International Journal of Pharmacy and Pharmaceutical Research (IJPPR)
Volume 32, Issue 1, January 2026 ijppr.humanjournals.com ISSN: 2349-7203

Comprehensive Insights into Liver Diseases: Pathophysiology, Experimental Models, Diagnostic Approaches, and Emerging Therapeutic Strategies

Tudi Mani[1], Kavya Manjunath[1*]

[1]KLE College of Pharmacy, Bengaluru, A Constituent unit of KLE Academy of Higher Education and Research, Belagavi, Karnataka, India

Received: 20 November 2025 Revised: 29 November 2025 Accepted: 21 December 2025

ABSTRACT

Liver diseases constitute a major global health burden, contributing significantly to morbidity and mortality worldwide. The liver plays a pivotal role in metabolic homeostasis, detoxification, and immune regulation; consequently, disruption of hepatic function leads to diverse pathological outcomes ranging from steatosis and fibrosis to cirrhosis and hepatocellular carcinoma. This review provides a comprehensive overview of liver diseases, focusing on hepatic structure and function, etiology, epidemiology, and the complex pathophysiological mechanisms underlying disease progression, including oxidative stress, mitochondrial dysfunction, apoptosis, immune activation, and metabolic dysregulation. The article further summarizes commonly employed in vivo and in vitro experimental models used to study hepatotoxicity and liver injury. Current diagnostic modalities, including conventional biochemical markers, imaging techniques, elastography, and emerging molecular and genetic diagnostics, are critically discussed. In addition, existing therapeutic strategies such as lifestyle interventions, pharmacological treatments, surgical approaches, cellular therapies, and preventive measures are reviewed. Emphasis is also placed on novel and emerging therapies, including gene therapy, artificial intelligence–assisted diagnostics, pathogen-targeted interventions, and advanced pharmacological approaches. Collectively, this review highlights recent advances and future directions in liver disease research, offering valuable insights for researchers and clinicians involved in hepatology and translational medicine.

Keywords: Liver disease, Hepatotoxicity, Oxidative stress, Experimental models, Novel therapeutic strategies

INTRODUCTION

The liver has the massive responsibility and metabolic homeostasis maintaining in the body. This function includes the metabolism of carbohydrates , vitamins, dietary amino acid, lipids, synthesis of serum proteins detoxification and removal of xenobiotics and endogenous waste products into bile[1]. Liver as embodying many cell types including liver sinusoidal endothelial cells, hepatocytes, biliary epithelial cells, Kupffer cells and stellate cells. each of these cells exhibit its distinct function that ultimate regulate hepatic function. the key Hepatocytes are epithelial cell group of the liver stellate cells are dynamic cell that is present in passive or active state. In the passive state the vitamin A in lipids is stored in stellate cells. Activation of stellate cells and proliferate progressively is during the injury to the liver and loss of vitamin A storage. Which can advance to last stage of hepatic disease. The stationary macrophage is a Kupffer cells group of the tissue and which detects pathogen reactions and converts to pro or anti- inflammatory acts as wound healing in the liver, Eventually, unique functions characterized of the endothelial group liver in sinusoidal endothelial cells. at the sinusoidal lumen are critical for exchange of particles and proteins by forming sieve plates between cell types and plasma of the hepatic [2].

Function of the liver [1]

Lipid Metabolism: beta-oxidation is experience in hepatic, conversion of free fatty acids are breaks into acetyl coenzyme A (Acetyl CoA) and ketone bodies converted due to excess of this enzyme. instance to generate bile salts, cholesterol produce from hepatocytes to utilize.

Metabolism of Protein: the plasma proteins initiated by hepatocytes of the hepatic and which experiences process known as transamination . from an amino group converts to one amino acid into another. Through this method, the toxic ammonia is removed, transformed it into a urea which is harmless product forward in the form of urine is excreted.

Metabolism of Carbohydrate: for metabolism the key organ is liver where, it performs glucogenesis process, glucose is turned from specific amino acids, glycogenolysis by conversion of glycogen to glucose through negative feedback mechanism. Other process like lipogenesis and glycogenesis.

Other functions: detoxification of toxic chemicals like metals, drugs , alcohol, chemicals and excreted through bile. Generates the bile salts. Other Functions like the major vitamins and minerals are stored. it performs phagocytosis against the xenobiotics in the liver.

Etiology

liver disease is life-threatening for various reasons such as exposure to excess alcohol, diet, hepatitis virus, accumulation of environmental toxins, including heavy metals, hereditary metabolic liver diseases , metabolic stress. Even with stress, unhealthy diet and drug over doses leading to major cause of hepatotoxicity, liver cancer, and liver failure. symptoms are Characterized for chronic liver disease like muscle wasting, palmar erythema spider angiomas, weight loss, gynecomastia, hypogonadism, cholestasis, Hypoalbuminemia, hypogonadism, gynecomastia, jaundice, hyperammonaemia, hypoglycaemia.[3]

Epidemiology

One of the main global mortalities is Hepatotoxicity and liver disease. According to global cancer data 2020, the 6th most diagnosed cancer is liver cancer and about 4.7% new cases and Lung and colorectal cancers account for 8.3% of all new fatalities globally each year. third leading cancer is hepatic cancer deaths. [4] The worldwide burden of illness According to a 2019 study, cirrhosis and other chronic liver disorders claimed the lives of 1.26 million people in 2019, a 13% rise from 1990.[5] MASLD with increased alcohol intake, which accounted for about 70% in 2020. Fibrosis cases 42% in earlier dataset in 1988-1994 and about 9-16% in later dataset in 2017-2020.[6] all races and ages are diagnosed autoimmune hepatitis. where males are less commonly influence than females at a ratio of 4:1 in worldwide and Asia is less affected in autoimmune hepatitis. Combination of the therapy and diagnosis causes drug -induced liver injury in China, count for 27% of DILI cases and second most frequent cause in the US (16%), India (14%), Iceland (16%), and Spain (6%), behind antimicrobials and anti-tuberculosis medication.[7]

