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EVALUATION OF *CASCABELA THEVETIA* BARK EXTRACTS FOR HEPATOPROTECTIVE ACTIVITY AGAINST CCL_4 AND PARACETAMOL INDUCED HEPATOTOXICITY IN ALBINO RATS

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ABSTRACT

Cascabela thevetia bark is a poisonous plant native throughout Mexico and in Central America, and cultivated widely as an ornamental. It is a relative of Nerium oleander, giving it a common name yellow oleander, and is also called lucky nut in the West Indies. Therefore evaluated for safety and potential hepatoprotective activity in rodents. The extract (200, 400 mg/kg, p.o) administered to rats and mice over a 24-hour period did not show any signs of toxicity or mortality, suggesting that the oral LD50 of the hydroalcholic extract (in rats and mice) was beyond 400 mg/kg. Daily administration (200, 400 mg/kg; p.o) of extract for 9 days did not cause any changes in behavior or alterations in hematological parameters of the animalsthe results indicate that the hydroalcholic extract of Cascabela thevetia bark is toxic and may exhibit hepatoprotective activity at lower doses by enhancing antioxidant protection in the cell bioactivation of hepatotoxic agents.

KEYWORD: Hepatoprotective Activity, Cascabela Thevetia, Silymarin.

General

Your liver is your body's largest solid organ. On average, Weight is around 3 pounds, the liver is the second largest organ in the body; only the skin is big and heavy. The hepatic acts many basic functions related to absorption, metabolism, immunity, and the storage of beneficial within the body.

Fortunately the liver has an incredible capacity for regeneration of dead or damaged tissues,an organ only found
in vertebrates, detoxifies various metabolites, synthesizes proteins, and produces biochemicals necessary for digestion.[1,2,3]

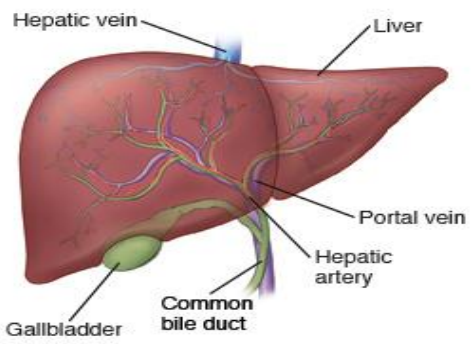


Figure 1.1 Structure of liver.

1.2 Anatomy of the Liver

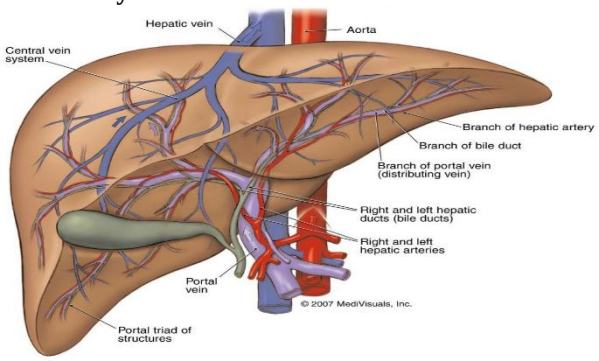


Figure 1.2: Structure of anatomy of liver

1.2.1 Gross Anatomy

The liver is a roughly triangular organ that extends across the entire abdominal cavity just inferior to the diaphragm. The mass of most liver is located on the right side of the body. The hepatic is divided into two parts when seen from above – one right and left lobe, and four parts are seen from the bottom (left lobe, right lobe, caudate and quadrate lobes).[4]

The falciform ligament, divides the liver into a left and right lobe. From the bottom, two additional lobes are located between the right and left lobes, front of each other. A line can be imagined to walk on the left side of

vena cava and in order to move forward to divide the liver and gallbladder into two halves.[5] This line is called "Cantlie's line"

Other anatomical landmarks include the ligamentum venosum and the round ligament of the liver (ligamentum teres), which further divide the left side of the liver in two sections. An important anatomical landmark, the porta hepatis, divides this left part into four segments, which can be started with the caudate lobe in an arbitrary manner. From this parietal view, seven sections can be seen from this family scene, because the eighth segment is visible view.[6]

1.2.2 Bile Ducts

The tubes transporting bile through the liver and gallbladder are known as bile ducts and are known as bile tree. Bile produced by liver cells gets drained into micro canals which is called bile canaliculi. The countless bile canaliculi joined several large bile ducts found in the whole the hepatic.

