



REVIEW ARTICLE

A Short Review on Hepatotoxicity and Hepatoprotective Herbs

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ABSTRACT

The liver plays a central role in transforming and clearing chemicals and is susceptible to the toxicity from these agents. Certain medicinal agents, when taken in overdoses and sometimes even when introduced within therapeutic ranges, may injure the organ. Other chemical agents, such as those used in laboratories and industries, natural chemicals (e.g., microcystins) and herbal remedies can also induce hepatotoxicity. Chemicals that cause liver injury are called hepatotoxins. Any agent/ compound that is able to prevent damage to the liver. Hepatoprotective drugs means the drugs that are prevent the liver disease. A number of synthetic hepatoprotective drugs are available in practice, however their effectiveness does not hold true with the entire range of population suffering from this disorder. Moreover, the side effects and the drug interactions are major restrictions in its clinical utility. On the other hand, herbal medicines are widely used across the globe due to their wide applicability and therapeutic efficacy coupled with least side effects, which in turn has accelerated the scientific research regarding the hepatoprotective activity. In this overview we have summarized the current herbal hepatoprotectives.

KEYWORDS

Ascites, Hepatoprotective, Hepatotoxins, Microcystins, Aflatoxins, Picroliv, Ellagic Acid, Phyllanthin, Hypophyllanthin, Kupffer Cells, Hemochromatosis.

INTRODUCTION

Liver is the largest internal organ in our body performing more than 5000 separate bodily functions- from cleansing the blood of toxins to converting food into nutrients to controlling our hormone levels. It detoxifies various metabolites, synthesizes proteins, & produces biochemicals necessary for digestion.

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Most people never give their Liver a thought until something goes wrong. Yet, Liver disease is on rise. In fact, there are many types of Liver

diseases that can be caused by various damages from drugs or chemicals, obesity, diabetic or an attack from your own immune system.

Hepatotoxicity has now become the most serious liver disorder, which accounts for about 15% of the world's burden of diseases.

Hepatotoxicity, or liver damage, is caused by hepatotoxins, which may source from chemicals, dietary supplements, pharmaceutical drugs, and medicinal plants.

The main causes of liver damage are-

- The major cause in India is Ethanol addicts. It is suspected that more than half of the cases of hepatotoxicity are caused by alcohol.
- Chemicals like CCl₄, phosphorous, Aflatoxins, Chlorinated Hydrocarbon, etc.
- Drugs i.e. DILI (Drug Induced Liver Injury)
- Autoimmune Disorders
- Infections like Viral Hepatitis

Mechanism of Hepatotoxicity

- Most of the hepatotoxic chemicals damage liver cells mainly by inducing lipid per oxidation & other oxidative damages in liver.
- By forming the reactive free oxygen radicals which directly induces hepatotoxicity
- Increasing the apoptosis
- Reducing glutathione stores (an antioxidant of Human body).

Markers of Hepatotoxicity

- a) AST- Aspartate Serum Transferase
- b) ALT- Alanine Amino Transferase
- c) ALP- Alkaline Phosphatase
- d) LDH- Lactate Dehydrogenase
- e) TB- Total Bilirubin
- f) TP- Total Protein
- g) TG- Triglycerides
- h) GGT- Gamma-glutamyl Transferase

A number of hepatoprotective agents are available in practice. However, their effectiveness doesn't hold true with the entire range of population suffering from disorder.

Hepatoprotective Agents:

Any agent/ compound that is able to prevent damage to the liver. Hepatoprotection or anti-hepatotoxicity is the ability to prevent damage to the liver. This is opposite to hepatotoxicity.

