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REVIEW ARTICLE **OPEN ACCESS**

A Systemic Approaches for Developing New Antihypertensive Drugs from Plant Source

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ABSTRACT
Hypertension is the risk key factor for cardiovascular disease and death. People with this medical condition might be a symptomatic for years before having a deadly heart attack or stroke, hypertension is frequently referred to as a "silent killer". WHO reports that natural herbs and shrubs are frequently utilised to increase in order to effectively address practically all human health issues. In addition to being utilised as an immunity booster to strengthen the body's natural ability to fight off various health issues, plants serve as the primary industrial sources for the creation of chemical components, herbal medications, and food products. Nearly 5.6 billion people worldwide, or 80% of the population, use natural plant-based medications to treat serious health problems. Finding and assessing unstudied medicinal plants with antihypertensive properties is necessary so that they can be utilised as an alternative to currently available synthetic medications. Animal models must accurately reflect human forms of disease in order to be useful in advancing our understanding of the pathogenesis, prevention, and treatment of hypertension and its comorbidities. Additionally, models are employed in the pharmacological evaluation of prospective antihypertensive drugs. In the past, investigating the antihypertensive potential of medications rarely used hypertensive animal models. Animal models are being used more frequently to evaluate novel compounds as they are being synthesised in vast quantities. As new information about the aetiology of hypertension is discovered, novel animal models of hypertension are being created.Many characteristics of human hypertension are present in the animal models of the disease as well.Creation of innovative approaches to treating and avoiding high blood pressure and its side effects. Animal models could be helpful in filling these gaps in knowledge.
Keywords*: Hypertension, plant source, animal models, treatment.*

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INTRODUCTION

A significant medical condition called hypertension can raise your chance of developing heart, brain, kidney, and other problems. It is a significant global cause of premature death. Synthetic medications can be replaced with natural herbal remedies that may have antihypertensive action and fewer adverse effects when combined with a change in lifestyle and some mild exercise, medications. Clinical hypertension is managed with a number of current medications, but it comes with a number of side effects. According to predictions, by 2025, the global prevalence of hypertension will have increased by 60% from its current level of 26.4%. A person's normal blood pressure is 120/80 mmHg.

Hypertension is mainly of two types:

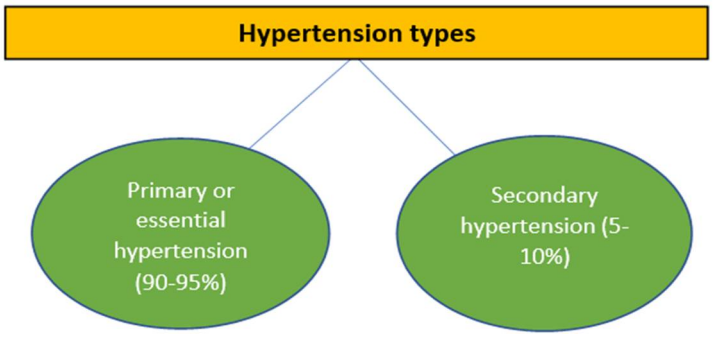

Fig no 1: Types of hypertensions

1)Primary or Essential Hypertension (90–95%): Patients' unclear causes, which could contribute to blood pressure increase.

2) Secondary Hypertension (5–10%):

Patients' elevated blood pressure is primarily caused by renal or adrenal illness. In addition, cardiac output, peripheral vascular resistance, and nitric oxide play significant roles in hypertension. Natural herbs and shrubs are being used more frequently worldwide to cure practically all physical illnesses, according to the WHO. The kind any natural plant can be used to cure a specific illness or group of illnesses because of the phytochemical components found in the plant. Compared to allopathic treatment, the use of medicinal herbs and shrubs is crucial since it is less expensive and has less adverse effects. A serious health issue, hypertension is made worse by other cardiovascular diseases. Diuretics are frequently used to lower elevated blood pressure by themselves or in combination with other antihypertensive medications. Booster to improve the body's inherent ability to fight off various health issues, as well as herbal remedies and nutritional items. Herbal plants are viewed as effective treatments for practically all diseases in cultural, religious, and folk traditions.

Native plant remedies have been a part of World Health Organization initiatives since 1970, mostly for developing nations. 80% of the world's population, according to the United Nations World Health Organization (around 5.6 billion people) uses herbal remedies for serious health issues. [1].

