Use of Herbal Drugs in Liver Disease and Disorders

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***Abstract*- Herbal drugs have become increasingly popular and their use is widespread. Licensing regulations and pharmacovigilance regarding herbal products are still incomplete and clear cut proof of their efficacy in liver diseases is sparse. Nevertheless, a number of herbals show promising activity including silymarin for antifibrotic treatment, phyllantus amarus in chronic hepatitis B, glycyrrhizin to treat chronic viral hepatitis, and a number of herbal combinations from China and Japan that deserve testing in appropriate studies. Apart from therapeutic properties, reports are accumulating about liver injury after the intake of herbals, including those advertised for liver diseases. Acute and/or chronic liver damage occurred after ingestion of some Chinese herbs, herbals that contain pyrrolizidine alkaloids, germander, greater celandine, kava, atractylis gummifera, callilepsis laureola, senna alkaloids, chaparral and many others. Since the evidence supporting the use of botanicals to treat chronic liver diseases is insufficient and only few of them are well standardised and free of potential serious side effects, most of these medications are not recommended outside clinical trials. Particularly with regard to the latter, adequately powered randomised-controlled clinical trials with well-selected end points are needed to assess the role of herbal therapy for liver diseases.**

***Index terms*- Alternative medicine, Antifibrotic therapy, Glycirrhizin, Hepatotoxicity, Herbal medicine, Liver disease, Silymarin**

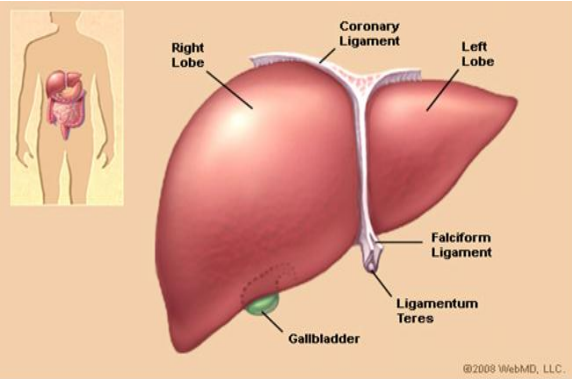
INTRODUCTION

The use of natural remedies for the treatment of liver diseases has a long history, starting with the Ayurvedic treatment, and extending to the Chinese, European and other systems of traditional medicines.
The 21st century has seen a paradigm shift towards therapeutic evaluation of herbal products in liver diseases by carefully synergizing the strengths of the traditional systems of medicine with that of the modern concept of evidence-based medicinal evaluation, standardization of herbal products and randomized placebo controlled clinical trials to support clinical efficacy.
The basic concept in these medicinal systems is that the disease is a manifestation of a general Imbalance of the dichotomous energies that govern life as a whole and human life in particular, and they focus on medicine that can balance these energies and maintain good health.
In Ayurveda of India, the forces are said to be Agni (strength, health and innovation) & Ama (weakness, disease and intoxication).In India there are also other systems of traditional medicine besides Ayurveda and these are called Siddha, Unani etc.
Which originated almost at the same time as Ayurveda from southern India, and Unani, which entered India during the Mogul dynasty periods. Like Ayurveda, practitioners of Siddha medicine believe in a perfect balance of three doshas known asvatha (space and air elements), pitta(fire and water elements) and kapha(water and earth elements).
All these Indian systems of medicine have primarily claimed a curative potential for their medicinal preparations for all kinds of liver diseases. In spite of the significant popularity of these medicinal systems, they are still to be recognized as being universally

acceptable treatment modalities for chronic liver disease.

The limiting factors that contribute to such an eventuality are:-

1. Lack of standardization of the herbal drugs;
2. Lack of randomized placebo controlled clinical trials; and
3. Lack of traditional toxicologic evaluations.



Anatomy and Physiology of the Liver:-

Anatomy:-

The liver is the largest organ of the human body, weighs approximately 1500 g and is located in the upper right corner of the abdomen.

The liver performs over 500 metabolic functions, resulting in synthesis of products that are released into the blood stream (e.g. glucose derived from glycogenesis, plasma proteins, clotting factors and urea),or that are excreted to the intestinal tract (bile).

