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**HERBAL AND HEPATOPROTECTIVE DRUGS ACTING ON PEPTIC ULCER AND LIVER DISEASE:
A REVIEW**

S.K.Gupta*¹ and I.J.Singhvi¹

¹Pacific College of Pharmacy, Udaipur.

Email: garg_s.kumar@yahoo.com

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ABSTRACT

Peptic ulcer disease is an imbalance between offensive and defensive gastric factors. A bacterium called *Helicobacter pylori* has been considered a major causative agent for gastric and duodenal ulcers. This is a major cause of mortality in developing countries. Today, we have a bunch of herbal drugs that have very good potential to treat peptic ulcer and other gastrointestinal disorders both from traditional knowledge and scientific data. This review includes physiological, pathophysiological aspects related to peptic ulcer and liver disease and list of herbal drugs for treatment of gastrointestinal ulcers.

Keywords: Herbal Drugs, Peptic ulcer, liver disease, *Helicobacter pylori*, etc.

INTRODUCTION

Peptic ulcer disease is an imbalance of aggressive gastric luminal factors like acid and pepsin and defensive mucosal barrier function may be environmental and host factors contribute to ulcer formation by increasing gastric acid secretion or weakening the mucosal barrier¹⁻³. Elaborately, peptic ulcer disease is characterized by the imbalance between gastric offensive factors like acid, pepsin secretion, lipid per-oxidation, nitric oxide and defensive mucosal factors like mucin secretion, mucosal cell shedding, glycoprotein, proliferation & antioxidant enzymes like catalase, superoxide dismutase & glutathione levels⁴. Peptic ulcers include both gastric and duodenal ulcers⁵. A bacterium called *Helicobacter pylori* has been considered a major causative agent for gastric and duodenal ulcers.

Herbal Medicine is defined as branch of science in which plant based formulations are used to alleviate the diseases. It is also known as botanical medicine or phytomedicine. Lately phytotherapy has been introduced as more accurate synonym of herbal or botanical medicine. Recently, treatment of diseases with herbal medicine has been addressed as phytopharmacotherapy. Moreover, herbal medicinal products have been included lately in dietary supplements.

Early in the twenty century herbal medicine was a prime healthcare system as antibiotics or analgesics were not available. With the development of allopathic systems of medicine, herbal medicine gradually lost its popularity among people and it was based on the fast therapeutic actions of synthetic drugs. Almost a century has passed and we have witnessed limitations of allopathic systems of medicine. Lately herbal medicine has gained momentum and it is evident from the fact that certain herbal remedies peaked at par with synthetic drugs.

According to a study from U.S., 60-70% patients living in rural areas are dependent on herbal medicine for their day to day diseases⁶. Substances derived from the plants remain the basis for a large proportion of the commercial medications used today for the treatment of heart disease, high blood pressure, liver disease, pain, asthma, and other problems.

Several authors have reported favorable results with herbal drugs either in animal or in human studies. Ginkgo biloba L., Echinacea purpurea L., Hypericum perforatum L. and Cimcifuga racemosa (L.) Nutt., were subjected to clinical trials.

Hepatoprotective drugs means the drugs that are used in the treatment of hepatic diseases; they improve the function of hepatic cells while protecting them from further impairment.

Silybum marianum L., the reputed hepatoprotective, has remained a golden standard in the treated of liver ailments. Several years have passed but status of this herbal drug remains unquestioned. In India, a study reported that Picrorrhiza kurroa Royle. is more potent than Silybum marianum as hepatoprotective agent (however, this study is not complete in all aspects). If the results of the study were true, then more clinical trials were warranted with Picrorrhiza kurroa.

Scope of the Herbal Therapy and Indian Herbal Market:

Traditional Indian practice held that certain drugs should be formulated through the addition of chosen substances that enhances bioavailability of anti-TB drug Rifampicin. Formulation of piperine with rifampicin will save the drug counter effects.

Herbal oriented pharmaceutical companies are investing crores of rupees on researching, developing and popularizing OTC remedies. India can be a major player in the global market for herbal product based medicines. Exports of herbal materials and medicines can jump from just Rs. 456 crore in 2000 to Rs.3000 crore in 2005 and with a “grand strategic plan” exports can shoot to Rs.10,000 crore by 2010.

The Significance of Quality for Efficacy and Safety of Herbal Drugs

The efficacy and safety of any pharmaceutical product is determined by the compounds (desired and undesired) which it contains. The purpose of quality control is to ensure that each dosage unit of the drug product delivers the same amount of active ingredients and is, as far as possible, free of impurities. As herbal medicinal products are complex mixtures which originate from biological sources, great efforts are necessary to guarantee a constant and adequate quality. By carefully selecting the plant material and a standardized manufacturing process the pattern and concentration of constituents of herbal medicinal products should be kept as constant as possible as this is a prerequisite for reproducible therapeutic results.

The major problem in quality control is the batch to batch variations in the quality of medicinal plants. This is mainly due to the existence of ecotype pharmacological variations in the case of many medicinal plants. Therapeutic value of medicinal plants could differ depending on soil conditions, nutritional status, climatic conditions, seasonal variations, diurnal variations and their association with other organisms.

The digestion system is essential part of the human physiology. If the digestion is distorted due to any reason then the disease will appear. The peptic ulcer also a disease which shows impaired digestion.

Peptic ulcer:

Peptic ulcer is a sore area or erosion on the lining of the digestive system. If it is in the stomach, it is referred to as a gastric ulcer. If it is in the duodenum (the part of the small intestine just after the stomach), it is called a duodenal ulcer.

It is the most common disease of upper G.I.T. system. It affects, 1 in 10 persons during life time ⁷

- Peptic ulcers affect both men and women.
- 5–10% of people worldwide suffer from a peptic ulcer at least once in their lifetime.
- Duodenal ulcers are more common than gastric ulcers and usually occur in people aged fewer than 50.

Gastric ulcers are more common in people aged over 50 ⁸.

Mankind has lived with peptic ulcers since ancient times. He incubated and saw a vision; the god seemed to order his followers to seize and hold him, that he might incise his stomach. Acid neutralization was recognized as effective treatment more than 12 centuries ago by Paulus Aeginata, who prescribed a mixture of Samian and Lemnian earths and milk, not unlike the milk-antacid regimens of the mid-twentieth century.

Since then of course, considerable advances in understanding the pathogenesis and in the treatment of acid-peptic conditions have occurred, culminating in the discovery of *Helicobacter pylori* and proton pump inhibitors. We now know that eradication of *H. pylori* effectively promotes healing of peptic ulcers and prevents their recurrence in most cases, it is reasonable to conclude that the battle against the ravages of gastric acid is finally turning in our factor ⁹.

