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MEDICINAL PLANTS IN HEPATOLOGY: ADVANCES IN EXPERIMENTAL AND CLINICAL RESEARCH

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ABSTRACT

The hepatic system plays a pivotal role in metabolic homeostasis and the processing of essential nutrients. Hepatic dysfunction and acute liver failure represent significant clinical challenges with substantial morbidity and mortality implications. Viral hepatitis, particularly hepatitis B virus (HBV) and hepatitis C virus (HCV) infections constitute the predominant aetiological factors in chronic liver disease globally. Pakistan bears a disproportionate burden of viral hepatitis, with epidemiological data indicating that approximately 20 million individuals are affected by these infections–15 million with HCV and 5 million with HBV. This prevalence positions Pakistan among the countries with the highest hepatitis burden worldwide. Globally, chronic hepatitis B affects an estimated 350 million individuals, while hepatitis C impacts approximately 170 million people. The annual mortality attributed to complications of chronic hepatitis B and C infections represents a substantial public health concern, with death rates varying significantly across different populations and healthcare settings. Despite advances in antiviral therapeutics, current pharmacological interventions demonstrate limited efficacy in promoting hepatocellular regeneration, preserving hepatic architecture, or comprehensively restoring liver function in patients with advanced disease. Consequently, there exists an urgent clinical need to identify novel therapeutic modalities that are both efficacious and demonstrate acceptable safety profiles for the management of chronic liver disease. The present investigation seeks to systematically evaluate indigenous phytochemical compounds derived from medicinal plants that have

demonstrated hepatoprotective properties through rigorous scientific evaluation, with particular emphasis on their potential therapeutic applications in hepatotoxicity management.

Keywords: *Liver; Hepatoprotective; Medicinal Plants; Hepatitis B; Hepatitis C; Liver Disease; Phytochemicals; Hepatotoxicity*

INTRODUCTION

The liver represents a critical organ in human physiology, orchestrating essential metabolic processes and maintaining physiological homeostasis (Mitra and Metcalf, 2009). This organ serves as the primary site for macronutrient metabolism, facilitating the biotransformation of carbohydrates, proteins, and lipids whilst simultaneously eliminating toxic metabolic by-products (Nguyen et al., 2008; Kumar et al., 2012; Marchesini et al., 2003; Bartosch et al., 2010; Block et al., 2015; Waheed et al., 2009; Otta et al., 2012; Li et al., 2025; Gower et al., 2014; Amersfoort et al., 2003; Jayton and Hall, 2006; Klammt et al., 2000; Apte and Krishnamurthy, 2010; Akinloye et al., 2011; Dorcas and Soloman, 2014; Atkinson & Camien, 1982; Shivananda et al., 2011; Scerif and Jarish, 2010). Liver dysfunction encompasses any pathological process that compromises hepatic architecture or physiological function, manifesting through diverse clinical entities including cirrhosis, non-alcoholic steatohepatitis, cholestatic disorders, alcoholic hepatitis, and hepatocellular carcinoma (Sarin and Choudhury, 2016). In developed nations, alcohol consumption and chronic infections represent the predominant aetiological factors for hepatic impairment, whilst in developing regions, environmental toxins, viral hepatitis (particularly HBV and HCV), and pharmaceutical agents including antibiotics, chemotherapeutic compounds, paracetamol, and industrial solvents constitute the primary causative mechanisms (Chopin and Best, 2008). The prevalence of hepatitis B and C infections demonstrates alarming increases across emerging economies (Messina et al., 2015; Patel et al., 2011), with epidemiological surveillance revealing 1,800 hepatitis B-positive blood samples in recent screening programmes (CUPEC, 2013). Many plants have hepatoprotective activities (Table 1). Regional variations in viral hepatitis prevalence are substantial, with Southern European and Japanese populations exhibiting higher rates than those observed in the United Kingdom, whilst Egyptian blood donor populations demonstrate a 19% hepatitis B prevalence (Buseri et al., 2009; Yazdani et al., 2012). Pakistani paediatric populations exhibit hepatitis B antibody prevalence of 2.4% and hepatitis C antibody prevalence of 2.1%, with both infections representing significant causes of morbidity and mortality in this demographic (Hamid et al., 2003). Transmission mechanisms frequently involve contaminated medical equipment, non-sterile injection practices, and inadequate sterilisation protocols, with Pakistan reporting among the highest rates of intramuscular injection procedures globally, contributing to HBV antigen positivity rates of 2.4% and HCV prevalence of 3.0% in healthy populations (Faiz et al., 2011). Historical perspectives on hepatic pathology trace back to Giovanni Battista Morgagni's initial observations in 1761, with René Laennec subsequently introducing the term "cirrhosis" in 1826, derived from the Greek word describing the characteristic orange coloration of cirrhotic tissue (Selmi et al., 2011). Contemporary pathological classification encompasses ulcerative lesions, degenerative changes, fibrotic transformation, parenchymal nodule formation, and vascular alterations as fundamental components of hepatic disease progression (Anna et al., 2015). The discovery of hepatitis B virus in 1967 (Block et al., 2015) and subsequent isolation of hepatitis C virus in 1989 (Waheed et al., 2009) revolutionised understanding of viral hepatitis epidemiology. Global HCV prevalence demonstrates significant geographical variation, ranging from 0.1% in Oceania to 5.4% in Central Asia, with regional distributions including 1.2% in East Asia, 1.1% in South Asia, 3.1% in North Africa/Middle East, 4.2% in Central Africa, and 5.3% in West Africa, yielding an overall global prevalence of 1.6% (Irene et al., 2014). Despite therapeutic advances,

