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REVIEW ARTICLE

Herbals as Antihypertensive Agent: A Review

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ABSTRACT

Hypertension is a chronic condition that is commonly characterised as a permanent rise in the level of blood pressure. Chronic cardiac disease, stroke, coronary heart disease, heart failure, peripheral artery disease, cerebrovascular disease, renal dysfunction, atrial fibrillation, left ventricular hypertrophy, retinal haemorrhage, and visual impairment are risk factors linked to hypertension. Smoking, stress, excessive salt consumption, obesity, and alcohol are primarily factors causing hypertension. As an antihypertensive agent, different groups of antihypertensive drugs such as diuretics, renin-angiotensin system inhibitors, calcium channel blockers (CCB) and beta blockers (BB) are used, although these drugs have side effects. Herbal therapies take on these therapies as the plants include a range of chemical components that are effective against different diseases, including cardiovascular diseases (CVDs), as well as showing fewer side effects. Prevention of ACE activity, reduction of vascular resistance, cholinergic mediated vasodilation, increase of nitric oxide (NO) synthesis, endothelium-dependent arterial contraction inhibitory effects are some of the expected mechanisms of action by which antihypertensive activity is demonstrated by these metabolites. We have tried in this analysis to summarize most of the metabolites that can be used as an antihypertensive agent, such as alkaloids, glycosides, terpenoids, etc.

KEYWORDS-*hypertension, chronic, herbal, metabolites, side effects*

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INTRODUCTION

Systemic arterial hypertension is commonly characterized as a permanent rise in the level of blood pressure [1].Hypertension is a subject of considerable concern since there is a growing prevalence of hypertension in the world. According to estimates, more than 1.4 billion people worldwide suffer from hypertension [2]. Chronic cardiac disease, stroke, coronary heart disease, heart failure, peripheral artery disease, cerebrovascular disease, renal dysfunction, atrial fibrillation, left ventricular hypertrophy, retinal hemorrhage, and visual impairment are some risk factors linked to hypertension [3,4].There are some beliefs that only older folks experience hypertension, but that's not the real case. Studies performed in 2015 on the people of England indicated that there was hypertension in over 2.1 million people less than 45 years old [5].In the research conducted by Franco and co-authors, it was proposed on the basis of Framingham data that "total life expectancy for normotensive males and females was 5.1 and 4.9 years longer compared to hypertensive patients [6].Even with advancements in science and the availability of medical studies, hypertension care in many parts of the world remains a problem [7].As far as prevalence of hypertension is concerned; it was found that individuals who have high body mass index, high waist to hip ratio were more prone to hypertension [8].Hypertension is mainly classified as primary hypertension and secondary hypertension [9].Primary hypertension refers to an unexplained explanation for a rise in blood pressure, while the causes of secondary hypertension are clearly apparent. Smoking, stress, excessive salt intake, obesity, and alcohol are some known variables that contribute to hypertension [10].

There are various outcomes of chronic hypertension, but left ventricular hypertrophy and coronary artery disease are the most serious outcomes, primarily caused by pressure overload and increased muscle mass and wall thickness [11].Studies have also suggested that the hypertension is also the cause of Nigerian "unexpected death" syndrome which causes sudden and unexplained deaths [12].Different types of antihypertensive medications are currently being used, such as diuretics, renin-angiotensin system inhibitors, calcium channel blockers (CCB) and beta-blockers (BB)but these drugs have their side effect like muscle cramps, dizziness, extreme tiredness, dehydration, blurred vision, abnormal heart rate, skin rash etc [13].In addition, certain requirements exist for the use of certain types of medicinal products, such as an ACE inhibitor, an angiotensin receptor blocker, a direct renin inhibitor, or atenolol, due to their fetotoxic nature, they are not administered to pregnant women [14].Usage of allopathic therapies is currently taken over by herbal therapies due to different side effects, as the plants contain a range of chemical components that are effective against various diseases, including cardiovascular diseases (CVDs), and there is also a reality that compared to certain allopathic medicines, herbal remedies display low side effects [15,16].There are different plants in folklore or traditional medicine that are used as an antihypertensive agent, but their mechanism of action is not fully known [17].Although various experimental studies indicated that these plants demonstrate their activity through certain metabolites that mainly have antioxidant and anti-inflammatory properties [18].In this review we tried to summarize most of the metabolites that can be used as an antihypertensive agent.