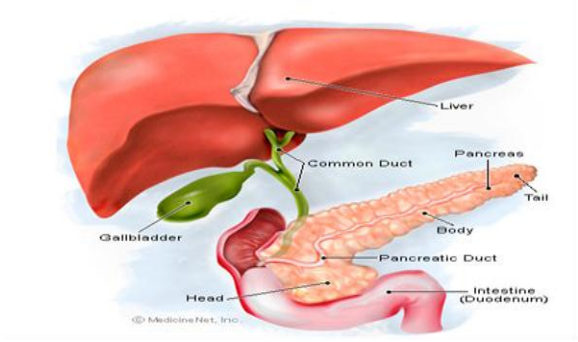
Also, several products are stored in liver parenchyma (e.g. glycogen, fat and fat soluble vitamins).

Almost all blood that enters the liver via the portal tract originates from the gastrointestinal tract as well as from the spleen, pancreas and gallbladder.

A second blood supply to the liver comes from the hepatic artery, branching directly from the celiac trunc and descending aorta.

Basic liver architecture:-

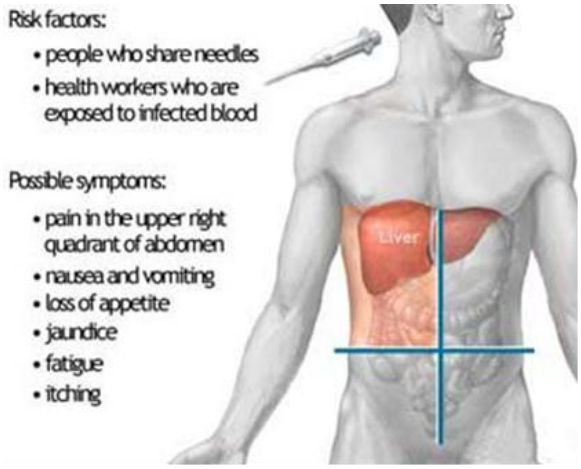
The major blood vessels, portal vein and hepatic artery, lymphatics, nerves and hepatic bileduct communicates with the liver at a common site, the hilus. From the hilus, they branch and rebranch within the liver to form a system that travels together in a conduit structure, the portal canal.



LIVER DISEASES

Hepatitis:-

Hepatitis (plural hepatitides) implies injury to the liver characterized by the presence of inflammatory cells in the tissue of the organ. The name is from ancient Greek hepar, the root being hepat , meaning liver, and suffix -itis, meaning "inflammation".



The condition can be self-limiting, healing on its own, or can progress to scarring of the liver. Hepatitis is acute when it lasts less than six months and chronic when it persists longer.

A group of viruses known as the hepatitis viruses cause most cases of liver damage worldwide. Hepatitis can also be due to toxins (notably alcohol), other infections or from autoimmune process. It may run a subclinical course when the affected person may not feel ill. The patient becomes unwell and symptomatic when the disease impairs liver functions that include, among other things, removal of harmful substances, regulation of blood composition, and production of bile to help digestion.

Viral Hepatitis:-

Viral hepatitis is liver inflammation due to a viral infection. It may present in acute (recent infection, relatively rapid onset) or chronic forms. The most common causes of viral hepatitis are the five unrelated hepatotropic viruses Hepatitis A, Hepatitis B, Hepatitis C, Hepatitis D, and Hepatitis E. In addition to the hepatitis viruses, other viruses that can also cause hepatitis include Cytomegalovirus, Epstein-Barr virus, and Yellow fever. A virus previously called Hepatitis G virus is now classified as GB virus C because it does not appear to cause hepatitis.

Hepatitis A:-

Hepatitis A or infectious jaundice is caused by hepatitis A virus (HAV), a picornavirus transmitted by the fecal-oral route often associated with ingestion of contaminated food.

It causes an acute form of hepatitis and does not have a chronic stage. The patient's immune system makes antibodies against HAV that confer immunity against future infection.

People with hepatitis A are advised to rest, stay hydrated and avoid alcohol.

A vaccine is available that will prevent HAV infection for up to 10 years. Hepatitis A can be spread through personal contact, consumption of raw sea food or drinking contaminated water.

This occurs primarily in third world countries. Strict personal hygiene and the avoidance of raw and unpeeled foods can help prevent an infection.

Infected people excrete HAV with their feces two weeks before and one week after the appearance of jaundice.

