HISTOPATHOLOGICAL EVALUATION OF AMLODIPINE AND TELMISARTAN ON HEPATIC TISSUE OF ALBINO RATS: A COMPARATIVE STUDY

BY

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SEPTEMBER, 2025.

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A PROJECT WORK SUBMITTED TO THE DEPARTMENT OF MEDICAL LABORATORY SCIENCE, SCHOOL OF MEDICAL SCIENCES, COLLEGE OF MEDICAL SCIENCES, UNIVERSITY OF BENIN, IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE AWARD OF BACHELOR OF SCIENCE DEGREE IN MEDICAL LABORATORY SCIENCE (B.MLS).

SUPERVISOR: DR. N.T. OMORODION

SEPTEMBER, 2025.

DECLARATION

I hereby declare that the research project titled "HISTOPATHOLOGICAL EVALUATION OF AMLODIPINE AND TELMISARTAN ON HEPATIC TISSUE OF ALBINO RATS: A COMPARATIVE STUDY" was carried out by me, IYEKEKPOLOR SILVIA. This work is the result of my personal effort, except where due acknowledgment has been made to other sources of information.

Mat No: _____

Submitted to the Department of Medical Laboratory Science, School of Basic Medical Sciences

Signature: _____

Date: _____

CERTIFICATION

This is to certify that **IYEKEKPOLOR SILVIA,** with matriculation number **BMS2001171,** a student of the Department of Medical Laboratory Science, Faculty of Basic Medical Sciences, University of Benin, Benin City carried out this project work under my supervision in partial fulfillment of the requirements for the award of Bachelor of Medical Laboratory Science (B.MLS) Degree.

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DR. N.T. OMORODION **DATE**

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(Head of Department)

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PROF. VICTOR .O. EKUNDINA **DATE**

(External supervisor)

DEDICATION

I dedicate this work to God, who has blessed me with the strength and perseverance to complete this work. I am also eternally grateful to my family and friends, whose love and encouragement have been a constant source of inspiration.

ACKNOWLEDGMENT

I am deeply grateful for the unwavering support I have received throughout the completion of this project.

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ABSTRACT

The prevalence of chronic elevation of blood pressure, and the resulting morbidity, are sufficiently high to justify viewing the condition as a serious global public health problem. Sometimes lifestyle changes are not enough to treat high blood pressure, in such cases medication is required. This study performed an Evaluation on Some High Blood Pressure Medications(Amlodipine and Telmisartan) on the hepatic tissues of albino rats. A total of 18 albino rats weighing 165g-195g with high blood pressure were distributed into 3 groups (A,B and C). Group A (Labelled as control group) were administered water and food only, Group B amlodipine was given in a dose of 10 mg/kg/day for 4 weeks (28 days), Group C Telmisartan was given in a dose of 10 mg/kg/day for(4 weeks). After 4 weeks, Animals were weighed, anesthetize and dissected and the liver harvested placed in 10% Neutral buffered formalin. A stain in hematoxylin for 3-5 minutes was done. Samples of selected sections of the liver was photographed and presented as plates. A significant increase in body weight was recorded in all groups of Amlodipine and Telmisartan treated animals. Microscopic examination of hepatic tissues from the albino rats demonstrated no obvious pathologic changes, including hypertrophy, and perivascular fibrosis, wall thickening hepatic atrophy and fibrosis, and vascular sclerosis in groups treated with Amlodipine. Histopathological examination showed no pathological glomerular, tubular, or blood vessel changes in groups treated with telmisartan during the weeks of the research. Thrust of public health policies should be primary prevention of hypertension. The long-term treatment with this combination could presents a beneficial effect on the reduction of BP, BPV, and the protection of end- in-depth study on the effect of these antihypertensive drug treatments on the antioxidant mechanisms involved as liver damage is highly recommended.

CHAPTER ONE

INTRODUCTION

1.1 Background of the study

Since the heart's pumping action is known to affect blood flow, the heart's pressure does not always remain constant (Amoah, 2023; Mendez et al., 2023; Ogun et al., 2020). It changes according on what is going on at a given moment. Long-term aberrant pressure in the major arteries leads to hypertension (Wang et al., 2018). According to Popkinet al. (2020), the incidence of chronic hypertension and the morbidity that follows are significant enough to warrant considering the illness a major worldwide public health issue. Three million individuals die each year from hypertension, which affects around 600 million people globally (Zhao et al., 2022). The most prevalent cardiovascular disease that affects people is high blood pressure, or hypertension, and for the majority of people, the lifetime chance of getting the disease is more than 50% (Rainforthet al., 2017). According to Madala (2019), hypertension is the highest quintile of a population's blood pressure distribution. Accordingly, the percentage of hypertensive individuals in a population is arbitrary as there is no clear boundary or standard that distinguishes those with high blood pressure (hypertensive) from those without the condition (normotensive) (Kelley and Abraham, 2023). The World Health Organization's definition of hypertension is the most often used criteria, which is systolic pressure more than 160 mm Hg and diastolic pressure greater than 95 mm Hg (Lionakiset al., 2020). The likelihood of end-organ damage is significantly increased by pressure levels higher than this. Hypertension is a major public health concern because of the impairment and death brought on by the damage it causes to the kidneys, brain, heart, and probably liver (Ford, 2023; Hussain et al., 2019).

To manage and control high blood pressure, healthy lifestyle choices are advised (Gardiner et al., 2019). If blood pressure is high or slightly over optimum, a healthy lifestyle may help decrease the need for medication. Medication is sometimes necessary to manage high blood pressure when lifestyle modifications are insufficient (Hart et al., 2020). The patient's general health and the level of high blood pressure in their system determine the kind of medication used to treat it. In many cases, two or more blood pressure medications are more effective than one. Finding the right medication or combination of medications may take some time (DiClemente et al., 2022). These medications use a variety of mechanisms to control blood pressure. These medications

eliminate excess salt and water from the body. As a result, less fluid is passing through the arteries and veins. As a result, the blood vessel walls experience less pressure. Others prevent the production of a naturally occurring substance that constricts blood vessels and aid in blood vessel relaxation (Engelfrietet al., 2018). Calcium channel blockers are medications that help prevent calcium from getting into the heart's and arteries' cells. The arteries might relax and open as a result. Renin inhibitors contribute to the cascade of events that raise blood pressure. Renin inhibitors reduce the production of this chemical. Alpha blockers are another kind of blood pressure medication that stops the norepinephrine hormone from tightening the muscles in the walls of smaller veins and arteries. This maintains the veins and arteries relaxed and open (McQueen et al., 2018).

According to Leighton et al. (2016), the liver is an essential organ in the human body that supports metabolism, immunity, digestion, detoxification, and vitamin storage, among other processes. About 2% of an adult's body weight is made up of it. The liver's dual blood supply from the hepatic artery (about 25%) and portal vein (roughly 75%) makes it a special organ (O'Connelet al., 2019).

It has been shown that the majority of blood pressure medications have a variety of effects on the body's vital organs, particularly internal organs like the liver (Kaplan et al., 2017). Amlodipine, a calcium channel blocker, is one such medication. It functions by altering the flow of calcium into the heart's and blood vessels' cells (Whelton et al., 2022). In addition to increasing the heart's supply of blood and oxygen while decreasing its strain, this relaxes the blood vessels and decreases blood pressure. Amlodipine is used to treat hypertension, or high blood pressure, either by itself or in combination with other medications. The strain on the heart and arteries is increased by high blood pressure (Bulpitt, 2019). The heart and arteries may not work correctly if it persists for an extended period of time. A stroke, heart failure, or kidney failure may follow from this injury to the blood arteries in the brain, heart, and kidneys (Bibbins-Domingo et al., 2020). Heart attacks may also be made more likely by high blood pressure. Controlling blood pressure may reduce the likelihood of these issues. Amlodipine often causes nausea, stomach

discomfort, fatigue, and edema as adverse effects. Heart attacks or low blood pressure are examples of serious adverse effects (Beeverset al., 2021). It's uncertain whether using it while pregnant or nursing is safe. Doses should be lowered for older patients and those who have liver issues. Amlodipine partially relaxes and widens the arteries via a process known as vasodilation. It is a dihydropyridine-type long-acting calcium channel blocker (Ansa et al., 2020).

Telmisartan is another blood pressure drug that is marketed under many brand names, including Micardis. This drug is used to treat diabetic renal disease, high blood pressure, and heart failure (Barr, 2019). It is a sensible first line of therapy for hypertension. It is consumed orally. Angiotensin II receptor blockers (ARBs) include telmisartan (Anand, 2018). It works by preventing the body's production of a chemical that tightens blood arteries. Telmisartan thus causes the blood vessels to relax (Asaria, 2017). As a result, the heart receives more blood and oxygen, lowering blood pressure. According to Alonso et al. (2016), telmisartan is a potent antihypertensive medication with a tolerability profile comparable to a placebo. According to comparative statistics, telmisartan lowers blood pressure just as well as other main families of antihypertensive medications. Telmisartan is linked to a noticeably decreased frequency of dry, persistent cough when compared to lisinopril. Telmisartan is thus a helpful treatment choice for the treatment of hypertensive individuals. (Van der Kuil and Altorf, 2022). Back discomfort, diarrhea, and upper respiratory tract infections are typical adverse effects. Angioedema, low blood pressure, and renal issues are examples of serious side effects. Use whilst nursing is not advised and during pregnancy may be harmful to the unborn child. It functions by preventing the effects of angiotensin I and is an antagonist of the angiotensin II receptor (Britton and McKee, 2020).

1.2 Statement of the problem

Millions of individuals worldwide suffer with hypertension, a chronic illness. Because it is linked to cardiovascular disease, stroke, and early death, it is sometimes referred to as a silent killer. If blood pressure is high or slightly over optimum, a healthy lifestyle may help decrease the need for medication. Medication is sometimes necessary to manage high blood pressure

when lifestyle modifications are insufficient (Campbell et al., 2021).

Several drugs have been prescribed to treat high blood pressure, including enalapril, lisinopril, perindopril, olmesartan, amlodipine, felodipine, and nifedipine. People in Edo North Iyamho continue to take amlpdopine and other blood pressure medications like telmisartan since they are reasonably priced and have similar effects on the heart and male reproductive system. Given that the liver is the body's primary detoxifying organ, prolonged exposure to certain medications or chemotherapeutic agents may cause liver damage, which can ultimately result in a number of liver illnesses (Chaturvediet al., 2022). Because the liver plays a crucial role in metabolism and has the capacity to concentrate and biotransform xenobiotics, it is much more vulnerable to harm from such agents than any other organ.

Therefore, in this study, we aim to perform an Evaluation of Some High Blood pressure Amlodipine and Telmisartan on The Hepatic Tissues of Albino Rats.

1.3 Justification of the study

Previous research in this field has primarily focused on lipid profiles. Certain studies have shown connections between liver enzymes (alanine aminotransferase (ALT) and gamma glutamyltransferase [GGT]) and metabolic syndrome, type 2 diabetes, and cardiovascular disease. However, the specific link to hypertension requires further investigation. There is limited information available regarding on the impact of Amlodipine in comparison withtelmisartan on Liver histology. Although previous research has examined the relationship between antihypertensive agents and the liver, these studies have typically focused on only one in single type medication in assessing the impact on the liver. Therefore, in this study, I aim to perform an Evaluation of Some High Blood pressure Amlodipine and Telmisartan on The Hepatic Tissues of Albino Rats.

1.4 Significance of the study

Since hypertension affects around one in four persons worldwide, it is a serious public health issue. It is a major avoidable cause of early mortality and disability globally and is a prevalent risk factor for a number of illnesses, including cardiovascular, cerebrovascular, and renal disorders. According to research, 8.5 million fatalities worldwide are attributable to hypertension, which also accounts for 7% of disability-adjusted life years and is caused by stroke, ischemic heart disease, other cardiac illnesses, and renal disease (Burrows and Muller, 2017).

Amlodipine, a calcium channel blocker, functions by interfering with calcium's entry into heart and blood vessel cells. In addition to increasing the heart's supply of blood and oxygen while decreasing its strain, this relaxes the blood vessels and decreases blood pressure. Angiotensin II receptor blockers (ARBs), including telmisartan, function by preventing the body from producing a chemical that tightens blood vessels. Telmisartan thus causes the blood vessels to relax. As a result, the heart receives more blood and oxygen, lowering blood pressure.

