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ROLE OF NUTRACEUTICALS IN MANAGEMENT OF LIVER DISEASE: A COMPREHENSIVE REVIEW

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ABSTRACT: Despite significant progress in the field of targeted medicine, no treatment is totally successful in promoting liver function, aiding in the regeneration of hepatic cells, or providing protection for the organ without having a toxic effect. Recognizing low toxic therapeutic alternatives is crucial for the management of liver illnesses as a result. Phytochemicals, which are found in plants and fruits, have been shown to have beneficial effects on liver protection, according to numerous scientific research. This has led to the usage of some natural remedies. For their anticipated safety, potential nutritional and medicinal advantages, nutraceuticals have attracted a lot of attention. These were employed as an alternative to modern medications that improve health, boost diet nutrient content, and lengthen life expectancy. Herbs, diverse nutrients, and dietary supplements are important components of nutraceuticals since they help prevent certain diseases and lessen their pathophysiology. Along with other health-promoting actions, it also has immune-stimulating, natural antioxidant, anticancer, anti-inflammatory, antidiabetic, cardioprotective, and organo protective properties. In the end, they guarantee a higher quality of life. The goal of the current review was to gather information from studies that looked at a variety of foods that humans frequently consume and that have been shown to have hepatoprotective properties, including grapefruit, cranberries, and grapes, as well as cactus pear (nopal) and cactus pear fruit, chamomile, silymarin, and spirulina.

INTRODUCTION: The largest glandular organ that regulates a variety of physiological and chemical processes in the human body is said to be the liver. In other words, it is crucial for metabolic regulation and detoxification, which affects how lipids, carbohydrates, alcohol, a variety of medications, and pollutants are metabolized¹⁻³.

The body's many physiological processes depend on the liver, which is the most significant organ in this regard. Another significant organ that plays a crucial part in the preservation of the body's homeostasis is the liver⁴⁻⁵.

The liver is particularly vulnerable to damage from a range of metabolic, infectious, immune-mediated, toxic, and carcinogenic sources due to its distinct anatomy, physiology, and metabolism. Numerous nutraceutical substances with antioxidant, anti-inflammatory, antifibrotic, antiproliferative, or antineoplastic properties have been suggested to support liver health maintenance or restoration⁶.

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Humans have been researching the health benefits of food for hundreds of years. Researchers have become quite interested in finding functional foods with nutraceutical benefit over the past few decades⁷. Nutraceuticals have been shown to offer protection against numerous chronic diseases as well as a variety of physiological benefits⁸. Nutraceuticals can include separated nutrients, plant-based phytochemicals, herbal goods, dietary supplements, and processed foods such as cereals, milk derivatives, soups, and drinks⁹. The idea of nutraceuticals has been increasingly well-known in recent years due to a noticeable shift in people's health consciousness, and its significance in the current medical and healthcare system has grown. The beneficial effects of nutraceuticals on liver function are the main topic of this review. Nutraceuticals are considered in relation to the liver's multiple activities, including oxidation,

detoxification, and the prevention of chronic liver disorders¹⁰. For ages, people in India's Ayurvedic medical system managed their fundamental healthcare needs by using medicinal plants¹¹⁻¹². For thousands of years, plant-based medicine has been used to prevent and treat a variety of health issues, including liver illnesses. Today, conventional medicine is focusing on using natural items, like herbs, to give the liver the everyday care it requires¹³. Investigating potential natural medications that could take the place of chemical ones is crucial. Antioxidants, which are known to avert several disease states, are abundant in Indian medicinal herbs. There are several degrees of antioxidant protection that are noted. Other advantageous substances, such as phytochemical components for functional foods, are also present in medicinal plants.

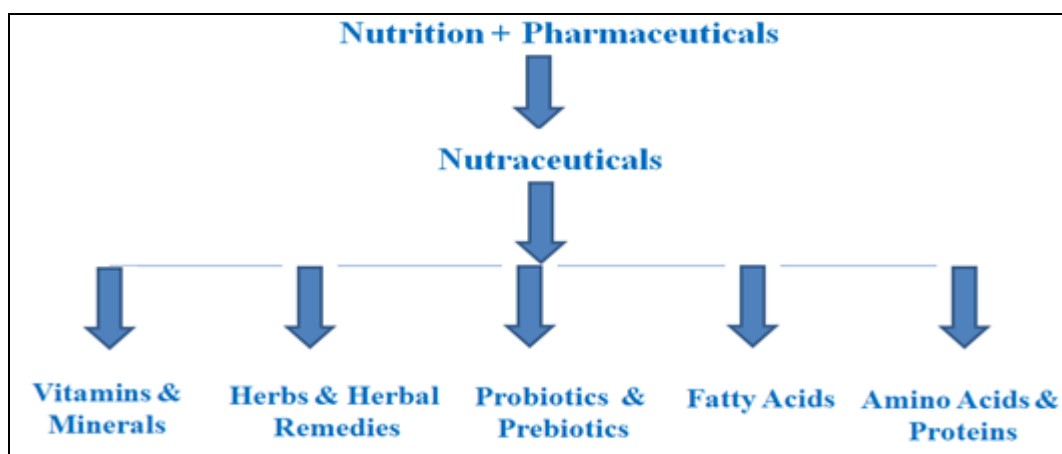


FIG. 1: CONCEPT OF NUTRACEUTICALS

Therefore, information on the evidence-base of these plants will hopefully contribute to the global understanding of Ayurveda and Indian herbals. Rich dividends will come from this in the upcoming years. Medicinal plants are thought to be more dependable and effective choices and they have also reportedly been used traditionally to cure liver conditions. In India's rural and tribal regions, a variety of traditional herbs are utilized to treat a wide range of illnesses¹⁴. Livers have been treated primarily using plant-based medicines. The human body heals itself naturally with the use of herbal ingredients. The global trend for the prophylaxis of illnesses has shifted from synthetic to natural medications. 4 billion people are estimated by the World Health Organization [WHO] to utilize herbal medicines for some form of basic healthcare¹⁵⁻¹⁶.

