



Development Of Herbal Drugs In The Treatment Of Jaundice– An Overview”

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Investigation of traditional medicine is very important for the welfare of rural and tribal communities for the conventional illness. In past few decades traditional medicine has been done in India. The manifestations of liver diseases such as Hepatitis–B, including Jaundice were treating by using herbals. Alternative approaches of herbal medications are increasingly sought by jaundice patients and health care professionals. The present review aims to give data about jaundice, how it can occurs, what are the drugs causing hepatotoxicity and present trends in research of medicinal plants accredited with anti-hepatotoxic activity. This may help to identify and develop appropriate compounds or plant products beneficial in the management of jaundice.

Key words: Hepatotoxicity, Herbal drugs, traditional uses, bilirubin, biliverdin.

Liver:

The liver is the largest organ in the body weighing 1400-1600 gm in males and 1200-1400 gm in females. There are two main anatomical lobes- right lobe and left lobe, the right is being about six times the size of left lobe. Liver is an important organ actively involved in many metabolic functions and it is the frequent target for the number of toxicants. Hepatic damage is associated with distortion of these metabolic functions. In the absence of a reliable liver protective drugs in modern medicine, there are number of medicinal preparations in Ayurveda recommended for the treatment of liver disorders. Liver is the vital organ of metabolism, detoxification and excretion from exogenous and endogenous challenges like xenobiotics, drugs viral infections. Hepatic damage is associated with distortion of these metabolic functions. About 20,000 deaths found every year due to liver disorders ¹.

Drug induced liver diseases:

Liver diseases are still world wide problem. Unfortunately, conventional and synthetic drugs used in the treatment of liver diseases are inadequate and some times can have serious side effects. Toxic liver injury produced by drugs and chemicals may virtually mimic any form of naturally occurring liver diseases. Hepatotoxicity from drugs and chemicals is the commonest form of iatrogenic diseases. Inorganic compounds producing hepatotoxicity are Arsenic, Phosphorus, copper and iron. Organic agents including certain naturally occurring plant toxins such as Pyrrolizidine alkaloids, mycotoxins and bacterial toxins ².

In general, drug reactions affecting the liver are divided into two main classes.

1. Direct or predictable.
2. Indirect or unpredictable or idiosyncratic.

Some common drugs which causes hepatotoxicity:

1) Acetaminophen (Paracetamol):

Hepatotoxicity caused by toxic doses of paracetamol is clinical important. Paracetamol is the fourth most common cause of death following self poisoning in the UK in 1989. Acetaminophen can cause severe

centrilobular hepatic necrosis when ingested in large amount. A single dose of 10-15 gm, occasionally less, may produce chemical evidences of liver damage. First 4-12 hours after ingestion nausea, vomiting, diarrhea, abdominal pain are the early manifestations, then 24 - 48 hours later, when these features are abating hepatic injury become apparent³. Acetaminophen is metabolized predominantly by a phase II reactions to innocuous sulfate glucuronide metabolites. A small portion of acetaminophen is metabolized by a phase I reaction to a hepatotoxic metabolite formed from the parent compound by the cytochrome p450. This metabolite, N-acetyl benzoquinone imide is detoxified by binding to hepatoprotective glutathione to become harmless, water soluble mercapturic acid which undergoes renal excretion^{4,5,6}.

2) Carbon tetrachloride (Tetrachloromethane):

It is one of the most potent hepatotoxin and is widely used in scientific research to evaluate hepatoprotective agents. It can also affect the CNS, after prolonged exposure it may be causes to coma and even death. Chronic exposure causes liver and kidney damage and could result in cancer. Throw the damage of liver cell mitochondria. It was suggested that lipid accumulation was due to failure of normal pathway of lipid oxidation and the death of liver cells resulted from interruption in energy transducing mechanism. The main evidence regarding the pathogenesis of hepatocellular necrosis was based on the observation that rats whose spinalcord had been divided were remarkably immune to the toxic agent. CCl₄ is also both ozone depleting and green house agent. It was widely used as dry cleaning solvent as refrigerant. CCl₄ is molecule; four chloride atoms are positioned symmetrically as corners in a tetrahedral configuration joined to a carbon atom^{7,8}.

