HYPERTENSION AND TREATMENT

A Project Report Submitted

In Partial Fulfillment of the Requirements

for the Degree of

BACHELOR OF PHARMACY

By

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GALGOTIAS UNIVERSITY

CERTIFICATE

This is to certify that project work entitled **"Hypertension and Treatment"** done by **Mr. Ashif Ahmad Khan** submitted to Department of Pharmacy, is a bonafide research work done by Mr. Ashif Ahmad Khan under the supervision and guidance of **Prof (Dr) Md Aftab Alam,** Professor, School of Medical and Allied Sciences, Greater Noida. The work is completed and ready for evaluation in partial fulfillment for the award of Bachelor of Pharmacy during the academic year 2021-2022. The project report has not formed the basis for the award of any Degree/Diploma/Fellowship or other similar title to any candidate of any University.

Date:

Prof. Pramod Kumar Sharma
Dean
School of Medical and Allied Sciences
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BONAFIDE CERTIFICATE

This to certify that the project work entitled **"Hypertension and Treatment"** is the bonafide research work done by **Mr. Ashif Ahamd Khan**, who carried out the research work under my supervision and guidance for the award of Bachelor of Pharmacy under Galgotias University, Greater Noida during the academic year 2021-2022. To the best of my knowledge, the work reported herein is not submitted for the award of any other degree or diploma of any other Institute or University.

Dr. Md Aftab Alam
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DECLARATION

I hereby declare that the work embodied in this project report entitled **"Hypertension and Treatment"** in Partial fulfillment of the requirements for the award of Bachelor of Pharmacy, is a record of original and independent research work done by me during the academic year 2021-22 under the supervision and guidance of **Prof (Dr) Md Aftab Alam**, Professor, School of Medical and Allied Sciences, Galgotias University, Greater Noida. I have not submitted this project for award of any other degree or diploma of any other Institute or University.

Date: **Mr. Ashif Ahmad Khan**

Place: **Name and Signature of candidate**

Acknowledgement

Praise to be almighty God who made me able to carry out the present study successful. I feel high privileged while starting my dissertation work with acknowledge of the genuine help and support received from others who made this research and project possible for me.

I deem it a great pleasure record my heartfelt gratitude to my supervisor **Prof (Dr) Md Aftab Alam**, for his valuable guidance.

I express my gratitude to my friends and my co-workers for their moral support, advice, affection, co-operation, and functional freedom that made me to set goal and achieved this task. The episode of my acknowledgement would not be complete without mentioning thanks to **Dr. P.K. Sharma**, Dean of our School and **Dr. GSN Koteswara Rao**, HOD, Department of Pharmacy for sculpting another milestone in my academic journey.

Last but not the least I wish to express my gratitude to my lovely parents for their patience and constant support. They provided me with every opportunity to succeed.

Mr. Ashif Ahmad Khan

ABSTRACT

Hypertension is a term that describes high blood pressure in conjunction with the presence of other disorders as a worldwide warning to address the most serious health concerns affecting the human body. Changes in the normal physiology of the heart such as blood circulation, contractile forces, blood volume, and many other distinguishing traits result in hypertension. It is mostly caused by human lifestyle with environmental factors as well as some genetic inheritance throughout time. These issues may be solved by maintaining a healthy lifestyle and using a chemotherapeutic strategy with natural or synthetic/semi-synthetic medication treatment while taking into consideration the diverse disease physiology in the human body. It also causes seizures, cardiac arrest, heart attack, renal failure, peripheral vascular disease, and in certain cases, dementia, among other things. There are various anti-hypertension classifications to control this problem as much as possible to some extent, such as beta-blockers, diuretics, ACE inhibitors (Angiotensin-converting enzymes), angiotensin- II receptor blockers, calcium channel blockers, receptor inhibitors, alpha-adrenergic antagonist, centrally acting agents, and direct-acting vasodilators, along with natural agents.

Keywords: Pathophysiology of hypertension, treatments with drug classification, and natural remedies for hypertension.

INTRODUCTION

Hypertension (High blood pressure) is defined as a fixed repeating systolic blood pressure more than 140 mmHg or diastolic blood pressure of more than 90 mmHg. The patient must simply sit for 5 minutes in order for blood pressure to be measured [1]. High blood pressure is a global health issue, and the World Health Organization (WHO) considers it to be one of the most serious health issues, killing over 9 million people each year [2]. In 2000, the worldwide prevalence of hypertension for those aged 20 and above was 26.4 percent (26.6 percent for males and 26.1 percent for females), and it is expected to increase to 29.2 percent for both males and females by 2025 [3].The volume of blood in the body and the contractile force of the heart keep blood pressure balanced. The sodium store/excretion balance regulates blood fluid. Both sympathetic neural activity and heart function maintain cardiac contractile force [4]. Researchers discovered a relationship between hypertension and dietary components such as fruits and vegetables. Evidence suggests that consuming a lot of dietary fibre reduces the risk of high blood pressure [5]. Overweight, obesity, greater salt consumption, and old age are all risk factors for hypertension [6]. Other risk factors include alcohol consumption, a lack of physical exercise, an unhealthy diet, cigarette smoking, psychological stress, and a sleep disorder [7]. Hypertension has been associated with heart attacks, seizures, cardiac arrest, kidney failure, peripheral vascular disease, and dementia (memory loss) [8]. It is most effective to prevent cardiovascular disease by quitting smoking, consuming a low-salt diet, meditating, and drinking alcohol. Aerobic exercise (paced breathing) and meditation are suggested because they have a physiological benefit on blood pressure [9].

Considering sodium in salt is an important factor in hypertension, the daily consumption of salt should not exceed 6gm. If both parents have hypertension, it is possible for their kid to develop it as well, as it may be passed down through DNA. Postmenopausal women can develop hypertension because hormones contribute an essential role in cardiovascular function. Hypertension, or an increase in blood pressure, can result from sympathetic nervous system activation. Hyperglycemia raises the circulatory fluid volume, which raises systemic blood pressure. The juxtaglomerular apparatus helps in the separation of renin, which converts angiotensinogen to inactive Angiotensin I, which is then converted by ACE into Angiotensin II,

a vasoconstrictor that causes hypertension.There are many classes of antihypertensive medications, with Beta-blockers having the fewest side hypertension in the Europe and United States. Lisinopril is more commonly used in the effects and is used in heart failure patients and low left ventricular ejection fraction, whereas Angiotensin-Converting Enzyme (ACE) inhibitors are widely used in patients suffering from pulmonary United States, while Ramipril is more commonly used in Europe. In acute and chronic disease conditions, loop diuretics such as furosemide and bumetanide are commonly used in the treatment of fluid overload. Angiotensin II blockers are also effective, but should not be used during pregnancy. Amlodipine is a generally used Calcium channel blocker. Direct-acting vasodilators, alpha-adrenergic receptor antagonists, renin inhibitors, and centrally acting agents are other anti-hypertensive medications used to treat hypertension.