These bile ducts next join to form the larger left and right hepatic ducts, which carry bile from the left and right lobes of the liver. Those two hepatic are involve in making normal hepatic canal which remove all the bile away from the liver. Biliary drainage is performed with a tube or catheter (called a biliary drain, biliary stent or biliary catheter) by a surgeon or, commonly, an interventional radiologist.[7] It can be used to rid of obstruction in the bile duct, either as permanent or temporary solution before some treatment like surgery. The drain can be placed percutaneously through the liver, with the procedure then being called percutaneous transhepatic biliary drainage (PTBD).[8]

1.2.3 Blood Vessels

The blood **v**essels are the part of the circulatory system, and microcirculation, that transports blood throughout the human body.[9] Spleen, stomach, pancreas, gallbladder, and blood traveling to the intestines pass through the capillaries in these organs and the hepatic portals are collected in the vein. The liver portal vein then transmits this blood to liver tissues where the contents of the blood are divided into smaller vessels. There are three major types of blood vessels: the arteries, which carry the blood away from the heart; the capillaries, which enable the actual exchange of water and chemicals between the blood and the tissues; and the veins, which carry blood from the capillaries back toward the heart. The word vascular, meaning relating to the blood vessels, is derived from the Latin vas, meaning vessel. A few structures (such as cartilage and the lens of the eye) do not contain blood vessels and are labeled. Except liver tissues, blood is collected in liver veins. Which leads to Vena Cava and comeback to the heart.

1.2.4 Lobules

The internal structure of the hepatic is composed of approximately 100,000 small hexagonal functional units is called as lobules. Every lobule has a central vein surrounded by 6 liver portal veins and 6 liver arteries. These blood vessels are linked to many capillary-like tubes which are called sinusoids, which are expanded to meet the portal central nerve such as the spokes from the portal nerves and arteries on a circle. A hepatic lobule is a small division of the liver defined at the histological scale. It should not be confused with the anatomic lobes of the liver (caudate lobe, quadrate lobe, left lobe, and right lobe), or any of the functional lobe classification systems.

The hepatic lobule is a building block of the hepatic parenchyma in which a portal tried, occurs, hepatocytes are arranged in linear wires between a capillary network, and a central vein.

The two-dimensional microarchitecture of the hepatic can be seen from many different perspectives.[10]

1.3 Physiology of the Liver

1.3.1 Digestion

In the human digestive system, food enters the mouth and mechanical digestion of the food starts by the action of mastication (chewing), a form of mechanical digestion, and the wetting contact of saliva. Saliva, a liquid secreted by the salivary glands, contains salivary amylase, an enzyme which starts the digestion of starch in the food; the saliva also contains mucus, which lubricates the food, and hydrogen carbonate, which provides the ideal conditions of pH (alkaline) for amylase to work. After passing through chew and starch digestion, the food will be in the form of a small, round slurry mass called a bolus. It will then travel down the esophagus and into the stomach by the action of peristalsis. Gastric juice in the stomach starts protein digestion. Gastric juice mainly contains hydrochloric acid and pepsin. As these two chemicals may damage the stomach wall, mucus is secreted by the stomach, to make it available a slimy layer that acts as a protection against the damaging effects of the chemicals. Protein digestion at the same time, mechanical mixture is done by peristalsis, which is waves of muscular contractions that move along the stomach wall. This make free digestion of the food mass with more enzymes.

After some time (usually 1–2 hours in humans, 4–6 hours in dogs, 3–4 hours in house cats), the resulting thick liquid is called chyme. When the pyloric sphincter valve opens, chyme enters the duodenum where it mixes with digestive enzymes from the pancreas and bile juice from the liver and then passes through the small intestine, digestion in which release. When the chyme is fully digested, it becomes absorbed in the blood. About 95% of the absorption of nutrients become in the small intestine. Water and minerals are brought back to the blood in the colon (large intestine) where the pH is

slightly acidic about 5.6 ~ 6.9. Some vitamins, such as biotin and vitamin K (K_2MK7) produced by bacteria in the colon are also absorbed into the blood in the colon. Waste material is eliminated from the rectum during defecation.[11]

1.3.2 Metabolism

Metabolism is usually divided into two categories: catabolism, the breaking down of organic matter for example, the breaking down of glucose to pyruvate, by cellular respiration, and anabolism, the building up of components of cells such as proteins and nucleic acids. Usually, breaking down releases energy and building up consumes energy.

The chemical reactions of metabolism are organized into metabolic pathways, in which the sequence of enzymes, a chemical is converted into another chemical through a series of steps. Enzymes are crucial to metabolism because they allow organisms to drive desirable reactions that require energy that will not occur by themselves, by coupling them to spontaneous reactions that release energy. Enzymes act as catalysts that allow the reactions to proceed more rapidly. Enzymes also allow the regulation of metabolic pathways in response to changes in the cell's environment or to signals from other cells.

The metabolic system of a particular organism determines which substances it will find nutritious and which poisonous. For example, some prokaryotes use hydrogen sulfide as a nutrient, yet this gas is poisonous to animals.[12] The speed of metabolism, the metabolic rate, affects how much food the food needs to eat, and also affects the food.

