Candidate's Name	:	RAM PRASAD
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Thesis Title	:	Screening of Hepatoprotective Potential of Certain Medicinal Plants in Liver Cirrhosis and Carcinoma
Supervisor	:	Prof. Luqman Ahmad Khan
Co-supervisor	:	Prof. Shakir Ali

Thesis Abstract

Liver is an important organ inside the human body and performs several vital activities, and its position in the metabolism makes it susceptible to various types of hepatic diseases. After numerous developments in medical science, liver diseases are still a world wide health problem. Unfortunately, conventional or synthetic drugs used in the treatment of liver diseases are inadequate and sometimes can have serious side effects. Therefore, it is necessary to search for alternative drugs in order to replace currently used drugs. Herbal drugs are traditionally used in various parts of the world to cure different diseases and an important source of potentially useful new compounds for the development of effective treatments to combat liver problems.

The present study is an attempt to elucidate the hepatoprotective properties of 50% hydroalcoholic extracts of *Valeriana jatamansi, Syzygium aromaticum,* and *Citrus sinensis* on thioacetamide induced hepatotoxicity in rats. Thioacetamide is a potent hepatotoxin and its mechanism to produce hepatotoxicity mimics alcohol induced liver injury in humans.

Animal models of hepatic injury (necrosis, cirrhosis, and carcinoma) were re-produced by using thioacetamide (single i.p injection of thioacetamide at a dose level of 400mg/kg body weight; 0.03% thioacetamide in drinking water for 16 weeks to induce cirrhosis, while 64 weeks for carcinoma) and validated biochemically. In the animal model of liver necrosis, *V. jatamansi*, *S. aromaticum* and *C. sinensis* were studied for their efficacy. These extracts were administered at a dose level of 800mg/kg body weight throughout the study. The results using the animal model of thioacetamide induced hepatotoxicity in rats demonstrated that all these three extracts reduced the level of AST, ALT, ALP, and GGT when given prior to thioacetamide intoxication. The decreased levels indicate the stabilization of plasma membrane and protection of hepatocytes against thioacetamide induced damage. This suggests hepatoprotective activities of theses plants and further supportive evidences were also observed.

Chronic form of liver diseases, cirrhosis and carcinoma were induced by thioacetamide. After successful completion of the experiments, all experimental rats were sacrificed and biochemical as well as histochemical parameters were studied. Percent liver weight body weight ratio increased in comparison to the normal control rats and decreased significantly in treated rats. ALP and GGT, which increased in liver cirrhosis almost normalized in the treated rats. Elevation of the plasma levels of cytoplasmic and mitochondrial enzymes is a sensitive indicator of liver damage. TAA induced liver damage has been reported to correlate with an increase in the activity of these enzymes. Among the various phosphatases, ALP has attained much attention because of its location in the plasma membrane and possible role in active transport. The efficacy of any hepatoprotective drug is essentially dependent on its capability of either reducing the harmful effects of a hepatotoxin or maintaining the normal physiological mechanism that is

disturbed by a hepatotoxin. Elevated level of lipid peroxidation (LPO) is an important factor for the development of liver fibrosis. LPO increased in the model group over the control group. Following the extract treatment, the value decreased in the range close to the normal control. Reduced glutathione (GSH), which decreased significantly ($p<0.05$) in the model group, was almost normal in the treated group. Glutathione reductase (GR), the enzyme required for the recycling of GSH (from its oxidized form, GSSG) also decrease in the model group, and attained the value similar to the control in treated rats. The peroxide metabolizing enzymes, catalase and GPx also decreased significantly ($p<0.05$) in the model group and tend to increase in the treated rats. Non-microsomal Phase I drug metabolizing enzyme xanthine oxidase (XO) increased in thioacetamide induced cirrhotic model when compared to normal control, and decreased in the group receiving the extracts. This effect can be correlated to the activity levels of peroxide metabolizing enzymes, oxidative stress markers, serum markers of liver cirrhosis and other signs and symptoms of hepatic injury. Further, GST, which is a phase II drug metabolizing enzyme, increased in the LC group and decreased significantly following the post-treatment. Deposition of collagen, which is secreted by the activated hepatic stellate cells (HSC), is a characteristic change during liver cirrhosis that results in gross morphological changes and changes in the hepatic tissue architecture. The whole organ and the sections from the treated and the control group show characteristic nodules on the liver in the model group. The texture of the liver in the control and extract treated rats was almost similar in comparison to the model group.

Anticancer activity of the herbal extracts was studied assaying DNA synthesis using ^{3}H thymidine. Increase in thymidine uptake was found in the hepatic tissue of treated rats. In the drug treated animals, increased level of hepatic DNA was reduced to normal. Other biochemical and histopathological changes were also recorded.

On the basis of biochemical and histopathological observations, it can be concluded that hydroalcoholic extracts of *V. jatamansi, S. aromaticum* and *C. sinensis* show hepatoprotective properties.

Key message of this study is that the herbal extracts and their isolated compounds are good candidates for developing therapies that can be used for the prevention and perhaps the treatment of acute and chronic liver diseases such as the necrosis, fibrosis/cirrhosis and carcinoma.