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Therapeutic Roles of Medicinal Herbs for the Treatment of Jaundice and Hepatitis-B

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ABSTRACT

In the developing countries like India, understating of traditional medicine or medicinal plants is very important for the welfare of rural and tribal communities in the treatment of conventional illness. In the last several years the use of medicinal plants has been on rise across the world, including India. The liver diseases like Jaundice, Hepatitis- B have been classically treated by several medicinal plants. Clinical treatment of Jaundice patients by the alternative approach of herbal medication is increasing day by day. Healthcare professionals are also advising the use of herbal medicines. The objective of our present work is to give an elaborate idea about jaundice, its occurrence, and the medicines which causes heptotoxicity and what is the present trend in the research of medicinal plants accredited with hepato-protective activities. It is very much beneficial in the identification and the development of relevant compounds or medicinal plant products which are valuable in the treatment of Jaundice and Hepatitis -B.

KEYWORDS: *Jaundice, Hepatitis- B, bilirubin, biliverdin, hepatotoxicity, herbal drugs, Liver*

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INTRODUCTION

In a human body, the liver is the largest organ having a weight of 1.4 kg to1.6 kg in males and 1.2 kg to 1.4 kg in females. There are two types of main anatomical lobes in a human body. One is right lobe and another is called left lobe. The right lobe is approximately six times larger than the size of the left lobe. Liver is a very important organ of human body which is actively involved in various types of metabolic functions and it is the soft target for the number of toxicants. Any distortion in the metabolic function of a body leads to hepatic damage. In the modern medicine system, the liver protective drugs are not so reliable; hence there are many herbal preparations available in Ayurveda which is recommended in the treatment of various disorders of liver. Liver is an important organ of human body which is involved in metabolism, excretion from exogenous, detoxification and endogenous problems like viral infections, xenobiotics. Approximately more than 20000 people lost their life every year due to different type of disorders occurred in the liver.[1,2]

Liver injury caused by synthetic compounds

If observed at worldwide level, we found that liver diseases are a big problem everywhere. However, advancement of medicine system is being taken place on the day to day basis but still the conventional and synthetic drugs are being used in the treatment of liver diseases and these drugs are not sufficient and even sometimes they are having very serious side effects on the human body. Toxic liver injuries produced due to the side effects of these medicines and chemicals may virtually mimic any form of naturally occurring live diseases. Hepatotoxicity due to drugs and chemicals is the most common form of iatrogenic diseases. The elements generally used in inorganic compounds which produce hepatotoxicity are copper, phosphorus, arsenic and iron. There are various organic agents like naturally occurring plant toxins such as mycotoxins, bacterial toxins and pyrrolizidine alkaloids. In general, we can classify the side effect of the drugs on the liver of human body into two main categories; one is direct or predictable and another is idiosyncratic or Indirect or unpredictable

There are some common drugs which produces or which causes hepatotoxicity are:

Acetaminophen (Paracetamol)

The toxic dose of Paracetamol causes hepatotoxicity. Paracetamol is very harmful to the human body. Paracetamol can cause serious centrilobular hepatic necrosis when it is consumed in a large amount. A single dose of around 15 gm may produce chemical evidences of liver damage. In the first 12 hours after injection, the human body starts showing the symptom of abdominal pain, nausea, diarrhea, vomiting then and after one or two days when these features are abating hepatic injury become apparent. Acetaminophen is metabolized via phase 2 reaction to innocuous sulphate glucuronide metabolites. In phase I reaction, a small volume of acetaminophen is metabolized to a hepatotoxic metabolite which is generated from its parent compound by the cytochrome. N-acetyl benzoquine amide, the metabolite is detoxified by binding to hepatoprotective glutathione so that it becomes harmless, water soluble mercapturic acid which further undergoes renal excretion.[3,4]

Carbon Tetrachloride (Chloromethane)

The ccl_4 is widely used chemical in scientific research to calculate the hepatoprotective agents and it is one of the most important hepatotoxin. If any person undergoes a prolonged exposure of CCL4 then it will affect the CNS, consequently that person may go in coma or in even worst condition. The liver and kidney get damaged by a chronic exposure and automatically which may lead to cancer. It is happened due to damage of liver cell called mitochondria. It has been observed that lipid accumulation takes place due to failure of normal flow of liquid oxidation and the death of liver cells is caused due to interruption in energy producing mechanism. An observation on the rats relating to the pathogenesis of hepatocellular necrosis and their spinal cord had been divided significantly immune to the toxic agent. CCl_4 is also known as ozone depleting and greenhouse agent. It is commonly used as dry cleaning agent or solvent as refrigerant. The internal structure of ccl_4 molecule is in such a way that four chloride atoms are symmetrically positioned at the corner of a tetrahedral and the carbon atom is placed at the centre of a tetrahedron.[5,6]

Isoniazid

This is the antibiotic which is used in the treatment of tuberculosis patient. Hepatotoxicity was increased by pyrazinamide, rifampin and alcohol. There are various drug allergies which are distinctly unusual such as rash, fever, eosinophilia etc. A metabolite of isoniazid may cause liver injury in a patient which are frequent acetylators and would more prone to such type of disease. Recent research has reported that hepatotoxicity due to Isoniazid and with the combination of anti-tuberculosis therapy is more likely in patients who undergo chronic hepatitis.