Pathogenesis

The concept of liver disease pathogenesis is caused by many hazards like apoptosis, cell degeneration, inflammatory cell infiltration, bile duct hyperplasia and focal necrosis. reactive oxygen species (ROS) production, CYP450 enzyme systems metabolism dysfunction which catalyse phase I of endogenous substances metabolism. circadian rhythms ,Sex differences and genetic polymorphisms[8]. hepatotoxicity mediates oxidative stress like mitochondrial oxidative stress in addition to this imbalance of antioxidant protect system enhances in liver disease and hepatotoxicity. Excessive apoptosis autophagy- mediated hepatotoxicity. The variety of metabolic pathway disorders induced liver-toxicity. Liver is filled with various type of immune cells that protects from drug-induced liver injury (DILI) [9]. Occurrence of hepatic damage is also by excessive of consumption of alcohol , smoking unhealthy diet, increase in fats intake and comorbidity which includes Cardiovascular condition, non-alcoholic fatty liver disease(NAFLD), type 2 diabetes and obesity. Other underlying leads to the liver disease is autoimmune hepatitis.[10]

Pathophysiology

Cascading principles of pathophysiology of liver disease

a) Proteins transport dysfunction: The intrahepatic bile enzyme ALP in serum is damaged in cholangiodestructive cholestasis. The bile duct is destroyed by prolong drug usage, which can result in fibrosis and proliferation.
b) Hepatocyte Disruption: due to toxic enzymes and oxidative stress on the cell membrane of the hepatocyte causes damage of architecture of cell integrity and leakage of enzymes into cytoplasma and activation of the neighbouring macrophages and progress to inflammation in liver. Kupffer cells express tumour necrosis factor (TNF) related apoptosis in hepatocytes leads to increase in serum level.[11]
c) Cytosolic-T-cell activation: the CD8-T cells generating virus-specific cells virus activates CD8-T cells. activated virus T cells are differentiated into effector cytotoxic T lymphocytes that specifically kill virus -infected cells, thus contributing to liver injury. High levels of IL-15,IL-18, and NK cells in the serum.[13]
d) Lipid metabolic dysfunction: fatty acids are absorbed from hepatocytes the circulation convert into triglycerides and synthesis triglycerides from non-carbohydrate sources through de novo lipogenesis (DNL). These lipids stored and fuel for peripheral organs. There is increased level in liver DNL and NEFA release from adipose tissue and causes accumulation of lipids, hence depletes lipid metabolism in many liver disease [14]

e) hepatocytes Apoptosis: Apoptosis is a single-cell process that is engaged in excretion of the damaged and old cells at the growth of normal tissue. under these circumstances, the hepatocytes absorb the apoptotic cells that are destroyed by the stellate cells Increased apoptosis results in subsequent hepatocyte necrosis because the apoptotic process is not completed.[16]
f) damage of Mitochondrial: toxic agents generate beta-oxidation and formation of NADH inhibited and decreases function of mitochondria which leading to decreased ATP production resulting in a restriction electron transport and buildup of electron respiratory chain complex which increases oxidative stress and ROS reacts with oxygen via upstream complex to superoxide anion radical (O^{2-}) form.[12]
g) Suppression of transcription factor of cytoprotective: Nuclear-factor erythroid 2-related factor 2 (Nrf2), Kelch-like-ECH-associated protein-1 (Keap-1) in the cytoplasm is facilitates by binding through proteasome ubiquitin in Nrf2 degradation. Nrf2 distracted from Keap-1, translocated from cytoplasm to nucleus this process is due to over production of free radical, electrophilic molecules and small Maf proteins complex is formed and antioxidant response element(ARE) combines with complex thus, increased regulation of antioxidant enzyme such as the nitrite oxidase, heme oxygenase-1(HO-1) and several detoxifying downstream.[15]

Alcoholic liver disease(ALD): chronic alcoholic will develop alcohol- related cirrhosis and hepatocellular carcinoma. The ALD advancement and its issues are poorly researched . The breakthroughs of understanding disruption of pathways. Extremely reactive molecule is acetaldehyde and additives are made with proteins, lipids, nucleic acids are involved in alcohol pathogenesis and physiology of cell. Prolong consumption of alcohol leads to overexpression of CYPs, specially CYP2E1, this enzyme as important role as ethanol oxidises into acetaldehyde which generates excess ROS and change in metabolism causes hepatic injury.[17]
Viral hepatitis**:** worldwide morbidity and mortality is caused by liver-related chronic viral hepatitis. The liver-related viruses are hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis A virus (HAV) hepatitis E virus (HEV) hepatitis D virus (HDV).[18] The sodium taurocholate co-transporting polypeptide (NTCP) detects the special receptor entries in viral hepatitis or Hepatitis was a significant discovery was improved knowledge on hepatitis virus(HV) pathogenesis. However, their interaction is complex and not fully understood. Mechanisms of Hepatitis Virus penetration into cells, connection of HV on the Cell membrane, NTCP Receptor as high-affinity binding, Low-Affinity Binding to Heparin Sulphate Proteoglycans, aspects of Viral Entry Host Cell incorporating in HV , Endocytosis Mediated by Receptor Binding Viral Escape from Endosomes pathway and it dissociates at the nuclear pore complex.[19]