Liver Disease⁶:

Liver disease is a term for a collection of conditions, diseases, and infections that affect the cells, tissues, structures, or functions of the liver. Also called: Hepatic disease

Types of liver disease:

- a) Necrosis
- b) Cirrhosis

c) Hepatitis – may be viral, toxic or deficiency type.

d) Hepatic failure

e) Chemical / Drug induced Hepatotoxicity: Generally may be hepatitis, jaundice and carcinogenesis.

f) Liver disorders due to impaired metabolic function. Generally the disorders associated with fat (liposis) and bilirubin (Jaundice) metabolisms are very commonly seen.

Signs and symptoms of the liver disease:

Symptoms partly depend on the type and the extent of liver disease. In many cases, there may be no symptoms.

Signs and symptoms that are common to a number of different types of liver disease include: Jaundice, or yellowing of the skin, Darkened urine, Nausea, Loss of appetite, Unusual weight loss or weight gain, Vomiting, Diarrhea, Light-colored stools, Abdominal pain in the upper right part of the stomach, Malaise, or a vague feeling of illness, Generalized itching, Varicose veins (enlarged blood vessels), Fatigue, hypoglycemia (low blood sugar), Low grade fever, Muscle aches and pains, Loss of sex drive, Depression

Liver Anatomy and physiology:

- The liver produces and secretes bile into the intestine where the bile assists with the digestion of dietary fat.
- The liver helps purify the blood by changing potentially harmful chemicals into harmless ones. The sources of these chemicals can be outside the body (for example, medications or alcohol), or inside the body (for example, ammonia, which is produced from the break-up of proteins; or bilirubin, which is produced from the break-up of hemoglobin).
- The liver removes chemicals from the blood (usually changing them into harmless chemicals) and then either secretes them with the bile for elimination in the stool, or secretes them back into the blood where they then are removed by the kidneys and eliminated in the urine.
- The liver produces many important substances, especially proteins that are necessary for good health. For example, it produces albumin, the protein building-block of the body, as well as the proteins that cause blood to clot properly.

- Through a vast network of biochemical reactions, the liver controls a major portion of the body's internal environment. Some of its major functions include carbohydrate, fat, and protein metabolism; formation and storage of vitamins and minerals; conjugation and excretion of steroid hormones; and detoxification of drugs and other toxins.

Problems associated with liver dysfunction can ultimately lead to serious illness such as *hepatitis*, *cirrhosis*, fatty liver, alcoholic liver disease, and *biliary cirrhosis*. *Symptoms and signs of liver disease* include yellow discoloration of the skin and eyes, dark urine, gray, yellow or light colored stools, nausea, vomiting and/or loss of appetite, vomiting of blood, bloody or black stools, abdominal swelling, prolonged generalized itching, unusual change of weight, abdominal pain, sleep disturbances, mental confusion, and fatigue

Today, as conventional medicine pursues a more integrated approach to managing disease, natural products and select herbs that influence liver function are being revisited and evaluated for their overall health promoting effects. In addition to the herbal treasure chest of ancient ayurveda offers a host of new phytochemicals that can be used both preventively and clinically to manage a spectrum of liver related imbalances.

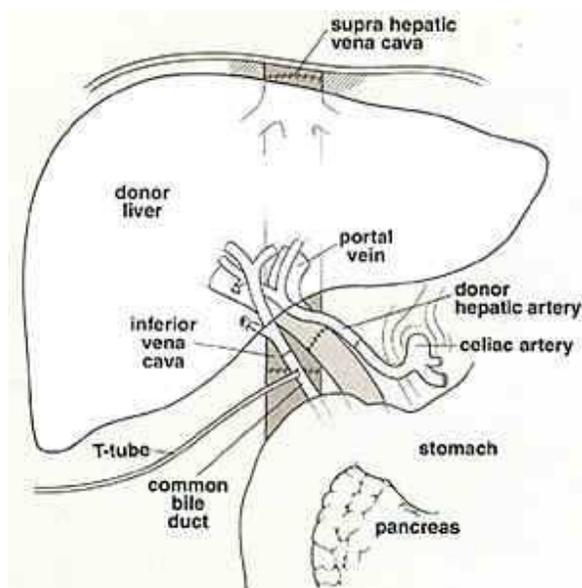


Figure-1: Liver

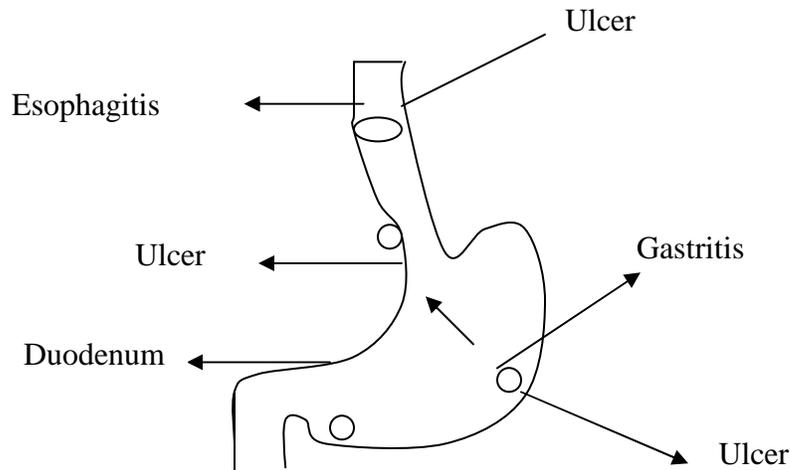


Figure-2: Stomach

Pathophysiology of Peptic Ulcer and Liver Disease¹⁰:

The pathogenesis is multifactor. These ulcers never occur in his absence of gastric acid only about 50% of patients with the disease secrete excessive quality of acid. This hyper secretion may be due to an increase parietal cell mass, excessive gastric release during meals, enhanced sensitivity to gastrin or to other factors. The disease occurs as often in socially disadvantaged manual laborers.

This disease is characterized by remissions and exacerbations relapse often occurs during spring and autumn. Relapses occur in 50 to 90% patients within a year of the first attack.

Gastric ulcer:

These ulcers occur with equal frequency in man and women. The average age of onset of gastric ulcers is between 40 to 55 years. The incidence is rising in the elderly due to the heavy use of aspirin and other non-steroidal anti-inflammatory drugs. Cigarettes smoking and aspirin ingestion increase the risk of developing gastric ulcers.