Determining the effect of high blood pressure medications (amlodipine and telmisartan) on the hepatic tissues required a combination of these two drugs, which operate via distinct methods.

1.5 Aim of the study

To perform an Evaluation of Some High Blood pressure(Amlodipine and Telmisartan) on The Hepatic Tissues of Albino Rats.

1.6 Objectives of the study

1. To determine the effect of Amlodipine on weight

2. To determine the effect of Amlodipine on histology of the liver

3. To determine the effect of Telmisartan on weight

4. To determine the effect of Telmisartan on liver histology of the liver

CHAPTER TWO

LITERATURE REVIEW

2.1 The liver

One of the most important organs in the human body, the liver supports metabolism, immunity, digestion, detoxification, and vitamin storage, among other processes (Djousse et al., 2019). About 2% of an adult's body weight is made up of it. The liver's dual blood supply from the hepatic artery (about 25%) and portal vein (around 75%) makes it a special organ (Fisher, 2022).

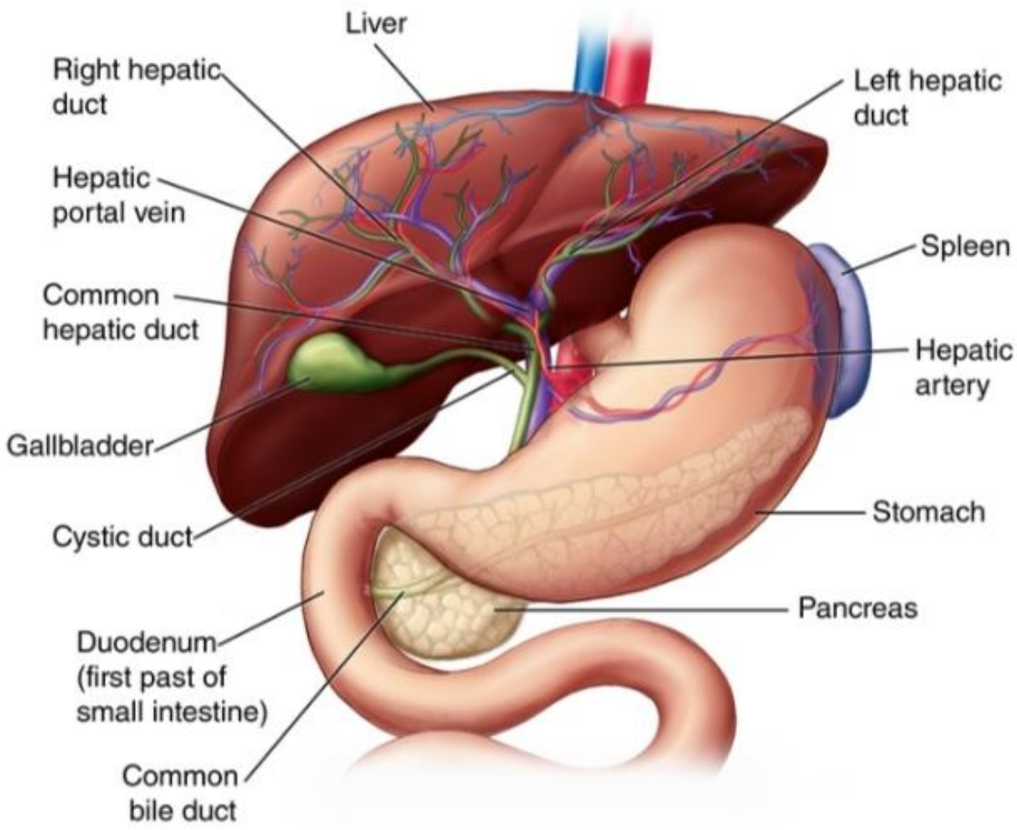

Figure 1: The anatomy of the liver (Casagrande*et al.,* 2017)

2.1.0 The anatomy of the liver

The lobule is the liver's functional unit. A portal triad (portal vein, hepatic artery, and bile duct) is located at each hexagonal corner of each lobule. Hepatocytes, which have physiologically different apical and basolateral membranes, make up the lobule's base. Hepatocytes are separated into three zones according to their perfusion and function (Byberg, 2019).

Because of their close proximity to oxygenated blood and nutrients, hepatocytes in zone I, also known as the periportal area, are the best perfused and regenerate earliest. Zone I is heavily involved in oxidative metabolisms such beta-oxidation, gluconeogenesis, bile synthesis, cholesterol creation, and amino acid catabolism because of its high perfusion (Brown, 2016).

The pericentral area of the hepatocytes is known as zone II, and it lies between zones I and III.

Because Zone III is farthest away from the portal triad, its perfusion is the lowest. According to

Freeman and Chapman (2020), it is most important for detoxification, drug biotransformation, ketogenesis, glycolysis, lipogenesis, glycogen synthesis, and glutamine production.

The apical membranes of nearby hepatocytes generate bile canaliculi, which further enhance bile flow. The canaliculi create a lattice-like network, or "chicken-wire pattern," as a result of the three-dimensional hepatocyte configurations, which aids in increasing the flow's surface area (Freeman and Chapman, 2020). It's critical to understand that blood and bile move in opposing directions. This is understandable as the liver generates bile, which is then expelled from the liver via the ducts while the dual blood supply enters the liver to perfuse it. Via the sinusoidal lumens of the lobule, blood flows into the hepatic vein branch located in the middle of the lobule (Huxley et al., 2019).

The space of Disse is the area between the sinusoidal lumen and the hepatocytes' basolateral membrane. Microvilli that extend from the hepatocytes' basolateral membrane and connect with the capillary occupy this location, enabling the hepatocyte to access its blood supply (Iqbal, 2018). A mixture of collagens, proteoglycans, and other proteins make up the extracellular matrix found in the space of Disse, which aids in providing scaffolding for the hepatocytes and, therefore, the lobule overall. Since hepatocytes lack a real basement membrane, the significance of the scaffolding that occurs in the Disse gap is further increased (Novo et al., 2019). Ito cells (stellate cells) and Kupffer cells (macrophages) are also found in the Disse space. The purpose of the Kupffer cells is to remove pathological or superfluous material from the bloodstream. Vitamin A and other fats are stored in the Ito cells. They may also function as myofibroblasts and support liver regeneration under the correct conditions.

2.1.2 Development

Part of the foregut is the liver. Around the fourth week of development, it begins as the hepatic diverticulum and is derived from endodermal cells. The falciform ligament, which emerges from the ventral mesentery, anchors it to the abdominal wall after it develops within the peritoneum. On its journey from the umbilical cord to the liver, the umbilical vein crosses the falciform ligament (Olatunbosune et al., 2020).

It is thought that a number of routes work together to generate the diverticulum, primarily the Wnt/B-catenin pathway and fibroblast growth factors (FGF), which are released by embryonic heart cells and are triggered by the MAPK pathway. After that, the diverticulum develops and engages with the septum transversum, which separates the heart from the abdominal cavity and subsequently aids in the diaphragm's creation. After then, the diverticulum develops into the liver or gallbladder's primordium. The primordium of the hepatic sinusoids is formed when the primordium liver matures into hepatic cords that anastomose around endothelium-lined gaps. The development of the hepatic sinusoids is significantly influenced by VEGF (Vasanet al., 2021).

The hepatic cords develop around the portal vein, which is the main conduit that emerges from the umbilical and vitelline veins. This explains why the portal vein, rather than the hepatic artery, serves as the liver's main blood supply. Alongside the biliary system, the hepatic artery grows and continues to do so after birth. Hematopoiesis is taken over by the liver about week six, and bile is produced by hepatocytes around week twelve (Vasanet al., 2021).

2.1.3 Involved Organ Systems

Almost all of the body's organ systems depend on the liver. By supporting digestion and metabolism, it interacts with the gastrointestinal and endocrine systems. The liver manages the homeostasis of cholesterol and stores fat-soluble vitamins. It holds copper and iron. It contributes to the creation of proteins and clotting factors in hematology (Williams et al., 2023). Heme is broken down into unconjugated bilirubin and then conjugated by the liver. It generates carrier proteins that are crucial for growth and reproduction and contributes to the metabolism of sex hormones. Lastly, Kupffer and Pit cells are crucial components of the body's immune system.

2.1.4 Hepatic physiology

Production of Bile

The release of bile salts and acids facilitates the absorption and digestion of lipids and helps eliminate material that the kidneys are unable to eliminate (Ogah and Rayner, 2023). This makes bile a vital fluid. Hepatocytes generate bile, which is mostly made up of phospholipids, bilirubin,

cholesterol, bile pigment, bile salts, bile acids, water, and electrolytes, among other materials. According to the duct and sphincter of Oddi pressures, bile is produced by hepatocytes into the bile canaliculi, where it passes from tiny ducts to the larger ducts before either ending up in the duodenum or being deposited in the gallbladder for concentration and storage. After bile is secreted into the duodenum, it travels through the enterohepatic circulation, where it does its function in the bowel. Bile components that are not eliminated are recycled by gut bacteria, who transform them into bile acids that can be absorbed in the ileum and returned to the liver (Ogah and Rayner, 2023).

Vitamins Stored in Fat and/or Metabolism

The majority of fat-soluble vitamins are absorbed via the intestines as VLDL or chylomicrons. Fat-soluble vitamins are stored and/or metabolized by the liver. Ito cells store vitamin A, as was previously mentioned. Retinoic acid may be converted into glucuronide and secreted into bile, or it can be oxidized into retinal and then retinoic acid for phototransduction. The hepatic CYP-450 system must 25-hydroxylate vitamin D3, which is then further hydroxylated in the kidney to reach its usable form, regardless of whether it originates from the skin, animal products, or plant sources. After then, carbon 24 is hydroxylated by the hepatic CYP-450 system, making vitamin D inactive (Stewart and Eales, 2022). The alpha and gamma forms of vitamin E are delivered to the liver. While the liver breaks down the gamma-tocopherol form for excretion, alpha-tocopherol is reintroduced into the bloodstream after integrating with VLDL or HDL. The liver enzyme gamma-glutamyl carboxylase needs vitamin K for gamma-carboxylation of coagulation factors II, VII, IX, X, and protein C and protein S, even though the liver does not store or metabolize it (Ogah and Rayner, 2023).

The Metabolism of Drugs

The liver's metabolism and/or detoxification of xenobiotics is another essential function. For some of these compounds, the liver employs lysosomes, although biotransformation is a key pathway for metabolism and detoxification. Phase I and Phase II processes are the primary means by which the liver changes xenobiotics from a lipophilic to a hydrophilic state (Ogah and

Rayner, 2023). Hepatocytes' smooth endoplasmic reticulum is where these reactions mostly occur. Using mostly the cytochrome P450 (CYP450) family of enzymes, phase I processes use oxidation, reduction, and hydrolysis to produce a more hydrophilic solute (Stewart and Eales, 2022). The oxygen species in the phase I product interacts more favorably with the enzymes engaged in phase II processes. The metabolites produced in phase I undergo conjugation in phase II processes, which increases their hydrophilicity for secretion into bile or blood. In phase II reactions, conjugation may occur in three major ways: to glucuronate, glutathione, or sulfate. In the smooth endoplasmic reticulum, conjugation to glucuronate occurs, as with bilirubin. Because the necessary enzymes are located in the cytosol, substances undergoing sulfate conjugation, including alcohols, often undertake this process there. A small percentage of glutathione conjugation takes place in the mitochondria, whereas the majority takes place in the cytosol (Stewart and Eales, 2022). Glutathione must be reduced for conjugation to occur, and if reduced glutathione is depleted, hazardous metabolites may accumulate, as in the case of an acetaminophen overdose. Phase III is the term used to characterize the movement of metabolites resulting from these events. The stomach and kidney are two other organs that may help in medication metabolism. Drug metabolism is affected by a number of variables, including age, gender, drug-drug interactions, diabetes, pregnancy, liver or kidney illness, inflammation, and heredity, to mention a few.

metabolization of bilirubin

The breakdown of heme is significantly influenced by the liver. The liver, spleen, and bone marrow are among the several places in the body where hemolysis occurs. Biliverdin is produced from heme and then converted to unconjugated bilirubin (Welch et al., 2016). Unconjugated bilirubin attached to albumin is transported from the bloodstream to the liver. The unconjugated bilirubin subsequently becomes hydrophilic by conjugation, a phase II step, using the uridine diphosphate glucuronyltransferase (UGT) mechanism. The newly conjugated bilirubin is subsequently filtered by the kidneys for excretion after being released into the bile via bile

canaliculi or dissolving in trace quantities in the blood (Welch et al., 2016). Since the intestinal wall cannot absorb conjugated bilirubin, the majority of it enters the bile and is expelled along with the bile in feces. According to Beilin and Puddey (2016), gut bacteria transform some bilirubin into urobilinogen or unconjugated bilirubin for reabsorption and enterohepatic circulation.

