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Review Article

Current Status on Hepatotoxicity and Natural Hepatoprotective Agents

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ABSTRACT

Nutrition is processed and energy is produced by the liver in the body, which is an essential organ. As an essential part of the kidney's function, it facilitates the processing and elimination of exogenous medicines and toxic chemicals.Hepatotoxicity, which can result from a variety of environmental pollutants, pathogenic microorganisms, viruses, drugs, and chemical compounds, can cause cirrhosis, fibrosis, hepatitis, necrosis, and jaundice, among other liver-related disorders.India's ancient medical tradition, Ayurveda, has long been used as a means of treating countless health issues in humans. The plant medicines serve as a significant source of therapeutic compounds used in creating effective medications for various human illnesses, including liver disorders. As a result, the pharmaceutical industry is becoming more interested in using therapeutic plants to develop secure and efficient cures for recently discovered illnesses.The primary objective of this review is to aggregate data on medicinal herbs that have been studied for their potential to prevent drug-induced hepatic injury.

Keywords: Liver, Hepatotoxicity, Hepatoprotective, Herbal remedies.

INTRODUCTION

The liver functions as the principal organ for the metabolism of vital substances. In addition to its metabolic functions, it is crucial for detoxifying and eliminating both internal and external harmful substances, thus safeguarding the body [1]. However, prolonged exposure to foreign compounds and their metabolites can lead to liver damage [2]. The liver is also integral to nearly every biochemical process related to growth, disease defence, nutrient distribution, and energy metabolism. What distinguishes the liver from other organs is its remarkable ability to regenerate after sustaining damage [3]. A variety of substances, including medications such as paracetamol, antibiotics, antituberculosis drugs, and chemotherapeutics, can cause liver injury. Furthermore, other chemicals, such as alcohol and heavy metals like lead and arsenic used in industrial settings, also contribute to this risk [4,5]. Extensive research into chemical-induced liver toxicity has been conducted using animal models, documenting the alterations in biochemical pathways connected to liver disease progression [6,7]. Liver injuries can manifest as necrosis, jaundice, fibrosis, cirrhosis, hepatitis, and liver cancer [8]. Liver-related illnesses rank as one of the leading causes of illness and death globally, according to estimates from the World Health Organisation (WHO) that approximately 1.4 million fatalities result from liver diseases annually. While modern medicine can address liver disorders, it often leads to various side effects.

Herbal plants have been used for ages to treat basic healthcare needs in the Ayurvedic school of Indian medicine. For thousands of years, plant-based treatments have been relied upon for preventing and managing health issues, including liver conditions [10]. The field of conventional medicine has now begun investigating the potential benefits of natural compounds, such as herbs, in providing everyday support for liver health [11]. Hence, it is vital to investigate appropriate herbal remedies that could serve as alternatives to synthetic chemicals.

Indian medicinal herbs have having variety of antioxidant-rich substances, which have been found to help prevent different health disorders. Antioxidant benefits occur at multiple levels, while medicinal plants also contain other advantageous components like phytochemicals that contribute to functional food products. Increasing global awareness of Ayurveda and Indian herbal medicine is anticipated to strengthen understanding of the evidence supporting these plants, bringing fruitful results in the future. Medicinal plants are often viewed as more dependable and effective options and have a long-standing history of traditional use for treating liver-related problems. Many local and tribal communities in India have traditionally turned to these plants for curing various ailments [12]. Mainly, herbal remedies have been employed for tackling liver disorders. Herbal compounds naturally facilitate healing processes within the body. There is a noticeable global trend shifting from synthetic to herbal medicines for preventing diseases and maintaining health. The WHO estimates that 4 billion individuals incorporate herbal medicines into their primary healthcare routines [13,14]. Extensive research is currently being carried out in the field of

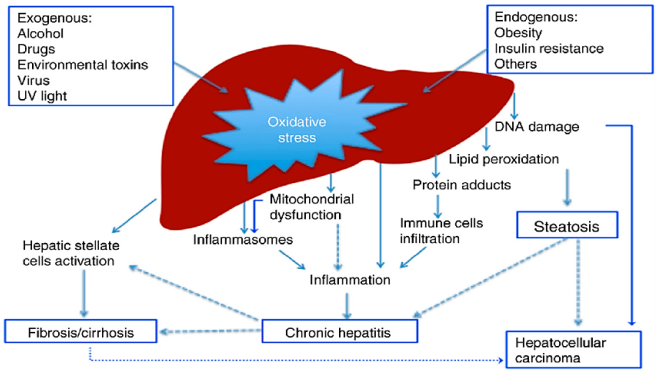

Fig. 1: Risk factors of liver diseases[15].

ethnopharmacology focused on herbal treatments, with efforts underway to discover new herbal drugs that could offer greater efficacy.