A striking facility of metabolism is the similarity to original metabolic pathways and components, which are even among different species.[13] For example, the set of carboxylic acids that are best known as the intermediates in the citric acid cycle are present in all known organisms, being found in species as diverse as the unicellular bacterium Escherichia coli and huge multicellular organisms like elephants.[14] These striking similarities in metabolic pathways are likely due to their early appearance in evolutionary history, and their retention because of their efficacy.[15,16]

1.3.3 Detoxification

As blood from the digestive organs passes through the hepatic portal circulation, the hepatocytes of the liver monitor the contents of the blood. It's the physiological or medicinal removal of toxic substances from a living organism, including the human body, which is mainly done by the liver. It can refer to the period of withdrawal during which an organism returns to homeostasis after long-term use of an addictive substance.[17,18] In medicine, detoxification can be achieved by decontamination of poison ingestion and the use of antidotes as well as techniques such as dialysis and (in a limited number of cases) chelation therapy.[19,20]

Sense about Science, a UK-based charitable trust, determined that most such dietary "detox" claims lack any supporting evidence.[21,22,23]

1.3.3.1 Storage

The liver provides storage of many essential nutrients, vitamins, and minerals obtained from blood passing through the hepatic portal system. Glucose is transported to hepatocytes under which the effect of hormone insulin and stored in polysaccharide glycogen. Hepatocytes expand as well and store fatty acids from digestive triglycerides. The storage of their nutrients make free the liver to maintain the homeostasis of blood glucose. To provide continuous supply of these essential substances to our liver body tissues, Vitamin A, D, E, K, and B12, and minerals also store vitamins and minerals such as iron and copper.[24,25,26,27,28]

1.3.3.2 Production

The liver is liable for the manufacture of many important protein components of blood plasma like fibrinogen, prothrombin and albumins, prothrombin and fibrinogen proteins are coagulation factors involved in the formation of blood clots. Albumins are proteins that preserve the isotonic a of the blood so that cells of the body do not get water or lose in the presence of fluid in the body.

1.4 About the Liver

Liver is a body weight of 1.5 kg on the right side of the body. This is clearly the largest organ and a major part of the human body, which is specialized by its muddy red color. It is strategically the first port of entry from the process of digestion before nutrients leave for the rest of the body. It is the only organ in the human body that can regenerate unless struck by disease.

Essential Functions of the Liver are

- Using Food to make chemicals for essential functions of the body
- Processing drugs to modified forms that are easily absorbed
- Manufacturing essential materials
- Nutrients Storage for various processes
- Detoxification and immersion of substances which are no longer required by the body.

The liver's key role as a member of the human body

- Production of Energy instantly
- Making proteins for body building and tissue repair
- Vitamins, minerals, and sugars storage for various functions
- Regulate fat transport across the body
- Regulate Blood fatigue activities
- Regulate the levels of chemicals and medicine in the blood
- Hormone balance regulate

- Help digestion with production of bile
- Helps eliminate excess cholesterol levels
- Deactivation of toxic substances
- Metabolism of alcohol
- A vital organ in blood formation before birth
- Helping to resist infection
- Regenerating its own damaged tissue
- Resisting infections by helping to remove bacteria from blood
- Cleansing Blood by discharging waste products

1.5 The Liver and Blood Flow

1.5.1 Systemic circulation: Oxygenated blood that has returned from the lungs to the left ventricle of the heart is pumped to all of the tissues of the body.[29]

1.5.2 Pulmonary circulation: After arriving the tissues, blood is come back to the right side of the heart, from where it is pumped to the lungs and then come back to the left side of the heart and which carries deoxygenated blood away from the right ventricle of the heartreturns oxygenated blood to the left atrium and ventricle of the heart.[30]

1.5.3 Portal circulation: Blood from the gut and spleen flow to and through the liver before returning to the right side of the heart. The portal vein and hepatic arteries form the hepatic dual blood supply. About 75% of liver blood flow is taken from the portal vein, while the rest is with the hepatic arteries.[31] Blood flows into the liver vein, which goes to the less vena cava on the right side of the heart. The hepatic get some blood directly from the heart through the liver artery. In the stomach, esophagus, rectum, small intestine and, portal diffusion and nerves of the systemic diffusion are added. Under normal circumstances, there is no back flow from the portal circulation into the systemic circulation.

1.6 Biochemical Functions of the Liver

The hepatic display several biochemical functions. Blood clotting factors are synthesized in the hepatic. Albumin, the major protein in the blood are synthesized as well and secreted with the hepatic. The modification and/or synthesis of gall components also occurs in the hepatic. Many of the body's metabolic functions mainly in the hepatic which involves the conversion of cholesterol metabolism and glucose into proteins and fats. The liver is also where most drugs and toxins, including alcohol, are metabolized.