Many natural plants have antihypertensive benefits, including garlic, oats, green tea, ajwain, tomato, sesame, ginger, cocoa, roselle, basil, black cumin, sarpagandha, parsley, celery, and cardamom. Many of these natural plants increase the level of nitric oxide (NO), which is a vasodilator that helps blood vessels widen or dilate, resulting in reduced blood pressure. Few acts as ACE inhibitors, while others act as calcium channel blockers to reduce blood pressure and demonstrate antihypertensive properties.

1. PATHOPHYSIOLOGY

1.1 Salt cause hypertension

Modern human consumes four times more salt than 10,000 years ago which is due to the salt farming method. Dhal discovered in the 1960s that the population of Alaska Inuit who consumed 1.6 grams of sodium daily had no high blood pressure, but 8.6 percent of Americans who consumed 3.9 grams of salt daily had high blood pressure [10]. The WHO suggests taking less than 200mg of salt per day, which is equivalent to less than 6gm of NaCl. Researchers discovered that Indians consume approximately 11gm of salt each day, while the country's hot climate causes salt loss of up to 6gm from perspiration [11]. Guyton's formula states that BP = pulse volume * peripheral resistance.

Salt consumption raises the intravascular volume and cardiac preload, resulting in an increase in pulse volume. Blood pressure will rise if there is a long-term imbalance between salt intake

and salt excretion, together with an increase in pulse volume [12]. High salt consumption induces an imbalance in renal sodium processing, in which the kidney reabsorbs a higher quantity of sodium and water, leading in hypovolemic shock (too much fluid in the blood), which eventually causes an increase in blood pressure [13].

1.2 Genetics

African Americans and African descendants have been reported to have higher prevalence of high blood pressure than other racial groupings in the United States. Several genes have been identified as playing an important function in the maintenance of blood pressure, resulting in hypertension [14]. The study of hypertension in animal studies, along with breakthroughs in human genome research, aid in the discovery of genes that cause hypertension. The research on the genetics of hypertension is extensive but not complete [15]. Researchers discovered that if both parents had high blood pressure, the odds of getting hypertension increased. The following are some gene-related researches on hypertension:

1) Genetic variations in the thiamine transporter were discovered to boost cardiac output while decreasing peripheral resistance.

2) The UMOD gene helps in the coding of Uromodulin, a protein that stimulates the Furosemide sensitive renal sodium Cotransporter NKCC2. The use of furosemide helps in the inhibition of NKCC2, which decreases blood pressure.

3) GWAS investigations revealed that any genetic impairment in eNOS activity results in hypertension.

4) A shift in net sodium reabsorption is caused by many single-gene disorders, resulting in a rare form of hypertension [16].

The genetic information for all racial groups causing hypertension is incomplete, but breakthroughs in DNA sequencing technology are quickly enhancing the effectiveness to do upscale genomics research. In the future, this will aid in getting a thorough understanding of the genetic contribution to hypertension in various racial groups, as well as the treatment of hypertension [17].

1.3 Menopausal

Female hormones such as estrogen and progesterone are essential in the lives of women. These hormones cause puberty, enabling a woman to enjoy the joys of motherhood while also helping

in the proper functioning of the cardiovascular system and healthy bones [18]. Menopause is the cessation of menstruation due to the permanent decline in ovarian follicular activity, and it signals the cessation of a woman's reproductive life, which normally begins when she reaches the age of 50. Hot flashes, lethargy, discomfort, night sweats, reduced libido, and mood changes are the most common menopausal symptoms reported by three-quarters of all women [19-20]. Estrogen and progesterone are key sex hormones during the menstruation periods, and these hormone changes may have different effects on women [21]. Postmenopausal women develop hypertension as a result of changes in sex hormone levels. Estrogen causes vasodilatation in the blood vessels, improves the bioavailability of nitric oxide, and modulates the Renin-Angiotensin-Aldosterone System (RAAS) [22]. Endothelial-dependent vascular dilation is caused by progesterone [23]. On the pathogenetic basis, it is concluded that the decline in estrogen concentration, i.e., the estrogen to androgen ratio, in menopause causes the production of specific Vaso-constructive elements like angiotensinogen and endothelin, likely to lead to upregulation of renin-angiotensin system, renal sodium absorption, and vasoconstriction. Early menopause is connected with smoking, a lack of physical work, and socioeconomic level, whereas smoking is also associated with a loss in ovarian reserve with time [24-25].

1.4 Sympathetic nervous activity

Sympathetic nerve activity is essential in maintaining the cardiovascular system's physiological homeostasis as well as in the pathogenesis of hypertension. The sympathetic system plays a significant part in the pathophysiology of hypertension, which can be caused by a number of reasons. Researchers discovered that adrenergic drive could be measured either indirectly, by measuring adrenergic neurotransmitters epinephrine and norepinephrine levels in the blood, or directly, by evaluating postganglionic efferent muscular sympathetic nerve activity in peripheral nerves, and also regional noradrenaline generation and absorption by adrenergic neurons using noradrenaline radioactivity. The two most important effectors in neural blood pressure regulation are systemic vascular resistance and cardiac output. The balance of vasoconstriction and vasodilation of vessels can be used to express vascular tone. The sympathetic nervous activity is influenced by neurotransmitters such as norepinephrine, epinephrine, and dopamine. Nerve terminals release norepinephrine (noradrenaline), while the adrenal medulla secretes epinephrine (adrenaline). Noradrenaline is released into synaptic clefts in response to a stimulus,

causing vasoconstriction and an increase in blood pressure. Increased sympathetic activity increases blood pressure by increasing the release of neurotransmitters like adrenaline [26-30]. Parasympathetic activity rises while sympathetic activity drops during sleep, resulting in a natural nocturnal "dip" in blood pressure [31]. Negative pressure against blockage and repetitive hypoxia produces chemoreceptor activation in the kidneys, adrenals, and peripheral nerves [32].

1.5 Insulin (Diabetes)

The occurrence of type-2 diabetes mellitus is continuously growing globally, owing mostly to people's lifestyles in which they do not put in much physical activity in comparison to the calories they consume from their food [33]. Type-2 diabetes is linked to an increased prevalence of earlier deaths from heart disease such as hypertension [34]. Hypertension is caused by an increase in the volume of blood in the circulatory system and peripheral vascular resistance. Diabetes mellitus patients have increased peripheral arterial resistance owing to vascular remodelling, as well as elevated body fluid content due to insulin resistance induced hyperglycemia and hyperinsulinemia, resulting in hypertension [35]. Insulin resistance would be defined as a natural reaction in animals to a given concentration of the hormone that is less than expected, and it serves an important part in the aetiology of type-2 diabetes. Insulin production in the body causes vasodilation via nitric oxide generation, whereas diabetes or insulin resistance impairs nitric oxide production, resulting in vasoconstriction or increased blood pressure [36]. When hyperinsulinemia is caused, salt reabsorption from the renal tubules increases, resulting in hypertension [37]. Hyperosmolarity caused by hyperglycemia increases circulatory fluid volume [38]. Diabetes causes an increase in plasma glucose levels, which changes the extra-cellular osmolarity on the side with the highest glucose level. Hyperglycemia raises the circulatory fluid volume, which increases systemic blood pressure [39].

