1. INTRODUCTION

In recent years, focus on plant research has increased all over the world and a large body of evidence has been collected to show immense potential of medicinal plants used in various traditional systems\(^1\). Medicinal plants constitute a source of both traditional and modern medicines. Natural compounds that reduce the chemical activating enzymes might be good candidates for protecting against chemically induced toxicity. Herbal medicines derived from plant extract, are increasingly being utilized to treat a wide variety of clinical diseases, with relatively little knowledge of their modes of action\(^2\). About 80% of the rural population depends on it as primary health care. With the introduction of sophisticated techniques, scientists started exploring the plant flora for active constituents. In 1803 morphine, a crystalline alkaloid was isolated from opium poppy papaver somniferum that still remains a priced drug in medicine as analgesic. Later on antitussive alkaloid, codeine was isolated and it proved the fact that a medicinal herb can exert different pharmacological activities due to the presence of number of constituents. Later on drugs like atropine, arecoline, muscarine and hyoscine were purified from the plant extracts for medicinal applications.

A large number of medicinal plants and their purified constituents have been shown beneficial therapeutic potentials. The oil and seed constituent of the plant Nigella Sativa contain active constituent
Thymoquinine possessing anti-oxidant activity\(^{3}\). To explore the possibility of using the traditional medicine with proper chemical and pharmacological profile, in recent days, there has been a large volume of work aimed at scientific validation of efficacy of herbal drugs used in the traditional medicine. The modern medicine does not have suitable answer for many conditions such as liver disorder, asthma, cardiovascular disorder etc. Herbal drugs are playing an important role in health care programmes world wide and there is a resurgence of interest in herbal medicines for treatment of various hepatic ailments \(^{4}\). The diverse culture of our country is a rich source of traditional medicines, many of which are of plant origin. Scientific data on such plant derivatives could be of clinical use \(^{5}\).

In Indian Flora a number of medicinal plants possess hepatoprotective potential \(^{6}\). About 600 commercial preparations are available all over the world, which were claimed for liver protection. In India about 33 patent herbal formulations are available for liver ailments and these preparations represent a variety of combination of 100 Indian medicinal plants belonging to about 40 families\(^{7}\). Some of the polyherbal formulation Liv-52, Livol, Jigrine etc. are available in Indian market for treatment of various liver diseases and verified for their anti-hepatotoxic effect against chemically induced liver damage in experimental animals\(^{8}\). In ancient system of medicines, herbal preparations are being used for treating duodenal ulcers \(^{9}\). In the last few years, efforts have been taken
to identify new anti-ulcer drugs from natural sources. Plants are the sources of certain known anti-ulcer drugs \(^{(10)}\).

Active phytoprinciples such as flavonoids, terpenoids and saponins are known to be responsible for diuretic activity \(^{(11)}\).

In view of growing demand of herbal drugs, the quality control assurance is primarily important. The standardized herbal extracts are considered to be more scientific than crude drugs. The commonly employed technique for removal of active substances from the crude drug is called extraction. Selection of the solvent is very critical in preparing the extract because the active constituents of plants have affinity for certain solvents.

Human beings used parts of plants, animals and minerals as sources of food and medicine from time immemorial. Primitive man discovered the nutritive and medicinal value of different plant materials by trial and error.

In recent years, development of new synthetic drugs and their introduction has become a very costly affair. Hence a lot of time and money can be saved if natural resources are channeled towards identification, extraction and isolation of plant constituents with a view to explore their medicinal value. It is a much cheaper method of treatment compared to the synthetic and semi synthetic drugs.

People will get the true benefit of phytochemical studies, of plants that are used as Folklore medicine only when pharmacological and
clinical investigations are also done. These studies reveal the importance of active ingredients that are responsible for the observed therapeutic activity. The active ingredients can also serve as lead molecules in designing drugs by synthetic means.

In the present work, the author has carried out phytochemical investigations for organ protection activity of *Boswellia serrata* Roxb plant extracts in view of its reputed medicinal uses in folklore. The author has tried to isolate and identify different constituents and study of different pharmacological actions was carried out. The parts of plants such as Bark, Leaves & Gum are investigated for this purpose.

1.1 LITERATURE FOR *BOSWELLIA SERRATA*

1.1.1 Taxonomy of *Boswellia serrata*

<table>
<thead>
<tr>
<th>Kingdom</th>
<th>Plantae-Plants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Division</td>
<td>Angiospermae</td>
</tr>
<tr>
<td>Class</td>
<td>Dicotyledoneae</td>
</tr>
<tr>
<td>Order</td>
<td>Geraniales</td>
</tr>
<tr>
<td>Family</td>
<td>Burseraceae</td>
</tr>
<tr>
<td>Genus</td>
<td>Boswellia</td>
</tr>
<tr>
<td>Species</td>
<td>Serrata</td>
</tr>
</tbody>
</table>
Plate 1.1: Boswellia serrata plant
Plate 1.2: Boswellia serrata bark

Plate 1.3: Boswellia serrata leaves
1.1.2: **Vernacular names:**

English: Sallaki guggul, Indian Olibanum tree

Hindi: Kundur, Salai, Salga

Bengali: Kundur, Salai

Gujarati: Dhup, Gugali

Kannada: Chitta, Guguladhuph

Malayalam: Parangi, Saambraani, Kunduruhkamaram

Tamil: Parangi, Saambraani, Kunturucam, Kunturu

Telugu: Phirangi, Saambraani, Anduga, Anduku

Sanskrit: Ashramoorti, Kundru, Shallkai

Plate 1.4: Boswellia serrata Oleo-Gum-Resinta
1.1.3: Botanical Description

It is a deciduous, medium sized tree which grows up to 12-15 feet in height. It has ash colored bark, peeling off in thin flakes, shoots are young and leaves pubescent. Leaves are long, opposite, sessile variable in shape ovate or lanceolate, obtuse flowers in auxiliary racemes, shorter than leaves. Calyx is pubescent outside. Petals long and ovate. Drupe is trigonous.

1.1.4: Geographical Distribution

The tree is common at the foot of the Western Himalayas and in dry hilly areas of Aravalli hill in Rajasthan, Vindhya & Satpura hill in Madhya Pradesh, Bihar, Orissa, Central peninsula regions, Andhra Pradesh, Assam, other eastern states and North Gujarat. In many places, the tree forms almost pure forests yielding an abundant supply of timber. Large forests of this tree occur in the Khandesh and Nagpur-Wardha Divisions in Maharashtra and Khandwa-Nimar Division in Madhya Pradesh and in Andhra Pradesh\(^ {12}\).

1.1.5: Traditional Uses

Traditionally the plant is reported to have anti-inflammatory astringent, anti-pyretic, anti-dysenteric, expectorant, diuretic, anti-ulcer. It is useful in fevers, convulsions, dysentery, bronchitis, asthma, cough,
stomatitis, syphilitic diseases, chronic laryngitis, jaundice and arthritis\(^{(13)}\).

