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A Review on Experimental Animal Models Used for Evaluation of Anti-Hypertensive Drugs in Rats and Mice

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Abstract:

Hypertension is one of the leading cardiovascular disorders responsible for significant morbidity and mortality worldwide. The continuous rise in hypertensive patients has increased the demand for effective and safer anti-hypertensive therapies. Experimental animal models play a crucial role in understanding the pathophysiology of hypertension and in the preclinical evaluation of anti-hypertensive drugs. Among different laboratory animals, rats and mice are widely preferred because of their genetic similarity to humans, ease of handling, reproducibility, and cost-effectiveness. Various experimental models have been developed to mimic human hypertension, including genetic, pharmacological, dietary, and surgically induced models. Commonly used models include Spontaneously Hypertensive Rats (SHR), DOCA-salt induced hypertension, L-NAME induced hypertension, renovascular hypertension models, and Angiotensin-II induced hypertension. Each model exhibits distinct pathological and physiological characteristics that help researchers evaluate the efficacy, safety, and mechanism of action of anti-hypertensive agents.This review summarizes the major experimental animal models used in hypertension research and highlights their applications in anti-hypertensive drug screening. The article also discusses methods for blood pressure measurement, biochemical and histopathological assessment, advantages and limitations of rodent models, and recent advancements in hypertension research. Furthermore, emerging therapeutic strategies such as nanotechnology-based drug delivery systems, herbal medicines, and gene-targeted therapies are briefly addressed. Understanding the appropriate selection and utilization of animal models is essential for improving translational research and accelerating the development of novel anti-hypertensive drugs with better therapeutic outcomes.

Keywords: Hypertension; Anti-hypertensive drugs; Experimental animal models; Rats; Mice; Spontaneously hypertensive rats; DOCA-salt model; L-NAME induced hypertension; Blood pressure; Preclinical evaluation; Rodent models; Cardiovascular research; Pharmacological screening; Hypertension research

1. Introduction

Hypertension is a chronic cardiovascular disorder characterized by a persistent elevation in arterial blood pressure and is considered one of the major risk factors for heart disease, stroke, renal dysfunction, and premature death worldwide. According to global health reports, the prevalence of hypertension has increased significantly due to sedentary lifestyle, unhealthy dietary habits, stress, obesity, alcohol consumption, and genetic predisposition. Despite the availability of numerous anti-hypertensive drugs, effective management of hypertension remains a major clinical challenge because of drug resistance, adverse effects, and patient non-compliance. Therefore, continuous research is required for the discovery and development of safer and more effective anti-hypertensive agents.

1.1 Overview of Hypertension

Hypertension, commonly known as high blood pressure, is a chronic medical condition in which the force exerted by circulating blood against the walls of arteries remains consistently elevated. It is one of the most prevalent cardiovascular disorders worldwide and represents a major public health concern due to its association with severe complications such as myocardial infarction, stroke, heart failure, renal impairment, and vascular diseases. Blood pressure is generally expressed in terms of systolic blood pressure (SBP) and diastolic blood pressure (DBP). According to international guidelines, a persistent blood pressure reading of 140/90 mmHg or higher is commonly considered hypertensive in adults.Hypertension is broadly classified into primary (essential) hypertension and secondary hypertension. Primary hypertension accounts for nearly 90–95% of cases and develops gradually without any identifiable cause. Genetic factors, obesity, excessive salt intake, smoking, alcohol consumption, stress, sedentary lifestyle, and aging are considered important contributors to its development. Secondary hypertension occurs due to underlying medical conditions such as renal disorders, endocrine abnormalities, cardiovascular diseases, or the use of certain medications.

The pathophysiology of hypertension is complex and involves multiple physiological systems including the renin–angiotensin–aldosterone system (RAAS), sympathetic nervous system, vascular endothelial function, and renal sodium regulation. Overactivation of these systems leads to vasoconstriction, fluid retention, oxidative stress, and increased peripheral vascular resistance, ultimately resulting in elevated blood pressure. Persistent hypertension may damage vital organs such as the heart, kidneys, brain, and blood vessels, commonly referred to as target organ damage. Hypertension is often called a “silent killer” because many individuals remain asymptomatic during the early stages of the disease. Common symptoms observed in severe or uncontrolled hypertension include headache, dizziness, fatigue, blurred vision, chest pain, and shortness of breath. Early diagnosis and appropriate treatment are therefore essential to prevent long-term complications and improve patient outcomes. Management of hypertension involves both pharmacological and non-pharmacological approaches. Lifestyle modifications such as reduced sodium intake, regular physical activity, weight management, smoking cessation, and balanced diet play an important role in controlling blood pressure. Pharmacological treatment includes the use of anti-hypertensive agents such as diuretics, beta-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers. Continuous research and preclinical studies using animal models remain essential for the development of safer and more effective therapies for hypertension.

1.2 Global Burden of Hypertension

Hypertension has emerged as one of the most significant global public health challenges due to its increasing prevalence, associated complications, and economic burden on healthcare systems. It is recognized as a major modifiable risk factor for cardiovascular diseases, stroke, kidney failure, and premature mortality. According to the World Health Organization (WHO), approximately 1.4 billion adults aged 30–79 years worldwide were living with hypertension in 2024, and nearly two-thirds of these individuals belonged to low- and middle-income countries. The prevalence of hypertension has increased substantially over the past few decades because of urbanization, population aging, sedentary lifestyle, obesity, excessive salt intake, alcohol consumption, smoking, and psychological stress. Although hypertension can be effectively managed through lifestyle modifications and pharmacological therapy, awareness, treatment, and control rates remain inadequate in many countries. Reports indicate that nearly 44% of hypertensive individuals are unaware of their condition, while only a small proportion achieve adequate blood pressure control. Hypertension contributes significantly to the global burden of cardiovascular diseases (CVDs). Cardiovascular disorders are currently the leading cause of death worldwide, accounting for approximately 19.8 million deaths annually. Elevated blood pressure is strongly associated with myocardial infarction, heart failure, stroke, peripheral vascular disease, and chronic kidney disease. Persistent hypertension also causes structural and functional damage to vital organs including the heart, brain, kidneys, and blood vessels.