Currently, a lot of research is being done on the ethnopharmacology of herbal remedies. The present focus of research is on finding novel herbal medications with a good safety profile and improved healing potential. This review primarily compiled the drug-induced hepatotoxicity and hepatoprotective medicinal plants that have been assessed *in-vivo* and *in-vitro* models. Many medicinal plants and their bioactive compounds have been studied and found to have hepatoprotective property against various types of drug-induced hepatotoxicity **Table 1**. The current review on hepatoprotective plants based on various target cells for liver treatment or hepatoprotective activities of several was reviewed, and its future was also considered.

Pathogenesis of Disease: Hepatic stellate cell activation (HSC activation) is a crucial step in the fibrosis process. Hepatic dysfunction in liver cirrhosis is primarily caused by the liver sinusoidal endothelial cells' defenestration and capillarization¹⁷⁻¹⁸. Hepatocytes are destroyed by activated Kupffer cells, which also encourage the activation of HSCs. Encapsulation or replacement of damaged tissue by a collagenous scar is referred to as fibrosis¹⁹. Liver fibrosis is caused by the normal wound healing response continuing, which leads to an inappropriate continuation of fibrogenesis (the creation and deposition of connective tissue)²⁰⁻²¹. Depending on the origin of liver illness, environmental factors, and host factors, fibrosis advances at varying rates²². Cirrhosis is an advanced form of liver fibrosis that is characterised by hepatic vascular distortion. This compromises communication between hepatic sinusoids and the surrounding liver parenchyma, or hepatocytes, by causing the portal and arterial blood supply to be shunted straight into the hepatic outflow (central veins)²³. Hepatic stellate cells (HSC) and a few mononuclear cells border the hepatic sinusoids, which are lined with fenestrated endothelia that lie on a layer of permeable connective tissue (the gap of Disse)²⁴. The hepatic vascular changes and the ensuing portal hypertension are closely related to the general circulatory abnormalities in cirrhosis. Although recent studies reveal that cirrhosis regression or even reversal is feasible, the condition and the vascular distortion it causes are usually thought to be irreversible²⁵⁻²⁶.

Hepatoprotective Herbal Plants:

Lawsonia inermis L. (Henna): The use of *Lawsonia inermis* L. (henna) for medicinal and cosmetic purposes is inextricably linked for treatment of liver and digestive disorders, reduction of tissue loss in leprosy, diabetic foot disorders and ulcers. Henna is a pharmacologically important plant with significant in vitro and in vivo biological activities. Although a myriad of pharmacological activities have been documented, the antioxidant and antimicrobial activities are the most thoroughly investigated. Some incidents of adverse reactions following application to the skin have been reported, but these are mainly confined to cases involving individuals with glucose-6-phosphate dehydrogenase deficiency and reactions to adulterants added to henna products²⁶.

Adulteration of henna is very common and may have resulted in unwarranted scientific findings. Phytochemical profiling studies of the plant, which are crucial for the establishment of proper quality control protocols, are lacking and hamper the development of medicinal products²⁷.

Although many *in-vitro* studies have been conducted to evaluate the pharmacological activities and many *in-vivo* studies have focussed on the toxicity of extracts, more *in-vivo* studies to validate pharmacological activities are needed. The roles of specific compounds and their synergies have not been comprehensively investigated.

Moringa oleifera Lam. (M. oleifera): *Moringa oleifera* Lam. (*M. oleifera*) is consumed not only for its nutritional values but also its medical benefits. *M. oleifera* leaves are rich in beta-carotene, vitamin C, vitamin E, and polyphenols and are a good source of natural antioxidants²⁸. Currently, *M. oleifera* is reported to enhance a broad range of biological functions including anti-inflammatory, anti-cancer, hepatoprotective, and neuroprotective functions.

In addition, many studies have revealed its therapeutic value including anti-diabetes, anti-rheumatoid arthritis, anti-atherosclerosis, anti-infertility, pain relief, anti-depression, and diuretic and thyroid regulation. Due to these reported functions, the bioactivity of *M. oleifera* has gained tremendous attention over the last decade, thereby leading to the increasing exploration and understanding of its pharmacological functions and underlying mechanisms²⁹.

Adansonia digitata L.: *Adansonia digitata* L. (Malvaceae), the baobab fruit pulp is used in African traditional medicine as an antipyretic or febrifuge, anti-dysenteric, diaphoretic, immunostimulant, anti-inflammatory, analgesic, and probiotic remedy. In Mali, baobab fruit pulp flour is also used to treat the diarrhoea of children and to stimulate the milk production in breastfeeding women. Baobab leaves are known in folk medicine as an antipyretic or febrifuge. Biological studies reported that baobab fruit pulp exhibited antioxidant activity, hepatoprotective effect, cardioprotective, antidiabetic, and antitumor action³⁰⁻³¹.