1.1.6: PHYTOCHEMISTRY:

The oleo-gum-resin obtained from plant *Boswellia serrata* contains not less than 1.0% of total 11-keto-boswellic acid and acetyl-11-keto-β boswellic acid.

![KETO β-BOSWELLIC ACID](image)

Gum is mainly composed of arabinose with small amount of xylose and galactose. Gum also contains oxidizing and diastatic enzymes.

Salai guggal is an oleo-gum-resin containing essential oil, gum and resin which is valued for alleviating various human sufferings. It has been used for variety of therapeutic purposes\(^{(14)}\) such as in treatment of inflammation\(^{(15)}\), arthritis\(^{(16)}\), asthma\(^{(17)}\), colitis\(^{(18)}\), hyperlipidemia\(^{(19)}\), Psoriasis\(^{(20)}\), cancer\(^{(21)}\) and Crohn’s disease\(^{(22)}\).
The alcoholic extract of salai guggal was reported to possess anti-inflammatory and anti-arthritic activities in animals (23) due to the presence of boswellic acids, an ursane type compound with pentacyclic triterpenes.

Selective inhibition of leukotriene synthesis by boswellic acid (24,25) by inhibiting 5-Lox (26,27) was reported. Salai guggal contains 8-9% essential oil, 20-23% gum and resin 50% (28, 29).

The non-phenolic fraction of Boswellia serrata showed analgesic and Psychopharmacological effects (27). The drug also showed anti-diabetic activity in rats against streptozocin induced diabetes (30).

Essential oil is a mixture of monoterpenes, diterpenes and sesquiterpenes. Also phenoilc compounds and diterpene alcohol (serratol) is found in essential oil. Gum portion of the drug contains pentose and hexose sugars with some oxidizing and digestive enzymes. Resin portion of salai guggal is composed of pentacyclic triterpene acid of which boswellic acid is the active moiety (31). By fractionation of methanolic extract of Boswellia serrata resin together with boswellic acids a new lupane triterpene was isolated (32). This fraction on further purification with ethanol-hexane (1:1) yielded 3 alpha-hydroxy-lup 20 (29) ene-24-oic acid whose structure was confirmed by NMR and mass spectroscopy (33).
HPLC analysis of *Boswellia serrata* gum-resin yielded 12 different pentacyclic triterpene acids \(^{[34-36]}\). This method provides differentiation and standardization of gum-resin of different origin and gum-resin phytopharmaceuticals \(^{[37]}\).

A highly sensitive reverse phase HPLC method was developed for detection and analysis of boswellic acids in *Boswellia serrata* using acid mobile phase at 60 °C at 210 and 250 nm \(^{[38]}\).

Essential oil fraction from steam distillation of n-hexane extract of salai guggal on GC-MS analysis revealed 33 components \(^{[39, 40]}\) containing esters, alcohol, monoterpenes and diterpenes \(^{[41]}\).

A pure compound is obtained following alumina column chromatography with n-hexane and ethyl acetate as eluent. This compound on IR, NMR and Mass spectroscopy was found to be serratol \(^{[42]}\).

![Serratol](image)
**Boswellia serrata** oleo-resin on gas chromatography using poly-dimethyl siloxane/divinyl benzene fibre yielded 50 monoterpenes \(^{[43-47]}\).

GC-MS study of samples of methanolic extract of **Boswellia serrata** oleo-resin after trimethylation yielded 15 triterpenes \(^{[48]}\) i.e. boswellic acid, boswellic acid, 3-acetyl boswellic acid, 3-acetyl-boswellic acid, amyrin,3-epi- amyrin, 3 amyrin, lupeol, 3-epi-lupeol, amyrnonone, lupenone, 3 hydroxy lup-20en-24 oic acid and 3-0-acetyl hydroxy lup-20 en-24-oic acid on GC-MS studies.

Apart, three characteristics degradation products- 24-noroleana-3,12-diene (a), 24-norursa-3,12-diene (b) and 24-norlupa-3,20 diene (c) were also found \(^{[49]}\).

**1.1.7: Pharmacological actions of Boswellia serrata**

1. **Anti-inflammatory:** It was found that alcoholic extract of salai guggal possess anti-inflammatory activity in carrageenan induced paw oedema in rats and mice \(^{[50-53]}\). It was reported that the boswellic acids exert their action by inhibiting the synthesis of 5-Lox. They also inhibit topoisomerase, elasase and C-3 convertase enzyme \(^{[54]}\).

2. **Anti-arthritic activity:** **Boswellia serrata** reduced the infiltration of polymorphonuclear leukocytes in to knee joints and pleural cavity caused by bovine serum albumin (BSA) induced arthritis in rabbits \(^{[55-56]}\).
3. **Analgesic and Psychopharmacological activity:** The non-phenolic portion of *Boswellia serrata* showed sedative and analgesic effect \(^{(57-58)}\).

4. **Anti-asthmatic activity:** In a double blind placebo control clinical study, it was found that 300 mg. of alcoholic extract of salai guggal thrice daily for 6 weeks showed improvement in dyspnea, bronchi and number of attacks in 70% of asthma patients \(^{(59)}\).

5. **Immuno modulatory activity:** *Boswellia serrata* showed anti-anaphylactic and mast cell stabilizing activity \(^{(60,61)}\).

6. **Crohn’s disease:** *Boswellia serrata* was found to be superior on efficacy and safety aspects compared to masalazine, which is the drug commonly used for treating crohn’s disease \(^{(62)}\).

7. **Anti-diarrhoeal activity:** *Boswellia serrata* was found effective in treating diarrhoea in patients with inflammatory bowel syndrome without causing constipation \(^{(63)}\).

8. **Muscle relaxant activity:** Essential oil of oleo-gum-resin of *Boswellia serrata* on muscles revealed stimulatory effect on skeletal muscles and spasmogenic effect on smooth muscle of guinea pig ileum\(^{(64)}\).

9. **Hypolipidemic activity:** In an animal study it was found that feeding of 100 mg/kg of salai guggal significantly reduced cholesterol level in wistar rats \(^{(65)}\).
10. **Hypoglycaemic activity:** - Herbal formulation containing *Boswellia serrata* oleo-gum resin as one of the ingredient has been reported to produce significant anti-diabetic activity on Non-insulin-dependant Diabetes mellitus in streptozocin induced diabetic rat model (66).

11. **Hepatoprotective activity:** - Studies on alcoholic extract of salai guggal revealed hepatoprotection in galactosamine/endotoxin induced liver damage in mice. The hepatoprotection was probably through inhibition of 5-Lipoxygenase (5-Lox) activity (67).

