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Mechanism of action of herbs present in the Siddha formulation Veppampoo mathirai against hypertension - A Review

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Abstract

Background

Hypertension is one among the leading non communicable disease that affects the people worldwide. It is the most prevalent trigger for morbidity and mortality associated with CVD's and its complications. Although, so many conventional drugs are prevalent for high blood pressure, people are still in search for traditional herbal medicines due to their safety and efficacy. The different constituents in herbal medicine plays a multitarget and synergistic role in the treatment of Hypertension. Veppampoo mathirai, a polyherbal siddha formulation containing fifteen herbs was found to be effective in reducing blood pressure which had been practised since decades. But, the mechanism of action is not known yet. However, it is very important to validate the potential of the herbal medicines scientifically, which are in practise, so that it might help them to establish with authentication for further use.

Objective

The objective of the study was to explore the mechanism of action of individual herbs present in the polyherbal siddha formulation Veppampoo mathirai through literature search in relation with modern aspect.

Material and Methods

This study reviewed databases like PubMed, Google scholar, and science direct with search terms, Antihypertensive herbals, mechanism of action, Blood pressure. Animal study, clinical study, in-vivo study to recapitulate the mechanism of the herbs that has antihypertensive action present in Veppampoo mathirai were collected.

Result

It was found that most of the herbs present in the formulation Veppampoo mathirai has antihypertensive activity related with modern aspect.

Conclusion

This study gave an idea that traditional herbal medicines indicated for specific diseases has relevant action indicated for that disease when analysed for modern aspect, apart from their traditional aspect. Hence, the active potential of the traditional medicines can be highlighted scientifically for further research.

Key words: Hypertension, Veppampoo mathirai, mechanism of action, literature search.

Background

Hypertension is one of the most challenging non communicable disease that affects the public worldwide. It is the most prevalent trigger for morbidity and mortality associated with cardiovascular diseases (CVD's) and its complications. If the rise in blood pressure (BP) can be prevented or controlled, many cardiovascular diseases (CVDs), cerebrovascular diseases, and its complications could be preventable. It is estimated to affect 1.13 billion people worldwide, and this is predicted to increase by 15–20% by 2025[1,2]. Prevalence of hypertension in India is about 27% in men and 24% in women. According to statistics cases of hypertension increased 10 times in last 4 decades in rural India and almost 30 times in urban India[3].

Although, many preventive and therapeutic pharmacological interventions are prevalent on the market, for high blood pressure, people are still in search for traditional herbal medicines due to their safety and efficacy. The different bio active constituents in herbal medicine plays a multitarget and synergistic role in the treatment of Hypertension. According to historical records, the first medicines with the characteristics that we know today, began only in the twentieth century-nineteenth century. More than 50% of existing medicines are synthesized from substances extracted from plants and herbs, thus creating the search for active ingredients present in plants[4]. Among the drugs used in clinical practice whose origin comes from natural products, we can mention, for example, ephedrine (from *Ephedra sinica*), aspirin (from *Salix alba*), lovastatin (from *Monascus purpureus*), and reserpine (from *Rauwolfia serpentina*)[5].

Indian traditional medicinal systems are considered as one of the oldest treatments in human history and it plays an important role in encountering global health care needs[6]. Siddha system practised in southern India, since centuries is well known for its preventive and therapeutic medicines. Veppampoo mathirai, a polyherbal formulation, consisting fifteen herbs remarkably reduces blood pressure but the mechanism of action is not known yet. Hence, a review was done to understand the mechanisms of antihypertensive action of the individual herbs present in the above formulation to establish its efficacy scientifically.

Material and Methods

Databases like PubMed, Google scholar, and science direct with search terms, Antihypertensive herbals, mechanism of action, Blood pressure were applied for literature

search. Animal study, clinical study, in-vivo study related to the mechanism of the herbs that has antihypertensive action present in Veppampoo mathirai were collected.