Reason of gastric ulcer:

1. *Helicobacter pylori*: Helicobacter Pylori is a curved or “s” shaped gram-negative bacillus with 4-6 lophotrichous sheathed flagella. Pylori is found primarily in the deep portions of the mucus gel layer that coats the gastric mucosa and between the mucus gel layer and apical mucosal epithelial cells. It may adhere to the luminal surface of gastric epithelial cells but does not invade the gastric mucosa⁴

Pathophysiology:

H. Pylori produce a variety of proteins that appear to mediate or facilitate its damaging effect on the gastric mucosa.

Urease produced by H. Pylori catalyzes the hydrolysis of urea to ammonia and carbon dioxide.

H. Pylori urease



Production of urease is required for gastric colonization by H. Pylori and may protect it from the effect of gastric acid, which normally prevents gastric colonization by either bacterium, hydroxide ion generated by the equilibration of water with ammonia may contribute to gastric mucosal epithelial damage.

2. Decrement in gastric Defense:

The stomach protects itself from damage by gastric acid through several mechanisms such as the presence of intercellular tight junctions between the gastric epithelial cells, the presence of a mucin layer overlying the gastric epithelial cells, the presence of prostaglandins in the gastric mucosa, and secretion of bicarbonate ions into the mucin layer. Prostaglandins, E₂ and I₂ inhibit gastric acid secretion by a direct effect on the parietal cell mediated by the EP₃ receptor¹¹.

THERAPY/TREATMENT:

(A) Therapy for liver disease includes allopathic and herbal drug treatment

(1) Hepatoprotective allopathic treatment: Specific drugs used in the management of liver disease:

(i) Ursodeoxycholic acid (Ursodiol):

Mechanism of action:

Ursodeoxycholic acid decreases intestinal absorption and suppresses hepatic synthesis and storage of cholesterol. This is believed to reduce cholesterol saturation of bile and thereby allowing solubilization of cholesterol-containing gall stones. It has little effect on calcified gallstones or on radiolucent bile pigment stones and therapy is only successful in patients with a functional gall bladder. Ursodeoxycholic acid, a relatively hydrophilic bile acid, is also believed to protect the liver from the damaging effects of hydrophobic bile acids, which are retained in cholestatic disorders. The immunomodulatory effects of ursodeoxycholic acid are believed to involve decreased immunoglobulin production by B lymphocytes, decreased interleukin-1 and interleukin-2 production by T lymphocytes, decreased expression of hepatocyte cell surface membrane HLA class I molecules and possibly stimulation of the hepatocyte glucocorticoid receptor.

Clinical applications:

Ursodeoxycholic acid has been used in the management of chronic hepatic diseases in humans such as primary biliary cirrhosis, biliary disease secondary to cystic fibrosis, nonalcoholic steatohepatitis, idiopathic chronic hepatitis, autoimmune hepatitis, primary sclerosing cholangitis, and alcoholic hepatitis. However, its therapeutic efficacy in some of these disorders has not been firmly established.

(ii) Penicillamine: Penicillamine is a degradation product of penicillin but has no antimicrobial activity. It was first isolated in 1953 from the urine of a patient with liver disease who was receiving penicillin

Mechanism of action:

Penicillamine chelates several metals including copper, lead, iron, and mercury, forming stable water soluble complexes that are renally excreted. It also combines chemically with cystine to form a stable, soluble, readily excreted complex. Although it usually takes months to years for hepatic copper levels to decrease, clinical improvement is often seen in Bedlington Terriers after only a few weeks suggesting the drug has other beneficial effects other than copper depletion. Penicillamine induces hepatic metallothionein, which may bind and sequester copper in a nontoxic form. It may also have antifibrotic effects as it inhibits lysyl oxidase, an enzyme necessary for

collagen synthesis and directly binds to collagen fibrils, preventing cross-linking into stable collagen fibers. However, its efficacy as an antifibrotic agent in humans is doubtful and it has not been evaluated in veterinary medicine. Penicillamine may have immunomodulatory effects and has been demonstrated to reduce IgM rheumatoid factor in humans with rheumatoid arthritis. However, its mechanism of action in this disease remains uncertain.

(iii) Other drugs include:

Liver disease treatment will depend on the type and the extent of disease. For example, treating hepatitis B, hepatitis C, and hepatitis D may involve the use of medications such as the antiviral medication alpha interferon. Other medications used to treat liver disease may include ribavirin, lamivudine, steroids, and antibiotics. Wilson's disease is treated by trientine or penicillamine. Other drugs are: Alphamethyldopa, halothane, INH (isoniazid), rifampicin, pyrazinamide, phenylbutazone, allopurinol, chlorpromazine, methyltestosterone, erythromycin, glibenclamide.

Side Effects:

It will depend on the treatments used for the liver disease. Antibiotics may cause stomach upset or allergic reactions. Side effects of interferon include a flu-like illness with fever, and body aches.

A liver transplant can cause many complications, including failure or rejection of the new liver. After a liver transplant, a person will need to take powerful anti-rejection medications for the rest of his or her life. Because these medications interfere with normal immune system functioning, they increase the person's risk for infections and certain types of cancer.

A person with hepatitis B, hepatitis C, or hepatitis D needs to be monitored for side effects and benefits during and after interferon treatment. Alpha interferon treatment might be repeated if the disease flares up again. A person who has received a liver transplant is checked for further disease, as well as for function of the new liver.

Cirrhosis can lead to a number of complications, including liver cancer. In some people, the symptoms of cirrhosis may be the first signs of liver disease.

(2) Herbal treatment:

Classification:

These are generally classified into 3 categories without any strict delineation amongst them.

1. Anti hepatotoxic agents: These generally antagonise the effects of any hepatotoxin causing hepatitis or any liver disorder or disease.
2. Hepatotrophic agents: These generally support or promote the healing process of the liver. In practice these two activities cannot be easily distinguished from each other.
3. Hepatoprotective agents: These generally prevent various types of liver affections prophylactically. In general any hepatoprotective agent can act as an antihepatotoxic or hepatotropic agent but the vice versa is always not true.

Hepatoprotective Natural Plants Treatmentt: Some of the crude drugs with activity against liver diseases are listed in table no 1.

Some Herbal Formulations Used In Liver Disorder:

1. Liv-52: It is non-toxic hepatoprotective substance from The Himalaya Drug Co. Liv.52 can improve the subjective condition and clinical parameters in patients with liver damage, in particular in alcoholic liver damage.
2. LIMARIN®: Capsules and Suspension: It has a potent hepatoprotective and free radical scavenging (antioxidant) action. LIMARIN® is developed from the active extract of the fruit of silybum marianum, or the milk thistle. Basically a European herbal product.
3. Cirrhitin: Cirrhitin is a natural medicine formulated specifically to treat Cirrhosis of the liver. Marketed by CCNOW. Some other polyherbal preparations such as Livex, HD-03, Hepatomed, Live 100 and Hepatoguard with proven efficacy are also use in different types of liver disorders.

