innocuous If untreated, it can raise the risk of CVD, including myocardial infarction, stroke, hypertension, and atrial fibrillation. This risk is attributed to multifactorial factors such as systemic inflammation, metabolic dysfunction, endothelial dysfunction, and hyperactive sympathetic dysfunction. Few of the factors responsible for HTN are depicted in figure 4. Approximately 425 million people globally have moderate OSA, while 936 million people worldwide have mild OSA, according to recent research [28].

4.4 RENIN-ANGIOTENSIN ALDOSTERONE SYSTEM ABNORMALITIES

The aberrant activation of the RAAS is what leads to HF, chronic HTN & RAAS. The vital human body system known as the renin-angiotensin-aldosterone system (RAAS) controls extracellular volume, arterial blood pressure, and plasma sodium concentration. Renin (also known as angiotensinogen's) is released by the kidney's granular cells [33]. RAAS inhibitors, such as ACE inhibitors & ARBs,are frequently used to treat high BP since there is a significant relationship between HTN an overactive RAAS [29] Clinically, because both ACE inhibitors and ARBs are used to treat CVD, decrease BP, prevent stroke, and treat the symptoms of HF, they may appear to be the same. [30].

4.5 OXIDATIVE STRESS

The pathophysiology of HTN is linked to OS represent with Figure 3. A change in the ratio of the generation of ROS (free radicals) to antioxidant defence is referred to as oxidative stress. Reduced NO bioavailability is one of the variables associated in pathophysiology. Redox imbalance has been defined in hypertension patients as an elevated level of oxidative stress [31]. Alternately, this redox imbalance can be induced by a decrease in NO's antioxidant capacity, which happens as a result of a decline in NO production. Oxidative stress appears to be a significant contributor to hypertension in each of these cases [32].