The present focus of research is on remedies that promote healing and possess a strong safety record. A variety of medicinal herbs and their active components have been examined and shown to protect the liver from different kinds of damage caused by drugs. This review primarily outlines instances of drug-induced liver damage (hepatotoxicity) as well as the medicinal plants recognized fortheir protective effects, as assessed through both *in-vivo* and *in-vitro* studies (Fig. 1).

Hepatotoxity Classification or Hepatotoxicants

Acetaminophen (Paracetamol)

Acetaminophen, commonly called paracetamol or N-acetyl-p-aminophenol (APAP), is a safe and effective analgesic and antipyretic medication when used within recommended limits [16,17]. The advised dosage of APAP is 325 to 650 mg every 4 to 6 hours in adults, with a max of 4 grams/day. In children, the dosage is 10 to 15 mg/kg every 4 to 6 hours, with a daily max of 50 to 75 mg/kg [18,19]. At therapeutic doses, APAP is predominantly metabolised in the liver. The cytochrome P-450 enzyme system converts around 5 to 9% into the reactive metabolite N-acetyl-p-benzoquinoneimine (NAPQI). However, the bulk, approximately 80 to 90%, undergoes phase II metabolic transformation via glucuronidation and sulfation pathways. In this process, conjugation with reduced glutathione

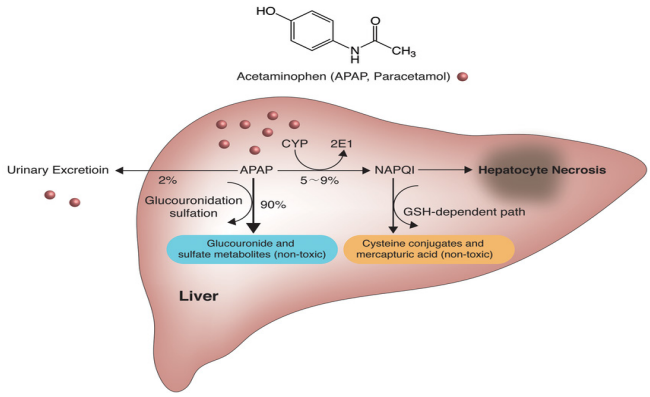

Fig. 2: Acetaminophen (APAP) metabolic pathway.[112]

(GSH) is facilitated by UDP-glucuronosyltransferases (UGT) and sulfotransferases (SULT), converting APAP into non-toxic glucuronidated and sulfated substances that are then eliminated in urine.[20]

APAP-induced hepatotoxicity is a common type of direct liver injury that can cause immediate and serious damage to the liver in both humans and experimental animals. Currently, it is the primary cause of acute liver failure worldwide, accounting for a significant number of deaths [21,22]. Extensive studies have documented the metabolic toxicity of APAP in both human and experimental models [23]. From 1997 to 2002, more than 50% of all acute liver failure cases in the US were linked to drug exposure, with approximately 40% specifically attributed to acetaminophen consumption [24] (Fig. 2).

Carbon Tetrachloride (CCl_4)

Carbon tetrachloride (CCl_4) is an organic solvent that has been chlorinated, and excessive exposure to it can be harmful to several organs. This substance appears as a colourless, highly volatile liquid that emits a sweet, ether-like scent. When subjected to heat, it decomposes into extremely toxic phosgene fumes. Its main use is in the manufacturing of chlorofluorocarbons, which serve as refrigerants. Additionally, it has been used as a treatment for parasites, a dispersant for insecticides, a cleaning solvent, a grain fumigant, and a fire suppressant [25]. Carbon tetrachloride can enter the body through oral ingestion, inhalation through the lungs, and skin contact in both humans and animals (Fig. 3).