Hypertension is classified as either essential hypertension (EH) or secondary hypertension, and EH accounts for about 90–95% of the cases characterized by high blood pressure with no underlying cause whereas secondary Hypertension results from any underlying disease condition[6]. Thus, the goals of antihypertensive treatment are to limit end-organ injury and so reduce CVD morbidity and mortality. Indeed, meta-analyses demonstrate that a 10-mmHg reduction in SBP, or a 5-mmHg reduction in DBP, reduces the relative risk of all major CVD events by 20%[7.8]

Hypertension Pathophysiology

Blood pressure is determined by the product of cardiac output (CO) and peripheral vascular resistance (PVR), and regulated by neural, renal, humoral, endothelial, and local control mechanisms of cardiovascular and renal functions. In this way, Systemic arterial hypertension (SAH) can develop from abnormalities in any homeostatic control mechanisms of PVR and/or CD [9].

The major contributing factors identified by previous researches for hypertension were (i) increased sympathetic nervous system activity; (ii) increased levels of long term high sodium intake, inadequate dietary intake of potassium and calcium; (iii) altered renin secretion related to elevated activity of the Renin aldosterone system (RAS); (iv) increased activity of Angiotensin converting enzyme (ACE) resulting over production of angiotensin II (Ang II) and deactivation of kallikrein kinin-system (KKS); (v) endothelial dysfunctions and deficiencies of vasodilators including reduced nitric oxide (NO) bioavailability; (vi) abnormalities in vessel resistance due to vascular inflammation, increased activity of vascular growth factors and altered cellular ion channel[10,11,12,13,14]. Although all of the above factors clearly contribute to the pathogenesis of hypertension, the hyperactivity of the RAS, endothelial dysfunction, enhanced activation of sympathetic nervous system and structural abnormalities in resistance vessels play critical roles in the development and progression of this disease[14,15,16].

Classification of Antihypertensive drugs

Antihypertensives may be divided into two broad groups, the first group being those which directly or indirectly block the renin–angiotensin system (RAS), for example, ACEIs,

angiotensin receptor antagonists (ARAs), direct renin inhibitors (DRIs), and to a lesser extent β-blockers. While these drugs have multiple mechanisms of action, their predominant effect is to cause vasodilatation. The second group of drugs works by increasing water and sodium excretion, thereby reducing intravascular volume, or by causing vasodilatation through non-RAS pathways, for example, diuretics and calcium channel blockers (CCBs). The actions of this second group increase RAS activity through negative feedback, a result of which is that they can potentiate the activity of drugs which target and inhibit the RAS.

Siddha formulation Veppampoo Mathirai

The polyherbal formulation VPM consists of 15 herbs - *Azadirachta indica, Solanum trilobatum, Phyllanthus niruri, Eclipta prostrate, Zingiber officinale, Piper nigrum, Piper longum, Terminalia chebula, Terminalia bellerica, Emblica officinalis, Eugenia caryophyllata, Cinnamom zeylanicum, Elatteria cardamomum, Coeus vettiveroides,* and *Citrus lemon* described in classical Siddha text, Noigaluku Siddha parigaaram, part I, by author Shanmugavelu indicated for reducing blood pressure[17].

Fig.1. Herbs present in Veppampoo mathirai

I J K L

M N O

A, *Azadiracta indica* B. *Solanum trilobatum* C. *Phyllanthus niruri* D. *Eclipta prostrata*

E. *Zingiber officinale* F. *Piper nigrum* G.*Piper longum* H.*Terminalia chebula*

I.*Terminalia bellerica* J. *Emblica officinalis* K. *Eugenia caryophyllata*, L. *Cinnamom zeylanicum*