Additional Roles

Since the liver is where T4 is deiodinated to T3, it has an impact on thyroid hormone activity. Almost all of the body's plasma proteins, including albumin, binding globulins, protein C, protein S, and all of the clotting factors of the intrinsic and extrinsic routes save factor VIII, are synthesized by the liver (Welch et al., 2016).

2.1.5 Pathophysiology

Chronic liver damage, inflammation, fibrosis, and necrosis lead to cirrhosis. Cirrhosis is often brought on by alcoholism and chronic hepatitis B and C. The most harmful kind is hepatitis C. The Ito cells in the Disse space secrete TGF-beta, which causes the fibrosis seen in cirrhosis. Cirrhosis often indicates end-stage liver disease, which significantly impairs liver function (Dickson and Sigmund, 2016). The symptoms of portal hypertension, hyperestrinism, and hypoalbuminemia are caused by the decreased capacity to make protein and detoxify chemicals. Coagulation is caused by decreased production of clotting factors. It manifests itself as symptoms of portal hypertension and impaired hepatic function. Hemorrhoids, caput medusae, and portosystemic shunts that cause varices in different places are sequelae of portal hypertension. Ascites, spider angiomas, hepatic encephalopathy, hepatorenal syndrome, and splenomegaly are further signs of portal hypertension. The most frequent cause of mortality for people with cirrhosis is esophageal varices. Patients with cirrhosis are evaluated and their prognosis is determined using the Child-Pugh score and the Model for End-Stage Liver Disease (MELD) score. Both evaluate a number of factors in order to provide a score to the patient.

Ascites, hepatic encephalopathy (HE), total bilirubin, albumin, and prothrombin time, or INR, are all assessed by the Child-Pugh score. INR, bilirubin, and creatinine are used in the MELD score. The MELD score is the preferred metric for assessing liver transplant recipients, even if both are used to develop a prediction model for cirrhotic patients (Dickson and Sigmund, 2016).

A change in bilirubin metabolism is often indicated by jaundice. Yellowing behind the tongue is often the first symptom of jaundice, which is followed by scleral icterus, or yellowing of the sclera. Jaundice may have many different causes, however it can usually be categorized by measuring indirect bilirubin (unconjugated bilirubin) and direct bilirubin (conjugated bilirubin) in a fractionated bilirubin test. The fractionated bilirubin result may be used to determine if the cholestasis has prehepatic, intrahepatic, or extrahepatic origins. Prehepatic jaundice is often caused by hemolysis, in which the liver's conjugating ability is overloaded, leading to an accumulation of unconjugated bilirubin and jaundice. Congenital conditions like Crigler-Najjar syndrome and Gilbert syndrome may be the cause of intrahepatic cholestasis. UGT, the enzyme that catalyzes bilirubin conjugation, is either severely or severely impaired in many congenital disorders. Due to a malfunction in the canalicular transport of conjugated bilirubin, Dubin-Johnson and Rotor syndrome are the causes of direct bilirubinemia. Post-hepatic cholestasis may also result from obstructions like cancer or stones. Both direct and indirect hyperbilirubinemia may be caused by viral hepatitis (Wetzelset al., 2016).

2.1.6 Importance for Clinical Practice

Liver damage may result from a number of infections. While hepatitis E may cause fulminant hepatitis in pregnant individuals, hepatitis viruses A and E only cause acute hepatitis without developing chronic hepatitis. Travelers and contaminated water or shellfish are the main causes of hepatitis A and E (Thalacker, 2021). These are often self-limiting conditions that manifest as vomiting and jaundice. The viruses hepatitis B, C, and D may cause acute hepatitis that progresses to chronic hepatitis. Hepatitis B is necessary for the generation of hepatitis D. It may develop together with hepatitis B (coinfection) or concurrently with hepatitis B (superinfection).

Given that superinfection may result in more severe illness, the difference is crucial. Contaminated needles, such as those used in tattooing, intravenous drug use, or iatrogenically, may cause both hepatitis B and C. Sexual contact is another way that hepatitis B may spread. IgG is a sign that indicates vaccination or previous exposure, whereas IgM indicates acute infection. Vaccination is the best therapy for hepatitis A, B, and C (Thalacker, 2021). Hepatitis C can now be treated with combination antiviral drugs like sofosbuvir/velpatasavir thanks to breakthroughs in therapy. Previously referred to as primary biliary cirrhosis, primary biliary cholangitis (PBC) is thought to be an autoimmune condition that causes chronic liver damage, which in turn causes end-stage liver disease and cirrhosis (Thalacker, 2021). Women in their middle years are more likely to have it. Similar to other liver conditions, PBC may manifest as pain in the right upper quadrant. Elevations in liver enzymes that are not specific may be found with laboratory workup. The most specific marker for PBC is anti-mitochondrial antibodies, which may be found via ELISA. Ursodeoxycholic acid, which slows the course of the illness, and other drugs that target immunological regulation, such methotrexate, steroids, and in some cases, calcineurin 2 inhibitors, are used to treat PBC. There is no cure other than a liver transplant (Thalacker, 2021).

The liver suffers long-term harm from alcoholism. Alcohol is broken down by the liver, and prolonged alcohol use damages cells over time by accumulating harmful metabolites, most often from acetaldehyde. The liver develops cirrhosis as a result of this process, exhibiting all of the previously mentioned characteristics of cirrhosis (Ohlin et al., 2017). Clinical history, physical examination results, test results, and questionnaires may all be used to make a diagnosis. The CAGE questionnaire may be used for screening in clinics. The AUDIT is a questionnaire that may be given out using paper and pencil. As previously noted, alcohol withdrawal, delirium tremens, portal hypertension, and consequences including Wernicke encephalopathy, Korsakoff syndrome, and hepatic encephalopathy may all be signs of alcoholism. Blood alcohol, GGT, MCV, ethyl glucuronide, AST, ALT (the traditional AST/ALT ratio is 2:1), and other laboratory indicators are used to screen for alcoholism. The mainstay of treatment is behavioral change,

often with the help of anonymous alcoholics, and drugs like disulfiram may be added (Nwaneli, 2021).

There are many types of benign liver lesions in addition to malignant ones. The four most often addressed conditions are hepatocellular adenomas, hepatic cysts, focal nodular hyperplasia (FNH), and hemangiomas, which are the most prevalent. FNH is often seen in conjunction with hemangiomas and occurs in the context of congenital vascular formations or vascular disturbances (Nwaneli, 2021). These have a lower risk of rupture than hemangiomas and may be distinguished macroscopically from them by the presence of a central stellate scar. If the previous workup is unclear, sulfur colloid imaging or the use of eovist are examples of imaging workups particular for FNH. Hepatocellular adenomas are distinct growths that may develop during pregnancy and are often brought on by oral contraceptives and anabolic steroids. The main goal of treatment is to stop using identified causes. In the healthy population, they are seldom ever premalignant. Hepatocellular adenomas are linked to glycogen storage diseases, and these adenomas are more harmful since they are more likely to develop into hepatocellular carcinoma. Serial imaging allows for cautious overall therapy; but, if the adenoma is more than 5 cm, the lesion is bleeding, or the patient is male, it must be removed. Embolization may be used if the patient is not a good candidate for surgery. Nwaneli (2021).

Cancer may develop in the liver. Because the liver receives blood from so many parts of the body, metastases to the liver account for the majority of liver cancer cases. Hepatocellular carcinoma is the most prevalent primary liver cancer. As was said, cirrhosis, which may result from a number of conditions such primary biliary cirrhosis, alcoholism, nonalcoholic fatty liver disease, chronic hepatitis B or C, and more, can also cause HCC in addition to hepatocellular adenomas (Makusidiet al., 2023). The clinical picture of the patient and the extent of liver involvement determine the course of treatment for any malignant lesion; if the liver is not too heavily affected, resection and embolization or microwave ablation may be used. If not, systemic radiation and chemotherapy may be used to reduce the tumor burden. The range of liver diseases known as non-alcoholic fatty liver disease (NAFLD) includes cirrhosis that necessitates a liver transplant as well as benign steatosis. It is among the most prevalent long-term liver diseases that

need a liver transplant. NAFLD may be caused by a number of factors, including metabolic syndrome, pregnancy, diet, medications, pollutants, and more. Patients with diabetes and obesity are more likely to experience it (Makusidi et al., 2023). Asymptomatic patients undergoing workup for various reasons may also exhibit it. It may sometimes manifest as pain and/or discomfort in the right upper quadrant.

2.2 Hypertension and Blood Pressure

The force of blood pushing outward on the arterial walls is known as blood pressure (BP), according to the American Heart Association (2020). It is a measurement of the force that blood flowing throughout the body, delivering essential oxygen and other nutrients, exerts on the artery walls. According to the American Heart Association (AHA, 2020), blood pressure is caused by two factors. The circulatory system transports blood throughout the body, and the initial force is the heart's pumping blood into the arteries. The top number, or systolic blood pressure, is used to measure it. The heart's rest period in between heartbeats produces the second force. The diastolic blood pressure, or bottom number, is used to measure it. Systolic blood pressure of less than 120 mmHg and diastolic blood pressure of less than 90 mmHg are considered optimal. According to Zhao (2017), HBP is referred to as hypertension, which is a public health issue. This condition arises when blood pressure consistently rises beyond 140 over 90 mmHg, with a systolic pressure above 140 and a diastolic pressure above 90. However, normal blood pressure is below 120/80; values between 120/80 to 139/89 is considered pre-hypertension. While diastolic blood pressure refers to the pressure that results from the relationship of the arteries after contraction, systolic blood pressure is the pressure in the arteries when the heart contracts and pushes blood forward into the arteries. Since it often exhibits no symptoms, it has been dubbed a silent killer. According to Zhao (2017), it takes a long time to diagnose hypertension, which leads to serious health issues like stroke and other cardiovascular diseases. The long-term effects of high blood pressure sickness include harm to organs such as the heart, brain, kidneys, eyes, and so on. A sphygmomanometer is often used to test blood pressure in order to diagnose high blood pressure. This includes electronic blood pressure monitors, an inflated rubber cuff, an air pump, and either a mercury column or a digital readout that shows the pressure in an air column. A common unit

of measurement for the measurements is millimeters of mercury, or mmHg. With the exception of very high blood pressure (over 170-180 systolic and diastolic of 105-110), high blood pressure cannot be diagnosed simply on a single measurement.