12. **Anticancer activity:** - The alcoholic extract of salai guggal (AESG) was found to be Anti-carcinogenic in mice by inhibiting cell proliferation and cell growth due to the interference with biosynthesis of DNA, RNA and proteins (68). Boswellic acid, Keto boswellic acid and Acetyl keto boswellic acid showed anti-proliferative and apoptotic effect HT-29 on colon cancer cell and caspase-8 activation pathway leading to apoptosis (69-72). *Boswellia serrata* extract containing 60% BAs inhibited tumor and inflammation in mice (73).

Alcoholic extract of salai guggal inhibited the synthesis of DNA, RNA and protein in HL-60 cells. AKBA was most potent inhibitor and its inhibitory effect on DNA synthesis was irreversible (74).

Boswellic acid treatment to female wistar rats inoculated with C-6 tumour cells not only showed significant reduction in brain tumour
volume but also enhanced the survival time of animals in dose dependent manner\(^{(75-78)}\).  

Boswellic acids induce concentration dependent inhibition of glioma cell proliferation and show anti-edema effect in glioblastoma patients\(^{(79)}\). Acetyl keto boswellic acid impairs the motility of meningioma cells by impaired signal transduction and tumorigenesis thus causing cytotoxicity against meningioma cells\(^{(80)}\).
1.2 LITERATURE FOR LIVER

Plate 1.5: External Anatomy Of Liver

1.2.1 ANATOMY:

The liver is the heaviest gland of the body weighing about 1.4kg in an average adult, and after the skin it is the second largest-organ of the body (81). It is a soft, pinkish-brown, triangular organ. It is inferior to the
diaphragm and occupies most of the right hypochondriac and part of the epigastric region of the abdominopelvic cavity.

### 1.2.2 Internal Anatomy of Liver

The liver is almost completely covered by visceral peritoneum and is completely and completely covered by dense irregular connective tissue layer that lies deep in to the peritoneum. The liver is divided into two principal lobes—a large **right lobe** and smaller **left lobe** by falciform ligament.

Based on internal morphology the **quadrate lobe** and **caudate lobe** belong to **left lobe**.

**Histology of Liver:** The lobes of the liver are made of many functional units called **lobules** which contain specialized epithelial cells called **hepatocytes** arranged in irregular, branching, interconnected plates around a **central vein**. Liver has large endothelium-lined space called **sinusoids** through which blood passes. Fixed phagocytes called **Kupffer cells** are also present in sinusoids.

**Biliary tract:**

Bile, which is secreted by hepatocytes, enters **bile canaliculi** which are narrow intercellular canals that empty into small bile ductules. The ductules pass bile to bile ducts. The bile ducts merge to form large **right** and **left hepatic ducts** which unite to form **common hepatic**
duct. The common hepatic duct joins the cystic duct from gall bladder to form the common bile duct.

**Blood supply:**

The liver receives blood from two sources. It obtains oxygenated blood from the hepatic artery and deoxygenated blood from hepatic portal vein. Branches of these arteries carry blood in liver sinusoids. Branches of hepatic portal vein, hepatic artery, and bile duct accompany each other in their distribution through the liver. Collectively, these three structures are called portal triad.

**Plate: 1.6 Internal Anatomy Of Liver**
1.2.3 PHYSIOLOGY

The various functions of the liver are carried out by the liver cells or hepatocytes. The functions of the liver are so numerous and important that we cannot survive without it\(^{(82)}\). It plays a major role in detoxification and excretion of many endogenous and exogenous compounds, any injury to it or impairment of its functions may lead to many implications on one’s health\(^{(83)}\).

1. CARBOHYDRATE METABOLISM:-

The liver maintains normal blood glucose levels by performing following functions:-

- *Gluconeogenesis* (the synthesis of glucose from certain amino acids, lactate or glycerol)
- *Glycogenolysis* (the breakdown of glycogen into glucose) (muscle tissues can also do this)
- *Glycogenesis* (the formation of glycogen from glucose)

2. LIPID METABOLISM:

i. Synthesis of lipoproteins which help in transportation of fatty acids, triglycerides, and cholesterol to body cells.

ii. It breaks down fatty acid and generates ATP.

iii. It produces bile salts which are useful for emulsification of fats.
3. PROTEIN METABOLISM:-

i. Deamination of amino acids for production of ATP or conversion to carbohydrates and fats. The resulting toxic ammonia is then converted to less toxic urea for excretion in urine.

ii. Synthesis of plasma proteins such as albumin, globulin prothrombin and fibrinogen.

4. DRUG METABOLISM :-

It can detoxify drugs such as alcohol, penicillin and erythromycin. It can break down Insulin and other hormones.

5. EXCRETION OF BILIRUBIN:-

Bilirubin derived from worn out RBC is absorbed by the liver and secreted in the bile. It is metabolized in intestine by the bacteria and eliminated in the faeses.

6. SYNTHESIS OF BILE SALTS:-

Bile salts are used for emulsification and absorption of Lipids, Cholesterol, Phospholipids and Lipoproteins.

7. STORAGE:-

The Liver is the primary organ for the storage of the vitamins(A, B₁₂, D, E and K) and minerals(iron and copper) which are released when required.
8. PHAGOCYTOSIS:-

The reticulo – endothelial cells of the liver (kupffer cells) phagocytize aged RBC and WBC and some bacteria.

9. ACTIVATION OF VITAMIN D:-

The skin, liver and kidneys participate in the activation of Vitamin D.

1.2.4 Drug Induced Hepatotoxicity

The liver plays a central role in the metabolism of a large number of organic and inorganic chemicals and drugs which gain access to the body by inhalation, injection, or most commonly via the intestinal tract. The main drug metabolizing system is present in the microsomal fraction of smooth endoplasmic reticulum of the liver cells via P-450 cytochrome and cytochrome reductase enzyme systems. Other steps involved in the drug metabolism are its conjugation with an endogenous molecule, its active transport from the hepatocytes and ultimately its excretion in the bile or urine depending upon the molecular weight of the substance.

A number of risk factors predispose an individual to hepatic drug injury such as pre-existing liver disease, ageing, gender, and genetic inability to perform a particular biotransformation.

Toxic liver injury produced by drugs and chemicals may virtually mimic any form of naturally occurring liver diseases (84). Hepatotoxicity
from drugs and chemicals is the commonest form of iatrogenic disease. Severity of hepatotoxicity is greatly increased if the drug is continued after symptoms develop.

Drug reactions affecting the liver are divided into two main classes:

1. Direct or predictable: If the drug or its metabolites is directly toxic to liver or it lowers the host immune defense mechanism. This reaction is dose dependent. Ex: carbon tetra chloride.