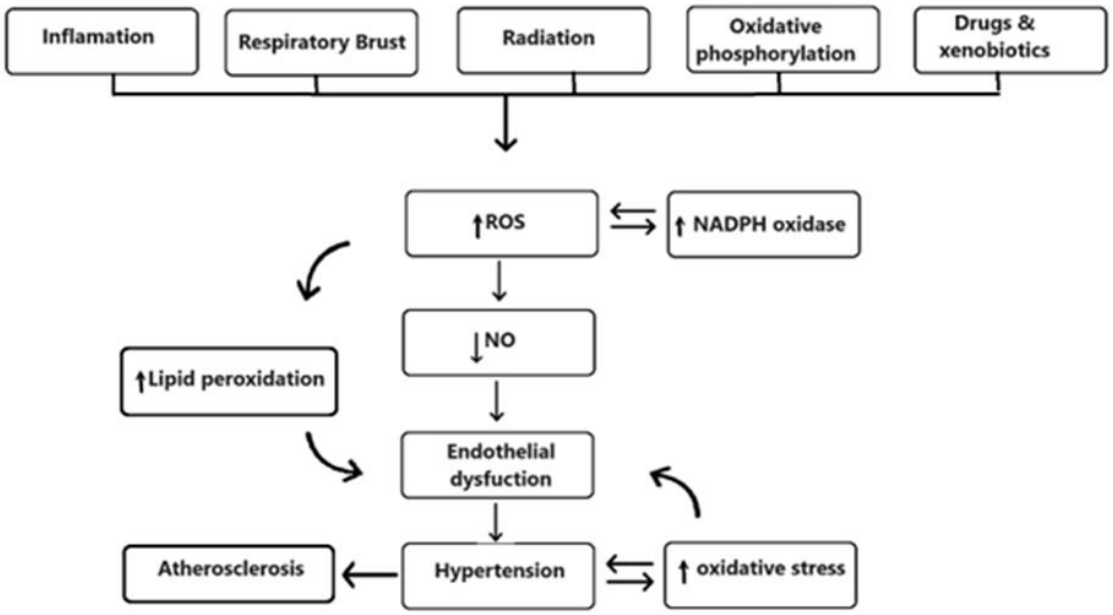

Figure 3. ROS, Oxidative stress induced hypertension

Angiotensin-II-induced hypertension is first reduced by redox-dependent signal cascades and ROS produced by NADPH oxidase [33]. SOD, catalase (Cat), (GPx) are the three primary endogenous antioxidant enzymes that neutralize ROS [34]. Excessive quantities of ROS, such as peroxides, superoxide hydroxyl radical, etc., can harm nucleic acids, membrane lipids, and cellular proteins, impairing cellular function and damaging the myelin sheath of neurons. OS, which is connected to HTN, might begin as a result of chronic inflammation. Anti-inflammatory drugs may somewhat lower systolic BP in those with hypercholesterolemia. Patients are more vulnerable to the effects if their blood pressure is greater. The removal of oxidative stress from biological systems is accomplished by antioxidants. Lipoic acid, glutathione, -arginine, and coenzyme Q10 are a few examples of nonenzymatic antioxidant compounds that are all naturally occurring antioxidants [35].

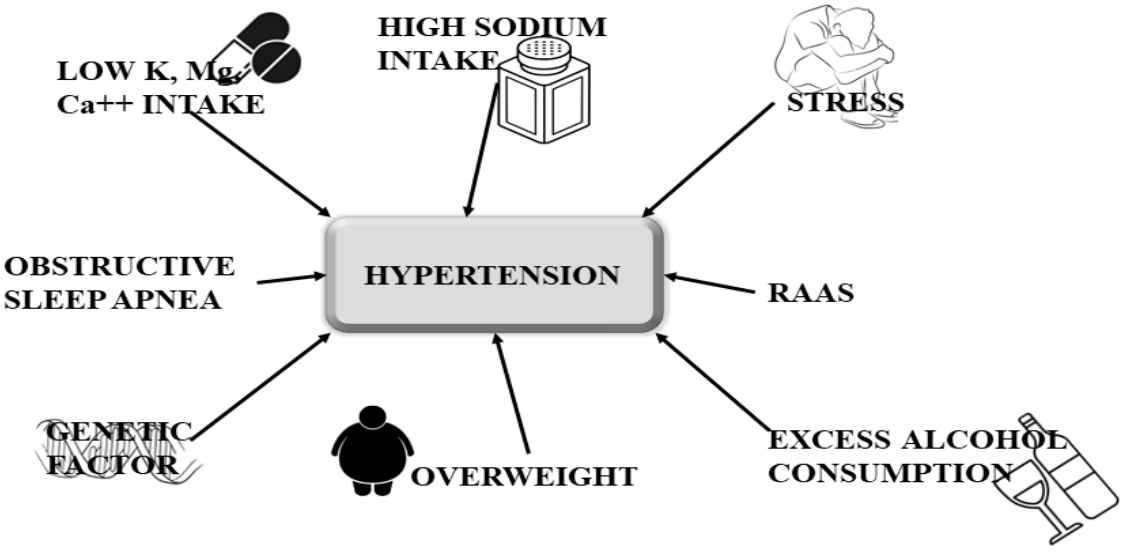

Figure 4. Few factors responsible for Hypertension

5. ROLE OF PHYTOCONSTITUENTS FOR THE MANAGEMENT OF HTN

The management of hypertension is greatly aided by antihypertensive phytoconstituents, which are bioactive substances present in plants that have the ability to reduce blood pressure. Figure 5 illustrates the range of disorders that can be treated with these natural compounds. Active phytochemicals are active substances such as flavonoids, glycosides, terpenes, and alkaloids that act on the target site and demonstrate therapeutic effect, and their structures are given below. ACE inhibitors, beta blockers, calcium channel blockers, vasodilators, angiotensin-2 antagonists, and diuretics are medically recommended drugs. nonetheless, these exhibit side effects. Phytochemicals may be more successful in treating these disorders and have less adverse effects than current drugs. which is why we must replace medicines with phytoconstituents and their bioactive. According to studies conducted on humans, there is evidence that allium species and their active components reduce the risk of diabetes and cardiovascular disease, bolster the immune system to prevent infections, and possess qualities that include antibacterial, antifungal, anti-aging, and anti-cancer [36]. The figure 6a and b showed the chemical structure of few commonly used phytoconstituents to treat the HTN.