The burden of hypertension is particularly high in developing and economically weaker regions where healthcare infrastructure, awareness programs, and access to essential medicines are limited. The WHO Eastern Mediterranean and African regions report higher prevalence rates compared to several developed nations. In addition, socioeconomic inequality, poor dietary habits, and lack of routine screening contribute to delayed diagnosis and treatment in these

populations. Hypertension also imposes a considerable economic burden through increased healthcare expenditure, long-term medication use, hospitalization, and loss of productivity. Uncontrolled hypertension often leads to severe complications requiring expensive medical interventions and prolonged treatment. Therefore, early diagnosis, preventive healthcare strategies, public awareness programs, and continuous research on novel anti-hypertensive therapies are essential to reduce the global impact of hypertension.Recent global initiatives emphasize strengthening primary healthcare systems, improving access to affordable anti-hypertensive medications, and promoting lifestyle interventions such as reduced salt intake, regular physical activity, healthy diet, and smoking cessation. Continued advancements in experimental hypertension research and preclinical drug evaluation are expected to contribute significantly toward the development of safer and more effective therapeutic approaches for hypertension management.

1.3 Need for Experimental Animal Models

Experimental animal models play a fundamental role in hypertension research and are widely used for the discovery, development, and evaluation of anti-hypertensive drugs. Hypertension is a multifactorial disorder involving complex interactions among genetic, environmental, neural, renal, vascular, and hormonal factors. Due to this complexity, direct investigation of disease mechanisms in humans is often difficult, time-consuming, and ethically restricted. Therefore, experimental animal models provide a controlled and reproducible platform for studying the pathophysiology of hypertension and assessing the therapeutic potential of novel drug candidates.

Rats and mice are the most commonly used laboratory animals in hypertension research because of their physiological and genetic similarities to humans, short life cycle, ease of breeding, and relatively low maintenance cost. In addition, advances in molecular biology and genetic engineering have enabled the development of transgenic and knockout mouse models that closely mimic human cardiovascular disorders. These animal models allow researchers to investigate the molecular mechanisms involved in blood pressure regulation and target organ damage.Experimental models are essential for understanding the progression of hypertension and evaluating the pharmacological actions of anti-hypertensive agents under controlled laboratory conditions. They help in studying parameters such as systolic and diastolic blood pressure, heart rate, vascular resistance, renal function, oxidative stress, and inflammatory responses. Animal studies also provide valuable information regarding drug absorption, distribution, metabolism, toxicity, and long-term safety before initiating clinical trials in humans.

Different animal models have been developed to simulate various forms of human hypertension. Genetic models such as Spontaneously Hypertensive Rats (SHR) mimic essential hypertension, whereas chemically induced models like DOCA-salt and L-NAME induced hypertension reproduce secondary hypertension associated with endothelial dysfunction and hormonal imbalance. Renovascular and salt-sensitive models are also commonly used for investigating specific mechanisms related to renal and dietary factors in hypertension. The availability of diverse models enables researchers to select the most appropriate system according to the objective of the study and the mechanism of action of the test drug.

Experimental animal models also contribute significantly to the identification of novel therapeutic targets and biomarkers associated with cardiovascular diseases. Many currently available anti-hypertensive drugs, including ACE inhibitors, beta-blockers, calcium channel blockers, and angiotensin receptor blockers, were developed and validated through preclinical studies using animal models. Furthermore, modern research involving herbal medicines, peptide-based therapies, nanotechnology-based drug delivery systems, and gene-targeted approaches heavily depends on experimental hypertension models for preliminary evaluation.Despite their advantages, animal models have certain limitations because no single model can completely replicate human hypertension. Variations in species physiology, genetic background, and environmental factors may influence experimental outcomes. Nevertheless, experimental animal models remain indispensable tools in cardiovascular pharmacology and continue to provide critical insights for the advancement of anti-hypertensive drug research and development.

1.4 Importance of Preclinical Evaluation of Anti-Hypertensive Drugs

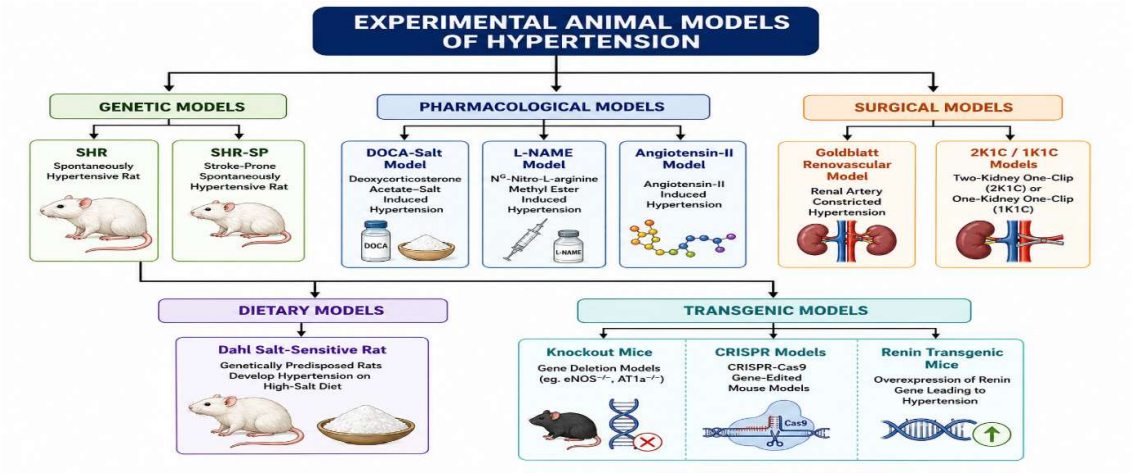
Preclinical evaluation is a crucial stage in the development of anti-hypertensive drugs because it provides essential information regarding the efficacy, safety, pharmacological activity, and toxicity profile of new therapeutic agents before their administration in humans. Hypertension is a complex cardiovascular disorder associated with multiple physiological mechanisms, and therefore extensive laboratory investigations are necessary to ensure that newly developed drugs are both effective and safe for long-term clinical use. Preclinical studies primarily involve in vitro experiments and in vivo testing using experimental animal models such as rats and mice.The major objective of preclinical evaluation is to identify compounds capable of reducing elevated blood pressure without producing significant adverse effects. Experimental studies help researchers determine the mechanism of action of anti-hypertensive agents by assessing their influence on physiological systems involved in blood pressure regulation, including the renin–angiotensin–aldosterone system (RAAS), sympathetic nervous system, vascular endothelial function, and renal sodium balance. These studies also assist in understanding the effects of drugs on cardiac output, vascular resistance, electrolyte balance, and organ protection.