It is a well-known liver toxin, which is used to cause liver injury in experimental animals, including rats and mice, for the purpose of assessing the protective effects of herbal remedies. In the liver, it is processed by a nicotinamide adenine dinucleotide phosphate [NADPH]-dependent CYP450-2E1 enzyme, resulting in the creation of free radicals, including the trichloromethyl radical ($\bullet CCl_3$). Further oxidation causes the generation of trichloromethylperoxy radicals($\bullet O-O-CCl_3$) [26,27]. These free radicals target fatty acids in cellular membranes, triggering lipid peroxidation that generates additional reactive aldehydes, such as formaldehyde and acetaldehyde. These aldehydes subsequently interact with reduced glutathione (e.g., GSH), leading to a decrease in GSH levels within liver cells. GSH acts as an intracellular antioxidant, preventing free radical damage to cells [28]. An excess of free radicals from CCl_4 metabolism can also result in DNA damage, contributing to the genotoxic effects of CCl_4. Lipid peroxidation further disrupts cell membranes, resulting in the leakage of hepatic enzymes like aspartate transaminase [AST] and alanine transaminase [ALT], as well as high bilirubin levels in the bloodstream [29,113]. This process subsequently stimulates protein breakdown, inflammation, and cell death, which can all heighten cytotoxic effects [30].

Alcohol (Ethanol)

Alcohol use is a common activity among individuals all over the planet. It is estimated that around 2.4 billion people engage in drinking, with about 960 million of them falling into the category of heavy drinkers [32]. While moderate alcohol intake might lower the risk of heart disorders, excessive and prolonged ethanol use can lead to damage to the liver and nerves [33]. The World Health Organization's Global Report on Alcohol and Health from 2018

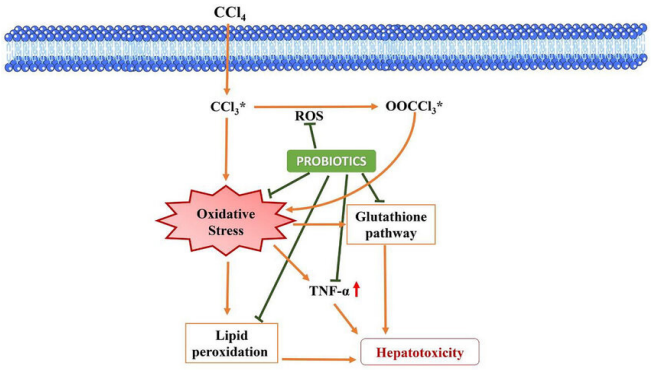

Fig. 3: Schematic diagram of hepatotoxicity induced by Carbon tetrachloride (CCl_4) and reduction by probiotics.[31]

indicates that about 3 million people die each year due to excessive drinking, which constitutes 5.3% of total deaths, and accounts for nearly half of all liver-related fatalities. Ethanol is the primary ingredient found in alcoholic drinks. It is largely absorbed in the intestines, and when it enters the blood circulation, the liver converts it into acetaldehyde and acetic acid. This chemical process generates a considerable amount of reactive oxygen species (ROS) and disrupts the normal functioning of the liver. With time, these alterations can lead to alcoholic liver disease (ALD).

ALD is distinguished by liver damage, inflammation, scarring, cirrhosis, and/or cancer resulting from long-term or excessive alcohol consumption [34]. ALD is divided into various phases based on the pathogenic conditions of the liver. The most common initial stage is alcoholic fatty liver (AFL), which occurs due to an increase in fat buildup within the liver. The next phase, alcoholic hepatitis (AH), is identified by changes in liver cells that make them look swollen, along with the presence of Mallory-Denk bodies and infiltration of inflammatory cells like monocytes and neutrophils [35,36]. While early-stage ALD can be improved with abstention from alcohol, once heavy drinking continues, ALD becomes irreversible. The third phase is alcoholic liver fibrosis, where collagen fibers infiltrate the liver lobules. Finally, cirrhosis and hepatocellular carcinoma are the final two stages of the disease. Though nearly all long-time drinkers develop AFL, only about 10 to 35% progress to alcoholic steatohepatitis (ASH). Additionally, between 8 and 20% of chronic heavy drinkers develop cirrhosis, with approximately 2% acquiring hepatocellular cancer [34]. Despite the growing concern regarding ethanol-related liver injury, the mechanisms behind such damage are intricate and involve various signaling pathways. As a result, it's crucial to understand these mechanisms in order to enhance the treatment options for ALD. Liver injury due to alcohol primarily entails damage to liver cells, the buildup of fat, and inflammation. According to research, transcription factors, kinases, and microRNAs (miRNAs) all play important roles in ALD regulation. In this article, we will discuss the enzymes that regulate ethanol metabolism, the molecular pathways thought to be important in ALD, and an overview of the various treatment approaches.

