Review Article

Medicinal Plants as Calcium-channel Blockers Against Hypertension

Nachiket Jitendra Joshi*, Shivani Ashok Shelke
Department of Pharmaceutical chemistry, Department of Quality Assurance
Vivekanand Education Society's College of Pharmacy, Chembur (East), Mumbai, India.
***Corresponding author's E-mail:** nachiketjoshi7441@gmail.com

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ABSTRACT

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

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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.[1]

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.[2]

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

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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. [1,3,4,5]

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.[6,7]

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.[8,13]

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.[12,14] 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.[15]

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

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5. Angiotensin converting enzyme inhibitors
6. Calcium channel blockers

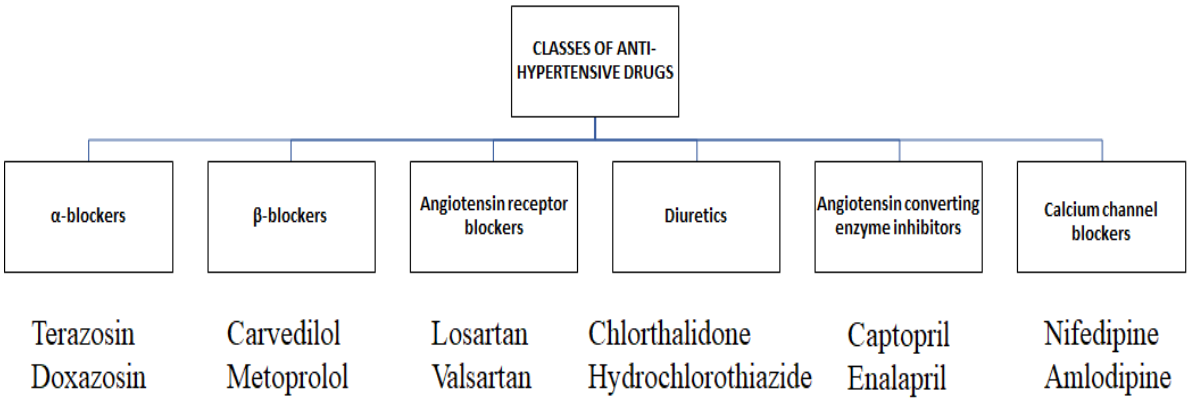

Figure 1: Various classes of anti-hypertensive agents along with FDA approved drugs of each class

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.[16,17,17,18,19]

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* [20]	Asteraceae	aerial part	Carvacrol, luteolin, apigenin 1,8-cineole	Hydroalcoholic extract
Celery *Apium graveolens* [18,21]	Apiaceae	seed	Apiin, apigenin, isoquercitrin sesquiterpene	Hexanic, methanolic and aqueous-ethanolic extracts
Shell ginger *Alpinia zerumbet* [18,22]	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 [23,24]	Aceraceae	Leaves, bark	Scopoletin, Cleomiscosin A, Aquillochin	Methanolic extract

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Soursop, Graviola *Annona muricata* [25,26]	Annonaceae	Leaves	Reticuline, quercetin, beta-caryophyllene, coreximine, anomurin	Ethanolic, aqueous extract
Sweet flag, flagroot *Acorus calamus L.* [27,28]	Acoraceae	Rhizome	β- asarone, β- gurjunene, sequesterpenes, xylose, β- daucosterol, d- galacturonic acid	Aqueous- methanolic extract
Punarnava Hogweed *Boerhavia diffusa* [18,27]	Nyctaginaceae	Whole plant, root	Liriodendron, boeravinone, hypoxanthine	Methanolic extract
Cape periwinkle, periwinkle *Catharanthus roseus* [18,29]	Apocynaceae	Leaves, roots, flowers	Vinblastine, vincristine	Ethanolic extract
Ajwain *Carrom copticum* [30,31]	Apiaceae	Seeds	Thymol, p-cymene, γ-terpinene, o-cymene, carvacrol β-phellandrene	Aqueous- methanolic extract
Saffron *Crocus sativus* [32,33,34]	Iridaceae	Stigma	Crocin, picrocrocin, safranal, crocetin	Aqueous extract
Carrot *Daucus carota* [35,36]	Apiaceae	Aerial parts	Coumarin glycosides (DC-2 and DC-3)	Ethanolic extract
Wu-Chu-Yu *Evodia rutaecarpa L.* [23,37,38]	Rutaceae	Fruits	Rutaecarpine	Methanolic extract
Roselle *Hibiscus sabdariffa* [18,32,35,39,40]	Malvaceae	Calyx, leaves, corolla	β-carotene, ascorbic acid, β sitosterol, cyaniding-3-rutinose, pectin	Aqueous extract
French Lavender *Lavandula stoechas* [18,38,41]	Lamiaceae	Flower and oil	Fenchone, p-cymene, lavandulyl acetate, a-pinene	Methanolic extract
White horehound *Marrubium vulgare L* [18]	Lamiaceae	Whole plant	Marrubenol	Hydroalcoholic extract
Mu Dan Pi *Moutan Cortex* [42]	Paeoniaceae	Whole plant	Paeoniflorin, benzoyl paeoniflorin, mudanpioside C, paeonol, 1,2,3,4,6-o-pentagalloylglucose	Methanolic extract
Black Cumin, Seed of Blessing	Ranunculaceae	Seed	Thymoquinone, dithymoquinone,	Dichloromethane extract

