Pathophysiology and risk factors related to hypertension and its cure using herbal drugs

Hipertansiyonun fizyopatolojisi, ilişkili risk faktörleri ve bitkisel ilaçlarla tedavisi

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SUMMARY

Hypertension is a term used to denote chronic disease that is related to high blood pressure due to the exertion of force of blood against the walls of arteries. It can be categorized into two types i.e. primary and secondary hypertension on the basis of variation from systolic/diastolic blood pressure of 120/80 mmHg. There are several risk factors contributing in the onset and severity of hypertension including changing life style pattern, sodium and potassium content, alcohol consumption, calcium deficiency, obesity etc. The disease can be prevented by the use of drugs but excessive use of antihypertensive is related to different side effects. In such instances, use of herbal drugs is promoted as these act on the same mechanism to prevent hypertension, as are therapeutic agents as well as are having metabolism enhancing effects. In this review, an attempt has been made to summarise the pathophysiology of hypertension, factors contributing in the onset and widespread occurrence of disease along with role of herbal drugs and formulations used to prevent the risk of disease.

Key words: Hypertension; Pathophysiology; Risk Factors; Herbal Drugs.

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Hypertension and herbal drugs

INTRODUCTION

Hypertension is a medical term used to denote high blood pressure. Scientifically, blood pressure refers to force of blood exerted against the walls of arteries during its circulation from the heart throughout the body. The normal blood pressure usually has systolic/diastolic blood pressure of 120/80 mm Hg or lowers than this. High blood pressure refers to a condition of elevated blood pressure over a time and if systolic/diastolic blood pressure falls in the range of 120/80 and 140/90, the condition is denoted as pre-hypertension [1, 2]. Clinically hypertension is classified into two types: Primary and Secondary. Primary hypertension, also known as essential hypertension, is the most frequent one and accounts for 90-95% incidences related to increasing blood pressure. The etiology of this form is not known and is mainly linked to obesity and family history. Secondary Hypertension, on the other hand, is less frequent with 5-10% incidences and is linked to diseases of central nervous system, kidneys, lungs, vascular and endocrine system [3]. Hypertension usually arises as a result of change in life style patterns including sedentary lifestyle, stress, potassium deficiency (hypokalemia) and sodium sensitivity, obesity, (more than 85% of cases occur in those with a body mass index greater than 25), excessive alcohol intake and vitamin D deficiency. Risk also increases with aging, some inherited genetic mutations, and having a family history of hypertension [4]. However, in certain cases renal artery stenosis, thyroid disorders, chronic kidney disease and sleep disorders also lead to the onset of hypertension. Hypertensive conditions can also lead to other conditions such as congestive heart failure, kidney disease, and blindness. The disease is also referred as silent killer disease as it accounts for 13.5% deaths worldwide. The disease is prevalent worldwide but majority of hypertensive patients belongs to low economic status. The Farmingham study reported that residual life time risk of developing hypertension is approximately 90% in middle aged and elderly persons. According to World Health Statistics report 2012, 33% of Adults has raised blood pressure that causes around half of all deaths from stroke and heart diseases [5]. In Africa, more than 40% of adults suffered from high blood pressure. In India, the prevalence of hypertension is low as compared to worldwide condition with 23.10 per cent men and 22.60 per cent women over 25 years old suffer from hypertension [5]. The increased blood pressure accounted for approximately 51 per cent deaths from stroke and 45 per cent from coronary artery disease in India.

Many health organizations including the American Society of Hypertension, Asian Hypertension League, World Stroke Organization, International Diabetes Federation, and others have endorsed the global call to action for recognizing high blood pressure as a major public health priority. The disease can be prevented by the use of drugs but it has been found that drug intervention need not be the only option for lowering the moderately high blood pressure. The excessive use of antihypertensive is associated with many side effects. Herbal remedies are helpful in most instances in addition to a change in lifestyle that can be sufficient to control or prevent mild or moderately high blood pressure, stress and enhancement of metabolic health. In present review, an attempt has been made to summarize the pathophysiology of hypertension, factors contributing in the onset and widespread occurrence of disease along with role of herbal drugs and formulations used to prevent the risk of disease.

Pathophysiology of hypertension

Hypertension is also known as silent killer disease and is associated with a number of diseases including coronary heart, cerebrovascular and renal diseases. Due to its association with different organs and its severe consequences including myocardial infarctions, strokes and heart failures, it is considered as main contributing factor for morbidity and mortality. In medical terms, hypertension occurs due to disrupted vascular regulation resulting from malfunction of arterial pressure control mechanisms (central nervous system, rennin-angiotensin-aldosterone system (RAAS), extracellular fluid volume).