SAFER HERBAL MEDICINE OF HYPERTENSION:

Sr.no	Common name	Botanical name
1	Garlic	*Allium sativum*
2	Ginkgo	*Ginkgo biloba*
3	Passionfruit (Passiflora)	*Passiflora edulis*
4	Rudraksha	*Elaeocarpus ganitrus*
5	Roselle	*Hibiscus sabdariffa*

Table1.Listof Botanicals for the Treatment of Hypertension

HERBS & NATURAL REMEDIES WITH HYPOTENSIVE & HYPERTENSION PROPERTIES:

Agathosma betulina:

(Family: Rutaceae; Common name: Buchu). It is a South African medicinal plant that has been used for ages to heal a variety of maladies by the local aboriginal population. It is a successful both a diuretic and an anti-inflammatory. Using buchu, early Dutch immigrants created a brandy tincture that is still used today to cure a variety of ailments [2].

Annonam uricata (Family: Annonaceae; Common name: Prickly Custard apple):

muricata is a species of the genus Annona, which is well known for its edible fruits, and a member of the Annonaceae family of custard apple trees. The tree naturally grows in both Central America and the Caribbean. According to reports, the plant's leaf extract can lower high blood pressure by reducing peripheral vascular resistance [3].

Aristolochiam anshuriensis (Family: Aristolochiaceae; Common name: Guan Mu Tong):

This Chinese plant is used to treat edoema and rheumatic pain as a diuretic and antiphlogistic. Aristolochic acid has reportedly been found in this plant's extract. tannins, oleanolic acid, hederagenin, aristoloside, and magnoflorine. It has been discovered that magnoflorine has hypotensive qualities [4].

Blond psyllium (Family: Plantaginaceae; Common name: Indian plantago):

According to preliminary clinical studies, ingesting 15 g of B. psyllium (Plantago species) daily will somewhat lower blood pressure, systolic by roughly 8 mmHg and diastolic by 2 mmHg [5].

Ajwain (CarumcopticumL.):

The A piaceae family includes Carumcopticum, which thrives in a variety of habitats throughout Central Europe, Iran(especially in the eastern Baluchistan region),India, Afghanistan, and Pakistan. Because of its ability to inhibit calcium channels, C. copticum plays a significant part in controlling blood pressure and heart rate.

In normotensive (NMT) rats, the aqueous-methanolic extract of C. copticum Benth. seeds (CSE) (1-30 mg/kg) lower blood pressure and heart rate (HR). There have been reports of bradycardia at higher doses (10–30mg/kg) [6].

PLATFORMS OF EXPERIMENTAL HYPERTENSION: GENETIC

SHR Strain: By mating an outbred Wistar male rat with spontaneously raised blood pressure with a female rat who also had mildly elevated blood pressure

Following brother-sister mating, animal selection was continued with systolic blood pressure greater than 150 mm Hg After 20 generations of inbreeding at the National Institutes of Health, the inbred strain was subsequently introduced to the United States in the late 1960s and spontaneously develops hypertension in adult animals. The SHR is frequently utilised as a rat model of primary or essential hypertension in many research. The investigations of stroke, vascular function, autonomic regulation, renal function, therapeutic treatments, and the genetics of primary hypertension have all benefited from using this strain or its sub-strains, such as the stroke-prone SHR [7].

DSS rats:

Lewis Dahl, who recognised the health benefits of low-sodium diets in the 1950s and studied the impact of various salt diets on blood pressure in outbred SD rats, produced the DSS rat. selecting just the rats that matured after being fed a high salt diet.

The inbred DSS rats, which are frequently employed in studies looking at the kidney, vascular, and genetics in hypertension, were developed as a result of hypertension. The inbred Dahl salt-resistant rats were created through selective breeding of rats resistant to salt-sensitive hypertension [8].

FHH Rat:

The outbred fawn-hooded (or fawn headed) rat, which was first noted for its bleeding condition, was inbred to create the FHH model. Inbred the outbred rats after finding that they had higher mean arterial pressure than Wistar rats, resulting in two strains known as the normotensive fawn-hooded (also known as FHL) rat and the hypertensive FHH. The genetics of hypertension and chronic kidney disease have been studied using the FHH rat [9].

Milan Hypertensive Strain:

The Milan hypertensive breed of rats was developed from Wistar rats that were found to have increased blood pressure; the rats were inbred for several generations. To research primary hypertension, Milan hypertensive strain rats have been employed. Recently, the Milan normotensive strain has been valuable for examining the genetic pathways behind poor myogenic responses, sensitivity to the onset of proteinuria, and vulnerability to renal damage [10,11].

Lyon Hypertensive Rats:

In the late 1960s, researchers in France chose outbred SD rats for high, normal, or low blood pressure [12,13]. These rats were then repeatedly inbred into strains with low, normal, or high blood pressure.