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Nigella sativa [16,18,19,27,43]			thymohydroquinone, thymol, 4-terpineol	
Basil *Ocimum basilicum* [18,32,44]	Lamiaceae	Leaves, stem	Eugenol, α- cubebene, caryophyllene, rosmarinic, estragole	Aqueous extract
Olive leaf *Olea africana and Olea europaea* [18]	Oleaceae	Leaves	Oleuropein	Aqueous extract
Ginseng *Panax ginseng* [45,46,47]	Araliaceae	Roots	Ginsenosides Rg1, Rg3, Rh1, Re and Rd	Methanolic extract
Fen Fang Ji *Radix stephaniae tetrandrae* [48,49]	Menispermaceae	Roots	Tetrandrine	Aqueous extract
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.

REFERENCES

1. Hall JE, Granger JP, do Carmo JM, da Silva AA, Dubinion J, George E, Hall ME. Hypertension: Physiology and pathophysiology. Comprehensive Physiology 2012; 2(4): 2393-2442.
2. Lewis JR. Pathology and pathophysiology of primary pulmonary hypertension 1, American journal of cardiology 1995; 75(3): 51A-54A.
3. Carey RM. Pathophysiology of Primary Hypertension. Microcirculation. 2, Academic Press, Virginia, 2008; 794-895.
4. Saxena T, Ali AO, Saxena M. Pathophysiology of essential hypertension: an update. Expert Review of Cardiovascular Therapy 2018; 16(12): 879-887.
5. El-Atat F, McFarlane SI, Sowers JR. Diabetes, hypertension, and cardiovascular derangements: Pathophysiology and management. Current Hypertension Reports 2004; 6(3): 215-223.
6. Folkow B. The fourth Volhard lecture: Cardiovascular structural adaptation; its role in the initiation and maintenance of primary hypertension. Clinical Science and Molecular Medicine 1978; 55(4): 3s-22s
7. Folkow B. The Pathophysiology of Hypertension: Differences between Young and Elderly Patients. Drugs 1993; 46(2): 3-7.
8. Akpunonu BE, Mulrow PJ, Hoffman EA. Secondary hypertension: Evaluation and treatment. Disease-a-Month 1996; 42(10): 609-722.
9. Charles L, Triscott J, Dobbs B. Secondary Hypertension: Discovering the Underlying Cause. American Family Physician 2017; 96(7): 453-461.

