

The Liver: Mechanisms of Toxic Injury and Therapeutic Prevention

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Introduction

In the environment, there are a great many agents that are potentially toxic to the cells of the liver, ranging from the poison on toadstools, ingestion of alcohol, to commonly prescribed drugs. These agents can damage the delicate muralium structure of the liver through a number of different mechanisms. Fortunately, specific information from the research community continues to accumulate suggesting ways to realize some adaptive protection against liver injury.

Development

The liver embryologically develops from an outpouching of the embryonic primary foregut. Throughout life its delicate connection to the digestive system is through the common bile duct, which empties into the duodenum.

The parenchyma of the liver is perfused by two large vessels. The hepatic portal vein carries nutritional elements from the stomach and the intestines. Another vessel of great importance is the smaller hepatic artery. The hepatic artery services the liver and in particular the hepatocytes with a rich supply of oxygen. The hepatocytes are very versatile and dynamic cells. They are responsible for a number of different functions attributed to the liver. These multifunctional cells are responsible for: storage of glucose, glycogen, fats, proteins and vitamins, synthesis of blood clotting and blood thinning factors, synthesis and secretion of bile as well as the detoxification of metabolic wastes. It is this detoxification role performed in the cytochrome P450 enzyme system that

is so crucial to the detoxification process.

Classification of Liver Injury

An noxious agent that attacks the liver, is most likely to enter through the hepatic portal vein system, emerging from the central zone of the liver acini. There are several ways of classifying hepatic injury. The most comprehensive system describing liver injury is based on a morphological classification. Popper and Schaffner in 1959¹ elaborated an elegant scheme that comprised five categories of liver injury. The categories described are:

1. Zonal hepatocellular alterations without inflammatory reaction (necrosis or steatosis ie. fat accumulation)
2. intrahepatic cholestasis
3. hepatic necrosis with inflammatory reaction (can have progression to massive necrosis)
4. an "unclassified group" of injuries that do not fit any scheme
5. those agents that produce hepatic cancer.

A useful example of a disease that focuses on the categories of liver injury described by Popper and Schaffner is the transformation of normal hepatic tissue into the alcoholic cirrhotic liver.

Naturopathic Regimen Encouraging and Aiding the Healing Process of Hepatic Tissue

In treating alcoholic liver injury, the naturopathic approach involves detoxification and regeneration. Detoxification is the metabolic processing of endogenous and exogenous compounds which are destined to be eliminated from the body. In the case of alcohol abuse, the detoxification pathways have been overloaded by chronic ethanol consumption. Regeneration is the correction of morphological, biochemical and physiological abnormalities, leading to a restoration of normal hepatocyte function

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and structure of the liver parenchyma.

Support of the detoxification enzymes can be achieved by providing the essential nutrients. Excessive alcohol consumption is associated with multiple vitamin deficiencies. Poor dietary intake of essential nutrients, irritation of the gastrointestinal tract by alcohol and increased metabolic demand for certain vitamins all complicate matters. For example, nicotine adenine dinucleotide (B₃) is a part of alcohol dehydrogenase, yet may be deficient due to the above factors.

The stimulation of bile flow can help the liver to dispose of wastes. Botanical medicines which stimulate the production of bile are called cholagogues. Those that support the excretion of bile from the gall bladder are cholegogues. *Chelidonium majus* is a botanical with a long history of use. Also known as great celandine, it is widely distributed in Europe and Western Asia. A member of the Papveraecea family, it is rich in specific alkaloids. These are isoquinoline alkaloids, and include chelidonine, chelerythrine, sanguinarine, berberine and coptisine. *Chelidonium* is a versatile plant medicine with multiple biological actions including antiviral, antitumour, antibacterial/antifungal and anti-inflammatory effects. It also has demonstrated cholagogue activity.² It is available in ethanol extract, dried or freeze dried form, and in Europe in OTC preparations.³