There is a BP difference between the strains. observable at a young age (5 weeks) and persists after that. These strains have been employed in genetic, autonomic, metabolic, renal, and cardiac research [14].

HYPERTENSION: INDUCED PLAT FORMS OF EXPERIMENTAL:

Renovascular hypertension:

several of these models' substantial RAAS involvement may help to identify Beyond their anatomical, physiological, and pathological similarities to humans, large animal models of renovascular hypertension may offer a number of benefits. Both small and large animal models now allow for tailored therapies to treat the vascular occlusion.

These types of models may be used to determine the mechanism that causes hypertension, investigate the possibility of target- organ injury being reversible, and pinpoint organ damage processes that might not be related to hypertension [15,16].

AngII–Dependent Hypertension:

A crucial part of healthy salt and water balance is played by the RAAS. As a result, long-termsubcutaneousinfusionofAngIIisoneofthemostoftenusedpreclinicalmodelsofhypertension, particularly in rodents. The RAAS is extensively active in human hypertension. The level of BP elevation attained with routinely used dosages of Ang II in mice is comparable to that found in uncontrolled stage 2 hypertension. Target-organ damage is strikingly similar to that reported in human patients with sustained elevations in BP after 4 weeks of long-term Ang II infusion in susceptible rodent strains, including cardiac injury. chronic renal disease, vascular remodeling, and hypertrophy [17,18]. However, long-term Ang II infusion more accurately simulates the renal damage that results from Ang II because the renal vasoconstriction it causes might cause ischemia, especially at larger doses. Human hypertension than that from barotrauma is persistent renal ischemia [19]. Radiotelemetry is the most recent cutting-edge technique for measuring BPs during long-term Ang II infusion [20].

Nitric oxide system:

nitro-L-argininemethyl ester (L-NAME), a nonselective nitric oxide synthase inhibitor, causes time- and dose-dependent hypertension in SHRs when administered for 4 weeks.[21].

Three different types of hypertension can result from the Goldblatt technique:

Two kidney, one clip (2K1C) hypertension: Itis characterized by the constriction of only one renal artery, leaving the other kidney unaffected. Due to elevated plasma renin activity (PRA), which raises the level of circulating angiotensin-II, a powerful vasoconstrictor, this causes a persistent rise in blood pressure. The

other normal kidney, on the other hand, being undamaged, there is no salt or water retention. As a result, renin-angiotensin is required for the development of hypertension at this stage. At this point, the resulting hypertension is renin-angiotensin dependent. After around 6 weeks, the elevated angiotensin-II causes the adrenal cortex to release aldosterone, which gradually causes a retention of salt and water. Renin production is lowered as a result of salt and water retention. As to this point, hypertension is volume dependent. As a result, the balance between salt and water plays a crucial role in the pathophysiology of renovascular hypertension. Unclipping or removing the damaged kidney restores normal blood pressure and renin activity.

1K1C, or one kidney, one clip hypertension: The opposite kidney is removed and the renal artery is constricted on one side. The blood pressure rises after a short while. There is rapid salt and water retention since there is no second kidney, which prevents pressure diuresis and natriuresis. The activity of plasma renin is typically normal. Over time, hypertension becomes volume dependent.

2K2C (2 kidney, 2 clip) hypertension: Aorta or both renal arteries are constricted. Patchy ischemic kidney tissue secretes renin, which raises blood pressure. Salt and water are retained by the renal tissue that is left. Indeed, a patchy ischemic kidney disease is one of the most prevalent causes of renal hypertension in humans.

Hypertension induced by external compression of renal parenchyma:

Two kidney, one ligature (2K1L):

One kidney is ligated, while the opposite kidney is left unaffected**.**

One kidney, one ligature (1K1L):

The contralateral kidney is removed and the ligature is attached to one kidney [25].

Dietary hypertension:

Increased salt intake (Mineralocorticoid-Salt Hypertension):

When administered to large and small animals, mineralocorticoids and a high-salt diet can cause hypertension. Deoxycorticosterone administration, typically in the form of DOCA, has been the most popular treatment for animals that consume a lot of salt for causing hypertension caused by mineralocorticoid salts. Although deoxycorticosterone appears to have both glucocorticoid and mineralocorticoid qualities, the DOCA-salt model appears to be more focused on this hormone's propensity to produce sodium retention.