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10. Cicala MV, Mantero F. Hypertension in Cushing's syndrome: From pathogenesis to treatment. Neuroendocrinology 2010; 92(1): 44-49.
11. Sharma S, Meyers KE, Vidi SR. Secondary forms of hypertension in children: Overview. Pediatric Hypertension. Springer international publishing, 2018; 431-449.
12. Chiong JR, Aronow WS, Khan IA, Nair CK, Vijayaraghavan K, Dart RA, Geraci SA. Secondary hypertension: Current diagnosis and treatment. International Journal of Cardiology 2008; 124(1): 6-21.
13. Freihage JH, Nanjundappa A, Dieter RS. Secondary hypertension: Etiology and mechanism of disease. Therapy 2008; 5(6): 787-790.
14. Seeman T, Palyzová D, Dušek J, Janda J. Reduced nocturnal blood pressure dip and sustained nighttime hypertension are specific markers of secondary hypertension. Journal of Pediatrics 2005; 147(3): 366-371.
15. Rizzoni D, Muiesan ML, Porteri E, Salvetti M, Castellano M, Bettoni G, Agabiti-Rosei E. Relations between cardiac and vascular structure in patients with primary and secondary hypertension. Journal of the American College of Cardiology 1998; 32(4): 985-992.
16. Landazuri P, Chamorro NL, Cortes BR. Medicinal Plants Used in the Management Hypertension. Journal of Analytical & Pharmaceutical Research 2017; 5(2): 1-3
17. Marjina, Singh A, Sharma A, Narang RK, Singh G. Management of Hypertension with Conventional and Herbals Drugs. Journal of Drug Delivery and Therapeutics 2020; 10(3): 280-287.
18. Modak P, Halder S, Sarkar KB, Das A, Sarkar PA, Kundu K. Traditional Antihypertensive Medicinal Plants: A comprehensive review. World Journal Of Pharmacy and Pharmaceutical Sciences 2020; 9(9): 884-912.
19. Chrysant SG, Chrysant GS. Herbs Used for the Treatment of Hypertension and their Mechanism of Action. Current Hypertension Reports 2017; 19(9): 1-10.
20. Niazmand S, Harandi Zadeh F, Mahmoudabadi M, Hosseini M, Hasanzadeh M, Fereidouni E. Mechanism of vasorelaxation induced by *Achillea wilhelmsii* in rat isolated thoracic aorta Advanced Biomedical Research 2014; 3(1): 91.
21. Moghadam MH, Imenshahidi M, Mohajeri SA. Antihypertensive effect of celery seed on rat blood pressure in chronic administration. Journal of Medicinal Food 2013; 16(6): 558-563.
22. Xiao T, Huang J, Wang X, Wu L, Zhou X, Jiang F, He Z, Guo Q, Tao L, Shen X. *Alpinia zerumbe*t and Its Potential Use as an Herbal Medication for Atherosclerosis: Mechanistic Insights from Cell and Rodent Studies. Lifestyle Genomics 2020; 13(5): 138-145.
23. Maione F, Cicala C, Musciacco G, Feo VD, Amat AG, Ialenti A, Mascolo N. Phenols, alkaloids and terpenes from medicinal plants with antihypertensive and vasorelaxant activities. a review of natural products as leads to potential therapeutic agents. Natural Product Communications 2013; 8(4): 539-544.
24. Iizuka T, Nagumo S, Yotsumoto H, Moriyama H, Nagai M. Vasorelaxant effects of Acer nikoense extract and isolated coumarin lignans on rat aortic rings. Biological and Pharmaceutical Bulletin 2007; 30(6): 1164-1166.
25. Ismail S, Hayati N, Rahmawati N. Mechanism of action vasodilation *Annona muricata L*. leaves extract mediated vascular smooth muscles. IOP Conference Series: Earth and Environmental Science 2018; 144(1): 1-6.
26. Nwokocha CR, Owu DU, Gordon A, Thaxter K, Mccalla G, Ozolua RI, Young L. Possible mechanisms of action of the hypotensive effect of *Annona muricata* (soursop) in normotensive Sprague Dawley rats. Pharmaceutical Biology 2012; 50(11): 1436-1441.
27. Khanal H, Joshi RK, Upadhyay A. Anti- hypertensive activity of Ayurvedic medicinal plants. International Journal of Complementary and Alternative Medicine 2020; 13(1): 7-12.
28. Shah AJ, Gilani AH. Blood pressure-lowering and vascular modulator effects of Acorus calamus extract are mediated through multiple pathways. Journal of Cardiovascular Pharmacology 2009; 54(1): 38-46.
29. Ara N, Rashid M, Amran MS. Comparison of hypotensive and hypolipidemic effects of *Catharanthus roseus* leaves extracted with nifedipine on adrenaline induced hypertensive rats. Journal of Biological Sciences 2008; 8(6): 1082-1086.
30. Gilani AH, Jabeen Q, Ghayur MN, Janbaz KH, Akhtar MS. Studies on the antihypertensive, antispasmodic, bronchodilator and hepatoprotective activities of the Carum copticum seed extract. Journal of ethnopharmacology 2005; 98(1-2):127-35.
31. Boskabady MH, Alitaneh S, Alavinezhad A. Carum copticum L.: A herbal medicine with various pharmacological effects. BioMed Research International 2014; 1-11.
32. Rawat P, Singh PK, Kumar V. Anti- hypertensive Medicinal Plants and their Mode of Action. Journal of Herbal Medicine 2016; 6(3): 107-118.
33. Singh P, Mishra A, Singh P, Goswami S, Singh, A. Hypertension and herbal plant for its treatment : a review. Indian Journal of Research in Pharmacy and Biotechnology 2015; 3(5): 358-366.
34. Imenshahidi M, Hosseinzadeh H, Javadpour Y. Hypotensive effect of aqueous saffron extract (*Crocus sativus* L.) and its constituents, safranal and crocin, in normotensive and hypertensive rats. Phytotherapy research : PTR 2010; 24(7): 990-994.
35. Tabassum N, Ahmad F. Role of natural herbs in the treatment of hypertension. Pharmacognosy Reviews 2011; 5(9): 30-40.
36. Gilani AH, Shaheen F, Saeed SA. Cardiovascular actions of *Daucus carota*. Archives of Pharmacal Research 1994; 17: 150-153.
37. Jayakumar T, Sheu JR. Cardiovascular Pharmacological Actions of Rutaecarpine, a Quinazoline Carboline Alkaloid Isolated From Evodia rutaecarpa. Journal of Experimental and Clinical Medicine 2011; 3(2): 63-69.
38. Jiang JK, Chiu JH, Yu IT, Lin JK. In vitro relaxation of rabbit and human internal anal sphincter by rutaecarpine, an

