GASTROENTEROLOGY IN INDIA

Indigenous Drugs and Liver Disease

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Introduction
Liver disease, acute or chronic, is a cause of significant human morbidity. Although the liver has a tremendous capacity of regeneration, acute liver illnesses often lead to serious chronic sequelae such as chronic hepatitis, cirrhosis and even carcinoma. The modern medical armamentarium includes simple remedies like vitamin supplements, strong agents like steroids, and sophisticated therapies like liver transplantation. Several new compounds such as colchicine, cyanidanol-3, sylimarin, malonate, ursodeoxycholic acid and prostaglandins appear promising. These however need further clinical evaluation before they can be recommended for routine clinical use. Thus the search for a specific remedy continues.

The inability of the modern synthetic approach to provide a satisfactory answer has led to a shift in focus to alternative forms of therapy based on drugs derived from plants. Internationally, there are more than 600 commercial preparations with claims of liver protective activity. In India, several combinations of about 100 Indian medicinal plants are available as hepatoprotective formulations. A monograph published by the Central Council for Research in Ayurveda and Siddha concluded that indigenous, plant-based drugs have a role in the treatment of hepatocellular jaundice. A review of literature published between 1986 and 1993 discussed the data on 43 plants and about 23 herbal drugs showing hepatoprotective activity. These conclusions are based on research data which are not easily available to a medical practitioner. Unfortunately, much of the information on indigenous hepatoprotective drugs is published in non-peer reviewed journals with a bias for natural products/alternative medicines or non-clinical journals. Many pharmaceutical companies have used these studies to further their marketing claims of natural products. A physician prescribes these agents more often empirically than as an intellectual therapeutic choice.

There is thus a need for a balanced look at the literature on hepatoprotective agents in order to provide a framework for assessing the potential of these therapies in clinical practice. With these objectives, we have attempted to review the Indian literature on hepatoprotective indigenous drugs/plants.

Assessment of hepatoprotective agents
Three experimental approaches have been used to assess hepatoprotective activity: in vivo animal studies, in vitro assay methods, and clinical trials.

In animal model (in-vivo) studies, liver injury is produced, usually in mice or rats, by a toxin, viz carbon tetrachloride (CCL4) ethanol, galactosamine or paracetamol. This leads to induction of processes like cell injury, necrosis, regeneration of liver cell mass, reorganization of liver structure, control of blood flow, etc. The hepatoprotective ability of the plant extract is assessed using parameters like levels of transaminases, alanine amino- aspartate (AST), and albumin aminotransferase (ALT) serum bilirubin, glutathione, lipid peroxidation and triglycerides, and changes in the histopathology of the liver. Another commonly used parameter is barbiturate sleeping time. This test is a measure of enzyme induction.

Animal studies pose a number of problems. First, these are based on acute chemical injury whilst the most common form of clinical liver disease is viral in etiology. Liver damage caused by toxins may be different from the effect of natural hepatotoxins. Second, chronic liver disease is hard to mimic in the laboratory. Finally, the herbal extract is usually administered along with or before the injection of toxin, and hence the focus is on preventing the damage due to a toxin. In contrast, patients present after the liver injury has set in. It is thus difficult to extrapolate the information from animal studies to the human situation. In vitro assay methods of hepatotoxicity use cultured rat hepatocytes. These methods score over in vivo methods in having better reproducibility, however, they are less applicable to humans.
Table: Hepatoprotective Medicinal Plants in Clinical Use

