Hypertension is a problem plaguing globally developed, developing and under-developed countries alike. It is of two types- Primary Hypertension which accounts for 95% of overall cases of hypertension and Secondary hypertension which accounts for 5% of hypertension cases. Various synthetic drugs have been approved for its treatment by FDA, but these drugs have various side-effects. Hence, herbal drugs which are cheaper, more compatible and safer in comparison with the synthetic drugs provide for a great alternative. Calcium channel makes for an effective and proven drug target and thus, calcium channel blockers act as potent anti-hypertensive agents. In this review, medicinal plants which are composed of phytoconstituents which can act as calcium channel blockers have been listed for treatment therapy of hypertension.

KEYWORDS: Hypertension, Blood pressure, Medicinal plants, Calcium channel blockers

INTRODUCTION

FDA terms hypertension as a “Silent killer”, because often people who have hypertension do not know about it. Hypertension is a serious illness which affects numerous individuals throughout the world. It is associated with increased systolic and diastolic blood pressure. A systolic/diastolic blood pressure of 120/80 is considered to be normal while anything greater than 140/90 is considered to be requiring medical care and attention. Hypertension is primarily classified into two classes:

1. Primary Hypertension
2. Secondary Hypertension

Primary Hypertension is also called “Essential Hypertension”. This type accounts for 95% of the overall hypertension cases in the world. It is a type of hypertension for which no secondary cause of disorder can be deciphered.

There are three vivid subtypes of Primary hypertension namely-

A. Plexogenic arteriopathy, which involves abnormalities in the pre-capillary structures.
B. Veno-occlusive disease, which is caused due to injury to the veins and venules.
C. Capillary hemangiomatosis, which involves proliferation of capillary network.

A wide range of physiological mechanisms have been identified which lead to primary hypertension. They are:

1. Genetic factors: It was noted that families having a history of hypertension have shown to pass them on to the next generation. Minor changes in the alleles cause the genes which control cardiac output and total peripheral resistance to contribute to hypertension. Genetic mutations, variations and defects can negatively affect the normal blood pressure thereby causing hypertension.

2. Sympathetic nervous system overactivity: Excessive sympathetic nervous activity is associated with increased heart rate, cardiac output, peripheral resistance, plasma and urinary noradrenaline levels. It occurs at an early stage in this disease. Emotional and physical stress leads to hypertension too.

3. Renal dysfunction: This is associated with the kidney’s inability to excrete sodium which is present in excess in the body due to high salt intake from the daily diet. There is resetting of the pressure-sodium curve which causes hypertension.

4. Obesity: Increase in body weight has been hypothesized to sympathetic overactivity which in turn causes hypertension.

5. Endothelial cell dysfunction: Endothelium is responsible for production of nitric oxide and endothelin which regulates blood pressure. In hypertension, nitric oxide is inactivated by reactive oxygen species and thus deficiency of nitric oxide is thought to cause hypertension. Also chronic
endothelin-1 activation is thought to be responsible for hypertension.

6. Renin-angiotensin-aldosterone system: Elevated renin levels are also said to be associated with hypertension.

7. Obstructive sleep apnea: Obstructive sleep apnea consists of apnea episodes in sleep along with hypoxia. Recurrent hypoxia causes an increase in sympathetic activity which thereby causes increase in blood pressure.

8. Metabolic syndrome: It was found that diabetes and hypertension have a core Metabolic syndrome which is characterized by an increase in insulin resistance. Insulin leads to hypertension via increased sodium reabsorption by the kidneys, sympathetic nervous system activation and increase in the size of resistance vessels.

9. Uric acid overproduction: Uric acid causes activation of nicotinamide adenine dinucleotide phosphate oxidase that causes increased oxidative stress in vascular smooth muscle and kidney contributing to hypertension.

10. Environmental factors: Exposure to air-pollution can also cause increased sympathetic activity which in a way also causes hypertension. This is because small particulate matter can cause oxidative stress and vascular inflammation.

Primary hypertension causes cardiac changes like thickening and stiffening of the wall of the heart and also reduction in the speed and strength of cardiovascular contraction. There are advanced structural changes in the large arteries and precapillary resistance vessels. Atherosclerotic and thrombotic degenerations can be seen as a result of primary hypertension. Hypertrophy of the left ventricle is also a characteristic of primary hypertension.

Secondary hypertension is a type of hypertension for which the causes are known. It accounts for 5% of hypertension cases. It is also called a “treatable or curable” form of hypertension. The causes for this type of hypertension are:

1. Renal parenchymal disease: It includes conditions like diabetes mellitus, polycystic kidney disease, renin secreting tumor, renal venous thrombosis, post-renal transplant hypertension and reflux nephritis.

2. Renovascular diseases: Hypertension is caused in young children due to fibromuscular dysplasia and in older patients due to atherosclerosis. Fibromuscular dysplasia is an arterial disease which affects carotid and renal arteries. Renal venous thrombosis and renal artery thrombosis can also cause hypertension.