Generally, blood pressure is the result of cardiac contraction against the vascular contraction and is defined as the product of cardiac output and systemic vascular resistance [6]. The cardiac output is regulated by heart rate and stroke volume that is affected by pre-load, after-load and contractility of left ventricle. The systemic vascular resistance (SVR) refers to the resistance to blood flow offered by all of the systemic vasculature, excluding the pulmonary vasculature. This is sometimes referred as total peripheral resistance (TPR). SVR is affected by humoral and local factors that influence vascular resistance in individual vascular beds. The humoral factors include the balance between the vasoconstrictors and vasodilators including serotonin (platelet derived factors) and nitric oxide (endothelium derived relaxing factors).
Table 1. Main factors involved in the regulation of blood pressure (Foex and Sear, 2004)[7]

<table>
<thead>
<tr>
<th>Regulatory Systems</th>
<th>Factors (Effectors/Modulators)</th>
<th>Functions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurogenic System</td>
<td>Arterial baroreceptors</td>
<td>Vasodilation due to the decreased efferent sympathetic activity occurring as a result of increased afferent impulse.</td>
</tr>
<tr>
<td>Renin-Angiotensin System located in the Juxtaglomerular Apparatus of Kidney</td>
<td>Active octapeptide angiotensin II produced from inactive peptide angiotensin I (formed as a result of cleavage of angiotensin by protease renin)</td>
<td>• Detects the renal perfusion pressure and sodium concentration in distal tubular fluid.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• High angiotensin II concentration suppresses renin secretion.</td>
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<tr>
<td></td>
<td></td>
<td>• Acts on specific angiotensin AT1 and AT2 receptors causing smooth muscle contraction.</td>
</tr>
<tr>
<td>Atrial Granules</td>
<td>Atrial natriuretic peptide (ANP)</td>
<td>• Produces natriuresis, diuresis</td>
</tr>
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<td></td>
<td></td>
<td>• Decrease plasma renin and aldosterone</td>
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<tr>
<td></td>
<td></td>
<td>• Reduction on blood pressure</td>
</tr>
<tr>
<td>Kallikrein Kinin System</td>
<td>Vasoactive peptides (Kinin) especially bradykinin produced due to the action of kallikrein on kininogen</td>
<td>• Regulate renal blood flow</td>
</tr>
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<td></td>
<td></td>
<td>• Regulate sodium and water excretion</td>
</tr>
<tr>
<td>Endothelial Mechanism</td>
<td>Nitric oxide (NO)</td>
<td>• NO mediates vasodilation produced by acetylcholine, bradykinin, sodium nitroprusside and nitrates</td>
</tr>
<tr>
<td></td>
<td>Endothelin</td>
<td>• Vasoconstrictor</td>
</tr>
<tr>
<td>Adrenal Glands</td>
<td>Adrenal steroids including mineralocorticoids and glucocorticoids</td>
<td>• Increase blood pressure due to sodium and water retention</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Increase vascular reactivity</td>
</tr>
<tr>
<td>Renomedullary Interstitial Cells</td>
<td>Medullipin I transformed to medullipin II in the liver</td>
<td>Prolonged hypotensive effect by direct vasodilation, diuretic action and inhibition of sympathetic drive.</td>
</tr>
</tbody>
</table>

The regulatory function of these factors depends on the condition of endothelium i.e. whether it is intact or damaged [7]. In spite of this, there are a number of other mechanisms that regulate the coronary vascular tone including metabolic demands (i.e. hypoxia), neurologic control, and endothelial factors and potential role of adenosine in vasodilation of small and medium sized resistance arterioles [7]. The condition of arterial hypertension is the result of increase in cardiac output, increase in systemic vascular resistance or both. The cause of arterial hypertension is different in different age groups as in youth, it is the result of elevated cardiac output whereas in older group increased SVR and stiffness of vasculature are important [5, 8]. The two major types of hypertension are categorized depending upon the stage of occurrence i.e. primary (essential) hypertension, in which systolic/diastolic pressure is 140/90 mm/Hg or higher in absence of other causes of hypertension (approximately 95% of patients); and Secondary hypertension, which results primarily from renal disease, endocrine disorders, and coarctation of the aorta. Alongwith these two types i.e. primary and secondary hypertension, a third condition i.e. accelerated hypertension might occur due to elevated blood pressure that rapidly threaten one or more of the target organs: the brain, kidney, or the heart. It has been emphasized that increase in diastolic pressure is the outcome of increase in total peripheral resistance due to alterations in the arterioles. However, changes in arteries resulted in the decreased vascular compliance that is related to the increase in systolic and a decrease in diastolic blood pressure [9].

Risk factors related to the development of hypertension

The control of blood pressure is a complex process and is regulated by number of factors as mentioned in Table 1. Hypertension arises as a result of abnormal functions of these factors including neurohumoral, renal, metabolic, race, genetic, and environmental factors that leads to the multifactorial hypothesis of the pathophysiology of hypertension. The pathogenic processes that resulted from the abnormalities in vasculature tone are affected by several factors that act together or independently during the early phases of hypertension. These factors turn neurohumoral systems on and off and produce transient exacerbated alterations in pressure-flow with a hyper responsive cardiovascular system due to altered vascular properties [9]. Giles et al. (2009) mentioned the main risk factors of hypertension including age, alcohol consumption, obesity, low potassium intake, high sodium intake, stress, smoking and family history important one [1]. These risk factors are discussed in the following sections:

The older age groups are more prone to hypertension due to reduced flexibility of blood vessels. Life style patterns including excessive intake of sodium, decreased intake of potassium and
calcium and excess body fats accelerates the hypertension. The presence of excessive sodium in the diet resulted in fluid retention that leads to high blood pressure whereas low potassium in diet increases the sodium in cells due to sodium potassium pump.