***Cannabis sativa* L.:** *Cannabis sativa* L. has been used as a psychoactive drug, as a folk medicine ingredient. The taxonomic classification of this plant has always been difficult, due to its genetic variability³². Firstly, the genus *Cannabis* has been divided into three main species: a fibre-type one, named *C. sativa* L., a drug-type one, characterised by high levels of the psychoactive compound Δ^9 -tetrahydrocannabinol (Δ^9 -THC), named *C. indica* Lam., and another one with intermediate properties, named *C. ruderalis* Janisch. Due the easy crossbreeding of these species to generate hybrids, a monotypic classification has been preferred, in which one species (*C. sativa*) is recognised and it is divided into different chemotypes. On the basis of their cannabinoid profiles, five chemotypes have been recognised: chemotype I comprises drug type plants with a predominance of Δ^9 -THC-type cannabinoids; chemotypes III and IV are fibre-type plants containing high levels of nonpsychoactive cannabinoids and very low amounts of psychoactive ones; chemotype II comprises plants with intermediate characteristics between drug-type and fibre-type plants; chemotype V is composed of fibre-type plants which contains almost no cannabinoids³³.

***Khaya senegalensis* (Desr.):** *Khaya senegalensis* (Desr.) A. Juss. is a common component of the pharmacopoeia's of multiple African groupings which inhabit the areas in which it grows. Amongst these groups there is a myriad of medicinal uses in the treatment of a wide variety of bacterial, fungal and protozoal infections, liver infections as well as in the treatment of cancers³⁴.

***Raphanus sativus* (Radish):** *Raphanus sativus* (Radish) extracts prepared from the aerial and underground parts of radishes have been used in the treatment of stomach disorders, urinary infections, hepatic inflammation, cardiac disorders and ulcers in folk medicine since the ancient times³⁵. The pharmaceutical potential of radishes is attributed to the presence of its beneficial secondary metabolites, such as glucosinolates, polyphenols and isothiocyanates³⁶.

***Solanum nigrum* L. (SN):** *Solanum nigrum* L. (SN) belongs to the *Solanaceae* family to Europe, Asia, and North America and was introduced in

South America, Australia, and Africa. It represents one of the largest and most variable species groups of the genus. SN, well known as "Black Nightshade" (the English name), is an herbal plant widely distributed throughout the world, extending from tropical regions to temperate regions³⁷. In many developing countries, SN constitutes a minor food crop, with the shoots and berries not only used as vegetables and fruits but also for various medicinal and local uses. SN serves mainly as vegetables for soup preparation in different parts of the world. Several studies have investigated the nutritive value of the 'vegetable black nightshade', which put forward evidence that this species constitutes a nutritious vegetable³⁸. This plant was chosen not only for being nutritive, but also for their folkloric reports of medicinal properties. Studies document potential health benefits of different parts of this vegetable. SN leaves have been reportedly used in traditional medicine for the management of several diseases including seizure and epilepsy, pain, ulcer, inflammation, diarrhea, some eye infections, and jaundice. In folklore medicine, the leaves are used to treat oral ulcers in India where an interesting pharmacological investigation has been performed by using an aqueous extract of SN leaves³⁹.

***Sterculia setigera* Del.:** In traditional African communities, majority of the population still use medicinal plants for observing primary health care. Natural products derived from plants contain physiologically active principles that have been exploited in traditional medical practice over the years for the treatment of various ailments⁴⁰. The use of *Sterculia setigera* Del. in the treatment of severe diarrhea, dysentery, and jaundice has been reported by several researchers over the years. Replacement for already existing pain killers, hematinics and antibiotics are sought for globally due to the cost of already existing drugs and its associated side effects⁴¹.

***Tamarindus indica* (T. indica):** *Tamarindus indica* (T. indica) is evergreen tree that can reach 24 m height and 7 m girth that has pale yellow and pink flowers. It needs dry climate so the region it is commonly seen extends Africa to Senegal in west, Sudan and Ethiopia in east, Mozambique and Madagascar in South.

It is also thought that the plant came to India from Africa. Thailand, Bangladesh, Indonesia in Asia; Mexico, Costa Rica in America are some of the countries in which this plant is mostly encountered⁴².

Every part of *T. indica* plant (root, body, fruit, and leaves) not only has rich nutritional value and broad usage area in medicine but also has industrial and economic importance. Tamarind can be the most acidic and sweet fruit according to its growing season. In traditional medicine, it is used in wound healing, abdominal pain, diarrhea, dysentery, parasitic infestation, fever, malaria and respiratory problems. It is also commonly used in tropical countries because of its laxative and aphrodisiac properties⁴³.

Andrographis paniculata Nees: *Andrographis paniculata* Nees is a herbaceous plant, commonly known as “King of Bitters”, in the family Acanthaceae (Jarukamjorn and Nemoto, 2008). *A. paniculata* grows erect to a height of 30 – 110 cm

with glabrous leaves and white flowers with rose-purple spots on the petals⁴⁴. *A. paniculata* has been used in Asia to treat variety of chronic and infectious diseases⁴⁵. It has been traditionally used as a remedy against diabetes⁴⁶, hypertension⁴⁷, and inflammation⁴⁸ and cobra bite⁴⁹.