Halothane

This is an example of idiosyncratic hepatotoxicity. It can cause huge amount of necrosis of hepatic cells. Jaundice is identified in 7 to 10 days after exposure but occur earlier in the previously exposed patients. Liver tenderness is common though the hepatomegaly is often mild. The serial aminotransferase levels are enhanced up to certain extent.[7,8]

Phenytoin

Phenytoin is earlier known as diphenylhydantoin. In the liver of human body, Phenytoin is converted into metabolites with the help of cytochrome p450. The metabolites include the highly reactive electrophilic arene oxide. Genetic defect or acquired defect in epoxide hydrolase activity can permit the covalent bindings of arene oxides to hepatic macromolecules which consequently lead to hepatic injury.

Amiodarone

Amiodarone is an antiarrhythmic medicine. When this is used in combination with other drugs then it can interfere with hepatic mixed function oxidase metabolism of other medicines. The catabolic amphiphilic drug and its major metabolite disethylamiodarone gathered in hepatocyte lysosomes and mitochondria and in bile duct epithelium. Hepatic granulomas are generally observed. This has also been observed that liver injury may occur even after stopping the drugs for many months.[9,10]

Oral Contraceptives

This is a combination of estrogenic and other steroids. The use of oral contraceptives may lead to intrahepatic colitis and jaundice. This antibiotic combination is used for urinary tract infections in immuno competent persons. Histologically and biochemically, It is seen that hepatocellular necrosis predominates but cholestatic features are quite frequent in the patient. The Hepatitis C is attributed to the sulfomethoxazole component of the medicine and is very much similar in properties to that seen with other sulfonamides.

Sodium Valproate

Sodium valproate is used in the treatment of seizure disorders and petitmal. It is associated with the development of serious hepatotoxicity and at the sometimes fatalities mainly in the children as well as in adults also. Hepatic tissue reveals microvescicular fat and bridging hepatic necrosis which is predominant in centrilobular zone. Valproate

hepatotoxicity is most commonly found in those persons who have mitochondria enzyme deficiencies.[11,12]

Methyldopa

It is being reported in the patient that there is minor alteration in the liver test when the patients are treated with this hypertensive agent. In about 15 % - 20% patient with methyldopa hepatotoxicity. The histological, biochemical and clinical features are those of moderate to severe chronic hepatitis with or without necrosis and macronodular cirrhosis.

Some other medicines which can causes hepatic injury

There are several other medicines which can cause hepatic injuries apart from those above discussed. Salicylates, tetracyclines, yellow phosphorus produces micro vascular fatty change in the hepatic cells. Ethanol Methotroxate causes fibrosis, cirrhosis of hepatic cells and various other injuries. Thorotrast, Vinylchloride, Apolotoxin are the main cause of hepatocellular carcinoma. Some other drugs which can cause hepatic injury: Tetracyclins, salicylates, yellow phosphorus, methanol etc these are induces microvescicular fatty change in the hepatic cells. Ethanol, Methotroxate- causes fibrosis, cirrhosis of hepatic cells. Vinyl chloride, Aplotoxin, Thorotrast- these drugs are causes hepatocellular carcinoma.[13,14]

Discussion

Jaundice:

Jaundice is turmoil occurs due to accumulation of bilirubin and its increase in serum level and is identified by yellow color pigmentation mainly in sclera of eye and skin. In a human body, normal levels of bilirubin should be in between 0.3 to 1.2 mg/dl. When any person has the problem of jaundice, then the bilirubin level can increase up to 2 to 2.5 mg/dl.

Causes of jaundice:

Excess production of bilirubin (Hemolytic anemia, Typhoid, Malaria), reduction of hepatic uptake, impaired bilirubin conjugation, and obstruction of Gallstones in bile ducts, genetic enzyme deficiency, viral and chemical induced liver damage, blood type incompatibility, food habituation.[15,16]

Types of Jaundice:

The jaundice is of three types_

1. Hemolytic jaundice or pre hepatic jaundice
2. Hepatocellular jaundice or hepatic jaundice
3. Obstructive jaundice or post hepatic jaundice

Hemolytic Jaundice

This type of jaundice occurs when there is a large number of destruction of RBC and due to this, liver cells are not able to conjugate all the increased bilirubin formed. This jaundice is also known as prehepatic jaundice. In this type of Jaundice, the unconjugated bilirubin level is increased in the blood of a human body. The generation of urobilirubin is also more resulting in the excretion of more volume of urobilinogen in urine. There is also a reason called hemolytic anemia which may leads to hemolytic jaundice.[17,18]

Hepatocellular Jaundice

In this type of Jaundice, there is an impairment of parenchymal cells of the liver. Due to that, the liver is no longer able to process the bilirubin. This is due to the damage of liver cells is called hepatocellular hepatic or cholestatic jaundice. In this type of jaundice, bilirubin is conjugated. But the conjugated bilirubin is not excreted. The main cause of damage of liver cells is the toxic substances or by infection commonly the river is affected by virus resulting in hepatitis.