1.6.1 Bilirubin Secretion

The hepatic is the site of the build. Bile contains fatty acids, bile salts, bilirubin, cholesterol and other compounds. The bile organ are synthesized and modified in hepatocytes (the main cell type in the liver) and hidden in small bile ducts within the hepatic. These small bile ducts form a branch network of progressive larger tubules which eventually from a common bile duct, which bind in the small intestine. Bilirubin is a yellow pigment that originated from old red blood cells. Bilirubin is taken by hepatocytes from the blood, in a hepatocytes, a water is modified in a soluble from and is secreted in the bile.The bileproduced in the liver is collected in bile canaliculi, small grooves between the faces of adjacent hepatocytes. The canaliculi radiation on the edge of hepatic lobule, where they merge to from bile nozzles. Within the liver, these ducts are termed intrahepatic bile ducts, and once they exit the liver they are considered extra hepatic. The intrahepatic ducts eventually drain into the right and left hepatic ducts, which exit the liver at the transverse fissure, and merge to form the common hepatic duct. The cystic duct from the gallbladder joins with the common hepatic duct to form the common bile duct.[32]

1.7 What Is Liver Disease

Liver disease (also called hepatic disease) is a type of damage to or disease of the liver. Liver disease is serious damage to the liver, usually caused due infection that can be viral or non-viral, abnormal changes through development of processes like tumor, changes or abnormalities in the metabolic process or naturally through a congenital process.

Diseases of the liver can also be categorized by the effect. Hepatitis is inflammation of the liver, scarring and progressive cell death in cirrhosis, stones develop and block, change affect the fatty liver and cancer caused by genetic defects, lifestyle, environment, or other diseases. All these prevent vital functions of the liver and may cause a build-up of damaging substances to the liver itself that could even be a threat to life.[33]

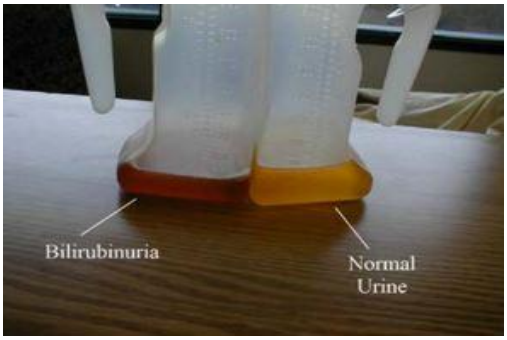


Figure 1.3: Picture Of Bilirubinuria And Normal Urine.

1.7.1 Signs and Symptoms

- Fatigue
- Loss of appetite
- Nausea
- Vomiting
- Joint pain
- Stomach discomfort or pain
- Nose bleeds
- Abnormal blood vessels on the skin (spider angiomas)
- Itchy skin

- Weakness
- A low sex drive

More serious symptoms include

- Yellowing of the skin and eyes (jaundice)
- Confusion and difficulty thinking clearly abdominal swelling (ascites)
- Swelling of the legs (edema)
- Impotence
- Gynecomastia (when males start to develop breast tissue
- Enlarged Liver (hepatomegaly
- Dark urine
- Pale-Colored Stools

If you're experiencing any of the symptoms mentioned above, see your doctor immediately [34, 35, 36].

1.7.2Detecting liver disease

1.4 Figure: Picture of normal and jaundice.

1.7.2.1Jaundice

Jaundice, also known as icterus, is a yellowish or greenishpigmentation of the skin and whites of the eyes due to high bilirubin levels.[37,38] Diagnosis of a liver disease considers history, of the patient, symptoms, physical examination, laboratory testing, often a radiological investigation and biopsy are conducted when experiencing. A Hepatologist will be the specialist to make the most reliable diagnosis and recommendations.

commonly associated with itchiness.[39] The feces may be pale and the urine dark.[40] Jaundice in babies occurs in over half in the first week following birth and in most is not a problem.[41,42] If bilirubin levels in babies are very high for too long, a type of brain damage, known as kernicterus, may occur.[43]

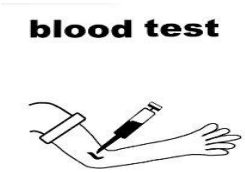
Three types of tests are often used to detect liver disease; these tests measure the levels of specific enzymes, bilirubin, or protein present as part of assessing the liver function. A test sample is usually a blood sample. This sample is extracted from the body using a syringe.

1.7.2.2 Enzymes

Are proteins that help cells do their work. When cells are injured, enzymes tend to leak into the blood stream to produce higher-than-normal levels. All liver enzymes are measured by the amounts in the serum (blood), which is why they may be referred to as Serum ALT, AST, ALP. Three common enzymes which detect liver disease.

➢ **Alanine aminotransferase (ALT)** – an enzyme found mainly in hepatic cells. Raised ALT levels can be due to loss or death of a liver causing leakage in the blood stream. All forms of hepatitis damage the liver cells where the doctor may suspect liver disease from a raised ALT level. Its severity, however, will be subject to other tests as part of confirmation. Reduced glucose tolerance, and increased free fatty acids and triglycerides. Bright liver syndrome (bright liver on ultrasound suggestive of fatty liver) with raised ALT is suggestive of metabolic syndrome.[44]