Extensive research revealed that *A. paniculata* has a surprisingly broad range of pharmacological effects and some of them are extremely beneficial and include anticancer, anti HIV, anti AIDS, hepatoprotective and immunostimulatory. Other pharmacological effects include; antimalarial, antityphoid, antiviral, antifungal, antibacterial, antidiarrhoeal, antipyretic, antiinflammatory, antidiabetic, antithrombotic, cardiovascular, antivenom, antifertility and psychopharmacological activity. *A. paniculata* may be a promising treatment for the alleviation of subjective symptoms of respiratory tract infections. It may also be beneficial for those with chronic fatigue syndrome and fibromyalgia⁵⁰⁻⁵².

TABLE 1: HEPATOPROTECTIVE ACTIVITY OF SOME MEDICINAL PLANTS

Botanical names	Part used	Parameters estimated	Uses	Ref.
Acacia mellifera	Leaves	AST, ALT, GGT, ALP, bilirubin, TP	Cured the tissue lesions	53
Achillea millefolium L.	Leaves, flowers	AST, ALT, GGT, ALP, bilirubin, TP	Use leaves and flowers powder 3–5 g twice a day. Extract of <i>Achillea millefolium</i> also use in hepatitis.	54
Anogeissus leiocarpus (DC) Wall	Bark	AST, ALT, ALP, bilirubin, total protein, albumin	Less hepatocyte vacuolation and cellular regeneration	55
Argemone Mexicana L.	Aerial parts	SGOT, SGPT, ALP	100 mg/kg methanolic extract more effective in healing liver parenchyma than other doses; 400 mg/kg aqueous extract showed a good result than the corresponding dose of methanol extract	56
Artemisia absinthium L.	Leaves	AST, ALT, ALP, bilirubin, total protein, albumin	Leaves 3–5 g of powder of dried leaves use twice a day.	57
Azadirachta indica A.Juss	Leaves	AST, ALT, ALP, bilirubin, total protein, albumin	Take 30 ml leaf extract with honey and use once a day on empty stomach for a week.	58
Balanites aegyptiaca L.	Bark	AST, ALT, ALP, bilirubin	Both extracts decrease centrilobular degenerative changes	59
Capparis decidua (Forsk)	Branches, Stems, Roots	AST, ALT, ALP, bilirubin, total protein, albumin	Aqueous and methanolic extracts masked the liver fatty changes, Less hepatocyte vacuolation and cellular regeneration	60, 61
Carica papaya L.	Seeds	AST, ALT, ALP	Take extract of 1 table spoon of seeds of Carica papaya. Add 2 tea spoon of lemon juice, mix well. Take twice a day for one month.	62
Chenopodium album L.	Leaves	AST, ALT, ALP, bilirubin, total protein, albumin	Extract from 500 g leaves of <i>Chenopodium album</i> , <i>Solanum nigrum</i> and <i>Cichorium intybus</i> each. Boil the juice, mix sugar and make syrup. Use 2 teaspoon twice a day for two weeks.	63
Combretum hartmannianum (Schweinf)	Leaves	AST, ALT, ALP, bilirubin, total protein, albumin	-	64, 65