Animal models play a significant role during preclinical assessment because they simulate various forms of human hypertension under controlled conditions. Through these models, researchers can evaluate pharmacodynamic parameters such as systolic and diastolic blood pressure reduction, heart rate changes, vascular reactivity, and improvement in endothelial function. In addition, pharmacokinetic studies are performed to investigate the absorption, distribution, metabolism, and excretion of the drug candidate. These findings are important for dose optimization and selection of appropriate routes of administration.Preclinical evaluation is also essential for detecting possible toxicological effects and ensuring drug safety before human clinical trials. Long-term administration studies in rodents help identify adverse reactions such as hepatotoxicity, nephrotoxicity, cardiotoxicity, and metabolic disturbances. Histopathological examination of organs including the heart, kidneys, liver, and blood vessels further provides evidence regarding tissue protection or damage caused by the investigational drug. Such studies minimize the risk of unexpected complications during clinical development.

Another important aspect of preclinical evaluation is the screening of novel therapeutic approaches for hypertension management. Recent advancements in pharmaceutical research have introduced herbal medicines, nanotechnology-based drug delivery systems, peptide therapeutics, and gene-targeted therapies as potential anti-hypertensive strategies. Experimental animal models are extensively used to evaluate the efficacy and safety of these innovative treatments before their transition into human studies. Furthermore, regulatory authorities require comprehensive preclinical data prior to granting approval for clinical trials. Reliable preclinical findings improve the probability of clinical success and reduce the financial burden associated with drug development. Although animal models cannot fully replicate human hypertension, they provide valuable scientific evidence that contributes significantly to the discovery and advancement of effective anti-hypertensive therapies.Therefore, preclinical evaluation remains an indispensable component of cardiovascular drug research, enabling the development of safer, more efficient, and clinically relevant anti-hypertensive medications.

2. Classification of Experimental Animal Models of Hypertension

Experimental animal models are indispensable tools in hypertension research and preclinical evaluation of anti-hypertensive drugs. Since hypertension is a multifactorial disease involving genetic, environmental, renal, vascular, neural, and endocrine factors, no single animal model can completely reproduce all aspects of human hypertension. Therefore, a variety of experimental models have been developed to mimic different forms of the disease and to facilitate the investigation of underlying mechanisms and therapeutic interventions. These models are generally classified into genetic models, pharmacological models, surgically induced models, dietary models, stress-induced models, and transgenic models.



2.1 Genetic Models of Hypertension

Genetic models are developed through selective breeding of animals that naturally exhibit elevated blood pressure. These models closely resemble human essential hypertension and are extensively used to study the hereditary and molecular basis of blood pressure regulation. Among the various genetic models, the Spontaneously Hypertensive Rat (SHR) is considered the gold standard for hypertension research. Hypertension develops naturally in SHR without any external intervention, making it highly suitable for evaluating long-term anti-hypertensive therapies. Other important genetic models include Stroke-Prone Spontaneously Hypertensive Rats (SHR-SP), Dahl Salt-Sensitive Rats, Milan Hypertensive Rats, and New Zealand Genetically Hypertensive Rats. These models provide valuable information regarding genetic susceptibility, vascular remodeling, cardiac hypertrophy, and target organ damage associated with hypertension.

2.2 Pharmacologically Induced Models

Pharmacological models are produced by administering chemical agents that interfere with normal physiological mechanisms involved in blood pressure regulation. These models are simple, reproducible, and widely used for screening anti-hypertensive compounds. One of the most frequently employed pharmacological models is the L-NAME-induced hypertension model, in which nitric oxide synthase inhibition leads to endothelial dysfunction and elevated blood pressure. Another widely used model is the Angiotensin II-induced hypertension model, where chronic administration of angiotensin II causes vasoconstriction, oxidative stress, and activation of the renin–angiotensin system. Similarly, administration of deoxycorticosterone acetate (DOCA) combined with high salt intake produces mineralocorticoid-dependent hypertension characterized by sodium retention and vascular dysfunction. These models are particularly useful for studying specific pathophysiological pathways involved in hypertension.

2.3 Surgically Induced Models

Surgically induced models are designed to mimic secondary forms of hypertension associated with renal vascular abnormalities. The most commonly used surgical model is the Goldblatt renovascular hypertension model, which involves partial constriction of one or both renal arteries. Reduced renal blood flow stimulates renin release and activates the renin–angiotensin–aldosterone system, resulting in persistent hypertension. Common variants include the two-kidney one-clip (2K1C), one-kidney one-clip (1K1C), and two-kidney two-clip (2K2C) models. These models are highly valuable for investigating renal mechanisms of hypertension and evaluating drugs that target the renin–angiotensin system.

2.4 Dietary-Induced Models

Dietary factors play a significant role in the development of hypertension, and several animal models have been established using nutritional interventions. High-salt diet models are among the most commonly used dietary models and are particularly relevant for studying salt-sensitive hypertension. Excessive sodium intake causes fluid retention, increased vascular resistance, and elevated blood pressure. Fructose-induced hypertension models are also widely employed to investigate the relationship between metabolic syndrome, insulin resistance, and hypertension. In addition, high-fat diet models contribute to obesity-associated hypertension and provide insight into the cardiovascular complications of metabolic disorders.