<table>
<thead>
<tr>
<th>Plant</th>
<th>Common name</th>
<th>AnimalClinical studies</th>
<th>studies</th>
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<tbody>
<tr>
<td>Acrimony asocaera</td>
<td>Latjira</td>
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<tr>
<td>Andrographis paniculata</td>
<td>Kalmegh</td>
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<td>Aloe indicia</td>
<td>Gkankar</td>
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<td>Boerhaavia diffusa</td>
<td>Punarnava</td>
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<tr>
<td>Berberis aristata</td>
<td>Daru haridra</td>
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<td>Cleome endivia</td>
<td>Kasani</td>
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<tr>
<td>Curcuma longa</td>
<td>Haldi</td>
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<tr>
<td>Emblica officinalis</td>
<td>Amalaki</td>
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<tr>
<td>Emblica ribes</td>
<td>Vindang</td>
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<td>Eclipta alba</td>
<td>Bhringraja</td>
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<tr>
<td>Fumaria officinalis</td>
<td>Pitapara</td>
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<tr>
<td>Gljyrrhiza glabra</td>
<td>Yasagandh</td>
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<td>Luffa echinata</td>
<td>Bindaal</td>
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<tr>
<td>Phyllanthus niruri/amarus</td>
<td>Bhuamal</td>
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<tr>
<td>Picrolivis kurroa</td>
<td>Kutakki</td>
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<tr>
<td>Piper longum</td>
<td>Pipali</td>
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<tr>
<td>Piper nigrum</td>
<td>Katinbreh</td>
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<tr>
<td>Ricinus communis</td>
<td>Erand</td>
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<tr>
<td>Solenum nigrum</td>
<td>Maks, Kakamari</td>
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<tr>
<td>Tephrosia purpurea</td>
<td>Sharpunaka</td>
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<tr>
<td>Terminaria chebula</td>
<td>Hariaki</td>
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<tr>
<td>Tinospora cordifolia</td>
<td>Gato</td>
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<tr>
<td>Withania somnifera</td>
<td>Asongdh</td>
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(* = Studies published in literature)

Most clinical studies are conducted in patients of viral hepatitis, acute or chronic. Efficacy is judged by clinical improvement and change in biochemical parameters of liver disease. However, usually these studies are open and uncontrolled. As most acute liver conditions have a natural recovery, it is difficult to link the improvement to the natural product.

Hepatoprotective plants

Many Indian plants are claimed to have hepatoprotective activity. The available market formulations in India contain one or more these plants in varying proportions. A partial list is given in the Table. However, not all of these plants have been well researched. The following discussion focusses only on selected plants which have undergone animal testing and/or clinical trials.

*Picrolivis kurroa (Ptk)*

This plant is a constituent of many marketed formulations. Since the pioneering work of Pandey in 1966, many investigators have shown hepatoprotective effects of Ptk in diverse models of liver injury. Ptk, in a dose of 2 g/Kg, reversed the increase in AST and ALT caused by CCl4 and improved BSP retention time. In CCl4, paracetamol and allopurinol models, Ptk significantly reduced liver transaminases and restored the levels of Na+/K+ ATPase to normal.

Picrolivis, a standardized fraction of alcoholic extract of Ptk containing 55-60% of a mixture of picoroside-I and kuttikoside, has been studied in animals. When given before the toxin, picrolivis showed hepatoprotection against injury induced by paracetamol, thioacetamide, galactosamine and CCl4.10 Thioacetamide-induced cholestasis was reversed by pre-treatment with picrolivis, with hepatoprotective activity comparable to that of silymarin.11 In partially hepatectomized rats, picrolivis and silymarin improved liver regeneration as judged by enhancement of increase in DNA, RNA synthesis and mitotic of hepatocytes.12

There are only a few clinical trials with Ptk. In an early open study,3 Ptk 1 g thrice daily, given for a mean period of 26 days to 20 patients with hepatocellular jaundice, showed significant improvement in serum bilirubin AST and ALT. Vaidya et al13 conducted a double-blind, randomized, placebo-controlled trial with Ptk in patients with viral hepatitis who had symptoms for less than 10 days. Ptk (375 mg thrice daily for 2 weeks) gave a significant reduction in serum bilirubin, AST and ALT. The time required for serum bilirubin to drop to 2.5 mg/dl, as calculated from extrapolation on a semilog graph, was 75.9 days with placebo and 27.4 days with Ptk. There was marked improvement in anorexia, malaise, nausea, vomiting, liver size and tenderness with Ptk. No side-effects were noticed.

These experimental and clinical data support the claim of hepatoprotection with Ptk and its chemical constituent picrolivis. Ptk may thus appear to be a good therapeutic option in early viral hepatitis.