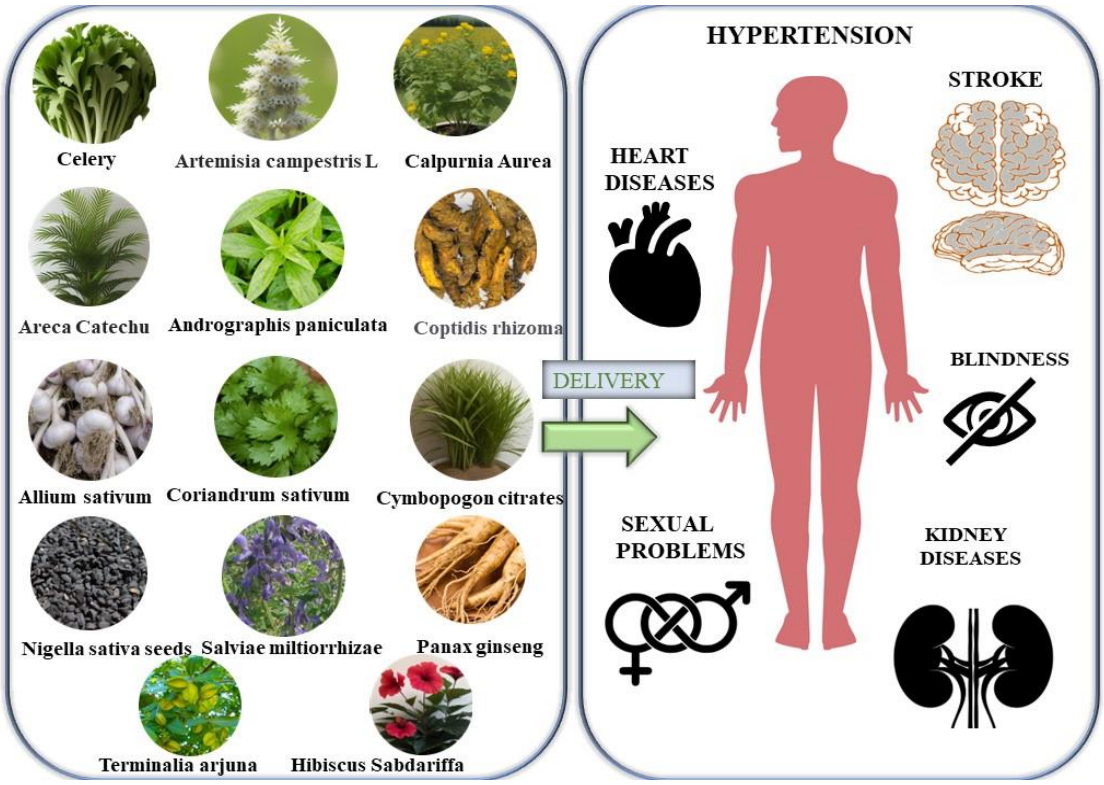

Figure 5. Phytoconstituent targets for hypertension management

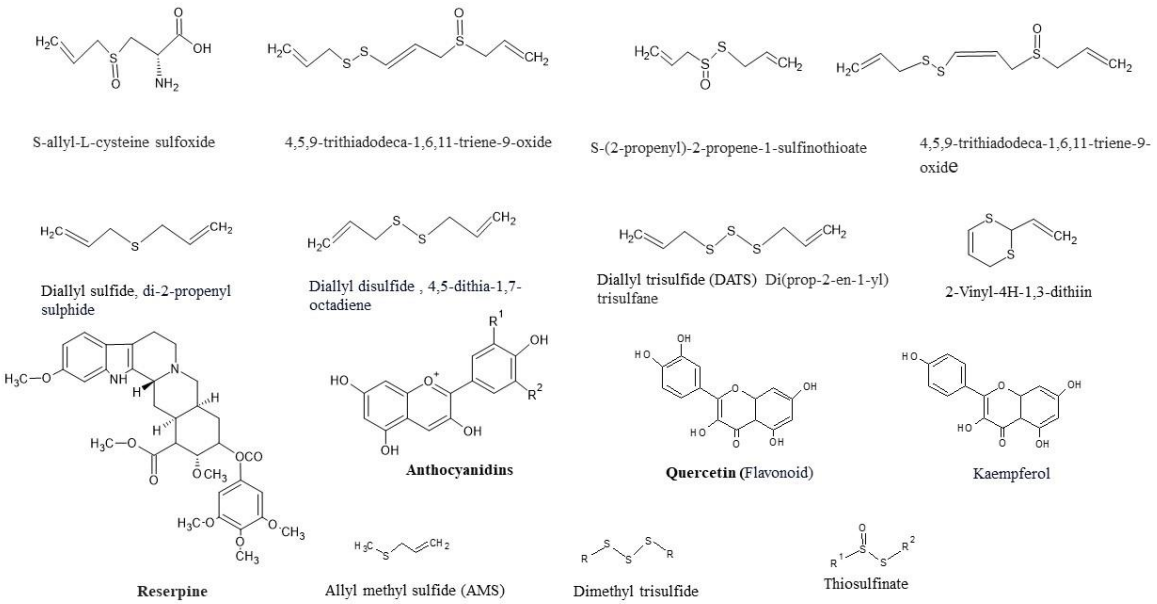

Figure 6a. Chemical structure of commonly used phytoconstituents

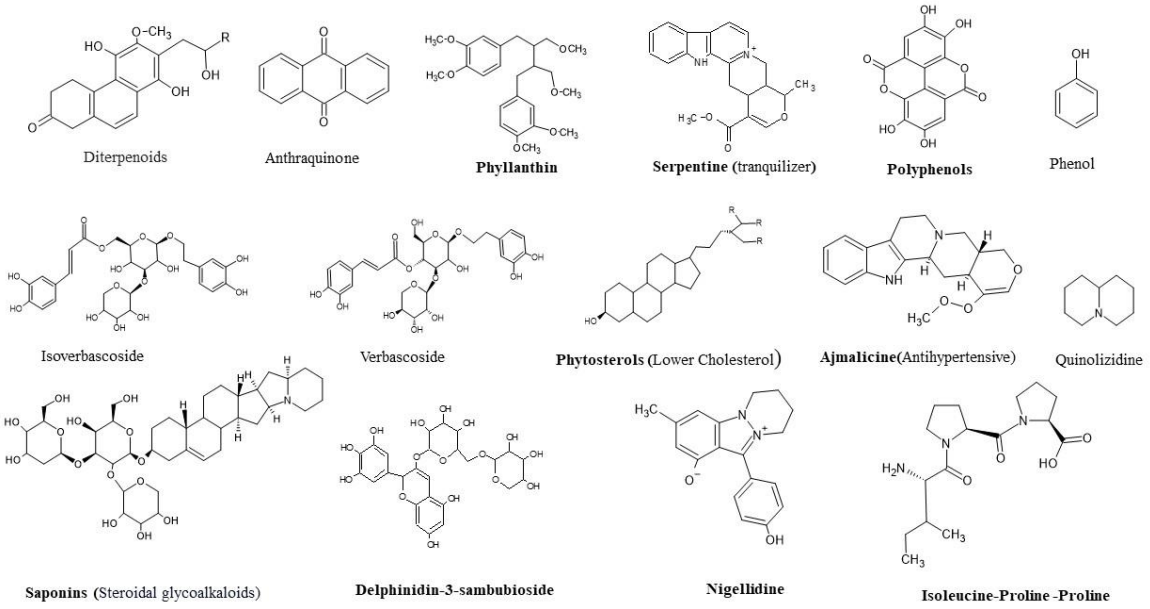

Figure 6b. Chemical structure of commonly used phytoconstituents

The most well-known medications made from medicinal plants in modern medicine are artemisinin, quinine, and emetine, all of which are widely marketed. Due to their amazing biological activity, secondary metabolites from plants have historically been used in traditional medicine, and it is these molecules that are responsible for the therapeutic actions of plants see table 2 [37].