2.5 Stress-Induced Models

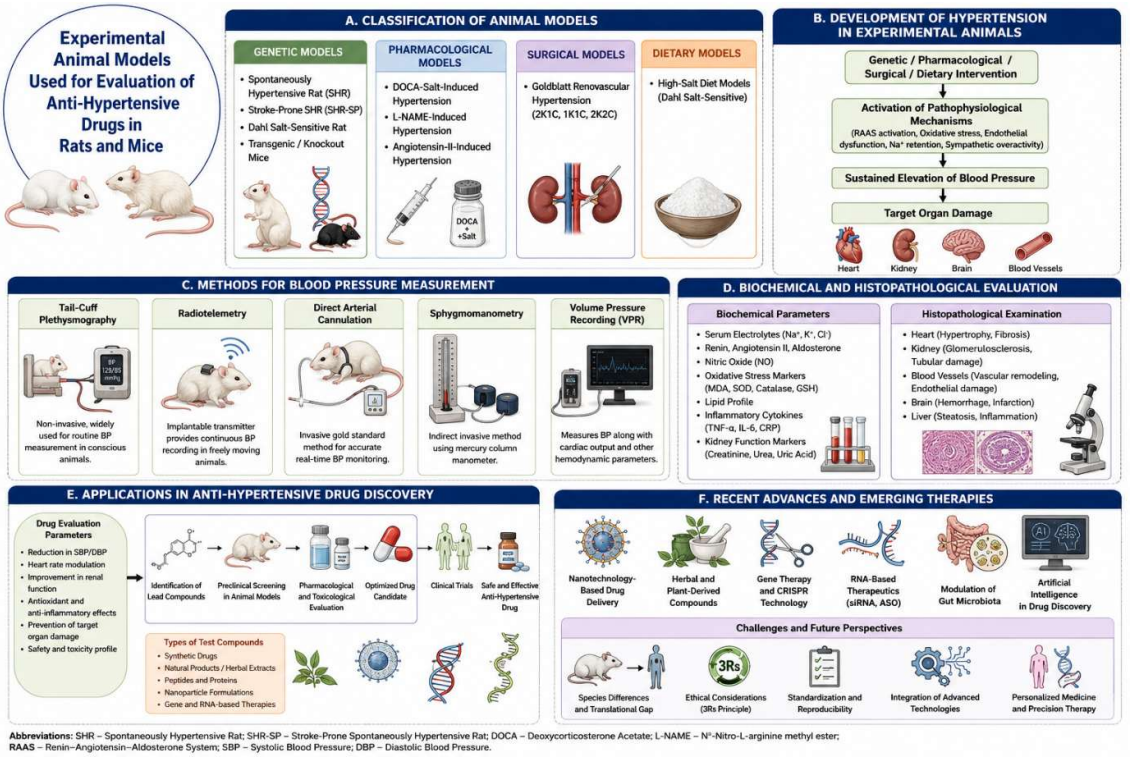
Chronic stress is recognized as an important contributor to hypertension in humans. Stress-induced animal models are developed through repeated exposure to physical or psychological stressors such as cold exposure, restraint stress, social isolation, noise stress, or overcrowding. These stressors activate the sympathetic nervous system and hypothalamic–pituitary–adrenal axis, leading to increased catecholamine release, vasoconstriction, and sustained elevation of blood pressure. Such models are useful for investigating neurogenic hypertension and evaluating drugs that modulate sympathetic activity.

2.6 Transgenic and Genetically Engineered Mouse Models

Recent advances in molecular biology and genetic engineering have facilitated the development of transgenic and knockout mouse models for hypertension research. These models enable researchers to selectively manipulate genes involved in blood pressure regulation and cardiovascular function. Gene-editing technologies such as CRISPR-Cas9 have further enhanced the precision of these models. Transgenic mice overexpressing renin, angiotensinogen, or angiotensin-converting enzyme exhibit elevated blood pressure and are valuable tools for studying the genetic basis of hypertension. These models provide detailed mechanistic insights and contribute significantly to the identification of novel therapeutic targets.

2.7 Selection of Appropriate Animal Models

The choice of an experimental hypertension model depends on the objectives of the study and the pharmacological profile of the investigational drug. Genetic models are generally preferred for studying essential hypertension, whereas pharmacological and surgical models are useful for investigating specific pathophysiological mechanisms. Dietary and stress-induced models help researchers understand environmental influences on blood pressure regulation. Selection of an appropriate model improves the reliability, reproducibility, and translational relevance of preclinical findings. Since no single model fully replicates human hypertension, researchers often employ multiple models to comprehensively evaluate the efficacy and safety of anti-hypertensive agents.



5. Major Experimental Animal Models Used for Evaluation of Anti-Hypertensive Drugs

Experimental animal models are essential tools in hypertension research because they provide valuable information regarding disease pathogenesis, target organ damage, and therapeutic responses to anti-hypertensive agents. Since hypertension is a heterogeneous disorder influenced by genetic, environmental, hormonal, neural, and renal factors, a variety of animal models have been developed to mimic different forms of human hypertension. These models enable researchers to evaluate the efficacy, safety, pharmacokinetics, and mechanisms of action of investigational anti-hypertensive drugs before clinical trials. Among laboratory animals, rats and mice are most commonly employed due to their physiological similarities to humans, short reproductive cycles, ease of handling, and availability of genetically modified strains.

5.1 Spontaneously Hypertensive Rat (SHR) Model

The Spontaneously Hypertensive Rat (SHR) is one of the most widely accepted and extensively used animal models for studying essential hypertension. This model was developed through selective breeding of Wistar rats exhibiting elevated blood pressure and is considered the gold standard for hypertension research. Unlike chemically induced models, hypertension develops naturally in SHR without the need for surgical or pharmacological intervention. Blood pressure begins to increase at approximately six to eight weeks of age and reaches hypertensive levels by adulthood.

The pathogenesis of hypertension in SHR involves enhanced sympathetic nervous system activity, endothelial dysfunction, oxidative stress, altered renal sodium handling, and activation of the renin–angiotensin–aldosterone system. These animals exhibit cardiovascular abnormalities similar to those observed in human essential hypertension, including left ventricular hypertrophy, vascular remodeling, and renal impairment. Due to its close resemblance to human hypertension, SHR is extensively used for evaluating ACE inhibitors, angiotensin receptor blockers, beta-blockers, calcium channel blockers, and novel therapeutic agents. Although the model offers excellent translational relevance, maintenance costs are relatively high and the development of hypertension requires several weeks.

5.2 Stroke-Prone Spontaneously Hypertensive Rat (SHR-SP)

The Stroke-Prone Spontaneously Hypertensive Rat (SHR-SP) is a specialized strain derived from SHR through selective breeding. This model exhibits severe hypertension and a high susceptibility to cerebrovascular accidents, making it particularly useful for studying the relationship between hypertension and stroke. Blood pressure in SHR-SP animals rises more rapidly and reaches higher levels than in conventional SHR.

The pathological features of SHR-SP include severe vascular damage, cerebral hemorrhage, ischemic stroke, renal dysfunction, and cardiac hypertrophy. High salt intake further accelerates disease progression and increases the incidence of stroke. Researchers frequently utilize this model to investigate neuroprotective and anti-hypertensive therapies capable of preventing cardiovascular and cerebrovascular complications. The SHR-SP model provides valuable insights into target organ damage associated with uncontrolled hypertension and is especially relevant for evaluating drugs aimed at reducing stroke risk.