Narkiewicz (2006) postulated that obesity particularly the central obesity have been consistently associated with hypertension and increased cardiovascular risk [10]. The excessive deposition of fats in adipose tissue has been implicated in the pathogenesis of different ailments including coronary artery disease, sleep apnoea, stroke, chronic kidney diseases and congestive heart failure [11]. Early phases of obesity are characterized by the increase in renal tubular reabsorption that resulted in increase sodium retention that resulted in the expansion of extracellular-fluid volume [12, 13]. Dorrestein et al. (2012) reported that eventual development of hypertension due to obesity is the result of adipose tissue dysfunction, characterized by enlarged hypertrophied adipocytes, increased infiltration by macrophages and marked changes in secretion of adipokines and free fatty acids that leads to chronic vascular inflammation, oxidative stress, activation of the renin-angiotensin-aldosterone system and sympathetic overdrive, eventually leading to hypertension [14]. The weight loss has been found to result in the significant reduction of hypertension and protect from the risks associated with hypertension by reducing the activity of the renin–angiotensin–aldosterone systems in the circulation and in adipose tissue which makes a major contribution to the blood pressure decrease. Furthermore, weight loss has been shown to improve endothelial function, decrease sympathetic nerve activity and improve baroreflex function [10].

It has been reported that heavy alcohol consumption enhances the risk of hypertension whereas light to moderate alcohol consumption from 1 drink per month to 1 drink per day is associated with significant 8% to 21% reductions in the risk of hypertension. However, the relationship between light-to-moderate alcohol consumption and incident hypertension remains controversial and it has been found that additional adjustment for Body Mass Index (BMI), diabetes, and history of high cholesterol attenuated these risk reductions [15]. The intake of beer, red wine, and white wine between 2 and 7 drinks per week resulted in significant reduction in the risk of hypertension [16, 17]. Alcohol enhances the risk of hypertension due to the stimulation of the sympathetic nervous system and alteration of renin-angiotensin-aldosterone system, induction of cortisol levels and intracellular calcium especially in vesicular smooth muscles, inhibition of nitric oxide, depletion of ions, mediated by changes in electrolyte transport and alteration of insulin resistance [18].

Lifton (1993) reported that genetic approaches to hypertension have the potential to identify many of the primary abnormalities that underlie this disorder [19]. According to Seedat, hypertension is a specific middle age disorder that occurs due to abnormality in single autosomal dominant gene and proposed the hypothesis of incomplete dominance. This hypothesis proposed the existence of three population groups, including groups that lack hypertensive gene, heterozygous form of moderate hypertension resulting from inheritance of the hypertensive gene from one parent, and homozygous groups having severe hypertension resulting from inheritance of the gene from both parents [20]. In animals and humans, the mapping of a number of loci led to the identification of several mutations that contributed in the pathogenesis of disease. Relationship between sodium intake and blood pressure regulation is controlled by a number of genes that ultimately have influence on the hypertension. Renal sodium excretion emerges as a keystone mechanism to regulate the blood pressure level and is affected by α-adducin (ADD1) and aldosterone synthase genes (CYP11B2) gene. The angiotensin converting enzyme (ACE) gene is also important as it act as modulator of renin-angiotensin system (RAS) [21]. Beside the above mentioned genes, the other genes related to the processes linked with renal reabsorption of sodium, calcium and affecting the cardiac output and systemic vascular resistance has influence on the development of hypertension.

Therapies available and potential targets of therapeutic agents

A number of therapeutic drugs are available in order to control the hypertension. These drugs are categorized into different classes depending on the target and their mode of action (Table 2). However, these drugs are having different side effects that make the people rely on the herbal formulations for the treatment of hypertension. Herbal medicines are used by about 75 to 80% of the world population, mainly in developing countries, for primary health care because of their better acceptability with human body and lesser side effects. In the last three decades, a lot of concerted efforts have been channeled into researching the local plants with hypotensive and antihypertensive therapeutic values. The hypotensive
## Table 2. Therapeutics used for the treatment of hypertension (adopted and modified from Foex and Sear, 2004) [6]

