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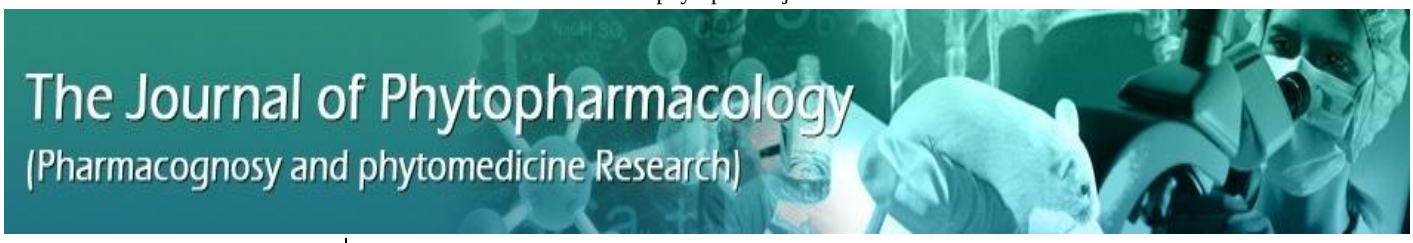

Review Article

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

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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 for treating 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 hepato-toxins [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 [8]. His most notable pieces, *De Causis Plantarium* and *De Historia Plantarium* distinguished over five hundred medicinal plants: cinnamon, cardamom, mint, et cetera. During the eighteenth century, Linaeus 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 affects 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 [18]. 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 P_{450} 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 hepatotoxin-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.

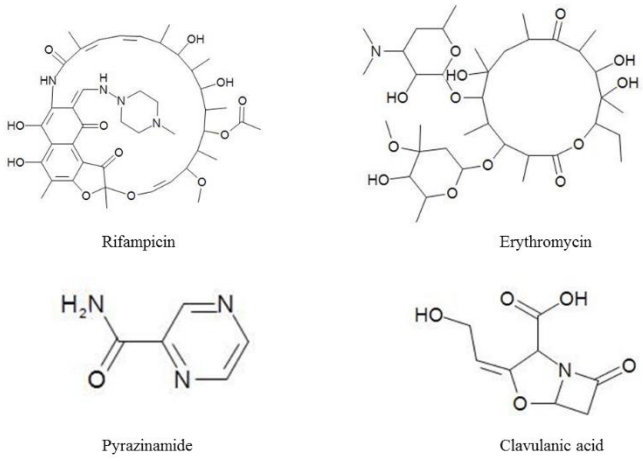

Figure 1: Structures of some reported hepatotoxic agents

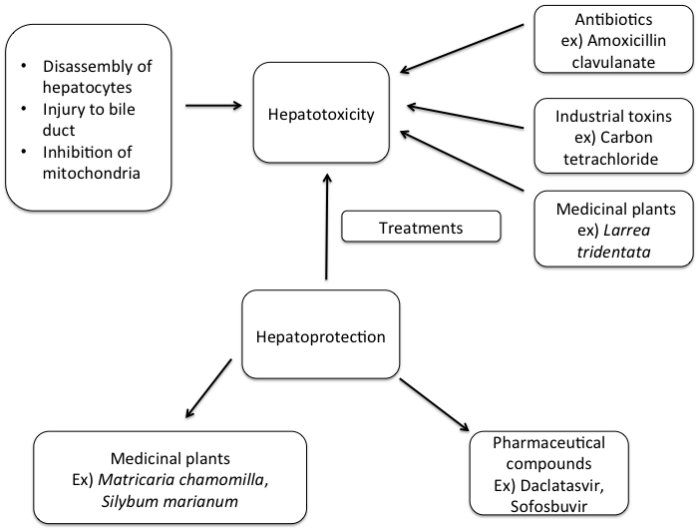

Figure 2: Mechanisms and treatments for hepatoprotection and hepatotoxicity

Table 1: Causative Agents of Hepatotoxicity

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

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*[43]. Ayurveda considers the physical, psychological, philosophical, ethical, and spiritual well-being of the individual [44]. Five basic elements exist to maintain equilibrium, *Prithvi*, *Jala*, *Teja*, *Vayu*, and *Akash*. When equilibrium is disturbed, disease results [45]. Based upon one's psychosomatic constitution, there are specific daily, *Dinacharya*, and seasonal, *Ritucharya*, routine to maintain optimal human health [46]. 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. In Sanskrit, turmeric, *sarvoshadhi*, means 'medicine for all diseases.' The principle constituent *Curcumin* gives turmeric its yellow appearance. 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 CCl_4 (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 [47]. Garlic, *Allium 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 [48]. Furthermore, garlic strengthens the immune system by fighting diseases such as cancer, particularly stomach, colon, prostate, and breast cancer [49]. Aged garlic extract demonstrates the delay of ischaemia-induced neuronal injury [50]. It has low toxicity, although the following adverse reactions have been reported: upset stomach and skin rashes [45]. Most notably, garlic provides hepatoprotection against gentamycin-induced hepatotoxicity in rats. Adult male rats were fed 2% and 4% garlic for 27 days pre-gentamycin administration. Rats adhering to a garlic diet demonstrated a restoration of antioxidants due to the presence of sulpur-containing compounds and flavonoids [51]. Amla, *Emblica*