5.3 DOCA-Salt-Induced Hypertension Model

The Deoxycorticosterone Acetate (DOCA)-salt model is one of the most commonly employed pharmacological models of hypertension. In this model, animals receive repeated administration of DOCA, a synthetic mineralocorticoid, in combination with high sodium chloride intake. The treatment promotes sodium and water retention, resulting in increased blood volume and elevated arterial pressure. In many experimental protocols, unilateral nephrectomy is performed to enhance the hypertensive response.

The development of hypertension in this model is associated with volume overload, oxidative stress, inflammation, endothelial dysfunction, and vascular remodeling. Blood pressure generally increases within two to four weeks following treatment. The DOCA-salt model is particularly useful for studying mineralocorticoid-dependent hypertension and evaluating drugs that influence sodium balance, vascular function, and oxidative stress pathways. However, because the mechanism differs from primary hypertension in humans, the model primarily represents secondary hypertension rather than essential hypertension.

5.4 L-NAME-Induced Hypertension Model

The L-NAME-induced hypertension model is based on chronic administration of Nω-Nitro-L-arginine methyl ester (L-NAME), a non-selective inhibitor of nitric oxide synthase. Nitric oxide is a potent vasodilator that plays a critical role in maintaining vascular homeostasis. Inhibition of nitric oxide production results in vasoconstriction, endothelial dysfunction, oxidative stress, and sustained elevation of blood pressure.

Hypertension develops rapidly in animals receiving L-NAME and is accompanied by structural and functional changes in the cardiovascular system. This model is particularly useful for investigating the role of endothelial dysfunction in hypertension and assessing drugs that enhance nitric oxide bioavailability or reduce oxidative stress. Researchers frequently employ the L-NAME model for evaluating antioxidant compounds, herbal medicines, endothelial protective agents, and novel anti-hypertensive therapies. The simplicity and reproducibility of this model make it highly attractive for pharmacological studies.

5.5 Angiotensin-II-Induced Hypertension Model

The Angiotensin-II-induced hypertension model is widely used to investigate the role of the renin–angiotensin–aldosterone system in blood pressure regulation. Hypertension is induced by continuous administration of angiotensin II through osmotic mini-pumps or repeated injections. Elevated angiotensin II levels cause vasoconstriction, sodium retention, oxidative stress, inflammation, and vascular remodeling.

This model closely mimics RAAS-mediated hypertension observed in humans and is particularly valuable for evaluating ACE inhibitors, angiotensin receptor blockers, renin inhibitors, and other drugs targeting the renin–

angiotensin system. Chronic exposure to angiotensin II also produces cardiac hypertrophy, endothelial dysfunction, and renal injury, allowing researchers to assess organ-protective effects of investigational therapies. Due to its well-defined mechanism, the Angiotensin-II model remains an important tool in cardiovascular pharmacology.

5.6 Dahl Salt-Sensitive Rat Model

The Dahl Salt-Sensitive Rat is a genetically predisposed model that develops hypertension in response to a high-salt diet. These animals exhibit an exaggerated blood pressure response to sodium intake due to abnormalities in renal sodium handling and vascular regulation. Hypertension develops progressively and is often accompanied by cardiac hypertrophy, renal injury, and vascular dysfunction.

The model closely resembles salt-sensitive hypertension observed in humans and is therefore highly relevant for studying the impact of dietary sodium on cardiovascular health. Researchers use this model to evaluate anti-hypertensive drugs that influence renal function, sodium excretion, and vascular reactivity. Furthermore, the Dahl model is useful for investigating interactions between genetics, diet, and hypertension. One limitation is that disease severity may vary depending on dietary conditions and experimental protocols.

5.7 Goldblatt Renovascular Hypertension Model

The Goldblatt renovascular model is one of the oldest and most widely recognized surgical models of hypertension. It is produced by partial constriction of one or both renal arteries, resulting in reduced renal perfusion and activation of the renin–angiotensin–aldosterone system. Several variations exist, including the two-kidney one-clip (2K1C), one-kidney one-clip (1K1C), and two-kidney two-clip (2K2C) models.

Reduced blood flow to the kidney stimulates renin release, leading to increased production of angiotensin II and aldosterone. These hormonal changes promote vasoconstriction, sodium retention, and elevated blood pressure. The Goldblatt model closely resembles renovascular hypertension in humans and is frequently used for studying renal mechanisms involved in blood pressure regulation. It is particularly valuable for evaluating ACE inhibitors, angiotensin receptor blockers, and renin inhibitors. Although highly informative, the model requires surgical expertise and careful postoperative management.

5.8 Transgenic and Knockout Mouse Models

Advances in molecular biology and genetic engineering have led to the development of transgenic and knockout mouse models that provide detailed insights into the genetic basis of hypertension. These models are created by overexpressing, deleting, or modifying genes involved in blood pressure regulation. Examples include mice overexpressing renin, angiotensinogen, or angiotensin-converting enzyme genes, which develop hypertension due to excessive activation of the renin–angiotensin system.

Knockout models lacking genes associated with nitric oxide synthesis, vascular function, or renal regulation have also contributed significantly to understanding hypertension pathogenesis. Modern gene-editing technologies such as CRISPR-Cas9 have further expanded the possibilities for creating highly specific disease models. These genetically engineered animals allow researchers to investigate molecular pathways, identify novel therapeutic targets, and evaluate precision medicine approaches for hypertension management. Despite their high scientific value, transgenic models are often expensive and require specialized facilities and expertise.

Table 1. Major Experimental Animal Models Used for Evaluation of Anti-Hypertensive Drugs