Table 2. Commonly used Phytoconstituents for the management of Hypertension

Common name	Scientific name	Family	Phytoconstituents	Medicinal use
Basil	Ocimum basilicum	Lamiaceae	Vitamin A, vitamin C, calcium, phosphorus, and pigments such as β-carotene.	Combats the common cold, respiratory issues, soothes irritated skin, lessens heart issues, and lowers stress.
Parsley	Petroselinum crispum	Apiaceae	Limonene, myristicin, phthalides, coumarins, flavonoids, and volatile oil.	Applications include bladder infection, constipation, kidney stones, and GI disorders.
Celery seeds	Apium graveolens	Apiaceae	Caffeic acid, apigenin, ocimene, bergapten, isopimpinellin, beta-selinene, and limonene.	Capacity to conceive, anti-hypertensive, and anti-cancer qualities.
Chinese cat's claw	Uncaria rhynchophylla	Rubiaceae	Tannins, quinovic acid, sterols, oxindole.	Enhances immunity, relieves rheumatoid arthritis, HTN, etc.
Water hyssop	Bacopa monnieri	Plantaginaceae	nicotinine, herpestine, bacosides A and B, saponins A, B and C, triterpenoid saponins, stigmastanol, β-sitosterol, betulinic acid, D-mannitol, stigmasterol, α-alanine, aspartic acid, glutamic acid, and serine and pseudojujubogenin	Protects against ulcers, improves liver health, improves cognition, and has anti-asthmatic and anti-diabetic properties.
Thyme	Thymus vulgaris	Lamiaceae	Thymol, p-cymene, linalool, carvacrol,	Fighting acne vulgaris, boosting mood, aromatherapy.
Cinnamon	Cinnamomum verum	Lauraceae	Eugeno, linalool, Beta-caryophyllene, cinnamaldehyde, cinnamyl acetate	Protect against heart problems, improve sensitivity to insulin, effective on neurodegenerative diseases.
Ginger	Zingiber officinale	Zingiberaceae.	6- gingerol, 6-shogaol, 6-paradol	Treat persistent dyspepsia, morning sickness, osteoarthritis, and hypertension.

Cardamom	Elettaria cardamomum	Zingiberaceae	α-terpineol, 1, 8-cineole, 1, 8-cineole and α-terpineol 38 α-terpinyl acetate, 1, 8-cineole, sabinene, linalyl acetate.	Diuretic properties, lower blood pressure, contain cancer fighting compounds.
Ajwain	Trachyspermum ammi	Apiaceae	β-pinene, α-terpinene, α-pinene, p-cymene, γ-terpinene	Potentially use in respiratory problems, diabetes, migraine, arthritis, diarrhoea.
Green oat	Avena sativa	Poaceae	β-glucan, neokestose, bifurcate, neobifurcose, and kestose	For cancer, dry skin, and hypertension.
Flaxseed	Linum usitatissimum	Linaceae	*α*-linolenic, palmitic acid, phosphatidylinositol, lysophosphatidylcholine	Used for constipation, hypertension, high cholesterol, lumps in kidney.
Lotus	Nelumbo nucifera	Nelumbonaceae	(E)-Sinapate-4-O-β-D-glucopyranoside, 3-Hydroxymegastigm-7-en-9-one.	Antioxidant properties, fight inflammation, antibacterial, lower sugar level
Golden seal	Hydrastis canadensis	Ranunculaceae	sideroxylin, 8-desmethyl-sideroxylin, hydrastinine, neochlorogenic acid	Helps in the treatment of common cold, UTI, CS, hyperuricemia.
Black cohosh	Actaea racemose	Ranunculaceae	N-Feruloyl arginine; N-Feruloyl tyramine glucoside, β-Carbolines; γ-Guanidinobutyric acid	Reduce musculoskeletal pain, support liver function, tonify the kidney and uterus.
Hawthorn	Crataegus	Rosaceae	Vitexin, procyanidins, hyperoside, D-isoquercitrin	Antihypertensive, lower total cholesterol level, treat health problem.
King of bitter	Andrographis paniculata	Acanthaceae	Deoxyandrographolide, tetramethyoxyflavanone,	Prevent infections, prevent cancer, antioxidant, anti-inflammation, treat diabetes.
Black -Jack	Bidens Pilosa	Asteraceae	7-Phenylhept-2-ene-4,6-diyn-1-yl acetate, Luteolin 7-O-β-d-glucopyranoside, β-trans-Ocimene	Reduce inflammation, battles microbes and fungi, antioxidant defence, supporting digestive health
Coriander	Coriandrum sativum	Apiaceae	cis-dihydrocarvone, β-carotene, Trideca-1,11-diene-3,5,7,9-tetrayne.	Lower blood sugar, immune booting anti-oxidant, protect skin.

