Hepatotoxicity: Treatment, causes and applications of medicinal plants as therapeutic agents

Meagan Thompson, Yogini Jaiswal, Ilya Wang, Leonard Williams

ABSTRACT

Hepatotoxicity, or liver damage, is caused by hepatotoxins, which may source from chemicals, dietary supplements, pharmaceutical drugs, and medicinal plants. Notably, numerous medicinal plants are used to alleviate illness, particularly in traditional systems of medicine, such as Ayurveda and Traditional Chinese Medicine. These systems of medicine have been implemented for centuries to treat various ailments. Some medicinal plants serve as hepatoprotectors against liver damage, while others induce hepatotoxicity. Recent advances in instrumentation and knowledge of active components have allowed research scientists to study the drug metabolic pathways of these phytopharmaceuticals to establish a causal relationship between medicinal plants and their pharmacological effects on the human liver, as a hepatoprotector or a causative agent for hepatotoxicity. The human liver metabolizes substances via oxidation, reduction, hydration, hydrolysis, condensation, conjugation, or isomerization. Interruption of these processes can lead to hepatotoxicity, causing liver cancer, cirrhosis and Hepatitis C, respectively. Such diseases are responsible for higher mortality rates worldwide. The present review focuses on highlighting various plants that are hepatoprotective, hepatotoxic and the challenges faced by phytopharmaceuticals. The article also emphasizes on various agents (bioactives from medicinal plants, industrial toxins and pharmaceutical compounds) that have been reported to cause hepatotoxicity. The article proposes views and beneficial medicinal plants that can help in identification of natural hepatoprotective agents for future natural product based drug discovery.

Keywords: Hepatotoxicity, hepatoprotection, phytopharmaceuticals, medicinal plants, drug metabolism, Ayurveda.

INTRODUCTION

Since ancient times, humans have used medicinal plants to alleviate diseases. Modern analytical technologies and knowledge of active compounds found in plants have allowed greater insights into pharmaceutical plants. Hepatotoxicity is medicinal, chemical, dietary, or herb-induced liver damage via hepatotoxins [1]. The global burden of hepatotoxicity affects over fifty million people worldwide [2]. Traditional systems of medicine include diverse cultural health care practices that are passed from ancient times. The World Health Organization defines traditional medicine as ‘diverse health practices, approaches, knowledge, and beliefs incorporating plant, animal and/or mineral based medicines, spiritual therapies, manual technique, and exercises applied singularly or in combination to maintain well-being, as well as to treat, diagnose or prevent illness’ [3,4]. Practitioners of Traditional Chinese Medicine believe that Disease results due to imbalance in Yin and Yang of the body [5]. All sensations of the human body can be represented with five elements: fire, wood, metal, earth, and water. Ayurveda originated in India over 3000 years ago and emphasizes a universal connectedness between humans and the universe. Life forces are called dosha, and the constituents of the human body are called prakriti[6]. Compared to synthetic drugs, which have established mechanisms of action, the arena of phytochemicals faces challenges in establishing the mechanism of action of plant extracts. The interaction between various constituents, synergism or inhibition in their activity, differences in their in-vivo and in-vitro effects, and the cost and duration associated with isolation and screening of active compounds are the challenging aspects for success of phytopharmaceuticals.

Historical perspective

Ancient societies consumed medicinal plants to propitiate ill health conditions. A Sumerian clay slab dated to be made in 3000 B.C. in Nagpur, India, is the oldest written account of medicinal plants composed of two hundred and fifty plants and twelve preparations, including henbane, mandrake, and poppy [7]. The Ebers Papyrus, originating in 1550 B.C. Egypt, encompasses seven hundred species of plants for eight hundred prescriptions. During the first century A.D., Dioscorides, the ‘father of
pharmacognosy” and physician in the Roman military, studied the restorative properties of medicinal plants. His work De Materia Medica included 657 medicinal plants, including chamomile, onion, ivy, sage, and coriander. During the third century B.C., Theophrast, the “father of botany,” created botanical science [9]. His most notable pieces, De Causis Plantarum and De Historia Plantarum distinguished over five hundred medicinal plants: cinnamon, cardamom, mint, et cetera. During the eighteenth century, Linnaeus composed Species Plantarium that classified medicinal plants according to a binomial naming system: the genus with an initial capital letter and the species in lowercase letters. During the nineteenth century, scientific pharmacology allowed researchers to discover active substances within medicinal plants, such as tannins, vitamins, glycosides, hormones, and flavonoids [9]. Immemorial interest in medicinal plants produced advancements in research and led to the modern field of medicinal plants, with several applications to human disease [10].