M. *Elatteria cardamomum* N. *Coeus vettiveroides* O.*Citrus lemon*

Mechanism of action of herbs present in Veppampoo Mathirai

Azadiracta indica

Common name is Neem and Tamil name is Vembu, belongs to the Family Meliaceae. The flowers are the main ingredient used in the medicine and hence it was named after the flowers as Veppampoo mathirai, Flowers bloom in bunches and the flowering season is April to June every year. The plant posseses bioactive components Azadiractin, Nimbin, Nimbidin, Flavonoids, Tannins. A study by Abdul et al, 2014, showed that neem extract possesses combination of vasodilator and cardiac depressant constituents. The vasodilatory effect is mediated through Ca^{++} channel blockade and Nitric oxide (NO) pathway linked to muscarinic vascular receptors while the cardiac depressant effect is probably the outcome of Ca^{++} antagonist effect which possibly explain its blood pressure lowering effect. Effects of *Azadirachta indica* leaf extract on serum lipid profile changes in normal and streptozotocin - induced diabetic rats have been studied by *RR Chattopadhyay*, 2005, with a view to elucidate its possible effect on cardiovascular disease induced by hyperglycemia[18]. It was observed that *A.indica* leaf extract significantly reduced the total cholesterol, LDL- and VLDL-cholesterol, triglycerides and total lipids of serum in streptozotocin induced diabetic rats but HDL-cholesterol levels remained unchanged. Thus, *A.indica* leaf extract may be helpful in controlling the blood pressure, development of hyperlipidemia as well as atherosclerosis[19].

Solanum trilobatum

Tamil name is Thoothuvelai and common name is climbing brinjal. It belongs to the family Solanaceae. Phytochemical screening of the dried leaves showed alkaloids, triterpenoids, phenolics, tannins, flavonoids, anthoquinones, phytosterols, saponins, cardiac glycosides, soladunalinidine, tomatidine, solanine, sobatum, solasodine, diosgenin, and β-solamarine[20] *S. trilobatum* displayed potent antioxidant properties and alleviate oxidative stress induced hepatotoxic effects and possible engross mechanisms related to free radical scavenging properties[21]. It exhibits cardio protective activity and the aqueous leaves extract has antihyperlipidaemic activity in streptozotocin induced diabetic rats[22,23].

Phyllanthus niruri

Tamil name Keezha nelli, and common name Carry me seed. Family Euphorbiaceae. In Spontaneously Hypertensive Rats (SHRs), Corilagin, a tannin constituent present in *P. niruri*, has been reported to reduce the blood pressure (Cheng et al., 1995). The stonebreaker is reported to decrease BP in rabbits (Amaechina and Omogbai, 2007). Antihypertensive activity of *P. niruri* extract is mediated by vasoactive phytoconstituents that dilate the arterial wall via endothelium-dependent pathways and β-adrenoceptor activity which, in turn, cause vasorelaxation and reduce blood pressure[24]. A study supports the traditional use of aqueous leaves extract of Cynodon dactylon and P. niruri for the treatment of diabetes and arterial hypertension, in rats with simultaneous type 2 diabetic and hypertension and indicate that they may have a beneficial effect in patients with co-existing diabetic hypertension[25]. The antihypertensive effect is likely related to its diuretic, antioxidant, and anti-inflammatory activities (Kassuya et al., 2005; Maity et al., 2013). In a clinical trial, P. niruri, increased urinary output as well as levels of Na+ in urine (Srividya and Periwal, 1995). These actions were without any noticeable harmful side effects in the mild hypertensive subjects of the above study. In addition, the aqueous extract of P. amarus (200 mg/kg) was shown to increase plasma antioxidants like reduced glutathione (GSH), Glutathione peroxidase (GPx), superoxide dismutase (SOD), and catalase (CAT) in rats (Karuna et al., 2009).