METABOLITES

Allicin

Allicin is an organosulfur compound present mainly in *Allium sativum* which belongs to family Alliaceae. Various pharmacological activities reported in allicin mainly include antithrombotic, antidiabetic, antitumor genetic, antioxidant, anticarcinogenic, anti-atherosclerosis, and antihypertensive activities. In order to establish its antihypertensive activity, comparative studies were carried out using nicorandil and allicin on dexamethasone induced hypertension in wistar rats. It was found that the blood pressure in Allicin-treated rats was decreased as compared to hypertensive control group. The proposed mechanism of action behind antihypertensive activity of allicin is decrease in vascular resistance and a corresponding decrease in total peripheral resistance, which finally leads to activation of NO synthase [19].

Linalool

Linalool (an open chain monoterpene tertiary alcohol) is generally found as a major constituent of essential oils in many aromatically herbal species. Previous studies confirmed that it shows various activities like anxiolytic, anticonvulsant, sedative and hypotensive activities. In the present study for evaluating antihypertensive activity of linalool, Paulo J. C. Anjos et al has recorded the changes in the heart rate and mean arterial pressure before and after the rats were exposed to linalool and atropine separately. Linalool [200 mg/kg BW; oral (v.o.)] lowered blood pressure without changing the heart rate in hypertensive rats. Linalool induced concentration-dependent relaxation in intact rings of the rat mesenteric artery, which did not improve after atropine administration. The contractions caused by CaCl2 were also antagonized by Linalool. From these experiment results, authors suggested that linalool shows antihypertensive activity by directly acting on smooth muscles that contributes to vasodilation [20].

Puerarin

Puerarin, found in the roots of *Pueraria lobata,* is mainly used as an antidiabetic, anti-inflammatory, anti-oxidant agent. To evaluate antihypertensive activity of puerarin, systolic blood pressure (SBP) of Dahl Salt Sensitive rats was monitored by using tail-cuff method. It was observed that puerarin statistically reduced the SBP and it may be due to cardiac and vascular remodeling by restoring multiple endothelium derived vasoactive substances such as NO, ET1, inhibition of vascular inflammation and activation of ERK1/2 by Puerarin. These above results indicate that puerarin can be used as a potent antihypertensive agent [21].

Eugenol

Eugenol is a phenylpropanoid compound which is mainly extracted from dietary plants like *Syzygium aromaticum*, *Ocimum Gratissimum*, *Ocimum basilicum*, *Cinnamomum zeylanicum* and *Myristica fragrans*. Kamatou GP et al in their studies showed many pharmacological actions of eugenol, some of which includes antimicrobial, antioxidant and anti-inflammatory actions.Dieniffer Peixoto-Neves et al conducted in vitro studies on the cerebral arteries of male sprague-dawley rats by using patch-clamp electrophysiology and it was observed that eugenol inhibits the voltage-dependent calcium (Ca2+) currents in the arteries. Conclusively, this experimental study suggested that eugenol dilates cerebral

arteries via multimodal inhibition of voltage-dependent Ca2+ channels so it can be used as a potential antihypertensive agent [22].

Epicatechin

Epicatechin is a natural flavonoid which is generally found in green tea, black berries, black grapes, apples, black tea, cocoa etc. In order to establish its antihypertensive activity, an experimental study was carried out on spontaneously hypertensive rats. It was observed that epicatechin improved erythrocyte deformability in the blood, increased total antioxidant potential and decreased concentrations of nitrotyrosine. In the aorta, it substantially increased the activity of nitric oxide synthase (NOS) and increased vasorelaxation based on NO. In the left heart ventricle, without altering gene expressions of nNOS, iNOS, and eNOS, it increased NOS activity. Moreover, epicatechin administration resulted in a decline in blood pressure and reduction in heart rate (571.8±17 bpm in control versus 524.8 ± 8.2 bpm in epicatechin). The outcome of experiment suggested that epicatechin modulates BP in hypertensive rats by proliferating NO levels in vasculature thus acts as a potent antihypertensive agent [23].

Tetrahydropalmatine

Tetrahydropalmatine (THP) is an alkaloid class chemical agent which is mainly isolated from *Corydalis yanhusuo*. Major reported actions of this metabolite are cardio protection, neuroprotection, anti-oxidant, anti-apoptosis, and anti-inflammation. In order to determine antihypertensive activity of THP, an experimental study was conducted on Male Wistar rats, in which their aortas were isolated and the aortic rings were subjected to THP, KCl, Phenylephrine and Nifedipine. The plateaued contraction force values were recorded and it was observed that KCl and Phenylephrine subjected to aortic rings contraction was reduced by TPH resulting in the relaxation of rat aorta. This study suggested that THP shows antihypertensive action by different contractors such as PI3K/Akt/eNOS/NO/cGMP signaling pathway, Ca2C channels and KC channels. Thus, with these uncovering, it is stipulated that THP might be a good alternative for treatment of hypertension [24].