Examples ^[01]:

Mangifera indica, Berberis vulgaris, Myristica fragrans, Cinnamomum zeylanicum, Crocus sativus, Aquilaria agallocha, Eupatorium cannabinum/agrimonia eupatoria, Syzygium aromaticum, Ruscus aculeatus, Acorus calamus, Elettaria cardamomum, Pistacia lentiscus, Commiphora opobalsamum, Lavandula stoechas, Rosa damascene, Acokanthera schimperi, Acacia concina, Aconitum rotundifolium, Acalypha fruticosa, Acalypha indica, Acalypha racemosa, Acalypha torta, Adiantum capillus-veneris, Aerva lanata, Agastache Mexicana, Alhagi graecorum boiss, Alhagi maurorum medic, Aloe vera, Amaranthus spinosus, Amomum subulatum, Andrographis paniculata, Anthocleista djalensis, Ardisia japonica, Ardisia paniculata, Argemone mexicana, Artemisia abrotanum, Artemisia capillaris, Artemisia vulgaris, Artemisia scoparia, Asparagus racemosus, Asphodelus microcarpus, Astragalus fasciculifolius, Averrhoa carambola, Averrhoa sp.,

Azadirachta indica, Baliospermum solanifolium, Benincasa hispida, Berberis jaeschkeana, Berberis aristata, Berberis integririma, Berberis vulgaris, Betula utilis, Bidens andicola, Bromelia laciniosa, Cajanus cajan, Canscora lucidissima, Capparis spinosa, Carica papaya, Cassia fistula, Cassytha filiformis, Centella asiatica, Boerhavia diffusa, Bidens pilosa, Chonemorpha fragrans, Cicer microphyllum, Cichorium intybus, Cirsium japonicum, Cissampelos pareira, Clematis chinensis, Cistanche tubulosa, Cochlospermum tinctorium, Coriandrum sativum, Costus speciosus, Cotoneaster nummularius, Crepis flexuosa, Cucumis dispsaceus, Curculigo orchiodis, Curcuma zedoaria, Curcuma aromatic, Cuscuta chinensis, Cuscuta reflexa, Cynara scolymus, Cynodon dactylon, Cyperus rotundus, Datura stramonium, Daucus carota, Dendrocnide sinuate, Descurainia Sophia, Desmostachya bipinnata, Dichondra repens, Dillenia indica, Descurainia Sophia, Ecballium elaterium, Eclipta prostrata, Ehretia laevis, Elephantopus scaber, Embelia ribes, Eupatorium chinense, Fibraurea recisa, Ficus religiosa, Ficus tikoua, Flacourtia indica, Fumaria vaillantii, Galium rotundifolium, Gardenia jasminoides, Gentiana moorcroftiana, Gentiana tubiflora, Gentianopsis detonsa, Geranium pretense, Glechoma hederacea, Glechoma hirsute, Glycosmis pentaphylla, Glycyrrhiza spp, Gossypium barbadense, Gynura conyza, Haldina cordifolia, Hibiscus rosa-sinensis, Hippocratea Africana, Hippophae rhamnoides, Hippophae tibetana, Holarrhena pubescens, Inula cappa, Ipomoea purpurea, Juncus effuses, Lagenaria siceraria, Lagerstroemia speciosa, Lannea acida, Laportea crenulata, Lawsonia inermis, Leptadenia pyrotechnica, Leucas aspera spreng, Lippia gracilis, Lobelia angulata, Lonicera japonica, Luffa acutangula, Lysimachia christinae, Marsilea quadrifolia, Mallotus roxburghianus, Malva sylvestris, Malva verticillata, Mangifera indica, Momordica charantia, Nandina domestica, Musa superb, Nelumbo nucifera, Nephrolepis cordifolia, Nerium oleander, Ocimum americanum, Oroxylum indicum, Oxalis corniculata, Passiflora spp., Pavetta indica, Peganum harmala, Peumus boldus Molina, Phyllanthus amarus, Phyllanthus emblica, Phyllanthus fraternus, Phyllanthus niruri, Phyllanthus urinaria, Physalis alkekengi, Physalis divaricata, Picrorhiza kurroa, Piper betle,