2. Indirect or unpredictable or idiosyncratic: If the drug or its metabolites act as hapten and induces hypersensitivity in the host. This reaction is usually not dose related. Ex: Paracetamol.
**Table 1.1:** Classification of Hepatic Drug Reactions:

<table>
<thead>
<tr>
<th>PATHOLOGIC CHANGES</th>
<th>DRUGS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. Acute liver diseases</strong></td>
<td></td>
</tr>
<tr>
<td>1. Zonal necrosis</td>
<td>Paracetamol</td>
</tr>
<tr>
<td></td>
<td>Carbon tetra chloride</td>
</tr>
<tr>
<td></td>
<td>Halothane</td>
</tr>
<tr>
<td>2. Massive necrosis</td>
<td>Paracetamol</td>
</tr>
<tr>
<td></td>
<td>Halothane</td>
</tr>
<tr>
<td></td>
<td>Methyl dopa</td>
</tr>
<tr>
<td>3. Fatty change</td>
<td>Tetracycline</td>
</tr>
<tr>
<td></td>
<td>Salicylates</td>
</tr>
<tr>
<td></td>
<td>Methotrexate</td>
</tr>
<tr>
<td></td>
<td>Ethanol</td>
</tr>
<tr>
<td>4. Hepatitis</td>
<td>Methyl dopa</td>
</tr>
<tr>
<td></td>
<td>Isoniazid</td>
</tr>
<tr>
<td></td>
<td>Halothane</td>
</tr>
<tr>
<td></td>
<td>Ketoconazole</td>
</tr>
</tbody>
</table>
| 5. Granuloma formation | Sulfonamide  
Methyl dopa  
Quinidine  
Allopurinol |
|------------------------|-----------------------------------|
| 6. Cholestasis          | Oral contraceptives  
Chlorpromazine  
Nitrofurantoin |
| 7. Veno-occlusive disease | Cytotoxic drugs |
| 8. Hepatic /portal vein thrombosis | Oral contraceptives |
| B. Chronic liver disease | |
| 1. Fibrosis-cirrhosis | Methotrexate |
| 2. Focal nodular hyperplasia | Vinyl chloride  
Vitamin A  
Sex hormones |
| 3. Adenoma              | Sex hormones |
| 4. Hepatocellular carcinoma | Sex hormones |
The above table represents important drug reactions and the agents causing them. The changes produced by hepatotoxic agents may vary from mild to massive necrosis and death.

The pathologic changes by hepatotoxins include 2 large categories:

1. Acute liver disease characterized by cholestasis, hepatocellular necrosis, fatty change, granulamatous reaction or vascular disease.

2. Chronic liver disease characterized by variable degree of fibrosis, cirrhosis or neoplasia (86).

1.2.5 Diagnosis and treatment:-

Drug-induced hepatotoxicity is suspected when patients have unusual pattern of liver disease. (ex; - mixed or atypical pattern of cholestasis and hepatitis).

Treatment for drug-induced hepatotoxicity consists of with drawing the drug and providing supportive therapy.
Table 1.2: Normal values of serum enzymes with their significance

<table>
<thead>
<tr>
<th>Measurement (ALT)</th>
<th>Significance</th>
<th>Reference range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alanine transaminase</td>
<td>Alanine transaminase (ALT), also called Serum Glutamic Pyruvate Transaminase (SGPT) or Alanine aminotransferase (ALAT) is an enzyme present in hepatocytes (liver cells). When a cell is damaged, it leaks this enzyme into the blood, where it is measured. ALT rises dramatically in acute liver damage, such as viral hepatitis or paracetamol (acetaminophen) overdose. Elevations are often measured in multiples of the upper limit of normal (ULN).</td>
<td>5 to 40 ZU/L</td>
</tr>
<tr>
<td>Aspartate transaminase</td>
<td>Aspartate transaminase (AST) also called Serum Glutamic Oxaloacetic Transaminase (SGOT) or aspartate aminotransferase (ASAT) is similar to ALT in that it is another enzyme associated with liver parenchymal cells. It is raised in acute liver damage, but is also present in red blood cells, and cardiac and skeletal muscle and is therefore not specific to the liver. The ratio of AST to ALT is sometimes useful in differentiating between causes of liver damage. Elevated AST levels are not specific for liver damage, and AST has also been used as a cardiac marker.</td>
<td>10 to 40 IU/L</td>
</tr>
<tr>
<td><strong>Alkaline phosphatase (ALP)</strong></td>
<td>Alkaline phosphatase (ALP) is an enzyme in the cells lining the biliary ducts of the liver. ALP levels in plasma will rise with large bile duct obstruction, intrahepatic cholestasis or infiltrative diseases of the liver. ALP is also present in bone and placental tissue, so it is higher in growing children (as their bones are being remodelled) and elderly patients with Paget’s disease.</td>
<td>30 to 120 IU/L $^{11}$</td>
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<tr>
<td>-----------------------------</td>
<td>-------------------------------------------------------------------------------------------------</td>
<td>-------------------------</td>
</tr>
<tr>
<td><strong>Total Bilirubin (TBIL)</strong></td>
<td>Bilirubin is a breakdown product of heme (a part of haemoglobin in red blood cells). The liver is responsible for clearing the blood of bilirubin. It does this by the following mechanism: bilirubin is taken up into hepatocytes, <em>conjugated</em> (modified to make it water-soluble), and secreted into the bile, which is excreted into the intestine. Increased total bilirubin causes jaundice, and can signal a number of problems:</td>
<td>2 - 14 μmol/L</td>
</tr>
<tr>
<td></td>
<td>- 1. <strong>Prehepatic</strong>: Increased bilirubin <em>production</em>. This can be due to a number of causes, including haemolytic anaemias and internal hemorrhage.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- 2. <strong>Hepatic</strong>: Problems with the liver,</td>
<td></td>
</tr>
</tbody>
</table>
which are reflected as deficiencies in bilirubin metabolism (e.g. reduced hepatocyte uptake, impaired conjugation of bilirubin, and reduced hepatocyte secretion of bilirubin). Some examples would be cirrhosis and viral hepatitis.

- **3. Posthepatic:** Obstruction of the bile ducts, reflected as deficiencies in bilirubin excretion. (Obstruction can be located either within the liver or in the bile duct.)

<table>
<thead>
<tr>
<th>Direct bilirubin</th>
<th>The diagnosis is narrowed down further by looking at the levels of direct bilirubin.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>- If direct (i.e. conjugated) bilirubin is normal, then the problem is an excess of unconjugated bilirubin, and the location of the problem is upstream of bilirubin excretion. Hemolysis, viral hepatitis, or cirrhosis can be suspected.</td>
</tr>
<tr>
<td></td>
<td>- If direct bilirubin is elevated, then the liver is conjugating bilirubin normally, but is not able to excrete it. Bile duct obstruction by gallstones or cancer should be suspected.</td>
</tr>
<tr>
<td></td>
<td>0 - 4 μmol/L</td>
</tr>
</tbody>
</table>
Coagulation test:-

The liver is responsible for the production of coagulation factors. The international normalized ratio (INR) measures the speed of a particular pathway of coagulation, comparing it to normal. If the INR is increased, it means it is taking longer than usual for blood to clot. The INR will only be increased if the liver is so damaged that synthesis of vitamin K-dependent coagulation factors has been impaired: it is not a sensitive measure of liver function.