<i>Cucurbita pepo</i> L.	Fruit	AST, ALT, ALP, bilirubin, total protein, albumin	Take pulp of <i>Cucurbita pepo</i> 62 g, <i>Tamarindus indica</i> 25 g and 37 g sugar. Boil all in 900 ml water. Reduce to 225 ml, filter and use for one week.	66
<i>Cuminum cyminum</i> L.	Seeds	AST, ALT, ALP	Seeds of <i>Pipiper nigrum</i> , <i>Elletaria cardamom</i> , <i>Cuminum cyminum</i> , rhizome of <i>Zingiber officinale</i> take in equal quantity then roast, grind and use with water once a day.	67
<i>Daucus carota</i> L.	Root	AST, ALT, ALP, bilirubin, total protein, albumin	Extract of 5 in no. <i>Daucus carota</i> , 5 leaves of <i>Taraxacum officinale</i> , 1Beta vulgaris and 1 <i>Malus domestica</i> use twice a day for 60 days.	68
<i>Dobera glabra</i> (Forsk.)	Leaves	AST, ALT, ALP, bilirubin	Diffuse centrilobuar necrotic lesions in liver cells	69
<i>Foeniculum vulgare</i> Mill	Seeds	AST, ALT, ALP	Boil <i>Foeniculum vulgare</i> seeds, leaves of <i>Borago officinalis</i> and flowers of <i>Delphinium zalil</i> in 100ml water then strain, use 5–7 ml with lemon syrup.	70
<i>Fumaria officinalis</i> L.	Whole Plant	AST, ALT, ALP, bilirubin, total protein, albumin	Use 15 ml decoction of whole plant twice a day.	71
<i>Glycyrrhiza glabra</i> L.	Rhizome	AST, ALT, ALP, bilirubin, total protein, albumin	Mix 1 teaspoon of rhizome powder with 2 teaspoon of honey on daily basis. Take 50 g <i>Glycyrrhiza glabra</i> root and <i>Silybum marianum</i> plant each, make powder. Take 1 teaspoon of powder with water twice a day	72
<i>Grewia asiatica</i> L.	Fruit	AST, ALT, ALP, bilirubin, total protein, albumin	Use its raw fruit or extract.	73
<i>Hordeum vulgare</i> L.	Seeds	AST, ALT, ALP	Take 1 tbsp dried plant powder with water, twice a day.	74
<i>Kigelia africana</i> Lam.	Seeds	AST, ALT, ALP	Cytoplasmic fatty vacuolation, haemorrhages, and necrosis of the centrilobular hepatocytes	75
<i>Lepidium sativum</i> L.	Seeds	AST, ALT, ALP, bilirubin.	Mild-to-moderate changes in hepatocytes in both doses	76
<i>Mentha spicata</i> L.	Leaves	AST, ALT, ALP, bilirubin	Use infusion of leaves 2–4 spoon. Take dry leaves powder 2 g	77
<i>Momordica charantia</i> L.	Fruit	AST, ALT, ALP, bilirubin, total protein, albumin	Use ½ cup of fruit juice along with honey once a day.	78
<i>Nigella sativa</i> L.	Seeds	AST, ALT, ALP, bilirubin, total protein, Blood ions, antioxidant enzymes, e.g., SOD, GSH, and MDA	Less centrilobular vacuolation and inflammatory cell infiltration. Less hepatocyte changes. Improvement of lesions observed in CCl ₄ such as necrosis, loss of hepatocytes architecture, and cellular infiltration	79, 80
<i>Nymphaea alba</i> L.	Flower	AST, ALT, ALP, bilirubin, total protein, albumin	Take 10 g flowers to make decoction and use twice a day.	81
<i>Occimum basilicum</i> L.	Whole plant	AST, ALT, ALP, bilirubin, total protein, albumin	Less vacuolated hepatocytes and cellular regeneration	82, 83
<i>Physalis alkekengi</i> L.	Leaves, Flower and pods	AST, ALT, ALP, bilirubin, total protein, albumin	Make powder of leaves, flowers and pods. Take equal quantity of <i>Physalis alkekengi</i> powder and <i>Piper nigrum</i> powder. Use 2.91 g powder twice a day along with 58.3 g arq-e-Kasni.	84
<i>Picrorrhiza kurrooa</i>	Root	AST, ALT, ALP, bilirubin, total protein, albumin	Take 1–2 mg dry root powder with yogurt on empty stomach.	85
<i>Polygonum bistorta</i> L.	Bark	AST, ALT, ALP, bilirubin	Use 2.91 g plant powder twice a day.	86
<i>Phoenix dactylifera</i> Linn	Pollen grain powder	AST, ALT, ALP	Mild changes in hepatocytes	87
<i>Punica granatum</i> L.	Fruit	AST, ALT, ALP, bilirubin, total protein, albumin	Make syrup of fruit and sugar, Take its 3 spoon twice a day.	88
<i>Rosa damascena</i> Mill.	Flower	AST, ALT, ALP, bilirubin, total protein, albumin	Use syrup 2–3 spoon. Use flower powder 5 mg twice a day	89

<i>Saccharum officinarum</i> L.	Stem	AST, ALT, ALP, bilirubin, total protein, albumin	Take a glass of stem juice, mix 1 tea spoon lemon juice. Use 2–3 times a day.	90
<i>Syzygium cumini</i> (L.) Skeels.	Fruit	AST, ALT, ALP, bilirubin, total protein, albumin	Soak <i>Syzygium cumini</i> fruit in earthenware pot and mash with hand. Later strain, cook sap until half then mix half of material white sugar (mishri) and make Khamira. Use 1 spoon twice a day with water.	91
<i>Tamarindus indica</i> L.	Seeds	AST, ALT, ALP, bilirubin, total protein, Blood ions, antioxidant enzymes, e.g., SOD, GSH, and MDA	25–50 g seeds soaked in earthenware pot over night. Next morning drink this water on empty stomach.	92
<i>Tephrosia purpurea</i> (L.) Pers.	Whole plant	AST, ALT, ALP, bilirubin, total protein, albumin	Take 3 mg <i>Tephrosia purpurea</i> plant, <i>Tamarindus indica</i> seeds, <i>Prunus domestica</i> fruit, <i>Solanum nigrum</i> seeds each and 6 mg <i>Withania coagulans</i> fruit. Boil all in 1000 ml water and reduce to 125 ml water, strain, mix sugar and drink.	93
<i>Terminalia arjuna</i> (Roxb) Wight and Arn.	Bark	AST, ALT, ALP, bilirubin	Boil 23.32 g bark in 100 ml of water, strain and use this on empty stomach.	94
<i>Viola odorata</i> L.	Flower	AST, ALT, ALP, bilirubin, total protein, albumin	Take 7 g flower of <i>viola odorata</i> , nine in number of dry <i>Vitis vinifera</i> and 7 g seeds of <i>Cichorium intybus</i> . Boil all in 500 ml of water when boil down 250 ml, strain and use.	95
<i>Zingiber officinale</i> L.	Root	AST, ALT, ALP, bilirubin, total protein, albumin	Use root powder 1–2 g twice a day.	96

Table 1 Plants Used in Hepatoprotective Remedies in Traditional Indian Medicine:

Traditional Indian medicine has long utilized herbal-based therapeutics for liver disorders, which have gained worldwide recognition and popularity through leading pharmaceutical companies⁹⁷. Despite their widespread use and popularity, herbal medicines for liver diseases face challenges in being accepted as mainstream treatment options. Several factors contribute to this limitation, including:

1. The lack of standardization in herbal drug production, which can result in variable quality and efficacy.
2. The need for further research to identify and isolate active ingredients and principles in herbal remedies.
3. The absence of rigorous randomized controlled clinical trials (RCTs) to establish the safety and efficacy of herbal treatments.
4. Inadequate toxicological evaluation to ensure the long-term safety of herbal remedies for liver diseases⁹⁸.