Evaluation of Hepatoprotective activity: The liver function tests are employed for accurate diagnosis, to assess the severity of the damage, to judge the prognosis and to evaluate the therapy. The routinely performed liver function tests (LFTS) and various models are presented in table no 2 and 3.

(B) Therapy for peptic ulcer

Herbal Drug Therapy of Peptic Ulcer Disease:

Astragalus: Astragalus (*Astragalus membranaceus*) has been used in Traditional Chinese Medicine for thousands of years, often in combination with other herbs, to strengthen the body against disease. It contains antioxidants, which protect cells against damage caused by free radicals, byproducts of cellular energy. Astragalus is used to protect and support the immune system, for preventing colds and upper respiratory infections, to lower blood pressure, to treat diabetes, and to protect the liver.

Astragalus has antibacterial, anti-inflammatory, and diuretic (helps eliminate fluid from the body) properties. It is sometimes used topically for wounds. In addition, studies have shown that astragalus has antiviral properties and stimulates the immune system, suggesting that it is indeed effective at preventing colds.

In the United States, researchers have investigated astragalus as a possible treatment for people whose immune systems have been compromised by chemotherapy or radiation. In these studies, astragalus supplements have been shown to speed recovery and extend life expectancy. Research on using astragalus for people with AIDS has produced inconclusive results.

Recent research in China indicates that astragalus may offer antioxidant benefits to people with severe forms of heart disease, relieving symptoms and improving heart function at low to moderate doses ¹².

Barberry (*Barberis vulgaris*): Medicinal use of barberry dates as far back as ancient Egypt, and it has been used in Indian folk medicine to treat diarrhea, reduce fever, improve appetite, relieve upset stomach, and promote vigor as well as a sense of well-being. Today, it is widely used for medicinal purposes in Iran, including for biliary disorders (such as gallbladder disease) and heartburn.

Barberry and goldenseal (*Hydrastis canadensis*) are often used for similar medicinal purposes because both herbs contain the chemical berberine. Berberine has been shown to inhibit the growth of bacteria in test tubes, and also may help the immune system function better ¹².

Bilberry (*vaccinium mirtilus*): Bilberry has been used for centuries, both medicinally and as a food in jams and pies. It is related to the blueberry and is native to Northern Europe. Bilberry fruit contains chemicals known as anthocyanosides, plant pigments that have excellent antioxidant properties. They scavenge damaging particles in the

body known as free radicals, helping to prevent or reverse damage to cells. Antioxidants have been shown to help prevent a number of long-term illnesses such as heart disease, cancer, and an eye disorder called macular degeneration. Bilberry also contains vitamin C, which is another antioxidant.

Bilberry extracts are used in Europe to treat this condition, which occurs when valves in veins in the legs that carry blood to the heart are damaged. Some studies have reported improvements in symptoms, but most of the studies were of poor design. on similar antioxidants, or from test tube and limited animal studies¹³.

Calendula (*calendula officinalis*): the flower petals of the calendula plant (*calendula officinalis*), or marigold, have been used for medicinal purposes since at least the 12th century. Calendula is native to mediterranean countries but is now grown as an ornamental plant throughout the world. It is important to note, however, that not all household plants called marigold are members of the calendula family.

Calendula contains high amounts of flavonoids, plant-based antioxidants that protect the body against cell-damaging free radicals. Researchers are not sure what active ingredients in calendula are responsible for its healing properties, but it appears to have anti-inflammatory, antiviral, and antibacterial effects¹³.

Cat's claw (*Uncaria tomentosa*): Cat's claw (*Uncaria tomentosa*) is a woody vine native to the Amazon rainforest and other tropical areas of South and Central America. It is named after the hook-like thorns that grow along its vine. The bark and root of this herb have been used by South Americans going back to the Inca civilization to treat a variety of health problems including arthritis, stomach ulcers, inflammation, dysentery, and fevers. It was also used as a form of birth control.

Test tube studies indicate that cat's claw may stimulate the immune system, help relax the smooth muscles (such as the intestines), dilate blood vessels (helping lower blood pressure), and act as a diuretic (helping rid the body of excess water). It also has antioxidant properties, helping rid the body of particles known as free radicals that damage cells¹⁴.

Cayenne (*Capsicum annuum*): Cayenne pepper is an important spice, particularly in Cajun and Creole cooking, and in the cuisines of Southeast Asia, China, Southern Italy, and Mexico. Cayenne has also been used in traditional

Indian Ayurvedic, Chinese, Japanese, and Korean medicines as an oral remedy for digestive problems, poor appetite, and circulatory problems. It has also been used as a topical remedy for arthritis and muscle pain. Today, topical preparations of capsaicin are used in the United States and Europe primarily to relieve pain associated with conditions such as arthritis and shingles (Herpes zoster). Capsaicin is also a key ingredient in many personal defense sprays ¹⁵.

Evening primrose oil (*Oenothera biennis*): Evening primrose has served as food and medicine at throughout poultices from the plant for bruises and hemorrhoids. European settlers took the root back to England history, often for upset stomach and respiratory infections. Native Americans ate the boiled, nutty-flavored root, and used leaf and Germany, where it was introduced as food and became known as German rampion because it grew as a crawling vine. The plant was also a Shaker medicine, sold commercially ¹⁵.

Garlic (*Allium sativum*): Garlic has been used as both food and medicine in many cultures for thousands of years, dating as far back as the time that the Egyptian pyramids were built. Later, gravediggers in early 18th century France drank a concoction of crushed garlic in wine they believed would protect them from the plague that killed many people in Europe. More recently, during both World Wars I and II, soldiers were given garlic to prevent gangrene. Today garlic is used to help prevent heart disease, including atherosclerosis (plaque buildup in the arteries that can block the flow of blood and possibly lead to heart attack or stroke), high cholesterol, high blood pressure, and to improve the immune system. Garlic may also protect against cancer ¹⁵.

Liquorice (*Glycyrrhiza glabra*): Liquorice (*Glycyrrhiza glabra*) is a flavorful herb that has been used in food and medicinal remedies for thousands of years. Also known as "sweet root," liquorice root contains a compound that is roughly 50 times sweeter than sugar. Liquorice root has been used in both Eastern and Western medicine to treat a variety of illnesses ranging from the common cold to liver disease. This herb has long been valued as a demulcent (soothing, coating agent) and expectorant (rids phlegm and mucous from the respiratory tract) and continues to be used by health care professionals today to relieve respiratory ailments (such as allergies, bronchitis, colds, sore throats, and tuberculosis), stomach problems ¹⁶.