3. Coarctation of the aorta: It is commonly found in the adolescent and paediatric population. It is a congenital heart disease. It is usually manifested as a discrete constriction of ductus arteriosus.

4. Cushing’s syndrome: A chronic exposure to glucocorticoids causes cushing’s syndrome. Glucocorticoids in turn cause hypertension by affecting the renin-angiotensin system, activating vasoactive substances in the body and by inhibiting the vasodilatory system of the body. Also mechanisms like inhibition of prostacyclin and binding of cortisol to glucocorticoid receptors contribute to hypertension.

5. Primary hyperaldosteronism: The two main causes of hyperaldosteronism are Conn’s syndrome and idiopathic hyperaldosteronism. Increased aldosterone in a way suppresses renin levels and thereby affecting the renin-angiotensin-aldosterone pathway. Such a change leads to hypertension.

6. Pheochromocytoma: It is a condition in which a tumour causes elevation of catecholamines like norepinephrine or epinephrine. Imbalance of catecholamines leads to hypertension.

7. Hyperparathyroidism: Parathyroid hormone regulates serum calcium levels and hence hyperparathyroidism causes an imbalance in the serum calcium levels and thereby causes hypertension.

8. Thyrotoxicosis: It is a condition which involves excess presence of thyroid hormones. Hyperthyroidism can alter vascular reactivity, circadian blood pressure rhythm and normal functioning of the kidney, thereby causing hypertension. Hypothyroidism is associated with increase in diastolic pressure while hyperthyroidism is predominantly associated with systolic hypertension.

Secondary hypertension is accompanied by nocturnal and sustained increase in blood pressure. Prevalence of reduced femoral pulses as in coarctation of aorta, abdominal striae as in case of Cushing’s syndrome, pallor and palpitations as in case of pheochromocytoma are certain markers which help to distinguish a secondary hypertension from a primary one. Carotid plaques were commonly observed in patients having renovascular hypertension and those with pheochromocytoma. Also the carotid artery thickness was greatly increased in patients with secondary hypertension than primary ones. Various synthetic drugs have been approved by FDA to treat hypertension. These drugs have been classified into classes depending upon their target of action:

1. α-blockers
2. β-blockers
3. Angiotensin receptor blockers
4. Diuretics
5. Angiotensin converting enzyme inhibitors

6. Calcium channel blockers

**Figure 1:** Various classes of anti-hypertensive agents along with FDA approved drugs of each class

**Need for Herbal Variants in Treatment of Hypertension**

The side-effects of synthetic anti-hypertensive drugs has made researchers search for safer therapies to resolve the plaguing issue of hypertension. The selection of herbal variants to the conventional, synthetic ones stems from the fact that herbal drugs are actually safer and less costly than their synthetic contemporaries. Not only that, the medicinal plants also have better compatibility with the human body. Medicinal plants have a plethora of phytoconstituents which act on the various drug targets involved in hypertension. These plants can be used in the form of infusions, decoctions, fresh fruits or can be eaten raw.

**Calcium channels** are gated channels which are involved in transport of calcium ions into the cell. L-type calcium channels are involved in cardiac excitation and relaxation. These channels are also present in skeletal muscles, smooth muscles and adrenal cortex apart from cardiac muscles. It is one of the most well-established and potent drug targets for hypertension. Calcium channel blockers are one of the most effectively used classes of antihypertensives.

In this review, various medicinal plants which have phytoconstituents which act as calcium channel blockers have been described for treatment of hypertension.

**Medicinal plants as calcium channel blockers**

**Table 1:** Medicinal plants, their botanical names, chemical constituents responsible for activity and the type of extracts used.