<table>
<thead>
<tr>
<th>Therapeutic class</th>
<th>Drugs</th>
<th>Mechanism of action</th>
<th>Common clinical uses</th>
<th>Comments</th>
<th>Examples of adverse drug reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitors</td>
<td>Lisinopril</td>
<td>Inhibits ACE, preventing conversion of angiotensin I to angiotensin II, leading to:</td>
<td>Hypertension</td>
<td>Pharmacokinetics vary widely</td>
<td>Hypotension, Persistent angioedema, Rash, Dry cough</td>
</tr>
<tr>
<td></td>
<td>Enalapril</td>
<td>• reduced peripheral arterial resistance</td>
<td>Ischaemic heart disease</td>
<td></td>
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<td></td>
<td>Ramipril</td>
<td>• aldosterone secretion</td>
<td>Heart failure</td>
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<td></td>
<td>Captopril</td>
<td>• accumulation of bradykinin</td>
<td>Diabetic nephropathy</td>
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<td></td>
<td>Perindopril</td>
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<td>Trandolapril</td>
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<td></td>
<td>Fosinopril</td>
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<td></td>
<td>Quinalapril</td>
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<tr>
<td>Angiotensin II</td>
<td>Candesartan</td>
<td>Antagonist at angiotensin II receptor, leading to:</td>
<td>Hypertension</td>
<td>Pharmacokinetics vary widely</td>
<td>Hypotension, Persistent angioedema, Hyperkalaemia</td>
</tr>
<tr>
<td>receptor blockers</td>
<td>Losartan</td>
<td>• reduced peripheral arterial resistance</td>
<td>Ischaemic heart disease</td>
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<tr>
<td>(ARBs, A2RAs)</td>
<td>Irbesartan</td>
<td></td>
<td>Heart failure</td>
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<td></td>
<td>Valsartan</td>
<td></td>
<td>Diabetic nephropathy</td>
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<td></td>
<td>Olmesartan</td>
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<td></td>
<td>Telmisartan</td>
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<td></td>
<td>Eprosartan</td>
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<tr>
<td>Renin inhibitors</td>
<td>Aliskiren</td>
<td>Directly inhibits renin, which decreases plasma renin activity and inhibits conversion</td>
<td>Hypertension</td>
<td>Metabolized by hepatic CYP4A, leading to interactions</td>
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<tr>
<td></td>
<td></td>
<td>of angiotensinogen to angiotensin I</td>
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<td>Very long half-life</td>
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<td></td>
<td></td>
<td></td>
<td>Relatively new class/drug</td>
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<td>Usually reserved for third line use</td>
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<tr>
<td>Loop diuretics</td>
<td>Furosemide</td>
<td>Blocks the reabsorption of sodium and chloride in kidney tubules (proximal and distal</td>
<td>Resistant hypertension Heart failure Oedema</td>
<td>Quick onset of action</td>
<td>Mild gastrointestinal effects, Hypokalaemia, Hyperglycaemia, Headache, Dizziness</td>
</tr>
<tr>
<td>Thiazide diuretics</td>
<td>Bendrofluamizide</td>
<td>Directly inhibits the mechanism for transport of Na’ from the tubule lumen into the cells of the tubule wall, and hence enhance the amount of Na’ lost in the urine</td>
<td>Hypertension Oedema</td>
<td>Slower onset of action and longer duration</td>
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<tr>
<td></td>
<td>Chlortalidone</td>
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<td></td>
<td>Indapamide</td>
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<tr>
<td>Calcium channel</td>
<td>Dihydropyridines:</td>
<td>Antagonist at calcium channel blocks the influx of calcium ions via calcium channel into cardiac and vascular smooth muscles</td>
<td>Hypertension Angina</td>
<td>Dihydropyridines act predominantly on vascular smooth muscle Verapamil acts on heart whilst diltiazem is intermediate. Diltiazem and verapamil metabolized by hepatic cytochrome P450 system</td>
<td>Abdominal pain, Nausea, Palpitations, Oedema</td>
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<tr>
<td>blockers</td>
<td>amlopidine</td>
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<td></td>
<td>nifedipine</td>
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<td>felodipine</td>
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<td>lercanidipine</td>
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<td>nisoldipine</td>
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<td>Non-</td>
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<tr>
<td></td>
<td>dihydropyridines:</td>
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<tr>
<td></td>
<td>verapamil</td>
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<tr>
<td></td>
<td>diltiazem</td>
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</tbody>
</table>
Hypertension and herbal drugs

**Selective α1-adrenoceptor antagonists**
- Doxazosin
- Prazosin
- Indoramin

- Selectively inhibits the post synaptic α1 and α1a adrenergic receptors, causing arterial and venous dilation
- Binds highly to α1c adrenoceptor subtype predominant in the prostate

**Non-selective α1 and α2-antagonists**
- Phenoxymazine
- Phentolamine

- Blocks the effect of adrenaline and noradrenaline at α1 and α2 receptors both pre and post synaptically, leading to arterial and venous vasodilation and inhibition of catecholamine-mediated vasconstriction

**β-adrenoceptor antagonists**
- Propranolol
- Bisoprolol
- Atenolol
- Metoprolol
- Nebivolol
- Carvedilol
- Labetalol

- Competitively block β-receptors in heart, peripheral vasculature, bronchi, pancreas, uterus, kidney, brain, and liver, resulting in reduced cardiac output and antihypertensive effect

**Direct Vasodilators**
- Sodium nitroprusside
- Minoxidil
- Hydralazine
- Diazoxide

- A pro-drug that releases nitric oxide, a potent vasodilator that increases cGMP levels, leading to phosphorylation of protein kinase, which causes relaxation of vascular smooth muscles
- Causes direct relaxation of vascular smooth muscle, leading to vasodilation in the periphery

**Central adrenergic inhibitors**
- Methyldopa
- Clonidine
- Moxonidine

- Directly stimulates α2-receptor in the vasomotor centre of the medulla, leading to reduced sympathetic outflow from the brain.
- Agonist at central imidazoline-I-1 and α2 receptor

ACE: Angiotensin Converting Enzyme; MI: Myocardial Infarction; PE: Pulmonary Embolism; BPH: Benign Prostate Hypertropy

and antihypertensive effects of some of these medicinal plants have been validated and others disproved. However, ayurvedic knowledge needs to be coupled with modern medicine and more scientific research needs to be done to verify the effectiveness, and elucidate the safety profile of such herbal remedies for their antihypertensive potential [4]. These herbal formulations and plants due to the presence of wide range of secondary metabolites are able to control blood pressure and resulting complications. These herbal plants are discussed in the following section.
Table 3. Different plants and herbs in combating hypertension and associated mechanism of action.