Regeneration is dependent upon reversing the antioxidant depletion of the liver and reversing lipid accumulation. In terms of regeneration, the best botanical is *Silybum marianum*. Known traditionally as milk thistle, it also has a long use in the treatment of hepato-biliary disorders. Pliny the Elder (AD 23-79) recommended a mixture of the plant juice and honey for "carrying off bile".⁴ The Eclectics, a school of practitioners who were the forerunners to today's naturopathic physicians, used milk thistle extracts for treating "liver congestion".⁵

The active constituents of *Silybum* is *silymarin* a mixture of the flavonolignans silydianin, silychristine, and silybin.⁶ These compounds exert a powerful antioxidant effect, preventing lipid peroxidation in the hepatocyte,⁷ and increase hepatocyte protein synthesis by stimulating the activity of ribosomal RNA polymerase.⁸

Clinically, silymarin has shown usefulness in treating alcoholic liver disease. In a six month, double blind trial of patients who had histologic documentation of chronic alcoholic hepatitis, silymarin demonstrated the ability to decrease total bilirubin, AST, ALT and GST levels. Positive effects were seen in the histological evaluation, lymphocyte proliferation, and lipid peroxidation. The dose used was 140 mg b.i.d. of silymarin extract for six months.⁹ A double blind, randomized, placebo controlled trial of patients with acute alcoholic hepatitis showed that patients receiving silymarin had their AST, ALT and GGT levels normalize sooner than controls, significantly more often. In a high number of treated patients, all three parameters normalized.¹⁰

Fatty liver in alcohol abuse is a combination of decreased β oxidation, increased synthesis of triglyceride and impaired export of VLDL from the hepatocyte. L-carnitine is an amino acid involved in the β oxidation of fatty acids in the mitochondria. It may be useful in treating alcoholic fatty liver. Its functions as a lipotropic factor in alcohol induced fatty liver has been studied in the rat model.¹¹ That is, it significantly lowered the hepatic lipid and triglyceride content in the studied rat livers.¹² Interestingly, its use may be deleterious in obesity associated fatty liver.

Another promising agent is phosphatidylcholine, a lipid found in cell membranes. Commercially derived from vegetable oils, it is biologically very important in humans as part of cell and organelle membranes. These membranes, while essential for the physiologic roles of the hepatocyte,

are also susceptible to toxic injury. Phosphatidylcholine has been found to prevent hepatocyte dystrophy and necrosis in rats after carbon tetrachloride administration.¹³ Phosphatidylcholine is manufactured in the body from phosphatidylethanolamine. This conversion is strikingly depressed by alcohol consumption, but can be reversed by giving a polyenylphosphatidylcholine mixture (a form of phosphatidylcholine). In studies with baboons given toxic amounts of ethanol, polyenylphosphatidylcholine provided total protection against alcohol induced septal fibrosis and cirrhosis.¹⁴

During the detoxification phase, associated nutrients for detoxification, especially the B vitamin complex should be used. Dried or freeze dried *Chelidonium* can be given as a choleric. In order to regenerate the parenchyma of the liver, extracts of *Silybum marianum* (70% Silymarin) should be given at a dose of 140mg per day, for at least 6 months. Phosphatidylcholine or polyenylphosphatidylcholine can be administered. Some manufacturers produce a silymarin extract which is bound to phosphatidylcholine. This enhances absorption of the Silymarin, but also provides a source of phosphatidylcholine. In various treatment regimens, supplementation with L-Carnitine 1000mg per day may also be helpful.

Conclusion

Restoration of normal liver function may be achieved through a treatment protocol that involves both detoxification and regeneration. Paying attention to the interplay of various organ systems, it is imperative to support the liver during the transformational phase. Prevention of morbidity and mortality as well as improved liver function can be achieved through the clinician educating themselves as to the particular phytochemical therapeutic actions of specific botanical extracts. This algorithm of treatment is needed in order to activate the specific healing qualities inherent in the liver tissue.

Acknowledgment

The authors would like to acknowledge that this manuscript was diligently typed by Ms. Marina De Bona.

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