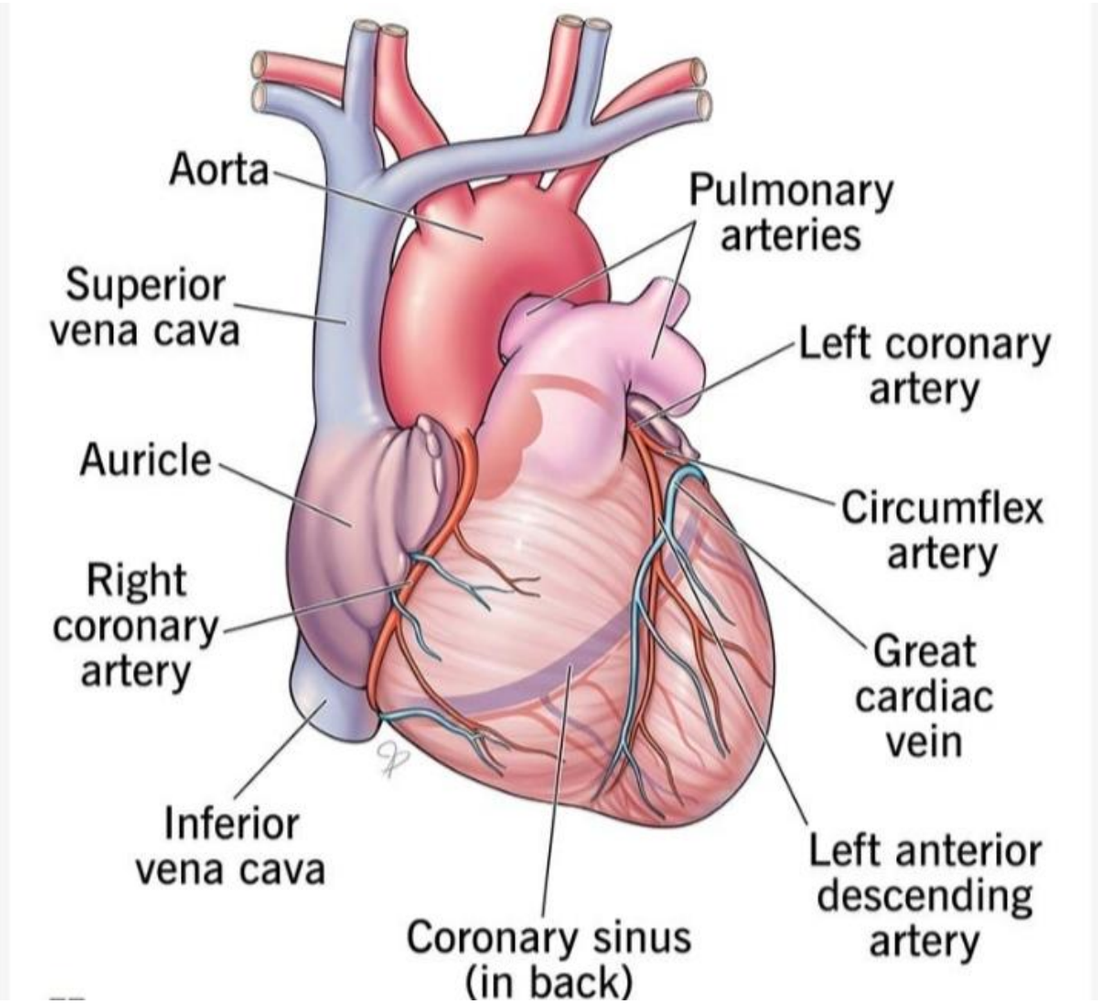

Figure 2: A well labelled exterior of the heart

The World Health Organization (2023) defines hypertension, often known as high blood pressure, as a condition in which the pressure within the blood arteries is continuously elevated. When the systolic blood pressure is 140 mm Hg or more and the diastolic blood pressure is 90 mm Hg or higher, the blood pressure is deemed elevated or high. It is the leading risk factor for death worldwide and is regarded as the most important modifiable risk factor for cardiovascular disease. Although the exact causes of high blood pressure are unknown, Campbell et al. (2021) noted that correlations with obesity, physical inactivity, salt and alcohol use point to a significant

role for behavioral variables. For instance, up to 30% of all instances of hypertension are brought on by excessive salt intake. According to Breen (2018), hypertension has a multifactorial and very complicated etiology and pathophysiology. Simply explained, blood pressure is determined by the balance between peripheral vascular resistance (the degree of arteriole dilatation or constriction) and cardiac output (the volume of blood the heart pumps out each minute). Blood pressure will rise if either variable rises significantly. Breen (2018) agreed that the sympathetic nervous system, endothelial dysfunction, and the rennin-angiotensin system are physiological processes that contribute to the maintenance of normal blood pressure in addition to cardiac output and peripheral resistance.

According to Alonso et al. (2019), high blood pressure contributes significantly to the worldwide burden of illness and is disproportionately greater in low-income nations than in high-income ones. Half of this load is borne by hypertensive individuals; the remaining portion is borne by those with less severe forms of high blood pressure. More precisely, high blood pressure causes more than 50% of ischemic heart disease and over 60% of strokes (American Heart Association, 2017). According to Burrows and Muller (2017), pre-hypertension increases the risk of cardiovascular disease. According to Alonso et al. (2019), individuals with high normal blood pressure (systolic blood pressure (SBP) between 120 and 139 mmHg and/or diastolic blood pressure (DBP) between 80 and 89 mmHg) are more likely to develop hypertension and cardiovascular disease. According to Health Statistics International (2021), hypertension is one of the most common chronic diseases. Approximately one billion individuals worldwide suffer from high blood pressure, and by 2025, that figure is predicted to rise to 1.56 billion. According to the World Health Organization (2018), hypertension is one of the leading causes of premature mortality globally and is becoming worse every day. In 2008, around 40% of persons aged 25 and older had elevated blood pressure.

According to the Centers for Disease Control and Prevention (2018), high blood pressure costs the US economy $47.5 billion annually. The cost of medical services, high blood pressure medication, and lost work days are all included in this sum. According to the World Health

Organization (2021), hypertension affects around 125 million people in the Eastern Mediterranean Region, where its prevalence is 29%. More concerning is the rising prevalence of cardiovascular problems brought on by high blood pressure, such as heart failure, stroke, and end-stage renal disease. According to study, medication non-compliance is the primary cause of poorly managed hypertension, according to Health Stats International (2021). "The extent to which a person's behavior does not coincide with medical or health advice" is the definition of non-compliance. Ikeda et al. (2018) claimed that research on hypertension varied significantly in their estimations of compliance, with values ranging from 20 to 80% being reported. Over the last three decades, the number of persons with uncontrolled hypertension has risen to over 1 billion globally. In a Karachi research, Almas et al. (2022) showed that 43% of people did not comply, with 53.4% having mild non-compliance, 24.4% having severe non-compliance, and 22% having moderate non-compliance.

Only 13.5% of patients in a different research by Mant and McManus (2016) at the Civil Hospital in Karachi had regulated blood pressure, while the remaining hypertensive patients had uncontrolled blood pressure. Christian (2018) also found that just 54% of patients reported having excellent treatment compliance, and fewer than half (43.8%) of the hypertensives had routine blood pressure checks. The fact that 22.5% of patients received subtherapeutic dosages of antihypertensive medications is significant. According to Health Statistics International (2021), uncontrolled hypertension is a prevalent cause of uncontrolled hypertension and a significant risk factor for CVDs. Noncompliance is a complicated behavioral process that is influenced by a number of variables, including the patient's personality, the connection between the patient and the physician, and the healthcare system. According to the World Health Organization (WHO, 2018), 50–70% of individuals do not take their antihypertensive medicine as directed, and poor adherence is the main reason why blood pressure is not under control. According to Joho (2018), there are a number of elements that are linked to it, and these factors differ depending on the research. They often include characteristics relating to health services, certain demographics, and

pharmaceutical choice. The majority of research on this topic, however, has focused on secondary analyses of administrative databases and examined factors that contribute to non-compliance, or non-persistence.

Cunha and Marks (2021) state that the etiology of hypertension is unknown at this time unless it is secondary hypertension. Nonetheless, the prevalence is linked to other underlying causes. These variables include aging, smoking, drinking alcohol, leading a sedentary lifestyle, eating too much salt, and genetics. According to Keaney et al. (2017), a research found that high blood pressure was prevalent in persons between the ages of 20 and 79. According to Hart, Fahey, et al. (2020), high blood pressure may strike anybody, and its reasons may be idiopathic, meaning they are not known. Patients with consistently elevated blood pressure are diagnosed with hypertension. A significant factor in determining who develops high blood pressure and who does not is a family history of the condition. In general, information of blood pressure in parents, siblings, and sisters may predict at least half of the variation in blood pressure among large groups of individuals. According to Rosendorff (2018), stress may result in a significant spike in blood pressure that lasts for minutes or even hours. These increases are common and happen to everyone. They are short-term enhancements to the typical average pressure, regardless of how high or low it is. According to Chaturve et al. (2022), being of Afro-Caribbean or South Asian heritage, being obese, not exercising, smoking, consuming excessive amounts of alcohol or salt, and eating a high-fat diet are all variables that might contribute to hypertension.

2.2.1 Hypertension Physiology

According to Hypertension (2005), the pathophysiology of hypertension is significantly influenced by the renal system. The kidneys filter blood selectively in order to eliminate extra fluid and preserve essential components. Blood volume rises and blood pressure rises when too much fluid is retained, as occurs with excessive salt consumption. Similarly, blood pressure was

reduced if extra fluid was expelled. In reaction to decreased blood volume, the kidney's juxtaglomerular apparatus secretes renin, which is in charge of converting renin substrate (angiotensinogen) to angiotensin I (Beevers, Lip, and O'Brien, 2021). In the lungs, the angiotensin converting enzyme (ACE) swiftly changes angiotensin I into angiotensin II. A strong peripheral vasoconstrictor, angiotensin II raises blood pressure. The renin-angiotensin system is the name given to this sensitive feedback mechanism.

According to Beevers, Lip, and O'Brien (2021), the sympathetic nervous system, which is a part of the autonomic nervous system, plays a significant function in preserving normal blood pressure since it may produce both arteriolar dilatation and constriction. It is a crucial factor to take into account while treating transient variations in blood pressure brought on by stress or physical activity. Through the production of many strong local vasoactive agents, including the vasoconstrictor peptide endothelin and the vasodilator molecule nitric oxide, vascular endothelial dysfunction plays a crucial role in blood pressure control. Numerous different vasoactive systems and processes have an impact on vascular tone and salt transport, which are crucial for maintaining normal blood pressure (Beevers, Lip, and O'Brien, 2021). The interaction between the autonomic and rennin-angiotensin systems, which is impacted by circulating volume, salt consumption, and hormones that impact vascular resistance, is probably the cause of hypertension (Beevers, Lip, and O'Brien, 2021). The muscle and semi-flexible tissue that line arteries stretch like elastic when they are healthy, according to Breen (2008) (Makusidi et al., 2023). The pressure is maximum when the heart contracts and pumps blood through the arteries. The systolic blood pressure is the resultant force. Diastolic blood pressure is the lowest level of arterial circulation pressure that occurs when the heart relaxes. The arteries will widen as the blood beats harder, making it easier for blood to pass through. According to the American Heart Association (AHA, 2020), prolonged and/or frequent episodes of high blood flow will eventually cause the tissue lining artery walls to extend above its safe limit.

2.2.2 The Causes of High Blood Pressure

Primary or essential hypertension and secondary hypertension are two etiological types of hypertension.

Approximately 95% of hypertensive patients are classified as primary or essential hypertension, which is defined as hypertension for which no known cause can be identified (Colledge and Walker, 2020). This kind of hypertension takes time to develop. The pathophysiology of primary hypertension is not well known, although putative contributing variables include renal dysfunction, endothelial dysfunction, insulin resistance, and other neurohumoral factors (Makusidiet al., 2023).

Secondary hypertension: This kind of hypertension usually appears suddenly and has a blood pressure level greater than primary hypertension. It is caused by underlying problems. The disorders listed below have the potential to cause secondary hypertension (NIH 2018).

• renal disorders, such as renal vascular diseases, kidney parenchymal illnesses, including glomerulonephritis (GN), and kidney cystic diseases, such as polycystic kidney disease (PKD).

• Endocrine system disorders such as acromegaly, thyrotoxicosis, Conn's syndrome, hyperparathyroidism, hypothyroidism (primary), tumors of the adrenal medulla (particularly pheochromocytoma), etc.

• Some drugs, such as over-the-counter pain relievers, corticosteroids, anabolic steroids, estrogen-containing oral contraceptive pills (OCP), etc. as well as other illicit substances like amphetamines and cocaine.

2.2.3 Hypertension Symptoms

According to Hypertension (2017), the majority of hypertension individuals do not exhibit any symptoms, therefore the illness is often identified during a normal checkup or a visit to the doctor to treat another ailment. Because so many people do not exhibit any signs that would suggest their blood pressure is high, hypertension has been aptly dubbed "the silent killer."