3) Isoniazid:

Isoniazid is antibiotic which is used for anti-tuberculosis agent. Hepatotoxicity was enhanced by alcohol, rifampin and pyrazinamide. Fever, rash, eosinophilia and other manifestations of drug allergy are distinctly unusual. A reactive metabolite of acetyl hydrazine, a metabolite of isoniazid may be responsible for liver injury, and patients who are rapid acetylators would be more prone to such injury. Slow acetylators are more likely to experience hepatotoxicity and more severe hepatotoxicity than rapid acetylators. A recent study suggested that hepatotoxicity due to isoniazid as well as to combination anti tubercular therapy that includes isoniazid is more likely in patients with underlying chronic hepatitis B⁹.

4) Halothane:

It is example for idiosyncratic drug hepatotoxicity. It can causes massive necrosis of hepatic cells. Jaundice is usually noted 7 to 10 days after exposure but occur earlier in previously exposed patients. Hepatomegaly is often mild, but liver tenderness is common. The serum aminotransferase levels are elevated¹⁰.

5) Phenytoin:

Phenytoin, formerly diphenylhydantoin. A main stay in the treatment of seizure disorders has been associated in rare instances with the development of severe hepatitis- like liver injury leading to fulminant hepatic failure. In the liver, phenytoin is converted by the cytochrome p450 system to metabolites, which include the highly reactive electrophilic arene oxide. A defect (genetic or acquired) in epoxide hydrolase activity could permit covalent binding of arene oxides to hepatic macromolecules, thereby leading to hepatic injury¹¹.

6) Amiodarone:

It is an antiarrhythmic drug. It can interfere with hepatic mixed function oxidase metabolism of other drugs. The catabolic amphiphilic drug and its major metabolite diethylamiodarone accumulate in hepatocyte lysosomes and mitochondria and in bile duct epithelium. The relatively common elevations in aminotransferase levels are also considered a predictable dose dependent, direct hepatotoxic effect. Hepatic granulomas have occasionally been observed. Liver injury may persist for months after the drug is stopped¹².

7) Oral contraceptives:

The administration of oral contraceptive combinations of estrogenic and progestational steroids leads to intrahepatic cholestasis and jaundice. Especially susceptible seem to be patient with recurrent idiopathic jaundice of pregnancy. Ex- Norethynodrel, Trinethoprim- Sulfamethoxazole: This antibiotics combination is used routinely for urinary tract infections in immunocompetent persons. Biochemically and histologically, acute hepatocellular necrosis predominates, but cholestatic features are quite frequent. The hepatotoxicity is attributed to the sulfamethoxazole component of the drug and is similar in features to that seen with other sulfonamides¹³.

8) Sodium valproate:

It is an anti-convulsant useful in the treatment of petit mal and other seizure disorders, has been associated with the development of severe hepatotoxicity and rarely, fatalities, predominantly children's as well as adults. Hepatic tissue reveals microvesicular fat and bridging hepatic necrosis, predominantly centrilobular zone. Valproate hepatotoxicity is more common in persons with mitochondrial enzyme deficiencies¹⁴.

9) Methyldopa:

Minor alterations in liver tests are reported in about 5% patients treated with this hypertensive agent. In about 15% of patients with methyldopa hepatotoxicity. The clinical, biochemical and histological features are those of moderate to severe chronic severe hepatitis with or without necrosis and macronodular cirrhosis¹⁵.

10) Some other drugs which can causes hepatic injury:

Tetracyclins, salicylates, yellow phosphorus, methanol etc these are induces microvesicular fatty change in the hepatic cells. Ethanol, Methotrexate- causes fibrosis, cirrhosis of hepatic cells. Vinylchloride, Aflatoxin, Thorotrast- these drugs are causes hepatocellular carcinoma¹⁶.