6. CONCLUSION

Natural antihypertensive phytoconstituents exert their effects through diverse mechanisms. These mechanisms encompass vasodilation, inhibition of angiotensin-converting enzyme (ACE), reduction of oxidative stress, and modulation of ion channels involved in the regulation of blood pressure. Additionally, these phytoconstituents possess properties such as vasodilation, ACE inhibition, antioxidant properties, and diuretic effects. Antihypertensive compounds found in nature have the potential to cause fewer side effects than synthetic drugs. Moreover, they may offer other health benefits due to their antioxidant and anti-inflammatory properties. Nevertheless, it's important to note that more research is required to determine the long-term effectiveness, safety, and recommended dosages of these plant-based substances for treating hypertension.

7. CONSENT FOR PUBLICATION

Not applicable.

8. FUNDING

None.

9. CONFLICT OF INTEREST

The authors declare no conflicts of interest, financial or otherwise.

10. ACKNOWLEDGMENTS

Declared none.

11. REFERENCE

1. Song JJ, Ma Z, Wang J, Chen LX, Zhong JC. Gender Differences in Hypertension. J Cardiovasc Trans Res. 2020 Feb;13(1):47-54. Doi 10.1007/s12265-019-09888-z. E pub 2019 May 1. PMID: 31044374.
2. Krishna A, Murali S, Moran AE, Saxena A, Gill SS, Hering D, Kaur P. Understanding the Role of Staff Nurses in Hypertension Management in Primary Care Facilities in India: A Time-Motion Study. Prev Chronic Dis. 2023 May 18;20: E39. Doi 10.5888/pcd20.220232. PMID: 37200503; PMCID: PMC10199685.
3. Kjeldsen SE. Hypertension and cardiovascular risk: General aspects. Pharmacol Res. 2018 Mar; 129:95-99. Doi 10.1016/j.phrs.2017.11.003. E pub 2017 Nov 7. PMID: 29127059.
4. G. Behrens, M.F. Leitzmann The association between physical activity and renal cancer: systematic review and meta-analysis
   Br J Cancer, 108 (2013), pp. 798-811
5. Rubin LJ. Primary pulmonary hypertension. *N Engl J Med.* 1997;**336**(2):111–7.

6. Anchala R, Kannuri NK, Pant H, Khan H, Franco OH, Di Angelantonio E, Prabhakaran D. Hypertension in India: a systematic review and meta-analysis of prevalence, awareness, and control of hypertension. J Hypertension. 2014 Jun;32(6):1170-7. Doi 10.1097/HJH.0000000000000146. PMID: 24621804; PMCID: PMC4011565.

7. Mills KT, Stefanescu A, He J. The global epidemiology of hypertension. Nat Rev Nephrol. 2020 Apr;16(4):223-237. Doi 10.1038/s41581-019-0244-2. E pub 2020 Feb 5. PMID: 32024986; PMCID: PMC7998524.
8. Pathak A, Kumar P, Pandit AK, Chakravarty K, Misra S, Yadav AK, Prasad K. Is Prevalence of Hypertension Increasing in First-Ever Stroke Patients? A Hospital-Based Cross-Sectional Study. Ann Neurosci. 2018 Dec;25(4):219-222. Doi 10.1159/000487066. E pub 2018 Jul 25. Erratum in: Ann Neurosci. 2018 Dec;25(4):278. PMID: 31000960; PMCID: PMC6470354.
9. Lauder L, Mahfoud F, Azizi M, Bhatt DL, Ewen S, Kario K, Parati G, Rossignol P, Schlaich MP, Teo KK, Townsend RR, Tsioufis C, Weber MA, Weber T, Böhm M. Hypertension management in patients with cardiovascular comorbidities. Eur Heart J. 2023 Jun 20;44(23):2066-2077. Doi 10.1093/eurheartj/ehac395. PMID:36342266.
10. Romano S, Rigon G, Albrigi M, Tebaldi G, Sartorio A, Cristin L, Burrei G, Fava C, Minuz P. Hypertension, uncontrolled hypertension and resistant hypertension: prevalence, comorbidities and prescribed medications in 228,406 adult Resident in urban areas. A population-based observational study. Intern Emerg Med. 2023 Aug 2. Doi 10.1007/s11739-023-03376-8. E pub ahead of print. PMID: 37530942.
11. Deussen A, Kopaliani I. Targeting inflammation in hypertension. Curr Opin Nephrol Hypertension. 2023 Mar 1;32(2):111-117. Doi 10.1097/MNH.0000000000000862. E pub 2022 Dec 7. PMID: 36476561; PMCID: PMC9872860.
12. The World Heart Federation is a non-governmental organization based in Geneva, Switzerland, formed in 1978. WHF is recognized by the World Health Organization as its leading NGO partner in cardiovascular disease prevention
13. The Indian Express Limited is an Indian news media publishing company. It publishes several widely circulated dailies, including The Indian Express and The Financial Express in English, the Loksatta in Marathi and the Jansatta in Hindi.
14. Delong C, Sharma S. Physiology, Peripheral Vascular Resistance. [Updated 2023 May 1]. In: Stat Pearls [Internet]. Treasure Island (FL): Stat Pearls Publishing; 2023 Jan-. Available from:
15. InformedHealth.org [Internet]. Cologne, Germany: Institute for Quality and Efficiency in Health Care (IQWiG); 2006-. What is blood pressure and how is it measured? 2010 Jun 24 [Updated 2019 May 23]. Available from:
16. A'Court C, Stevens R, Sanders S, Ward A, McManus R, Heneghan C. Type and accuracy of sphygmomanometers in primary care: a cross-sectional observational study. Br J Gen Practice. 2011 Sep;61(590) e 598-603. Doi 10.3399/bjgp11X593884. PMID: 22152749; PMCID: PMC3162183.