Metabolic dysfunction-associated steatotic liver disease(MASLD) and Non-alcoholic fatty liver disease (NAFLD)**:** MASLD is chronic condition is hallmark of which is fat accumulation in the liver. MASLD associated with Chronic inflammation is determined in pro-inflammatory cytokines levels, including IL-6 and TNF-α . TNF-α produces and acts by upregulation of many pro-inflammatory cytokines eventually nuclear factor kappa-B (NF-kappa B) signaling pathway starts to activation causes liver inflammation and NAFLD. Or else, JAK/STAT signaling pathway is activated by IL-6 and transcriptional upregulation of short-term reactants are CRP and serum amyloid A. The liver inflammatory response was further enhanced by this mechanism, which exhibits systemic implications apart from liver Obstructive sleep apnea (OSA) can progress to liver failure[20].

Fibrosis and cirrhosis**:** excessive growth of extracellular matrix (ECM) proteins which results in Liver fibrosis mostly collagens, fibrous marks formation, which can eventually compromise normal hepatic function. In liver fibrosis causing cell type is Hepatic Stellate Cells HSCs. This cell decreases gene expression such as peroxisome proliferator-activated receptor gamma (PPAR-γ) and glial fibrillar acidic protein (GFAP), generates myofibroblasts and reduced lipid storage. hepatocytes generate several fibro genic variables like as NADPH oxidase 4 (NOX4), TAZ, osteopontin, damaged hepatocytes are released by activated HSCs. The core transforming growth factor-β (TGF-β) by Kupffer cells of liver macrophages, which as significant function in liver fibrogenesis. the development of fibrosis to liver cirrhosis are more intense in death rate related in liver disease. Liver cirrhosis is also developed through alcoholic liver disease are faster than in non-alcoholic fatty liver disease and complex condition like hepatic carcinoma.[21]
hepatotoxicity: the responsible for liver damage are called hepatotoxins, hepatotoxins may be classified as intrinsic (common) agent's behaviour is predictable, the injury is dose-dependent such as chemical induced liver injury like ethanol, carbon tetrachloride, thioacetamide. Drug induced hepatotoxicity are acetaminophen, anti-tubercular drugs etc. metal induced hepatotoxicity are cadmium, lead, mercury etc.[22] the mechanism of causing hepatotoxicity and relationship between signalling pathways is poorly understood and signalling pathway are nearly relevant to the progress of hepatotoxicity. Includes LPS-toll-like receptor (TLR)4-NF-B signalling pathway, nuclear factor-kappa b (NF-B) inflammatory signalling pathway, silencing regulatory protein (SIRT)1/ AMP- activated protein kinase (AMPK) and Kelch-like-ECH-associated protein-1 (Keap-1) oxidative stress signalling pathways. These pathways intermediate link to cause hepatotoxicity and various hepatic disease into cirrhosis even hepatocytes carcinoma , at length causes serious threatening the life of patients.[23]

International Journal of Pharmacy and Pharmaceutical Research (IJPPR)
Volume 32, Issue 1, January 2026 ijppr.humanjournals.com ISSN: 2349-7203

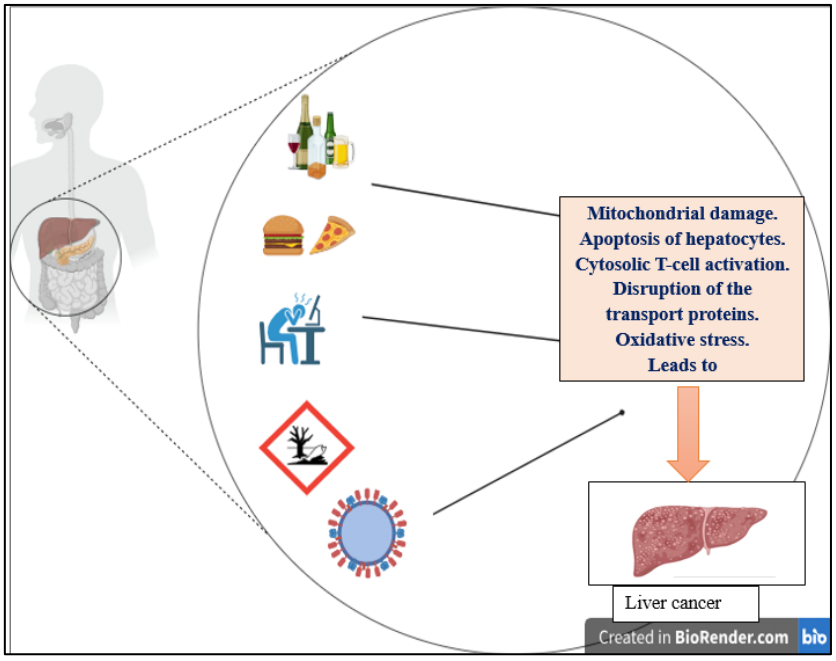

Fig no.1 pathophysiology of liver disease above diagram illustrates the sequence of cellular events and inflammation that lead from initial hepatic injury to advanced fibrosis and eventual cancer. This image was created using BioRender tool.