Phytomedicinals and challenges in their global acceptance

Various parts of medicinal plants have been used traditionally to mitigate and treat human ailments. Researchers have studied plant extracts and isolated secondary metabolites to establish their pharmacological effects in in-vivo, ex-vivo, and in-vitro models. [11, 12, 13] Medicinal plant products are used as dietary supplements and phytopharmaceuticals, and the formulations include: extracts, essential oils, ointments, syrups, salves, capsules, and tablets. As an example, galantamine, is a patented isoquinoline alkaloid that alleviates the effects of Alzheimer’s disease via neurogenesis and neuroprotection [14, 15]. Galantamine provides neuroprotection against amyloid-β peptides, a precursor to Alzheimer’s disease [16, 17, 18]. Razadyne, an acetylcholinesterase inhibitor, is a commercially available medication that decelerates the breakdown of acetylcholine, a neurotransmitter responsible for learning and memory [19]. Medicinal plant discoveries have immensely contributed to pharmaceutical drugs, including digoxin from Digitalis purpurea, a cardiac stimulant, and reserpine, an antihypertensive drug from Rauwolfia spp. [10]. However, researchers lack longitudinal data on their efficacy. Formidable tasks await the concerted efforts of ethnobotanists, pharmacists, physicians, and anthologists using new research techniques and clinical studies. Recently, the access, quality control, and efficacy of medicinal plants have become popular topics. Challenges facing research scientists include: standardization and regulation of herbal formulations, uncertainty of quality, identity, authenticity, deficient efficacy, establishment of plausible synergistic effects, multiple drug reactions, and intrinsic toxicity. A gateway for progress would be facilitation of pre-clinical studies in animal models followed by clinical trials of successful investigational compounds. Genetic variation due to such factors as gene flow, reproductive mode, environmental conditions, geographical locations and genetic drift cause qualitative and quantitative variations in the same plant [19, 20]. The systematic use of medicinal plants would require identical genetics and taxonomic documentation of species, genus, and their standardization [10]. The World Health Organization, the European Scientific Cooperative on Phytotherapy, and the European Agency for the Evaluation of Medicinal Products are scientific organizations that develop protocols to determine the safety and effectiveness of phytoconstituents of herbal drugs [21].  

Drug metabolic pathways of liver and hepatotoxicity

The liver is the most prominent digestive gland that metabolizes drugs via oxidation, reduction, hydration, hydrolysis, condensation, conjugation, or isomerization [22]. Two stages of hepatic drug metabolism convert pharmaceuticals into conjugated water-soluble substances via P450 enzymes, which are excreted via urine or bile [23]. Although the liver metabolizes drugs, disruption of these processes can lead to hepatotoxicity. Hepatotoxicity occurs through numerous mechanisms: disassembly of hepatocytes, apoptosis of hepatocytes, injury to bile duct, inhibition of mitochondria, and cytolytic T-cell activation. Data regarding herbal hepatotoxicity can be found in case series and case reports. The expression of hepatotoxicity originates with weight loss, malaise, jaundice, dyspepsia, blood coagulation, oedema, and pruritus [24, 25, 26]. Hepatic symptoms scope from clinically asymptomatic to chronic symptoms [27, 28, 29]. Mechanisms and treatments for hepatoprotection and hepatotoxicity are depicted in Fig. 2. Once hepatotoxicity is initiated, patients express the following symptoms: hepatic necrosis, fibrosis, vomiting, bleeding, swelling of the legs and feet, elevated serum transaminases, bilirubin, or cholestasis, liver cirrhosis, liver failure, and hepatic veno-occlusive disease [30]. Cirrhosis is marked by the degeneration of nodules enclosed by the fibrous glands of the liver, causing high portal blood pressure, and ultimately liver disease, due to deformity of hepatic vasculature. There are two forms of hepatotoxic-induced liver injury: Idiosyncratic injuries result from the formation of reactive metabolites and activation of the immune system. It is dose-independent and predictable. Intrinsic liver injuries are dose-dependent and reproducible [31, 32, 33]. Numerous factors make determination of herbal hepatotoxicity difficult and include: production and storage processes, contamination, pharmacodynamics properties, and pharmacokinetic properties [34]. Drug-induced liver injury occurs in many patients with acute liver injury, and without obvious etiology. Known information regarding the hepatotoxicity of the causative agent is helpful in diagnosis. However, documentation of hepatotoxicity in the medical literature is variable. Researchers need accurate information on the diagnosis, frequency, causes, and patterns of liver injury attributable to herbal medicines [35]. Structures of hepatotoxic agents are depicted in Fig. 1.