Patients who have a sudden, severe increase in blood pressure are more likely to develop symptoms. Headache, lightheadedness, ringing in the ears, chest discomfort, dyspnea, nausea, vomiting, convulsions, and unconsciousness are some of these symptoms. Unfortunately, only a small percentage of patients with hypertension experience these signs and symptoms, and most of them depend on having access to high-quality healthcare services in order to manage their condition and lower the morbidity and mortality that may arise from having high blood pressure for an extended period of time (Hypertension, 2017).

2.2.4 Blood Pressure Classification

Normal, prehypertension, stage 1 hypertension, stage 2 hypertension, and isolated systolic hypertension are the different classifications for blood pressure (NIH 2018; Madhur 2023).

• Typical

A SBP of less than 120 mmHg and a DBP of less than 80 mmHg are indicative of normal blood pressure.

Prehypertension

Systolic blood pressure of 120–139 mmHg or diastolic blood pressure of 80–89 mmHg are indicators of prehypertension.

• Hypertension in stage one

An SBP of 140–159 mmHg or a DBP of 90–99 mmHg indicates stage 1 hypertension.

• Hypertension in stage two

When the SBP is larger than or equal to 160 mmHg or the DBP is greater than or equal to 100 mmHg, it is considered stage 2 hypertension.

• Systolic hypertension that is isolated

A DBP of less than 90 mmHg and an SBP of more than or equal to 140 mmHg are indicative of isolated systolic hypertension.

2.2.5 Types and Classification of Hypertension

Blood pressure may be divided into four groups, according JNC 7 (The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure): Normal or Optimal, Pre-hypertension, Stage 1 Hypertension, and Stage 2 Hypertension. In order to lower blood pressure and stop the progressive development of hypertension in the general population, Chobania et al. (2023) claimed that the "Pre-hypertension" category, which was introduced with JNC 7, acknowledges the necessity of prevention strategies and the promotion of healthy lifestyles by medical and public health professionals. Another way to classify hypertension is by its cause or origin. Ninety to 95 percent of adult instances of high blood pressure are "primary" or essential hypertension. There are no clear-cut reasons for primary hypertension, which often develops gradually over several years. The remaining 5–10% of instances of high blood pressure are known as "secondary" hypertension, which is caused by illnesses including aortic coarctation and renal failure and often manifests abruptly.

According to Hypertension (2017), hypertension comes in a variety of forms. When assessed by a doctor or other healthcare professional, "white coat hypertension," often referred to as anxiety-induced hypertension, is defined by an increase in blood pressure that is apparently normal at other times. When the diastolic blood pressure stays below 90 mmHg and the systolic blood pressure continuously exceeds 160 mmHg, this condition is known as isolated systolic hypertension (ISH). ISH patients have a markedly elevated risk of cardiovascular and cerebrovascular illness, despite the fact that they are often asymptomatic (Hypertension, 2005). The occurrence of high blood pressure brought on by raised estrogen levels during pregnancy is known as gestational hypertension. Since blood pressure typically returns to normal after 12 weeks of giving birth, this condition is temporary (Hypertension, 2017). Pre-eclampsia and eclampsia are two more severe types of high blood pressure that occur during pregnancy. With the possibility of seizures and coma due to hypertensive encephalopathy, eclampsia is regarded as potentially fatal (Hypertension, 2005). The term "labile hypertension" describes a condition

where blood pressure often and suddenly changes, frequently leading to headaches or tinnitus when the blood pressure is high. Emotional stress may be the cause of labile hypertension, which makes it more susceptible to anti-anxiety drugs and less responsive to conventional blood pressure-lowering treatments (Hypertension, 2005). Lastly, a sudden and severe rise in blood pressure that quickly causes end-organ damage is known as malignant or accelerated hypertension. The one-year death rate is more than 75% if malignant hypertension is not treated immediately (Hypertension, 2017).

According to Harvard Medical School (2020), high blood pressure damages the cells lining the coronary arteries over time, creating the conditions for plaque and inflammation. Vascular weakening, vascular scarring and an elevated risk of blood clots, increased plaque accumulation, and tissue and organ damage due to constricted and blocked arteries are some of the issues that may result from this. Heart attacks and other heart conditions like cardiomyopathy, cardiac arrhythmias, congestive heart failure, aortic dissection, and atherosclerosis are among the long-term effects of uncontrolled high blood pressure, according to the American Heart Association (2010). Stroke, kidney damage, eyesight loss, lung fluid, memory loss, and erectile dysfunction may all result from poorly treated or controlled hypertension.

Based on data from 2005–2008, 79.6% of people with hypertension aged 20 and over were aware that they had the condition, and 70.9% of them received treatment, according to the Heart Disease and Stroke Statistics, 2022 update. About 52% did not have their hypertension under control, whereas 48% had it under control (<140/<90 mmHg) (Roger et al., 2022). According to prospective research, lowering blood pressure would reduce the incidence of cardiovascular disease and other vascular problems (Prospective Studies Collaboration, 2022). According to Burrows and Muller (2007), reducing blood pressure may decrease the risk of myocardial infarction (heart attack) by 20–25%, the risk of stroke by 35–40%, and the risk of heart failure by 50%. From their research on multiple risk factor controls, the CDC (2016) and Bozovic et al. (2023) came to the conclusion that a number of factors, including behavior, habits, and nutrition, may contribute to hypertension as a risk factor for cardiovascular disease. These factors may also

be indirectly impacted by depressive states. Maintaining a healthy mood is one of the many risk factors for the management of cardiovascular disease. According to Smith and Blumenthal (2021), cardiac patients' emotions, including stress, anxiety, despair, and rage, were linked to the development and advancement of the negative consequences of cardiovascular disease. In contrast to individuals who demonstrated control over these general emotions, Smith and Blumenthal found that cardiac patients diagnosed with or experiencing "negative moods" including anger, worry, stress, and sadness had double the death risk from cardiovascular disease. Like Bozovic et al., they provided more robust suggestions for future integrated behavioral changes that emphasize many risk factor controls and a closer examination of their interrelationships. According to Bozovicet al. (2023), identifying a single risk factor that may impact many other risk variables might be crucial to preventing illness in the future.

2.2.7 Risks of hypertension for the heart

According to Alwan (2020) and Yusuf (2018), abnormal lipids, hypertension, diabetes, tobacco use, abdominal and overall obesity, psychological stress, a lack of physical exercise, alcohol abuse, and poor nutrition are among the modifiable risk factors for cardiovascular disease. Tobacco use, poor nutrition, sedentary lifestyles, and excessive alcohol consumption may be the main lifestyle risk factors that contribute to a significant amount of the illness burden, according to WHO (2021) (Bakrhuet al., 2021).

According to Reddy and Katan (2016), elevated blood pressure is another significant risk that leads to cardiovascular disease. According to the WHO (2023), high blood pressure increases the risk of both coronary heart disease and hemorrhagic and ischemic stroke. According to Alwan (2020), the chance of dying from cardiovascular disease rises as blood pressure steadily rises. Van den Hoogen (2020) emphasized that although the absolute risk of death from CHD at any given blood pressure may vary, the relative increase in mortality from CHD across various groups was comparable with rising blood pressure. According to Yusuf (2004), controlling hypertension may result in a 15% decrease in myocardial infarction and a 40% decrease in stroke. According to Alwan (2020), 40% of persons aged 25 and older worldwide suffer from

hypertension, which is thought to be the cause of over 7.5 million fatalities annually. According to Rosendorff (2015), a key component of a person's clinical evaluation for first-time or recurring cardiovascular events is the risk factor concept. Anything that raises the risk of cardiovascular disease is called a risk factor. The likelihood of acquiring cardiovascular disease increases with the number of risk factors. Although signs of the initial incident's intensity often influence the likelihood of a recurring occurrence, other influencing risk variables still play a crucial role. Risk variables might be classified as changeable or non-modifiable based on risk assessment. Diabetes, high cholesterol, hypertension (high blood pressure), obesity, sedentary lifestyles (physical inactivity), smoking, and exposure to ambient tobacco smoke are among the modifiable risk factors. However, non-modifiable risk variables (such a high family history of cardiovascular disease) may improve risk assessment and influence how urgently modifiable risk factors need to be corrected (Bagnardiet al., 2018).

According to Zipes et al. (2017), smoking and high cholesterol are the two most significant modifiable cardiovascular risk factors in the globe. According to Yusuf, Cairns, and Camm (2023), the next most significant variables in the general population are obesity, diabetes, hypertension, and psychosocial factors; however, the relative importance of these factors varies depending on the location of the individual. According to Emberson et al. (2023), excessive alcohol use is another significant risk factor for smokers. The most disadvantaged populations are often exposed to the greatest risks due to the uneven distribution of many of these risk variables across society. According to the British Heart Foundation (2019), cardiovascular disease contributed to over 150,000 deaths in England in 2017, accounting for nearly 34% of all deaths. Other major independent risk factors include age, diabetes, cigarette smoking, blood pressure greater than 140/90 mm Hg, high-density lipoprotein (HDL) less than 1 mmol/l, elevated low-density lipoprotein (LDL) concentrations, and family history of premature coronary artery disease (first-degree male relative). Additionally, Murray and colleagues (2013) evaluated the UK's health performance using the Global Burden of Diseases, Injuries, and Risk Factors (GBD) data in a recent paper published in The Lancet. They found that ischemic heart disease was the leading cause of years of life lost due to premature mortality in the UK in 2010 and that

stroke came in third. Murray and others (2022). said that, above drinking and a high body mass index (BMI), hypertension has been shown to be the primary risk factor for this significant burden. The GBD architecture that is used to evaluate the health performance of the United Kingdom is intricate. The most comprehensive attempt to characterize the epidemiology of several serious illnesses, injuries, and risk factors has ever been made with GBD 2010. Millions of observations have been gathered, evaluated, and compiled on risk factors, illness and injury prevalence and incidence, mortality, and causes of death (Baglietto et al., 2016).

2.3 Hypertension management

Changes in Lifestyle

Lifestyle changes are recommended by JNC-7 for all patients with hypertension or prehypertension. These changes include cutting down on salt, exercising, drinking less alcohol, losing weight, and adopting the Dietary Approaches to Stop Hypertension (DASH) diet (AHA, 2017). Researchers evaluated the effects of behavioral changes without DASH ("established" group), with a "advice-only" group, and with full lifestyle changes that include the JNC-7 guidelines ("established plus DASH" group) in the PREMIER clinical study. When compared to the advice-only group, the established group's systolic and diastolic blood pressure decreased more (mean reductions were 11.1 mm Hg, 10.5 mm Hg, and 6.6 mm Hg for systolic blood pressure, and 6.4 mm Hg, 5.5 mm Hg, and 3.8 mm Hg for diastolic blood pressure, respectively). The biggest reductions were observed when DASH was also included (AHA, 2017).

The use of pharmaceuticals

If lifestyle changes are insufficient to raise blood pressure to the desired level, medication treatment is required. Angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), beta-blockers, calcium channel blockers (CCBs), and diuretics are first-line drugs used to treat hypertension (AHA, 2017). To reach their blood pressure goal, some individuals may need to take two or more antihypertensive drugs. Antihypertensives or a combination hypertensive may be introduced right away to newly diagnosed individuals whose

blood pressure is more than 20/10 mm Hg over target. Before taking the first medication at the highest prescribed dosage, a second medication with a complimentary mechanism of action should be taken to reduce adverse effects.

2.3.1 Diuretics

An accumulation of fluid in the blood vessels brought on by too much salt may increase blood pressure. By boosting urine production, diuretics assist the body in getting rid of extra water and salt (Alshubaily and Almotairi, 2020). Diuretics come in a variety of forms. Examples include furosemide (Lasix), amiloride hydrochloride (Midamar), and chlorthalidone (Hygroton) (Trusted Source). Weakness, lightheadedness or dizziness, increased sensitivity to sunlight, skin rashes, cramping in the muscles, vomiting, diarrhea, constipation, low blood pressure, and electrolyte imbalances are among the possible adverse effects of diuretics (Aziziet al., 2022). Although it is less often, people on diuretics may also have diminished libido. A patient should make sure their doctor is aware of all the medicines they are taking since some of them might interact with diuretics. Digoxin and digitalis are two medications that may interact with diuretics. Diuretics may not be appropriate for those who lose fluids easily. Additionally, they may exacerbate diabetes, pancreatitis, renal issues, gout, irregular menstruation, and anuria, which is characterized by little to no urine production (Alshubaily and Almotairi, 2020).