1.6 Renin angiotensin aldosterone system (RAAS)

The RAAS maintains fluid volume, cardiac output, and salt balance, and RAAS overactivity can result in several cardiovascular problems such as atherosclerosis, hypertension, heart attack, and cardiac arrest [40]. By regulating the extracellular fluid volume and arterial pressure, this mechanism maintains vascular tonicity. This system regulates water, blood, plasma, lymph, and interstitial fluid for the heart's function and kidney function [41]. The RAAS is an important vasoactive system in the physiological regulation of blood pressures. Inhibiting RAAS is

considered to be a therapeutic approach for hypertension [42]. The juxtaglomerular apparatus helps in the separation of renin, which converts angiotensinogen to inactive Angiotensin-I, which then is converted to Angiotensin-II by ACE, constricting blood vessels and causing hypertension [43]. Direct renin inhibitors, angiotensin-converting enzyme inhibitors, angiotensin-II type I receptor blockers, and mineralocorticoid receptor antagonists are some of the medications used to inhibit the RAAS at different levels. These medicines decrease the action of RAAS at different levels, resulting in dilatation of blood vessels and thereby reducing blood pressure [44-46].

2. Treatments

Table: Pharmacological class of Antihypertensive drugs [47].

S.NO	Pharmacological class	Subclass	Drugs	Adverse effect
	Major class			
1)	Beta-blocker	Non-vasodilating with beta 1-selectivity	Acebutolol, Bisoprolol, Betaxolol, Atenolol	Depression, fatigue, sexual dysfunction
		Non-vasodilating without beta 1-selectivity	Carteolol, Esmolol, Propranolol, Nadolol, Oxprenolol, Penbutolol, Timolol, Metoprolol	
		Vasodilating	Celiprolol, Labetalol, Nebivolol, Carvedilol, Pindolol	
2)	Diuretics (water pills)	Loop diuretic	Furosemide, Torsemide Bumetanide	Hypokalemia, hyponatremia, hypercalcemia, hyperuricemia,
		Thiazide diuretic	Chlorothiazide, Bendroflumethiazide, Chlortalidone,	

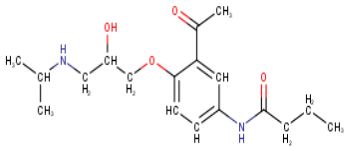
			Hydrochlorothiazide, Trichlormethiazide, Indapamide	hyperglycemia, hyperlipidemia
		Potassium-sparing diuretics	Spironolactone, Amiloride, Triamterene, Eplerenone	
3)	Angiotensin Converting Enzyme inhibitor		Ramipril, Benazepril, Quinapril, Captopril, Trandolapril, Cilazapril, Fosinopril, Imidapril, Enalapril, Lisinopril, Moexipril, Perindopril, Zofenopril	Angioedema, cough, renal dysfunction, hyperkalemia
4)	Angiotensin-II receptor blocker		Telmisartan, Candesartan, Losartan, Eprosartan, Irbesartan, Olmesartan, Valsartan	Cough, dizziness, fetal toxicity
5)	Calcium Channel blocker	Non Dihydropyridines	Diltiazem, Verapamil	Peripheral edema with diuretic
		Dihydropyridines	Lercanidipine, Felodipine, Lacidipine, Manidipine, Isradipine, Nicardipine, Nifedipine, Nitrendipine, Amlodipine,	
	Other class			
6)	Renin inhibitor		Aliskiren	Hyperkalemia, renal impairment

7)	Alpha adrenergic receptor antagonist		Doxazosin, Terazosin, Prazosin	Stress, idiopathic cystitis, lethargy, diarrhea
8)	Centrally acting agents		Clonidine, Rilmenidine, Methyldopa	bronchospasm, bradycardia, headache, constipation
9)	Direct-acting vasodilator		Hydralazine, Minoxidil	Weight gain

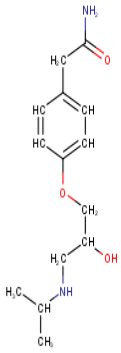
2.1 Beta-blockers and Diuretics

Beta-blockers are an important drug for treating increased blood pressure, cardiac angina, cardiac arrest, and decreasing cardiac blood flow in adults [48]. Beta-blockers can help reduce morbidity and mortality in those who have had a cardiac arrest and have a low left ventricular ejection fraction [49]. Beta-blockers are medications that inhibit endogenous catecholamine from interacting with beta-adrenergic receptors [50].Catecholamines like adrenaline and norepinephrine bind to B1 receptors, increasing cardiac automaticity, and conduction velocity. B1 receptors also stimulate renin release, which raises blood pressure. Catecholamines bind to B2 receptors, inducing smooth muscle relaxation and an increase in metabolic impact. Beta-blockers are medications that bind to the B1 and B2 receptors, blocking epinephrine and norepinephrine activity and reducing blood pressure, renin, and cardiac output. Propranolol, carvedilol, sotalol, labetalol, atenolol, bisoprolol, and metoprolol are examples of Beta-blockers [51-52]. Most clinical guidelines consider beta-blockers as the most important medications in hypertension [53]. Depression, exhaustion, bradycardia, bronchoconstriction, dizziness, diarrhoea, constipation, confusion, cardiac arrest, nauseous, peripheral chills, rashes, difficulty sleeping, visual impairment, and sexual dysfunction are among the side effects of beta-blockers [54-55].

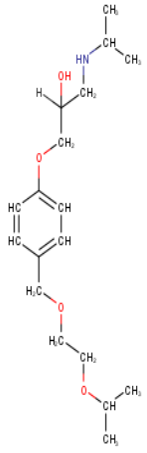
1. Beta-Blockers



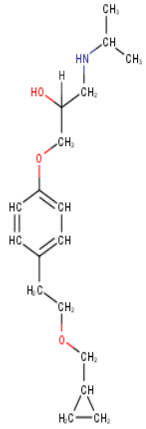
Acebutolol



Atenolol

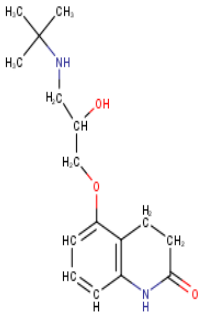


Bisoprolol

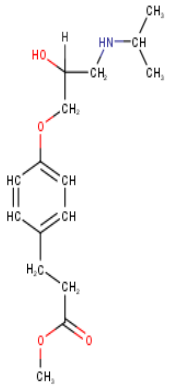


Betaxolol

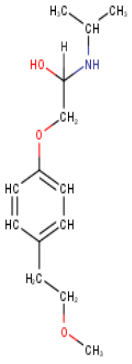
1.1 Non-vasodilating with beta 1-selectivity