Eclipta prostrata

Eclipta prostrata belongs to the Family Asteraceae and is commonly known as False daisy or Ink plant in English and in tamil as Karisalai, The antioxidant effects of *E. prostrata* were evaluated in Charles River Sprague-Dawley rats. The extract at 50 mg/kg and 100 mg/kg dose significantly reduced the oxidative biomarkers such as serum lipid peroxide, serum hydroxyl radical levels[26] *Eclipta alba* and its active constituents culumbin exhibit remarkable

anti-hypertensive activity on anesthesized rats. Diuretic effect which contributes its antihypertensive action can be due to the potassium content of the leaves, due to diuresis and increased sodium excretion.[27]

Zingiber officinale

Common name Ginger, Tamil name Inji and belongs to the family Zingiberaceae. Ghayur in his study has reported that the crude extract of ginger induces the Ca^{2+} channel-blocking (CCB) activity that lowers the blood pressure which ultimately reduces the hypertension in the patients[28]. Zingiber officinale's (ZO) BP lowering effect was mediated through the blockade of voltage-dependent calcium channels. Another suggested mechanism may involve the serotonergic antagonistic property of ZO (Ghayur & Ghilani; 2005) Human trials for the hypotensive effects of ZO have been few and generally used on low dose with inconclusive results (Nicroll & Tenien; 2009)[29]. A study by Fugh-Berman,2000, conclusively showed that consumption of ZO at doses has a blood pressure lowering effect and that this effect is dose-dependent.[30]

Piper nigrum, Piper longum

The common name for Piper nigrum is Pepper and Tamil name as Milagu while for piper longum, common name is long pepper and Tamil name is Thippili. Both belongs to the family Piperaceae. Piperine is the major phytoconstituent present in these plants. Administration of piperine intravenously caused a dose-dependent (1 to 10 mg/kg) decrease in mean arterial pressure (MAP) in normotensive anesthetized rats. In rat aorta, piperine demonstrated endothelium-independent vasodilator effect and was more potent against high K+ precontractions than phenylephrine (PE). In bovine coronary artery preparations, piperine inhibited high K+ precontractions completely. These data indicate that piperine possesses a blood pressure-lowering effect mediated possibly through Calcium channel blockade (CCB), while consistent decrease in BP was restricted by associated vasoconstrictor effect. Additionally, species selectivity exists in the CCB effect of piperine[31].

Terminalia chebula

Tamil name Kadukkai, common name chebulic myroblan and belongs to the family Combretaceae. Studies showed that T.chebula has various biological activities, including antimicrobial, antiinflammatory, antioxidant and antitumor (Zhang et al., 2016)[32]. The

antioxidant and antihypertensive properties of Pestalotiopsis isolates from T. chebula were determined in a study (Tejeswi et al 2008) by measuring 1,1-diphenyl-2-picrylhydrazyl inhibitory activity, lipid peroxidation, and angiotensin-converting enzyme inhibition activity. The antioxidant, antibacterial, and antihypertensive activities demonstrated the potential of *Pestalotiopsis* extracts as therapeutic targets[33].

Terminalia bellerica

Tamil name Thandrikkai, common name belleric myroblan and belongs to the family Combretaceae. *Terminalia bellerica* extract was found to contain flavonoids, sterols and tannins. Flavonoids and tannins are reported to possess Ca++ antagonist effect and the presence of such compounds in *Terminalia bellerica* might be contributing in its cardiovascular effects. In isolated guinea-pig atria, Terminalia bellerica crude extract inhibited the force and rate of atrial contractions. These results indicate that *Terminalia bellerica* lowers BP through Ca++ antagonist mechanism and thus provides a sound mechanistic background for its medicinal use in hypertension. A study by Khan A, 2008, showed that *Terminalia bellerica* exhibits BP-lowering effect possibly mediated through inhibition of Ca++ influx via membranous calcium channels and its release from the intracellular stores and thus explains its medicinal use in hypertension[34].