![Figure 1: Structures of some reported hepatotoxic agents](image-url)
Figure 2: Mechanisms and treatments for hepatoprotection and hepatotoxicity

Table 1: Causative Agents of Hepatotoxicity

<table>
<thead>
<tr>
<th>Causative Agent</th>
<th>Product</th>
<th>Type of Hepatotoxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotic</td>
<td>Amoxicillin-clavulanate</td>
<td>Hepatocellular, cholestatic or mixed hepatocellular-cholestatic hepatitis[^36, 37].</td>
</tr>
<tr>
<td>Antibiotic</td>
<td>Macrolidesketolides erythromycin</td>
<td>Cholestatic pattern of injury with evidence of portal and bullous inflammation, eosinophilia and mild hepatocellular necrosis[^37].</td>
</tr>
<tr>
<td>Antibiotic</td>
<td>Pyrazinamide</td>
<td>Centrolobular cirrhosis and cholestasis[^38, 37].</td>
</tr>
<tr>
<td>Antibiotic</td>
<td>Rifampicin</td>
<td>Cholestatic hepatitis[^39, 40, 37].</td>
</tr>
<tr>
<td>Industrial Toxin</td>
<td>Carbon tetrachloride</td>
<td>Centrolobular necrosis[^40, 37].</td>
</tr>
<tr>
<td>Industrial Toxin</td>
<td>Mercury</td>
<td>Interference of bile excretion and destruction of hemoglobin[^37].</td>
</tr>
<tr>
<td>Medicinal Plant</td>
<td>Larreatridentata</td>
<td>Fulminant hepatitis, subacute hepatic necrosis, cholestatic hepatitis, acute liver failure[^41].</td>
</tr>
<tr>
<td>Pharmaceutical Drug</td>
<td>Corticosteroids or glucocorticoids and anabolic androgenic steroids</td>
<td>Glyogen storage in liver, enlarged liver[^37].</td>
</tr>
<tr>
<td>Pharmaceutical Drug</td>
<td>Non-steroidal anti-inflammatory drugs</td>
<td>Acute, cytolytic, cholestatic or mixed hepatitis[^42, 37].</td>
</tr>
</tbody>
</table>

Ayurveda: A traditional system of medicine originating in India

Ayurveda, *Science of Life*, is a traditional system of medicine from around 1500 B.C. with distinct concepts of integrated medicine, derived from the Indian philosophies *Samkhya* and *Nyaya vaisheshika*. Ayurveda considers the physical, psychological, philosophical, ethical, and spiritual well-being of the individual. Five basic elements exist to maintain equilibrium, *Prithvi*, *Jala*, *Teja*, *Vayu*, and *Akash*. When equilibrium is disturbed, disease results. Based upon one’s psychosomatic constitution, there are specific daily, *Dinacharya*, and seasonal, *Ritucharya*, routine to maintain optimal human health. Of the several medicinal plants used in Ayurveda, some well-studied plants related to hepatotoxicity are discussed below. Turmeric, *Curcumin longa*, is of the Zingiberaceae family and curcuma genus. Humans consume the root, a rhizome, most commonly consumed as a powder. Ayurvedic medicine utilizes turmeric for its antibacterial, antiseptic, and anti-inflammatory properties, as well as a pain-killer, weight-reducer, cosmetic cream, and hepatoprotector. Researchers demonstrated that curcumin protects the liver against carbon tetrachloride-induced liver injury in rats. Research scientists induced hepatic stress via an intraperitoneal injection of CCL₄ (0.1 ml/hg bw). Also administered were turmeric and curcumin extracts once per day for four weeks at 100, 200, and 300 mg/kg/d. The extracts provided protection against hepatic damage by suppressing oxidative stress and lowering levels of serum aspartate aminotransferase and alanine aminotransferase. This yields higher levels of hepatic glutathione, reducing lipid peroxidases. Garlic, *Ailum sativum*, is of the Liliales family and Allium L. genus. Humans consume all parts of the plant, except the rhizome, wrappers of the garlic bulb, and the root cluster. The cloves are most commonly consumed either raw or cooked. Ayurvedic medicine uses garlic as an antibiotic to lower diuretic, expectorant, antitussive, lipid, and blood pressure levels. Garlic lowers systolic blood pressure, and thus treats hypertension. Furthermore, garlic strengthens the immune system by fighting diseases such as cancer, particularly stomach, colon, prostate, and breast cancer. Aged garlic extract demonstrates the delay of ischaemia-induced neuronal injury. It has low toxicity, although the following adverse reactions have been reported: upset stomach and skin rashes. Amla, *Emblica*, is a traditional Indian medicine, rich in antioxidants. It is used in the treatment of liver diseases.
officinalis, is of the Phyllanthaceae family and Phyllanthus genus. Human consume the dry powder of the fruit, and as a topical cream. In Ayurvedic medicine, Amla is believed to maintain the balance between all three doshas. Amla has great amounts of vitamin C. One hundred grams of amla contains 700 mg of vitamin C, thirty times that of an orange.[45] Amla alleviates the adverse effects of hyperacidity and ulcers, as well as strengthens immunity, improves vision, scavenges free-radicals, and reduces cholesterol. Amla fruit extracts provided hepatoprotection against alcohol-induced hepatic injury in rats as demonstrated by in-vivo administration of 5 g/kg bw for 60 days into two-month-old male albino Wistar rats, (120-140 g) and result in an increase in liver lipid peroxidation, nitrite plus nitrate levels, and protein carbonyls. The administration of alcohol at 250 mg/kg bw was found to lower superoxide dismutase, glutathione peroxidase, catalese, glutathione, and glutathione S-transferase.[52]