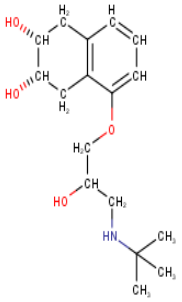
Carteolol



Esmolol

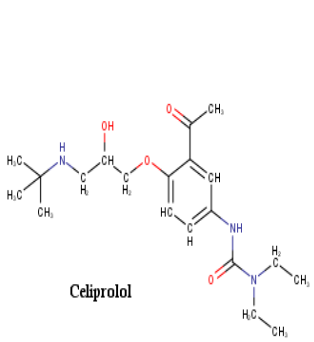


Metoprolol

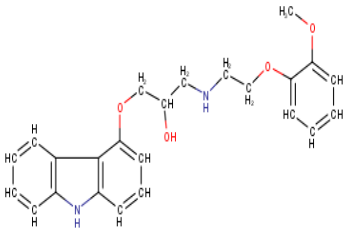


Nadolol

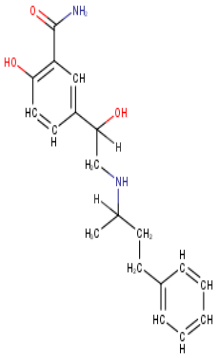
1.2 Non-vasodilating without beta 1-selectivity



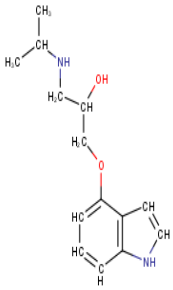
Celiprolol



Carvedilol



Labetalol

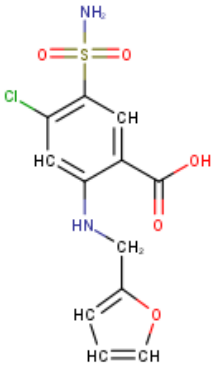


Pindolol

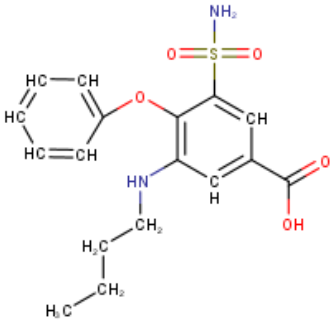
1.3 Vasodilating

Diuretics are categorized according to where diuretics act in the kidney: loop diuretics, thiazide diuretics, and potassium-sparing diuretics. Diuretics assist to reduce blood pressure by increasing renal salt and water excretion. By blocking the distal tubule Na+/Cl- cotransporter, thiazide diuretics as hydrochlorothiazide, cyclothiazide, bendroflumethiazide, and chlorothiazide decrease sodium and chloride re-absorption. Thiazide-like diuretics, such as metolazone, chlorthalidone, and indapamide, are sulfonamide diuretics that function in the same way as thiazide diuretics but have a distinct molecular structure [56-57].

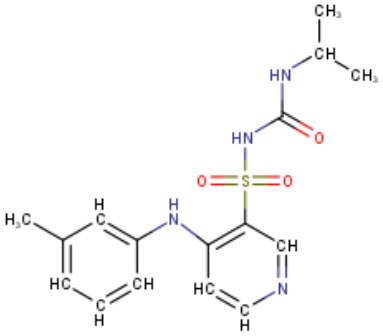
2. Diuretics (water pills)



Furosemide

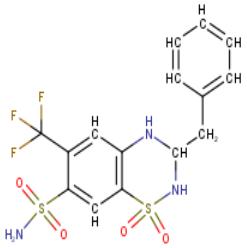


Bumetanide

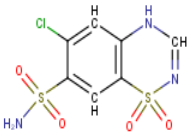


Torsemide

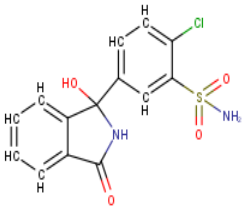
2.1 Loop diuretics



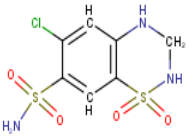
Bendroflumethazide



Chlorothiazide

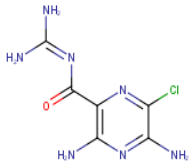


Chlorthalidone

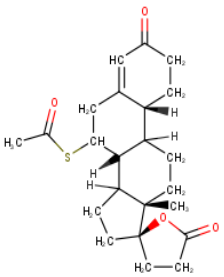


Hydrochlorthiazide

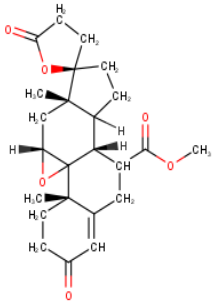
2.2 Thiazide diuretics



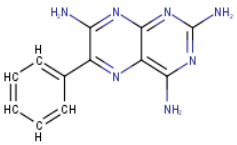
Amiloride



Spironolactone



Eplerenone



Triamtrene

2.3 Potassium-sparing diuretics

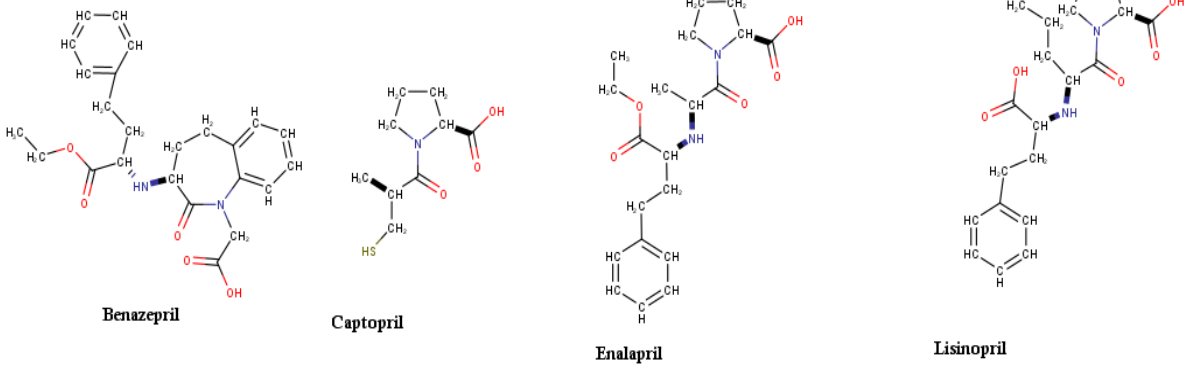
Loop diuretics increase free water excretion by inhibiting NaCl reabsorption. When the Na-K-2Cl cotransporter is blocked, K+ cannot be reabsorbed into the lumen, resulting in Ca++ and Mg++ loss [58].In acute and chronic illness situations, the loop diuretics furosemide and bumetanide are most commonly used to treat fluid overload [59]. A diuretic helps in volume management, blood pressure regulation, and the prevention of long-term cardiovascular morbidity and mortality [60]. Diuretics can cause hypokalemia, hyponatremia, metabolic alkalosis, hypercalcemia, hyperuricemia, hyperglycemia, hyperlipidemia, and other side effects [61].