Early research demonstrated that animals made particularly sensitive to the effects of mineralocorticoids like DOCA by a high salt intake (0.6%–1% NaCl in drinking water is normal) and frequently by uninephrectomy. Despite the fact that earlier studies focused on low dosages of DOCA reproducibly cause hypertension, hence extremely high doses are required; average current doses range from 20 to 50 mg/kg (in rats) [22].

OBESITY:

Up to 75% of the risk for primary hypertension and the majority of cases of treatment-resistant hypertension can be attributed to overweight and obesity. Several experimental obesity animals develop hypertension on their own when they put on weight. The obese Zucker rat, ZSF1 rat, Wistar fatty rat, and ob/ob mice are genetically generated obesity models that produce hypertension that obstruct leptin transduction and signalling. These models are the most popular and have the benefit of reducing the influence of confounding variables, allowing mechanistic investigations to examine the part that certain genes play in obesity-induced hypertension. In big animal models, genetically induced obesity-hypertension can also be accomplished. For instance, increased blood pressure is linked to DNA transposition of the D374Y gain-of-function cDNA of chimp proprotein convertase subtilisin/kexin type-9 [23]. In both rodents, diets high in saturated fats and refined carbohydrates cause weight gain, changes in body composition, and cellularity of adipose tissue [24] as well as a number of large animals, such as pigs [25] dogs [26] and rabbits [27].

Purified-ingredient diets are the best option due to their minimal batch-to-batch variability and lack of plant-derived ingredients, even though a combination of chow and added fat may be enough to promote obesity-hypertension. phytochemicals, which may change how a disease develops.

High quantities of carbs, which are essential to achieving various characteristics of the metabolic syndrome, including hypertension, are present in purified diets. Pigs fed a high- fat diet on their own exhibit vascular dysfunction and dyslipidemia but not elevated blood pressure. On the other hand, giving farmed pigs a diet heavy in fat, cholesterol, and carbs for 16 weeks results in spontaneous hypertension.

Although high-fructose diets appear to be more effective than high-sucrose diets at causing metabolic syndrome, the rises in blood pressure that these diets cause are equivalent. Last but not least, substances like monosodium glutamate that are primarily employed to cause obesity might cause spontaneous hypertension. However, these models frequently have poor associations between obesity and hypertension. To respond to the fundamental question of whether obesity exacerbates pre-existing

hypertension, models of contemporaneous, independently obtained hypertension in addition to models of primary obesity are essential. For instance, fat loading in DSS rats exacerbated kidney impairment brought on by high blood pressure and salt, which was preceded by body weight gain, visceral fat deposition, and insulin resistance [28]. In the same way, research on Ossabaw pigs with obesity and renal artery stenosis showed that fat enhances both renal and cardiac damage, but that blood pressure levels were unaffected. These findings imply that an essential predictor of the impact of obesity is the fundamental mechanism associated with the development of hypertension. Despite the fact that fat makes blood pressure more sensitive to salt, the impact on hypertension. In models of surgically induced hypertension, may be separated from obesity [29,30]. Alternately, genetic or dietary modifications could be used to study how fat affects hypertension. Obesity and hypertension are brought on by separate genetic changes in the spontaneously hypertensive (Koletsky) rat.

According to BP values, genetically induced hypertension is not made worse by fat, which is shown by the fact that these levels are similar to those of salt-sensitive hypertensive rats. On the other hand, obese Zucker rats treated with DOCA-salt see a 4-day increase in blood pressure.

Therefore, these models are appropriate to investigate whether fat affects animals' sensitivity to artificially generated pain. The sensitivity of the models to concomitant obesity and hypertension is likely to depend on the participation of the RAAS, oxidative stress, or other processes. When deciding between small and big animal models for obesity-hypertension, numerous factors should be taken into account. Particularly, the development of spontaneous hypertension in big animal models of diet-induced obesity may take a long time, increasing the expense of the experiment. In addition, considerable increases in body size, length, and fat content may restrict animal mobility and raise the danger of infections and surgical complications [31,32].