6-Gingerol

The Investigation was carried out to study the change in impression of biomarkers associated with emergence of hypertension through PPARδ in HUVECs, HEK293, and differentiated 3T3-L1 Cells. The effect of 6-gingerol were assayed via various methods like reverse transcription polymerase chain reaction (RT-PCR), western blotting, and immunocytochemical staining for biomarkers involved in hypertension in human umbilical vein endothelial cells (HUVECs), human embryonic kidney cells (HEK293 cells), and mouse preadipocytes (3T3-L1 cells). It was revealed that 6-Gingerol treated HEK293 cells shows reduction in assertion of epithelial sodium channel proteins (ENaC). It was also found that it attenuates vascular cell addition protein and TNFx in HUVECs, aggregation of lipids in differential (3T3-L1 cells). The authors have concluded that 6-Gingerol improves the level of biomarkers via PPARδ in various cell lines (HUVECs, HEK293, and Differentiated 3T3-L1 Cells) thus acts as an antihypertensive agent [25].

Citronellol

Citronellol is generally obtained from antihypertensive properties possessing medicinal plants like *Cymbopogon winterianus*, *Cymbopogon citratus*, and *Lippia alba*. Previous studies suggested that citronellol shows antibacterial, antifungal, antispasmodic and anticonvulsant activity. The experimental studies on this volatile oil constituent were carried out using Male Wistar normotensive rats which were subjected to Citronellol (1–20 mg/ kg, i.v.) and Nifedipine. Mean arterial pressure (MAP) and heart rate (HR) in these non-anaesthetized rats was measured and it was found that Citronellol caused non-dose dependent hypotension and relaxations in intact rings of rat mesenteric artery, moreover it strongly antagonized the contractions induced by CaCl2. The results of this experimental study suggested that Citronellol shows calcium-blocking as well as vasorelaxant activity, thus can be used as a potential antihypertensive agent [26].

Anthocyanin

Previous studies on anthocyanin showed that they have various pharmacological effects such as antihypertensive, anticancer, anti-inflammatory, antimicrobial and anti-obesity effects. To demonstrate its antihypertensive activity, an experimental study was carried out using spontaneously hypertensive rats. Anthocyanin containing pigments were introduced in experimental rats and their heart rate, SBP and DBP were observed with the help of tail cuff method. It was observed that the SBP, DBP and heart rate was reduced as compared to the controlled group. Mendes et al (13) also reported that anthocyanin shows endothelium dependent inhibitory effect on arterial contraction. These results elucidate that plant derived colors that contains anthocyanin shows antihypertensive activity and can be used as a potent antihypertensive agent [27].

Citral

Citral, which is also called lemongrass, is the major component of *Cymbopogon citratus*. Borrelli et al in their studies suggested that citral shows various activities like sedative, analgesic, anti-inflammatory, antispasmodic and diuretic activity. In order to establish its antihypertensive activity, studies were carried out on Visceral Smooth muscle of Rabbit Ileum by observing the effect of citral on Acetylcholine and KCl-induced compressions. It was observed that citral decreases the instantaneous Ach and KCl-induced Ileal compressions and produces a calcium antagonist action. In conclusion, it was suggested that citral may acts as a calcium antagonist and therefore can be used as an antihypertensive agent [28].

Kaempferol-3-O-rutinoside-

Kaempferol-3-O-rutinoside is a flavonoid which is isolated from the flowers of *Syringa vulgaris.* An experimental study was carried out on wistar rats to establish the role of kaempferol-3-O-rutinoside as an antihypertensive agent by using kaempferol-3-O-rutinoside, acetylcholine, atropine, norepinephrine and phentolamine. During this study, changes in blood pressure and heart rate was recorded after administration of each mentioned drug. It was observed that kaempferol-3-0-rutinoside showed a dose dependent decrease in systolic, diastolic and mean arterial blood pressure and authors suggested that it causes cholinergic mediated vasodilation. The results of this experimental study suggested that kaempferol-3-0-rutinoside can acts as a potent antihypertensive agent [29,30].