<table>
<thead>
<tr>
<th>S.No</th>
<th>Plant Name</th>
<th>Botanical Name (Family)</th>
<th>Active Compound</th>
<th>Mechanism of Action</th>
</tr>
</thead>
</table>
| 1.   | Garlic           | *Allium sativum* L. (Liliaceae)               | Allicin                                                                         | • Relax lining of blood vessels  
       |                  |                                 | • Reduction in the ability of blood to clot                                      |
| 2.   | Onion            | *Allium cepa* L. (Liliaceae)                  | Organo-sulfur compounds, flavonoids especially quercetin                      | • Elasticity of arteries  
       |                  |                                 | • Reduction in blood viscosity  
       |                  |                                 | • Interaction with Renin-Angiotensin System  
       |                  |                                 | • Improvement of endothelial and vascular function  |
| 3.   | Arjuna           | *Terminalia arjuna* Roxb. (Combretaceae)      | Triterpene glycosides (arjunoside, arjunetoside and arjunin etc.), saponin  
       |                  |                                 | and e-enzyme factor Q10                                                       | • Increase the strength of cardiac muscles by acting on myocardium layer  
       |                  |                                 |                                                                                           | • Promotes thinning of blood  
       |                  |                                 |                                                                                           | • Inhibit platelet aggregation  |
| 4.   | Sarpgandha       | *Rauwolfia serpentina* (L.) Benth. Ex Kurz. (Apocynaceae) | Reserpine, resepiline, ajmaline, rauwolfinine                               | • Reduce the levels of hormonal group catecholamines (dopamine and epinephrine)  
       |                  |                                 |                                                                                           | • Promotes vasodilation  |
| 5.   | Punarnava        | *Boerhaavia diffusa* L. (Nyctaginaceae)       | Punarnevine                                                                     | • Diuretic  
       |                  |                                 |                                                                                           | • Act as ACE (angiotensin converting enzymes) inhibitor  |
| 6.   | Coriander        | *Coriandrum sativum* L. (Aptiaceae)           | Dietary fibres, vitamins and minerals                                          | • Cholinergic  
       |                  |                                 |                                                                                           | • Diuretic  
       |                  |                                 |                                                                                           | • Ca²⁺ channel blocker  |
| 7.   | Hawthorn’s berry | *Crataegus laevigata* (Poir.) DC. (Rosaceae)   | Flavonoids such as quercetin and oligomeric procyanidin                       | • Strengthen blood vessels and cardiac muscles  
       |                  |                                 |                                                                                           | • Reduction in blood clots  
       |                  |                                 |                                                                                           | • Lower cholesterol level  |
| 8.   | Saffron          | *Crocus sativus* L. (Iridaceae)               | Picrocrocin, crocin and safranal                                               | • Calcium channel blocker  |
| 9.   | Ginger           | *Zingiber officinalis* Rosc. (Zingiberaceae)   | 6-Gingerol and 6-shogaol                                                       | • Calcium channel blocker  
       |                  |                                 |                                                                                           | • Anti-thrombotic effect  
       |                  |                                 |                                                                                           | • Promotes vasodilation  |
| 10.  | Olives           | *Olea europaea* L. (Oleaceae)                 | Oleuropein, hydroxytyrosol, oleacein, ursolic and oleamic acids.              | • Effect on arterial resistance and stiffness  
       |                  |                                 |                                                                                           | • Improve endothelial function  
       |                  |                                 |                                                                                           | • Calcium channel blocker  |
| 11.  | Cardamom         | *Elettaria cardamomum* (L.) Maton (Zingiberaceae) | Essential oil, rich in 1,8-cineole, terpinyl acetate, limonene, terpinolene and myrcene. | • Enhances fibrinolysis  
       |                  |                                 |                                                                                           | • Calcium channel blocker  |
| 12.  | Carrot           | *Daucus carota* L. (Aptiaceae)                | Pectin, potassium, vitamins, beta-carotene                                     | • Improves endothelial function  
       |                  |                                 |                                                                                           | • Regulate fluid balance  |
| 13.  | Chrysanthemum    | *Chrysanthemum morifolium* (Asteraceae)       | Flavonois including apigenin and luteolin                                      | • Inhibit plaque formation  |
| 14.  | Tea              | *Camellia sinensis* (L.) O. Kuntze (Theaceae)  | Catechin and their derivatives, L-theanine                                     | • Anti-thrombotic activity  
       |                  |                                 |                                                                                           | • Inhibitor of angiotensin converting enzyme  
       |                  |                                 |                                                                                           | • Calcium channel blocker  
       |                  |                                 |                                                                                           | • Diuretic  |
| 15.  | Banana           | *Musa acuminata* Colla (Musaceae)             | Potassium and minerals                                                          | • Maintain electrolyte balance  
       |                  |                                 |                                                                                           | • Inhibitor of angiotensin converting enzyme  |
**Herbal Drugs and their mechanism of action**