Tulsi, Ocimum sanctum Linn, is of the family Labiate and genus Ocimum.[53] Humans consume the raw or prepared leaves as a tea or powder. In Ayurvedic medicine, tulsi is used to lessen the effects of respiratory diseases like bronchitis and bronchial asthma, malaria, diarrhoea, arthritis, heart disease, insect bites, and chronic fever. The active component in tulsi is eugenol, and gives it its therapeutic properties.[54] Lahonet al. proved the hepatoprotective effects of tulsi against paracetamol-induced liver damage in albino rats (150-200 g) when combined with silymarin. Three rat groups were given the following preparations: alcoholic extract of Ocimum Sanctum leaves at 200 mg/kg/bw/d, silymarin at 100 mg/kg/bw/d and OSE 100 mg/kg/bw/d and silymarin 50 mg/kg/bw/d p.o. for ten days. On day eight, 2g/kg/bw/d of paracetamol was administered to induce hepatotoxicity. Results demonstrated that Ocimum sanctum alcoholic leaf extract provided hepatoprotection, as demonstrated by normal levels and maintained normal levels of liver enzymes and albumin globulin.[55] Ginger, Zingiber officinalis, is of the Zingiberaceae family and Zingiber officinalis Roscoe species. The rhizome, or underground stem, is consumed in the form of powder, teas, oils, and extracts. The active ingredients, the gingerols in particular 6-gingerol, alleviate the following symptoms: motion sickness, nausea, vomiting, vertigo, respiratory congestion, and hypoglycemia.[56] Researchers have studied the effects of the hydroalcoholic extract of ginger on the liver of epileptic female rats that have been treated with lamotrigine. Lamotrigine is an anti-epileptic drug. Prolonged use contributes to hepatotoxicity. To investigate, forty-eight female Wistar rats were given 10 mg/kg/d of lamotrigine via gavages for four weeks. Researchers induced epilepsy via injections of pentylentetrazol at 40 mg/kg. This demonstrates that the hydroalcoholic extract of ginger advances liver function in lamotrigine-induced hepatotoxicity.[57]