***In-vivo* and *in-vitro* experimental models for hepatotoxicity[24,25]**

Hepatotoxicity refers to hepatic dysfunction, which related with medicinal drugs and chemicals, radiation, metals and genetic factors . The experimental model serves as a road map for the identification of novel molecular processes and worthwhile avenues for the advancement of humanity. Described below Table no1:

Types of experimental models	**Description**
Drug-induced hepatotoxicity models	The drug which causes hepatotoxicity NSAIDs like paracetamol, anti-cancer like Cisplatin Methotrexate, Adriamycin. Antibiotics like Erythromycin, Azathioprine are the most commonly causing liver injury. anti TB drug such as Isoniazid , rifampicin pyrazinamide. Ranitidine. Over 75% of idiosyncratic medication reactions end in death or liver transplantation.
Chemicals - induced hepatotoxicity models	These hepatotoxic substances also cause oxidative stress by activating certain cytochrome p450 system enzymes, such as CYP2E1 and disruption of mitochondria that generates harmful enzyme. Toxins or chemicals such as Thioacetamide Carbon tetrachloride (CCl4) Alcohol Galactosamine Bromobenzene (BB) Lithocholic Aflatoxin B1 (AFB1) Allyl alcohol Halothane Acryl amide (AA) Microcystin Alpha-naphthyl isothiocyanate (ANIT), DEN(diethyl nitrosamine) GSH and neutrophils play a significant part in the chemical induction of liver injury.
Radiation – induced hepatotoxicity models	It is produced by machines in industry and diagnostics centre in the form of waves particles. ere are two kinds of radiation: ionizing and non-ionizing. such as Gamma rays of 5Gy were induces leads to damage of centrilobular hepatic cells and result in liver dysfunction.
Hormone – induced hepatotoxicity models	Intrahepatic cholestasis is a risk associated with androgens, which are still utilized in the hormonal treatment of breast cancer. Prolong administration of 17-alkyl androgen has ability to progress liver cancer. Hepatotoxicity was caused by the anti-androgen medications flutamide for prostate cancer, megestrol acetate for breast cancer.
Metals – induced hepatotoxicity models	Metals are more toxic to our body especially hepatic. this toxic metal present in the crust of the earth and spreads all over the surrounding by many human activities. such metals are cadmium, lead, mercury and manganese lead to cell membrane oxidative damage and production of ROS like singlet oxygen, hydro-peroxides, and hydrogen peroxide and decrease in level of antioxidant production produced by heavy metals.

Invasive model	It is a classic secondary biliary fibrotic experimental model. Cholestasis and apoptosis followed by generation of ROS and necrosis in hepatic cells and liver injury is caused due to obstruction in the biliary system. Such models are ligation of the bile duct and Ligation of portal-vein.
Genetic model	genetically modified models are used to assess the fibrogenesis part of the specific factors. Transgenic mice Mice/Abcb4(Mdr2/mice), Transgenic mice PDGF and TGF-1, Mice/ Bcl-xL. The removal of specific anti-apoptotic gene or phospholipid transporter and overexpressing upregulate , bile duct damage arise in intoxication-based liver.
Invitro experimental models[26]	Introduced various novel in vitro techniques and innovation options, such as HepG2 cells, HUVEC-T1 cells , three-dimensional(3D) cell spheroid cultures, human hepatic stellate cells and THP-1-originated macrophages components and coculture liver spheroid models showed prognostic capability and greater with benefits as the classifying method.

Diagnosis of liver disease

The demand for early identification and careful observation of hepatic disease explores for novel biomarkers and diagnostics. This approach could enhance conventional liver biopsies, providing important findings into pathological diagnosis and therapeutic efficacy. Such as Multi-source Feature Fusion based Tongue Diagnosis (MFF-TDF) Framework for fatty liver disease diagnosis. An outline of four steps such as multi-scale feature extraction, image preprocessing, training or validation and multi-source feature fusion diagnosis. application for fatty liver disease (FLD) screening to enhance in poor rural communities.[27]emerging technologies for liver diagnostics such as diffusion-weighted imaging (DWI), three- dimensional (3D) imaging techniques provides understanding on microstructure and tissue cellularity of liver health. Diagnostics of Molecular level, in this investigation of genetic parameters provide a distinctive opportunity into our complicated genetic makeup affects liver function. genetic markers, specific variations in DNA, act as check posts related to health of the liver. The diagnostics molecular as advancement in this stage of tailored therapy, predict disease trajectories, personalized diagnostic approaches and potential therapy plan for individual patient. genetic predictive testing: anticipating illness trajectories, allows fast identification for treatments to overcome risk factors associated to liver disease.[28] other diagnosis are non-invasive imaging-based investigations in suspected people in cirrhosis, ultrasound (US) is classical first- generation radiological diagnosis for chronic liver disease ultrasonography with different impedance indices to measure indirectly the spread of liver disease, magnetic resonance elastography creating an elastogram that shows the supersonic shear imaging, elasticity condition of the liver tissue to detect liver disease, transient elastography, liver elastography. Liver biopsy is to diagnosis the morphological signs of liver disease. Some of non-invasive evaluation parameters are laboratory blood serum tests such as platelet count, prothrombin index, aspartate aminotransferase, alanine aminotransferase and score of hepatic health.[29]

Existing treatments for liver disease

Existing specific therapeutic interventions and strategies for management of liver disease covers a wide spectrum from life style changes, drug therapy, Surgical treatment, Cellular therapies, Prevention therapy, Liver function tests, and other emerging and supportive therapies for liver disease. Existing treatments and examples were descried below table no 2:

Types of existing treatments	**examples**
Life style changes[30]	Weight reduction, reducing liver fat, low carbohydrate diet reducing caloric intake, diet enriched with PUFA, MUFA, omega -3 fatty acid and olive oil. maintaining body mass index, physical activity, total aerobic and cardiorespiratory fitness resistance training was greater beneficial effect in liver health. This implies that systematic weight loss program can be beneficial for the patient, it might be worthwhile to encourage patients to receive more training and help with weight loss.
Drug therapy[31,32]	Microbiome-based tools**:** the development of diagnostic and prognostic tool for microbiota on gut-liver axis for the treatment of liver disease that includes farnesoid x receptor (FXR), faecal microbial transplantation, postbiotics(bacterial metabolites), generations of probiotics which target specific bacteria therapies. Hepatocyte targeting therapy: oxymatrine, SiRNA apoB, quercetin, SiRNA against gp46, vismodegib antisense oligodeoxynucleotide against collagen I, silibinin and sicoL1a1. Hepatocyte growth factor. Different strategies have been created for medication of targeting cells of the liver disease. some other drug therapies are glucocorticoids, anti-TNF therapy, nutritional supplements like antioxidants vitamin c. Herbal drug therap**y:** silymarin, curcumin, resveratrol, green tea polyphenols, ginseng & coffee these pointed out herbals have significant potential for the treatment of liver diseases.
Surgical treatment [33,34]	Minimally invasive liver resections have been wining popularity over last decades. Recent developments, are intraoperative ultrasound(IOUS), liver transplantation, transarterial chemoembolization (TACE), portal vein

	embolization, radiofrequency ablation(RFA) modalities of ablation . Microwave ablation(MWA) has developed into a secure and successful treatment for a liver cancer across a spectrum of pathologies. Surgical treatment care concern Preoperative optimization, intraoperative monitoring and postoperative care this is to enhance recovery after surgery.
Cellular therapies[35,36]	advanced therapeutic medicinal products (ATMPs) products are categorized cellular therapies which utilize cells to treat immune-mediated disease with focus on promoting endogenous repair mechanisms. Such as cell therapy for autoimmune hepatitis (AIH): delivery of exosomes produced from mesenchymal stromal cells(MSC) was able to repair hepatic damage, cell therapy for primary sclerosing cholangitis (PSC) and primary biliary cholangitis (PBC). MSC combination of MSC and PBS which significant decreased in antibodies serum levels. Cell therapy for coeliac disease: to exert cytoprotective effect, maintain ratio of the anti-apoptotic and pro-apoptotic factors cellular therapy for IBD: HSCT as beneficial therapy for IBD. Cellular therapy for GvHD : the steroid therapy later T-cell therapy is first generation treatment for GvHD is a viable path showed beneficial outcomes to prevention of acute and chronic GvHD. These recently developed technologies will accelerate the advancement of liver disease in cell therapy
Prevention therapy[37,38]	Preventive care plays crucial part in public with long term liver disease. The methods of prevention are hepatitis vaccination, Limit alcohol intake, beta-adrenergic blockade, avoidance of NSAIDs drugs, in variceal bleed of prevention. A hypocaloric diet combined with moderate intensity exercise to maintain weight loss was linked to improvements in NAFLD activity score and ALT levels. Abnormal physical examination, abnormal liver function tests, ultrasonographic evidence of liver, liver biopsy and screening for hepatocellular cancer. To reduce the need for liver transplantation and postpone death by preventing more liver damage.
Liver function tests(LFT) [39]	The liver function tests one of most popularly ordered laboratory tests are alanine aminotransferases[ALT], Serum gamma-glutamyl transferase (γ-GT), aspartate aminotransferases [AST], alkaline phosphatase (ALP) and bilirubin. secondary liver parameter tests are alpa-fetoprotein (AFP) and synthetic function tests such as albumin and prothrombin time (PT) and other serological tests ultimately, LFT gives early detection and medical intervention based on these tests improve outcome for liver diseases.

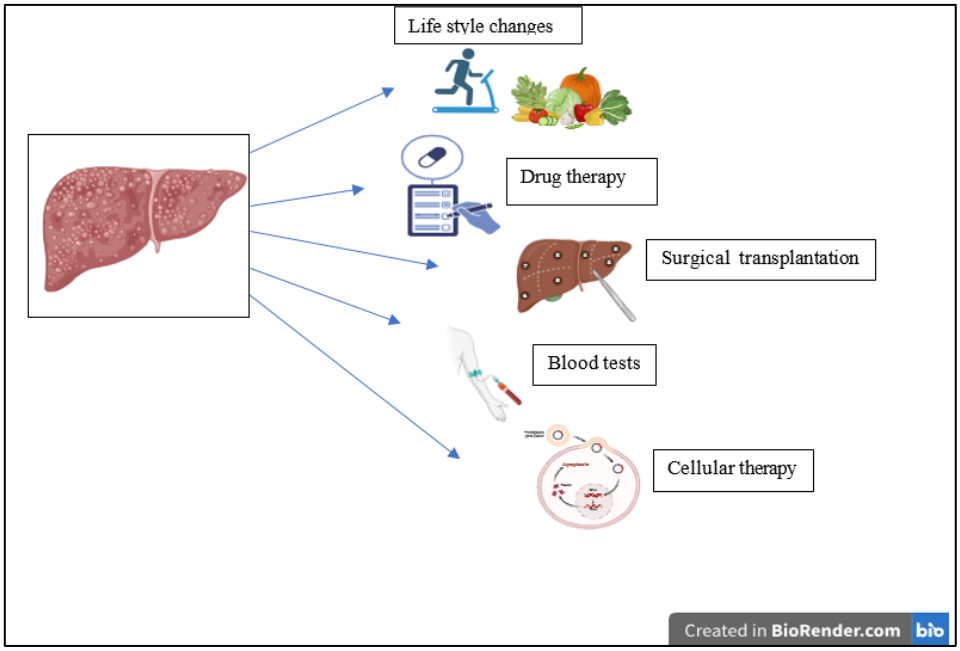

Fig no:2 existing treatment options for liver disease, this diagram is outlining structured approach to treat various liver disease. This image was created using BioRender tool.