Drug intervention need not be the only option to help lower your moderately high blood pressure. Herbal remedies such as garlic, Arjuna, sarpagandha etc. are helpful in combating hypertension and complexities related to it. The alternative therapy includes the use of herbs and supplements that might result in significant interactions or effects on hypertension and other cardiovascular disorders and needs to be considered by clinicians. The indigenous Indian herbs and formulations that are used for the treatment of hypertension include garlic, onion, arjuna, sarpagandha, punarnava, coriander, ashwagandha, Hawthorn’s berry, ginger, olives, cardamom, licorice, Chrysanthemum, green tea etc. These plants and herbs are helpful in reducing hypertension and exert their effect by different mechanism of action as mentioned in Table 3.

**Garlic**

Garlic, botanically known as *Allium sativum* L., has been used worldwide for lowering the blood pressure. It is a perennial herb originated from Asia and belongs to family *Liliaceae*. The bulb of plant is of utmost medicinal importance due to the presence of sulfur containing compounds or volatile compound Allicin. The bulb of plants as such or in the form of garlic supplements has been shown to lower cholesterol and reduce high blood pressure in those with untreated hypertension. In the recent study conducted by researchers from the University of Adelaide, Australia, it has been found that systolic blood pressure has been lowered by 10 mmHg in the group given garlic compound with those given a placebo [22]. In these garlic supplements, key compound is allicin that is broken down into sulphur compounds. These compounds react with red blood cells and produce hydrogen sulphide which relaxes the lining of blood vessels, and keeps blood flowing easily. But at low concentrations, it plays a vital role in helping cells to communicate with each other. The garlic also reduces the ability of blood to clot due to thinning of blood. Garlic also exert its effect as a result of its interaction with many drugs and supplements such as Coumadin (warfarin) or Trental (pentoxifylline), aspirin, vitamin E, gingko [23, 24].

**Onion**

Onion, botanically known as *Allium cepa* L., belongs to family *Liliaceae*. It has widely been used around the world as a food product and has also been used for medical applications. The onion either in raw form or cooked form provides protection against many chronic diseases including hypertension. The protective properties of onion is due to the presence of organo-sulfur compounds and flavonoids especially quercetin. Organ-sulfur compounds have been linked to lowering blood pressure by maintaining the elasticity (flexibility) of the major arteries that pump blood from the heart to the rest of the body (i.e. the aorta) along with reducing the blood’s viscosity (stickiness), thus preventing blood clotting. Quercetin, the compound most commonly associated with onions, may reduce blood pressure by an average of 5mm Hg, indicates new research in this direction [25]. The blood pressure lowering effects of quercetin is due to its tendency to reduce oxidative stress by reacting with free radicals, interaction with the RAS, and improvement of endothelial and/or vascular function [26]. Edwards and coworkers (2007) reported that blood pressure lowering potential of quercetin is related to the inhibition in the production of blood vessel constricting compound called angiotensin II that leads to increased blood pressure. 730 milligram supplementation of quercetin per day leads to the reduction in systolic pressure by 7 mmHg and 5mmHg diastolic compared to those patients who had been given the placebo [27].

**Arjuna**

Arjuna, botanically known as *Terminalia arjuna* Roxb., belongs to family *Combretaceae*. It is one of the important heart tonics that has been mentioned in traditional herbal system of Indian herbal medicines as the basic cure of cardiovascular diseases. Arjuna exerts its effect due to the presence of chemical compound triterpene glycoside such as arjunoside, arjunetoside and arjunix [28]. These glycosides increase the strength of cardiac muscles and improve the pumping activity of heart by reducing the LDL level and stabilizing the palpitation rate. The main target of action of arjuna is the muscular layer of heart i.e. myocardium layer and is also reported to have diuretic properties. The presence of co-enzyme factor Q10 along with arjuna is helpful in preventing heart attack problems [29].

The bark of plant is reported to rich in saponins including arjunic acid, arjunolic acid, arjungenin, arjunglycosides, flavonoids, arjunone, arjunolone, letelin, ellagic acid, oligomeric proanthocyanidins, phytosterols and minerals such as calcium, zinc copper, and magnesium. These components are helpful in removing blockade of the arteries by thinning the blood. It can be used as an anti-coagulant which works deep inside the tissues and works in cardiac related problems. Experimental studies and clinical trials indicate the usefulness of
the active constituents of Arjuna bark in treating coronary artery disease and congestive heart failure. The phytochemicals known as saponin glycosides exert the heart protective effects by improving the contraction of the heart muscles. Oligomeric proanthocyanidins and flavonoids boost the natural antioxidant defense system of the heart and strengthen the vascular system of the body. The researchers suggest that Terminalia arjuna might prevent atherothrombosis by inhibiting platelet aggregation in coronary artery disease patients [30-32].