Plants that cause hepatotoxicity

There are three types of hepatotoxicity: cholestatic,hepatocellular, and mixed. Cholestasis occurs when substances expelled via bile are disrupted due to impaired excretion of hepatocytes. Hepatocellular damage occurs when infection or cancer affects liver cells. Substances that result in hepatotoxicity include pharmaceuticals drugs and medicinal plants. Researchers have documented numerous pharmaceutical drugs that induce liver damage. As an example, overdose on acetaminophen is a common cause of drug-induced hepatotoxicity caused due to its metabolite NABQINABQI diminishes glutathione, leading to apoptosis of hepatocytes and hepatocellular necrosis. Anticoagulants, such as ximelagatran, acenocoumarin, heparin, and warfarin, are used to prevent venous thromboembolism. Patients begin with elevated serum transaminases, and subsequently develop hepatitis, and liver failure.[58] Antimalarial pharmaceuticals such as amodiaquine, contributes to hepatotoxicity due to oxidation of a reactive metabolite, named iminoquinone. This metabolite binds irreversibly to proteins, disturbing cellular functions.[59] In addition to pharmaceutical drugs, research scientists have discovered medicinal plants that contribute to hepatotoxicity. Links between hepatic damage and herbal medicines are concerning to research scientists. Liver damage includes the following disorders: elevated liver enzymes, acute or chronic hepatitis, cholestasis, hepatic necrosis or fibrosis, cirrhosis, liver failure, and hepatic veno-occlusive disease.[60] Actearacemosa is a perennial woodland herb native to North America. The active constituents include terpene glycosides like actein, cimicifugoside, and 27-deoxyactein, alkaloids, flavonoids, and tannins. This plant is associated with acute hepatitis and liver failure.[62] Symphytum officinale L. is a common garden plant belonging to the Boraginacea family. Pyrrolizidine alkaloids are a major content of this plant and the main hepatotoxic effect is hepatic veno-occlusive disease.[63] Germander contains diterpenoids, which cause hepatocyte apoptosis. Green tea is extracted from Camellia sinensis leaves and is safe in average amounts, however excessive catechins causes hepatocellular injury. Extracts from symphytum causes veno-occlusive disease as it contains pyrrolizidine alkaloids. Moreover, piper methysticum used for anxiety and sleep disorders and leads to hepatotoxicity. Cinicifugaracemosa is used for menopause and dysmenorrhea, and contains glucosamine supplements and causes severe hepatotoxicity. Chelidoniummajus is used for dyspeptic symptoms, and cascara sagrada, a herbal laxative containing anthracene glycoside. The liver is the main organ of drug metabolism, so it is the target organ of drug-induced injuries. In the liver, foreign chemicals are transformed by the metabolizing enzymes; microsomal cytochrome P450, mixed-function monooxygenases, UDP-glucuronosyltrans-ferases, sulphotransferases, and glutathione-S-ferases. Medicinal plants are self-prescribed and widely available so they are difficult to control.[65]

Establishing a causal relationship between pharmaceutical drugs, medicinal plants, and liver injury is challenging due to the variable composition of the plants, and their respective ingredients. To assess the causal relationship, other causes of liver injury must be excluded, such as hepatitis, autoimmune diseases, metabolic, and genetic diseases. Two methods are used to assess liver injury: expert opinions, and the RousselUclaf assessment method. This method calculates a score based on clinical, and biochemical parameters. High scores indicate increased chance of hepatic injury.[66]

Mortality and morbidity statistics

Hepatitis C is marked by inflammation of the liver due to a virus in the blood, usually from the use of blood-to-blood contact, shared needles, or mother-to-offspring transmittal. Left untreated, Hepatitis C causes liver cancer, liver disease, and cirrhosis. The Centers for Disease Control’s study of Hepatitis C demonstrated that the mortality rate of Hepatitis C in 2013 exceeded the total collective deaths from sixty infectious diseases, including tuberculosis and HIV. In 2014, the CDC reported 19,659 total deaths. An estimated three and a half million Americans have the disease, with those born between 1945-1965 showing the highest risk due to medical procedures involving needles and blood transfusions. Approximately 175 million worldwide test positive for Hepatitis C and 350,000 die per year. Three to four million people are diagnosed each year. Chronic hepatitis C is the eminent cause of cirrhosis at 27% and hepatocellular carcinoma at 25%. Chronic Hepatitis C kills 2.4 million worldwide
per year [67, 68]. Patients with alcoholic cirrhosis comprise 30-50% for liver transplants [2]. The incidence of cirrhosis worldwide is unclear. However, in the United States of America, is accounts for 0.15%, or 400,000 cases, as well as more than 25,000 deaths and 373,000 hospital visits in 1998. The European nation reflect similar values, with Asian and African countries demonstrate higher values due to the prevalence of Hepatitis B and C [61]. Global mortality and morbidity rates due to hepatitis C are depicted in Fig. 3.

![Figure 3: Global mortality and morbidity rates due to hepatitis C](image)