Novel therapy for liver disease

This table describing New and novel therapy beyond existing treatment for liver disease typically emerging therapy that target specific liver injury are as follows gene therapy, Artificial intelligence, targeting specific pathogen therapy and Novel pharmacological therapy are overview of these therapies below Table no 3:

Novel therapies	Examples
Gene therapy [40,41]	Gene Therapy (GT) shown to provide potential therapeutic effects approaches using viral vectors and non-viral in many liver-directed clinically demonstrated animal models. Numerous gene therapy products with unique features have been approved: RNA interference (Givosiran, Lumasiran, Patisiran), lentiviral-transduced cells (brexucabtagene, Autologous CD34+, autoleucel, Tisagenlecleucel, Axicabtagene Ciloleucel) or recombinant adeno-associated viral (AAV) vectors (Onasemnogene abeparvovec, Alipogene tiparvovec, voretigene neparvovec-rzyl, Onasemnogene abeparvovec), antisense oligonucleotides (ASOs: Etaplirsen, Golodirsen, Nusinersen, Mipomersen). The miRNA as essential function in the hepatic which helps in immunity, regulation of metabolic pathways, viral hepatitis, liver fibrosis, and cancer. The role of MicroRNAs, miR-122 as modulating liver disease were emphasised in HCV infection and increases in RNA abundance and viral 5′ non-coding region was targeted and disease-specific target linked to progress in liver histology. The function of Kupffer cells (KCs) and inflammation causes increased level of TNFα production in alcoholic liver disease has been deep rooted. miR-155 via NF- kappa B activation leading to stabilization of TNFα mRNA. gene editing techniques and hepatic-directed gene therapy have become a viable substitute to various hepatic disease and orthotopic liver transplantation (OLT) for Inherited Metabolic Liver Diseases(IMLDs).
Artificial intelligence(AI)[42,43]	Artificial intelligence (AI) techniques in liver health. Show the variety of AI techniques widely applicable in hepatic conditions. pathophysiology of MASLD and metabolomics have been explore using Machine learning techniques. The current applicable in structure prediction of protein, uses diffusion models, a type of generative AI. transcriptomics data and paediatric liver transplantation in machine learning techniques combining and they identify network module. Omics technologies play role in the treatment and recognition of starting-stage fibrosis to reduced disease progression such as decrease mortality and liver tumour. These components of the network are better suited for antirejection targeting drug. For chronic hepatic condition, prediction of disease courses and treatments through AI systems with optimizing management and atypical accuracy strategies. AI can improve post-operative care and progress in long term graft survival ratio in the liver transplantation, diagnosis and therapy for hepatic conditions is applicable in AI. medical imaging analysis, and interpretation, in personalized treatment planning, in drug response prediction AI-assisted monitoring and evaluation of treatment effects, Surgical assistance and robotic surgery, in postoperative complication and prediction Data analysis and patient follow-up management. The fusion of AI with other advanced medical technologies will further promote the comprehensive management of liver diseases. Hepatology AI-enabled future holds great potential for improve liver health outcomes worldwide.
Targeting specific pathogen therapy [44,45,46]	Targeting Organ Immunopathology and Organ Support devices on liver are bioartificial (cell-based devices) and artificial (mechanical). It works on the albumin dialysis principle and Molecular Adsorbent Recirculation System (MARS) which helps in protein-bound toxins removal. The receptor-interacting protein kinase 1 inhibitor(RIP1) also therapy for liver target pathogen have shown improve reconstitution and decreased GVHD death rate and immune, another effective target to ameliorate inflammations and reduced activation of macrophages and T-cells is bromodomain and extra-terminal domain inhibitors (BET) and shows anti-inflammation activity. Targeting Toll-like Receptor 4 and Inflammasome Pathways, Targeting Albumin Dysfunction, Targeting Mitochondrial Dysfunction, Targeting Ammonia, Targeting Hepatic Regeneration, Targeting Endothelial Dysfunction etc. at present, targeting on metabolism of mitochondrial and proteomic mutation are the relevant research, specifically, mutation in present in normal cell of mitochondria was extracted and differentiated on health cells. Improvement of mitochondrial architecture, reduction of ROS generation, and stimulation of autophagy in various liver disease.
Novel pharmacological therapy[47]	Novel pharmacological therapy is Based on the complex pathophysiology and various pathways of liver diseases are engaged in their development, combination medicines or multifactorial treatments that take part in many targets in demand. Presently Many are explored follows. ruxolitinib is selective JAK-1/2 inhibitor, used in therapy for SR-aGVHD steroid-refractory acute graft-versus-host disease (SR-aGVHD), cytokine-mediated inflammatory pathways are potentially inhibited and reduce pro-inflammatory cytokines generations. Combination strategies of FXR with PPAR ligands in PBC. Expansion of dual PPAR-α/γ and Fatty acid beta oxidation was elevated by α/δ agonists. Progress in inflammation and resistance of insulin, dual FXR/PPAR-δ agonists are refined progressive for medication of liver disease. Some drug therapies are advanced in monoclonal antibodies, immune modulation and nonpharmacologic interventions.