**Sarpgandha**

Sarpgandha (Indian snakeroot) botanically known as *Rauwolfia serpentina* (L.) Benth. Ex Kurz. (Family: Apocynaceae) is used in Indian folklore medicine as remedy for high blood pressure and mental disorders. The blood pressure lowering effect of sarpgandha is due to the presence of alkaloid reserpine that exert its protective effect by lowering the levels of hormonal group known as catecholamines (dopamine, epinephrine also known as adrenaline and noradrenaline). Adrenaline and noradrenaline alleviates the blood pressure in response to physical and emotional stress by constricting the blood vessels and increasing the heart rate and metabolism respectively. The lowering of catecholamines, stores in adrenergic nerves and in the heart, by reserpine slows down the heart rate and helps open up capillaries and arterioles which in turn cause a reduction in blood pressure.

The alkaloids including reserpinine, ajmaline, iso-ajmaline, rauwolfinine present in *R. serpentina* roots, exert their protective effects by acting on the vaso-motor centre that leads to generalized vasodilatation and thus lowered the blood pressure. Another alkaloid rescinnamine obtained from *Rauwolfia serpentina* and other *Rauwolfia* species, is an ACE inhibitor that competes with angiotensin I for binding to ACE and effectively inhibits the conversion of angiotensin I to angiotensin II, resulting in decreased concentrations of angiotensin II and blood pressure lowering effects. In addition to this, increased bradykinin levels resulting from decreased bradykinin inactivation may also contribute to the effects of rescinnamine [33-35].

**Punarnava**

Punarnava, botanically known as *Boerhaavia diffusa* L., belongs to family Nyctaginaceae. The plant is mentioned in Ayurveda for blood pressure lowering effects. The presence of alkaloid punarnevine is major contributing factor in maintaining blood pressure due to its diuretic properties and tendency to act as ACE inhibitor [36,37].

**Coriander**

Coriander, botanically known as *Coriandrum sativum* L. (Family: Apiaceae), is a powerful herb with many health benefits. The plant is traditionally used for various gastrointestinal and cardiovascular disorders. The protective properties are due to the presence of dietary fiber, vitamins and minerals like calcium, magnesium, sodium and potassium. The coriander fruit is reported to exhibit gut stimulatory, inhibitory and hypotensive effects by mediating the cholinergic, Ca$^{2+}$ antagonist and the combination of these mechanisms respectively. The diuretic property of coriander is also responsible for its antihypertensive action [38].

**Ashwagandha**

Ashwagandha, botanically known as *Withania somnifera* (L.) Dunal. (Family: Solanaceae), is one of the most important ayurvedic medicinal plants due to its immense medicinal properties. It is also known as Indian Ginseng as it improves the body’s ability to maintain physical effort and helps to get relieve from stress, fatigue and sleeplessness. It has been widely used as a sedative, an anti-inflammatory agent, aphrodisiac, a diuretic, a rejuvenating tonic, and an immune booster. It is especially beneficial in stress related disorders such as diabetes, general debility arthritis, hypertension, etc. The protective properties of ashwagandha are due to the presence of phytochemicals such as, withanamine, choline and alkaloids. The anti-stress properties of ashwagandha help to alleviate high blood pressure [32].

**Hawthorn’s Berry**

Hawthorn berries, botanically known as *Crataegus laevigata* (Poir.) DC. or *Crataegus mongyna*, belonging to family Rosaceae, are of immense medicinal importance due to its potential to treat heart disorders including high blood pressure and circulatory issues, cardiac arrhythmia, and even chronic heart failure. The blood pressure lowering effects of hawthorn berries are due to the presence of flavonoids such as quercetin and oligomeric procyanidins. It has been reported that heart protective effects of Hawthorn’ berries are related to blood vessel strengthening abilities, to remove vascular insufficiency and blood clots and restoring the heart muscle wall, lowering cholesterol and to aid digestion [39, 40].
Saffron

Saffron, botanically known as *Crocus sativus* L. (Family: *Iridaceae*), is a popular spice of Arabic cooking. The plant is reported to have blood pressure lowering effects due to the presence of chemical constituent known as picrocrocin, crocin, crocetin and safranal, the safranal being most important constituent of hypotensive nature. These constituents have calcium antagonistic activity that prevent the influx of Ca$^{2+}$ ions [41].

Ginger

Ginger, botanically known as *Zingiber officinalis* Rosc. (Family: *Zingiberaceae*), is a spice commonly used in Asian and Indian cuisine. The spice is known to reduce hypertension, or high blood pressure due to the presence of different chemical constituents (6-shogaol and 6-gingerol) that act by maintaining the levels of low density lipoproteins and cholesterol. Cholesterol and low density lipoproteins can contribute to sticky plaque along the walls of arteries and blood vessels, creates blockages that could contribute to high blood pressure by restricting the inner diameter of blood vessels and arteries and reducing the elasticity of arteries. The dissolution of blood clots also helps in lowering the high blood pressure as blood clots lead to hypertension by restricting the blood from flowing through circulatory system [42].

