



Hepatoprotective Potentials of Some Emerging Indian Medicinal Plants

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ABSTRACT

When more organs are added to the vertebrate system, metabolites such as bile are generated, as well as glycogen, which is then detoxified and liver proteins are made. Because of the effect on the hepatic control system, you may have some severe difficulties with your general functioning if you have liver failure. Our present emphasis is on controlling the liver's adverse effects, particularly the damage to hepatic tissues caused by conventional medications. We also went through individual signs and symptoms of liver disease, such as lipid catabolism, concurrent viral hepatitis, retained cell water, catabolism, and fibrosis and inflammation, all over the liver, in the liver, and excess, as well as inflammation and liver sickness, in particular. Different plant extracts (such as flavonoids, tannins, and vitamins) that have hepatoprotective properties, as well as the components that contribute to them, are discussed in this review article.

Key Words: Liver, Natural, Plants, Extracts, Hepatotoxicity, Hepatoprotective

INTRODUCTION

In metabolism, the liver has three well-known abilities: It has a strong capacity to regenerate after being damaged, as well as a better ability to recover from injuries. Jaundice, coagulopathy, and a liver that is acutely or seriously damaged may cause catastrophic diseases including ascites and mortality. [1] Pathophysiological mechanisms and effective treatment for severe hepatic damage are still being researched, as is the degree of complexity required to do such jobs. Multiple herbal remedies have traditionally been a focus of study in terms of health maintenance and prevention, and the treatments have been proven to be effective. [2] Toxicity in the liver is common and may be caused by a variety of factors, the majority of which can be addressed before therapy begins. To determine the source of the symptoms, a lab test should be performed. In reality, there have been a lot of measures taken by professionals to be aware of hepatotoxicity and to take action to prevent it. [3]

MONITORING OF THE SYMPTOMS

There are chronic symptoms such as nausea, anorexia, malaise, and upper-right abdominal discomfort. When

one or more particular adverse symptoms, such as itching or jaundice, appear or develop, you should look into the potential of liver damage while on the drug. [4]

CONSIDERING A CAREFUL HISTORY

Patients' medical and over-the-counter (herbal and OTC) records should be investigated to collect and preserve reference material, which will serve as a comparison of their current health and the kind of health they may lose over time, as well as any recovery issues that may arise. [5]

DRUG-INDUCED HEPATIC INJURY

If an allergic reaction occurs, it is assumed that the underlying medicine (and perhaps additional medications) is to blame. Long-term administration and potential adverse effects (such as cholestasis and metabolic problems, including hepatopathy) cannot be addressed with a single allergic corticosteroid, which is frequently used in cholestasis instances. During acetaminophen poisoning, however, only N-acetyl cysteine is given. If coagulopathy or encephalopathy

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ISSN: 2231-2188 (Print)

ISSN: 2231-685X (Online)

Received: 08.04.2021

Revised: 06.05.2021

Accepted: 18.08.2021

Published: 01.04.2022

is present, the last option is utilised to attempt to re-expand the liver. [6]

MECHANISMS OF LIVER DAMAGE

Increasing oxidative stress

Some of the body's main lignification activities, such as protection and strength, need the expansion of the lignified stems. Alcohol may cause oxidative stress and harm to the body as a consequence of free radicals. Oxygen metabolites such as superoxide (O₂) and hydroxy radicals (OH) are thought to have a major role in the development of alcoholic liver damage based on the data. [7]

Disturbing protein metabolism

An indirect impact on the mechanism is one of the most common causes for a disturbance in the liver's protein production process. As a result, acetaldehyde (alcohol's primary metabolite product) interacts with and negatively affects the fibrous and membrane structures. As a result, it often serves as an oxidant source for protein adducts, resulting in progressive oxidation and lipid peroxidation). Alcohol induces an immune attack on the changed liver cells that target hepatocytes, as well as an immunological reactivity in specific cells against those cells. [8] If one or more of the following circumstances occur, liver dysfunction may develop: As alcohol dehydrogenase and acetaldehyde-dehydrogenase are extremely active, nicotinamide and acetoin synthetase may lose their ability to generate more nicotinamide and create adenyadenosine (generating acetate). The assembly and secretion of lipoprotein function are impaired when lipid concentrations drop. [9]