Nantenine

Nantenine is an alkaloid mainly found in *Nandina Domestica* and *Corydalis species*. Experimental studies were carried out by Francisco Orallo to identify potential activity of Nantenine on CVS of rats. It was observed that Nantenine administration caused dose-related reduction in Mean Arterial Pressure (MAP) along with a subsequent fall in heart rate. Moreover, it was observed that it modified the cardiovascular effect induced by phenylephrine (selective alpha-1- adrenergic receptor agonist) and 5-HT. Therefore, author suggested that nantenine is an antagonist of alpha-1- adrenergic receptor and 5-HT2A serotonin receptor, so can be used as an antihypertensive agent [31].

Hirsutine

Hirsutine is an indole alkaloid which is eluted out from *UncariaRhynchophylla*. Hirsutine shows various pharmacological effects such as antihypertensive, sedative and antiarrhythmic effects. To demonstrate its antihypertensive potential, experimental studies were carried out on smooth muscle of separated rat aorta and cytosolic Ca2+ level were observed. In this experimental study Noradrenaline and high K+ solution produced an elevation of cytosolic Ca2+ level which was decreased on administration of hirsutine, which suggested that hirsutine inhibits Ca2+ influx by voltage gated ion channels. Moreover, in a comparative study of hirsutine and caffeine, it was observed that hirsutine reduced the caffeine induced contractions. Conclusively, it was suggested that hirsutine reduces intracellular Ca2+ ions by acting on voltage-dependent Ca2+ channel and Ca2+ stores, thus acts as a potent antihypertensive agent [32].

Myricetin

Myricetin is a flavonoid found in seeds of *Vitis vinifera*. Some wide range of activities is shown by this compound that includes antioxidant, anticancer, ant diabetic and inflammatory activities. In order to establish its antihypertensive activity, an experimental study was carried out on albino rats in which hypertension was induced by fructose administration and with the help of tail-cuff method changes in blood pressure was monitored. It was observed that myricetin administration prevented increase in blood pressure in the fructose treated rats. Moreover, it also shifted cumulative concentration–response curve (CCRC) of Ang II towards the right which suggested that myricetin may prevent the development of fructose-induced high blood pressure, potentially by reversing fructose-induced metabolic changes. Myricetin, in conclusion, shows antihypertensive action [33].

Diterpenoid

Diterpenoid (isolated from *Salvia cinnabarina*) is known for its different pharmacological properties, including antifungal, antioxidant, antibacterial and anti-inflammatory. In order to test the effect of Diterpenoid on arterial blood pressure, the Male Wistar rats were anesthetized and the effect of diterpenoid was observed before and after the infusion of nitric oxide inhibitor (L-NAME). It was observed that diterpenoid causes fall in mean arterial blood pressure which was not modified by infusion of nitric oxide inhibitor. These experimental results suggested that diterpenoid shows antihypertensive activity by peripheral mechanism which is independent of nitric oxide release [34].

OPLE Catechins

Palm oil (*Elaeis Guineensis*) leaf extract (OPLE) has excellent ex Vivo dilation and defoliant characteristics. In order to establish its antihypertensive activity, Juliana M. Jaffri et al conducted a comparative experimental study on Male Wistar Kyoto Rats which OPLE and it was observed OPLE catechin was administered to normal hypertensive eats and L-NAME induced NO deficient hypertensive rats. In NO-

deficient hypertensive rats, OPLE significantly attenuated blood pressure rises, increased serum NO, decreased lipid peroxidation, demonstrated antioxidant impact and reduced the coronary arteriole wall-to-lumen ratio to near normal values. While OPLE showed strong antihypertensive and antioxidant effects with NO deficiency, normal rats were not hypotensive. Conclusively, OPLE catechins have been found to increase the deficiency of NO hypertension by stabilizing serum NO levels, showing the effects of antioxidants, increasing the probability of endothelial NO bioactivity. Therefore, OPLE Catechins can be used as potent antihypertensive agent [35].