**Plants with hepatoprotective properties**

Plants contain compounds that confer hepatoprotection including: carotenoids, glycosides, phenols, coumarins, lignans, essential oils, monoterpenes, alkaloids, flavonoids, xanthines, and organic acids [69]. Out of several classes of hepatoprotective plants reported till date, some well-studied plants are described in this section. The genus *Opuntia* possesses great capacity for protection of the liver. *Opuntia* plants are commonly used to treat ulcers, glaucoma, dyspnea, and liver disease. Ncibi et al. demonstrated that *Opuntia indica* reduced the hepatotoxicity of the organophosphorus insecticide chlorpyrifos [70]. *Opuntia indica* *f. inermis* prickly pear juice was studied to determine its affects against ethanol-induced liver injury in rats. The study reported that pre-treatment of ethanol fed rats with prickly pear juice reduced liver protein, and lipid oxidation, and decreased histopathological markers. It is postulated these effects are exerted due to its ability to end free-radical chain reactions, or enhance endogenous antioxidant activities [71]. *Matricaria chamomilla*, one of the most popular teas consumed, contains over 100 components identified for the biological activity. Namely, *Matricaria chamomilla* controls the activity of cytochrome P450. Malaiakal et al. reported that rats fed with a 2% chamomile solution for four weeks, decreased CYP1A2 isofrom activity by 39% versus that of the control group, who received only water [72]. Grupa et al. used an aqueous ethanolic extract of *Chamomile* for the paracetamol-induced damage in albino rats. Their results established that the ethanolic extract of one kilogram of *Chamomile* provided hepatoprotection. *Silybum marianum* is of the Asteraceae family and has been widely studied for its oral treatment of liver disease [73, 74, 75]. Different mechanisms allow for its protective abilities including the following: increasing SOD activity, subduing toxin penetration of hepatocytes, impeding lipid peroxidation, increasing glutathione tissue concentrations, and augmenting hepatocyte protein production. Moreover, *Silybum marianum* stimulates hepatocyte regeneration and stabilization of the cell membrane. This prevents hepatotoxic agents from entering the hepatocytes [76, 77].

### Table 2: List of representative hepatoprotective plants studies

<table>
<thead>
<tr>
<th>Plants</th>
<th>Dose Administered</th>
<th>Geographical source location</th>
<th>Animal Model Studied</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Opuntia robusta</em> and <em>O. streptacantha</em></td>
<td>800 mg/kg/d oral dose</td>
<td>Semi-arid region of Mexico</td>
<td><em>Opuntia robusta</em> and <em>Opuntia streptacantha</em> fruits to alleviate acetaminophen-Induced Acute Liver Damage in rats [79].</td>
</tr>
<tr>
<td><em>Matricaria chamomilla</em></td>
<td>5-7 mg/kg bw, hot liquid extract</td>
<td>Najaf city, Iraq</td>
<td>Hepatoprotective effect of <em>Matricaria chamomilla</em> hot aqueous extract against methyoxyl 90%- induced hepatotoxicity in 3 month old albino mice [79].</td>
</tr>
<tr>
<td><em>Silybum marianum</em></td>
<td>100-200 mg/kg/bw/d</td>
<td>Extracts of milk thistle</td>
<td><em>Silybum marianum</em> favors hepatobiliary elimination of various drugs in rats [80].</td>
</tr>
<tr>
<td>3,4',5-trihydroxystilbene</td>
<td>5 g/kg daily injection of ethanol and resveratrol</td>
<td>Resveratrol from Selmedica healthcare, Korea</td>
<td>Protective effects of resveratrol on ethanol-induced lipid peroxidation in adult male wistar rats (200-230 g) [81].</td>
</tr>
<tr>
<td><em>B. orellana</em>, <em>C. cajan</em>, <em>G. pentaphylla</em>, and<em>C. equisetifolia</em> (Achiote, Pigeon pea, Glycocomspentaphylla, <em>Casuarinaequisetifolia</em>)</td>
<td>500 mg/kg bw</td>
<td>Rajshahi City, Bangladesh</td>
<td>Methanol extract of <em>B. orellana</em>, <em>C. cajan</em>, <em>G. pentaphylla</em>, and<em>C. equisetifolia</em> displays hepatoprotection via lowering serum levels of ALT, SGPT, AST, and SGOT in Swiss albino rats (80-90 g) [82].</td>
</tr>
<tr>
<td><em>Vaccinium macrocarpon</em></td>
<td>200, 400, 800 mg/kg oral for 7 days daily</td>
<td>State of Puebla, Mexico market of Zacatlan</td>
<td>Protection of cranberry via ethanolic extract of DNA damage due to benzo[alpyrene using <em>in-vivo</em> mouse peripheral blood micronucleous assay [83].</td>
</tr>
<tr>
<td><em>Alchornea cordifolia</em></td>
<td>2 g/kg oral acetaminophen, 0.22 mg/ml phenolic content</td>
<td>Federal University of Technology, Akure, Nigeria</td>
<td>Hepatoprotection of <em>Alchornea cordifolia</em> extract in Wistar albino rats against acetaminophen-induced liver damage [84].</td>
</tr>
<tr>
<td><em>Andrographis lineata</em></td>
<td>Subcutaneous injection 50% v/v CCl4, liquid paraffin 3 ml/kg alternate days for 4 weeks A. <em>lineata</em> oral 845 mg/kg/d</td>
<td>Jhansi, India</td>
<td>Hepatoprotective effects of <em>Andrographis lineata</em> in male Wistar rats with chronic liver damage [85].</td>
</tr>
</tbody>
</table>
As not been documented regarding reliance used alone, but rather used with viral protease inhibitor, inhibits the function of the viral replication complex by viral reproduction.