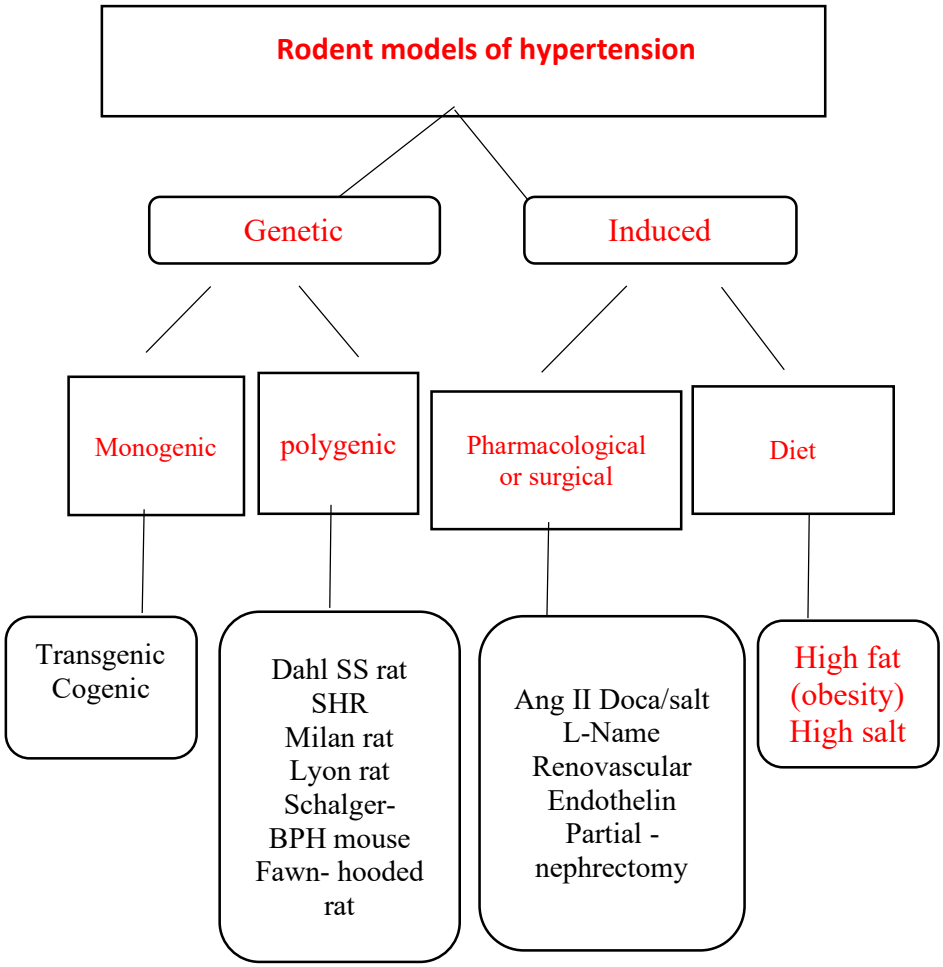

Fig no 2: Rodent models of hypertension

DISCUSSION AND CONCLUSION

A key contributing factor to cardiovascular diseases, which impact of individuals globally, is hypertension. Essential or primary hypertension is a high blood pressure condition brought on by an unidentified or unknown disease. An underlying condition or specific medications may be to blame for secondary

hypertension. There are numerous allopathic medications used to treat hypertension. However, these medications might cause adverse effects include skin rashes, muscle cramps, dizziness, excessive fatigue, dehydration, blurred vision, and irregular heartbeats. Herbs are becoming a part of evidence-based medicine since studies in this review show that they can moderately lower blood pressure whether used alone or in combination with existing antihypertensive medications. The management of high blood pressure Through their effects on vascular smooth muscle cells, endothelial cells, ROS, and inhibition of RAAS, their pharmacological actions appear to favorably influence various parameters implicated in the a etiology of hypertension. The focus of this review is not on the toxicity profile of the plants, it was found that some plants that are still being used conventionally to treat hypertension despite being thought to be hazardous. To reach prescribed blood pressure targets, safe and efficient interventions are required. Additionally, this review article offers assistance in the identification of B.P. and in the choosing a certain antihypertensive medication in combination with natural remedies.

Natural plants' and their isolates' pharmacological effects on the aetiology of hypertension through modifying a number of factors, including endothelial function, ROS generation, pro-inflammatory signalling, platelet activation, various ion channel opening and shutting, ACE inhibition, gene expression, etc. Herbal medicines will undoubtedly receive more attention in the future because they have a wide range of benefits and have undergone necessary clinical and experimental research. Additionally, it is advised that patients receive sufficient education regarding the usage of long-used herbs like ginseng, blackcumin, coriander & garlic. As there are medications accessible that can cause individuals harm and elevate blood pressure.

Animal models of hypertension have been and most likely will continue to be very helpful in shedding light on the disease's pathophysiology and cutting-edge therapeutic possibilities. It is obvious that researchers need to make knowledgeable decisions regarding the best animal model for experiments need to be properly planned, carried out, and analyzed for a particular application. In this scientific statement, we highlight a few crucial ideas that are particularly important for individuals working in the subject and could help advance it.

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