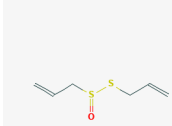
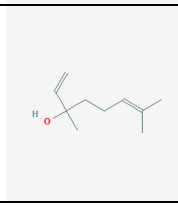
Quercetin

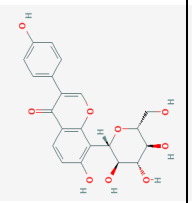
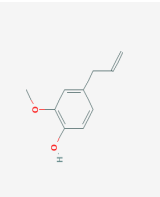
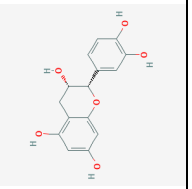
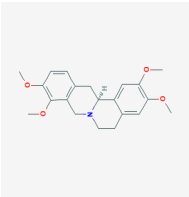
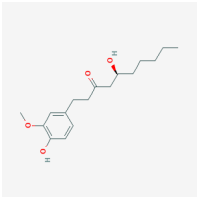
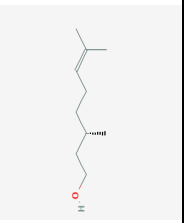
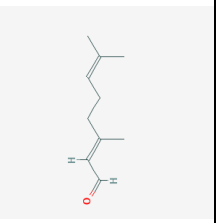
Quercetin is one of the richest flavonoids found in fruits and vegetables like apples, corpus, cocoa powder, berries, ref grapes, red wine, citrus fruits, broccoli, onions, bark roots, flowers, black tea and green tea. Quercetin is responsible for averting syllable structure and serviceable changes in heart, vessels and kidney. Important outcomes of this particular flavanol are adiposity, antioxidant, antidiabetic, immune and inflammatory modulating actions. Effects like arteriosclerosis, antineoplastic and anti-inflammatory responses were also reported. Quercetin's first positive response on hypertension was reported on voluntary hypertensive rats, in a fact finding that imitates human hypertension. After many studies it is found that quercetin employs vasodilative effect, antithrombotic, antineoplastic effects, reduced blood pressure etc. For this clinical trial were conducted in 587 random individuals in which 299 individuals were exposed to quercetin and 288 individuals were assigned to a controlled group. Study Carried on Meta- Analysis was assigned by employing the Comprehensive Meta-analysis (CMA) V2 Software in which SBP & DBP was accumulated in mm Hg. Mean difference of SDs was calculated. Remarkable depletion in SBP and similarly the effects of Quercetin on DBP by combined analysis was observed which also reflects a noteworthy depletion in DBP. On interpretation the final results of Meta-analysis exhibit notable outcome of Quercetin supplementation in depletion of blood pressure and the mechanism suggested is that it decreases intracellular Ca2+level by its action on Ca2+ store along with actions on voltage-dependent Ca2+ channel, which showed that this particular nutraceutical is effective as therapy to antihypertension [36].

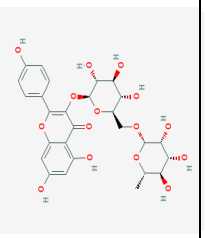
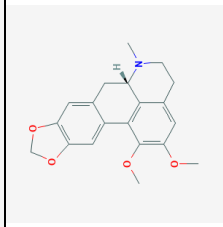
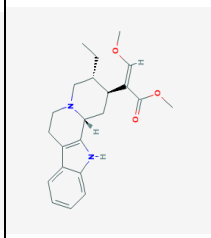
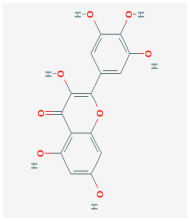
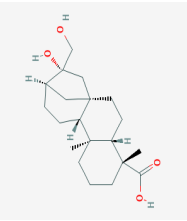
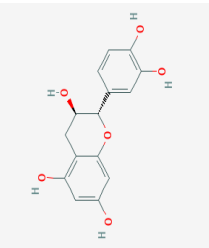
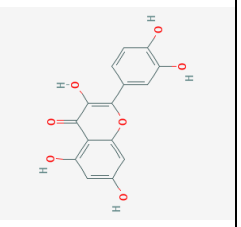
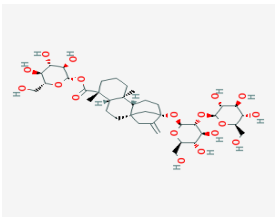
Stevioside

Stevioside is isolated from the plant *Stevia rebaudiana* which originated from Japan. An experimental study was conducted to observe the effect of stevioside on human hypertension. In this study Chinese hypertensive candidates were chosen which belongs to the age group of 28 to 75 years and their diastolic blood pressure ranges from 95mmHg to 110 mmHg. Out of these Chinese hypertensive candidates, some candidates were subjected to the treatment by stevioside (250 mg), whereas other candidates were subjected to Placebo treatment. After duration of 3 months it was observed that the stevioside treated group showed decline in blood pressure (systolic: 166.0±9.4 to 152.6±6.8 mmHg; diastolic: 104.7±5.2 to 90.3±3.6 mmHg, $P<0.05$). The results of this experimental study suggested that stevioside can be used as a potential antihypertensive agent in humans which acts by inhibition of Ca (2+) influx [37].