Peppermint (*Mentha piperita*): Peppermint (*Mentha piperita*), a popular flavoring for gum, toothpaste, and tea, also serves as a calming agent to soothe an upset stomach or to aid in digestion. Because it has a calming and numbing effect, it has been used to treat headaches, skin irritations, anxiety associated with depression, nausea, diarrhea, menstrual cramps, and flatulence. It is also widely used to treat symptoms of the common cold. These and other conditions for which peppermint may be beneficial are listed below ¹⁷.

***Nigella sativa* Linn. (In Rats):** It is a plant belonging to the family Ranunculaceae grows as a small herb and is cultivated throughout India and other tropical regions of the world. Mechanism of antiulcer action of *Nigella sativa* may be due to its flavonoid content. Alcoholic extract significantly reduces the total volume of gastric juice, free and total acidity of gastric secretion ¹⁷.

***Asparagus racemosus* (Hindi-satavari):** *Asparagus racemosus* (AR) is commonly mentioned as a rasayana in the ayurveda. Rasayanas prevent aging, increase longevity and offer resistance to disease by augmenting the immune system. The anti-ulcerogenic activity of juice of fresh roots of *Asparagus racemosus* against cold-restraint stress and pylorus ligation induced gastric ulcers ¹⁸.

***Zingiber officinale* (Roscoe):** Water decoction of ginger making up one of the constituents of mahakasaya drugs along with water decoction of *Piper longum* and colloidal solution of *Ferula asfoetida* has been reported to protect against gastric ulcers in rats. Several anti-ulcers compounds have been isolated from ginger, including 6-gingerol, 6-gingerol sulphonic acid, 6-shogaol and arcurcumene ^{19, 20}.

***Pluchea indica*:** The effect of methanolic fraction of *pluchea indica* is less. Root extract evaluated a various models of inflammation and ulcer in vivo to assess the role of *P. indica* on the 5-lipoxygenase pathway of prostaglandin synthesis. It has significant antiinflammatory activity of fraction on arachidonic acid, platelet activation factor and compound 48/80 induced paw oedema.

Ulcer studies revealed significant protective action of fraction on idoxethacin, alcohol and indomethacin alcohol induced ulceration. It has significant decrease of gastric volume and acidity in pylorus ligated rats and has significant protection action of the same on gastric mucosa ²¹.

***Dalbergia monetaria* (Linn.):** The lyophilized aqueous extract (LAE) of *D. monetaria* has significant antiulcerogenic activity and inhibited gastric ulcers lesions induced by *pylorus* ligation, ethanol and hypothermic restraint stress. To identify the antiulcerogenic mechanism of action of LAE of *D. monetaria*, the effect of LAE on prostaglandin E₂ synthesis and on the characteristic (pH volume and total acid) content of gastric juice.

The protective effect of the LAE on induced gastric lesion might be because of synergistic effect increased PGE₂ synthesis and antagonism of H₂ histamine and beta adrenergic receptors, reducing gastric acid secretion, increase PGE₂ synthesis results in increase protection and antagonism of H₂ histamine and beta receptor reduced aggressive factors against the gastric mucosa²².

***Mikania cordata* root:** The effect of methanolic fraction of *Mikania cordata* root alcoholic extract investigated for its possible ulcer protective activity in male Sprague dawley rats. Oral administration of this extract significantly prevented the occurrence of water immersion stress induced gastric ulcer in dose responsive manner.

The extract also dose dependently inhibited gastric ulcers induced by ethanol aspirin and phenylbutazone. The gastric mucus secretion in normal as well as stress and ethanol induced ulcerated animal increased dose dependently.

Therefore, *M. cordata* extract possess antiulcer activity and that the observed activity may be due to modulation of defensive factor through an improvement of gastric cytoprotection²³.

***Ocimum sanctum* L. (Labiatae):** *O. sanctum* found to possess significant antiulcer activity against aspirin, indomethacin, alcohol, histamine, reserpine, serotonin and stress induced ulceration experimental animal model. Significant inhibition also observed gastric secretion and aspirin-induced gastric ulceration in pylorus-ligated rats. The lipooxygenase inhibitory histamine antagonistic and antisecretory effect of oil could probably have contributed towards antiulcer activity *O. sanctum* fixed oil may be considered to be a drug natural origin which possesses both anti-inflammatory and antiulcer activity²⁴.

***Centella asiatica* (Linn.):** Extract of *C. asiatica* inhibited significantly gastric ulceration induced by cold and restraint stress in Charles fosters rats, antiulcer activity of plant extract compared with famotidine (H₂ antagonist)

and sodium valproate (antiepileptic). Plant alcoholic extract, formotidine and sodium valproate showed a dose dependent reduction of a gastric ulceration²⁵.

Dombeya buettneri The effects of an aqueous extract of leaves of D. between on gastric acid secretion and ethanol induced gastric mucosal damage studied in rats. Gastric acid secretion measure by continuous perfusion in urethane anaesthetized

Intragastric perfusion with extract caused significant reduction in basal and histamine stimulated gastric acid secretion. Pretreatment with extract also reduced the extent of gastric mucosal damage induced by oral ethanol (75% V/V) but have no effect on mucus secretion.

Therefore, consumption of an extract of the leaves of D. buettneri may be beneficial prevention and treatment of peptic ulcer disease²⁶.

Neurolaena lobata: The hexane fraction (H_XF) chloroform fraction (CIF) and aqueous fraction (H₂OF) fractions of a hydro alcoholic extract (HE) of N. lobata aerial parts were investigation there ability to prevent ulceration gastric mucosa. The pylorus ligation experiment demonstrated that HE, H_XF and CIF fraction changed significantly the gastric juice parameters such as pH value (increase to 5.4, 4.9. and 4.8 respectively) and acid output (decreases by 4.6, 5.3 and 6.2 (--) 4th respectively) and gastric content (increased by 400, 410 and 390 mg, respectively) in animals.

M. lobata present significant antiulcer effect when assessed in this ulcer, induced models by increased activity of defensive mechanism of stomach, such as prostaglandin synthesis and mucus production²⁷.