Serum glucose test :-

The liver’s ability to produce glucose (gluconeogenesis) is usually the last function to be lost in the setting of fulminant liver failure.

Lactate dehydrogenase (LDH) test:-

Lactate dehydrogenase is an enzyme found in many body tissues, including the liver. Elevated levels of LDH may indicate liver damage.

Uribilinogen test:-

The protein urobilinogen is formed in the intestines by bacterial action from the protein bilirubin. This is then absorbed and passed to the liver and urine. An above normal level of urobilinogen in the urine is indicative of liver disease.
**1.2.6 LIV-52:-**

Liv-52\(^{(89)}\) was introduced in 1955 by Himalaya Herbal Health Care. Since then it has been sold world wide and is recognized by thousands of health professionals as one of the most effective liver protective, with beneficial effects reported in over three hundred studies on a variety of cases. Liv-52 ensures optimum liver function through the protection of the hepatic parenchyma and by way of its potent anti oxidant properties. Liv-52 neutralises all kinds of toxins and poisons from food, water, air and medications, all sources of detrimental effects on the liver. Alcohol users in particular find Liv-52 helpful in maintaining a healthier liver.

Liv-52 is a unique all natural complex multi ingredient formula. It is safe and effective in protecting the liver against harmful toxins from drugs, alcohol, food and water\(^{(90)}\). Liv-52 helps to regulate the levels of enzymes and optimizes assimilation. Liv-52 has also been found to be associated with increase in serum albumin which is another indication of the liver protection.

Protein energy malnutrition work shows that Liv-52 has cholesterol-regulation action. Clinically it helps to maintain healthy levels of serum cholesterol, Lipo proteins, Phospholipids and triglycerides.
Liv-52 restores the functional efficiency of the liver by protecting the hepatic parenchyma and promoting hepato cellular regeneration. The anti-peroxidative activity of Liv-52 prevents the loss of functional integrity of the cell membrane, maintains cytochrome P-450, hastens the recovery period and ensures restoration of hepatic functions in infective hepatitis. Liv-52 facilitates rapid elimination of acetaldehyde, the toxic intermediate metabolite of alcohol metabolism, and ensures protection from alcohol-induced hepatic damage. Liv-52 diminishes the lipotropic activity in chronic alcoholism, and prevents fatty infiltration of the liver. In pre-cirrhotic conditions, Liv-52 arrests the progress of the disease and prevents further liver damage.

Liv – 52 Benefits :

- Viral hepatitis.
- Alcoholic liver disease.
- Pre cirrhotic conditions
- Loss of appetite.
- Radiation and Chemotherapy induced liver damage.
- As adjuvant with hepatotoxic drug.
1.3. LITERATURE FOR GASTRO INTESTINAL TRACT:

Plate: 1.7 THE STOMACH

Plate: 1.8 The stomach
1.3.1 ANATOMY OF STOMACH

The stomach is a J-shaped dilated portion of the alimentary tract situated in the epigastric, umbilical and left hypochondriac regions of the abdominal cavity. The stomach is continuous with the oesophagus at the cardiac sphincter and with the duodenum at the pyloric sphincter. It has two curvatures. The lesser curvature and the greater curvature. The stomach is divided into three regions: the fundus, the body and the antrum. Pyloric sphincter is present at the distal end of Pyloric antrum which regulates the movement of food from the stomach in to duodenum.
The walls of the alimentary tract are formed by four layers of tissue:

- Adventitia or outer covering
- Muscle layer
- Submucosal layer
- Mucosal layer

**Gastric Juice**

About 2 litres of gastric juice are secreted by special secretory glands in the mucosa. It consists of:

- Water & Mineral salts secreted by gastric glands
- Mucus secreted by goblet cells
- Hydrochloric acid & Intrinsic factor secreted by parietal cells
- Pepsinogens secreted by chief cells

**1.3.2 Phases of gastric juice secretion:**

1. **The Cephalic Phase** – The flow of gastric juice occurs before food reaches the stomach and is due to reflex stimulation of vagus nerves initiated by the sight, smell, or taste of food.

2. **The Gastric Phase** – It is stimulated by the presence of food. The enteroendocrine cells present in pyloric antrum and duodenum secrete gastrin which stimulate the gastric glands.

3. **The Intestinal Phase** – When the food enters small intestine a hormone called enterogasterone is produced which inhibits the secretion of gastric juice. The hormone is a complex of secretin and cholecystokinin\(^ {91} \).
1.3.3 Regulation of Gastric Acid Secretions:

There are 3 main stimulus on parietal cells.

- Gastrin
- Acetylcholine
- Histamine

Prostaglandins E$_2$ and I$_2$ inhibits acid secretion.

GASTRIN:

Gastrin is a peptide hormone synthesized in endocrine cells of the mucosa of the gastric antrum and duodenum, and secreted into portal blood. The main action is stimulation of the secretion of acid by the parietal cells. Gastrin also indirectly increases pepsinogen secretion and stimulates blood flow and gastric motility.

Gastrin secretion is inhibited when the pH of the gastric contents falls to 2.5 or lower.

An excessive secretion of gastrin resulting in excessive secretion of acid is seen with rear tumors of gastrin-secreting cells, gastrinomas – the complex of signs and symptoms constituting the Zollinger-Ellison syndrome.

ACETYLCHOLINE:

Acetylcholine is released from neurones and stimulates specific receptors on the surface of parietal cells and on the surface of histamine containing cells.
HISTAMINE:
The parietal cells are stimulated by acting on H₂ receptors. They respond to amounts that are below the threshold concentration that acts on H₂ receptors in blood vessels. The histamine is derived from mast cells (or histamine containing cells similar to mast cells) that lie close to the parietal cells. There is a steady basal release of histamine which is increased by gastrin and acetylcholine.

Plate 1.10: THE REGULATION OF GASTRIC ACID SECRETIONS BY PARIETAL CELLS:
1.3.4 PEPTIC ULCER DISEASE

Gastric hyperacidity and gastro duodenal ulcer is a very common global problem today. Peptic ulcer is a lesion of gastric or duodenal mucosa. The modern approach to control gastric ulceration is to inhibit gastric secretion, to promote gastric protection, block apoptosis and stimulate epithelial cell proliferation for effective healing (92).

Peptic ulcer disease is one of the common gastrointestinal disorders in clinical practice.