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 presents 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 resulted 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, catalase, 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, diarrhea, arthritis, heart disease, insect bites, and chronic fever. The active component in tulsi is eugenol, and gives it its therapeutic properties [54]. Lahon*et 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 officinale*, is of the *Zingiberaceae* family and *Zingiber officinale 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 pentylenetetrazol 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, andmixed. 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, 61]. *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 Boraginacaea family. Pyrrolizidine alkaloids are a major content of this plant and the main hepatotoxic effect is hepatic veno-occlusive disease [63, 64]. 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*is used for anxiety and sleep disorders and leads to hepatotoxicity. *Cimicifugaracemosa* 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, sulfotransferases, and glutathione-S-transferases. 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, while Asian and African countries demonstrate higher values due to the prevalence of Hepatitis B and C [1]. Global mortality and morbidity rates due to hepatitis C are depicted in Fig. 3.

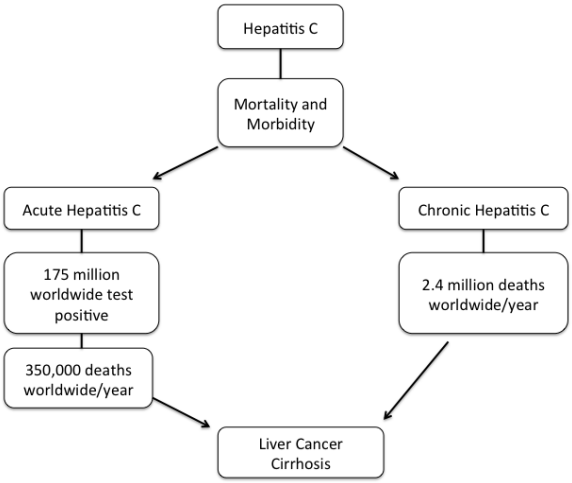

Figure 3: Global mortality and morbidity rates due to hepatitis C

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 *Opuntiaficus-indica* reduced the hepatotoxicity of the organophosphorus insecticide chlorpyrifos[70]. *Opuntiaficus-indica f. inermes* 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]. *Matricariachamomilla*, one of the most popular teas consumed, contains over 100 components identified for the biological activity. Namely, *Matricariachamomilla* controls the activity of cytochrome P450. Maliakal *et al*. reported that rats fed with a 2% chamomile solution for four weeks, decreased CYP1A2 isoform activity by 39% versus that of the control group, who received only water [72]. Grupa *et al*. used an aqueous ethanolic extract of *Chamomile recutitacapitula* for the paracetamol-induced damage in albino rats. Their results established that the ethanolic extract of one kilogram of *Chamomile capitula* extract provided hepatoprotection. *Silybummarianum* 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, *Silybummarianum* stimulates hepatocyte regeneration and stabilization of the cell membrane. This prevents hepatotoxic agents from entering the hepatocytes [74, 76, 77].

Table 2: List of representative hepatoprotective plants studies

Plants	Dose Administered	Geographical source location	Animal Model Studied
Opuntiarobusta and *Opuntiastreptacantha*	800 mg/kg/d oral dose	Semi-arid region of Mexico	*Opuntiarobusta* and *Opuntiastreptacantha* fruits to alleviate acetaminophen-Induced Acute Liver Damage in rats [78].
Matricariachamomilla	5-7 mg/kg bw, hot liquid extract	Najaf city, Iraq	Hepatoprotective effect of *Matricariachamomilla* hot aqueous extract against methomyl 90%- induced hepatotoxicity in 3 month old albino mice [79].
Silybummarianum	100-200 mg/kg/bw/d	Extracts of milk thistle	*Silybummarianum* favors hepatobiliary elimination of various drugs in rats [80].
3,4',5-trihydroxystilbene	5 g/kg daily injection of ethanol and resveratrol	Resveratrol from Selmedica healthcare, Korea	Protective effects of resveratrol on ethanol-induced lipid peroxidation in adult male wistar rats (200-230 g) [81].
B. orellana, *C. cajan*, *G. pentaphylla*, and*C. equisetifolia* (Achiote, Pigeon pea, Glycosmispentaphylla, *Casuarinaequisetifolia*)	500 mg/kg bw	Rajshahi City, Bangladesh	Methanol extract of *B. orellana*, *C. cajan*, *G. pentaphylla*, and*C. equisetifolia* displays hepatoprotection via lowering serum levels of ALT, SGPT, AST, and SGOT in Swiss albino rats (80-90 g) [82].
Vacciniummacrocarpon	200, 400, 800 mg/kg oral for 7 days daily	State of Puebla, Mexico market of Zacatlan	Protection of cranberry via ethanolic extract of DNA damage due to benzo[a]pyrene using *in-vivo* mouse peripheral blood micronucleus assay [83].
Alchorneacordifolia	2 g/kg oral acetaminophen, 0.22 mg/ml phenolic content	Federal University of Technology, Akure, Nigeria	Hepatoprotection of *Alchornea cordifolia* extract in Wistar albino rats against acetaminophen-induced liver damage [84].
Andrographislineata	Subcutaneous injection 50% v/v CCl_4 liquid paraffin 3 ml/kg alternate days for 4 weeks*A. lineata* oral 845 mg/kg/d	African Tradtional Medicine Jhansi, India	Hepatoprotective effects of *Andrographis lineata* in male Wistar rats with hronic liver damage [85].