Obstructive Jaundice

This type of jaundice is also known as extra hepatic cholestatic jaundice. In this type of jaundice, there is an obstruction in the bile flow in the extra hepatic ducts. This is the reason, why it is also known as extra hepatic cholestatic jaundice. The bile cannot pour into small intestine due to the obstruction of normal flow of bile. In this type of jaundice, there is more conjugated bilirubin in the blood of a human body.[19,20]

Implications

Metabolism and Production of bilirubin:

1. Source of bilirubin:

This is derived from catabolism of hemoglobin. The destruction of defeat erythrocytes at the end of their normal life span which is of 120 days takes place in the reticuloendothelial system in the liver, spleen and bone marrow. This is about 85% of the total volume of the bilirubin. The remaining part of bilirubin is in partially from non-hemoglobin organs containing pigments such as cytochromes, catalase and myoglobin and also partially ineffective erythropoiesis. In a human body and in normal physiological condition erythrocytes destroyed at the rate of 1.2×10^{8}. If we take an approximation, then we can say that in one day a 72 kg man turnover approximately 7 gram of hemoglobin. In the process of hemolysis, hemoglobin is divided into heme and globin. It undergoes hydrolysis which converts it into amino acids and is utilized for heme biosynthesis. Bilirubin is formed in reticuloendothelial cells are virtually insoluble in water and the reason behind that is the tight hydrogen bonds between the water-soluble moieties of bilirubin.

2. Transport of bilirubin

The circulation of bilirubin on the release from macrophages takes place as unconjugated bilirubin in the form of plasma which is tightly bound to albumin and transported to hepatocytes.[21,22]

3. Hepatic phase

The unconjugated bilirubin when comes in the contact of hepatocyte surface it gets metabolized in 3 steps as follows:

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

Hepatic uptake:

The solubility of bilirubin in water is not so easy but it is soluble in plasma increased by non-covalent binding to albumin. In the molecule of albumin there are two affinity sites. One site has high affinity for bilirubin and the other one is having low affinity for it. In 100 ml of plasma approximately 25 milligram of bilirubin is bounded to albumin on the high affinity sites. There are other compounds whose affinity is comparable with bilirubin for high affinity ending side on albumin for example antibiotics and other medicines. The bilirubin from albumin and taken up at the surface of the hepatocytes through carrier mediated saturated system which can also be called facilitated diffusion. The bilirubin gets bonded to cytoplasmic glutathione s- transferase.

Conjugation:

As we know that if bilirubin is in unconjugated form then it is not soluble in the water. So it is converted into water soluble form by adding glucuronic acid molecules into it. This process is called conjugation and we can also use polar molecules in place of glucuronic acid for example sulphate. The conjugation of bilirubin is catalysed by a particular enzyme called bilirubin-UDP-Glucuronosyl transference. This enzyme is mainly located in the the endoplasmic reticulum. In the bile of mammals most of the bilirubin excreted is in the form of bilirubin diglucoranide. In human plasma biirubin conjugates exist abnormally. Number of clinically useful drugs such as Phenobarbital can get induced by bilirubin UGT.[23,34]

Bilirubin is secreted into bile:

The emission of conjugated bilirubin into the bile happened due to an active transport mechanism which is the rate limiting for the entire process of hepatic bilirubin metabolism. The protein which is involved in this process is MRP-2 (Multidrug resistance like protein 2). It is also called multi specific organic anion transporter (MOTA). It is situated in the plasma membranes of the bile canaliculated and handles a number of organic anions. It is the member of the family of ATP- binding cassette (ABC) transporters.

Diagnosis:

Jaundice can be diagnosed in the following ways:

- On the basis of previous history of the patient.
- By the physical examination
- By the biochemical analysis

History of the patient

In this process first we have to identify the causes to the jaundice. There may be various causes like whether he/she is alcoholic, when he/she shared the injectable needles, habitual to consume drugs, regularly using the synthetic medicines, regularly taking normal diet or not.[25,26]

Physical examination

In the physical examination to identify the jaundice one should observe yellow coloration of skin, eyes, tongue and urine, loss of appetite, weight loss, weakness, fever, nausea, vomiting etc.