Emblica officinalis

Common name Gooseberry and Tamil name Nellikkai, belongs to the family Phyllanthaceae. *Emblica officinalis* (EO) has antioxidant properties. The antihypertensive activity of EO was also linked with increased serum NO, K(+) levels and decreased Na(+) levels. Moreover, EO robustly increased activated eNOS expression in heart. EO reduces oxidative stress, prevents development and progression of hypertension as well as cardiac and renal hypertrophy in DOCA/High Salt -induced hypertension rat model via modulation of activated eNOS, endogenous antioxidants, serum NO and electrolyte levels. EO is rich in phenols (gallic acids, methyl gallate, ellagic acid, and trigalloyl glucose) and flavonoids (quercetin and kaempferol) EO can be effective in the prevention or treatment of hypertension through its strong antioxidative properties[35]. More importantly, EO is a plant with the ACE (angiotensin-converting enzyme) inhibitor and diuretic activity which can explain its antihypertensive effect.[36,37]

Eugenia caryophyllata, Cinnamom zeylanicum

Common name clove and Tamil name kirambu for *Eugenia caryophyllata* and belongs to the family Myrtaceae whereas *Cinnamom zeylanicum* belongs to the family Lauraceae, Tamil name Lavangapattai, Common name Cinnamon. Methanol extract of *Cinnamomum zeylanicum* stem bark (MECZ) possesses antihypertensive and organ protective effects that may result from its ability to increase the production of the endogenous NO and/or to regulate dyslipidemia. Pre-treatment of rats with L-NAME inhibited the sustained plant antihypertensive effects,[38] suggesting a possible active vasodilatation, which might be partly mediated by an endothelial l-arginine/nitric oxide pathway. In isolated rat aortic rings pre-contracted with KCl (60mM), the extract exhibited cumulative vasodilating effects, which were attenuated with either L-NAME, vascular endothelium removal or both tetraethylammonium and glibenclamide pre-treatments. The vasorelaxant effects may be involved in the extract antihypertensive mechanism, partially by increasing the endothelial nitric oxide and by activating the KATP channels in vascular smooth muscle[39]

Elatteria cardamomum

Elettaria cardamomum is commonly known as cardamom and in Tamil as Elam belongs to the family Zingiberaceae. In powder form (3 g), it decreases mean arterial blood pressure (MAP), as well as SBP and DBP in pre-hypertensive (Stage 1) subjects. SBP and DBP were significantly decreased by 19 and 12 mmHg, respectively. The mechanism for this hypotensive action appears to be due to cardamom's ability to increase the total antioxidant status (Verma et al., 2009)[40]. In anesthetized rats, 3– 100 mg/kg of E. cardamomum crude extract was also able to reduce BP. In the same model, 1–10 mg/kg of the crude extract exhibited diuretic effects. It also relaxed pre-constricted rat aortic rings with a concentration of 2.94 mg/ml, possibly by inhibiting Ca2+ movement through transmembrane calcium channels (Gilani et al., 2008)[41].

Coeus vettiveroides

Tamil name Vettiver, common name kuskus grass, belongs to the family Poaceae. The methanolic extract of Coleus vettiveroides Jacob possesses potent antioxidant and lipid peroxidation activity that can be employed in protecting tissue from the oxidative stress[42]

Citrus lemon

Tamil name Elumichai, Common name Lemon, belongs to the family Rutaceae. In a study by Shahabeddin Bahrani et al, 2020, it was concluded that the short-term effects of lemon

juice are greater than those of garlic and the long-term effects of garlic consumption are greater than those of lemon juice, but these results can be very useful for hypertensive patients who can benefit from these substances and eat more in their diet and thus have better control over their blood pressure[43]. C. limon juice is capable to lower blood pressure when this is elevated in hypertensive patients, without influencing on the blood pressure in normotensive patients (Avello, 2014)[44]. Lemon causes clinically significant interactions with a variety of drugs including calcium antagonists. The antioxidant activities of lemon juice are associated with the actions of flavonoids and coumarin, which act as radical scavengers[45].

Conclusion

This review was able to provide the various mechanism of action of the individual ingredients of Siddha formulation Veppampoo mathirai against hypertension that was perfomed in animal model and clinical trials to substantiate the potential antihypertensive effect of the formulation with scientific basis.