These limitations highlight the need for further scientific investigation and validation to fully

harness the potential of herbal-based therapeutics for liver disorders. By addressing these challenges, we can work towards developing evidence-based herbal remedies that can be integrated into mainstream healthcare for the benefit of patients worldwide.

The treatment of liver diseases has a rich history of leveraging natural remedies, dating back to ancient Ayurvedic practices and extending to traditional Chinese, European, and other systems of medicine. In recent years, there has been a significant shift towards integrating traditional knowledge with modern scientific methods to evaluate the therapeutic potential of herbal products in liver disease models. This synergy combines the strengths of traditional medicine with evidence-based approaches, including standardization, randomized placebo-controlled clinical trials, and rigorous evaluation to support clinical efficacy. By bridging the gap between traditional wisdom and modern science, we can harness the full potential of natural remedies to develop effective treatments for liver diseases⁹⁹.

Grape Seeds: The hepatoprotective effects of Grape Seed Extract (GSE) were investigated in Wistar rats fed a cholesterol-rich diet (HCD) to

induce hypercholesterolemia. To assess the effects of GSE, a separate group received a cholesterol-rich diet supplemented with 0.3% GSE for 8 weeks. The study evaluated serum lipid levels, antioxidant status, liver and kidney function, and histopathological changes in the liver. Notably, oral administration of GSE significantly normalized liver function, as indicated by reduced glutamic pyruvate transaminase (GPT) and increased albumin serum levels. Histological examination of liver sections revealed that GSE-treated animals showed minimal liver damage, characterized by mild microvesicular vacuolation of hepatocytes in the peripheral zone of the hepatic lobule (<50%), compared to the HCD group, which exhibited more extensive fatty changes, including microvesicular and macrovesicular vacuolation in >50% and <70% of liver sections¹⁰⁰⁻¹⁰¹.

***Annona squamosa*:** The hepatoprotective potential of *Annona squamosa* (custard apple) extracts was investigated in a study aimed at exploring its therapeutic application in human hepatotoxicity treatment. Alcoholic and water extracts of the plant were used to assess their protective effects in an isoniazid and rifampicin-induced hepatotoxicity model. The results showed a significant reduction in total bilirubin levels, accompanied by an increase in total protein levels, and a decrease in ALP, AST, ALT, and γ -GT levels in the treatment group compared to the hepatotoxic group. Histopathological examination revealed that the hepatotoxic group exhibited hepatocytic necrosis and inflammation in the centrilobular region, with portal triaditis. In contrast, the treatment group showed minimal inflammation, moderate portal triaditis, and normal lobular architecture. While the extracts of *Annona squamosa* did not completely reverse hepatic injury induced by isoniazid and rifampicin, they did mitigate the effects of these drugs on the liver. The efficacy of the extracts was compared to the standard drug silymarin, providing valuable insights into their potential as a natural hepatoprotective agent¹⁰²⁻¹⁰³.

***Apium graeolens* Linn:** The hepatoprotective effects of *Apium graveolens* Linn (Apiaceae) against carbon tetrachloride (CCl₄)-induced hepatotoxicity were investigated in albino rats. The study evaluated the degree of protection offered by the plant extracts using biochemical markers such

as serum transaminases (SGOT and SGPT), alkaline phosphatase, total protein, and albumin. The results showed that the methanolic extract exhibited the most significant hepatoprotective activity, comparable to the standard drug silymarin. Additionally, the petroleum ether and acetone extracts also demonstrated potent hepatoprotective effects, indicating the potential of *Apium graveolens* Linn as a natural remedy for liver damage¹⁰⁴.

***Fumaria indica*:** *Fumaria indica* (Fumariceae) was investigated for its hepatoprotective properties against carbon tetrachloride, paracetamol, and rifampicin-induced hepatotoxicities in albino rats. The study revealed that the petroleum ether extract effectively mitigated carbon tetrachloride-induced hepatotoxicity, while the total aqueous extract showed protective effects against paracetamol-induced toxicity, and the methanolic extract exhibited hepatoprotective activity against rifampicin-induced damage. Notably, these extracts demonstrated a similar reduction in elevated serum biochemical parameters, comparable to the standard hepatoprotective agent silymarin, suggesting *Fumaria indica*'s potential as a natural hepatoprotective agent¹⁰⁵.

***Wedelia calendulacea* (Bhanra):** The hepatoprotective effects of the ethanol leaf extract of *Wedelia calendulacea* (Asteraceae) (EEWC) were investigated by assessing serum enzyme activities, including aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), protein, and bilirubin. Treatment with EEWC resulted in a dose-dependent decrease in carbon tetrachloride (CCl₄)-induced elevated serum enzyme levels, accompanied by a parallel increase in total protein and bilirubin. This suggests that the extract may help maintain the normal functional status of the liver, indicating its potential as a hepatoprotective agent¹⁰⁶.