Olive

Olive, botanically known as *Olea europaea* L. belonging to family *Oleaceae*, is a core constituent of the Mediterranean diet. The plant is reported to have wide array of health benefits due to the presence of beneficial compounds including oleuropein, hydroxytyrosol, oleacein, ursolic and oleanic acids. The oleuropein, main constituent of olive tree leaves, is largely responsible for beneficial effect on high blood pressure due to the reduction in nitric acid produced by polyphenols. Oleuropein lower the high blood pressure by targeting the arterial resistance and stiffness, improving endothelial function and modulating the flow of calcium channel. It has been found that olive oil and its formulation reduced systolic blood pressure by an average 11.5 points mmHg, and diastolic blood pressure by 4.8 points in just eight weeks. Olive leaf extract also help to maintain healthy blood pressure [43-46].

Cardamom

Cardamom, botanically known as *Elettaria cardamomum* (L.) Maton (Family: *Zingiberaceae*), is reported to have have antihypertensive potential and effect on cardiovascular risk factors linked with stage 1 hypertension. Verma and coworkers reported that small cardamom effectively reduces blood pressure, enhances fibrinolysis and improves antioxidant status, without significantly altering blood lipids and fibrinogen levels in stage 1 hypertensive individuals [47]. The protective properties are due to the presence of essential oil, rich in 1,8-cineole, terpinyl acetate, limonene, terpinolene and myrcene. The cardamom exerts its protective effect in lowering high blood pressure by acting as calcium channel blocker [48].

Carrot

Carrot, botanically known as *Daucus carota* L. (Family *Apiaceae*), is reported to be act as antihypertensive agent due to the presence of pectin, potassium, vitamins and antioxidants like beta-carotene. The pectin or calcium pectate binds with cholesterol in the bile in gut and helps to sweep it out of body. Carrot juice is rich in antioxidants such as beta-carotene and vitamins A and C that reduce oxidative stress resulting from free radicals and improve insulin resistance and the function of endothelial cells, which regulate the function and structure of blood vessels, including helping blood vessels to dilate. The carrots also help to normalize blood pressure due to the presence of potassium, a well-known mineral for its ability to regulate fluid balance in the body. The potassium is also helpful in countering the effects of sodium, an electrolyte that increases blood pressure [49].

Chrysanthemum

Chrysanthemum, botanically known as *Chrysanthemum morifolium* belonging to family *Asteraceae*, is a useful remedy for the treatment to high blood pressure related problems. Chrysanthemum in the form of tea known as Chrysanthemum tea, appears to affect oxidation of low-density lipoprotein that leads to the plaque formation due to the presence of flavonoids including apigenin and luteolin [50].

Tea

Tea, botanically known as *Camellia sinensis* (L.) O. Kuntze and belonging to family *Theaceae*, is a widely-consumed beverage in Asia and has been regarded to possess significant health-promoting effects. It is consumed either as black tea or green tea and both these forms differ with respect to oxidation process. Black tea is oxidized form of *C. sinensis* and green tea is unoxidized. Both forms of tea are
Effective to attenuate the increased blood pressure [51]. The protective properties of tea are due to the presence of polyphenols especially flavanols, which represent approximately 30% dry weight of the fresh leaf. The major polyphenols include epigallocatechin gallate (EGCG), epigallocatechin (EGC), epicatechin gallate (ECG), and epicatechin (EC). Due to the presence of chemical constituents, tea has been shown to relieve high blood pressure by preventing thrombosis and strengthening blood vessels. L-theanine an important component of Japanese green tea, help to normalize blood pressure by targeting the peripheral nervous system through the formation of inhibitory neurotransmitter, gamma amino butyric acid (GABA). Green tea has high blood pressure lowering properties due to the presence of polyphenolic compounds that act as an inhibitor of Angiotensin Converting Enzyme (ACE), calcium channel blockers and diuretics [52-54]. Caffeine is also an important constituent of tea (predominant in black tea than green tea) and is reported to enhance blood pressure. However, Winkelmayer et al. (2005) reported that habitual consumption of caffeine in the form of tea or coffee has not any association with hypertension [55].

**Banana**

Banana, botanically known as *Musa acuminata* Colla (Family: *Musaceae*), because of their potassium content, are helpful in lowering high blood pressure. Potassium works with sodium to help in regulating the electrolyte balance. Due to the presence of minerals, bananas inhibit the action of angiotensin converting enzyme (ACE) which is responsible for forming a substance, angiotensin-2 that constricts blood vessels and raises the pressure inside them [56,57].

Besides the above mentioned herbs, a lot of other herbs and herbal formulations including potassium rich spinach (*Spinacia oleracea*), celery (*Apium graveolens*), tomatoes (*Solanum lycopersicum*), sulforaphane glucosinolate rich broccoli (*Brassica oleracea* var. *italica*), amino acid known as glutamic acid rich cabbage (*Brassica oleracea* var. *capitata*) has been used to reduce the high blood pressure.

**CONCLUSION**

Hypertension or elevated high blood pressure is a disease related to changed life style pattern. The disease can be cured or kept under control by the use of wide range of therapeutic agents but these drugs are having a lot of side effects. Fortunately, in most instances drug intervention may not be necessarily required, just a change in lifestyle can be sufficient to control or prevent mild or moderately high blood pressure. In such instances, use of herbal drugs and formulations are effective as these help to control blood pressure at desired levels without exerting any side effect, reducing stress and enhancing metabolic health.

**REFERENCES**