| Common name | Botanical name | Family | Plant part used | Chemical constituents | Extract used |
|-------------|----------------|--------|-----------------|-----------------------|--------------|
| Yarrow      | Achillea wilhelmsii | Asteraceae | aerial part     | Carvacrol, luteolin, apigenin 1,8-cineole | Hydroalcoholic extract |
| Celery      | Apium graveolens | Apiaceae | seed            | Apiin, apigenin, isoquercitrin sesquiterpene | Hexanic, methanolic and aqueous-ethanolic extracts |
| Shell ginger| Alpinia zerumbet | Zingiberaceae | Whole plant    | Catechin, epicatechin, rutin, quercetin, kaempferol 3-o-rutinoside, kaempferol dihydro-5, 6-dehydrokawain, 5,6-dehydrokawain | Hydroalcoholic extract |
| Nikko Maple | Acer nikoense (Miq.) Maxim | Aceraceae | Leaves, bark | Scopoletin, Cleomiscosin A, Aquillochin | Methanolic extract |
| Plant Name                     | Family          | Part                | Active Constituents                                                                 | Extraction Method               |
|-------------------------------|-----------------|---------------------|-------------------------------------------------------------------------------------|----------------------------------|
| Soursop, Graviola             | Annonaceae      | Leaves              | Reticuline, quercetin, betacyrophylleone, coreximine, anomurin                      | Ethanol, aqueous extract         |
| Annona muricata               |                 |                     |                                                                                     |                                  |
| Sweet flag, flagroot          | Acoraceae       | Rhizome             | β-asarone, β-gurjunene, sequesterpenes, xylose, β-daucosterol, δ-galacturonic acid   | Aqueous-methanolic extract       |
| Acorus calamus L.             |                 |                     |                                                                                     |                                  |
| Punarnava Hogweed             | Nyctaginaceae   | Whole plant, root   | Liriodendron, boeravinone, hypoxanthine                                             | Methanolic extract               |
| Boerhavia diffusa             |                 |                     |                                                                                     |                                  |
| Cape periwinkle, periwinkle   | Apocynaceae     | Leaves, roots, flowers | Vinblastine, vincristine                                                            | Ethanolic extract                |
| Catharanthus roseus           |                 |                     |                                                                                     |                                  |
| Ajwain Carrom copticum        | Apiaceae        | Seeds               | Thymol, p-cymene, γ-terpinene, o-cymene, carvacrol β-phellandrene                    | Aqueous-methanolic extract       |
| 30,31                         |                 |                     |                                                                                     |                                  |
| Saffron Crocus sativus        | Iridaceae       | Stigma              | Crocin, picrocrocin, safranal, crocin                                                | Aqueous extract                  |
| 32,33,34                      |                 |                     |                                                                                     |                                  |
| Carrot Daucus carota          | Apiaceae        | Aerial parts        | Coumarin glycosides (DC-2 and DC-3)                                                  | Ethanolic extract                |
| 35,36                         |                 |                     |                                                                                     |                                  |
| Wu-Chu-Yu Evodia rutaecarpa L.| Rutaceae        | Fruits              | Rutaecarpine                                                                         | Methanolic extract               |
| 23,37,38                      |                 |                     |                                                                                     |                                  |
| Roselle Hibiscus sabdariffa   | Malvaceae       | Calyx, leaves, corolla | β-carotene, ascorbic acid, β-sitosterol, cyaniding-3-rutinose, pectin               | Aqueous extract                  |
| 18,32,35,39,40                |                 |                     |                                                                                     |                                  |
| French Lavender              | Lamiaceae       | Flower and oil      | Fenchone, p-cymene, lavandulyl acetate, α-pinene                                     | Methanolic extract               |
| Lavandula stoechas           |                 |                     |                                                                                     |                                  |
| White horehound              | Lamiaceae       | Whole plant         | Marrubenol                                                                           | Hydroalcoholic extract           |
| Marrubium vulgare L           |                 |                     |                                                                                     |                                  |
| Mu Dan Pi Moutan Cortex       | Paeoniaceae     | Whole plant         | Paeoniflorin, benzoyl paeoniflorin, mudadpioside C, paeonol, 1,2,3,4,6-o-pentagalloylgucose | Methanolic extract               |
| 42                            |                 |                     |                                                                                     |                                  |
| Black Cumin, Seed of Blessing | Ranunculaceae   | Seed                | Thymoquinone, dithymoquinone                                                        | Dichloromethane extract         |
| Plant                | Scientific classification | Part Used | Constituents                                                                 | Preparation            |
|---------------------|---------------------------|-----------|------------------------------------------------------------------------------|------------------------|
| Nigella sativa      | 16,18,19,27,43            |           | thymohydroquinone, thymol, 4-terpineol                                      |                        |
| Basil Ocimum basilicum | 18,32,44                  | Lamiaceae | Leaves, stem                                                                | Aqueous extract        |
| Olive leaf Olea africana and Olea europaea | 18 | Oleaceae | Leaves                                                                      | Oleuropein             |
| Ginseng Panax ginseng | 45,46,47                  | Araliaceae | Roots                                                                      | Ginsenosides Rg1, Rg3, Rh1, Re and Rd | Methanolic extract|
| Fen Fang Ji Radix stephaniae tetrandrae | 58,49 | Menispermaceae | Roots                                                                      | Tetrandrine            |
| Cat’s Claw herb Uncaria rhynchophylla | 18,32,35 | Rubiaceae | Leaves                                                                      | Hirsutine, rhynchophylline, isorhynchophylline | Methanolic extract|
| Jatamansi, Indian valerian Valeriana jatamansi | 27,50 | Valerianaceae | Roots, rhizomes                                                            | Jatamansika, jatamansine | Ethanolic extract|
| Ginger Zingiber officinale | 27,51 | Zingiberaceae | Rhizomes                                                                  | Gingerol, gingerdiol, gingerdione, β-carotene, capsaicin, caffeic acid | Aqueous extract|

**CONCLUSION**

Synthetic anti-hypertensive drugs have shown to have various side-effects. Hence, there is an increasing need to develop new molecules which can be made safer and active as anti-hypertensive agents. Various synthetic calcium-channel blockers useful in hypertension have been approved by FDA, which suggests that calcium channel is a potent and proven drug target for developing molecules against hypertension. Various medicinal plants listed in this review have certain phytoconstituents which are adept at blocking calcium channels and thereby have potential for treating hypertension. We therefore hypothesize the use of these medicinal plants as a monotherapy or in combination with other drugs.

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