➢ **Aspartate aminotransferase (AST)** – another enzyme found in the liver and a few other places, particularly the heart and other muscles. It is less specific for liver disease alone as a raised AST could also be one early indication for a heart attack. Usually where the liver is inflamed, raised ALT and AST levels are in the ratio of 1:1. However, in specific diseases such as alcoholic hepatitis or liver shock, AST levels could be higher than blood ALT levels. some pregnancy conditions such as hyperemesis gravidarum, AST 73 IU/L, 66 IU/L in pre-eclampsia, can reach 81 IU/L in HELLP syndrome.[45]



➢ **Alkaline phosphatase (ALP)** – an enzyme respective to the bile ducts; often rise when they are blocked. Alkaline phosphatase is also produced by the kidneys, intestine, placenta and bone. Increased levels of ALP in the presence of normal or moderately elevated AST and ALT are suggestive of an obstruction in the bile duct or a bile duct disease such as primary biliary cirrhosis or primary sclerosing cholangitis. ALP elevated can also be an indication of a bone disorder as it is also produced in bones.low levels of ALP is found in hypothyroidism, pernicious anemia, zinc deficiency, and hypophosphatasia.[46]

➢ **Gamma-glutamyltranspeptidase (GGT)** - another enzyme produced in the bile ducts which may be high in the blood with ALP in patients with bile duct diseases GGT is very sensitive test. There is also the possibility of increased GGT due to drugs and alcohol, especially if there is no liver damage or swelling in heavy drinkers. In pregnancy conditions GGT activity is reduced in 2nd and 3rd trimesters. In hyperemesis gravidarum, the price GGT level can reach 45 IU/L, 17 IU/L pre-eclampsia, and 35 IU/L in HELPP syndrome.[47]

1.7.3 *Bilirubin*

Waste product made from destruction of old red blood cells. It is a yellow compound that causes the jaundice and dark yellow coloured urine when present in increased amounts. Bilirubin is removed from the blood by the liver which is chemically modified by the processing it and make it cryptic in the form of bile.

Bilirubin is a yellow compound that occurs in the normal catabolicpathway that breaks down heme in vertebrates. This synthesis is an essential process in the extraction of waste products of the body, which is produce from the destruction of the old red blood cells. First the hemoglobin gets stripped of the heme molecule which thereafter passes through various processes of porphyrin catabolism, depending on the part of the body that has break. For example, the molecules emitted in the urine are different from those in the stools.[48] Tests for bilirubin are

- Total bilirubin measures all the bilirubin in the blood (direct + indirect)
- Conjugated or direct bilirubin - measures a form produced in the liver
- Un-conjugated or indirect bilirubin- measures an indirect form of bilirubin that was not converted to the ligament conjugated form.
- A Variation in the direct and indirect bilirubin can be an indicators for liver disease
- increased production
- decreased uptake by the liver
- decreased conjugation
- decreased secretion from the liver
- due to blockage in the bile duct

1.7.4 Protein tests

1.7.4.1 ***Albumin*** – explain that liver is synthesizing this protein. Low albumin levels are suggest bad liver function. Chronic liver diseases that are compensated may show normal albumin levels. The levels of albumin are common in cirrhosis or where significant liver damage exist. Low levels of albumin may also be sign of other diseases such as malnutrition and some kidney disorders. A number of blood transport proteins are evolutionarily related, including serum albumin, alpha-fetoprotein, vitaminD-binding protein and afamin.[49,50,51]

1.7.4.2 ***Serum Protein electrophoresis*** – it is a test where the principle proteins in the serum differ in an electric field to determine concentrations. The four major types of serum proteins are albumin, alpha-globulins, beta-globulins and gamma-globulins. Serum protein electrophoresis is a useful test for patients with liver diseases as it can give the physician several diagnostic possibilities. For instance: in cirrhosis the albumin can be decreased but the gamma-globulin level may be elevated. High gamma-globulin levels can also be found in types of autoimmune hepatitis while low alpha-globulin level may suggest metabolic disease such as alpha-1-antitrypsis deficiency.The most common indications for a serum protein electrophoresis test are to diagnose or monitor multiple myeloma, a monoclonal gammopathy of uncertain significance, or check an inconsistency between a low albumin and relatively high total protein. There are also symptoms of unstable bone pain, anemia, proteinuria, kidney dfficiency, and hypercalcemia, many myeloma, and sign of Serum Protein electrophoresis.[52]

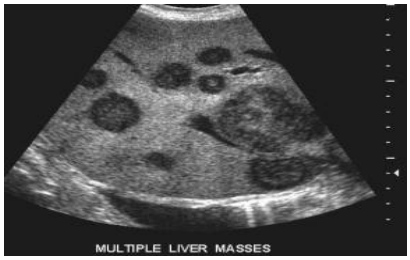
1.7.4.3 ***Prothrombin time (PT)***- Factors needed for blood clotting are made in the liver. In cases where the function of the liver is abnormal, the secretion of synthesis these factors in the blood decreased. PT is a test where the factor performed by the liver are found less in the blood, then the knee length becomes longer. Compensation is not reduce in chronic liver diseases, unless the liver cirrhosis or stage of significant damage reaches the slaughter factor. An elevated PT can also be seen in acute liver diseases where severe liver damage can occur after the recovery of the patient. PT time can also be extended for a long time by medicines in vitamin deficiency and warfarin (which is used as anti-congestants) and other non-liver diseases.Blood is drawn into a test tube containing liquid sodium citrate, which acts as an anticoagulant by binding the calcium in a sampleThe blood is mixed, then it is concentrated to isolate the blood cells separated from the plasma (because prothrombin time is usually measured using blood plasma). In newborns, a capillary whole blood specimen is used.[53]