Jaundice:

Jaundice is a disorder occurs due to deposition of bilirubin and its elevation in serum level and is characterized by yellow color pigmentation particularly in sclera of eye and skin¹⁷.

Normal levels of bilirubin - 0.3 - 1.2 mg/dl

Elevated levels of bilirubin - 2 - 2.5 mg/dl

Etiology:

- Excess production of Bilirubin (Hemolytic anemia, Typhoid, Malaria)
- Reduction of hepatic uptake
- Impaired Bilirubin Conjugation
- Obstruction of Gallstones in Bile ducts
- A Genetic Enzyme Deficiency
- Viral and Chemical Induced liver damage.
- Blood type incompatibility
- Food habituation

Types of Jaundice :

Rollestan and mc Nee, differentiates Jaundice into 3 types.

Hemolytic Jaundice (or) Pre Hepatic Jaundice
Hepatocellular Jaundice (or) Hepatic Jaundice

1. **Obstructive Jaundice** (or) Post Hepatic Jaundice

1. Hemolytic Jaundice :

It can be occurring due to the excessive destruction of R.B.C. so liver cells are unable to conjugate all the increased Bilirubin formed. It is also called as Prehepatic jaundice. In this type of jaundice, the free (unconjugated) bilirubin increased in blood. The formation of urobilinogen also is more resulting in the excretion of more amount of urobilinogen in urine. Any condition that causes Hemolytic anemia can leads to hemolytic jaundice.

2. Hepatocellular Jaundice:

There is an impairment of parenchymal cells of liver. So liver is unable to process Bilirubin. It is due to the damage of liver cells is called as hepatocellular or hepatic or cholestatic jaundice. Here bilirubin is conjugated. But the conjugated bilirubin cannot excreted. The damage of liver cells occur because of toxic substances (toxic jaundice) or by infection (infective jaundice) commonly the liver is affected by virus resulting in hepatitis.

3. Obstructive Jaundice:

There is an obstruction of bile flow in the extra hepatic ducts thatswwhy it is called as extra hepatic cholestatic jaundice or post hepatic jaundice. Due to obstruction the bile cannot poured into small intestine. In this, blood contains more conjugated bilirubin¹⁸.

Production and metabolism of bilirubin:

1. Source of bilirubin: Bilirubin is derived from catabolism of hemoglobin. The destruction of defeat erythrocytes at the end of their normal life span of 120 days takes place in the reticuloendothelial system in the bone marrow, spleen and liver (80-85%). The remaining 15-20% of bilirubin comes partially from non-hemoglobin heme containing pigments such as myoglobin, catalase and cytochromes, partially from ineffective erythropoiesis. Normal physiological conditions in the human adults 1.2×10^8 erythrocytes destroyed per hour. That is one day 70 kg human turnover approximately 6 gm of hemoglobin.

When hemolysis occurring hemoglobin is converted into heme and globin. It is undergo hydrolysis converted into amino acids and is reutilized for heme biosynthesis. In the presence of microsomal enzyme Hemeoxygenase, oxidatively cleaves the α -bridges of porphyrin and opens the heme ring called as Biliverdin, then it is converted into bilirubin in the presence of a cytosolic enzyme Biliverdin reductase. (Reduces the central methylene bridges of Biliverdin and converts into bilirubin). Bilirubin formed in reticuloendothelial cells is virtually insoluble in water; this is due to tight hydrogen bonds between the water soluble moieties of bilirubin¹⁹.

2. Transport of bilirubin: Bilirubin on release from macrophages circulates as unconjugated bilirubin in plasma tightly bound to albumin and transported to hepatocytes.

3. Hepatic phase: On coming in contact with the hepatocyte surface, unconjugated bilirubin is preferentially metabolized which involves 3 steps.

- A. Hepatic uptake of bilirubin by the parenchymal cells.
- B. Conjugation of bilirubin with glucuronate in the endoplasmic reticulum.
- C. Secretion of conjugated bilirubin into bile.