The time between the infection and the start of the illnessaverages 28 days (ranging from 15 to 50 days), and most recover fully within 2 months, although approximately 15% of sufferers may experience continuous or relapsing symptoms from six months to a year following initial diagnosis

Hepatitis B:-

Hepatitis B is caused by hepatitis B virus, a hepadnavirus that can cause both acute and chronic hepatitis. Chronic hepatitis develops in the 15% of adults who are unable to eliminate the virus after an initial infection.

Identified methods of transmission include blood (blood transfusion, now rare), tattoos (both amateur and professionally done), sexually (through sexual intercourse or through contact with blood or bodily fluids), or via mother to child by breast feeding (minimal evidence of transplacental crossing).

However, in about half of cases the source of infection cannot be determined. Blood contact can occur by sharing syringes in intravenous drug use, shaving accessories such as razor blades, or touching wounds on infected persons.

Needle-exchange programmes have been created in many countries as a form of prevention

Patients with chronic hepatitis B have antibodies against hepatitis B, but these antibodies are not enough to clear the infection that establishes itself in the DNA of the affected liver cells.

Hepatitis B treatment vaccine is available that will prevent infection from hepatitis B for life. Hepatitis B infections result in 500,000 to 1,200,000 deaths per year worldwide due to the complications of chronic hepatitis, cirrhosis, and hepatocellular carcinoma. Hepatitis B is endemic in a number of (mainly South-East Asian) countries, making cirrhosis and hepatocellular carcinoma big killers. There are six FDA-approved Hepatitis B treatment options available for persons with a chronic hepatitis B infection: alpha-interferon, pegylated interferon adefovir, entecavir, telbivudine and lamivudine. About 65% of persons on Hepatitis B treatment achieve a sustained response.

Hepatitis C:-

e primarily in the liver. It is now classified as GB virus C.

LIVERFIBROSIS

Liver fibrosis is the scarring process that represents the liver’s response to injury. In the same way as skin and other organs heal wounds through deposition of collagen and other matrix constituents so the liver repairs injury through the deposition of new collagen. Over time this process can result in cirrhosis of the liver, in which the architectural organization of the functional units of the liver becomes so disrupted that blood flow through the liver and liver function become disrupted. Once cirrhosis has developed, the serious complications of liver disease may occur, including portal hypertension, liver failure and liver cancer. The risk of liver cancer is greatly increased once cirrhosis develops, and cirrhosis should be considered to be a pre-malignant condition. Cirrhosis

and liver cancer are now among the top ten causes of death worldwide, and in many developed countries liver disease is now one of the top 5 causes of death in middle-age.1,2

Biology

The main liver cells that produce matrix are Hepatic Stellate Cells (HSC). This resident cell population exist in a resting phenotype as the body's major store of vitamin A. However on activation they transform to adopt a myofibroblast phenotype capable of secreting collagen. This fibrous tissue can then be remodelled through digestion of matrix by matrix metaloproteinases (MMPs). In turn the digestion of matrix is checked through the inhibition of MMPs by tissue inhibitors of matrixmetaloproteinases (TIMPs) of which TIMP-1 is of major importance. Liver fibrosis, previously thought to be merely the accumulation of scar tissue, is now recognised to be a dynamic process that can progress or regress over periods as short as months.3

Causes

All chronic liver diseases (CLD) can lead to liver fibrosis. Over many years the principle causes of CLD have been chronic viral hepatitis B (CHB) and alcoholic liver disease (ALD).

While rates of alcoholism and ALD are falling in many countries, hazardous drinking amongst young people is resulting in alarming rates of ALD in several northern European countries.4,5 Over the last few decades two other diseases have emerged to make a major contribution to the burden of CLD.

Chronic hepatitis C (CHC) and non-alcoholic fatty liver disease (NAFLD) are recognised to have already had a major impact on CLD incidence.

Hepatitis C virus (HCV) is transmitted in blood and blood products through unsafe injection practices and the therapeutic use of infected blood products. It is thought that the world prevalence of CHC is nearly 200 million people.6,7 In the developed world with rapidly increasing rates of obesity, NAFLD is considered to represent a major cause of significant fibrosis. Although it appears that only a minority of patients with NAFLD (maybe 20%) develop significant fibrosis, due to the vast prevalence of the at-risk overweight population, NAFLD may give rise to an epidemic of liver fibrosis.