***Spermacoce hispida*:** The ethanolic extract of *Spermacoce hispida* Linn (SHE) was investigated for its hepatoprotective effects against carbon tetrachloride (CCl₄)-induced liver damage in rats. Liver function was evaluated by assessing serum levels of SGOT, SGPT, ALP, and bilirubin. Additionally, histopathological examinations were

conducted. The results of the serum biochemical analysis revealed that the ethanolic extract of *Spermaceoce hispida* Linn exhibited a significant protective effect against hepatic damage in the CCl₄-induced hepatotoxicity model. Furthermore, histopathological studies demonstrated that co-administration of the extract with CCl₄ protected the liver, providing further evidence of its hepatoprotective activity¹⁰⁷.

***Momordica subangulata* and *Naregamia alata*:**

The hepatoprotective potential of *Momordica subangulata* (leaf) and *Naregamia alata* (whole plant) suspensions was investigated using a paracetamol overdose-induced liver damage model in rats. The effect of the plant suspensions on bile flow was also studied in anesthetized normal rats by surgically cannulating the bile duct with polyethylene tubing. The plant suspension was administered intraduodenally after a 1-hour bile collection period.

The results showed that *Momordica subangulata* leaf suspension (500mg/kg fresh weight or 50mg/kg dry weight) significantly protected rats from paracetamol-induced liver damage, as evidenced by reduced serum marker enzyme activities. Additionally, it stimulated bile flow in normal rats. In contrast, *Naregamia alata* suspension did not exhibit hepatoprotective activity against paracetamol-induced toxicity. These findings suggest that a suspension of *Momordica subangulata* leaf (fresh or dry) may offer protection against paracetamol-induced hepatotoxicity¹⁰⁸⁻¹⁰⁹.

***Leucas Aspera*:** The protective effects of *Leucas aspera* leaves' fresh juice against carbon tetrachloride (CCl₄)-induced liver damage were investigated. The study evaluated various biochemical markers, including GOT, GPT, alkaline phosphatase, glucose, bilirubin, cholesterol, and total protein. A single dose of CCl₄ significantly altered these markers, but treatment with *Leucas aspera* leaves' fresh juice effectively restored them to normal levels. Silymarin was used as a standard reference for comparison. The study's findings, supported by light and electron microscope photographs, indicate the regeneration of liver parenchyma, demonstrating the juice's promising potential against liver disorders¹¹⁰.

***Plumbago zeylanica*:** The petroleum ether extract of *Plumbago zeylanica* roots was assessed for its hepatoprotective effects against paracetamol-induced liver damage. To evaluate this, serum levels of total bilirubin, total protein, aspartate transaminase, alanine transaminase, alkaline phosphatase, lactate dehydrogenase, γ -Glutamyl transferase, total cholesterol, and serum triglycerides were measured. Additionally, histopathological examination of liver sections was conducted.

The results showed that paracetamol treatment led to significantly elevated serum markers, indicating severe hepatic damage. In contrast, animals treated with the petroleum ether extract of *Plumbago zeylanica* roots (300 mg/kg body weight) exhibited a substantial reduction in serum markers, suggesting the extract's ability to restore normal hepatocyte function. This study demonstrates that the petroleum ether root extract of *Plumbago zeylanica* offers significant protection against paracetamol-induced hepatocellular injury¹¹¹.

***Leucas ciliata* Leaves:** The ethanolic extract of *Leucas ciliata* leaves was assessed for its hepatoprotective effects using a carbon tetrachloride (CCl₄)-induced liver damage model in rats. The extract exhibited a significant, dose-dependent antioxidant activity comparable to ascorbic acid. In the hepatoprotective activity study, CCl₄ significantly elevated serum levels of SGPT, SGOT, ALP, and total bilirubin. However, pretreatment with the ethanolic extract of *L. ciliata* (100, 200, and 400mg/kg po) substantially inhibited these increases, with an effect comparable to silymarin (100mg/kg po). This study reveals that *L. ciliata* leaves possess significant hepatoprotective activity, warranting further investigation into its potential as a natural remedy for liver disorders.¹¹²

***Coptidis Rhizoma* (Huanglian):** Berberine, a bioactive compound found in *Coptidis rhizoma* (Huanglian), has been extensively studied for its diverse pharmacological properties, including antimicrobial, antiviral, anti-inflammatory, cholesterol-lowering, and anticancer effects. This study investigated the hepatoprotective effects of berberine on serum and tissue superoxide dismutase (SOD) levels, as well as liver histology, in a tetrachloride (CCl₄)-induced liver injury

model. Seven-week-old Sprague-Dawley rats were intraperitoneally injected with 50% CCl₄ in olive oil, and berberine was administered orally before or after CCl₄ treatment in various groups. Twenty-four hours after CCl₄ injection, serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) activities, as well as serum and liver SOD activities, were measured. Additionally, liver histological changes were examined under microscopy. The results of this study demonstrate that berberine possesses significant hepatoprotective effects, highlighting its potential as a natural remedy for liver disorders ¹¹³.

Careya arborea: The methanol extract of *Careya arborea* bark (Myrtaceae) was evaluated for its antioxidant and hepatoprotective properties in *Ehrlich ascites* carcinoma (EAC) tumor-bearing mice. Tumor-bearing control animals exhibited significant alterations in antioxidant and hepatoprotective parameters. However, oral administration of the extract at doses of 50, 100, and 200 mg/kg body weight caused a significant reversal of these biochemical changes, returning them to near-normal levels in serum, liver, and kidney tissues, compared to tumor control animals. This suggests that the standardized extract possesses potent antioxidant and hepatoprotective properties, warranting further investigation into its potential therapeutic applications ¹¹⁴.