References

1.WHO. Hypertension. World Health Organisation. https://www.who.int/news-room/fact-sheets/detail/hypertension. Published 2019. Accessed 2 October 2020.Google Scholar

2.Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J. Global burden of hypertension: analysis of worldwide data. *Lancet*. 2005; **365**(9455): 217– 223.

3.Kishore J. Gupta N. Kohli C.Kumar N. Prevalence of hypertension and determination of its risk factors in rural Delhi. International journal of hypertension 2016

4.J. B. Calixto and J. M. Siqueira Júnior, "Drug development in Brazil: challenges. Bahia Medical Gazette," *Bahia*, vol. 78, 2008.View at: Google Scholar

5.B. Baharvand-ahmadi, M. Bahmani, P. Tajeddini, M. Rafieian-kopaei, and N. Naghdi, "An ethnobotanical study of medicinal plants administered for the treatment of hypertension," *Journal of Renal Injury Prevention*, vol. 5, no. 3, pp. 123–128, 2016.View at: Publisher Site | Google Scholar

6.Chitra SM, Mallika P, Anbu N, Narayanababu R, Sugunabai A, David Paul Raj RS, Premnath D. An open clinical evaluation of selected siddha regimen in expediting the management of COVID-19 -a randomized controlled study. J Ayurveda Integr Med. 2022 JanMar;13(1):100397.

7.O. A. Carretero and S. Oparil, "Essential hypertension. Part I: definition and etiology," *Circulation*, vol. 101, no. 3, pp. 329–335, 2000.View at: Google Scholar

8. Ettehad D, Emdin CA, Kiran A, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. *Lancet*. 2016; **387**(10022): 957– 967.CrossrefPubMedWeb of Science®Google Scholar

9. Thomopoulos C, Parati G, Zanchetti A. Effects of blood pressure lowering on outcome incidence in hypertension. 1. Overview, meta-analyses, and meta-regression analyses of randomized trials. *J Hypertens*. 2014; **32**(12): 2285– 2295.
CrossrefCASPubMedWeb of Science®Google Scholar

10.A. F. Sanjuliani, "Fisiopatologia da hipertensão arterial: conceitos teóricos úteis para a prática clínica," *SOCERJ Magazine*, vol. 15, no. 4, pp. 210–218, 2002.

11. Schulz, E.; Gori, T.; Munzel, T. Oxidative Stress and Endothelial Dysfunction in Hypertension. Hypertens. Res. 2011, 34, 665–673. 46.

12. Paravicini, T.M.; Touyz, R.M. Redox Signaling in Hypertension. Cardiovasc. Res. 2006, 71, 247–258

13. Cuzzocrea, S.; Mazzon, E.; Dugo, L.; di Paola, R.; Caputi, A.P.; Salvemini, D. Superoxide: A Key Player in Hypertension. FASEB J. 2004, 18, 94–101.

14. Intengan, H.D.; Schiffrin, E.L. Vascular Remodeling in Hypertension: Roles of Apoptosis, Inflammation, and Fibrosis. Hypertension 2001, 38, 581–587.

15. Hall, J.E.; Granger, J.P.; do Carmo, J.M.; da Silva, A.A.; Dubinion, J.; George, E.; Hamza, S.; Speed, J.; Hall, M.E. Hypertension: Physiology and Pathophysiology. Comp. Physiol. 2012, 2, 2393–2442.

16. Beevers, G.; Lip, G.Y.H.; O'Brien, E. The Pathophysiology of Hypertension. BMJ 2001, 322, 912–916.

17. Shanmugavelu M. Noigaluku Siddha parigaaram, Part I. 3rd ed. Chennai, India: Venkateshwara Publications; 2012. p. 146-7

18. Shah AJ, Gilani AH, Hanif HM, Ahmad S, Khalid S, Bukhari IA. Neem (Azadirachta indica) lowers blood pressure through a combination of Ca" channel blocking and endothelium-dependent muscarinic receptors activation. Int J Pharmacol. 2014;10(8):418-28.