Model	Type of Model	Method of Induction	Major Pathophysiological Features	Applications in Drug Screening	Advantages	Limitations
Spontaneously Hypertensive Rat (SHR)	Genetic Model	Selective breeding of Wistar rats with elevated blood pressure	Enhanced sympathetic activity, endothelial dysfunction, oxidative stress, RAAS activation, left ventricular hypertrophy, vascular remodeling	Evaluation of ACE inhibitors, ARBs, beta-blockers, calcium channel blockers, and novel antihypertensive agents	Closely mimics human essential hypertension; highly reproducible	Expensive maintenance; hypertension develops gradually
Stroke-Prone Spontaneously Hypertensive Rat (SHR-SP)	Genetic Model	Selective breeding from SHR strain	Severe hypertension, cerebral hemorrhage, ischemic stroke, renal dysfunction, cardiac hypertrophy	Evaluation of neuroprotective agents, antihypertensive drugs, and stroke-prevention therapies	Useful for studying hypertension-related stroke and target organ damage	High mortality rate; disease progression influenced by dietary salt
DOCA-Salt-Induced Hypertension	Pharmacological Model	Administration of DOCA with high-salt intake, often combined with unilateral nephrectomy	Sodium retention, volume overload, oxidative stress, endothelial dysfunction, vascular remodeling	Screening of drugs affecting sodium balance, vascular function, and oxidative stress	Rapid induction; highly reproducible	Represents secondary rather than essential hypertension
L-NAME-Induced Hypertension	Pharmacological Model	Chronic administration of nitric oxide synthase inhibitor (L-NAME)	Nitric oxide deficiency, vasoconstriction, endothelial dysfunction, oxidative stress	Evaluation of antioxidants, endothelial protective agents, herbal medicines, and novel antihypertensive compounds	Simple, economical, and reproducible	Reflects mainly endothelial dysfunction-mediated hypertension
Angiotensin-II-Induced Hypertension	Pharmacological Model	Continuous Angiotensin-II infusion via osmotic pumps or repeated injections	RAAS activation, vasoconstriction, sodium retention, inflammation, oxidative stress, vascular remodeling	Screening of ACE inhibitors, ARBs, renin inhibitors, and RAAS-targeting therapies	Well-defined mechanism; clinically relevant	Requires specialized infusion systems and continuous monitoring

Model	Type of Model	Method of Induction	Major Pathophysiological Features	Applications in Drug Screening	Advantages	Limitations
Dahl Salt-Sensitive Rat	Genetic/Dietary Model	High-salt diet in genetically susceptible rats	Salt-sensitive hypertension, renal dysfunction, vascular injury, cardiac hypertrophy	Evaluation of drugs affecting sodium handling, renal function, and vascular reactivity	Closely resembles human salt-sensitive hypertension	Disease severity depends on dietary conditions and experimental protocols
Goldblatt Renovascular Hypertension (2K1C, 1K1C, 2K2C)	Surgical Model	Partial constriction of one or both renal arteries	Reduced renal perfusion, increased renin release, RAAS activation, vasoconstriction, sodium retention	Evaluation of ACE inhibitors, ARBs, renin inhibitors, and renal protective agents	Excellent model for renovascular hypertension research	Technically demanding surgical procedure; postoperative complications possible
Transgenic and Knockout Mouse Models	Genetic Engineering Model	Gene overexpression, deletion, mutation, or CRISPR-Cas9 editing	Altered expression of genes regulating RAAS, nitric oxide signaling, vascular function, and renal mechanisms	Identification of therapeutic targets, precision medicine research, gene therapy evaluation	High mechanistic relevance; useful for molecular studies	Expensive; requires specialized facilities and expertise

6. Methods for Blood Pressure Measurement in Experimental Animals

Accurate measurement of blood pressure is a critical component of hypertension research and is essential for evaluating the efficacy of anti-hypertensive drugs in experimental animal models. Reliable blood pressure assessment allows researchers to monitor disease progression, determine pharmacological responses, and assess the cardiovascular effects of investigational compounds. Several techniques have been developed for measuring blood pressure in rats and mice, each possessing specific advantages and limitations. The selection of an appropriate method depends on the objectives of the study, available resources, and the level of accuracy required. The tail-cuff plethysmography method is one of the most commonly employed non-invasive techniques for blood pressure measurement in rodents. In this method, a cuff is placed around the tail of a restrained animal, and blood flow is detected using a pressure sensor or volume-pressure recording system. As the cuff pressure is gradually released, the return of blood flow is recorded and used to calculate systolic blood pressure. The tail-cuff method is widely used because it is simple, inexpensive, and does not require surgical intervention. However, factors such as animal movement, stress, temperature fluctuations, and operator variability can influence the accuracy of measurements. Therefore, animals are usually acclimatized to the procedure before data collection to minimize stress-related variations.

Direct arterial blood pressure measurement is considered the gold standard technique due to its high accuracy and reliability. This method involves surgical cannulation of a major artery, such as the carotid or femoral artery, which is connected to a pressure transducer and recording system. Direct measurement provides real-time monitoring of systolic, diastolic, and mean arterial pressure and is particularly useful in pharmacological studies requiring precise hemodynamic evaluation. Despite its accuracy, the invasive nature of the procedure may induce physiological stress

and requires specialized surgical expertise.Radiotelemetry has emerged as the most advanced method for continuous blood pressure monitoring in experimental animals. In this technique, a miniature transmitter is surgically implanted into the animal, allowing wireless transmission of blood pressure data while the animal remains conscious and freely moving. Telemetry minimizes stress-related artifacts and provides long-term, continuous recordings of cardiovascular parameters. The method is particularly valuable for chronic studies involving circadian blood pressure variation and long-term drug administration. However, the high cost of equipment and surgical requirements limit its widespread use.

Additional cardiovascular parameters frequently measured during anti-hypertensive studies include heart rate, pulse pressure, vascular resistance, and electrocardiographic changes. Combining blood pressure assessment with biochemical and histopathological investigations provides a comprehensive evaluation of anti-hypertensive activity and cardiovascular protection.

7. Biochemical and Histopathological Evaluation

Biochemical and histopathological assessments are essential components of preclinical hypertension research because they provide detailed information regarding the mechanisms of disease progression and the therapeutic effects of anti-hypertensive agents. While blood pressure reduction remains the primary endpoint in hypertension studies, biochemical and tissue-level analyses help determine whether a treatment can prevent organ damage and improve overall cardiovascular health. Biochemical evaluation typically involves the measurement of serum and tissue biomarkers associated with hypertension, oxidative stress, inflammation, endothelial dysfunction, and organ injury. Oxidative stress markers such as malondialdehyde (MDA), thiobarbituric acid reactive substances (TBARS), and reactive oxygen species are commonly quantified because excessive oxidative stress contributes significantly to hypertension-induced vascular damage. Antioxidant enzymes including superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), and reduced glutathione (GSH) are also assessed to determine the antioxidant capacity of experimental treatments. Inflammatory biomarkers play an important role in hypertension pathogenesis and are frequently measured during preclinical studies. Commonly evaluated markers include tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), interleukin-1β (IL-1β), and C-reactive protein (CRP). Elevated levels of these cytokines indicate vascular inflammation and endothelial injury. Additionally, biochemical analysis often includes measurement of nitric oxide levels, endothelin-1 concentration, angiotensin II levels, aldosterone, plasma renin activity, and endothelial nitric oxide synthase expression to investigate mechanisms related to vascular function and blood pressure regulation.