Pistacia lentiscus, *Plantago asiatica*, *Plantago major*, *Plantago ovata* forssk, *Polygonum perfoliatum*, *Polygonum tortuosum*, *Polypodium vulgare*, *Portulaca oleracea*, *Pteris multifida*, *Reynoutria japonica*, *Rheum officinale*, *Rheum palmatum*, *Rheum ribes*, *Rheum turkestanicum*, *Rhus coriaria*, *Rosa sericea*, *Rosa webbiana*, *Rubus parvifolius*, *Rumex acetosella*, *Saccharum officinarum*, *Salix alba*, *Salix excels*, *Salvia macrosiphon*, *Scoparia dulcis*, *Senecio scandens*, *Scorzonera divaricata*, *Sigesbeckia orientalis*, *Silybum marianum*, *Solanum americanum*, *Solanum incanum*, *Solidago decurrens*, *Solidago virga-aurea*, *Sonchus oleraceus*, *Sphaeranthus indicus*, *Sphaeranthus senegalensis*, *Spinacia oleracea*, *Striga asiatica*, *Tamarindus indica*, *Tanacetum vulgare*, *Taraxacum officinale*, *Terminalia chebula*, *Teucrium chamardrys*, *Tinospora sinensis*, *Toddalia asiatica*, *Tribulus terrestris*, *Trichilia emetic*, *Trichosanthes cucumerina*, *Trigonella emodi*, *Urtica dioica*, *Uncaria rhynchophylla*, *Uvaria chamae*, *Veronica chamaedrys*, *Viola inconspicua*, *Viola odorata*, *Vitex negundo*, *Woodfordia fruticosa*, *Ziziphus jujube*, etc.

Herbs with potentially hepatoprotective constituents are:

1. *Astragalus membranaceus*
2. *Curcuma longa*
3. *Mangifera indica*
4. *Brassica napus*
5. *Silybum marianum*
6. *Andrographis paniculata*

Although herbal drugs are available for almost all ailments, hepatoprotective drugs have unique importance. Different herbal products representing different plant parts are able to act as hepatoprotective drugs by minimizing or preventing the hepatotoxicity through many mechanisms [108].

Mechanism(S) of Action:

The mechanism of hepatoprotection by these compounds is generally by exerting multiple effects [13]. The herbal drugs used for the management of chronic liver disease can regulate and strengthen the liver, gastrointestinal, and immune system [24]. The regulation of gastrointestinal system may improve the general

well-being of the patients, and the improvement of the constipation may prevent the absorption of harmful substances and indirectly decrease ascites [25]. The protection of liver cells against toxic materials including drugs, lipid peroxidation, and free radical injury may decrease inflammation, improve liver blood flow, and ultimately help in reduction in ascites and blood pressure [26]. They can suppress CYP2E1 enzyme that converts many drugs to their toxic metabolites [27]. They can protect normal structure of mitochondrial membrane and enhance the activity of ATPase in mitochondria, thereby modulating the balance of liver energy metabolism [28]. They also possess anti-inflammatory and antiprotozoal activities. Immune dysfunction is a component of liver disease, and thus, immunomodulation by herbal therapy (withaferin-A) prevents oxidative stress and inflammation and strengthens the detoxifying power of liver cells [29]. Antiviral properties of picroliv, ellagic acid, phyllanthin, and hypophyllanthin are reported [30]. Moreover, Herbal drugs can promote protein synthesis in hepatocytes or decrease formation of leukotrienes, prostaglandins, and TNF- α by Kupffer cells [31]. Drugs like picroliv (iridoid glycoside) can cause liver tissue regeneration, and ellagic acid can prevent liver fibrosis [31, 32]. Anticholestatic and choleretic effects of silymarin and andrographolide are well established [20]. Further, nuclear factor-kappa B-mediated inhibition of inflammatory cytokines and chemokines had been shown with silymarin, picroliv, curcumin, and ellagic acid [33-36]. Moreover, cyclo-oxygenase-2-mediated inflammatory response had been shown to be inhibited by curcumin and inducible nitric oxide synthase inhibition with silymarin and curcumin [34, 35]. The pro-inflammatory cytokines and chemokines had been exhaustively studied with curcumin by Nanji and coworkers [36]. Silymarin and picroliv had been shown to inhibit TNF- α -mediated apoptosis [37-39]. All these effects strengthen liver and regulate body metabolism and ultimately inhibit further liver cell damage in the favor of their regeneration [40].

Possible Hepatic Disorders:

There are many kinds of liver diseases:

- Diseases caused by viruses, such as hepatitis A, hepatitis B, and hepatitis C

- Diseases caused by drugs, poisons, or too much alcohol. Examples include fatty liver disease and cirrhosis.
- Liver cancer
- Inherited diseases, such as hemochromatosis and Wilson disease

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