contemporary medicine has yet to establish consistently effective interventions for complex hepatic disorders (Ravi et al., 2014), with the World Health Organization reporting that 80% of developing world populations rely on traditional medicinal approaches for hepatic conditions (Rahim and Khan, 2006). Current therapeutic strategies focus on addressing hepatitis-mediated, alcohol-induced, and drug-related hepatic injury through conventional and innovative treatment modalities aimed at enhancing clinical efficacy (Thyagarajan et al., 2002). Hepatocellular injury typically manifests through disruption of intercellular connections, compromise of plasma membrane integrity, and subsequent elevation of circulating hepatic enzymes, with increased alkaline phosphatase activity indicating membrane dysfunction and biliary obstruction, ultimately resulting in cholestasis and characteristic biochemical profile alterations (Tatiya et al., 2012).Novel biomarkers for early detection of liver dysfunction are being developed, like transmembrane glycoprotein GP73 ,midkine, and Von Willebrand Factor, improving diagnostic accuracy (Adugna, A. et al., 2025). Additionally, advances in gene editing technologies, such as CRISPR (Adlat et al., 2025), have shown promising results in treating genetic liver diseases, paving the way for personalized medicine.

THE SPREAD OF HEPATITIS B AND HEPATITIS C.

According to World Health Organization surveillance data, hepatitis B virus (HBV) and hepatitis C virus (HCV) infections rank amongst the leading ten causes of global mortality. Epidemiological stratification of HBV prevalence is characterised by hepatitis B surface antigen (HBsAg) seroprevalence rates, with high-endemic regions defined by prevalence exceeding 8%, intermediate-endemic areas demonstrating 2-7% prevalence, and low-endemic regions maintaining prevalence below 2% (Raminder and Sharma, 2014). Geographic distribution analysis reveals that Southeast Asia, China, sub-Saharan Africa, Pacific Islands, and Middle Eastern territories represent high-endemic zones, with approximately 8% of the population demonstrating HBsAg positivity. Intermediate endemicity characterises South Asia, Europe, Russia, and the United States, where prevalence ranges from 2-7%, whilst low-endemic regions include Western Europe, North America, and Australia, where prevalence remains below 2%. South Asian countries including Afghanistan, Bangladesh, Bhutan, India, Nepal, and Pakistan have been identified as priority regions for collaborative epidemiological research initiatives. Population-based studies demonstrate that HCV prevalence in Western Europe and North America remains below 2.5%, representing relatively lower burden compared to other global regions. British epidemiological investigations have identified HCV prevalence of less than 1% in low-risk populations, whereas high-risk cohorts, particularly individuals with intravenous drug use history, demonstrate substantially elevated prevalence rates ranging from 77% to 90% in Scottish populations. The World Health Organization's 2004 mortality projections estimated annual deaths attributable to HCV-associated complications at 308,000 cases for hepatocellular carcinoma and 785,000 cases for cirrhotic complications, highlighting the substantial global health burden imposed by chronic viral hepatitis infections (Wahid et al., 2009).