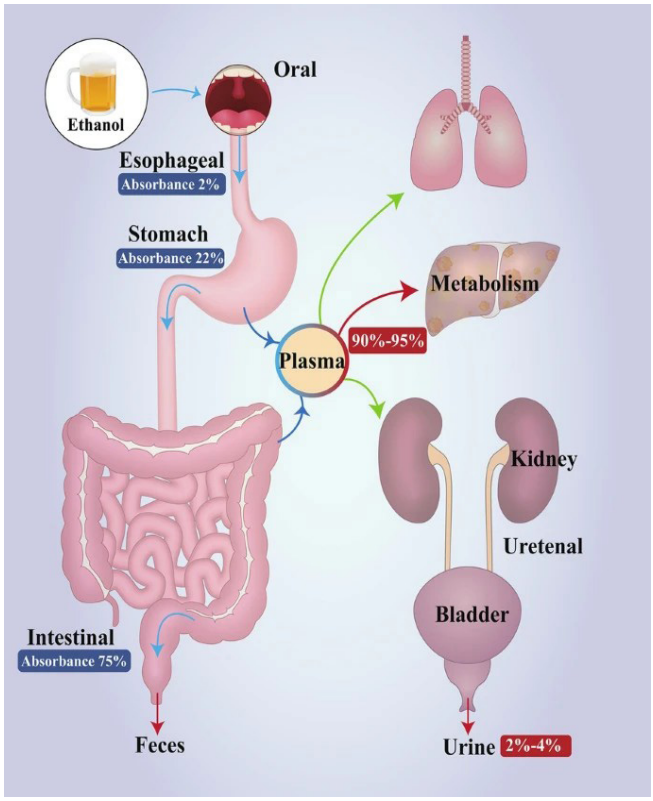

Fig. 4: Pathways of alcohol absorption, distribution, and metabolism in the human.[112]

Ethanol metabolism

Once ingested orally, only a minor quantity of ethanol (2%) gets absorbed in the mouth and esophagus. The majority of ethanol is absorbed in the stomach (22%) or in the intestines (75%). Any ethanol that is not absorbed is removed through the faeces. Approximately 1% of the alcohol that remains in the body is excreted unaltered in the faeces. After absorption, the majority of the consumed ethanol enters the bloodstream and is metabolised by the liver. A minor fraction is removed in its original form through urine or exhaled from the lungs as gas. (see Fig. 4). Ethanol, a small molecule with two carbon atoms and amphiphilic properties, is converted and broken down into an intermediate known as acetaldehyde by enzymes such as ethanol dehydrogenases, microsomal oxidases, and catalases within the liver (Fig. 5).

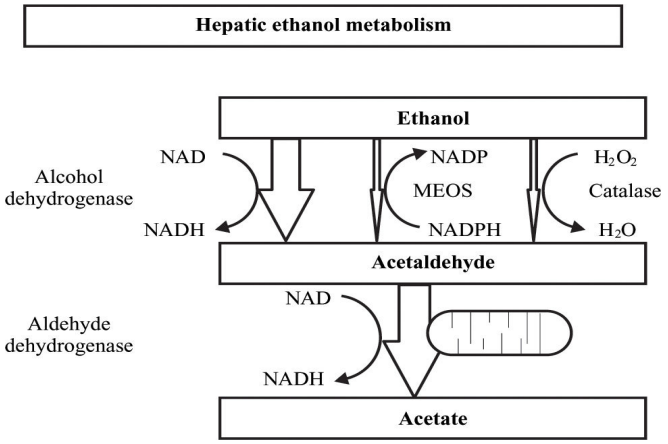

Fig. 5: The metabolic pathway of alcohol[115].