19. Chattopadhyay RR, Bandyopadhyay M. Effect of Azadirachta indica leaf extract on serum lipid profile changes in normal and streptozotocin induced diabetic rats. African Journal of Biomedical Research. 2005;8(2):101-4.

20. Amir M., Kumar S. Possible Industrial application of genus Solanum in twenty-first century—A review. *J. Sci. Ind. Res.*2004;63: 116–124. [Google Scholar]

21. Vijaimohan K., Mallika J., Shyamala D.C. Chemoprotective effect of Sobatum against lithium-induced oxidative damage in rats. *J. Young Pharm*. 2010;2: 68–73. doi: 10.4103/0975-1483.62217. [PMC free article] [PubMed]

22. Ganesan K, Sukalingam K, Xu B. Solanum trilobatum L. Ameliorate Thioacetamide-Induced Oxidative Stress and Hepatic Damage in Albino Rats. Antioxidants (Basel). 2017 Aug 22;6(3):68. doi: 10.3390/antiox6030068. PMID: 28829363; PMCID: PMC5618096.

23. Ganesan, Kumar & Ramasamy, Maheswaran & Banu, Gani. (2013). Antihyperlipideamic effect of Solanum trilobatum L. leaves extract on streptozotocin induced diabetic rats. 3. 51-57.

24. Idris Bello, Nasiba Salisu Usman, Aidiahmad Dewa, Kabiru Abubakar, Nafiu Aminu, Mohd Zaini Asmawi, Roziahanim Mahmud. Blood pressure lowering effect and vascular activity of Phyllanthus niruri extract: The role of NO/cGMP signaling pathway and β-adrenoceptor mediated relaxation of isolated aortic rings, Journal of Ethnopharmacology,Volume 250,2020,112461,ISSN 03788741,https://doi.org/10.1016/j.jep.2019.112461.

25. Bharati, Deepak & Rawat, swati rawat & Sharma, Paban & Shrivastava, Birendra. (2016). Comparative evaluation of antidiabetic antihypertensive activity of Cynodon dactylon L. and Phyllanthus niruri L in ratswith simultaneous type 2 diabetic and hypertension. 8. 255-263.

26. Kim, D.-I.; Lee, S.-H.; Choi, J.-H.; Lillehoj, H.S.; Yu, M.-H.; Lee, G.-S. The Butanol Fraction of *Eclipta prostrata* (Linn) Effectively Reduces Serum Lipid Levels and Improves Antioxidant Activities in CD Rats. *Nutr. Res.* **2008**, *28*, 550–554. [**Google Scholar**] [**CrossRef**]

27. Verma, Rakesh & Shankar, Pratap & Dwivedi, Shailendra & Dixit, Rakesh. (2012). Effects of eclipta alba and boerhaavia diffussa on normal blood pressure and hypertension in rats and their comparison with amlodipine. ijpsr. 3. 1832-.

28. M. N. Ghayur, A.H. Gilani, Ginger lowers blood pressure through blockade of voltage dependent calcium channels, Journal of Cardiovascular Pharmacology, 45, 2005, 74-80 [12].

29.R. Nicroll, M.Y. Henein, Ginger (Zinger offiicinale Roscoe): a hot remedy for cardiovascular disease? International Journal of Cardiology, 131, 2009, 408-9

30.A. Fugh-Berman, Dietary supplements in the prevention and treatment of cardiovascular disease, Preventive Cardiology, 2000, 24- 32 [11].

31. Taqvi SI, Shah AJ, Gilani AH. Blood pressure lowering and vasomodulator effects of piperine. J Cardiovasc Pharmacol. 2008 Nov;52(5):452-8. doi: 10.1097/FJC.0b013e31818d07c0. PMID: 19033825.