1.7.4.4 ***Platelet count***- These are the smallest units of blood cells that are involved in clotting In some individuals with liver disease, the spleen increases because blood flow in the liver is bad. After the development of cirrhosis, the calculation of platelet falls, however, in addition to liver diseases, the number of platelets in disorders can be abnormal.Platelets are found only in mammals, whereas in other animals (e.g. birds, amphibians) thrombocytes circulate as intact mononuclear cells.[54]

1.7.3 What types of imaging are used to detect the severity of a liver disease

Imaging is important for accurate diagnosis on various biliary tract diseases and for diagnosing focal liver lesions such as tumours. In diagnosing diffuse hepatic diseases such as cirrhosis or hepatitis,this damage is characterized by the replacement of normal liver tissueby scar tissue.[55]

1.7.3.1 Transabdominal Ultrasound- It is traditionally done throughout the stomach. The duration of fasting may be required for preparation for ultrasound. This gall system is particularly the most expensive, safe and quite sensitive for bile bladder imaging. It is often chosen as a process of choice for screening pathologic abnormalities and makes a difference between intrahepatic (which is within hepatic cells and can be managed medically). And (can be managed in surgery) Due to the detection of the people of the liver as well as the jaundice. On such ultrasound, kidneys, pancreas and blood vessels can also be seen. Generally, presence of intestinal gas or obesity can obscure visibility.



1.5 Figure: Picture of ultrasound.

Transbodominal ultrasound can detect centered liver lesions (1 cm in diameter) more precisely than spreading diseases (for example, fatty liver, cirrhosis).Generally, cysts is free rasonance; concrete wounds (eg, tumors, boils) that are **echogenic** (can reflect high-frequency sound waves which allows imaging by ultrasound techniques). ultrasound is used for cleaning, mixing, and to accelerate chemical processes. Animals such as bats and porpoises use ultrasound for locating prey and obstacles.[56] Scientist are also studying ultrasound using graphenediaphragms as a method of communication.[57]

1.7.3.2 Carcinoma is a type of cancer that develops from epithelial cells.Non-specific solid also appear as mass. Ultrasound is used to screen for hepatocellular carcinoma in high-risk patients (people with old hepatitis B).This ability to localize focal lesions can permits ultrasound-guided aspiration and biopsy.[58]

1.7.3.3 Doppler ultrasound is medical ultrasonographythat employs the Doppler effect to generate imagingof the movement of tissues and body fluids(usually blood) is a noninvasive method that assesses direction of blood flow and patency (the limit of any obstruction) of the major blood vessels around the liver. These are the portal vein and hepatic artery.70% of the blood and nutrients are supplied to the liver is through the portal vein and 30% through the hepatic artery. The portal with Doppler Ultrasound Collateral Flow can reveal evidence of hypertension, assesses the patency of liver shunts (for example, surgical portocaval, percutaneous transhepatic), and reveal hepatic artery thrombosis after liver transplantation is. It can detect any unusual vascular structures. Most patients with cirrhosis recommend a Doppler Ultrasound.[59]

1.7.3.4 Computerized Tomography (CT) – It is often used to refer to x-ray (CT) because it is the most commonly known form. But, many other types of (CT) are present, such as positron emission tomography (PET) and single-photon emission computed tomography (SPECT). X-ray tomography, a predecessor of CT, is one form of radiography, along with many other forms of tomographic and non-tomographic radiography. It is usually used to identify hepatic masses, especially small metastases. It accuracy is about 80%. Unlike an intravenous (IV), a CT is perfect for the detection of carvenous (deep-set) hemangiomas of the liver, as well as seprating from from other stomach paople. Unlike an ultrasound, neither obesity nor intestinal gas can nor intestinal gas can cloud a CT image.[60,61]

1.7.3.5 Magnetic Resonance Imaging (MRI)MRI was originally called 'NMRI' (atomic magnetic resonance imaging) and is a form of NMR, although to avoid negative associations with the word briefly the use of atom was dropped. It consists of imaging blood vessels (without using a contrast dye) and hepatic tissues. It is an expensive technique where its indications are still evolving. MRI fatty liver-like circulation is better than CT and ultrasound to diagnose liver diseases and hem ochromatosis and for clarifying some focal defects such as hemangiomas. MRI can expose blood flow and supplemental Doppler ultrasound and CT angiography to diagnose any vascular abnormalities and to perform vascular mapping prior to liver transplantation.[62]