Cytochrome p4503A is the mechanism by which SIM undergoes every genotype of hepatitis C, with the exception of genotype three. Daclatasvir, an HCV replication inhibitor of the viral NS5B or polymerase (NS5B). Daclatasvir is commonly used with pegylated interferon/ribavirin, and telaprevir or boceprevir, without ribavirin, in patients who had presented a failed triple therapy with pegylated interferon/ribavirin, and telaprevir or boceprevir, without ribavirin [102, 98].

SOF is a pan-structural proteins involved with embryo contraception during and six months post-treatment [104,105]. Significant drug toxicity has not been documented regarding Sofosbuvir, although two cases studies demonstrate that Sofosbuvir has been associated with jaundice, vomiting, and acute liver injury [106]. The hepatotoxicity of Daclatasvir is more difficult to ascertain because it is rarely used alone, but rather used with viral protease (NS3) or polymerase (NS5B). Daclatasvir is commonly used with Asunaprevir, an HCV protease inhibitor. This combination produced elevated serum ALT levels ranging from 3-11% and hepatitis [107].

Current pharmaceutical treatments

Pharmaceutical drugs in conjunction with antiviral therapy are typically used to treat herb-induced liver injury. For example, Hepatitis C virus is treated using a sustained virologic response, performed with ribavirin (RBV) and pegylated interferon (PegIFN)-alpha via intravenous administration one time per week with 800-1400 mg per day for forty-eight weeks [98]. Researchers recently discovered a novel oral drug, directly acting antiviral agents (DAAs) to cure Hepatitis C with a ninety percent success rate [99]. There are two types of developmental protease inhibitors, and one NS5A HCV replication inhibitor: Sofosbuvir (SOF), simeprevir (SIM), and daclatasvir (DCV) respectively. In particular, SOF is a pan-genotypic antiviral Hepatitis C-specific nucleotide inhibitor of the viral NS5B polymerase that terminates when the chain is integrated as a substrate by RNA polymerase in emerging HCV-RNA genome. Simeprevir is a macrocyclic NS3/4A protease inhibitor that presents activity against every genotype of hepatitis C, with the exception of genotype three. Cytochrome p4503A is the mechanism by which SIM undergoes hepatic metabolism [100]. The above-mentioned protease inhibitors achieve their affects by interfering with protein processing within the HCV genome targeting various non-structural proteins involved with viral reproduction [101]. Daclatasvir, a NS5A HCV replication inhibitor, inhibits the function of the viral replication complex by binding to the NS5A protein. Researchers have combined daclatasvir with sofosbuvir, discussed above. Results demonstrated a 100% sustained virological response at week twenty-four in genotype 1 patients who had presented a failed triple therapy with pegylated interferon/ribavirin, and telaprevir or boceprevir, without ribavirin, pegylated interferon/ribavirin, and telaprevir or boceprevir, without ribavirin [102, 98]. SOF is activated via phosphorylation once inside the hepatocytes, and is metabolized by dephosphorylation, producing an inactive metabolite GS-331007. The goal of treating Hepatitis is to avoid cirrhosis. New research aims to discover treatments using knowledge of direct-acting antivirals, such as pegylated interferon, as they produce several side effects. Sofosbuvir was the first drug to enter the market without NABQINABOQ [103]. Simeprevir capsules are associated with embryo-fetal toxicity with ribavirin therapy. Per these findings, female and male patients must use two methods of contraception during and six months post-treatment [104,105].