SYMPTOMS OF HEPATITIS B AND HEPATITIS C.

The clinical presentation of hepatitis B virus infection typically manifests within four to twelve weeks following exposure, with symptom severity ranging from mild constitutional symptoms to fulminant hepatic failure. In contrast, hepatitis C virus infection characteristically demonstrates an insidious onset with prolonged asymptomatic periods, often delaying clinical recognition until advanced disease stages. The acute phase of both

HBV and HCV infections presents with characteristic symptoms including abdominal discomfort, dark-coloured urine, pyrexia, arthralgias, anorexia, nausea, vomiting, malaise, fatigue, jaundice, and right upper quadrant pain (Omar et al., 2014). Progression to chronic hepatitis results in hepatic architectural damage and subsequent development of complications including gastrointestinal bleeding secondary to portal hypertension, altered bowel habits, ascites formation due to portal hypertension and hypoalbuminaemia, peripheral oedema, hepatic encephalopathy resulting from impaired ammonia metabolism, and the characteristic spider naevi reflecting altered vascular dynamics associated with chronic liver disease. (Thomas et al., 2000).

RISK FACTORS OF HEPATITIS B AND HEPATITIS C

The transmission of hepatitis B virus (HBV) and hepatitis C virus (HCV) is strongly linked to unsafe medical practices, particularly the reuse of contaminated needles. Needle sharing among people who inject drugs (PWID) is a major driver of HCV transmission (Altaf et al., 2007). In Pakistan, where annual per capita income is among the lowest in developing countries, unsafe blood transfusion practices remain widespread, with the World Health Organization estimating 1.2–1.5 million transfusions each year, many performed without adequate screening (Seyed et al., 2009). Blood transfusion is therefore a significant contributor to HBV and HCV transmission. The United Nations Office on Drugs and Crime (UNODC) has reported approximately 500,000 drug users in Pakistan, of whom 150,000 inject drugs, with up to 30% sharing injection equipment. The prevalence of HCV among PWID is alarmingly high—93% in Lahore (Punjab) and 75% in Quetta (Balochistan) (Asad et al., 2009). Unsafe practices also extend to barbers, where only 13% were aware of HBV transmission via contaminated razors; 46% of razors were reused, and some were disinfected using pesticides, an ineffective method (Janjua & Nizamy, 2004). Health care workers are another vulnerable group, with HBV and HCV prevalence rates of 6% and 5.5%, respectively, exceeding international averages (Asad et al., 2009). In addition, HBV carries a higher risk of vertical (transplacental) transmission compared with HCV, and unprotected sexual contact with infected individuals further contributes to HBV spread (Yaran et al., 2014).

HEPATITIS B AND HEPATITIS C DIAGNOSIS

Hepatitis B (HBV) and hepatitis C (HCV) are blood-borne viruses. Current diagnostic methods include enzyme-linked immunosorbent assay (ELISA) and polymerase chain reaction (PCR) for detecting HCV and HBV, respectively. These tests enable early detection in asymptomatic individuals, facilitating timely management and reducing disease-related complications. Screening programs for HBV and HCV, as well as individual testing, are integral to preventing adverse outcomes. (Khuwaja et al., 2002).

INVESTIGATION TEST

To diagnose hepatitis B, hepatitis B surface antigen (HBsAg) testing in blood samples is essential, as HBsAg is the marker for the virus. Detection of HBsAg typically occurs 2-3 months post-infection. A positive result indicates the presence of hepatitis B. For hepatitis C, reverse transcription PCR (RT-PCR) is used to detect hepatitis C viral RNA (HCV RNA). If HCV RNA is positive, the virus is present. The hepatitis C vaccine, however, does not prevent infection; it reduces the risk of progression to chronic infection and liver disease (Gilson et al., 2006).