Ezania chlorantha: Antiulcer action of novel protoberberine type alkaloid [7,8-dihydro-8 –Hydroxy palmatine (1)], obtained from bark of E.chlorantha using the HCl ethanol, absolute ethanol and pylorus ligation techniques. The healing effect on chronic acetic acid induced gastric ulcer that, dose dependently inhibited the formation of gastric ulcer induced by HCl/ ethanol

The significant inhibition of pylorus-ligated ulcers occurs at gastric acid concentration previously known to induce severe gastric ulceration in rats.

The prophylactic antiulcer effect is associated with enhanced mucus production, which is an important factor in mechanism of the local healing process of chronic gastric ulcers²⁸.

Calotropis procera: The role of chloroform fraction of *C. procera* root extract on different experimental ulcer models in rats investigated. The extract demonstrates significant antiulcer activity against aspirin, indomethacin ethanol, indomethacin + ethanol or stress- induced ulcerations.

Significant inhibition of gastric secretary volume and total acidity in pylorus ligated rats observed to occur with extract. It also observed that root extract significantly inhibited arachidonic acid metabolism induced by soybean lipoxygenase.

The result suggest that the antiulcer activity of exact might be attributable to the inhibition of 5-lipoxygenase²⁹

Chinese cinnamon: Two active compounds prevent serotonin-induced ulcerogenesis in rats isolate from Chinese cinnamon (the stem bark of *cinnamomum cassia*) and identified as 3-(2-hydroj-phenyl)- propanoic acid and it O-glucoside. The former compound, administered orally or parenterally to rats as remarkably low dose, also inhibited gastric ulcer induced by other ulcerogens such as phenylbutazone, ethanol and water immersion stress.

3- (2-hydroxyphenyl)-propanoic acid hardly inhibited secretion of gastric acid but promote gastric blood flow, attributable to potentiation of defensive factors through the improvement the circulatory disorder and gastric cytoprotection³⁰.

Turkish: The anti-helicobacter pylori of extracts and fraction obtain from seven Turkish plants, which are used in folk medicine for the treatment of gastric disorders including peptic ulcer, study against are standard strain and eight clinical isolates of pylori by using the agar dilution method. Flower of *cistus laurifolius* and *spartium jumceum*, cones of *cedrus libani*, herbs and flowers of *centaurea solstitialis* ssp. *Solstitialis*, fruits of *momordica charanta*, herbaceous parts of *sambucus ebulus*, and flowering herbs of *hypericum perforatum* evaluated in study.

Ocimum sanctum (linn.): The antiulcerogenic property of *Ocimum sanctum* linn (OSL) study on pyloric ligated and pyloric ligated and aspirin treated rats. The aquous extract of OSL reduce the ulcer index tree and total acidity an acidity and chronic administration.

Seven days pretreatment with drugs increase the mucosa secretion also. So, OSL extract has antiulcerogenic property against experimental ulcers³¹.

Chamomile (Matricaria recutita): Chamomile has been used in connection with colic, gastritis, indigestion and heartburn, peptic ulcer, ulcerative colitis and wound healing¹⁹.

Active constituents: The flowers of chamomile provide 1-2% volatile oils containing α -bisabolol, α -bisabolol oxides A and B, and matricin, bioflavonoids apigenin, luteolin and quercetin. These active ingredients contribute to chamomile's anti-inflammatory, antispasmodic and smooth muscle relaxing action, particularly in gastrointestinal tract³².

Benincasa Hispida

Extract : Methanolic fruit extract

Model : Inbred Male wistar rats Swiss albino mice

Antiulcer studies: HCl/ ethanol induced gastric lesions indomethacin-HCl/ethanol model Aspirin pylorus ligation model.

Rabdosia trichocarpa: A diterpane, trichorabdol A from *Rabdosia trichocarpa*, shows a very strong in vitro antibacterial activity against *Helicobacter pylori*. Regarding antibacterial activity of extract and constituents, treatment of gastritis is due to suppression of *pylori* since the extract of *R. trichocarpa* particularly inhibits the growth of *H. pylori*. It is a promising native herb treatment for patients with gastric complaints including gastric ulcer caused by *H. pylori*³³.

Neem: The antiulcer effect of aqueous extract of leaves of neem tree investigated on rats exposed to 2-hr. cold restraint stress or given ethanol orally for 7 days. Extracts administered in doses of 10, 40 or 160 mg level/kg body weight either as single or five dose treatment regimens.

Means dose-dependently reduced gastric ulcers severity in rats subjected to stress and decreased ethanol produced gastric mucosal damage. The extract appeared to prevent most cell deregulation and to increase the amount

of advent gastric mucus in stressed animals these effects may explain at least in parts, the mode of antiulcer action of neem³⁴.

Turmeric (*Curcuma longa*): An ethanol extract of turmeric study on rats for its ability to inhibit gastric secretion and to protect gastroduodenal mucosa against the injuries caused by pyloric ligation hypothermic restraint stress indomethacin reserpine and cysteamine administration and cystodestructive agent including 82% ethanol, 0.6 HCl, 0.2 M NaOH and 25% NaCl. An oral dose of 500mg/kg of the extract produced significant antiulcerogenic activity in rats subjected to hypothermic restraint stress, pyloric ligation and indomethacin and reserpine administration the extract has a highly significant protective effect against cystodestructive agents³⁵

***Tectona grandis*:** 70% of ethanol extracts of its defatted trunk bark and wood chips show significant antiulcerogenic effect against experimental ulcers in albino rats and guinea pigs. Napthaquinone and lapachol active principle lapachol 5mg/mg orally twice daily for three days have antiulcerogenic effect on experimental gastric and duodenal ulcer in rats and guinea pigs. Its significant antisecretery activity and reduction in total carbohydrate, protein ration gastric juice in pylorus ligated rats³⁶.

***Bupleurum falcatum L. (Roots)*:** Crude saponin fraction from *B. falcatum* showed weak antiulcerogenic activity in pylorus lighted ulcer model. Polysaccharides which are obtained by *Bupleurum posse*'s potent antiulcer activity against HCl ethanol induced lesions in mice. Acidic polysaccharide fraction from roots of *B. falcatum* and studied its effect an HCl-ethanol, ethanol and water immersion stress induced gastric lesions in mice and pylorus lighted ulcers in rats.

Dose of 50-200 mg/kg inhibit the formation of gastric lesion induced by necrotizing agent such as HCl ethanol and ethanol in dose dependent manner and ulcer induced by water immersion stress or pylorus ligation³⁶.

***Pistacia lentiseus (Mastic)*:** Mastic is the concrete resinous exudates obtained from tree *Pistacia lentiseus*. Action on induced gastric and duodenal ulcer by pyloric ligation, aspirin, phenylbutazone, reserpine and restraint and cold stress. Decrease of free acidity in 6th pylorus ligated rats. Cytoprotective effect given against rod ethanol in rats. It

may form complex with protein and produce cytoprotective layer, which protect the gastric mucosa against Injurious agent bite salt and pepsin³⁷.