2.2 ACE Inhibitor and Angiotensin II blocker

The juxtaglomerular apparatus helps in the separation of renin, which converts angiotensinogen to inactive Angiotensin-I, which then is converted to Angiotensin-II by ACE, constricting blood vessels and causing hypertension [43]. The ACE inhibitor is an effective antihypertensive medication because it reduces systemic vascular resistance, increases renal flow, and increases

the excretion of salt. ACE inhibitors are important antihypertensive medications used to treat hypertension in children [62]. Many Ace inhibitors are available, including zofenopril, ramipril, benazepril, trandolapril, enalapril, imidapril, captopril, lisinopril, quinapril, and others [63]. Angiotensin Converting Enzyme (ACE) inhibitors prevent angiotensin II formation. Captopril was the first ACE inhibitor, while losartan was the first Angiotensin receptor blocker [64]. ACE Inhibitors are typically prescribed to patients who have arterial hypertension. In the United States, lisinopril is the most often used ACE inhibitor, but in Europe, ramipril is the most commonly used ACE inhibitor [65]. Researchers discovered that zofenopril is more efficient than ramipril in treating comorbidities (like diabetes and high blood pressure) and that zofenopril is better than ramipril in the case of preserved ventricular function. Zofenopril helps in the prevention of cardiac arrest, particularly in men and the elderly [66]. Angioedema, cough, renal failure, and hyperkalemia are among the side effects of ACE inhibitors [67].

3. Angiotensin Converting Enzyme inhibitors



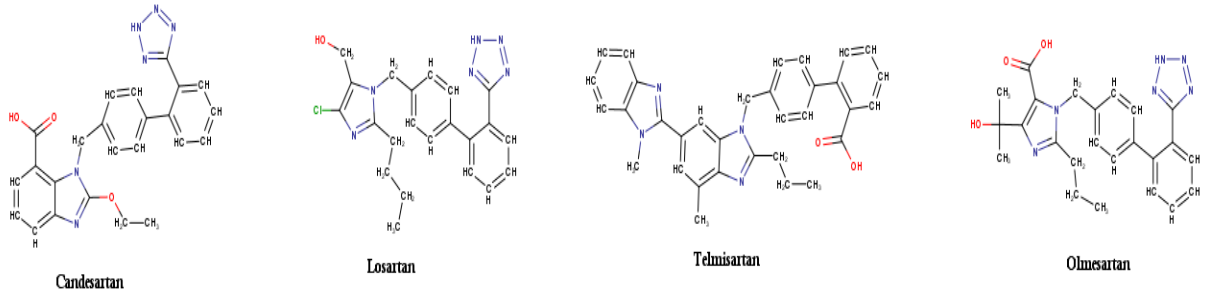
Benazepril Captopril Enalapril Lisinopril

Angiotensin II is important for cardiovascular physiology and pathology. Ang-II stimulation has been associated with myocardial remodellingg [68]. Renin (enzyme) is responsible for the conversion of angiotensinogen into angiotensin-I. ACE converts inactive decapeptide angiotensin-I to active octapeptide angiotensin-II. Angiotensin-II blockers decrease blood pressure by inhibiting the effects of angiotensin, which causes vasoconstriction [69].

Angiotensin-II Receptor Blockers (ARBs), also known as sartans, are highly selective antihypertensive medicines and work by inhibiting the activation of angiotensin II AT1

receptors. Olmesartan, eprosartan, irbesartan, candesartan, losartan, telmisartan, fimasartan, embusartan, and valsartan are some examples of ARBs [70-71]. In the beginning phases of hypertension, angiotensin-II blockers such as candesartan, losartan, telmisartan, and others with a similar feature, antagonists to Angiotensin type 1 receptor, should be administered [72].

4. Angiotensin-II receptor blockers



Losartan is effective in the elderly; however, it has side effects including coughing and dizziness. Losartan should not be used during pregnancy because it can result in serious fetal toxicity [73]. There are extremely few side effects observed in patients taking ARBs as an antihypertensive medication. These side effects include angioedema, coughing, and hypotension. ARBS can potentially cause kidney failure in individuals whose RAAS-dependent arterial pressure or kidney function [74].

2.3 Calcium channel blocker, Renin inhibitor and Alpha-adrenergic receptor antagonist

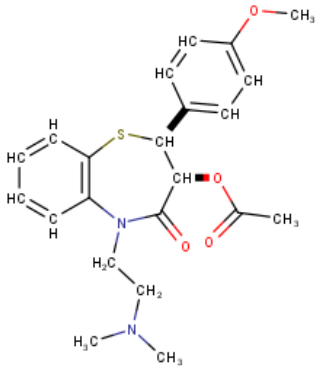
Calcium channel blockers (CCBs) are antihypertensive medications that widen arteries by decreasing calcium flow into cells and lowering blood pressure. Calcium channel blockers decrease blood pressure in all patient populations, irrespective of age, racial group, nationality, gender, or salt intake. The majority of calcium channel blockers are dilators of the peripheral arteries [75]. Calcium channel blockers are commonly used to treat heart problems such as angina pectoris, high blood pressure, supraventricular arrhythmias, and hypertrophic cardiomyopathy. Calcium channel blockers may be of different classes like:

a) Dihydropyridine derivatives: Nifedipine and Amlodipine
b) Benzodiazepine derivatives: Diltiazem

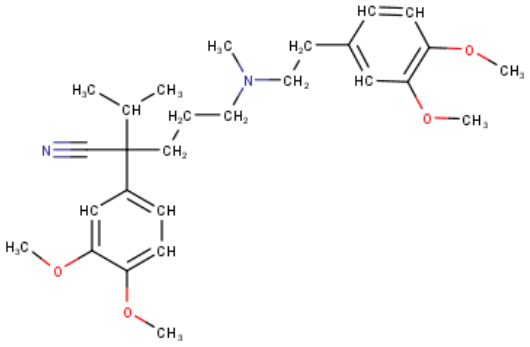
c) Phenylalkylaminederivatives: Verapamil

Dihydropyridine derivatives primarily influence arterial vascular smooth muscle cells, inducing vasodilation and thereby lowering blood pressure. The CCB phenylethylamine derivatives predominantly act on heart cells, where they exhibit chronotropic and inotropic actions. The actions of the preceding two derivatives are combined in the benzothiazepine derivatives of CCBs. Non-Dihydropyridine CCB classes include phenylalkylamine and benzothiazepine [76-77].