Evaluation of organ function biomarkers is equally important. Serum creatinine, blood urea nitrogen, and urinary protein excretion are commonly used indicators of renal function, whereas cardiac biomarkers such as creatine kinase-MB, lactate dehydrogenase, and cardiac troponins provide information regarding myocardial injury. Liver enzymes, lipid profiles, glucose levels, and electrolyte concentrations are also assessed to determine the systemic effects and safety profile of investigational drugs. Histopathological examination provides microscopic evidence of tissue damage and therapeutic protection. Following sacrifice, organs such as the heart, kidneys, aorta, liver, and brain are collected, fixed in formalin, processed, and stained using hematoxylin and eosin or specialized staining techniques. Microscopic analysis enables assessment of structural alterations associated with hypertension, including vascular wall thickening, endothelial injury, inflammatory cell infiltration, fibrosis, glomerular damage, and myocardial hypertrophy.

Cardiac histopathology often reveals left ventricular hypertrophy, myocardial fibrosis, and cellular degeneration in hypertensive animals. Renal tissues may exhibit glomerulosclerosis, tubular degeneration, interstitial fibrosis, and vascular damage. Examination of blood vessels frequently demonstrates smooth muscle proliferation, increased wall thickness, reduced lumen diameter, and endothelial disruption. The extent of these pathological changes is compared between treated and untreated groups to evaluate the protective effects of anti-hypertensive therapies. The integration of biochemical and histopathological analyses with blood pressure measurements enhances the reliability of preclinical findings and provides a comprehensive understanding of drug efficacy and safety. These assessments are particularly valuable for identifying organ-protective effects that may not be evident from blood pressure reduction alone.

8. Applications of Animal Models in Anti-Hypertensive Drug Discovery

Experimental animal models have contributed significantly to the discovery, development, and validation of anti-hypertensive drugs currently used in clinical practice. These models provide a controlled environment for investigating disease mechanisms, evaluating therapeutic efficacy, assessing safety profiles, and identifying novel pharmacological targets. The availability of diverse animal models enables researchers to study different forms of hypertension and select appropriate systems based on the mechanism of action of the investigational compound. One of the primary applications of animal models is the screening of new anti-hypertensive agents. Before clinical testing, potential drug candidates are evaluated in hypertensive rodents to determine their ability to reduce systolic and diastolic blood pressure, improve vascular function, and prevent target organ damage. Animal studies provide essential information regarding dose-response relationships, duration of action, therapeutic index, and potential adverse effects.

Animal models have played a pivotal role in the development of several major classes of anti-hypertensive medications. Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, beta-adrenergic blockers, direct vasodilators, and diuretics were extensively evaluated in experimental models before entering clinical practice. These studies established the efficacy, mechanism of action, and safety of these therapeutic agents.In addition to conventional pharmaceuticals, animal models are widely used for investigating natural products and herbal medicines with potential anti-hypertensive activity. Numerous medicinal plants and phytochemicals have demonstrated blood pressure-lowering effects in rodent models through antioxidant, anti-inflammatory, vasodilatory, and renin–angiotensin system-modulating mechanisms. Such studies contribute to the identification of novel bioactive compounds for future drug development. Recent advances in nanotechnology have introduced innovative drug delivery systems for hypertension management. Nanoparticles, liposomes, nanoemulsions, and polymeric carriers are being investigated to improve drug solubility, bioavailability, and targeted delivery. Experimental hypertension models provide a valuable platform for assessing the efficacy and safety of these advanced formulations before clinical translation.

Furthermore, animal models are increasingly used in gene therapy and precision medicine research. Genetically engineered rodents enable researchers to investigate specific molecular pathways involved in blood pressure regulation and identify novel therapeutic targets. Gene-editing technologies, including CRISPR-Cas9, have facilitated the development of customized hypertension models that closely mimic human disease conditions. These approaches offer promising opportunities for personalized anti-hypertensive therapy in the future.

Animal models also contribute significantly to the evaluation of combination therapies, long-term safety studies, and organ-protective interventions. By enabling detailed investigation of cardiovascular, renal, and vascular outcomes, these models continue to serve as indispensable tools in anti-hypertensive drug discovery and development. Their contribution remains essential for bridging the gap between basic scientific research and successful clinical application, ultimately leading to the development of safer and more effective therapeutic strategies for hypertension management.

9. Recent Advances and Emerging Therapies in Hypertension Research

The field of hypertension research has witnessed remarkable advancements over the past decade, driven by a better understanding of the molecular mechanisms underlying blood pressure regulation and the development of innovative therapeutic strategies. Although conventional anti-hypertensive drugs such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, beta-blockers, and diuretics remain the cornerstone of hypertension management, a substantial proportion of patients continue to experience uncontrolled blood pressure or treatment-related adverse effects. Consequently, researchers are exploring novel therapeutic approaches aimed at improving efficacy, reducing toxicity, and providing long-term cardiovascular protection. One of the most promising developments in hypertension therapy is the application of nanotechnology-based drug delivery systems. Nanocarriers such as nanoparticles, liposomes, nanoemulsions, solid lipid nanoparticles, and polymeric micelles have demonstrated the ability to enhance drug solubility, stability, bioavailability, and targeted delivery. These advanced systems enable controlled drug release and reduce systemic side effects, thereby improving therapeutic outcomes. Experimental studies in hypertensive animal models have shown that nanoformulations of anti-

hypertensive agents can achieve superior blood pressure control compared to conventional formulations. Herbal medicines and plant-derived bioactive compounds have also gained considerable attention as potential anti-hypertensive therapies.