Pinax ginseng: Pinax cinseng show a dose dependent inhibition of HCl/ethanol, induced ulcer in mice. GL-4 from the leaves of P. ginseng at doses of 50 to 200mg/kg inhibited the formation of gastric lesions induced by necrotizing agent such as HCl/ethanol³⁷.

GL-4 also inhibits the formation of gastric ulcers induced by water immersion stress indomethacin or pylorus ligation. P ginseng reduces both gastric acidity and pepsin activity of juice³⁸.

Andographis Aerial Parts (Andographis paniculata): Traditionally used for a variety of ailments including liver disorders and has also been shown to protect against toxin - induced hepatotoxicity. The diterpenes of andrographis were shown to increase glutathione (GSH), which may decrease susceptibility of the tissue to oxidative damage³⁹.

Hellebore Root (Picrorhiza Kurroa): Used traditionally in Ayurveda for centuries as a general liver tonic and for liver cleansing, hepatitis, biliousness, fevers and poisoning. In a randomized, double-blind, placebo-controlled trial in patients with acute viral hepatitis, hellebore root(375 mg/3 times daily for 14 days) led to rapid fall in serum bilirubin levels toward normal range and quicker clinical recovery with no side effects. Current evidence also indicates hellebore root protects against alcohol-induced hepatotoxicity³⁹

Ginger Rhizome (Zingiber officinal): Traditionally used to promote digestion. Ginger has been found to have a stimulatory effect on gastric secretions and has metabolic circulatory enhancing effects which reinforces the therapeutic activity of other herbs^{19,20}.

Embelia Fruit (Embelia officinal): Traditionally used for hepatic conditions and liver rejuvenation⁴⁰.

Trailing Eclipta Leaf and Root (Eclipta Alba): Traditionally used as a cholagogue (aids bile secretion) and deobstruent (removes functional obstructions in the body) in hepatic enlargement, for jaundice, and other ailments of the liver and gall bladder.

Two coumestans, wedelolactone and demethyl-wedelolactone were isolated as the main active principles present in trailing eclipta. Both constituents showed anti-hepatotoxic activity in assays using liver enzyme-induced cytotoxicity

in cultured rat hepatocytes. These constituents also showed a significant stimulatory effect on liver cell regeneration. Evidence suggests that trailing eclipta exerts its protective action through a reduction in GSH depletion⁴⁰.

Indian Gall Fruit (*Terminalia chebula*): Traditionally used in chronic diarrhea and dysentery, flatulence, vomiting, colic, and enlarged spleen and liver. In a study conducted on rabbits, Indian gall fruit had a hypocholesterolemic effect on cholesterol induced hypercholesterolemia⁴⁰

Chicory Seed (*Cichorium intybus*): Traditionally used for hepatic conditions and liver rejuvenation and has shown protective effects in mice with high levels of liver damaging enzymes⁴⁰.

Long Pepper Fruit (*Piper longum*): Piperine, an active alkaloid constituent, has been shown to exert a significant protection against liver toxicity induced by tert-butyl hydro peroxide and carbon tetrachloride by reducing in both vitro and vivo lipid peroxidation by decreasing the reduction of GSH⁴⁰.

Arjuna Myrobalan Bark (*Terminalia arjuna*): The powdered bark is traditionally used as a diuretic and general tonic in cases of cirrhosis of the liver⁴¹.

Amla Fruit (*Emblica officinalis*): Traditionally used for enlarged liver and for liver revitalizing⁴².

Spreading Hog Weed Whole Plant (*Boerhaavia diffusa*): Traditionally used for hepatic disorders and for internal inflammation⁴³.

Phyllanthus Aerial Parts (*Phyllanthus niruri*): The fresh root is traditionally given in peptic ulcer⁴⁴.

SUMMARY AND CONCLUSION:

Peptic ulcer is common gastro intestinal disorder and includes gastro esophageal reflux peptic ulcer and ZE-syndrome.

It is usually arising due to imbalance in aggressive (gastric juice, pepsin production, H. pylori, alcohol, NSAID'S) and defensive factor (endogenous prostaglandin, gastrial mucosal barriers). To treat this disease two categories of the drugs are used: Synthetic drugs, Herbal drugs. Herbal drugs in case of this disease play an important role owing to various protective and curing effects on stomach. These are not only effective in the peptic ulcer but also show different associated activities.

- Antistress activity: Abiexs pindrow

- Increase mucin secretion and life span of mucosa cell: *Bacopa monniera*.
- Increase PG production: *Flueggea microcarpa*.
- Cytoprotective action: *Zingiber officinale*, capsaicin.
- Acid neutralizing capacity: *Beninecosa lispida*.
- Decrease volume acidity of gastric juice: *Garcina Cambogia*.
- Antibacterial action against *H. pylori*: *Rabdosia trichocarpas*.
- H⁺K⁺ ATPase activity inhibitor: Kampo formulation.
- Anti histamines: *Atractylodes lancea*.
- Inhibition of 5- Lipoxygenase: *Calotropis procera*.

The drugs from the plant origin play very important role to treat the peptic ulcer.

To conclude it may be said that herbal drugs have provided us with potent weapons like atropine, codeine, taxol, vincristine and vinblastine. In the modern scenario, diseases are becoming drug-resistant and scientists are studying possible roles of plant based drugs for screening life saving drugs. The herbal system of medicine is a fully fledged system of medicine and it cannot be ruled out as quackery. Backing up this system is the fact that ancient findings and documentation have through the centuries provided us with leads on the development of life-saving drugs.

Liver disease appears to be on the increase. Part of this increase may be due to our frequent contact with chemicals and other environmental pollutants. The amount of medicine consumed has increased greatly with resulting dangers to the liver. The liver, the detoxifying factory in the body, has become an increasingly overworked organ. While those who smoke, abuse alcohol and drugs and live in severely polluted environments are at greatest risk, we all suffer some threat of damage or disease to the liver.

Several hundred plants have been examined for use in a wide variety of liver disorders. Just handfuls have been fairly well researched. The latter category of plants include: *Silybum marianum* (milk thistle), *Picrorhiza kurroa* (kutkin), *Curcuma longa* (turmeric), *Camellia sinensis* (green tea), *Chelidonium majus* (greater celandine), *Glycyrrhiza glabra* (licorice), and *Allium sativa* (garlic). *Silybum marianum*, *Picrorhiza kurroa*, *Andrographis paniculata*, *Phyllanthus niruri*, and *Eclipta Alba* are proven hepatoprotective medicinal herbs, which have shown

genuine utility in liver disorders. These plants are used widely in hepatoprotective preparations and extensive studies have been done on them.