Conclusion

Liver diseases represent a multifactorial and progressive group of disorders driven by complex interactions between metabolic imbalance, oxidative stress, immune dysregulation, mitochondrial injury, and genetic susceptibility. Understanding the intricate mechanisms involved in hepatotoxicity, fibrosis, cirrhosis, and liver cancer is essential for early diagnosis and effective therapeutic intervention. Experimental in vivo and in vitro models continue to provide critical insights into disease mechanisms and drug development. While conventional diagnostic tools and treatment strategies remain fundamental, recent advances in molecular diagnostics, imaging technologies, cellular therapies, gene therapy, and artificial intelligence offer promising avenues for precision medicine in hepatology. Future research focusing on targeted, multi-pathway therapeutic strategies and early predictive diagnostics may significantly reduce disease progression, improve patient outcomes, and lower the global burden of liver diseases.

REFERENCES

1. Tortora GJ. Principles of anatomy and physiology. 14th edition. Harper collins college publishers 1996;909-913.
2. Trefts E, Gannon M, Wasserman DH. The liver. Curr Biol. 2017;27(21):R1147-R1151.
3. Wang D, Tan M, Touch S, Kouy S, Sou S, Liu K, Zhu Y, Zhu H, Nov P. Burden of disease and risk factors for primary liver cancer by etiology in the United States, 1990-2021: Results from the Global Burden of Disease study, 2021. Ann Hepatol. 2025;30(2):101906.
4. Mondal D, Das K, Chowdhury A. Epidemiology of Liver Diseases in India. Clin Liver Dis (Hoboken).2022;19(3):114-117.
5. Gan C, Yuan Y, Shen H, Gao J, Kong X, Che Z, Guo Y, Wang H, Dong E, Xiao J. Liver diseases: epidemiology, causes, trends and predictions. Signal Transduct Target Ther. 2025;10(1):33.
6. Ma N, Bansal MB, Chu J, Woodward M, Branch AD. Heavy metals are liver fibrosis risk factors in people without traditional liver disease etiologies. J Environ Sci (China). 2025;155:329-342.
7. Devarbhavi H, Asrani SK, Arab JP, Nartey YA, Pose E, Kamath PS. Global burden of liver disease. 2023 update. J Hepatol. 2023;79(2):516-537.
8. Zhou WC, Zhang QB, Qiao L. Pathogenesis of liver cirrhosis. World J Gastroenterol. 2014;20(23):7312-24.
9. Horn M, Gumede N, Gamede M. The pathogenesis of metabolic dysfunction-associated steatotic liver disease and nucleoside reverse transcriptase inhibitors (NRTIs) -based HIV-antiretroviral regimens: A comprehensive narrative review. Biomed Pharmacother. 2025;192:118633.
10. Malhi H, Guicciardi ME, Gores GJ. Hepatocyte death. a clear and present danger. Physiol Rev. 2010;90(3):1165-94.
11. Hu Y, Wu Q, Wang Y, Zhang H, Liu X, Zhou H, Yang T. The molecular pathogenesis of triptolide-induced hepatotoxicity. Front Pharmacol. 2022;13:979307.
12. Wang M, Feng Z. Mechanisms of Hepatocellular Injury in Hepatitis A. Viruses. 2021;13(5):861.
13. Steinberg GR, Valvano CM, De Nardo W, Watt MJ. Integrative metabolism in MASLD and MASH: Pathophysiology and emerging mechanisms. J Hepatol. 2025;83(2):584-595.
14. He Q, Luo Y, Xie Z. Sulforaphane ameliorates cadmium induced hepatotoxicity through the up-regulation of/Nrf2/ARE pathway and the inactivation of NF-κB.J.funct.foods. 2021;77:104297.
15. Savneet Kaur, Dinesh M. Tripathi,Chapter 1 - An overview and pathophysiology of liver diseases,Editor(s): Savneet Kaur, Dinesh M. Tripathi,A Comprehensive Guide to Rodent Models of Liver Diseases. Academic Press,2025;1-42
16. Wu X, Fan X, Miyata T, Kim A, Cajigas-Du Ross CK, Ray S, Huang E, Taiwo M, Arya R, Wu J, Nagy LE. Recent Advances in Understanding of Pathogenesis of Alcohol-Associated Liver Disease. Annu Rev Pathol. 2023;18:411-438.
17. Usuda D, Kaneoka Y, Ono R, Kato M, Sugawara Y, Shimizu R, Inami T, Nakajima E, Tsuge S, Sakurai R, Kawai K, Matsubara S, Tanaka R, Suzuki M, Shimozawa S, Hotchi Y, Osugi I, Katou R, Ito S, Mishima K, Kondo A, Mizuno K, Takami H, Komatsu T, Nomura T, Sugita M. Current perspectives of viral hepatitis. World J Gastroenterol. 2024;30(18):2402-2417.
18. Herrscher C, Roingeard P, Blanchard E. Hepatitis B Virus Entry into Cells. Cells. 2020;9(6):1486.
19. Bharaj IS, Brar AS, Kahlon J, Singh A, Hotwani P, Kumar V, Sohal A, Batta A. Metabolic-dysfunction associated steatotic liver disease and atrial fibrillation: A review of pathogenesis. World J Cardiol. 2025;17(6):106147.
20. Berumen J, Baglieri J, Kisseleva T, Mekeel K. Liver fibrosis: Pathophysiology and clinical implications. WIREs Mech Dis. 2021;13(1):e1499.
21. Thakur S, Kumar V, Das R, Sharma V, Mehta DK. Biomarkers of hepatic toxicity: an overview. Curr.Ther.Res. 2024 ;100:100737.
22. Mao J, Tan L, Tian C, Wang W, Zhang H, Zhu Z, Li Y. Research progress on rodent models and its mechanisms of liver injury. Life Sciences. 2024;337:122343.
23. Bhatia D, Goyal P, Kabra A. Development on Animal Models for Drug/Chemical Induced Liver Injury. Biomedical and Pharmacology Journal. 2023;16(1):131-43.
24. Singh G, Dhadwal N, Harikumar SL. Experimental models for hepatotoxicity. Asian J Pharm Clin Res. 2015;8(2):70-4.
25. Sun B, Liang Z, Wang Y, Yu Y, Zhou X, Geng X, Li B. A 3D spheroid model of quadruple cell co-culture with improved liver functions for hepatotoxicity prediction. Toxicology. 2024;505:153829.