Peripheral catabolism of the fat increased

In most cases of patients with alcoholic hepatitis, infiltration of the liver increased the concentrations of interleukin-8 and alveolar granule exudate protein by about 40%, and the theory is that these mobilised neutrophils release oxygen metabolites (or poisons) that have an effect on the lung tissues. The use of alcoholic beverages contributes to the increase of liver fat. [10]

Concurrent viral hepatitis

Alcoholics are more likely to develop chronic hepatitis as well as acute liver injury as a result of their drinking habits. Hepatitis C is thought to be present in approximately 30% of individuals with alcoholic liver disease. [11]

Increased redox ratio

Lactic acidosis, which is caused by increased lactic acidity in the NADPH (redox ratio) and NAD (reduced phosphenyalanethiol) ratios, causes fatty liver, decreased

glucose production, and gout, as well as androgens. It differs from glucose intolerance in that it does not cause a rise in serum uric acid, but rather a decrease. [12]

Retention of liver cell water and proteins

Alcohol exacerbates the condition of liver accumulation and hepatocytes, and hepatomegaly is caused by a buildup of water in the liver. [13]

Hypoxia

Hepatocellular necrosis is produced by long-term alcohol absorption in the centrilobular [middle of the liver] tissue, which leads to hypoxia. [14]

Immunological mechanism

In alcoholic liver disease, cell-mediated immunity is compromised. Ethanol often causes a direct immunologic attack on liver cells. Furthermore, immunological experts think that alcohol-induced cytoskeleton instability may cause intermediate filaments to cluster, according to Mallory. [15]

Fibrogenesis and inflammation

The exact aetiology of fibrosis and the inflammatory response of alcoholic liver disease are unknown. Lymphokines and monokines are examples of mediating agents. The production of fibroblasts is significantly increased when cells die. Both of the three main kinds of collagen found in connective tissue expand, allowing myofibroblasts and fibrocytes to convert into muscle cells. Mediators important in inflammation, such as leukotrienes, which are utilised in the metabolic process, are produced by weaker hepatocytes, causing an inflammatory response in the areas where they are found. [16]

Anti-based tests may also be used because of the link between some hazardous substances and peroxidation of the liver cell membrane or DNA damage, as well as decreased glutathione losses. The usage of free radical molecules leading to cirrhosis, aggregation of parenchyma and cinoliths, and elastase study into the anti-oxidant carrying characteristics of liver membranes were all studied independently. As a result of the aforementioned study, the focus of the fight against cirrhosis has moved to finding variables that may prevent aberrant connective tissue formation in the liver. Proteolytic inhibitors may also be utilised to look for fibro-protective protein hydroxylation effects. [17]

MANAGEMENT OF HEPATOTOXICITY THROUGH HERBAL PRODUCTS

Because the liver is such an essential organ, it may be revived and regenerated by using natural medicinal herbs and altering one's diet, which is the most significant part of hepatotoxicity

management. This study's main aim is to investigate different processes and their impact on hepatotoxicity. Herbal medicines or polyherbal formulations are used to treat liver dysfunction caused by viral hepatitis, cigarettes, toxic medications, and plant poisons. [18] Silymarin extracted from *Silybum marianum*, andrographolide extracted from *Andrographis paniculata*, curcumin extracted from *Curcuma longa*, picroside and kutkoside extracted from *Picrorrhiza kurroa*, phyllanthin and hypophyllanthin extracted from *Phyllanthus niruri*, and glycyrrhiza glabra extracted from *Glycyrrhiza glabra* (Table 1). These plants provide hepatoprotection due to their anti-oxidant properties. [19] In free radical scavenger tests, the extracts reduced free radical oxygen in serum and liver due to anti-oxidant actions, which is supported by increased serum glutathione concentration and reduced lipid peroxidase in the liver. Silymarin is a plant-based compound that has been proven to protect the liver against harmful hepatotoxins in clinical trials. [20] The anti-oxidant, anti-inflammatory, and diuretic properties of silymarin's intrinsic components, as observed