Numerous medicinal plants possess antioxidant, anti-inflammatory, vasodilatory, and cardioprotective properties that may contribute to blood pressure reduction. Phytochemicals such as flavonoids, polyphenols, alkaloids, terpenoids, and phenolic acids have demonstrated beneficial effects in experimental models of hypertension. Natural compounds derived from plants including garlic, green tea, hibiscus, olive leaves, and various traditional medicinal herbs have shown promising anti-hypertensive activity through modulation of vascular function and oxidative stress pathways.Gene-targeted therapies represent another emerging area in hypertension research. Advances in molecular biology have identified several genes involved in blood pressure regulation, vascular remodeling, sodium transport, and neurohormonal signaling. Modern gene-editing technologies such as CRISPR-Cas9 have enabled researchers to selectively modify these genes and investigate their contribution to hypertension. Although still largely experimental, gene-based therapies may provide personalized treatment options for patients with genetically mediated forms of hypertension in the future.RNA-based therapeutics, including small interfering RNA (siRNA) and antisense oligonucleotides, have emerged as innovative approaches for targeting specific molecular pathways associated with hypertension. These technologies can selectively inhibit the expression of genes involved in renin-angiotensin system activation, inflammation, oxidative stress, and vascular dysfunction. Preliminary studies have demonstrated encouraging results, highlighting their potential as future anti-hypertensive interventions.Recent research has also focused on the role of gut microbiota in cardiovascular health. Alterations in intestinal microbial composition have been linked to hypertension through mechanisms involving inflammation, metabolic regulation, and vascular function. Modulation of gut microbiota using probiotics, prebiotics, dietary interventions, and microbial metabolites is being explored as a novel therapeutic strategy for blood pressure control. Experimental studies suggest that restoration of microbial balance may contribute to improved cardiovascular outcomes.

Artificial intelligence and machine learning technologies are increasingly being integrated into hypertension research and drug development. These computational approaches facilitate large-scale data analysis, biomarker identification, drug-target prediction, and personalized treatment planning. AI-assisted drug discovery has the potential to accelerate the identification of novel anti-hypertensive compounds while reducing the cost and duration of pharmaceutical development.Collectively, these advancements demonstrate that hypertension management is rapidly evolving beyond traditional pharmacotherapy. Continued integration of biotechnology, nanomedicine, precision medicine, and computational sciences is expected to contribute significantly to the development of safer, more effective, and individualized therapeutic approaches.

10. Challenges, Limitations, and Future Perspectives

Despite their substantial contribution to cardiovascular research, experimental animal models possess several limitations that must be carefully considered when interpreting preclinical findings. Although rats and mice provide valuable insights into the pathophysiology of hypertension and facilitate anti-hypertensive drug discovery, no single animal model can completely replicate the complexity of human hypertension. Differences in genetics, physiology, metabolism, environmental exposure, and disease progression often limit the direct translation of experimental results to clinical settings.One of the major challenges in hypertension research is the heterogeneity of the disease itself. Human hypertension arises from a combination of genetic, environmental, behavioral, metabolic, and socioeconomic factors. In contrast, most experimental models reproduce only specific aspects of the disease, such as salt sensitivity, endothelial dysfunction, renin–angiotensin system activation, or sympathetic overactivity. Consequently, therapeutic responses observed in animal studies may not fully predict clinical outcomes in human patients.Species-specific differences represent another important limitation. Variations in cardiovascular physiology, drug metabolism, receptor distribution, immune responses, and renal function may influence the pharmacological effects of investigational compounds. Certain drugs that demonstrate promising anti-hypertensive activity in rodents may fail during clinical trials due to differences in human biology. This discrepancy contributes significantly to the high attrition rate observed in cardiovascular drug development.

Ethical concerns regarding animal experimentation continue to influence biomedical research. Regulatory authorities and scientific organizations emphasize adherence to the principles of Replacement, Reduction, and Refinement (3Rs) to minimize animal use and suffering. Researchers are increasingly encouraged to adopt alternative methods whenever possible, including in vitro models, organ-on-a-chip technologies, computational simulations, and advanced cell culture systems.Technical challenges also affect the reliability and reproducibility of animal studies. Variations in experimental protocols, housing conditions, diet, age, sex, genetic background, and blood pressure measurement techniques can contribute to inconsistent results across laboratories. Standardization of experimental procedures and reporting guidelines is therefore essential for improving data quality and reproducibility.Another limitation involves the relatively short lifespan of rodents compared to humans. Chronic hypertension in patients often develops over several decades and is associated with multiple comorbidities such as diabetes, obesity, dyslipidemia, and chronic kidney disease. Most experimental studies are conducted over weeks or months and may not fully capture the long-term progression of the disease and its complications.

Future hypertension research is expected to benefit from advances in genetic engineering, systems biology, and precision medicine. The development of humanized animal models, transgenic rodents, and CRISPR-based gene-editing technologies will improve the ability to study disease-specific mechanisms. Integration of genomics, proteomics, metabolomics, and transcriptomics will facilitate identification of novel biomarkers and therapeutic targets.Emerging technologies such as organoids, tissue engineering, organ-on-a-chip platforms, and artificial intelligence-driven drug discovery may complement traditional animal studies and enhance translational accuracy. Personalized medicine approaches based on genetic profiling and molecular characterization are also likely to transform hypertension management in the coming years. By combining innovative technologies with carefully designed experimental models, researchers can improve the efficiency of drug development and increase the likelihood of successful clinical translation.

11. Conclusion

Hypertension remains one of the most prevalent and challenging cardiovascular disorders worldwide, contributing significantly to morbidity, mortality, and healthcare expenditure. The complex and multifactorial nature of hypertension necessitates extensive preclinical investigation to understand its underlying mechanisms and develop effective therapeutic interventions. Experimental animal models have played a fundamental role in advancing hypertension research by providing controlled and reproducible systems for studying disease pathogenesis, target organ damage, and pharmacological responses. Among the various models available, spontaneously hypertensive rats, stroke-prone hypertensive rats, DOCA-salt-induced hypertension, L-NAME-induced hypertension, angiotensin II-induced hypertension, Dahl salt-sensitive rats, renovascular hypertension models, and transgenic mouse models each offer unique advantages for investigating specific aspects of blood pressure regulation. These models have contributed substantially to the development of currently available anti-hypertensive drugs and continue to serve as essential tools for evaluating novel therapeutic candidates. Comprehensive assessment of anti-hypertensive activity involves not only blood pressure measurement but also biochemical, molecular, and histopathological evaluations that provide insights into cardiovascular protection and organ preservation. Advances in nanotechnology, gene therapy, RNA-based therapeutics, microbiome research, and precision medicine have expanded the scope of hypertension research and created new opportunities for innovative treatment strategies. Despite certain limitations related to species differences, ethical considerations, and translational challenges, animal models remain indispensable for cardiovascular drug discovery. Future research efforts should focus on improving model relevance, enhancing reproducibility, integrating advanced technologies, and developing alternative experimental systems that complement traditional animal studies. Such approaches will strengthen the translational value of preclinical findings and accelerate the development of safer, more effective, and personalized anti-hypertensive therapies.

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