26. Gao J, Chen T, Xu Y, Wu Y, Liu K, Qiu W, Ye W. Accurate fatty liver disease diagnosis with a multi-source feature fusion model on the segmented tongue image dataset. J. Adv. Res. 2025.
27. Wazir H, Abid M, Essani B, Saeed H, Ahmad Khan M, Nasrullah F, Qadeer U, Khalid A, Varrassi G, Muzammil MA, Maryam A, Syed ARS, Shah AA, Kinger S, Ullah F. Diagnosis and Treatment of Liver Disease: Current Trends and Future Directions. Cureus.2023;15(12):e49920.
28. Pavlov CS, Casazza G, Semenistaia M, Nikolova D, Tsochatzis E, Liusina E, Ivashkin VT, Gluud C. Ultrasonography for diagnosis of alcoholic cirrhosis in people with alcoholic liver disease. Cochrane Database Syst Rev. 2016;3(3):CD011602.
29. Zelber-Sagi S, Godos J, Salomone F. Lifestyle changes for the treatment of nonalcoholic fatty liver disease: a review of observational studies and intervention trials. Therap Adv Gastroenterol. 2016;9(3):392-407.
30. Albillos A, de Gottardi A, Rescigno M. The gut-liver axis in liver disease: Pathophysiological basis for therapy. J Hepatol. 2020;72(3):558-577.
31. Kumar V, Xin X, Ma J, Tan C, Osna N, Mahato RI. Therapeutic targets, novel drugs, and delivery systems for diabetes associated NAFLD and liver fibrosis. Adv Drug Deliv Rev. 2021;176:113888.
32. Alexandra B. Wells, Vincent W. Butano, Michael C. Phillips, Robert W.C. Young, Kathryn M. Cavallo, David Gutierrez Blanco, Iain H. McKillop, Erin H. Baker, John B. Martinie, David A. Iannitti.Surgical microwave ablation of 3035 liver tumors in 1416 patients: a retrospective analysis of 16 years of experience. J Gastrointest Surg.2025;29(12):102176.
33. Tripke V, Sommer N. An update on liver surgery - a new terminology and modern techniques. Innov Surg Sci. 2024;8(4):197-201.
34. Khan S, Khan RS, Newsome PN. Cellular therapies for the treatment of immune-mediated GI and liver disease. Br Med Bull. 2020;136(1):127-141.
35. Zhang L, Deng Y, Bai X, Wei X, Ren Y, Chen S, Deng H. Cell therapy for end-stage liver disease: Current state and clinical challenge. Chin Med J (Engl). 2024;137(23):2808-2820.
36. Huang DQ, El-Serag HB, Loomba R. Global epidemiology of NAFLD-related HCC: trends, predictions, risk factors and prevention. Nat Rev Gastroenterol Hepatol. 2021;18(4):223-238.
37. Riley TR, Smith JP. Preventive care in chronic liver disease. J Gen Intern Med. 1999;14(11):699-704.
38. lala V, Zubair M, Minter DA. Liver Function Tests. [Updated 2023 Jul 30]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK482489.
39. Maestro S, Weber ND, Zabaleta N, Aldabe R, Gonzalez-Aseguinolaza G. Novel vectors and approaches for gene therapy in liver diseases. JHEP Rep. 2021;3(4):100300.
40. P de Jong Y, Jacobson IM. Monitoring for liver cancer post-gene therapy-How much and how often? J Viral Hepat. 2024;31(1):35-40.
41. Ghosh S, Zhao X, Alim M, Brudno M, Bhat M. Artificial intelligence applied to 'omics data in liver disease: towards a personalised approach for diagnosis, prognosis and treatment. Gut. 2025;74(2):295-311.
42. Gao B, Duan W. The current status and future directions of artificial intelligence in the prediction, diagnosis, and treatment of liver diseases. Digit Health. 2025;11:20552076251325418.
43. Gyongyi Szabo, Peter Sarnow, Shashi Bala, MicroRNA silencing and the development of novel therapies for liver disease, Journalof Hepatology. 2012; 57(2):462-466.
44. Saeidinejad M, Elshabrawi A, Sriphoosanaphan S, Andreola F, Mehta G, Agarwal B, Jalan R. Novel Therapeutic Approaches in Treatment of Acute-on-Chronic Liver Failure. Semin Liver Dis. 2023;43(4):429-445.
45. Zheng Y, Wang S, Wu J, Wang Y. Mitochondrial metabolic dysfunction and non-alcoholic fatty liver disease: new insights from pathogenic mechanisms to clinically targeted therapy. J Transl Med. 2023;21(1):510.
46. Trauner M, Fuchs CD. Novel therapeutic targets for cholestatic and fatty liver disease. Gut. 2022;71(1):194-209.
47. Yishan Ye, Wenjing Hao, Florent Malard, Mohamad Mohty, Emerging novel therapies for steroid-refractory acute graft-versus-host disease: recent advances and future directions, Current Opinion in Immunology.2025;96:102649.

How to cite this article:
Kavya Manjunath et al. Ijppr.Human, 2026; Vol. 32 (1): 93-101.
Conflict of Interest Statement: All authors have nothing else to disclose.