1.7.3.6 Magnetic Resonance Cholangiopancreatography (MRCP). is a medical imagingtechnique that usesmagnetic resonance imaging to visualize the biliary and pancreatic ductsin a non-invasive manner.[63] This procedure can be used to determine if gallstones are lodged in any of the ducts surrounding the gallbladder. It was introduced in 1991. MRCP is more sensitive than CT or ultrasound in diagnosing common bile duct abnormalities, particularly stones. Its images are comparable to an ERCP and percutaneous transhepatic cholangiography, which are more aggressive. MRCP is a useful screening tool where the bile disorder is suspected and it is normal step before going to therapeutic ERCP.[64]

1.7.3.7 Endoscopic Retrograde Cholangiopancreatography (ERCP) ERCP is mainly used to diagnose and treat conditions of the bile ducts and main pancreatic duct.[65] It connects endoscopy through the second part of the Duodenum, which imaging the opposite of bile and pancreatic ducts. ERCP is the procedure of choice when bile duct stones are susceptible but not found on less aggressive tests. This test is especially valuable for the diagnosis of lesions of convertible biliary lesions, which causes persistent jaundice (for example, stone, hardening, crystallization of oddi dysfunction). In addition to providing excellent images of biliary tract and pancreatia, the ERCP reveals some of the upper GI tracts. This process allows for biopsy stone extraction such as biopsy and other intervention procedures.

.**1.7.3.8 Percutaneous transhepatic cholangiography (PTC):** In PTC the liver puncture is included with a needle along the needle under fluoroscopic or ultrasound guidance (a process involving a tube which is extracted to maximize the effect of the fluid process) Peripheral intrahepatic bile duct system. This is above normal hepatic canal where opposite material injection is given. A contrast medium is injected into a bile duct in the liver, after which X-rays are taken.PTC is highly

clinical for bile disease and may be medicinal as during the disintegration of the biliary system.[66]

1.7.3.9 Endoscopy An endoscopy (on the other side) is used in medicine to look inside the body. The endoscope used in the field of gastroenterology is a thin flexible tube that uses a lens or a miniature camera to see various areas of the gastrointestinal tract. When the procedure is done to examine certain organs such as bile ducts or pancreas, the organs are not seen directly, but indirectly through the injection of x-ray dye into bile duct.

The performance of an exam using an endoscope is referred by the general term endoscopy. Diagnosis through biopsies or other means and therapeutic procedures can be done.[67]

1.7.3.10 The Hepatic Venous Pressure Gradient (HVPG): The clinical measure of the pressure gradient between the HVPG WHHP and the free hepatic venous pressure, and thus the pressure slope between portal vein and infrared Vena Cava is estimated. An HVPG portal of ≥5 mmHg hypertension, and if the measurement exceeds 10 mmHg then it is called clinically significant portal hypertension. Above 12 mm Hg, variceal haemorrhaging may occur.[68] Although not widely performed, it is recommended to evaluate the reaction of treatment in people with chronic liver disease.[69] HVPG represents the gradient between portal vein and intra-abdominal vena cava pressure. The HVPG measurement is done rapidly, under conscious sedation and after monitoring for important signs (including heart rate, arterial blood pressure, digital oxygen saturation, and ECG).Under local anesthesia, central vein (for pressure monitoring) is punctured using the Seldinger technique.

There are four steps to the Seldinger technique

- Venepuncture is done with a introducer needle or trocar (a sharp hollow needle)
- A soft tipped guide is passed through the wire needle and the needle removed
- A cannula or dilator is passed over the guide wire
- Cannula or dilator is removed and catheter is passed on the wire using fluoroscopy so that its position can be established - The guide is removed

The Seldinger technique has been refined to help reduce complications such as infection, haemorrhage and accidental perforation during intervention into a vein. The advantage of this process is the probability of biopsy with the measurement of pressure in the portal vein. The use of Doppler ultrasound helps in reducing complications such as leakage, hematoma, and rarely, neural reaction, rupture of venous tract, or arterial arterial painter. The main measurement of the HVPG process is Free Hepatic Venus Pressure and Ways Hepatic Venus Pressure. The inter portal between the two measures will provide a pressure gradient in the liver to detect the severity of hypertension.

Grading of pressure

- Persons with normal portal pressure measurement between 1-5mmHg.
- A person with portal pressure above 5mmHg is classified as a hypertension in sub- clinical portal.
- Portal is rated equivalent to people with pressure and more clinically important portal hypertension than 10mmHg.
- Persons with a portal pressure over 12mmHg are at risk for a varaceal rupture.