TABLE 1 summarizes various phytoconstituents combating against hypertension-

S. No	Plant Name	Metabolite	Structure	Family	Animal used	Route of administration	MOA	Reference
1	*Allium sativum*	Allicin		Alliaceae	Wistar rats	Intravenous	Reduction in vascular resistance	38
2	*Cinnamon zeylanicum*	Linalool		Lauraceae	Male Wistar normotensive rats	Intravenous	Directly acting on smooth muscles	39

40	41	42	43	44	45	46	47
Vasodilatation	Vasodilatory activity by inhibition of voltage-dependent Ca2+ channels	Elevation of plasma TAC and reduction in superoxide production in the LHV and aortae	By different contractors such as PI3K/Akt/eNOS/NO/ cGMP signaling pathway, Ca2C channels and KC channels	Improves the level of biomarkers via PPARδ	calcium-blocking as well as vasorelaxant acting	Endothelium dependent inhibitory effect on arterial contraction	muscarinic receptor and ultimately by commanding the formation and action of second messenger, IP3 causes visceral smooth muscle to
Oral	Intravenous	Oral	In vitro study	In vitro studies	Intravenous	Oral	Invitro study
Six-week-old male DS rats	Male Sprague-Dawley Rats	SHR males	Male Wistar rats	Human umbilical vein endothelial cells, human embryonal kidney cells, and mouse preadipocytes	Male Wistar rats	Spontaneously hypertensive rats	Isolated Rabbit Ileum
Fabaceae	Myrtaceae	Fabaceae	Papaveraceae	Zingiberaceae	Poaceae	Poaceae, Convolvulaceae, Brassicaceae	Poaceae
							
Puerarin	Eugenol	Epicatechin	Tetrahydropalmatine	6-Gingerol	Citronellol	Anthocyanin	Citral
Pueraria lobata	*Syzygiumaromaticum*	Pterocarpus marsupium	*Corydalis yanhusuo*	Zingiber officinale	*Cymbopogon winterianus*	*Zea mays, Ipomea batatas, Raphanus sativus*	*Cymbopogon citratus*
3	**4**	**5**	**6**	**7**	**8**	**9**	**10**

48	49	50	51	52	53	54	55
Cholinergic mediated vasodilation	Antagonist of alpha-1- adrenergic receptor and 5-HT2A serotonin receptor	Blocks the Ca2+ movement by acting on voltage-dependent Ca2+ channel	Acts by preventing and reversing the development of hyperinsulinemia	Vasodilator mechanism due to a peripheral action	elevates the deficiency of NO hypertension by stabilizing the levels of Serum NO	β-glucuronidase activity	Calcium antagonist mechanism
Intravenous	Intravenous	Invitro studies	Oral	Intravenous	Oral	Oral	Oral
Wistar rats	Male Wistar rats	Rats	Male albino rats	Male Wistar rats	Male Wistar Kyoto Rats	587 random individuals	Chinese hypertensive candidates
Oleaceae	Berberidaceae	Rubiaceae	Vitaceae	Lamiaceae	Arecaceae	Theaceae	Asteraceae
							
Kaempferol-3-O-rutinosid	Nantenine	Hirsutine	Myricetin	Diterpenoid	OPLE Catechins	Quercetin	Stevioside
Syringa uulgaris	*Nandinadomestica*	*Uncaria rhynchophylla*	*Vitis vinifera*	*Salvia cinnabarina*	*Elaeisguineeais*	*Camellia sinensis*	*Stevia rebausdiana*
11	**12**	**13**	**14**	**15**	**16**	**17**	**18**

CONCLUSION

Hypertension is a chronic disease which is spreading worldwide at an alarming rate. Herbal therapies are currently taking over the use of allopathic therapies due to various side effects, as plants contain a variety of chemical components that are effective against different diseases, including cardiovascular diseases (CVDs), and there is also a fact that herbal remedies show low side effects compared to some allopathic medicines. In order to minimize the side effects, herbal remedies can be used on the basis of metabolites present in them. These metabolites show their antihypertensive action through various pathways and their exact mechanism of action is still an area that needs to be researched. Results of experimental studies of these metabolites suggested they can be used as an effective antihypertensive agent although antihypertensive effects produced by these metabolites were lesser than available allopathic medicines but the herbal medicines were suggested to be a better alternative in long term useas they produced lesser number of side effects.

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CONFLICT OF INTEREST

None.

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