OTHER INVESTIGATIONS

- CBC
- LFT see (ALT, ALP, AST and total bilirubin)
- Ultrasound

TREATMENT OF HEPATITIS B

n acute hepatitis B infection, treatment during the first 24 months is generally not required, as approximately 90% of immunocompetent adults achieve spontaneous viral clearance without medical intervention. Management in the early phase of infection is largely supportive, given the limited role of antiviral therapy in altering the natural course of the disease. Only in rare instances of severe or fulminant hepatitis is pharmacological intervention indicated, and even then, the primary goal is to mitigate hepatic inflammation and prevent progression to liver failure. For patients who progress to chronic hepatitis B, long-term antiviral therapy with agents such as tenofovir or entecavir is the standard of care (Tan et al., 2022). These treatments suppress viral replication, reduce the risk of cirrhosis and hepatocellular carcinoma (Nan et al., 2025), and improve long-term survival.
(Anais et al., 2014).

TREATMENT OF CHRONIC HEPATITIS B

Current therapeutic approaches for chronic hepatitis B virus infection do not achieve definitive viral eradication but rather modify disease progression and minimise hepatocellular injury rates. In patients presenting with mild disease activity, clinical surveillance with deferred treatment initiation may represent the optimal management strategy. Contemporary treatment modalities encompass both parenteral and oral therapeutic options, including pegylated interferon-alpha and nucleoside or nucleotide analogues. Interferon-alpha functions through immunomodulation, enhancing host immune responses against viral replication. The American Association for the Study of Liver Disease (AASLD) updated treatment guidelines in 2009, establishing tenofovir and entecavir as preferred first-line oral antiviral agents, with adefovir relegated to second-line therapy due to inferior efficacy and resistance profiles (Marcellin et al., 2008). For patients without established cirrhosis, pegylated interferon remains a viable first-line treatment option due to its finite treatment duration and potential for sustained virological response (Zhou et al, 2025). Common adverse effects of interferon therapy include constitutional symptoms such as fatigue, depression, anxiety, influenza-like illness, dermatological reactions, alopecia, and haematological abnormalities. The standard duration of interferon treatment ranges from 24 to 48 weeks; however, sustained virological response rates vary substantially across patient populations, with the most favourable outcomes observed in individuals with elevated transaminase levels, absence of cirrhosis, and hepatitis B e-antigen positivity accompanied by low viral loads. In contrast, nucleoside and nucleotide analogues inhibit viral polymerase activity and are particularly effective in patients with advanced fibrosis or cirrhosis. However, oral antiviral therapy typically requires prolonged administration ranging from several years to indefinite duration, with treatment modification necessitated by the emergence of drug resistance, requiring sequential therapy adjustments to maintain virological suppression. (Eric et al., 2010)

TREATMENT OF HEPATITIS C

Treatment options for hepatitis C traditionally included a combination of ribavirin and interferon, though these regimens were associated with prolonged duration and significant adverse effects. Advances in antiviral therapy have led to the development of direct-acting antivirals (DAAs), which target specific viral proteins—namely the NS3/4A protease, NS5B polymerase, and NS5A replication complex (McHutchison et al., 2008). DAAs have revolutionised management by enabling interferon-free regimens of 12 weeks or less, with markedly improved efficacy and tolerability. Currently available agents include protease inhibitors (e.g., simeprevir, paritaprevir, asunaprevir), polymerase inhibitors (e.g.,

sofosbuvir, dasabuvir), and NS5A inhibitors (e.g., ledipasvir, ombitasvir, daclatasvir), often used in fixed-dose combinations such as sofosbuvir-ledipasvir (Harvoni), (Stanislas et al., 2016).DAAs beside achieve cure rates exceeding 95% but also from the cornerstone of the World Health Organization's strategy to eliminate HCV as a public health threat by 2030 (Di Marco et al., 2025). Their widespread adoption has the potential to curtail the global burden of liver-related morbidity/