A. Hepatic uptake:

Bilirubin is sparingly soluble in water but it is soluble in plasma increased by non covalent binding to albumin. Each molecule of albumin appears to have one affinity site and one low affinity site for bilirubin. In 100 ml of plasma approximately 25 mg of bilirubin bounded to Albumin at its high affinity site. A number of compounds such as antibiotics and other drugs compete with bilirubin for high affinity binding site on albumin. The bilirubin from albumin and taken up at the sinusoidal surface of the hepatocytes by a carrier mediated saturated system (facilitated diffusion). The bilirubin gets bounded to cytoplasmic protein glutathione s- transferase.

B. Conjugation:

Unconjugated bilirubin is not water soluble but is alcohol soluble and is converted into water soluble form by adding glucuronic acid molecule to it. This process is called as conjugation and can employ polar molecules other than glucuronic acid (example – Sulfate). The conjugation of bilirubin is catalyzed by a specific enzyme Bilirubin-UDP-Glucuronosyl transferase (The enzyme mainly located in the endoplasmic reticulum. Most of the bilirubin excreted in the bile of mammals is in the form of bilirubin diglucuronide Bilirubin Conjugates exists abnormally in human plasma (obstruction jaundice). Bilirubin UGT actively can be induced by number of clinically useful drugs including Phenobarbital.

C. Bilirubin is secreted into Bile:

Secretion of conjugated bilirubin into the bile occurs by an active transport mechanism, which is probably rate limiting for the entire process of hepatic bilirubin metabolism. The protein involved is MRP – 2 (Multi drug resistance like protein 2) also called multi specific organic anion transporter (MOTA). It is located in the plasma membrane of the bile canalculated and handles a number of organic anions. It is the member of the family of ATP – binding cassette (ABC) transporters. The hepatic transport of conjugated bilirubin into the bile is inducible by these some drugs that are capable of inducing the conjugation of bilirubin. Conjugated bilirubin reaches the terminal ileum and the large intestine. The glucuronides are removed by specific bacterial enzymes (β – glucuronidases). The pigment is subsequently reduced by fecal flora to a group of colorless tetrapyrrolic compound called urobilinogen. Fecal flora oxidized into urobilins (color compound). Darkening of feces up on standing in air is due to the oxidation of residual urobilinogens to urobilins²⁰.

Diagnosis:

Jaundice can be diagnosed by the following ways.

- History of the patient.
- Physical examination.
- Biochemical analysis.

A) History of the patients:

First we should identify the causes to the jaundice.

- Whether he/she have the alcoholism.
- Whenever shared the injectable needles.
- Have habit of to consume drugs.
- Regularly using the synthetic medicines.

- Regularly taking balanced diet or not.

B) Physical examination:

- Yellow colorization of skin, eyes, tongue and urine.
- Abdominal pain.
- Fever.
- Loss of appetite.
- Nausea.
- Weight loss.
- Vomiting.
- Weakness.

Biochemical analysis:

Increased the concentration of bilirubin (direct & indirect).

- SGOT
- SGPT
- ALP
- GTT
- Albumin, Globulin ratio.
- Hemoglobin level.
- Prothrombin time
- Abdominal ultra sonography.
- CT scan (Computed Tomography).
- ERCPC (Endoscopic Retrograde Cholangio Pancreatic Creatography).
- Liver biopsy.

Use of plants in health and disease management.

Food and medicine have been the inseparable companion of mankind from the beginning of mans existence and man had to contend with diseases that affected his life. Among the different sources of medicines, plants have been widely used for their healing abilities for health purposes and have provided mankind with a large variety of potent drugs to alleviate suffering from various diseases. It is essential that natural products be documented and studied for systematic regulation and wide spread applications²¹.

In India, the Department of Biotechnology (DBT), Ministry of science and Technology, Government of India has sponsored a project on inventorizing medicinal plants, where in literatures on ethnobotanical, Chemical, Pharmacological and Toxicological details of around 1700 plants are being collected^{22,23}. Plants are the alternative medicines.