The common forms of peptic ulcer are:

1. Duodenal ulcer
2. Gastric ulcer
3. NSAID induced ulcer
4. Stress ulcer
Among these the duodenal ulcer is more common in adult males. Gastric ulcers occur commonly at old age and lower socio-economic class of individuals. Although the exact cause of ulceration is not known, gastric acid and pepsin are responsible for maintaining the lesion once it is produced. Peptic ulceration occurs only in areas which are bathed by acid gastric juice. Stomach and first portion of duodenum are bathed by acid gastric juice. In the second portion of duodenum bile and pancreatic juice flow. This is why; the term peptic ulcer refers to ulceration of the parts which might be acted upon by acid peptic juice namely the stomach, the first portion of duodenum \(^{(93)}\).

Peptic ulcers also occur at the lower end of the oesophagus, on the jejunal side of a gastroenterostomy, and in Meckel’s diverticulum\(^{(94)}\).

Plate: 1.12 HELICOBACTER PYLORI
1.3.5 Helicobacter Pylori

*H. pylori* are a gram negative bacillus that colonises the stomach and the duodenum. A high association between *H.pylori* infection of the stomach and duodenum and peptic ulcer disease has now been established. The infection is acquired by oral ingestion of the bacilli, the organism does not invade the mucosa but attaches itself to the epithelial cells.

*H.pylori* secretes enzyme urease which hydrolises urea into carbon dioxide and ammonia which permits the bacilli to survive in the acid environment of the stomach. It also secretes an exotoxin which directly damages the epithelial cells. Although *H.pylori* is present in the Gastro intestinal tract of 50% of adult population only 10-20% of the latter develop peptic ulcer disease. Therefore there must be a host factor in the pathogenesis of peptic ulcer disease.

*H.pylori* cause most duodenal and gastric ulcers and are strongly implicated in the pathogenesis of gastric carcinoma and gastric lymphoma. Eradication of *H.pylori* infection benefits patients with all these entities.

1.3.6 MANAGEMENT OF PEPTIC ULCER

Principles of peptic ulcer therapy are:

- Controlling gastric acidity, hyper motility and promoting ulcer healing.
- Prevention of complications and recurrence
- Treatment of *H.pylori* infection.
**Classification:**

1. Gastric Antacids
   a. Non-systemic antacids: Aluminium hydroxide gel
      Magnesium hydroxide
      Magnesium oxide
      Calcium carbonate etc.
   b. Systemic antacids: Sodium bicarbonate

2. Gastric acid secretion inhibitors in peptic ulcer
   i. H$_2$ receptor antagonists: Cimetidine, Ranitidine, Famotidine etc.
   ii. Proton pump inhibitors: Omeprazole, Lansoprazole, Pantoprazole etc.
   iii. Antimuscaranics: Pirenzepine.

The management of peptic ulcer is essential. It has undergone a major change with the discovery of the association of duodenal ulcer with H. pylori infection\(^{(95)}\). H. pylori infection can be confirmed by

(a) Detection of IgG antibody against H. pylori in the stool.
(b) Urea breath test
(c) Biopsy of normal appearing gastric mucosa at an endoscopy at which the ulcer is diagnosed.

■ **Rest:**
Clinical studies have clearly shown that bed rest promotes ulcer healing. An initial period of bed rest, therefore, may be useful in patients with recent ulcer and in those with severe symptoms.
- **Withdrawal of the offending agents:**

  Cessation of smoking, avoidance of NSAIDs, alcohol and caffeine containing beverages are definitely helpful in promoting ulcer healing.

- **Diet:**

  Contrary to common belief, there is no special merit in frequent, small meals, nor in the addition does night feed. In fact, peptic ulcers disease can be effectively treated with the usual 3-4 meals a day. Night feeds only stimulates further gastric acid secretion at a time when a patient is asleep and is unable to take antacids; hence they should be avoided. However, irritant such as chilly, other spices and fried food should be avoided. Edible vegetable oils, ghee and butter taken as such are helpful, as these have an inhibitory effect on gastric acid secretion.

- **Antacid and Anti-secretory drugs:**

  In humans, the mean diurnal gastric pH is about 1.4 – 2.0: low pH is found at night. For the treatment of duodenal ulcer, the pH has to be elevated to a level higher than 3.0 for about 16 – 18 hours a day. With this in mind a course of therapy with an H₂ receptor blocker or a proton pump inhibitor (PPI's) should be given for 6 – 12 weeks; such a therapy is more convenient than intensive therapy with antacids which is more probably as effective in inducing ulcer healing.
Compared to H$_2$ receptor antagonists, PPIs cause a more profound inhibition of acid secretion on once a day regimen. Patients may be given one nightly dose to same drug for an additional 6-12 weeks, as short term prophylaxis. If the ulcer recurs, another course of full therapy is indicated. Patients with Zollinger-Ellison syndrome who are resistant to H$_2$ receptor blockers should be treated with PPI.

H$_2$ receptor antagonists, as a class, are remarkably free from adverse reactions.

Full doses of these drugs are usually given after the evening meal. Cimetidine 800 mg is equivalent to 300 mg of Ranitidine, 40 mg of Famotidine and 300 mg of Nizatidine. Therapeutically, there is little to choose from among the various drugs of this class. The difference is mainly in the potency as on mg bases and the cost. PPIs produced rapid relief of symptoms and caused faster ulcer healing than the H$_2$ receptor antagonists.

**Treatment of H. pylori infection:**

Eradication of documented *H. pylori* infection is now considered the mainstay of treatment of documented duodenal ulcer and gastric ulcer. For this purpose, antibiotics are used in combination regimens using 3-4 drugs.
The concurrent administration of PPI or an H$_2$ receptor antagonist enhances the eradication of *H. pylori*. PPIs are superior in this respect. The organism may develop resistance to metronidazole in 20-30 cases.

The drug regimens mentioned in the table are effective in 70-90% of patients. Some side effects occur in 20-30% of patients. For ulcer healing and cure, antisecretory and antimicrobial therapy is usually given together for the first 10-14 days, followed by antisecretory therapy alone for 6-8 weeks. Efficacy of the antimicrobial therapy is assessed by a negative urea breath test. Once *H. pylori* infection is eradicated, maintenance antisecretory therapy is not needed. Less than 10% of the ulcer may recur after cure following eradication of *H. pylori* infection. However, recurrence may be precipitated by NSAIDs or some other ulcerogenic factor.

**Prevention of recurrence:**

Cimetidine (400mg daily) and Ranitidine (150mg daily), used prophylactically have been shown to reduce ulcer recurrence and prevent complications in resistant case. Patient should be advised moderation in living and in eating, and to avoid smoking, drinking and certain drugs in the cope of preventing recurrence. Up to 4/5$^{th}$ of gastric ulcers have been attributed to smoking and use of NSAIDs. Many elderly persons with osteoarthritis often receive potent anti-
inflammatory drugs in full doses whereas all that they require is an analgesic such as Paracetamol or low dose Ibuprofen (200mg).