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alkaloid isolated from *Evodia rutaecarpa*. Life Sciences 2000; 66(24): 2323-2335.

39. Singh AM, Sharma A, Narang RK, Singh G. Management of Hypertension with Conventional and Herbals Drugs. Journal of Drug Delivery and Therapeutics 2020; 10(3): 280-287.
40. Ajay M, Chai HJ, Mustafa AM, Gilani A, Mustafa MR. Mechanisms of the anti-hypertensive effect of *Hibiscus sabdariffa L*. calyces. Journal of Ethnopharmacology 2007; 109(3): 388-393.
41. Alaoui CE, Chemin J, Fechtali T, Lory P. Modulation of T-type Ca2+ channels by Lavender and Rosemary extracts. PLoS ONE 2017; 12 (10): 1-21.
42. Lu Y, Deng Y, Liu W, Jiang M, Bai G. Searching for calcium antagonists for hypertension disease therapy from *Moutan Cortex*, using bioactivity integrated UHPLC-QTOF-MS. Phytochemical Analysis 2019; 30(4): 456-463.
43. Shakeri F, Khazaei M, Boskabady MH. Cardiovascular Effects of *Nigella sativa L*. and its Constituents. Indian Journal of Pharmaceutical Sciences 2018; 80(6): 971-983.
44. Umar A, Imam G, Yimin W, Kerim P, Tohti I, Berké B, Moore N. Antihypertensive effects of *Ocimum basilicum L.* (OBL) on blood pressure in renovascular hypertensive rats. Hypertension Research 2010; 33(7): 727-730.
45. Agrawal M, Nandini D, Sharma V, Chauhan NS. International Journal of Pharmaceutical Sciences and Research 2010; 1(5): 1-21.
46. Kim JH. Cardiovascular diseases and panax ginseng: A review on molecular mechanisms and medical applications. Journal of Ginseng Research 2012; 36(1): 16-26.
47. Lee KH, Bae IY, Park SI, Park JD, Lee HG. Antihypertensive effect of Korean Red Ginseng by enrichment of ginsenoside Rg3 and arginine-fructose, Journal of Ginseng Research 2016; 40(3): 237-244.
48. Rossiert MF, Pythons CP, Ontario LN, Stephanie R. Blocking T-Type calcium channels with Tetrandrine Inhibits in Bovine Adrenal Glomerulosa cells. Endocrinology 1993; 132(3): 1035-1043.
49. Jiang Y, Liu M, Liu H, Liu S. A critical review: traditional uses, phytochemistry, pharmacology and toxicology of *Stephania tetrandra S. Moore* (Fen Fang Ji). In Phytochemistry Reviews 2020; 19(2): 449-489.
50. Dong FW, Jiang HH, Yang L, Gong Y, Zi CT, Yang D, Ye CJ, Li H, Yang J, Nian Y, Zhou J, Hu J M. Valepotriates from the roots and rhizomes of *Valeriana jatamansi* jones as novel N-type calcium channel antagonists. Frontiers in Pharmacology 2018; 9: 1-9.
51. Ojulari L, Olatubosun O, Okesina K, Owoyele B. The Effect of *Zingiber officinale* (Ginger) Extract on Blood Pressure and Heart Rate in Healthy Humans. IOSR Journal of Dental and Medical Sciences 2014; 13(10): 76-78.

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