METHODS OF PREVENTION

Chronic hepatitis B and C infections lead to severe hepatic complications, including cirrhosis, hepatic failure, systemic vasculitis, and anaemia (Fernando et al., 2014). Comprehensive prevention strategies are essential for controlling these infections. Universal hepatitis B vaccination at birth represents the cornerstone of prevention, with completion of the full vaccination schedule according to established protocols Noubiap, J. J., &Ndoula, S. T. (2022). Sexual transmission can be prevented through consistent condom use and avoidance of high-risk sexual behaviours with infected individuals.

For pregnant women with hepatitis B, counselling regarding vertical transmission risks is crucial. Newborns require both hepatitis B immunoglobulin (HBIG) and hepatitis B vaccine within 10 hours of birth to prevent mother-to-child transmission. Serological testing for hepatitis B surface antigen (HBsAg) and antibodies to hepatitis B surface antigen (anti-HBs) should be performed after 9 months of age to assess immunological status and determine the need for additional vaccination (Elamin and Abu-Aisha, 2011).

Complementary approaches using medicinal plants have shown promise in hepatoprotective therapy. Numerous bioactive compounds have been identified in plant extracts, including phenolic compounds, coumarins, lignans, essential oils, monoterpenes, carotenoids, glycosides, flavonoids, organic acids, lipids, alkaloids, and xanthines. These compounds demonstrate anti-inflammatory properties that may support liver function. Wedelia indica, a traditional Chinese medicinal plant, has undergone evaluation in hepatitis B patients. The compound dicoumarindaphnioretin has demonstrated ability to inhibit HBsAg expression in cellular studies through protein kinase C activation pathways (Kokate, 2007).

Given that approximately 25% of patients with liver disease utilise herbal medicines, there is significant potential for developing evidence-based phytotherapeutic interventions. However, rigorous clinical trials are urgently needed to establish the safety profiles and therapeutic efficacy of these botanical preparations before they can be recommended for clinical trials.
(Rakeshet al., 2014).

ARTEMISIA ABSINTHIUM

Artemisia absinthium L., commonly known as wormwood, belongs to the Asteraceae family and represents a significant botanical resource in traditional medicine systems. This perennial herb has been utilised across multiple traditional healing modalities including Ayurveda, Homeopathy, Unani, and Siddha medicine, with documented therapeutic applications dating back to ancient Greek civilisation. The genus Artemisia, named after the ancient physician-botanist Queen Artemisia of Caria, encompasses approximately 400 species distributed globally (Rafael et al., 2015).

Artemisia absinthium demonstrates widespread geographical distribution across North Africa, Asia (including India, Pakistan, Afghanistan, Iran, and Siberia), and South America, reflecting its adaptability to diverse climatic conditions (Busineni et al., 2015). .

SILYBUM MARIANUM

Biermer et al. (2012) investigated high-dose silymarin monotherapy (1,400 mg/day) in 20 patients with prior failure of multiple interferon-based regimens, including four previously exposed to triple therapy with protease inhibitors.