2.3.2 Inhibitors of peripheral adrenergic

The neurotransmitters in the brain that induce blood vessels to contract are blocked by peripheral adrenergic inhibitors, or PAIs. Blood pressure may be decreased by blocking these receptors, which keeps the blood vessels open and relaxed (Mohammed and Abosaif, 2016). PAIs are often only prescribed by doctors in cases when other blood pressure drugs have failed. Guanadrel (Hylorel), guanethidinemonosulfate (Ismelin), and reserpine (Serpasil) are a few examples of this class of medication. PAI comes in a variety of forms, and each kind has unique side effects. Nasal congestion, heartburn, diarrhea, lightheadedness, dizziness, or weakness on rising up, fainting, low blood pressure, erectile dysfunction, depression, and nightmares are some of the possible adverse effects. Alcohol, asthma medicines, diuretics, and other blood pressure drugs

are among the substances that certain PAIs may interact with. When using certain PAIs, stopping these drugs too soon might result in a hazardous decline in blood pressure (Mohammed and Abosaif, 2016).

People with certain medical issues may not be able to use some kinds of PAIs. Congestive heart failure, vascular disorders, asthma, peptic ulcers, fluid retention, pheochromocytoma, depression, and ulcerative colitis are some of these ailments.

2.3.3 Inducing Vasodilation

Vasodilators, also known as blood vessel dilators, relax and enlarge the blood vessel walls to facilitate easier blood flow. The arteries are the particular target of direct-acting vasodilators (Ohmori et al., 2022). Minoxidil (Loniten) and hydralazine hydrochloride (Apresoline) are two varieties of direct-acting vasodilators. The stronger of the two medications is minoxidil. It is often prescribed by doctors to patients with severe and chronic hypertension. The following adverse effects of hydralazine hydrochloride are possible and often go away a few weeks after starting treatment: headaches, joint discomfort, eye puffiness, and palpitations (Ohmoriet al., 2022). Weight gain from fluid retention and, in rare instances, excessive hair growth are possible adverse effects of minoxidil. Diuretics and other blood pressure medicines, as well as erectile dysfunction treatments like vardenafil (Levitra), tadalafil (Cialis), or sildenafil (Viagra), may intensify the effects of vasodilators. Combining a vasodilator with erectile dysfunction drugs might result in a potentially fatal reduction in blood pressure (Puddey and Beilin, 2017).

2.4 Amlodipine

Amlodipine is a calcium channel blocker that is taken orally. Amlodipine inhibits the first calcium influx by blocking voltage-dependent L-type calcium channels (Aniaguet al., 2021).

2.4.1 Amlodipine Benefits

Amlodipine has the longest half-life (30 to 50 hours) when compared to nifedipine and other drugs in the dihydropyridine family. One advantage of having a lengthy half-life is that it allows for once-daily dosage. Among the several antihypertensive medication alternatives, amlodipin is a great first-line option. It may be used either by itself or in conjunction with other antihypertensive medications. Amlodipin is used to treat persistent stable angina symptoms. According to Ammerman et al. (2016), amlodipin may be taken either by itself or in conjunction with other antianginal medications.

2.4.2 Amlodipin's Drawbacks

Long-term use of amlodipin may cause impotence in men, peripheral edema, heart failure, pulmonary edema, flushing, headache, sleepiness, skin rash, nausea, stomach discomfort, and constipation, among other serious side effects. In controlled clinical studies, researchers noted palpitations, flushing, dizziness, and edema in a dose-dependent manner (AHA, 2016). Edema, dizziness, flushing, and palpitations, for instance, occurred 10.8%, 3.4%, 2.6%, and 4.5% of the time at a dosage of 10 mg. Furthermore, the prevalence of headaches, exhaustion, nausea, and stomach discomfort was 7.3%, 4.5%, 2.9%, and 1.6%, in that order.

Rare cases of idiosyncratic drug-induced liver illness have been associated with calcium channel blockers, such as amlodipine (AHA, 2020). A common characteristic of liver damage brought on by amlodipine is a mixed hepatocellular-cholestatic pattern. After quitting the medication, full recovery is expected in 4–8 weeks. Because CYP3A4 metabolism is reduced when amlodipine and clarithromycin or erythromycin are taken together, there is a higher chance of hypotension and severe kidney damage. Additionally, there is a higher chance of myopathy and rhabdomyolysis when amlodipine is used with large dosages of statins. It's crucial to remember that amlodipine may result in peripheral edema. When a diuretic is recommended to treat edema because it is thought to be a new medical disease, this is known as a prescribing cascade.

2.5 Telmisartan

With its selective binding to the angiotensin II (subtype 1) receptor, telmisartan, a non-peptide angiotensin II receptor antagonist, inhibits pressor effects in the vasculature, aldosterone synthesis and release, and renal sodium reabsorption. It can be used alone or in combination with other antihypertensive medications to treat hypertension (Andy et al., 2022).

2.5.1 Telmisartan Benefits

1) Greater and longer-lasting antihypertensive action compared to other angiotensin II receptor blockers with a longer half-life

2) Increase the expression of important mitochondrial enzymes in skeletal muscle, decrease weight gain, and raise overall energy expenditure.

2.5.2 Telmisartan's drawbacks

1) Allergic responses (swelling of the cheeks, lips, or tongue; skin rash, itching, or hives)

2) Elevated potassium levels (muscle weakness, rapid, irregular pulse, and chest discomfort)

3) Kidney damage (difficulty urinating or altering urine production)

4) Low blood pressure (dizziness, lightheadedness, fainting, and unusual fatigue or weakness)

5) Additional drawbacks include headache, stuffy nose, diarrhea, back discomfort, and changes in sex desire or performance.

CHAPTER THREE

MATERIALS AND METHOD

3.1. Laboratory equipments

Dissecting materials, capillary tubes, hot plate, cotton wool, knives, measuring cylinder, digital weighing balance, scissors, lithium heparin bottles, haematocrit centrifuge, haematocrit reader,

cover slips, stainless steel, blender, tissue gauze, pyrex glass wares, 5mil syringe, forceps, binocular microscope, GFI Shaker, cutup board, universal container, tissue cassette, rotary microtones, lead pencil automatic tissue processor and 2ml syringe

3.1.1 Animals and Chemicals

Amlodipine was purchased from EHI Pharmaceutical Co Ltd (Lagos, Nigeria) and telmisartan was purchased from pamasodor Pharmaceutical Co Ltd (Lagos, Nigeria). Male and Female albino rats (used for preparation of hypertensive models) were purchased from the department of Anatomy. The rats were housed with controlled temperature (23–25 degrees Celsius) and lighting (8:00 AM to 8:00 PM light, 8:00 PM to 8:00 AM dark) and with free access to food and tap water. All the animals used in this work received humane care in compliance with institutional animal care guidelines.

3.2 Induction of High Blood Pressure In Rats

The rats were administered water rich in NaCl for a period of 2 weeks and the blood pressure of the rat was measured using the Tail- Cuff plethysmography

3.3 Tail Cuff Plethysmograph

A cuff was placed around the tail of the albino rats and changes in tail volume and recorded to estimate blood pressure of the rat. Using the sphygmomanometer reading (the number the mercury has reached), the pulse reading is done and recorded as the systolic pressure. While cuff is Deflated further until the pulse disappear to record the reading as the diastolic pressure.

3.4 Experimental Design

A total of 18 albino rats weighing 165g-195kg with high blood pressure was distributed into 3 groups (A, B, and C). Group A (Labelled as control group) was administered water and food only, Group B amlodipine was given in a dose of 10 mg/kg/day for 4 weeks (28 days) , Group C Telmisartan was given in a dose of 10 mg/kg/day for 4 weeks .

3.5 Animal Harvesting

After 4 weeks, Animals was weighed, anesthetize with chloroform upon inhalation and dissected and the liver harvested and placed in 10% Neutral buffered formalin for onward tissue processing

3.6. Histological processing

3.6.1. Liver tissue preparation

After animals were sacrificed using chloroform, The liver tissue were cut open and placed into tissue cassettes and processed using a 12-hour automatic tissue processor schedule; (it went through fixation , dehydration, clearing , infiltration). After processing, embedding, microtomy/ sectioning, floating of section , dewaxing with hot plate, staining was carried out.

3.7 Staining

Flame the slide on burner and place in the xylene. Repeat the treatment to remove the wax. Drain xylene and hydrate the tissue section by passing through decreasing concentration of alcohol baths (100%, 90%, 80%, 70%) and water. Stain in hematoxylin for 5 minutes. Wash in running tap water until sections “blue” for 5 minutes or less. Dip in 1% acid alcohol (1% HCl in 70% alcohol) for a few seconds. Rinse in running tap water. Dip in ammonia water until the sections become blue, followed by tap water wash. Stain in 1% Eosin Y for 10 minutes. Wash in tap water for 5 minutes. Dehydrate in increasing concentration of alcohols. Put slides in two xylene baths for clearing for 5 minutes each. Mount in DPX or other mounting media. Observe under compund microscope.

3.8 Slide Reading

The slides were read using the microscope, all cellular details were examined

3.9 photomicrograph

Samples of selected sections of the livers was photographed and presented as plates

CHAPTER FOUR

RESULTS

4.1 EXPERIMENTAL FINDINGS

Amlodipine and Telmisartan administration for 4 weeks reveals changes in weight and no histopathological damages was observed. The results are explained separately in different sections as follows.The collated values were expressed in mean ± SD. was considered significant. The average weight of animal after the 4 weeks administration of amlodipine

180.57± 26.621 and telmisartan 189.07± 24.889 shows significant increase (p≤0.05)when compared with the control as presented in table 1 and 2.

The histological sections of the liver after administration of amlodipine and telmisartan (10mg/kg dosage) did not present any degenerative changes as presented plate 2-4

Table 1: Effect of Telmisartan administration on weight of Albino rats

	N	Mean ±SD	Std.Error	Sig.P-value ***p≤0.05**
GroupA–nil	6	165.25 ±23.940	5.985	.002
GrpB- 10mg/kg	6	212.88 ±25.838	6.459	.005
Totalaverageweight	12	189.07±24.889	3.328	.006

Table 2: Effect of Amlodipin administration on on weight of Albino rats

	N	Mean ±SD	Std.Error	Sig.P-value ***p≤0.05**
GroupA–nil	6	165.25 ±23.940	5.985	.002
GrpC-10mg/kg	6	195.88 ±11.278	2.819	.004
Totalaverageweight	12	180.57 ±26.621	3.328	.006