17. Kario K, Hoshide S, Chia YC, Buranakitjaroen P, Siddique S, Shin J, Turana Y, Park S, Tsoi K, Chen CH, Cheng HM, Fujiwara T, Li Y, Huynh VM, Nagai M, Nailes J, Sison J, Soenarta AA, Sogunuru GP, Sukonthasarn A, Tay JC, Teo BW, Verma N, Wang TD, Zhang Y, Wang JG. Guidance on ambulatory blood pressure monitoring: A statement from the HOPE Asia Network. J Clin Hypertension (Greenwich). 2021 Mar;23(3):411-421. Doi 10.1111/jch.14128. E pub 2020 Dec 14. PMID: 33319412; PMCID: PMC8029567.
18. Turner JR, Viera AJ, Shimbo D. Ambulatory blood pressure monitoring in clinical practice: a review. Am J Med. 2015 Jan;128(1):14-20. Doi 10.1016/j.amjmed.2014.07.021. E pub 2014 Aug 12. PMID: 25107387; PMCID: PMC4877527.
19. Weinfeld JM, Hart KM, Vargas JD. Home Blood Pressure Monitoring. Am Fam Physician. 2021 Sep 1;104(3):237-243. Erratum in: Am Fam Physician. 2022 Feb 1;105(2):115. PMID: 34523884.
20. Eguchi K, Kuruvilla S, Ogedegbe G, Gerin W, Schwartz JE, Pickering TG. What is the optimal interval between successive home blood pressure readings using an automated oscillometric device? J Hypertension. 2009 Jun;27(6):1172-7. Doi 10.1097/hjh.0b013e32832a6e39. PMID: 19462492; PMCID: PMC2941726.
21. Armstrong D, Matangi M, Brouillard D, Myers MG. Automated office blood pressure - being alone and not location is what matters most. Blood Press Monit. 2015 Aug;20(4):204-8. [
22. He J, Ogden LG, Bazzano LA, Vupputuri S, Loria C, Whelton PK. Dietary sodium intake and incidence of congestive heart failure in overweight US men and women: first National Health and Nutrition Examination Survey Epidemiologic Follow-up Study. Arch Intern Med. 2002 Jul 22;162(14):1619-24. doi: 10.1001/archinte.162.14.1619. PMID: 12123406.
23. Johnson C., Praveen D., Pope A., Raj T.S., Pillai R.N., Land M.A., Neal B. Mean population salt consumption in India: A systematic review. *J. Hypertension.*2017;35:39.
24. Nijst P, Verbrugge FH, Grieten L, Dupont M, Steels P, Tang WHW, Mullens W. The pathophysiological role of interstitial sodium in heart failure. J Am Coll Cardiol. 2015 Feb 3;65(4):378-388. Doi 10.1016/j.jacc.2014.11.025. PMID: 25634838.
25. Kunes J, Zicha J. The interaction of genetic and environmental factors in the Etiology of hypertension. Physiol Res. 2009;58 Supply 2S33-S42. Doi 10.33549/physiolres.931913. PMID: 20131935.
26. Ayyaswamy S, Shi H, Zhang B, Bryan RM Jr, Durgan DJ. Obstructive Sleep Apnoea-Induced Hypertension Is Associated with Increased Gut and Neuroinflammation. J Am Heart Assoc. 2023 Jun 6;12(11)e029218. Doi 10.1161/JAHA.122.029218. E pub 2023 Jun 1. PMID: 37260032; PMCID: PMC10381979.
27. Mashaqi S, Gozal D. Obstructive Sleep Apnoea and Systemic Hypertension: Gut Dysbiosis as the Mediator? J Clin Sleep Med. 2019 Oct 15;15(10):1517-1527. Doi: 10.5664/jcsm.7990. PMID: 31596218; PMCID: PMC6778338.