1.8 Some Common Liver Disease Symptoms

While diagnosing liver disease, the doctor looks at the symptoms of the patient and conducts physical examination. In addition, the doctor may request liver biopsy, liver function test, ultrasound, or CT scan (computerized tomography scan). Some common liver disease symptoms include the following, each of which are described briefly below:

- Jaundice
- Cholestasis
- Liver enlargement
- Portal hypertension
- Ascites
- Liver encephalopathy
- Liver failure

1.8.1 Jaundice

Jaundice is a yellowish or greenishpigmentation of the skin and whites of the eyes due to high bilirubin levels. Urine is usually dark because of the bilirubin excreted through the kidneys. High levels of bilirubin can be attributed to inflammation of liver cells or other abnormalities or obstruction of bile ducts. Occasionally, due to the breakdown of large number of red blood cells, this can occur in newborns. Jaundice is usually the first sign of liver disease, and sometimes the only sign is.

1.9 RESULT AND DISCUSSION

1.9.1 FOR CCl_4

Liver is necessary organ for metabolic functions mainly in detoxification of toxicants.[70] CCl_4 is widely used for halogenated hydrocarbons which study most important intensively hepatoxicants.[71] CCl_4 can lead to severe necrosis and steatosis.[72] Liver damage by inducing CCl_4 are same as viral hepatitis.[73] The free radicals may react with O_2 to form CCL_3 trichloromethyl peroxyl radicals. When lipid attacks on the membrane of endoplasmic reticulum may be used to achieve lipid peroxide, long lasting results in cell necrosis and cell death.[74] Tagged increase in discharge of liver enzymes into the blood stream is often associated with massive necrosis of the liver. CCl_4 causes tagged height of serum enzymes. In general, CCl_4cause liver damage and levels of liver enzymes such as SGOT, SGPT, ALP, TP, Total albumin and also bilirubin discharge in circulation.[75,76] Administration of hepatotoxic CCl_4 high the serum levels of SGOT, SGPT, ALP and bilirubin also decreases total protein and total albumin significantly.[77,78] The increase in serum enzyme levels and bilirubin is responsible for

the structural damage of the liver, because they are cytoplasmic at the place of cellular damage and are in circulation.[79] In this study, After CCl_4 treatment various types of biochemical changes present which are observed in animal groups. Pretreatment with *C.T.* bark extract where the dose 200 and 400mg/kg (Group IV and V) also silymarin where the dose 100 mg/kg (Group III), resulted in significantly reduce the liver enzymes such as SGOT, SGPT, ALP& bilirubin also increased the total serum proteins and Total albumin when compared to rats treated with CCl_4 (Group II). The recovery is normal of serum enzymes caused by *C.T.* bark extractwas almost same as to that caused by silymarin in this study. Silymarin is a known as standard drug which are mainly use for hepatoprotection also called hepatoprotective compound.[79] Same results have also been reported.[80] The augmentation peroxidation can outgrowth in changes in cellular metabolism of the hepatic and more hepatic tissues whole cell abnormality and increase in cell death.[81] Administration of *C.T.* bark extract showed significantly lowered levels of their lipids toxic level compared to CCl_4 induced rats. Lipid-toxic levels occurring with bark removal administration suggest low impact of lipid membrane and therefore increase the safety against the injuries caused by CCL-4 induced liver.

1.8.2 For Paracetamol

Paracetamol is commonly used as an analgesic and antipyretic agent. Hepatotoxic doses of paracetamol deplenish the simple levels of liver glutathione, when NAPQI which bind covalently into cysteine groups on proteins to form 3-(cystein-S-yl) paracetamol adducts.[81] The glutathione protects to hepatocytes by combine with the reactive metabolite of paracetamol and their covalent binding to hepatic proteins.[82] In living organs, liver is agree to be highly susceptive agents. In which studies were considered high values in various types of enzyme activities like SGOT, SGPT, ALP, TB, TA and TP to assess clinical and experimental hepatic damage.[83] It was observed in this study that the animals treated with paracetamol resulted in significant liver loss due to high levels of serum markers. The increase in the SGOT is usually accompanied by high in the levels of SGPT, ALP, TB, which play role in the conversion of amino acids to keto acids.[84] Before treatment with hydroalcholic extract where the dose 200mg/kg and 400mg/kg, significantly dilute the high levels of the serum markers. The normal serum markers by hydroalcholic extract suggests that they are able to state the hepatocytes so as to defend the membrane integrity against paracetamol induced outflow of marker enzymes into the circulation. It can be considered as an expression of the functional improvement of hepatocytes, which may be caused by quick regenesis of parenchyma cells. Serum ALP and bilirubin levels which are related to liver cell damage. Rise in serum level of ALP is due to rise synthesis in presence of rising biliary pressure.[84]

1.10 CONCLUSION

The present investigation has been designed to study the hepatoprotective activity of *Cascabela thevetia* bark extracts in albino rats.

Our preparation was to develop Hepatoprotective preparation which could be safe without interactions and helpful in hepatoprotection, *Cascabela thevetia* barkextractshowed a dose dependent decrease in the levels of SGOT, SGPT, ALP and bilirubin whereas increase in the level of total protein and total albumin. Thus notifying the prominent significance of *Cascabela thevetia* barkin hepatoprotection against paracetamol & CCl_4 induced hepatotoxicity.

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