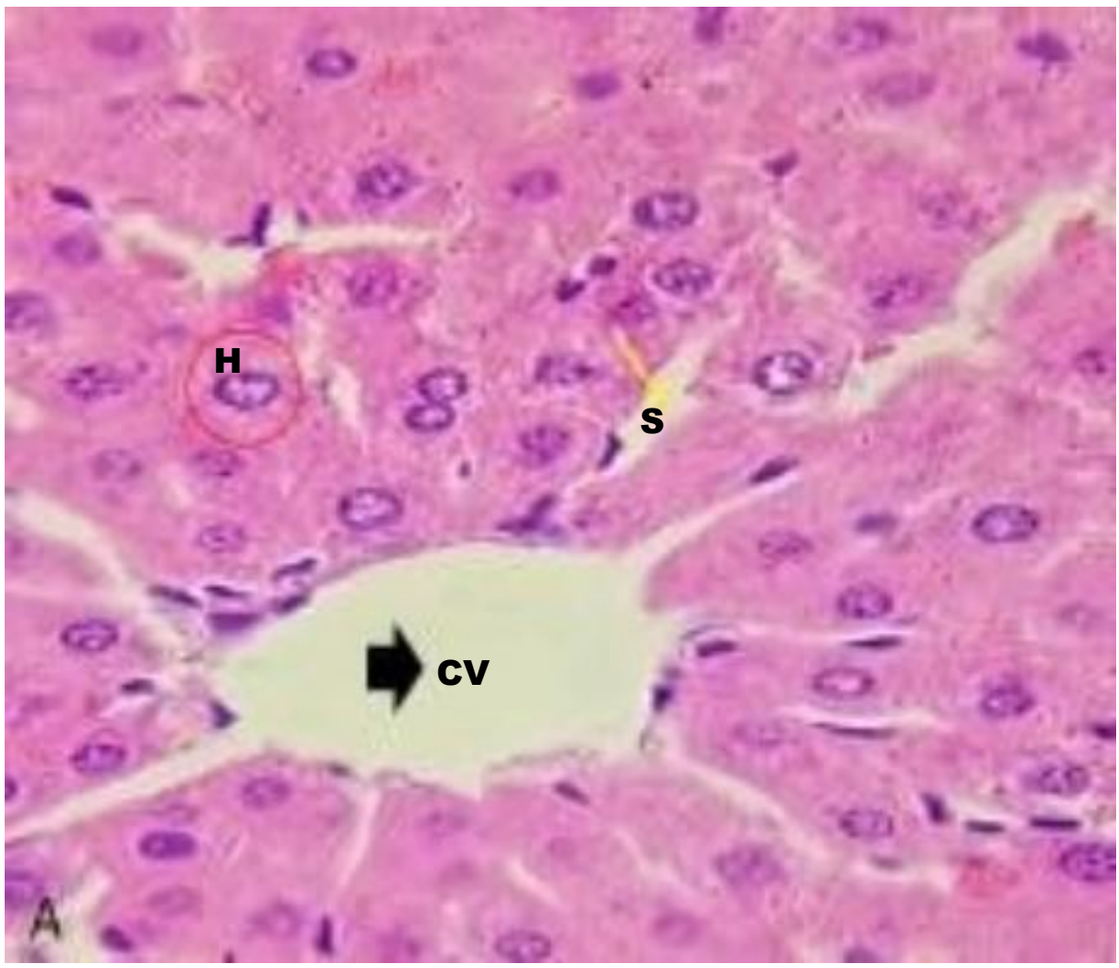

Plate 1: Section of rat hepatic tissue from the Control group A showing a well differentiated and organized hepatocytes (H) on the hepatic plates, central vein(CV) and sinusoids with Kupfer cells(S). Haematoxylin and Eosin X 400

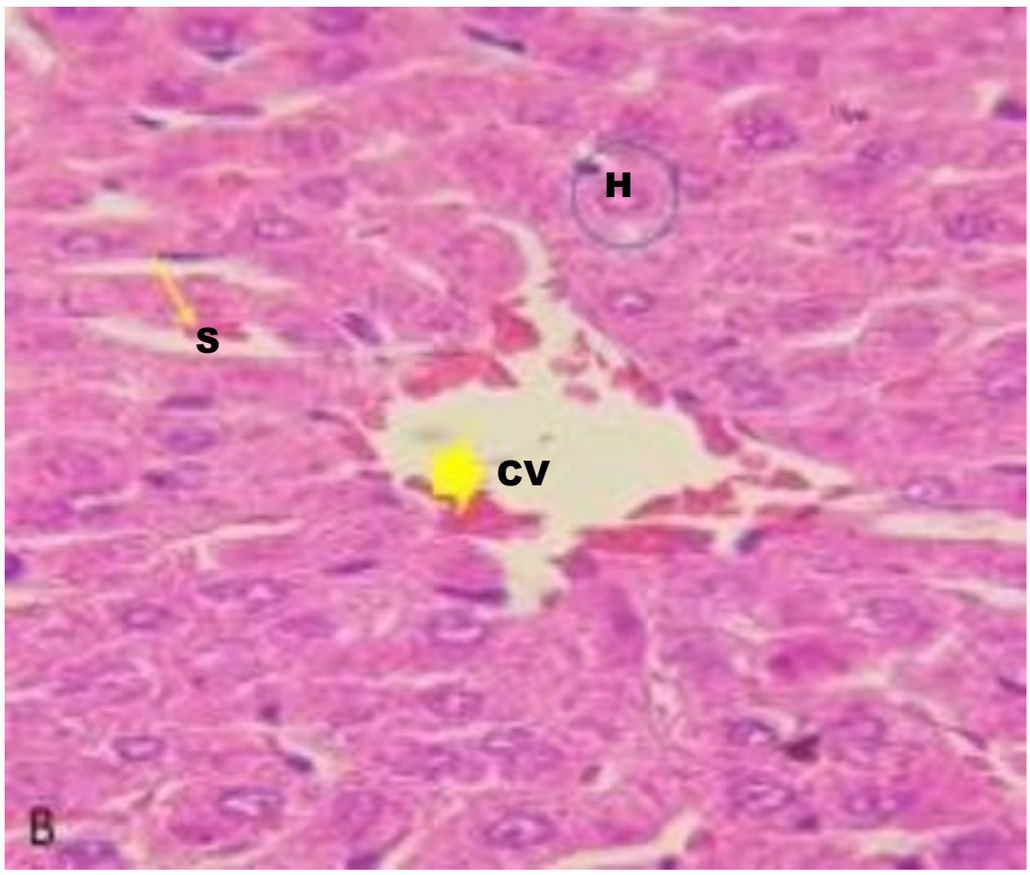

Plate 2: Section of rat hepatic tissue from the experimental Group B; Treated with 10mg/kg amlodipine showing irregularly distributed hepatocytes(H) on the hepatic plates, sinusoids(S) and slight congested central vein(CV).Haematoxylin and Eosin X 400

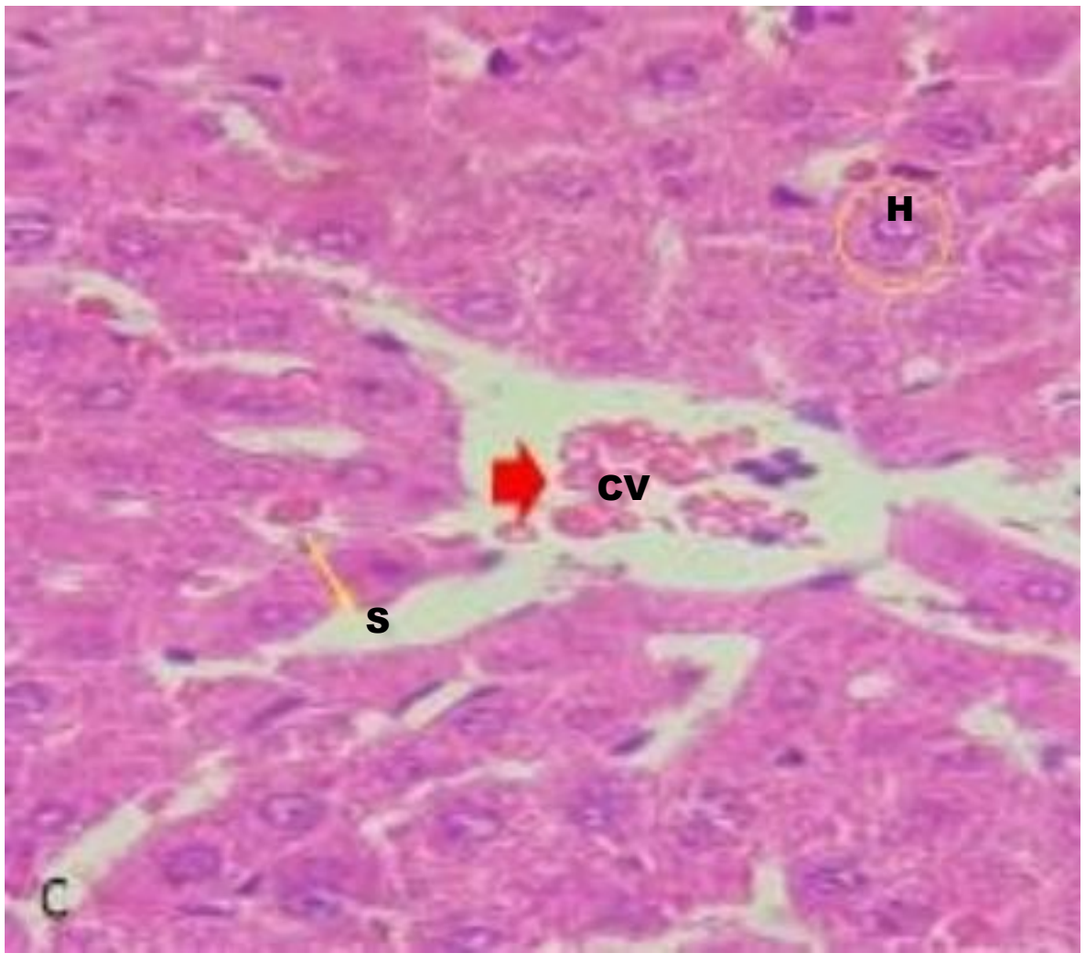

Plate 3: Section of rat hepatic tissue sample from the experimental Group B; Treated with 10mg/kg amlodipine shows irregularly distributed hepatocytes (H), congested central vein(CV) and dilated sinusoids(S).Haematoxylin and Eosin X 400

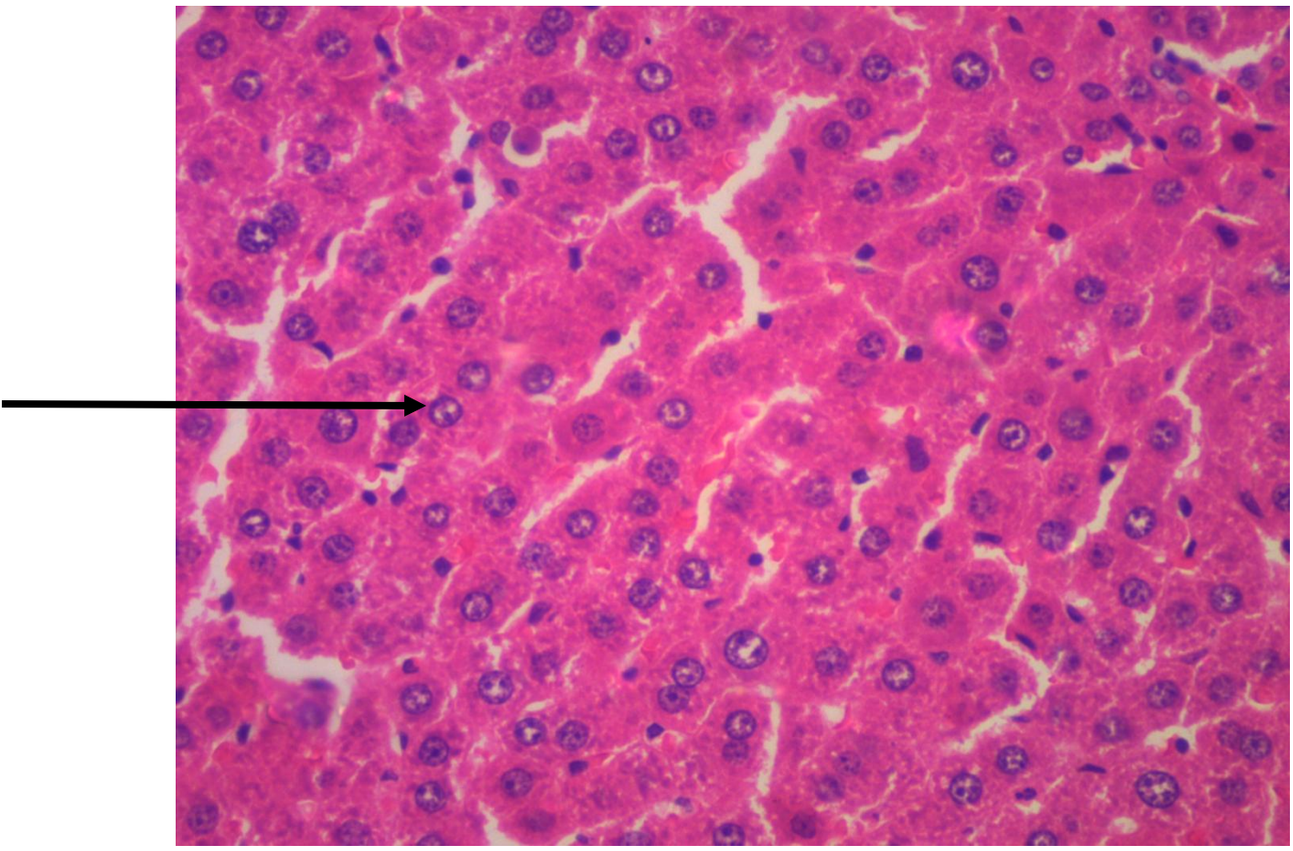

Plate 4 Section of rat hepatic tissue sample from the experimental Group C; Treated with 10mg/kg body weight of Telmisartan shows hepatocytes (arrow) with eosinophilic cytoplasm surrounding a centrally placed normochromic nuclei with indistinct nucleoli. FEATURES IN KEEPING WITH NORMAL HEPATOCYTES