in other therapeutic plants in nature, are attributed with its pharmacological efficacy. Silymarin is also a cell defender against glutathione, a reducer of leukotriene formation from unsaturated free acids, an amplifier of protein synthesis, a mast cell stabiliser, and an immune function regulator, as well as an anti-lipid peroxidation and mediated detoxification mechanism. It inhibits the cytochrome P450 detoxification pathway, which prevents hazardous chemicals like TAA from being metabolised. [21] The preliminary data collected in this study via observations and measurements indicates that using the PN extract may stop the development of hepatic cirrhosis induced by TAA in rats. This natural extract has shown the potential to protect the liver by preventing the occurrence of TAA-like side effects. [22] The results are similar to those of silymarin, and the PN extract's ability to maintain the liver's property, structure, and function in the face of toxic exposure is promising, necessitating more research into its pharmacologic potential in treating liver cirrhosis by mapping the molecular mechanisms of action. [23]

Table 1: Herbal resources with dominant hepatoprotective activity.

S. No.	PLANT	FAMILY	ACTIVE CONSTITUENTS	PARTS USED
	<i>Achillea millefolium</i>	Asteraceae	Isovaleric acid, Salicylic acid, Asparagines, Sterols, Flavonoids	Flower, Stem, Aerial part
	<i>Adhatoda vasica</i>	Acanthaceae	Glycosides, Flavonoids, Benzonoids, Phenolic compounds, Naphthoquinone, Triterpenoids	Leaves
	<i>Allium sativum</i>	Amaryllidaceae	Organosulfur compounds	Root
	<i>Andrographis paniculata</i>	Acanthaceae	Andrographolide, Kalmeghin, Flavanoids, Diterpenoids, Polyphenols	Leaves, Aerial part
	<i>Apium graveolens</i>	Apiaceae	Caffeic acid, Chlorogenic acid, Apiin, Apigenin, Rutaretin, Ocimene, Bergapten, Isopimpinellin, Alkaloids, Steroids	Seeds, Roots
	<i>Azardirchata indica</i>	Meliaceae	Glycoproteins, Triterpines, Limonoids, Flavonoids, Phenols, Tannins, Nimbins, Saponins, Catechins, Azadirachtin, Gallic acid	Plant
	<i>Berberis lyceum</i>	Berberidaceae	Alkaloids, Cardioactive glycosides, Saponins, Tannins, Anthocyanins, Vitamins, Phytic acid, Minerals	Roots
	<i>Boerrhavia diffusa</i>	Nyctaginaceae	Glycoside, Flavonoids, Sterols	Roots
	<i>Calotropis procera</i>	Asclepiadaceae	Procesterol, Cyclosadol	Flower
	<i>Camellia sinensis</i>	Theaceae	Polyphenols, Catechin	Leaves
	<i>Cassia occidentalis</i>	Solanaceae	Alkaloids, Glycosides, Tannins, Phenolics, Crysophenols, Emodin derivatives, Flavanoids, Occidentalins A and B	Roots, Leaves, Seeds
	<i>Cichorium intybus</i>	Asteraceae	Alpha-amyrin, Taraxerone, Baurenyacetate, Beta-sitosterol, Lactones, Vitamins, Minerals, Fats	Leaves, Roots
	<i>Cichorium intybus</i>	Asteraceae	Inulin, Sesquiterpene Lactones, Vitamins, Minerals, Fat, Mannitol, Latex	Whole plant

Table 1: (Continued)