5 Calcium Channel blockers

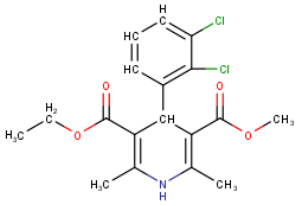


Diltiazem

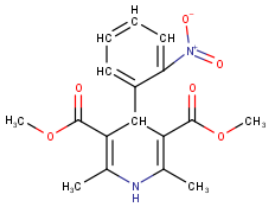


Verapamil

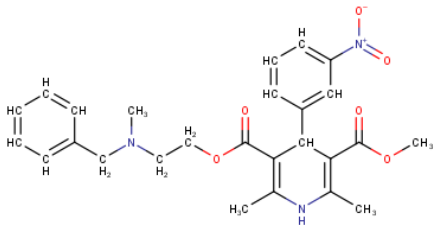
5.1 Non Dihydropyridines



Felodipine



Nifedipine



Nicardipine

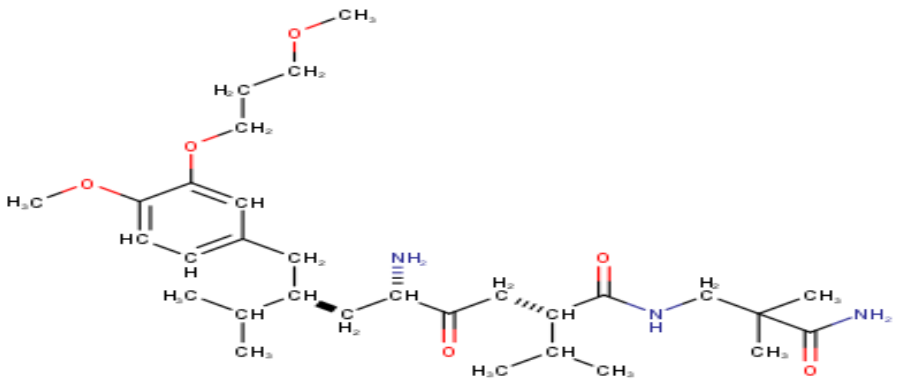
5.2 Dihydropyridines

Calcium channel blockers prevent calcium from entering the body via voltage-gated calcium channels (L-type). Vasodilation is achieved by inhibiting smooth muscle cell contraction and reducing myocardial conduction at the sino atrial (SA) and atrial ventricular (AV) nodes, where

there are no sodium-gated channels and conduction is mostly accomplished by calcium flux [78-79]. The effect of a calcium channel blocker on induced vascular contraction is dependent on the resting membrane potential [80]. T-type calcium channels open when the membrane depolarizes slightly, allowing Ca^{++} to enter electrically excitable cells, and T-type calcium channels modulate neuronal excitability [81]. Amlodipine is widely used which has adverse effects on peripheral edema with a diuretic [82]. Constipation, reduced cardiac output, bradycardia, lightheadedness, flushing, headaches, peripheral edema, and gingival hyperplasia are among the side effects of calcium channel blockers [83].

Renin is an aspartic protease that helps angiotensinogen breakdown. Several renin inhibitor drugs have been researched, but aliskiren is the only one that has been clinically tested [153]. Aliskiren is the first non-peptide, effective, and selective renin inhibitor used as an antihypertensive medication [154]. Aliskiren is an orally active medication that binds to rennin and non-proteolytically activated prorenin to block Angiotensinogen cleavage into Angiotensin I, which does not form Angiotensin II [155]. Aliskiren is also used to treat diabetic patients with proteinuria [157]. Aliskiren's side effects include hyperkalemia, renal impairment, and hypotension [158].

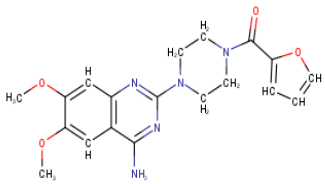
6. Renin inhibitor



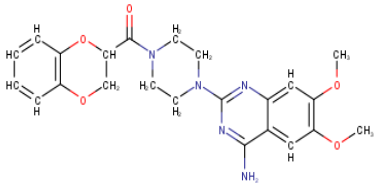
Aliskiren

Antihypertensive drugs that inhibit alpha-adrenergic receptors have proven to be effective. They reduce systolic and diastolic blood pressure by blocking norepinephrine's vasoconstriction activity and lowering peripheral vascular resistance [84].

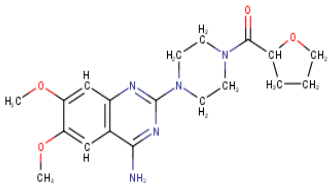
7. Alpha adrenergic receptor antagonists



Prazosin



Doxazosin



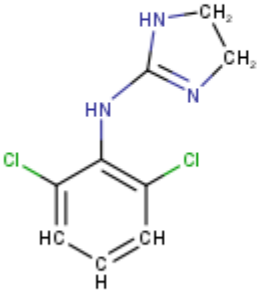
Terazosin

Doxazosin improves defective fibrinolysin by increasing Plasminogen activator activation, which is linked to hypertension [85]. Researchers discovered that blocking Alpha-adrenergic receptors with Prazosin and beta-adrenergic receptor that regulate exocytosis in mast cells shows a synergistic effect [86]. The adverse effect of Alpha-adrenergic receptor blocker is earlier voluntary urination, stress, idiopathic cystitis, lethargy, diarrhea, malodorous stool, and ptyalism [87].

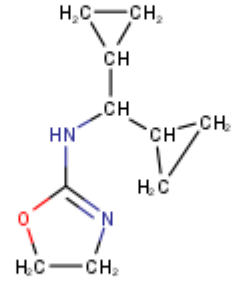
2.4 Centrally acting agent and direct acting vasodilator

Methyldopa is an antihypertensive medication that is often used during pregnancy and has a low frequency of medical problems [88]. Researcher suggests that methyldopa had a superior obstetrician result when used to manage blood pressure in pregnant women with pre-existing hypertension [89]. Clonidine is a centrally acting alpha-2 agonist that is utilized as a fourth-line treatment for hypertension [90]. Clonidine, a sedative, and anxiolytic agent is utilized as an alternative in pregnant women. Clonidine lowers the levels of catecholamines in the blood [91]. Edema, bronchospasm, bradycardia, headache, sleepiness, skin rash, and constipation are some of the side effects [92].

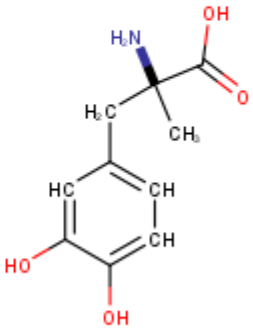
8. Centrally acting agents



Clonidine



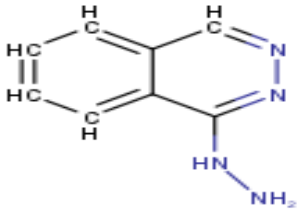
Rilmenidine



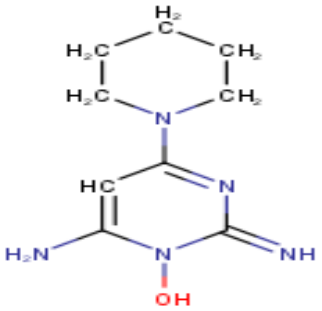
Methyldopa

Hydralazine is an important medication used to treat preeclamptic patients who have elevated blood pressure during pregnancy [93]. Parenteral hydralazine is considered an important medicine by the American College of Obstetricians and Gynecologists (ACOG) for the treatment of rapidly increasing blood pressure [94]. Hydralazine, Minoxidil, nitrates, and nitroprusside are examples of direct-acting vasodilators. Minoxidil's mechanism of action is that it directly relaxes arteriolar smooth muscle while having little impact on veins, with cyclic AMP mediating its effect [95].