Besides converting into acetaldehyde, the metabolism of ethanol also results in heightened levels of reactive oxygen species (ROS) and a reduction in the ratio of nicotinamide adenosine dinucleotide (NAD)+ to NADH. Under normal physiological circumstances, the majority of ethanol, roughly 80% to 90%, is broken down in the cytoplasm by enzymes known as alcohol dehydrogenases (ADHs) [36]. Multiple mechanisms may be linked to liver diseases caused by ethanol. For example, short-term ethanol use can cause oxidative stress, nitrification stress, endoplasmic reticulum (ER) stress, inflammation, and apoptosis. Long-term ethanol intake can disrupt lipid metabolism, promote lipid accumulation, and lead to alcoholic fatty liver (AFL). It also affects the gut-liver axis by weakening the integrity of the intestinal epithelium's connective structures.

Oxidative Stress and ROS Generation

CYP2E1 is critically involved in the damaging effects of alcohol caused by oxidative stress. Its activation upon prolonged exposure to ethanol results in the overproduction of reactive oxygen species, including superoxide radicals and hydrogen peroxide. These reactive oxygen species hold the capacity to inflict harm upon fats, proteins, and genetic material, eventually leading to the deterioration of cell operations and wholeness [37,38]. Furthermore, an excess of reactive oxygen species leads to a reduction in antioxidants inside cells, particularly glutathione. This weakening of glutathione impairs the liver's ability to protect itself from damage caused by oxidation [39].

Mitochondria dysfunction

When mitochondria don't work properly, it causes issues within the cell. Mitochondria often suffer damage because of alcohol exposure. Harmful molecules and a specific chemical compound cause damage to the structure of mitochondria, inhibit the process of energy synthesis in cells, and reduce the amount of cellular energy produced. This results in the mitochondria expanding, a shift in what can pass through their membranes, and the discharge of elements that encourage cell death, like cytochrome. These actions contribute to the self-destruction of liver cells [40,41].

Lipid Peroxidation and DNA Damage

Harm to fats can happen when they interact with harmful substances, and this can also hurt the genetic material inside cells. When the body processes ethanol, it leads to the creation of harmful substances that cause fats to break down. This process results in compounds like malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE) being produced. These aldehyde compounds create attachments to both DNA and proteins, disrupting how cells typically operate and encouraging mutations and cell death [42].

Pathways involved in inflammation

Cellular processes that trigger and manage inflammation involve intricate communication networks. Alcohol and the substances it breaks down into trigger reactions in the body's defense system. This happens through routes like the Toll-like receptor 4, or TLR4. This then causes nuclear factor-kappa B, or NF-κB, and mitogen-activated protein kinases, or MAPKs, to become active. These sequential reactions encourage the generation of inflammatory signalling molecules, like TNF-alpha and IL-6, which worsen liver swelling and harm [43,44].

Acetaldehyde Toxicity

Acetaldehyde presents a danger due to its harmful effects. Acetaldehyde can bind tightly to proteins and DNA, which disrupts their usual role. Additionally, it attaches itself to GSH, thereby lessening its ability to counteract harmful free radicals, while also encouraging the turning on of stress-related enzymes like c-Jun N-terminal kinase (JNK) and p38, which then worsen cellular injury and programmed cell death [45].

Disruption of Lipid Metabolism

Prolonged consumption of alcohol modifies how the liver processes fats, increasing the activity of fat-producing genes through the Wnt/β-catenin and PI3K/Akt signaling systems, which results in fatty liver disease. These alterations play a role in the shift from a liver filled with fat to a more inflamed and scarred liver [46,47].

Non-oxidative Metabolites and Extrahepatic Effects

Fatty acid ethyl esters, which are ethanol byproducts created without oxygen, similarly play a role in harming cells. Fatty acid ethyl esters negatively affect how mitochondria operate within liver cells, pancreatic cells, and cells lining the intestines; they're also thought to contribute to both pancreas inflammation and problems involving the connection between the digestive system and the liver [48,49].