Haematoxylin and Eosin X 400

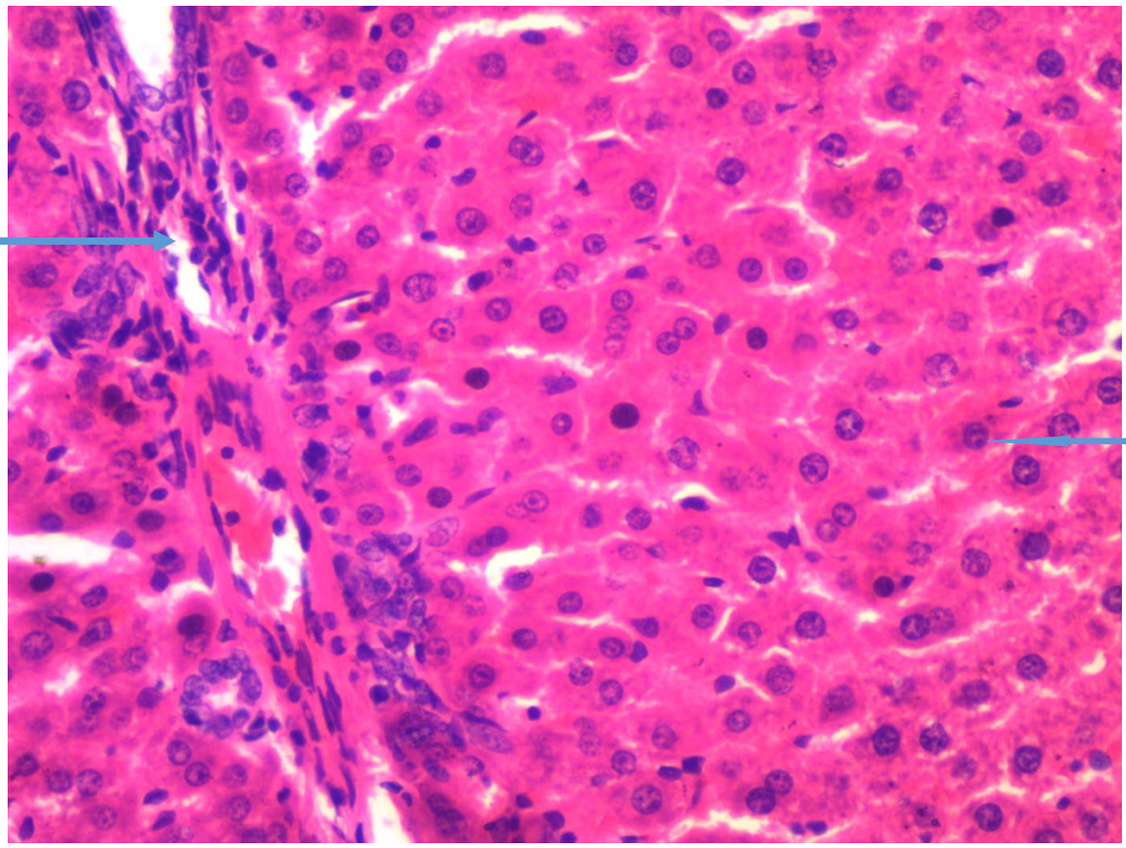

Plate 5:Section of rat hepatic tissue from the experimental Group C; Treated with 10mg/kg body weight of Telmisartan. see hepatocytes (thick arrow) with eosinophilic cytoplasm surrounding a centrally placed normochromic nuclei with indistinct nucleoli. Also present are some lymphocytic infiltrates around the portal triad. FEATURES IN KEEPING WITH NORMAL HEPATOCYTES

Haematoxylin and Eosin X

CHAPTER FIVE

DISCUSSION, CONCLUSION AND RECOMMENDATIONS

5.1 Discussion

Hypertension is a global health condition that has been increasing in prevalence around the world on an annual basis. Hypertension is a haemodynamic disorder, associated with a rise in peripheral vascular resistance, that can, in turn, lead to myocardial infarction, renal failure, strokes and death, if not identified early and treated effectively (Geleijnse *et al.,* 2023). Antihypertensive medications are the first line in managing high blood pressure. Some of this Antihypertensive drugs have been discovered to have negative impact on some vital internal organs. Patients with with liver conditions such as alcoholic liver disease (ALD) often suffer from high blood pressure and rely on antihypertensive treatment (Niaz *et al.,* 2018).

From the findings gotten from this research work, a significant increase in body weight was recorded in all groups of Amlodipine and Telmisartan treated animals. Hence, all treated animals

showed significant changes when compared with group A (hypertensive control) animals. The weight gained could be because of altered metabolism and decreased physical activity. Such as reduction in basal metabolic rate, reduction in the thermogenic response to meals, increased insulin resistance, and inhibition of lipolysis (Ohmori *et al.,* 2022). Another possible reason for the weight gained could be due to diminished exercise tolerance secondary to fatigue or dyspnea and decreased purposeless movements, also known as nonexercise-associated thermogenesis

In a similar study by Niaz *et al.,* (2018), using amlodipine and catopril, a significant ($P < 0.05$) increase in relative weight of the whole heart (15.06%), the left hepatic vein (19.87%), and the entire liver (30.51%) was observed in amlodipine compared to the control. Neither captopril nor amlodipine at doses of 200 and 400 mg/kg induced an increase in relative weight of the liver observed.

According to studies, antihypertensive drugs in the category of Calcium channel blocker such as Amlodipine, Nicardipine, Nifedipine Verapamil and Nisoldipine are known to increase weight in Hypertensive patients (Almas *et al.,* 2022). Pereira *et al* (2019), performed a similar research using 2 calcium channel blockers and obtained that the albino rats added significant weight from 15th to 18th weeks of the observation.

There was significant increase in weight among the control and the induced albino rats using telmisartan after few weeks. The body weight ratio was slightely increased after few weeks when compared to the control group. Angiotensin II receptor antagonists such as telmisartan taken to help control high blood pressure tend to cause a temporary increase in weight due to increase fluid. The body weights were also seen to slightly increased in similar findings reported by researchers experimenting on different animal models of hypertension (Raben *et al.,* 2022; Zhao *et al.,* 2017).

In plate 2 and plate 3, The microscopic examination of hepatic tissues from the albino rats in this research, demonstrated no obvious pathologic changes, including hypertrophy, and fibrosis, wall thickening hepatic atrophy and fibrosis, and vascular sclerosis in groups treated with Amlodipine.

A similar study by Andy *et al.,* (2022), demonstrated that the long-term use of amlodipine and 6 other drugs led to differing degrees of functional and pathological impairments in the kidneys and liver. Ramipril dopa were distinguished as drugs causing mild nephrotoxic effects, rilmenidine as causing moderate effects and amlodipine and clonidine as causing severe effects. This information indicates that clonidine and amlodipine should not be used in patients with glomerular cellularity, hyalinization, tubulo interstitial inflammation and tubular necrosis. They also reveal that hyalinization, tubulointerstitial inflammation and tubular necrosis are contraindications for rilmenidine. Methyldopa and ramipril should be used in a controlled manner in Kidney and the liver.

In plate 4 and plate 5, These characteristic changes were significantly attenuated by treatment with telmisartan. Histopathological examination showed no pathological glomerular, tubular, or blood vessel changes in groups treated with telmisartan during the weeks of the research

In this research, Telmisartan demonstrated to have higher hepatoprotective properties and a better drug to Amlodipin. Similar results were obtained by many researchers with discrepancies of negative and positive impact of antihypertensive drugs between the drugs used. Such as discrepancy regarding the weight gained or lost after antihypertensive drugs administration and histopathological changes in the vital internal organs of the body such as liver, kidney and heart (Singh and Ahluwall, 2021; Zilkens *et al.,* 2021; Aniagu *et al.,* 2019; Azizi *et al.,* 2022).

For instance, Almas et al., (2016), investigated the renal protective effect of nifedipine and efonidipine in streptozotocin (STZ)-induced spontaneously hypertensive rats (SHRs, 8 weeks of age). Diabetic SHRs were treated with 40 mg/kg/day of or efonidipine as controls for 16 weeks. Dosage of nifedipine or efonidipine was chosen after preliminary studies demonstrated that it showed moderate antihypertensive action (more than a 20% decrease in systemic blood pressure after treatment). In the diabetic SHR, the excretion of urinary albumin was increased and reached 4.41 ± 0.08 mg/day at 24 weeks. The levels of urinary albumin in the diabetic SHR after treatment with nifedipine were significantly less than those in the diabetic SHR at 24 weeks ($p < 0.01$). Levels of the ratio of creatinine clearance to body weight were significantly decreased in

the diabetic SHR after treatment with nifedipine. In light microscopy, the ratio of glomerular tufts to Bowman's areas was significantly decreased compared with those in the diabetic SHRs ($p < 0.05$). These findings suggest that nifedipine inhibits the development of albuminuria and glomerular enlargement in STZ-induced diabetic SHRs. There was no significant difference in the changes in antihypertensive or antialbuminuric effects between nifedipine and efonidipine. Thus, nifedipine, as well as efonidipine, may become a useful antihypertensive drug with a renal protective effect.

5.2 Conclusion

1) A significant increase in body weight was recorded in all groups of Amlodipine treated animals.

2) There was significant increase in weight among the control and the induced albino rats using telmisartan after few weeks

3) Amlodipine and Telmisartan treated albino rats had no histopathological changes observed during the cause of the research.

5.3 Recommendations

Hypertensive drugs could have negative impact on important systems in the body. Therefore, the thrust of public health policies should be primary prevention of hypertension. The long-term treatment with this combination could presents a beneficial effect on the reduction of Blood pressure, BPV, and the protection of end- in-depth study on the effect of these antihypertensive drug treatments on the antioxidant mechanisms involved as liver damage is highly recommended

5.4 Contribution to Knowledge

1. Therapeutic Effect: Long term therapy without the combination between amlodipine and telmisartan decreases the fibrotic changes associated with hypertension. Although the beneficial effects inInduced hypertension treatment, telmisartan and amlodipine can lead to some unexpected results like hepatocyte degeneration, hepatic tubular blockage and

inflammation**.**Telmisartan has been shown to be an effective antihypertensive agent at doses of 10–80 mg given

2. Histopathological Insight: This study has confirmed that Animal models have Over the years especially rats such as albino rats proven to be effective in histopathological studies. 60% of NIH extramural funding involves animal models, and approximately 80% to 90% of these are mouse models of human disease. It is critical to translational research that animal models are accurately characterized and validated as models of human disease. Pathology analysis, including histopathology, is essential to animal model studies by providing morphologic context to in vivo, molecular, and biochemical data; however, there are many considerations when incorporating pathology endpoints into an animal study. Mice, and in particular genetically modified models, present unique considerations because these modifications are affected by background strain genetics, husbandry, and experimental conditions. Comparative pathologists recognize normal pathobiology and unique phenotypes that animals, including genetically modified models, may present. Beyond pathology, comparative pathologists with research experience offer expertise in animal model development, experimental design, optimal specimen collection and handling, data interpretation, and reporting.

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APPENDIX

ETHICAL APPROVAL