9. Direct acting Vasodialators

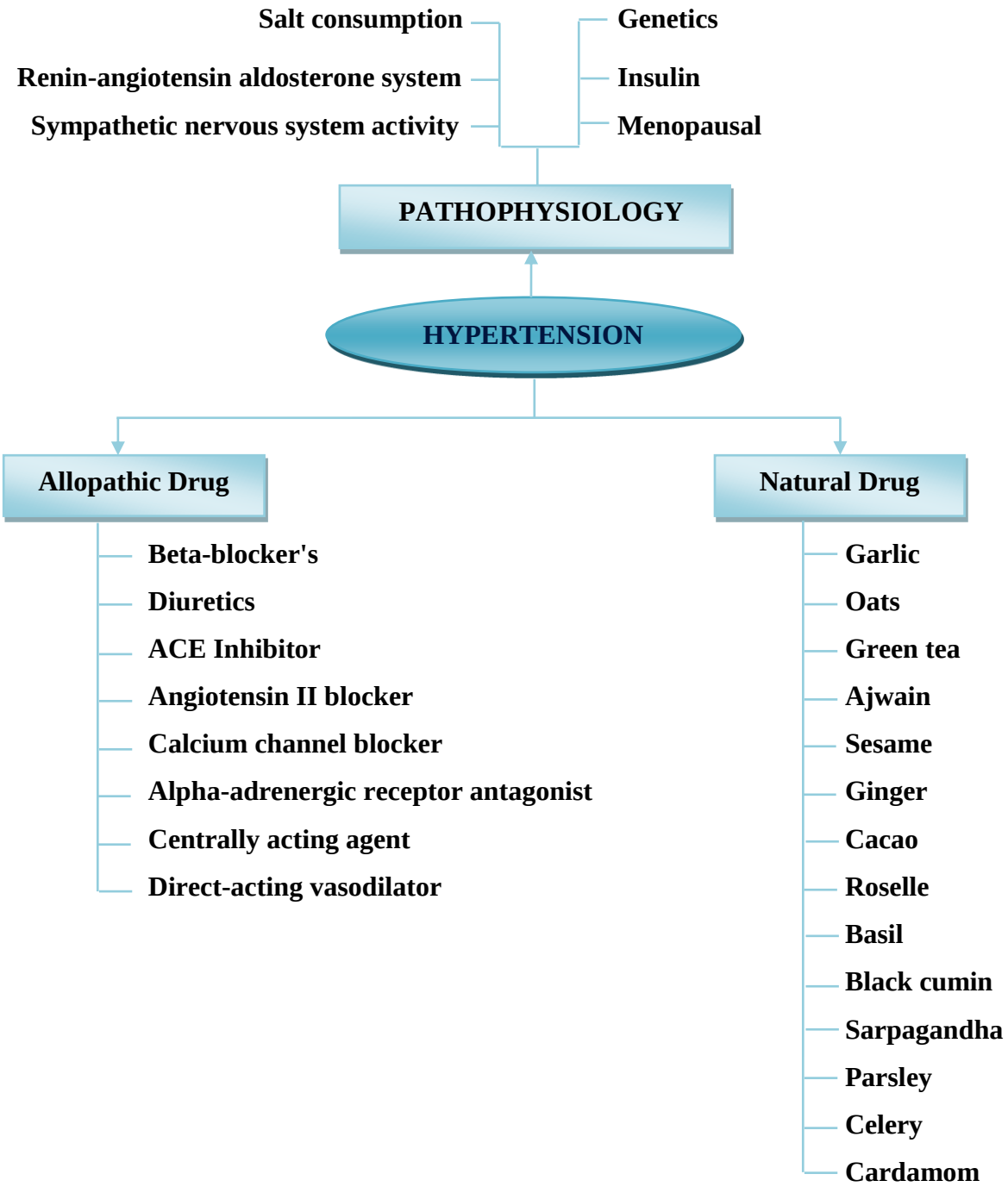


Hydralazine



Minoxidil

Minoxidil was developed in the 1970s as a therapy for people whose blood pressure could not be controlled or maintained while using other blood pressure medications, and it was utilized because of its significant vasodilation action [96]. Excess body weight is gained as a result of chronic minoxidil use [97]. All treatment strategies classify in figure.1.



3. Natural remedies for hypertension

3.1 Garlic and Oats

Garlic (*Allium sativum*) is an important and traditional medicinal herb in the Amaryllidaceae family. Garlic is utilized to treat cardiovascular diseases such as hypertension and arrhythmia [98]. Bioactive chemicals found in garlic include sulfur compounds, phenolic compounds, carbohydrates, and saponins. Garlic's bioactive components include alliin, ajoenes, Allyl sulfides, and 1,2-Vinyldithiin. Garlic is rich in many nutrients and vitamins (vitamin B complex and vitamin C), antioxidants, flavonoids, and minerals (potassium, phosphorus, and selenium) [99-100]. Garlic aqueous extract lowers blood Angiotensin I converting enzyme activity, whereas aged garlic extract lowers uncontrolled hypertension [101]. Garlic decreases oxidative stress while increasing NO and hydrogen sulfide (H2s) generation, both of which inhibit ACE [102]. Garlic is usually safe; nevertheless, there are a few effects that may cause minor discomforts, such as body odour, halitosis, and gut intolerabilities including flatulence, stomach ache, and gas. Some people are allergic to garlic, which may cause pemphigus, dermatitis, nasal congestion, asthma, itchy skin, and hypersensitivity [103].

Oats (*Avena sativa*) is a unique grain that contains protein, carbohydrates, crude fats, dietary fibre, antioxidants, vitamins, and minerals [104]. Oats have excellent therapeutic activity against the inflammatory state, diabetes, hypertension, and CVS disease [105]. Whole oats are high in B-glucan, which is beneficial to hypertension patients since it lowers blood pressure [106]. B-glucan degrades into short-chain fatty acids, causing arterial relaxation and lowering blood pressure. The hypotensive effect is related to endothelial dysfunction prevention and enhanced nitric oxide generation [107].

3.2 Green tea and Ajwain

Green tea (*Camellia sinensis*), a beverage made from the leaf of the plant's bud, has lately acquired popularity due to its health benefits and aroma [108]. Green tea’s primary ingredients include flavonoids, polyphenols, catechins, quercetins, kaempferols, and so on [109]. Green tea has an antioxidant impact owing to catechin as well as the influence of sympathoexcitation, which helps in blood pressure reduction [110].

Ajwain (*Trachyspermumammi*) is an important seed spice crop of the Apiaceae family that is also known as carom seed [111]. Ajwain's chemical ingredients include thymol, -terpene, -cymene, and others [112]. Researchers discovered that Ajwain had an antihypertensive effect, lowering both systolic and diastolic blood pressure [113]. Ajwain's vasorelaxation is similar to that of calcium channel blocker medications, which decrease extracellular Ca++ influx [114].