**Surgery:** Surgery is indicated when

- Malignancy is suspected in gastric ulcer.
- A duodenal ulcer becomes chronic and refractory to adequate medical management.
- A complication such as organic obstruction or perforation is present.
- The patient suffers from repeated attacks of gastrointestinal bleeding.

1.3.7 STANDARD DRUG

Ranitidine (Zantac, zinetac):-It is a H<sub>2</sub> receptor antagonist. H<sub>2</sub> receptor antagonists competitively inhibit the interaction of histamine with these receptors. They are highly selective and have little or no effect on H<sub>1</sub> receptors or other receptors.<sup>(96)</sup>

Ranitidine is chemically a nitromethane derivative of furan and is 5-10 times more potent than cimetidine.

It is adequately absorbed. Its plasma half life is 1.6- 2.4 hours. Its action is selective and long lasting.

A single oral dose of 150 mg controls gastric secretion for about 8-12 hours. It is also available as injection (25mg/ml) for slow IV administration.
Its advantages are:

- Does not inhibit hepatic metabolism
- Has less anti androgenic effects and less likely to cause gynecomastia and sexual dysfunction
- Cause little, if any, central effects.

Dose: The dose is 150mg 12 hours or 300mg once daily at bed time

**Omeprazole (Omezole, Lomac):**

It is a proton pump inhibitor. It irreversibly inhibits the gastric H+ - K+ ATPase proton pump which is a final common pathway for acid secretion in response to all varieties of stimuli. This is a substituted benzimidazole it has prolong action and a dose of 20-40mg once daily for seven days reduces the 24 hours gastric acid output by 90%.

It is useful in treatment of Zollinger- Ellison syndrome with severe gastric acid hyper secretion and recurrent duodenal ulcers. It has also been used in treating bleeding peptic ulcers in dose of 40mg 12 hourly

Adverse Reactions: GI disturbances, dizziness drowsiness, hypergastrinaemia due to prolonged achlorhydria.

In the last few years, efforts have been taken to identify new anti-ulcer drugs from natural sources. Plants are the sources of certain known anti-ulcer drugs.
1.4 Literature for Urinary System

Plate: 1.13 Urinary System

Urinary system helps to keep the body in homeostasis by both removing and restoring selected amounts of solutes and water from the blood.

The urinary system consist of

1. 2 kidneys
2. 2 ureters
3. 1 urinary bladder
4. 1 urethra.
The kidneys regulate the composition and volume of the blood and remove wastes from the blood in the form of **urine**. The urine consists of the metabolic waste urea excess water, excess ions and toxic wastes that may have been consumed with food. Urine is excreted from each kidney through ureters. It is then stored in the urinary bladder, until is expelled from the body through the urethra.

**1.4.1 Functions of urinary system:-**

- **Excretion:** The kidneys filter large amounts of fluid from the bloodstream. They are the major excretory organs of the body because they eliminate nitrogenous wastes, drugs and toxins from the body. In addition, the kidneys reabsorb needed substances and return them to blood.

- **Regulation of Blood volume and Blood concentration:** The kidneys control blood volume by regulating the proper balance in the blood between salts and water. They regulate the volume of urine produced. They also regulate the concentration of ions in the body fluids and blood, therefore the proper balance of sodium, chloride, potassium, calcium and phosphate ions is maintained.

- **pH regulation:** The kidneys control the balance of hydrogen ions in the blood, thus maintaining pH levels in Blood.

- **Blood pressure:** The kidneys produce the enzyme rennin which has vital role in maintaining Blood pressure.
- Erythrocyte regulation: The kidneys produce erythropoietin, a hormone that stimulates erythrocyte production in red bone marrow.
- Vitamin D production: The kidneys participate, along with liver and skin in vitamin D synthesis. Kidneys also convert vitamin D to its active form calciferol.

**Plate: 1.14 Internal Anatomy of Kidney**

**1.4.2 External Anatomy of the kidneys:** The kidneys are paired organs that are reddish in colour and resemble beans in shape. They are located just above the waist between the parietal peritoneum and posterior wall of abdomen. The average adult kidney measures about 11.2 cm.
inches) long, 5-7.5 cm. (2-3 inches) wide and 2.5 cm. (1 inch) thick. Near the center of the concave border of the kidney is a notch called hilum through which ureter leaves the kidney. Blood vessels, nerves and lymph vessels also innervate the hilum. The cavity is called renal sinus which consist of connective tissue and fat.

Three layers of tissue surround each kidney.

- Renal capsule: It is the innermost layer. It is smooth, transparent, fibrous connective tissue membrane which acts as barrier against infection and trauma to the kidney.
- Adipose capsule: It is a mass of fatty tissue which firmly holds the kidney in place and also protects it.
- Renal fascia: It consist of thin layer of fibrous connective tissue that anchors the kidneys to their surrounding structures and to abdominal wall.

### 1.4.3 Internal Anatomy of the kidneys:

It is divided in to two regions:-

- Renal Cortex: It is the outer region and appears reddish in colour.
- Renal Medulla: It is the inner region and appears reddish brown in colour.

Within the medulla there are 8-18 striated, triangular structures called **renal pyramids**. The bases of pyramids face the cortex and their
called renal papillae point towards the center of the kidney. Together **renal cortex** and **renal pyramids** are called **renal parenchyma**.

A funnel-shaped structure called minor calyx surrounds the tip of each renal pyramid. There can be 8-18 **minor calyces**. Each minor calyx collects urine from the ducts of pyramids. Minor calyces join to form **Major calyces**. There are 2-3 Major calyces in the kidney. The Major calyces join together to form large collecting funnel called **renal pelvis** which is found in renal sinus. Renal pelvis narrows to form ureter. Urine drains from tips of renal pyramids in to calyces, then in to renal pelvis and enters ureters.
Plate: 1.15 Structure of Nephron
1.4.4 NEPHRON

The Nephron is the functional unit of the kidney. Each kidney in the human contains about 1 million nephrons, each capable of forming urine. Each nephron contains (1) a tuft of glomerular capillaries called the glomerulus, through which large amounts of fluid are filtered from the blood, and (2) a long tubule in which the filtered fluid is converted into urine. The glomerulus is covered by Bowman’s capsule. Fluid filtered from the glomerular capillaries flows into Bowman’s capsule and then into proximal tubule, which lies in the cortex of the kidney.

From the proximal tubule, fluid flows into loop of Henle, which dips into renal medulla. Each loop consists of descending and ascending limb. The walls of descending limb and lower end of ascending limb are thin called thin segment of loop of Henle. The walls of ascending limb in cortex region is thick called thick segment of loop of Henle. At the end of thick ascending limb is a short segment called macula densa. From the macula densa fluid enters distal tubule followed by connecting tubule and cortical collecting tubule which lead to collecting duct. The collecting ducts merge to form larger ducts that drain in to renal pelvis.