S. No.	PLANT	FAMILY	ACTIVE CONSTITUENTS	PARTS USED
	<i>Cyperus rotundus</i>	Cyperaceae	Cyperene, Humulen, Beta-selinene, Zierone, Campholein aldehyde	Rhizomes
	<i>Eclipta alba</i>	Asteraceae	Hentricontanol, Heptacosanol, Protocatechuic acid, 4-Hydroxy-benzoic acid, Verazine, Ecliptalbine	Whole plant
	<i>Ginkgo biloba</i>	Ginkgoaceae	Polyphenols	Seeds
	<i>Gossypium herbaceum</i>	Malvaceae	Gossypol, Polyphenols	Roots
	<i>Hibiscus sabdariffa</i>	Malvaceae	Polyphenols, Protocatechuic acid, Vitamin C	Leaves, Fleshy red calyx
	<i>Ipomoea turpethum</i>	Convolvulaceae	Resins, Saponins, Flavanoids, Steroids, Triterpenes, Etulinic acid, Betulin acid, Sitosterol, Glucose, Rhamnose	Aerial part
	<i>Mangifera indica</i>	Anacardiaceae	Triterpene, Luoeol	Whole part
	<i>Moringa oleifera</i>	Moringaceae	Vitamin C, Calcium, Minerals	Leaves, Fruits, Seeds
	<i>Naragamia alata</i>	Meliaceae	Alkaloid, Steroid, Saponin	Plant
	<i>Nigella sativa</i>	Ranunculaceae	Polyphenols, Thymoquinone	Seeds
	<i>Ocimum basilium</i>	Lamiaceae	Phenolic acids, Rosmarinic acid	Flower, Seeds Leaves, Whole plant
	<i>Phyllanthus amarathus</i>	Phyllanthaceae	Polyphenols, Phyllanthin	Fruits, Whole plant
	<i>Phyllanthus niruri</i>	Euphorbiaceae	Gallic acid, Phyllanthin, Ellagic acid	Whole plant
	<i>Picrorrhiza kurroa</i>	Scrophulariaceae	Kurkin, Picroside, Vanilic acid, D-mannitol, Rosin, Apocynin	Roots, Whole plant
	<i>Plumbago zeylanica</i>	Plumbaginaceae	Plubagin, Isoshinolone, Plumbagic acid, Trans-cinnamic acid, Vanillic acid, Indole-3-carboxaldehyde	Roots
	<i>Rubia cordifolia</i>	Rubiaceae	Glycoside, Rubiadin, Hydroxytranquinone	Roots
	<i>Sida cordifolia</i>	Malvaceae	Fumaric acid, Organic compounds, Ephedrine, Pseudoephedrine	Roots, Leaves, Seeds, Whole plant
	<i>Silybum marianum</i>	Asteraceae	Silymarin, Lignans, Silybin, Silydianin, Silychristine	Seeds
	<i>Solanum nigrum</i>	Solanaceae	Gentisic acid, Luteolin, Kaempferol, m-coumaric acid, Glycosides, Glycoproteins, Polysaccharides	Fruits, Whole plant
	<i>Tephrosia purpurea</i>	Leguminaceae	Triterpenoids, Rotenoids, Sterols, Essential oils, Fixed oils, Flavonoids	Seeds, Roots, Bark, Whole plant
	<i>Terminalia chebula</i>	Combretaceae	Chebolic acid, Gallic acid, Punicalagin, Geraniin, Phyllanemblinin E, Chebulagic acid, Chebulinic acid	Fruits
	<i>Terminalia arjuna</i>	Combretaceae	Tannis, Phytosterols, Magnesium, Saponins, Flavanoids, Zinc, Arjunone, Luteolin, Gallic acid, Ellagic acid, Argugenin, Calcium, Copper	Stem, Bark
	<i>Trachyspermum ammi</i>	Apiaceae	Thymol, p-cymim, Gamma-terpinene, Beta-pinene, Alpha-terpine	Leaves, Seeds, Fruits
	<i>Trigonella foenum</i>	Lamiaceae	Vitamin A, Vitamin C, Tocopherol, Total phenol, Lycopene, Carotenoid, Flavonoids	Leaves

ROLE OF VITAMINS

Vitamins are important nutrients that the human body need in precise amounts. Because the human body is unable to manufacture them in sufficient amounts, they must be obtained through diet. Vitamins are classified into thirteen categories depending on their biological and chemical characteristics. [24] Any of them has a specific function in our bodies. Folic acid is required for cell development and synthesis in many reactions and processes in the body, including the histidine cycle, serine and glycine cycle, methionine cycle, thymidylate cycle, and purine cycle. Both of the aforementioned cycles become inactive when the body is deficient in folic acid, resulting in a range of problems such as megaloblastic anaemia, cancers, and neural tube abnormalities, among others. [25] Vitamin B12 is required for a number of physiological responses and activities, including cell growth and development. Because each step is interconnected, the whole process will fail if the quantity increases or falls above or below the average. Increased food intake or supplementation may be used to treat deficiencies. [26]