3.3 Sesame and Ginger

Sesame (*Sesamum indicum*) is a great edible oil crop rich in polyunsaturated fats and bioactive components including phytosterols, tocopherols (vitamin E), and lignans (sesamolin, sesamin, and sesamol) [115]. Polyunsaturated fatty acids (PUFA) and vitamins E have antioxidant, anti-inflammatory, and anti-hypertensive properties [116]. Sesame reduces endothelial dysfunction by increasing Nitric oxide (NO) and Ca++ antagonistic activity, which induces vasodilation and so lowers blood pressure [117].

Ginger (*Zingiber officinale*) is a significant plant that is the most commonly used ingredient in cooking. Ginger's fresh rhizome includes volatile oils as well as non-volatile components (Oleoresin, gingerol) [118]. Researchers discovered that gingerol, which is contained in ginger, lowers blood pressure by blocking ACE activity [119].

3.4 Cacao and Roselle

Cacao is derived from the plant *Theobroma Cacao* [120]. Flavonoids (catechin, epicatechin), procyanidin 2, methyl xanthenes, tannins, saponins, terpenoids, cardiac glycosides, and alkaloids are present in cacao [121]. Cacao's most important active phytochemicals are flavanols and methyl xanthene [122]. Cacao contains flavonoids and methylxanthines, which have been shown to improve blood pressure, cholesterol levels, and the risk of cardiovascular disease [123].

Roselle (*Hibiscus sabdariffa*) is a food, drink, and medicinal herb from the Malvaceae family, and every component of the plant provides therapeutic advantages [124]. Anthocyanins and flavonoids are the primary components. The crimson calyx is significant because it is utilized in the preparation of a health-promoting tea [125]. Roselle drink contains antioxidant, antihypertensive, anticancer, and antidiuretic properties. Researchers discovered that drinking 1

cup of Roselle drink twice a day can help reduce blood pressure [126]. Roselle has the same effect as captopril and lisinopril, both of which operate as ACE inhibitors and have antidiuretic effects, resulting in a synergy process that helps to reduce blood pressure [127].

3.5 Basil and Black cumin

Basil *(Ocimum basilicum*) is an annual herbaceous plant belonging to the Lamiaceae family [128]. It includes tannins, phenols, flavonoids, anthocyanins, and steroids, as well as essential oils. It has a high concentration of magnesium, potassium, and iron, which enhances CVS and is used as a diuretic [129]. Linalool, methyl chavicol, eugenol, and methyl cinnamate are the primary volatile components [130]. Basil extract was discovered to have vasorelaxant effects by researchers. Its crude extract includes quercetin, rutin, quercitrin, chlorogenic acid, and gallic acid, all of which inhibit the angiotensin I converting enzyme, which has an antihypertensive effect [131].

Black cumin (*Nigella sativa*), often known as black seed, is a member of the Ranunculaceae family. Black seed has a rich history in Indian and Arabian civilizations as food and medicinal [132]. Saponin, phenolic compound, alkaloids, sterols, novel lipid constituents, fatty acid, and volatile oil are the phytochemicals found in black cumin seeds. The most significant phytochemical found in cumin seed is thymoquinone [133]. Researchers discovered that black cumin increased plasma nitric oxide while decreasing systolic blood pressure [134]. Thymoquinone, a bioactive substance, helps in blood pressure reduction. By inhibiting voltage-gated ca^{++} channels and decreasing oxidative stress, black cumin exhibits a vasodilating effect [135].

3.6 Sarpagandha and Parsley

Sarpagandha (*Rauwolfia serpentine*) is a flowering plant in the Apocynaceae family which is also known as the Indian snakeroot and is utilized for its therapeutic properties [136]. Sarphagandha roots are used to cure a variety of ailments and disorders, including hypertension, sleeplessness, anxiety, excitation, schizophrenia, insanity, dysentery, menstruation problems, and even snakebite [137]. Flavonoids, phenolics, and alkaloids are among the phytochemicals present in Sarpagandha. The indole alkaloids present in Sarphagandha are widely recognized

[138]. The presence of indole alkaloids such as serpentine, ajmalicine, reserpine, and ajmaline in sarpagandha is attributed to its antihypertensive properties [139].

Parsley (*Petroselinum crispum l.*) is herbaceous species used as a food and medicinal plant [140]. Furanocoumarins, essential oils, flavonoids, carotenoids, vitamins, minerals, and fatty acids are all abundant in parsley [141]. People use parsley to treat gastritis, nasal haemorrhage, diabetes, and heart disease [142]. The researcher discovered that P.crispum extract lowers blood pressure via relaxing the aortic ring through the blocking of the Ca++ entrance, resulting in vasorelaxation [143].

3.7 Celery and Cardamom

Celery (*Apium graveolens l.*) is a herbal plant in the Apiaceae family that is utilized in both food and medicinal [144]. Selinene, bergapten, glycosides, furanocoumarins, flavonoids, psoralen, xanthoxin, furocoumarin, and limonene constitute the phytochemicals present in celery. Celery is used to treat cancer, as an antioxidant, an antihypertensive, an anti-inflammatory, and an anti-lipidemic (lipid-lowering) agent [145-146]. Researchers discovered that celery lowers blood pressure owing to the endothelium-dependent vasorelaxant action in the aortic ring, which is mediated by the inflow and release of Ca^{++}, cGMP, and nitric oxide [147-148].

Cardamom (*Elettaria cardamomum*) is a traditional medicine from the Zingiberaceae family. It is used to treat asthma, gum disease, cataracts, diarrhoea, and cardiac and digestive disorders [149]. Cardamom contains a variety of bioactive phytochemicals, the most important of which are monoterpenes such as 1,8-cineole, alpha terpineol, and sabinene, as well as the ester ingredient alpha terpinyl acetate [150]. Cardamom was discovered to have the ability to reverse the net effect of RAAS activation, such as vasoconstriction, sodium retention, and water retention, which raises arterial blood pressure and increases myocardial contractility with increased fluid volume, indicating its importance in hypertension management [151]. Cardamom has similar effects to verapamil, which is a calcium channel blocker that works by blocking the ca^{++} channels, decreasing blood pressure [152].

4. CONCLUSION

Hypertension is linked to a variety of disorders due to the involvement of variables such as lifestyle, environmental factors, heredity, and others with undesirable processes such as salt consumption, menopause, and the RAAS system for the onset of the hypertension state. To target hypertension, various aspects of medication have been proposed using natural and synthetic/semi-synthetic medicines. The study has discussed numerous hypertension subjects such as salt cause hypertension, heredity, menopause, sympathetic nerve activity, and insulin under the pathophysiological state. Treatments have been classified based on the development of mechanisms of action, such as the inhibition of endogenous catecholamine from interacting with beta-adrenergic receptors; inhibition of angiotensin II formation reduces systemic vascular resistance, increase renal flow; some agents decrease the calcium flow into cells which further lead the lowering of blood pressure; others also targeting to centrally like treating the catecholamine lowering the level in blood and, moreover natural remedies also help in lowering the blood pressure.

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