Careyaarborea	50, 100, 200 mg/kg bw orally	Jhansi, India	Methanol extract of *Careyaarborea* bark tested for antioxidant and hepatoprotection in mice with Ehrlich ascites carcinoma tumors[86].
Cassia fistula	400 mg/kg bw orally	Jhansi, India	Hepatoprotection of *Cassia fistula leaves* via extraction of n-heptane and induced paracetamol in rats to lower SGOT, SGPT, and ALP levels [87].
Phyllanthusamarus	0.3g kg/bw, 0.2 ml/dpost 30 min aflatoxin administration	Central andSouthern India	Ehtanolic extraction of *Phyllanthus amarus* to lower TBARS level and raise GPx, GST, SOD, and CAT over 3 months [88].
Phyllanthuspolyphyllus	200 and 300 mg/kg, p.o. plant extract	Pakistan	Methanolic extraction of *Phyllanthus polyphyllus* gives hepatoprotection and antioxidant benefits against acetaminophen-induced hepatotoxicity[89].
Picorhizakurroa	3-12 mg/kg/dfor 2 weeks	Jhansi, India	Animals given picroliv to protect against hepatic damage in Mastomysnatalensis via decrease of lipid peroxides and hydroperoxides[90, 91].
Pterocarpussantalinus	45 mg/ml plant and 30 mg/ml ethanol in 1% gum tragacanth oral for 14 days	Ayurvedic medicinal garden at Gajanur, Shimoga district	Hepatoprotection of CCl_4 induced hepatic damage model. Animals indicated recovered hepatic cells due to increase in protein and decrease in serum levels [92].
Ptrospermumacerifolium	0.1 ml/kg/d p.o. for 14 d $CCl_4$and 25 mg/kg/d p.o. for 14 days plant extract	Jhansi, India	Hepatoprotection of *Ptrospermumacerifoliu m*ethanol extraction in rats shown to restore levels of serum bilirubin and enzymes [93].
Vaccinium spp. (Rabbiteye Blueberry)	0.6 g/10 g oral for 21 days	Blueberry Production Field of Majiang, Guizhou	Blueberry in liver protection via increase liver antioxidants (Nrf2, HO-1, Nqol) [94].
Grape seed proanthocyanidin extract	100 mg/kg/ bw /d daily for 2 mon oral administration of GSPE	N/A	Grape seeds proanthocyanidin extract as hepatic-reno-protective agent against gibberellic acid induced oxidative stress in adult male abino rats [95].
Silybummarianum (Milk Thistle)	Ethyl acetate extract 100 mg/kg bwand ethanol extract 100 mg/kg bw 10 d against CCl_4 (100 mg/kg bw)	N/A	*Silybummarianum*shows antiradical properties and tested against $CCl_4$and showed decrease in liver enzymes [75].
Spirulinaplatensis and *Dunaliellasalina* (Carotenoids from microalgae)	Exracted in hexane:isopropynol (1:1 v/v) orally fed in olive oil 100 microg/kg bw/d	Egypt	Wistar albino rats (150-180g) tested for hepatoprotective activity of carotenoids showed higher protein levels [96].
β -(1-3)-D-glucan isolated from *Euglena gracillis Z* (Paramylon)	500, 1 000, 2 000, mg/kg bw extract and 50% CCl_4 2 ml/kg bw	Japan	Protective effect on CCl_4 induced liver injury in male Wistar stain rats [97].

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 the chain when integrated as a substrate by RNA polymerase in emerging HCV-RNA genome. Simpeprevir is a macrocyclic NS3/4A protease inhibitor that presents activity against every genotype of hepatitis C, with the exception of genotype three. Ctyochrome 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 NABQINABQI [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]. 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].

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 phytophamaceuticals that are standardized, regulated, and available in the clinical setting.

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