Cassia fistula (Amaltas): The hepatoprotective effects of the n-heptane extract of *Cassia fistula* (Fabaceae) leaves were assessed in a paracetamol-induced hepatotoxicity model in rats. Oral administration of the extract at a dose of 400 mg/kg body weight significantly mitigated hepatotoxicity, as evidenced by reduced serum levels of transaminases (SGOT and SGPT), bilirubin, and alkaline phosphatase (ALP). The extract's protective effects were comparable to those of a standard hepatoprotective agent, suggesting its potential as a natural remedy for liver damage ¹¹⁵.

Cleome viscosa Linn (Tickweed): The hepatoprotective potential of *Cleome viscosa* Linn (Capparidaceae) extract was evaluated in a carbon tetrachloride (CCl₄)-induced hepatotoxicity model in rats. Both in vivo and histopathological studies confirmed the extract's hepatoprotective effects. Additionally, the extract significantly reduced the

duration of thiopental-induced sleep in mice pretreated with CCl₄, indicating its ability to mitigate hepatic damage. Notably, the hepatoprotective activity of the ethanolic extract was comparable to that of silymarin, a well-established hepatoprotective agent, suggesting its potential as a natural remedy for liver disorders ¹¹⁶.

Morinda citrifolia (noni): The hepatoprotective effects of Noni juice (NJ) (Rubiaceae) were investigated against chronic liver damage induced by carbon tetrachloride (CCl₄) in female Sprague Dawley (SD) rats. Histopathological examination revealed that liver sections from the NJ + CCl₄ group showed minimal damage, similar to controls, whereas the placebo + CCl₄ group exhibited characteristic hepatic steatosis. Additionally, serum biomarkers of liver damage, including alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine transaminase (ALT), total cholesterol (TC), triglycerides (TG), low-density lipoprotein (LDL), and very low-density lipoprotein (VLDL), were significantly elevated in the placebo group compared to the NJ group. In contrast, high-density lipoprotein (HDL) levels were increased in the NJ group and decreased in the placebo group, suggesting a protective effect of NJ against chronic CCl₄-induced liver damage ¹¹⁷.

Phyllanthus amarus (Bhuimamala): The ethanolic extract of *Phyllanthus amarus* (Euphorbiaceae) was administered to all groups, excluding the control groups (I and V), at a dose of 0.3 g/kg body weight, 0.2 ml/day, 30 minutes after aflatoxin exposure. The study spanned three months, with animals sacrificed at 30-day intervals. The extract exhibited hepatoprotective properties by reducing thiobarbituric acid reactive substances (TBARS) content, increasing reduced glutathione levels, and enhancing the activities of antioxidant enzymes, including glutathione peroxidase (GPx), glutathione-transferase (GST), superoxide dismutase (SOD), and catalase (CAT) ¹¹⁸.

Sargassum polycystum: The ethanol extract of *Sargassum polycystum* was assessed for its protective effects against D-galactosamine-induced hepatitis in rats. Pre-treatment with *S. polycystum* extract (125mg/kg body weight/day for 15 days) significantly reduced (P<0.05) the D-galactosamine-induced elevation of plasma

diagnostic marker enzymes (AST, ALT, and ALP). Additionally, the extract exhibited antioxidant activity against D-galactosamine-induced hepatitis by inhibiting lipid peroxidation and preserving the hepatic enzymatic and non-enzymatic antioxidant defense system at near-normal levels. The antihepatotoxic potential of *S. polycystum* may be attributed to its antioxidant properties and membrane-stabilizing action, which warrant further investigation ¹¹⁹.

***Prostechea michuacana*:** The hepato-protective effects of *Prostechea michuacana* (PM) extracts were investigated against carbon tetrachloride (CCl₄)-induced hepatic injury and paracetamol-induced hepatotoxicity in albino rats. Pre-treatment with the methanolic extract of PM exhibited a dose-dependent reduction in CCl₄-induced peroxidation and significantly reduced biochemical markers of hepatic injury.

Additionally, the methanolic extract of PM demonstrated a significant hepatoprotective effect against paracetamol-induced hepatotoxicity, as evidenced by reduced serum enzyme activity and bilirubin levels. This protection was comparable to silymarin, a known hepatoprotective agent. In contrast, the hexane and chloroform extracts of PM did not show any apparent effect. These findings suggest that the methanolic extract of PM may be a potential source of natural hepatoprotective agents, warranting further investigation ¹²⁰.

CONCLUSION: Medicinal plants play a vital role in human healthcare, and numerous species have been identified as potential treatments for liver diseases. In this study, we conducted a comprehensive survey of herbalists in the study area to gather information on therapeutically useful plants for liver diseases. Our research revealed 69 plant species with anti-hepatic properties, with the Asteraceae family being the most dominant. The plants with high use value indicate the presence of valuable phytochemical substances, highlighting the need for further investigation into potential new drugs to treat various liver diseases. While all mentioned plants require pharmacological and phytochemical evaluation for efficacy and safety, priority should be given to herbal plants with high use value and relative frequency of citation for bioassay and allied pharmacological studies.

These plants hold promise for further investigation and potential development into effective treatments.

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