**Blood and nerve supply to the Nephrons**

Nephrons are richly supplied with blood vessels. The right and left renal arteries divide into branches and enter renal parenchyma. In renal columns these branches are called interlobar arteries which arch between the cortex and medulla. Here they are called arcuate arteries.
which produce a series of interlobular arteries that enter the cortex and divide to form afferent arterioles. The afferent arterioles divide into a capillary network in Bowman’s capsule. The glomerular capillaries then reunite to form efferent arteriole. Each efferent arteriole divide to form network of capillaries called peritubular capillaries which surround the convoluted tubules of the nephron. The peritubular capillaries reunite to form interlobular vein, then arcuate vein, then interlobar veins which unite to form right and left vein.

1.4.5 Physiology of urine formation:

- Urine is formed by three processes in the nephrons:
  - Glomerular filtration
  - Tubular reabsorption
  - Tubular secretion

In glomerular filtration, the glomerulus filters water and certain dissolved substances from the plasma of blood. This process of glomerular filtration results in increased blood pressure. This increased pressure forces the fluid to filter from the blood. The dissolved substances include positively charged ions of sodium, potassium, calcium and magnesium; negatively charged ions of chloride, bicarbonate, sulfate and phosphate; and glucose, urea and uric acid. This filtrate is mainly water with some of the same components as the blood plasma. No large proteins are filtered. Both kidneys filter about 45 gallons of blood plasma per day but
only a small portion of filtrate leaves the kidneys as urine. Most fluid gets reabsorbed in renal tubules and enters plasma.

In tubular reabsorption the substances are transported back into blood of peritubular capillary. Reabsorption of glucose, amino acids, ascorbic acid, sodium, potassium, calcium, chloride etc. will take place through renal tubule. Proximal convoluted tubule is the major site for reabsorption.

In tubular secretion substances from the peritubular capillary move in to renal tubule. The proximal convoluted tubule actively secretes penicillin, creatinine and histamine into tubular fluid. The entire renal tubule actively secretes hydrogen ions (H\(^+\)) thus maintaining pH of body fluids. The distal convoluted tubule and collecting duct secrete potassium ions (K\(^+\)) ions.

Urine is about 95% water with urea, uric acid, some amino acids and electrolytes. The daily production of urine is between 0.6-2.5 litres/day depending on fluid intake.

**URETERS**

The ureters begin as extension of renal pelvis of kidney and connect to urinary bladder. The function is to transport urine to urinary bladder.

**URINARY BLADDER**

The urinary bladder is held in position by folds of peritoneum in the pelvic cavity. Urine is expelled from the bladder by a process known as micturition. The bladder can hold 700-800 ml. of urine. When it reaches
200-400ml. stretch receptors in the bladder wall transmit impulses to lower spinal cord, which initiate a conscious desire to urinate and unconscious reflex called micturition reflex\(^{(98)}\).

**URETHRA**

Urethra is a small thin-walled tube connecting to the floor of urinary bladder that leads to outside.

**1.4.6 DIURETICS:**

Diuretics are commonly defined as drugs that increase the amount of urine produced by the kidneys. Diuretics can also be defined as agents which augment the renal excretion of sodium and either chloride or bicarbonate primarily and water excretion secondarily. The term “saluretic” is sometimes used to describe a drug that increases renal excretion of sodium and chloride ions.

Clinically diuretics are used for the treatment of hypertension and oedematous states like congestive heart failure, cirrhosis with ascites, nephrotic oedema and oedema of pregnancy.

**1.4.7 CLASSIFICATION**

1. Benzothiadiazides and related compounds

   Ex: - Chlorthiazide, Hydrochlorothiazide, Cyclothiazide,

   Metolazone.

2. High-Ceiling or Loop Diuretics

   Ex: - Furosemide, Bumetanide, Ethacrynic acid.

3. Carbonic Anhydrase Inhibitors
Ex: - Acetazolamide, Dichlorphenamide, Methazolamide.

4. Potassium-Sparing Diuretics

Ex: - Spironolactone, Triamterene, Amiloride.

5. Osmotic Diuretics

Ex: - Mannitol, Glycerol, Isosorbide.

6. Methyl Xanthines

Ex: - Aminophylline.

1. Benzothiadiazines and related compounds (Thiazides)

Thiazides are chemically related to sulphonamides. They are effective orally. Their main action is exerted on distal tubule and also on proximal tubule. They have saluretic action i.e., excretion of sodium and chloride ions. They also reduce reabsorption of bicarbonate ions.

2. High Ceiling or Loop Diuretics

The Loop Diuretics such as Furosemide, Bumetanide and Ethacrynic acid inhibit sodium and chloride reabsorption in thick segment of ascending limb of loop of Henle as well as in proximal convoluted tubule and distal tubule\(^{99}\). Thus they are very potent diuretics and the urine is rich in sodium chloride. The loss of potassium ions is also noted. Uric acid secretion is reduced and this may induce gout in susceptible individuals. There is rapid onset of action.
3. Carbonic Anhydrase Inhibitors

Acetazolamide competitively inhibits the enzyme carbonic anhydrase and interferes with ability of renal tubular cells to produce and secrete hydrogen ions. As a result few hydrogen ions are available for exchange with sodium. Therefore the sodium is eliminated along with bicarbonate ions and water. As there is a deficiency of H\(^+\) ions in tubular cells, more of K\(^+\) is exchanged for Na\(^+\) ions, and therefore there is loss of potassium from the body.

4. Potassium-Sparing Diuretics

The potassium-sparing diuretics, Spironolactone, Triamterene and Amiloride interfere with sodium reabsorption at distal tubule and promote sodium excretion by conserving potassium.

5. Osmotic Diuretics

Osmotic diuretics are non-electrolytes, which are freely filtered at the glomerulus. There presence in the urine causes increase in excreted electrolytes and volume flow. They inhibit sodium and water reabsorption in proximal tubules and Henle’s loop.

6. Methyl Xanthines

Methyl Xanthines inhibit reabsorption of Sodium, Chloride and water.
**1.4.8 GOUT**

Gout is a purine metabolism disorder resulting from excess of uric acid in blood (Hyperuricaemia), due to over production or faulty elimination. Crystals of monosodium urate get deposited in joints, skin, kidney and other tissues. Gouty arthritis involves single joint but some times may involve many joints. Classically the great toe is involved characterized by pain, swelling, tenderness.

Uric acid is filtered by the glomerulus, but 98% is actively reabsorbed in the proximal tubule. It is also excreted into the distal tubule. It is more soluble in alkaline urine. The formation of urate crystals is due to impaired ability to excrete alkaline urine. About two-third of uric acid is excreted in urine, and remainder is excreted in gut.

Uricosuric drugs such as Probenecid and sulphinpyrazine are used for long term control of gout. These drugs act by increasing excretion of uric acid by the kidneys. They inhibit tubular reabsorption of uric acid thereby greater amount of uric acid are eliminated in urine.