Within one week, 13 patients (65%) achieved undetectable viral loads, and sustained viral suppression was maintained during subsequent PegIFN/RBV therapy in all but one case. The hepatoprotective mechanisms of silymarin extend beyond antiviral activity to include direct cytoprotective effects. These encompass inhibition of hepatotoxin binding to hepatocyte membrane receptor sites, preservation of hepatocellular membrane integrity, elevation of glutathione (GSH) levels in hepatic and intestinal tissues through antioxidant pathways, stimulation of ribosomal RNA polymerase activity, and promotion of hepatocyte regeneration through enhanced protein synthesis (Govind and Sahni, 2011).Experimental studies have demonstrated silymarin's protective efficacy against diverse hepatotoxic agents. Administration of silymarin (100 mg/kg, intravenously) significantly reduced carbon tetrachloride-induced hepatotoxicity (0.15 ml/kg, orally), as evidenced by decreased sleeping time following hexobarbital challenge and reduced serum transaminase and sorbitol dehydrogenase elevations. Complete protection against phalloidin hepatotoxicity (3 mg/kg, intraperitoneally) was achieved with silymarin pretreatment (50 mg/kg, intravenously), while α-amanitin-induced liver damage (0.5 mg/kg, intravenously) was prevented with higher silymarin doses (75 mg/kg, intravenously). Similar protective effects were observed against thioacetamide-induced hepatotoxicity, with significant reductions in transaminase activity following silymarin administration (Govind and Sahni, 2011).The cytoprotective mechanisms involve inhibition of lipid peroxidation and preservation of hepatocyte membrane structure and function through modulation of phospholipid metabolism and restoration of serum alkaline phosphatase (SAP) and gamma-glutamyl transpeptidase (GGT) activities (Madani et al., 2008). These multifaceted protective effects, attributed to the flavonoid content and antioxidant properties of *Silybum marianum* extracts, support its therapeutic potential in various hepatic pathologies including acute hepatitis, drug-induced hepatotoxicity, cirrhosis, and chronic liver disease (Sif et al., 2008).

TYLOPHORA INDICA

A study investigated the hepatotoxicity of CCl_4 in methanol extracts of *Tylophora indica* leaves, resulting in increased liver damage and albino levels. The hepatoprotective effect of chamomile alcohol extract was found to counteract paracetamol-induced liver damage in albino mice. Blood and liver glutathione levels, Na+/K+ ATPase activity, serum enzymes, serum bilirubin, glycogen, and thiobarbituric acid-reactive compounds were all positively affected by the hepatoprotective properties of *Tylophora indica* (Gupta et al., 2006).

FICUS CARICA

Cytochrome p450 is found in the mitochondria of liver tissue, where it targets mitochondria through proteolysis, resulting in the production of two other types of mitochondrial CYP1A1 (mt1A1). In tissues, various ASTs and alkaline aminotransferases (ALTs) are concentrated in the cytoplasm, while ASTs remain in the mitochondria (Anil et al., 2013). Hepatotoxins can cause various types of liver damage, including genetic changes and damage from medications. Liver damage is often associated with elevated levels of AST, ALT, ALP, bilirubin, triglycerides, and cholesterol in the blood (Peter et al., 2010). Excessive steroid production can harm the body's defensive organs, such as glutathione and tocopherol, reducing low-density antioxidants, increasing peroxides and alkylation, stimulating free radical responses, and causing significant damage to skin function. (Baheti et al., 2006).

TABLE 1. SOME MEDICINAL PLANTS WITH HEPATO-PROTECTIVE ACTIVITIES

Name	Family	Chemical Constituents	Parts Used	Reference
Bassia Latifolia Roxb	*Sapotaceae*	Alkaloids, carbohydrates, anthraquinone glycosides, steroids, flavonoids, tannins, and phenolic chemicals are all examples of flavonoids.	Bark	Rizwan et al., 2012
Mimosa pudica	*Mimosaceae*	Sesquiterpenes, Flavonoids,	Leaves	Rekha et al., 2009
Juniperus phoenicea	*Cupressaceae*	Flavonoids	Leaves, fruits	Saleh et al., 2013
Andrographis lineate Nees	*Acanthaceae*	Isomers of flavonolignans, flavonoids, and fatty acids	Stems	Nikhil et al., 2015
Amaranthus tricolor Linn	*Amaranthaceae*	Flavonoids monoterpenes. Amentoflavone, cupressuflavone, hinokiflavone	Roots	Simran et al., 2013

CONCLUSION

Liver diseases are a significant health concern, exacerbated by changes in dietary habits and lifestyle. These diseases can impair various normal physiological functions, such as metabolism, synthesis, storage, and detoxification. The pathogenesis of liver toxicity involves multiple pathways, necessitating the development or identification of drugs that act through multiple pathways for effective treatment. Plant-derived chemicals offer an alternative, albeit limited, option for treating liver diseases, considering their efficacy, side effects, and cost. In this review, we have highlighted several herbal drugs and their hepatoprotective roles, as well as their potential advantages over allopathic medicines..

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