Non-alcoholic fatty liver diseases

Non-alcoholic fatty liver disease (NAFLD) is a contemporary liver disorder that affects people of any age, particularly those who are overweight or obese. It includes a wide variety of clinical disorders that are caused by an overabundance of fat accumulation in the liver [50]. The increase in obesity in India, especially among women and children in urban areas, is a growing worry for public health. Poor diet, excessive fat intake, unhealthy meal choices, lack of exercise, and genetic predisposition are among the contributing factors. One of the main factors in the growth of obesity and, as a result, NAFLD, is thought to be a high-fat diet (HFD). High-fat diets are the primary cause of non-alcoholic fatty liver disease, which is linked to high morbidity and mortality globally [51]. In India, liver ailments are particularly common, notably among obese people, where fatty liver affects between 8% and 30% of this population [52].Additionally, obesity-related insulin resistance may raise the chance of developing diabetes, which worsens liver disorders. A significant portion of the world's population suffers from NAFLD, a persistent liver condition that is a primary cause of liver disease-related problems such as steatosis, fibrosis, and cirrhosis. The buildup of liver lipids (triglycerides) under these circumstances causes oxidative stress and gradual liver injury [53,54].

D-galactosamine

In the liver, galactosamine treatment produces an inflammatory response that, both biochemically and histologically, mimics viral hepatitis [55]. A time course of therapy causes fatty liver and hepatocellular necrosis [56]. It leads to the emergence of specific liver cell abnormalities characterized by decreased protein and nuclear RNA production [57].

Table 1: Hepatoprotective activities of medicinal plants in paracetamol, carbon tetrachloride (CCL_4), D-galactosamine and thioacetamide-induced hepatotoxicity

Plant	*Family*	*Part Used*	*Extract Type*
Azima tetracantha[63]	Salvadoraceae	Leaves	Ethanol
Aloe vera[64]	Xanthorrhoeaceae	Leaves	Aqueous
Coccinia indica[65]	Cucurbitaceae	Fruits	Aqueous
Sida rhombifolia[66]	Malvaceae	Whole plant	Ethanol
Solanum pubscens[67]	Solanaceae	Leaves	Methanol
Abelmoschus moschatus[68]	Malvaceae	Seeds	Menthol
Carissa carandas[69]	Apocyanaceae	Roots	Ethanol
Eclipta alba[64]	Asteraceae	Leaves	Aqueous
Solanum indicum[64]	Solanaceae	Leaves	Aqueous
Maytenus emarginata[64]	Celastraceae	Leaves	Aqueous
Casuarina equisetifolia[70]	Casuarinaceae	Leaf & bark	Methanol
Lawsonia alba[71]	Lythraceae	Bark	50% Ethanol
Solanum trilobactum[72]	Solanaceae	Whole plant	Methanol
Glycyrrhiza glabra[73]	Fabaceae	Root	Crude powder
Luffa acutangula[74]	Cucurbitaceae	Fruit	Hydroalcohol
Glycosmis pentaphylla[70]	Rutaceae	Leaf, bark	Methanol
Bixa orellana[70]	Bixaceae	Seed	Methanol
Alchornea cordifolia[75]	Euphorbiaceae	Leaves	Chloroform
Morus alba[76]	Moraceae	Leaves	Chloroform, Alcohol
Pittosporum neelgherrense[77]	Pittosporaceae	Stem bark	Methanol
Sphaeranthus amaranthoides[78]	Compositae	Whole plant	Ethanol
Olenlandia herbaceae[79]	Rubiaceae	Whole plant	Methanol
Calotropis gigantean[80]	Ascelpiadaceae	Root bark	Ethanol
Coldenia procumbens[81]	Boraginaceae	Whole plant	Methanol
Polygala arvensis[83]	Polygalaceae	Leaves	Chloroform
Solanum tuberosum (purple potato)[84]	Solanaceae	Tubers	Formic acid, distilled water
Leucas lavandulaefolia[85]	Labiatae	Leaves	Methanol
Crassocephalum crepidioides[86]	Asteraceae	Whole plant	Aqueous
Pisonia aculeate[87]	Nyctaginaceae	Whole plant	Methanol
Phyllanthus niruri[88]	Phyllanthaceae	Whole plant	Ethanol
Vitex negundo[89]	Lamiaceae	Leaves	Ethanol
Orthosiphon stamineus[90]	Lamiaceae	Leaves	Ethanol
Momordica tuberose[91]	Cucurbitaceae	Tubers	Ethanol
Tinispora crispa[92]	Menispermaceae	Stem	Ethanol
Zizyphus jujube[93]	Rhamnaceae	Fruits	Methanol
Phoenix dactylifera[94]	Aracaceae	Fruits	Aqueous
Gardenia gummifera[95]	Rubiaceae	Roots	Methanol
Albizzia lebbeck[96]	Fabaceae	Leaves	70% Ethanol