*Tinospora cordifolia (Tc)*

In a CCl4 model, acute damage was enhanced by pre-treatment with Tc, but it proved effective in chronic injury models in prevention of fibrosis and in stimulating regeneration of hepatic tissue.14 In a rat model of choles-sis, treatment with an extract of Tc, 100 mg/Kg twice a day for 7 days, led to improvement in immune function.14 Tc was given 4 weeks after development of cholestasis and showed a trend towards normalization of phagocytic activity of macrophages, neutrophils and intracellular killing capacity of macrophages. The mortality in cholestatic rats on Tc was 16.7% as compared to 77.8% in control.
rats.\textsuperscript{15}

Rege et al studied the effect of addition of Tc to conventional treatment (Vitamin K, antibiotics and biliary drainage) in patients with malignant obstructive jaundice.\textsuperscript{16} After institution of biliary drainage, an aqueous extract of Tc was given in a dose of 16 mg/Kg/day for 3 weeks. Hepatic function was comparable in both groups. However, phagocytic and killing capacities of neutrophils normalized only in patients receiving Tc. Clinical evidence of septicemia was observed in 50% of patients on conventional treatment as against none of the Tc patients. Post-operative survival was 40% in the conventional treatment group and 92.4% in the Tc group.

In Ayurvedic texts, Tc is considered as Rasyana\textsuperscript{14} a plant which promotes longevity, increases body resistance and imparts immunity against disease. Tc has shown interesting properties of promoting regeneration of liver and immunomodulation.

\textit{Andrographis paniculata (Ap)}

In a CCl\textsubscript{4} injury model, pre-treatment with an aqueous extract of Ap resulted in an increase in biliary flow and liver weight and a decrease in hexobarbital sleeping time\textsuperscript{2,4,7,17} and ALT and AST.\textsuperscript{2} Andrographolide, the active principle, showed choleric action in rats\textsuperscript{18} and prevention of CCl\textsubscript{4} induced increase of ALT and AST.\textsuperscript{2} In an open trial, Chaturvedi et al\textsuperscript{19} treated 20 patients with viral hepatitis with a decoction of Ap in a dose of 60 mL/day (equivalent to 40 g of crude drug) for an average period of 24 days. There was a statistically significant decrease in serum bilirubin, AST ALT and serum alkaline phosphatase, and an increase in serum globulin. A formulation containingPk and Ap (Kanukshad Yoga) did not show any effect in patients with obstructive jaundice, chronic cholecystitis and cirrhosis of liver.\textsuperscript{2} Ap is a constituent of many commercial hepatoprotective formulations and deserves further clinical studies.

\textit{Eclipta alba (Ea)}

Pre-treatment with Ea reduced alcohol-induced hepatic necrosis in rats in a CCl\textsubscript{4} guinea pig model and caused significant decrease in AST, ALT and serum alkaline phosphatase, and an improvement in parenchymal damage.\textsuperscript{2} In an open clinical trial in 50 children with jaundice and 20 adults with viral hepatitis, Ea 50 mg/Kg per day gave biochemical recovery in 2-3 weeks.\textsuperscript{20} Thayagrajan \textit{et al} showed that extracts of Ea, when incubated with HBsAg positive sera in vitro showed inactivation of HBsAg.\textsuperscript{21} This widely used plant needs to undergo proper clinical evaluation.

\textit{Phyllanthus niruri (Pn)}

This plant, known also as Phyllanthus amarus (Pa), is commonly used for the treatment of jaundice and shows reversal of CCl\textsubscript{4} induced liver damage.\textsuperscript{22} Phyllanthus extracts inhibit the endogenous DNA polymerase of HBV virus, woodchuck hepatitis virus and duck hepatitis virus.\textsuperscript{22} Thayagrajan \textit{et al} treated 37 carriers of hepatitis B virus with Pa for 30 days. Of these, 59% lost HBsAg when tested 15-20 days after the end of treatment, compared with only 4% of placebo-treated controls. However, Leelarasamee \textit{et al} reported that Pa failed to eradicate HBsAg from symptomless carriers.\textsuperscript{23}

Other plants

In an open study in 7 patients, \textit{Kumari asawa} a formulation containing \textit{Aloe indica}, showed improvement in liver function tests.\textsuperscript{3} There was no effect on patients with cirrhosis of liver, chronic cholecystitis or obstructive jaundice. In patients with chronic cholecystitis, berberine, an alkaloid of \textit{Berberis aristata}, showed a decrease in bile bilirubin level and an increased gall bladder bile volume;\textsuperscript{24} there was no response in patients with cirrhosis of liver and obstructive jaundice.\textsuperscript{3} \textit{Luffa echinata}, as nasal drops, produced intense rhinorrhea and a significant drop in serum bilirubin and ALT.\textsuperscript{24} \textit{Piper longum} afforded no protection against acute damage or cirrhotic change but it improved regeneration process by restricting fibrosis in a rat model of CCl\textsubscript{4} induced hepatotoxicity.\textsuperscript{2}