It is suggested that consuming vitamin C and E aids liver regeneration. Vitamin E inhibits lipo-peroxidative chain reactions, which prevents lipid peroxidation. When vitamin C and vitamin E are combined, they produce an anti-oxidant effect that is synergistic. Vitamins C and E affect liver regeneration through increasing hepatocyte activity, according to the results. [27] Lu reported a metabolomics research in POFS rats caused by PH. The citric acid cycle, branched-chain amino acid metabolism, fatty acid transport and metabolism, phospholipid metabolism, tryptophan metabolism, phenylalanine metabolism, and purine metabolism were all identified as metabolic processes and potential biomarkers associated with POFS. According to these results, replacing branched-chain amino acids that are lost owing to fatigue-induced glycogen depletion is critical. [28] Vitamins C and E were given at dosages of 250 mg/kg body weight per day in this research to determine whether residual liver functions might be maintained. The ability of the liver to fully recover from the damage that follows is a remarkable phenomenon that is essential for the liver's vital function in metabolic control and xenobiotic detoxification. Histologically, the regeneration process is well known, but the genes that regulate liver regeneration are still a mystery. [29] Particularly concerning are cytokines and growth factors, which are involved in different phases of liver regeneration. Their potential involvement in this process have previously been explored by looking at their expression in rats' regenerated livers. Functional investigations have confirmed this anticipated involvement by employing neutralising antibodies or siRNAs before to liver damage or during liver regeneration, as well as systemic administration

of recombinant growth factors. [30] Using genetically modified mice in liver regeneration studies has often shown unexpected functions for growth factors like cytokines and their downstream liver regeneration signalling targets. The results of functional research into the roles and mechanisms of action of growth factors and cytokines in liver healing after acute damage are summarised in this paper. If a severe allergic response is discovered, corticosteroids may be administered, but no controlled trials have been performed to establish their efficacy. [31] Similarly, ursodiol is often used to treat cholestatic liver injury, despite the fact that it hasn't been well researched in this setting. Except for N-acetylcysteine, there are no particular antidotes for acetaminophen poisoning. The patient may be sent to a liver transplant centre if he or she develops coagulopathy (defined as an international normalised ratio of 1.5 or higher) or encephalopathy. [32]

OXIDATIVE STRESS

Ischemia-reperfusion injury (IRI), nonalcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH), liver fibrosis, liver cirrhosis, and hepatocellular cancer are all illnesses that impair liver function, and oxidative stress is a major factor to almost all of them (HCC). [33] The liver collects melatonin (N-acetyl-5-methoxytryptamine) and is the sole organ that metabolises circulating melatonin. Melatonin is one of the most effective anti-oxidants for liver protection, and its metabolites are also anti-oxidants. Melatonin's antioxidative impact is achieved both directly and indirectly by scavenging free radicals and activating antioxidant enzymes. [34] A variety of factors affect the anti-oxidative response of melatonin in the liver, including dosage, route, duration, and time of administration, the type of the oxidative-induced agent, and organisms. In addition to IRI, NAFLD, NASH, fibrosis, cirrhosis, and HCC in the liver, this indoleamine is an effective and promising anti-oxidant. [35]

ROLE OF NATURAL PRODUCTS

In-vivo and in-vitro anti-oxidant and hepatoprotective effects of aerial parts of *Bacopa monnieri* Linn (Schrophulariaceae), particularly the EBM and its ethanol extract, were investigated. The preparation of EBM and the calculation of total phenolics are both completed. In vitro models were used to study the anti-oxidant effect of EBM. [36] Per mg of extract, complete phenolics were calculated to be 47.7 g of pyrocatechol equivalent. The extract shows a decreasing force based on concentration dependency. With IC₅₀ values of 238.22 g/mL, 29.17 g/mL, and 22.92 g/mL, respectively, anti-oxidant generation, nitric oxide scavenging