What problems and symptoms does jaundice cause?

Jaundice or cholestasis, by themselves, causes few problems (except in the newborn, and jaundice in the newborn is different than most other types of jaundice, as discussed later.) Jaundice can turn the skin and whites of the eyes yellow.

In addition, stool can become light in color, even clay-colored because of the absence of bilirubin that normally gives stool its brown color. The urine may turn dark or brownish in color. This occurs when the bilirubin that is building up in the blood begins to be excreted from the body in the urine. Just as in feces, the bilirubin turns the urine brown Besides the cosmetic issue of looking yellow and having dark urine and light stools, the symptom that is associated most frequently with jaundice or cholestasis is itching, medically known as pruritus. The itching associated with jaundice and cholestasis can sometimes be so severe that it causes patients to scratch their skin "raw," have trouble sleeping, and, rarely, even commit suicide. It is the disease causing the jaundice rather than the jaundice itself that causes most problems associated with jaundice. Specifically, if the jaundice is due to liver disease, the patient may have symptoms or signs of liver disease or cirrhosis (cirrhosis represents advanced liver disease).

The symptoms and signs of liver disease and cirrhosis include fatigue, swelling of the ankles, muscle wasting, ascites (fluid accumulation in the abdominal cavity), mental confusion, coma, and bleeding into the intestines. If the jaundice is caused by blockage of the bile ducts, no bile enters the intestine. Bile is necessary for digesting fat in the intestine and releasing vitamins from within it so that the vitamins can be absorbed into the body. Therefore, blockage of the flow of bile can lead to deficiencies of certain vitamins. For example, there may be a deficiency of vitamin K that prevents proteins that are needed for normal clotting of blood to be made by the liver, and, as a result, uncontrolled bleeding may occur.

REFERENCES

[1] Paul Knekt, JormaKumpulainen, RitvaJarvinen, HarriRissanen, Heliovaara, AnttiReunanen, TimoHakulinen, and ArpoAromaa (September 2002), "Flavonoid intake and risk of chronic diseases". Am J ClinNutr 76 (3) : 560-8.

[2] Tsushida T, Suzuki, M. (1996) Content of flavonolglucosides and some properties of enzymes metabolizing the glucosides in onion. J. Jap. Soc. Food sci.Technol.,43,642-649.
[3] Slimestad R, Fossen T, Vagen IM (December 2007). "Onions: a source of unique dietary flavonoids". Nature 424: 1013.
[4] Serafini, M., Crozier, A., Bugianesi, R., Maiani, G., Valtuena, S., and Santis, S.D. (2003). "Nutrition: milk and absorption of dietary flavamp;s". Nature 424: 1013.
[5] VerveridisFilippos, F: TrantasEmmanouil, Douglas Carl, Vollmer Guenter, Kretzschmar Georg, Panopoulosnickolas (October 2007). "Biotechnology of flavonoids and other phenylpropanoid-derived natural products. Part I : Chemical diversity, impacts on plant biology and human health". Biotechnology Journal 2 (10); 1214.
[6] Burda S. and Oleszek W. (2001), Antioxidant and anti- radical activities of flavonoids. J. Agric. Food Chem. 49.
[7] Yokozawa T., Dong E. D., Liu Z., W. and Shimizu M. (1997), Antioxidative activity of flvones and flavo – nols in vitro. Phythotherapy Res. 11, 446D449.
[8] Ginter E. The role of antioxidants in prevention of tumors. BratislLekListy 1995;96:195-209
[9] Zheng R-L and Zhang H, "Effects of ferulic acid on fertile and asthenozoospermic infertile human sperm motility, viability, lipid peroxidation and cyclic nucleotides," Free Radical Biology & Medicine, 1997;22:581-586.
[10] Presentation by Steven Tenenbaum, Ph.D., and Julie Paul, Ph.D., Natural Foods Expo West, Anaheim, Calif., March 6, 1997.
[11] BastA,Haenen GR, Doelman CJ. Oxidants & Antioxidants: State of art. Am J Med 1991;91:2S- 13S.
[12] Campos AM, et al., "Total antioxidant potential of Chilean wines, Nutrition Research, 1996;16:385-389.
[13] Mann D, "Grape juice and beer may prevent heart disease," Medical Tribune News Service, March 18, 1997.