Table 2: Bioactive plant constituents with hepatoprotective effects

Plant Source	*Family*	*Phyto constituent*
Curcuma longa[97]	Zingiberaceae	Curcumin
Gingerber officinalis[98]	Zingiberaceae	Gingerol
Alium sativum[99]	Amaryllidaceae	S-Allyl-L-Cysteine
Glycine max[100]	Fabaceae	Genistein
Camelia sinensis[101]	Theaceae	Epicatechinsgallate
Vitis vinifera[102]	Vitaceae	Resveratrol
Picrorhiza kurroa[103]	Plantaginaceae	Picroside II
Ventilago madraspatana[104]	Rhamnaceae	Emodin
Anastatica hierochuntica[105]	Brassicaceae	Anastatins A
Acacia confuse[106]	Fabaceae	Galli acid
Cirsium japonicum[107]	Asteraceae	Apigenin-7-glucuronide
Nigella sativa[108]	Ranunculaceae	Thymoquinone
Capparis spinosa[109]	Capparaceae	Quercetin
Glycyrrhiza glabra[110]	Fabaceae	Glycyrrhizin
Clerodendrum[111]	Lamiaceae	Ursolic acid

Thioacetamide

The original thioacetamide is extremely hepatotoxic and has fungicidal properties. Centrilobular necrosis is caused by the bioactivation of sulfine (sulfoxide) and sulfene (sulfone) metabolites by flavin- and/or CYP450 with monooxygenase (FMO) systems [58,59].

This metabolite leads to liver fibrosis. Thioacetamide disrupts the mobility of RNA that travels from the nucleus to the cytoplasm and may cause membrane damage [60].

Hepatoprotective Agents

Phyto-compounds that have a (possibly) therapeutic and protective impact on liver cells are known as hepatoprotectants or hepatoprotective agents. For ages, medicinal herbs have been used in the Ayurvedic school of Indian medicine, address basic healthcare needs. For thousands of years, plant-based treatments have been relied upon for preventing and managing health issues, including liver conditions [10].

Indian medicinal plants are also a valuable source of antioxidants, which are known to help prevent various health issues. Antioxidant benefits occur at multiple levels, while medicinal plants also contain other advantageous components like phytochemicals that contribute to functional food products. Increasing global awareness of Ayurveda and Indian herbal medicine is anticipated to strengthen understanding of the evidence supporting these plants, bringing fruitful results in the future. Medicinal plants have a long history of conventional use in treating liver-related issues and are frequently thought of as more reliable and effective solutions. These plants have long been used by numerous Indian local and tribal cultures to treat a variety of illnesses [12]. Mainly, herbal remedies have been employed for tackling liver disorders. Herbal compounds naturally facilitate healing processes within the body. Herbal remedies are becoming more popular worldwide as a means of preventing illnesses and preserving health. According to WHO estimates, 4 billion people use herbal medicines as part of their primary healthcare regimens [13,14].

Herbal remedies

Modern Pharmaceuticals has a few plant-based solutions that are used to treat liver disorders, and it is designed to address certain conditions [61]. The most profitable sort of herbal medicine is conventional medicine, which is used by around 80% of the population The WHO's traditional medicine relies on the population, fact sheet number 134, published in December 2008. These have expanded as a result of their growing importance and appeal in recent years due to their affordability, safety, effectiveness, and ease of access. There are 33 plants in India that use more than 87 kinds. Plant with several components that are protected by a patent, about 40 commercial polyherbal preparations and formulations formulas said to be hepatoprotective, utilizing action. Approximately 160 phytochemicals from 101 medicinal plants have been reported to have hepatoprotective effects [62] (Tables 1 and 2).

CONCLUSION

This study compiles various pharmacological approaches for treating liver disorders, with a particular focus on medicinal plants that have undergone experimental evaluation. It highlights the need to isolate and identify key bioactive compounds from these plants that may provide liver-protective benefits. Herbal treatments are thought to have preventive effects because they can reduce oxidative stress and modify metabolic pathways linked to liver injury. Due to their high content of phytonutrients with potent antioxidant effects, medicinal plants are considered valuable allies in preventing liver damage. The results underscore the importance of continued pharmacological investigations and the systematic recording of traditional medicinal flora.

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