32. Zhang XJ, He LJ, Lu Q, Li DY. [Pharmacological activity of Terminalia chebula]. Zhongguo Zhong Yao Za Zhi. 2016 Feb;41(4):619-623. Chinese. doi: 10.4268/cjcmm20160412. PMID: 28871682.

33. Tejesvi MV, Kini KR, Prakash HS, Subbiah V, Shetty HS. Antioxidant, antihypertensive, and antibacterial properties of endophytic Pestalotiopsis species from medicinal plants. Can J Microbiol. 2008 Sep;54(9):769-80. doi: 10.1139/w08-070. PMID: 18772940.

34. Khan, A.-U. and Gilani, A.H. (2008) "Pharmacodynamic evaluation of Terminalia bellerica for its antihypertensive effect," *Journal of Food and Drug Analysis*: 2008, Vol. 16: Iss. 3, Article 8.Available at: https://doi.org/10.38212/2224-6614.2355

35. Khopde S. M., Indira Priyadarsini K., Mohan H., et al. Characterizing the antioxidant activity of amla (Phyllanthus emblica) extract. *Current Science.* 2001;81(2):185–190. [

36. Narasimhacharya A., Vasant R. A., Prajapati P. C. Angiotensin-converting enzyme inhibition by certain fruits: an in vitro study. *Current Trends in Biotechnology and Pharmacy.* 2010;4(3):801–808. [Google Scholar]

37. Sohgaura A., Bigoniya P., Shrivastava B. Diuretic potential of cynodon dactylon, emblica officinalis, kalanchoe pinnata and bambusa nutans. *Journal of Pharmacognosy and Phytochemistry.* 2018;7(3):2895–2900. [Google Scholar]

38. Nyadjeu P, Nguelefack-Mbuyo EP, Atsamo AD, Nguelefack TB, Dongmo AB, Kamanyi A. Acute and chronic antihypertensive effects of Cinnamomum zeylanicum stem bark methanol extract in L-NAME-induced hypertensive rats. BMC Complement Altern Med. 2013 Jan 31;13:27. doi: 10.1186/1472-6882-13-27. PMID: 23368533; PMCID: PMC3572416.

39. De Gruyter, Antihypertensive and Vasorelaxant Effects of Cinnamomum zeylanicum Stem Bark Aqueous Extract in Rats. Journal of Complementary and Integrative Medicine. January 2011; 8(1) DOI: 10.2202/1553-3840.1490

40. Verma SK, Jain V, Katewa SS. Blood pressure lowering, fibrinolysis enhancing and antioxidant activities of cardamom (Elettaria cardamomum). Indian J Biochem Biophys. 2009 Dec;46(6):503-6.

41. Gilani A. H., Jabeen Q., Khan A. U., Shah A. J. (2008). Gut modulatory, blood pressure lowering, diuretic and sedative activities of cardamom. *J. Ethnopharmacol.* 115, 463–472. 10.1016/j.jep.2007.10.015

42. Gopalakrishnan G, Dhanapal CK. Evaluation of in-vivo antioxidant activity of ursolic acid acetate isolated from methanolic extract of Coleus vettiveroides (jacob) in streptozotocin-induced oxidative stress in rats.

43. Shahabeddin Bahrani S, Abdulkarimi R, Gomar E, Afshari S, Mohamadi MA. The comparison of the effect of garlic and lemon juice on blood pressure and comfort in hypertensive patients. Revista Latinoamericana de Hipertensión. 2020;15(3):154-65.

44. Avello M, Jofré P, Pastene E, Fernández P. Use of Citrus limon l.(lemon) in treating blood pressure sudden rises. International Journal of Pharmacognosy and Phytochemical Research. 2014;6(3):606-11.

45. Kawakami K, Yamada K, Takeshita H, Yamada T, Nomura M. Antihypertensive effect of lemon juice squeezed residue on spontaneously hypertensive rats. Food Science and Technology Research. 2021;27(3):521-7.