Other plants with interesting hepatoprotective and/or choleric activities include \textit{Asafoetida indica}, \textit{Boswellia diffusa}, \textit{Cucumis longa}, \textit{Tephrosia purpurea}, \textit{Fumaria officinalis}, \textit{Salvia nigrum}, \textit{Withania somnifera}, \textit{Gynura zibbardii}, \textit{Ricinus communis}, \textit{Cichorium endivia}, \textit{Lewisia inermis} and \textit{Wedelia calendulacea}.\textsuperscript{7} However, there are very few clinical/experimental studies supporting their use.

Ayurvedic approach to liver disease

Clinical diagnosis based on signs and symptoms at different stages, and prognostication of jaundice (Kama) have been described in ayurvedic classics. Though the clinical picture described is similar to that available in present day medical texts, the understanding of pathogenesis is significantly different. In Ayurveda, jaundice is considered a disease of the circulatory system, involving both the liver and spleen, and is attributed to vitiated \textit{Pitta}.\textsuperscript{25,26} The liver and spleen are described as roots of the \textit{rakta vaha srotaas}, the channels of blood. The signs and symptoms of jaundice described in relation to the \textit{rakta vaha srotaas}, or those due to blood disorders, provide important information in terms of symptomatic manifestations of liver-related disorders. These include darkening of the skin, fever, burning sensation, redness of eyes, thirst, headache, fatigue, drowsiness, tremors, etc.\textsuperscript{27,28}
The therapeutic approach focuses on treatment of the vitiated pitta through dietary changes, cleaning processes and use of drugs. The dietetic approach includes the use of food articles like jaggery, turmeric, buttermilk, cabbage juice, cream of meat juice, coconut fibers, or even cow’s urine, which are prescribed with specifications depending on the stage of the disease. The drug therapy includes fresh juices or extracts of single plants or of several plant combinations. Many formulations containing more than one substance of herbal, mineral, or animal origin, and of different dosage forms like extracts, pills, medicinal wines, medicated ghee, etc are prescribed. Some of these formulations, like Arogyavardhini, Punarnavadi Kwatha, and Kusum-asaava, are experimentally and clinically proven to be effective. The role of other indigenous drugs, dietary items and pancha karma in the treatment of hepatic diseases is not well studied.

Several pharmacological preparations containing either known hepatoprotective or other plants are claimed to provide significant hepatoprotection in CCL4 damage. It is debatable whether the use of multiple plants in one formulation will provide synergistic effect or reduce unwanted effects. Besides, these formulations have different plants or the same plants with different names in varying dosages. There is a need to undertake studies for understanding the effects of these plants and to identify their role in different hepatic disorders. The current paradigm in the research of indigenous drugs is based in in vitro testing, animal models of liver injury, and clinical trials focused on a group of patients with a common allopathic diagnosis. While designing these experiments, there is a need to take into account the Ayurvedic approach to pathogenesis and treatment based on the three doshas theory and at least to conceptually correlate these with hepatic damage of different types as understood in modern medicine.

Conclusion
A wide variety of herbs and their active principles have undergone experimental studies in diverse models of liver injury, and cholestasis. Pretreatment with extracts of these plants has shown hepatoprotective activity and/or choleretic activity based on biochemical and/or histopathological assessment. However, only a few have undergone proper clinical trials, e.g. Pk and Te in viral hepatitis/obstructive jaundice. Most of these plants have a broad spectrum of activity on the cardiovascular and nervous systems gastrointestinal tract, etc.

Only well-planned, placebo-controlled, clinical studies with due attention to efficacy and safety parameters (effect on other organs) will allow us to judge the true potential of indigenous drugs in the treatment of liver disease. Current experimental approaches on indigenous drugs focus on the allopathic approach to jaundice and liver disease. We believe there is a need to discuss and develop clinical models of liver diseases based on Ayurvedic theory in order to provide new insights into hepatoprotection.

References