28. Arredondo E, DeLeon M, Masozera I, Panahi L, Udeani G, Tran N, Nguyen CK, Atphaisit C, de la Sota B, Gonzalez G Jr, Liou E, Mayo Z, Nwosu J, Shiver TL. Overview of the Role of Pharmacological Management of Obstructive Sleep Apnoea. Medicina (Kaunas). 2022 Feb 2;58(2):225. Doi: 10.3390/medicina58020225. PMID: 35208549; PMCID: PMC8874508.
29. Patel S, Rauf A, Khan H, Abu-Izneid T. Renin-angiotensin-aldosterone (RAAS): The ubiquitous system for homeostasis and pathologies. Biomed Pharmacother. 2017 Oct; 94:317-325. Doi 10.1016/j.biopha.2017.07.091. E pub 2017 Jul 31. PMID: 28772209.
30. Atlas SA. The renin-angiotensin aldosterone system: pathophysiological role and pharmacologic inhibition. *J Manag Care Pharm.*2007; 13:9–20.
31. Betteridge DJ. What is oxidative stress? Metabolism. 2000 Feb;49(2 Supply 1):3-8. Doi 10.1016/s0026-0495(00)80077-3. PMID: 10693912.
32. A.S. Hendre, A.K. Shariff, S.R. Patil, P.P. Durgawale, A.V. Sontakke, A.N. Suryakar Evaluation of oxidative stress and anti-oxidant status in essential hypertension J Indian Med Assoc, 111 (2013), pp. 377-381.
33. Redon J, Oliva MR, Tormos C, Giner V, Chaves J, Iradi A, et al. Antioxidant activities and oxidative stress byproducts in human hypertension. *Hypertension.* 2003;41,1096–101.
34. Touyz RM. Reactive oxygen species and angiotensin II signalling in vascular cells: Implications in cardiovascular disease. *Braz J Med Biol Res.* 2004;37,126373.
35. Pizzino G, Irrera N, Cucinotta M, Pallio G, Mannino F, Arcoraci V, Squadrito F, Altavilla D, Bitto A. Oxidative Stress: Harms and Benefits for Human Health. Oxid Med Cell Longev.2017;2017:8416763. Doi 10.1155/2017/8416763. E pub 2017 Jul 27. PMID: 28819546; PMCID: PMC5551541.
36. Rahman K. Historical perspective on garlic and cardiovascular disease. *J. Nutr.* 2001; 131:977S–979S. Doi10.1093/in/131.3.977S.
37. Hidayathula S, Chandra KK, Chandrashaker KR. Phytochemical evaluation and antibacterial activity of Pterospermum diversifolium blume. *Int J Pharma Sci.* 2011; 3:165–167.
38. Verma T, Sinha M, Bansal N, Yadav SR, Shah K, Chauhan NS. Plants Used as Antihypertensive. Nat Prod Bio prospect. 2021 Apr;11(2):155-184. Doi: 10.1007/s13659-020-00281-x. E pub 2020 Nov 11. PMID: 33174095; PMCID: PMC7981375.