### Table: Phytopharmacology

<table>
<thead>
<tr>
<th>Compound</th>
<th>Dosage and Route</th>
<th>Place of Origin</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Careyaarborea</td>
<td>50, 100, 200 mg/kg bw orally</td>
<td>Jhansi, India</td>
<td>Methanol extract of Careyaarborea bark tested for antioxidant and hepatoprotection in mice with Ehrlich ascites carcinoma tumors [96]. Hepatoprotection of Careyaarborea leaves via extraction of n-heptane and induced paracetamol in rats to lower SGOT, SGPT, and ALP levels [97].</td>
</tr>
<tr>
<td>Cassia fistula</td>
<td>400 mg/kg bw orally</td>
<td>Jhansi, India</td>
<td>Ethnologic extraction of Phyllanthus amarus to lower TBARS level and raise GPx, GST, SOD, and CAT over 3 months [99].</td>
</tr>
<tr>
<td>Phyllanthusamarus</td>
<td>0.3g kg/bw, 0.2 ml/d post 30 min aflatoxin administration</td>
<td>Central and Southern India</td>
<td>Ethnologic extraction of Phyllanthus amarus to lower TBARS level and raise GPx, GST, SOD, and CAT over 3 months [99].</td>
</tr>
<tr>
<td>Phyllanthuspolyphyllus</td>
<td>200 and 300 mg/kg, p.o. plant extract</td>
<td>Pakistan</td>
<td>Methanolic extraction of Phyllanthus polyphyllus gives hepatoprotection and antioxidant benefits against acetaminophen-induced hepatotoxicity [99]. Animals given picroliv to protect against hepatic damage in Mastomysnabatalensis via decrease of lipid peroxides and hydroperoxides [98, 92].</td>
</tr>
<tr>
<td>Pterocarpussantalinus</td>
<td>3-12 mg/kg/d for 2 weeks</td>
<td>Jhansi, India</td>
<td>Hepatoprotection of CCl4 induced hepatic damage model. Animals indicated recovered hepatic cells due to increase in protein and decrease in serum levels [92].</td>
</tr>
<tr>
<td><em>Proserpermaceriferiolium</em></td>
<td>45 mg/ml plant and 30 mg/ml ethanol in 1% gum tragacanth</td>
<td>Ayurvedic medicinal garden at Gajanur, Shimoga district</td>
<td>Hepatoprotection of Proserpermaceriferiolium methanol extraction in rats shown to restore levels of serum bilirubin and enzymes [93].</td>
</tr>
<tr>
<td><em>Vaccinium</em> spp. (Rabbiteye Blueberry)</td>
<td>0.1 ml/kg/d p.o. for 14 d CCl4and 25 mg/kg/d p.o. for 14 days plant extract</td>
<td>Jhansi, India</td>
<td>Blueberry in liver protection via increase liver antioxidants (Nrf2, HO-1, Nqo1) [94].</td>
</tr>
<tr>
<td>Grape seed proanthocyanidin extract</td>
<td>0.6 g/10 g oral for 21 days</td>
<td>Blueberry Production Field of Majiang, Guizhou</td>
<td>Blueberry in liver protection via increase liver antioxidants (Nrf2, HO-1, Nqo1) [94].</td>
</tr>
<tr>
<td><em>Silybummarianum</em> (Milk Thistle)</td>
<td>100 mg/kg/ bw d daily for 2 mon oral administration of GSPE</td>
<td>N/A</td>
<td>Silybummarianum shows antiradical properties and tested against CCl4 and showed decrease in liver enzymes [77].</td>
</tr>
<tr>
<td><em>Silphium</em> (Milk Thistle)</td>
<td>Ethyl acetate extract 100 mg/kg bw and ethanol extract 100 mg/kg bw 10 d against CCl4 (100 mg/kg bw)</td>
<td>N/A</td>
<td>Wistar albino rats (150-180g) tested for hepatoprotective activity of carotenoids showed higher protein levels [96].</td>
</tr>
<tr>
<td><em>Spirulina</em> and <em>Dunaliella</em> (Carotenoids from microalgae)</td>
<td>Extracted in hexane:isopropyl (1:1 v/v) orally fed in olive oil</td>
<td>Egypt</td>
<td>Protective effect on CCl4 induced liver injury in male Wistar strain rats [95].</td>
</tr>
<tr>
<td><em>Euglena gracilis</em> Z (Paramylon)</td>
<td>500, 1 000, 2 000, mg/kg bw extract and 50% CCl4, 2 ml/kg bw</td>
<td>N/A</td>
<td>Protective effect on CCl4 induced liver injury in male Wistar strain rats [95].</td>
</tr>
</tbody>
</table>
CONCLUSION

Herbal medicines have progressively become prevalent due to rising costs of treatments with synthetic western medicine, numerous side effects of allopathic drugs, drug resistance, unregulated purchase options for consumers on most herbal drugs and easy availability of these medicines. Since ancient times, human have employed medicinal plants to alleviate or cure diverse illnesses. Identification and isolation of the multitudinous components of medicinal plants pose a challenge to researchers and health care providers. With advancements in research techniques, the industry of phytopharmaceuticals has burgeoned to include new insights into medicinal plants to alleviate illness. The goal is to create novel phytopharmaceuticals that are standardized, regulated, and available in the clinical setting.

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REFERENCES