It can be concluded that knowledge of Alternative and Complementary Systems of Medicines like Ayurveda, botany, pharmacognosy and phytochemistry, biochemistry, ethno pharmacology and toxicology is integral part of herbal medicine.

Table-1: Some of the crude drugs with activity against liver diseases.

Plant name	Synonyms	Family	Origin	Chemical constituents	Use
Silybum marianum	Carduus marianus, mariane thistle	Asteraceae	indigenous to the Mediterranean region, North Africa & Western Asia	flavonolignans including silybin, silydianin, and silychristine, Silybum seeds also contain betaine (a proven hepatoprotector) and essential fatty acids,	liver disease, dyspepsia, disorders of biliary system, hepatoprotective and in chronic inflammatory hepatic disorders
Taraxacum officinale	Dandelion	Asteraceae	All parts of the northern hemisphere	Bitter constituents like taraxacerin and taraxacin, sesquiterpene lactones, phenolic acid, inulin, K	Hepatic & biliary disorders, kidney stones, remedy for jaundice diuretic, tonic
Cichorium intybus	Cichory	Compositae (asteraceae)		bitter glucoside, Cichorin	liver diseases, liver protection, chlorpromazine-induced hepatic damage
Solanum nigrum	Black nightshade	Solanaceae		solamargine, andsolasonine	liver disorders, hepatoprotective activity, cirrhosis of the liver emollient, diuretic, antiseptic, and laxative properties, Antimicrobial, antioxidants, cytotoxic properties, antiulcerogenic activity
Glycyrrhiza glabra		Leguminosae		triterpene saponin, known as glycyrrhizin, glucose, sucrose, bitter principle glycyramarin resin, aspargin and fat	anti-viral liver disease promote the regeneration of liver cells
Wilkstroemia indica	Aradon indica, wilkstromia	Thymelaeaceae		dicoumarin, daphnoretin	hepatitis B activator of protein kinase C
Curcuma longa	Curucuma, turmeric, Indian saffron	Zingiberaceae		Diarylhepatonoids including Curcumin, Curcuminoids volatile oil, starch	protect animal livers as anti-inflammatory drug

Tephrosia purpurea	basterd indigo, hoary pea sharpunkha	Fabaceae		tephrosin, deguelin and quercetin	treatment of liver and spleen diseases protective action against carbon tetrachloride and D-galalactosamine poisoning.
Fumaria officinalis	Fumatory	Papaveraceae	Europe, Mediterranean, Middle East, but has now become a weed all over the world	Alkaloids, flavonoids	Biliary & dyspeptic disorders, especially spastic discomfort of the GIT, the gall-bladder & bile ducts
Peumus boldus	Boldo	Monimiaceae	Chile and other south American regions	Alkaloids, volatile oils, flavonols and their glycosides	Dyspepsia, spastic complaints. It is the traditional anthemintic in Chile. It is also used in pharmaceutical slimming mixtures
Chionanthus virginicus	Fringe tree, old man's beard	Oleaceae	Southern parts of Northern America	Saponins, lignin glycoside	gall stones, hepatitis, jaundice & general tonic, diuretic & febrifuge. minor wounds, sores, bruises, inflammation
Andrograhis paniculata	Kalmeg	Acanthaceae	Andrographis leaves, as well as the fresh juice of the whole andrographis plant	andrographolide, a bicyclic diterpenoid lactone and Kalmeghin (upto 2.5%). andrographolide, deoxyandrographolide and neoandrographolide	Antipyretic, bacterial dysentery, arresting diarrhea and in upper respiratory infections tonsillitis, pharyngitis, laryngitis, pneumonia, tuberculosis, and pyelonephritis herpes, skin infections, and in helminthic (parasitic) infections, terminating pregnancies.
Elipta alba	Eclipta arecta, eclipta prostata	Compositae (asteraceae)		alkaloid known as ecliptin, nicotin, glucoside	Viral hepatitis, liver disorders, skin- and hair care, improves complexion, calm the mind, memory disorders, swollen glands, vision
Phyllanthus niruri/amarulus	Phyllanthus emblica, jonesiansoca	Euphorbiaceae		flavonoids and alkaloids	gall stones, hepatitis, jaundice & other ailments associated with poor liver function). general tonic, diuretic & febrifuge

Picrorrhiza kurrora	Indian gentian, kutki	Scrophulariaceae		irridoid bitter substances picroside, picroside and kutkoside	valuable bitter tonic, antiperiodic, febrifuge and stomachic and laxative jaundice potential hapatoprotectant
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Table-2: Liver function tests (LFTS) for Hepatoprotective Activity.

Type of Evaluation	Tests
Abnormalities of bile pigments and bile salts excretion tests	<ul style="list-style-type: none"> • Serum total direct and indirect bilirubin. • Urine bile salts, bile pigments and urobilinogen
Serum enzymes assays	SGOT (AST) <ul style="list-style-type: none"> • SGPT (AST) • Alkaline phosphatase (ALP) and if necessary • γ – Glutamyl transpeptidase (γ-GT) • Other enzymes
Changes in plasma protein tests	Thymol turbidity test. <ul style="list-style-type: none"> • Determination of total proteins, albumin globulins

Table-3: Various models for Hepatoprotective Activity.

Models	Discription
In vitro method	Hepatocytes are isolated by using in-situ under aseptic condition and placed in chilled HEPES (N-2-hydroxyethylpiperazine-N-2-ethanesulphonic acid). <ul style="list-style-type: none"> • These isolated hepatocytes than exposed to test samples and toxins like CCl₄, thioacetamide, ethanol and paracetamol etc. • After a specified time period the degree of toxicity or protection is assessed by viability tests (Trypan blue dye exclusion method) and enzyme levels such as SGOT and SGPT.
Ex vivo method	<ul style="list-style-type: none"> • In this method after completion of preselected in vivo test protocol hepatocytes are isolated and the percentage of viable cells and biochemical parameters are determined as liver function tests. • These methods are somewhat better correlated to clinical models than in vitro or in vivo methods.
In vivo method	These are of two types. <ul style="list-style-type: none"> •Based on bile parameters • Based on serum parameters
Experimental rat models	<ul style="list-style-type: none"> • CCl₄ model • Thioacetamide model • D-Galactosamine model • Paracetamol model • Chloroform model • Ethanol model

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Corresponding Author:

S.K.Gupta*¹

Email:garg_s.kumar@yahoo.com