Biochemical analysis

If there is any increase in the concentration of bilirubin whether it is direct or indirect. A person should get tested for SGPT, SGOT, hemoglobin level, abdominal ultrasonography, CT scan, ERCPC, albumin globulin ratio, GTT, liver biopsy etc.

Results

Role of medicinal plants in the treatment of various diseases

In health and disease management from the beginning of the human civilization it has been observed that food and medicine is the inseparable companion of mankind. Man has to content with different type of diseases that affects his life. However, there are different sources available for the medicines but the most widely used resources are plants. The plants are preferred over other resources due to their healing abilities for health purpose and they also provide a large variety of potent drugs to alleviate suffering from various types of diseases. This is necessary that natural herbal products should be documented and studied for widespread applications and systematic regulation. In our country, Department of Biotechnology under the ministry of Science and Technology, Government of India sponsored a very important project on inventorying of medicinal plants where in literatures on toxicological, chemical, ethnobotanical, pharmacological details of approximately 1800 plants are being collected. In other words, we can say that plants are the alternative drugs. However, there are a large number of specified pharmacological synthetic products are available to treat almost every disease but still the plants have a

different place in today therapy. [27,28]The importance of plants in the present days is due to the fact that Petrochemicals are the major source of aromas, drugs, insecticides, sweeteners, flavors, ant parasitic drugs and various other substances. Many of the drug molecules of present day's therapy are also produced from the plant sources for example, Anti-cancer drugs- vincristine is extracted from *Cathranthus roseus*, anti-malarial drugs – Artemisin is extracted from *Artemisia annua*, Cardiotonic drugs - Digitoxin is extracted from *Digitalis purpurea*. Many other plant products are also used in formulation that is sold over the counter in many countries.

Indian system of medicine

The Indian subcontinent has been rich expertise in local health edition. Alternative Medicine System is that offers independent therapy for almost all the diseases as allopathic does. The conventional medicine in India is common in two social streams. One level of conventional health care is classical or academic system. This system consists of organized medical wisdom with sophisticated theoretical foundations and philosophical explanations and this is codified. Other is local folk stream which is common in rural and tribal villages of our country and this is called as uncodified system of medicine. [29,30]The medicinal plants give a strong base for medical system. In human history of Galon and Hippocrates, herbal medicine is a triumph of common therapeutic diversity. Approximately 3000 medicinal plants have been investigated scientifically for their beneficial effects based on lads from traditional Medicine System. In the last many decades the growth of herbal medicine took place at exponential rate. It is equally popular in develop and developing countries.

Herbal medicines for liver diseases

If we consider worldwide, there are approximately 20000 deaths every year due to liver cirrhosis. This is mainly caused by hepatitis. Phototherapeutic approach in the development of modern medicine can provide many valuable drugs from traditional medicinal plant. In the treatment of liver diseases numerous plants and polyherbal formulations are used. Latest trends have proven there hepato-protective potential. Silymarin which is a flavonol ligan mixture extracted from the Silybum marianum (milk thistle) is widely used as a remedy for hepatic disease. For the treatment of liver disorders, hundreds of plants have been examined for use: Picroliv- *Picrorrhiza kurroa*, Andrographiloid- *Andrographis paniculata*, Silymarin- *Silybum marianum*, Phyllanthin- *Phyllanthus niruri*, Curcuminoids – *Curcuma longa*, Wed elolactone- *Eclipta alba*, Glycyrrhizin - *Glycyrrhiza glabra*.[31,32]

Conclusions

Presently available modern medicine for liver disorders

There are few modern drugs available for the treatment of liver diseases. Medicine such as Tricholinecitrate, Trithioparamethoxy phenyl propane, essential phospholipids, combination of L-ornithine, L- Aspartate and pancreatin, silymarin and ursodesoxycholic acid are commonly used in the treatment of hepatitis, cirrhosis and other liver diseases. However, performance of these modern drugs are still not up to the satisfactory level. Another liver disorder disease known as hepatitis C is also an infectious viral disease of the liver. The prescribed medicine for hepatitis C are Ribavarin, Amantadine, Interferon. In the treatment of HCV, a combination of interferon and ribavarin is used for 6 months and it is also very expensive. There are also some constraints in the use of these medicine like_ it cannot be used for the patients who is already pregnant or already having kidney and heart problem. The use of various plant products is also quite common all over the India. In spite of such widespread use of these herbal medicine for different type of disorders interest in hepatoprotective activity is kindled because in our country more than 20,000 people are affected with various type of liver disorders. Liver diseases are still a big problem at worldwide level. Based on the above facts, we may conclude that still there is a need of development of latest and safer plant medicinal plant based hepatoprotective drugs which can be used for the treatment of Jaundice and Hepatitis –B.[33,34]

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