activity, and superoxide radical scavenging activity were all concentration-based key-factors. [37] The observed behaviours were comparable to those seen with the reference medicines. The animals were now given paracetamol (500 mg/kg, p.o., once a day for 7 days) (Wistar albino rats). Rats administered paracetamol for seven days were given a combination of EBM 300 mg/kg/day and silymarin 25 mg/kg/day dosage absorption. In hepatotoxic rats, the effects of EBM and silymarin on serum transaminases (SGOT, SGPT), alkaline phosphatase (ALP), bilirubin (Direct and Complete), cholesterol (HDL and Total), and total protein were studied. The findings of the lipid peroxidation (LPO), glutathione (GSH), superoxide dismutase (SOD), and catalase (CAT) enzymes were then computed. EBM and silymarin protect the liver by decreasing serum enzymes, bilirubin, total cholesterol, and in-vivo lipid peroxidation, which raise GSH, CAT, SOD, and HDL cholesterol levels. EBM exerts anti-oxidant effects on FeCl₂-ascorbate-induced lipid peroxidation in paracetamol-induced rat liver homogenate. EBM has the potential to protect liver cells from paracetamol-induced liver damage because to its anti-oxidative activity on hepatocytes, allowing for the decrease of harmful effects caused by toxic metabolites produced by paracetamol. [38]

The study investigated into the hepatoprotective effects and mechanism of action of an aqueous extract of *Camellia sinensis* leaves. The extent of liver damage induced by intraperitoneal administration of carbon tetrachloride/olive oil (50 percent v/v, 0.5 mL/kg) once daily for 7 days in male Wistar rats (150-220 g) was investigated by measuring biochemical parameters like alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total protein, and albumin in serum and In addition, histopathological investigations were performed. Carbon tetrachloride significantly reduced serum hepatic enzymes and liver lipid peroxidation when *C. sinensis* levels were 100 mg/kg and 200 mg/kg, respectively. [39,40] There was a significant rise in serum total protein, albumin, and liver GSH, SOD, and CAT in rats given carbon tetrachloride. *C. sinensis* (100 mg/kg and 200 mg/kg) was compared to the anti-oxidant effects of vitamin E (100 mg/kg). In *C. sinensis*-treated rats, carbon tetrachloride-induced histological alterations (central vein congestion, centrilobular necrosis, and sinusoidal congestion) were somewhat decreased. *C. sinensis* protects the liver from the harmful effects of carbon tetrachloride. One potential mechanism of action is its anti-oxidant properties. [41]

Liv-52 and other Ayurvedic formulations have been proven to be helpful in the treatment of liver cirrhosis and other liver disorders. Phytochemicals have a wide range of actions that may help protect you against chronic illnesses. Alkaloids, for example, aid in the treatment of chronic illnesses. Saponins have both anti-hypercholesterolemic

and antibacterial activities. Steroids and triterpenoids have analgesic properties. [42] Vitamin B complex medicine aids the cytological regeneration of liver cells. Protein functions differently in distinct ALR isoforms, as shown by their subcellular location. The ubiquitous expression of ALR in the liver and other regions demonstrates that hepatic cellular regeneration is a dynamic process. [43] In addition to needing the protein, various ALR isoforms are generated via selective mRNA expression at different ATGs or as post-translational modifications products of the longest type (23 kDa). When it comes to acute cirrhosis, liver transplantation is the only option. [44] Herbal medicinal plants' phytochemical components are utilised as a supplement to pharmaceuticals as hepatoprotective medications, not only in treatment but also as a healthy supply to maintain one's health. The discovery of ALR gene expression will lead to a better understanding of ALR's different functions, making its prospective use as a therapeutic tool more realistic. [45]

CONCLUSION

The liver's self-healing properties, particularly its potential for regeneration, are being studied by researchers. Natural treatment outperforms pharmaceuticals whether used alone or in combination, according to this and other research. In this research, the intricacy of how liver recovery is managed has been taken into consideration. The capacity of liver cells to regenerate is influenced by a variety of variables. Several medicinal plants have been shown to be helpful in the treatment of liver illness, for the record. Herbal medications have been examined in this summary report to evaluate how well they function on their own and as part of a pair. Various studies have shown that flavonoids, glycosides, and other alkaloids have a unique defensive capacity that acts in the liver to repair oxygen radicals and alkaloids.

CONFLICTS OF INTEREST

No conflict of interest is declared.

ACKNOWLEDGEMENT

The author acknowledges the college management, principal, teachers, non-teaching staffs, and colleagues for their kind support.

FUNDING INFORMATION

No agency provided funds.

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