Even though a large number of very specific pharmacological synthetic products are available to treat almost every disease, plants still have an alternative place in today's therapy. The reason may be

- Phytochemicals are the major source of drugs, flavors, sweeteners, aromas, perfumes, insecticides, anti-parasitic drugs and many other substances.
- Many of the drug molecules of modern therapy are originated from the plant sources.

Ex. Anti-malarial drugs – Artemisinin from *Artemisia annua*.

Cardiotonic drugs - Digitoxin from *Digitalis purpurea*

Anti-cancer drugs- vincristine from *Catharanthus roseus*.

- Several other plant products are used in formulations that are sold over the counter in several countries. All this potential justifies the broadest and most exhaustive phytochemical research.
- Recognizing the merits of a wider usage of medicinal plants and of further integrated research on them, the WHO since 1977 has encouraged the study of traditional medicine in the hope of deriving the possible benefits for the needy world population²⁴.

Indian System of Medicine.

The Indian subcontinent is endowed with a rich expertise in local health traditions. Alternative medical systems are those that offer independent therapies for the full range of all the diseases, as Allopathy does.

The traditional medicine in India functions through two social streams.

1. One is the local folk stream which is prevalent in rural and tribal villages of India and is called an uncodified system of medicine.

2. The second level of traditional health care is the academic or classical system. This consists of codified and organized medical wisdom with sophisticated theoretical foundations and philosophical explanations.

Herbs are provided the basis of the great medical system. In human history of Hippocrates and Galen, Herbal medicine is a triumph of popular therapeutic diversity. About 3000 medicinal plants have been scientifically investigated for their beneficial effects based on leads from traditional medicine. In the last few decades there has been exponential growth in the field of herbal medicine. It is getting popularized in developing and developed countries²⁵.

Herbal Medicines for Liver Diseases

As per the global estimates, there are about 18000 deaths every year due to liver cirrhosis. Mainly caused by hepatitis. A phototherapeutic approach to modern drug development can provide many valuable drugs from traditional medicinal plants. Numerous plants and polyherbal formulations are used for treatment of liver diseases. Latest trends have proven their hepatoprotective potential. Silymarin, a flavonolignan mixture extract from the *Silybum marianum* (milk thistle) is a popular remedy for hepatic diseases^{26,27,28}. Several hundreds of plants have been examined for use in a wide variety of liver disorders.

Silymarin- *Silybum marianum*, Picroliv- *Picrorrhiza kurroa*, Andrographiloid- *Andrographis paniculata*, Phyllanthin- *Phyllanthus niruri*, Wed elolactone- *Eclipta alba*, Glycyrrhizin - *Glycyrrhiza glabra*, Curcuminoids – *Curcuma longa*.

Currently available modern medicine for liver disorders.

Few modern drugs are available for treating liver diseases. Drugs such as Tricholinecitate, Trithioparamethoxy phenyl propane, essential phospholipids, combination of L-ornithine, L- Aspartate and pancreatin, silymarin and ursodesoxycholic acid are generally prescribed for hepatitis, cirrhosis and other liver diseases. Hence these modern medical treatments are still far from satisfactory²⁹. Hepatitis C is an infectious viral disease of the liver. Prescribed drugs like - Interferon, Amantadine and Ribavarin. A combination therapy of interferon and ribavarin for 6 months is most commonly used for HCV treatment, it is also very expensive. The conditions like pregnancy, heart and kidney problems should not use. Usage of many folklore remedies mainly plant products, is also quite common through out India^{30,31}. In spite of such wide spread use of medicinal herbs for different disorders interest in hepatoprotective activity is kindled because in India more than 18000 people are affected with liver disorders.

Liver diseases are still a world wide problem. Based on the above facts there is need for the development of newer and safer plant based hepatoprotective (used for treatment for jaundice) drugs.

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