RESEARCH PAPER

Drug-Induced Liver Injury: A Comparative Evaluation of Conventional Biomarkers and Omics-Based Diagnostic Signatures

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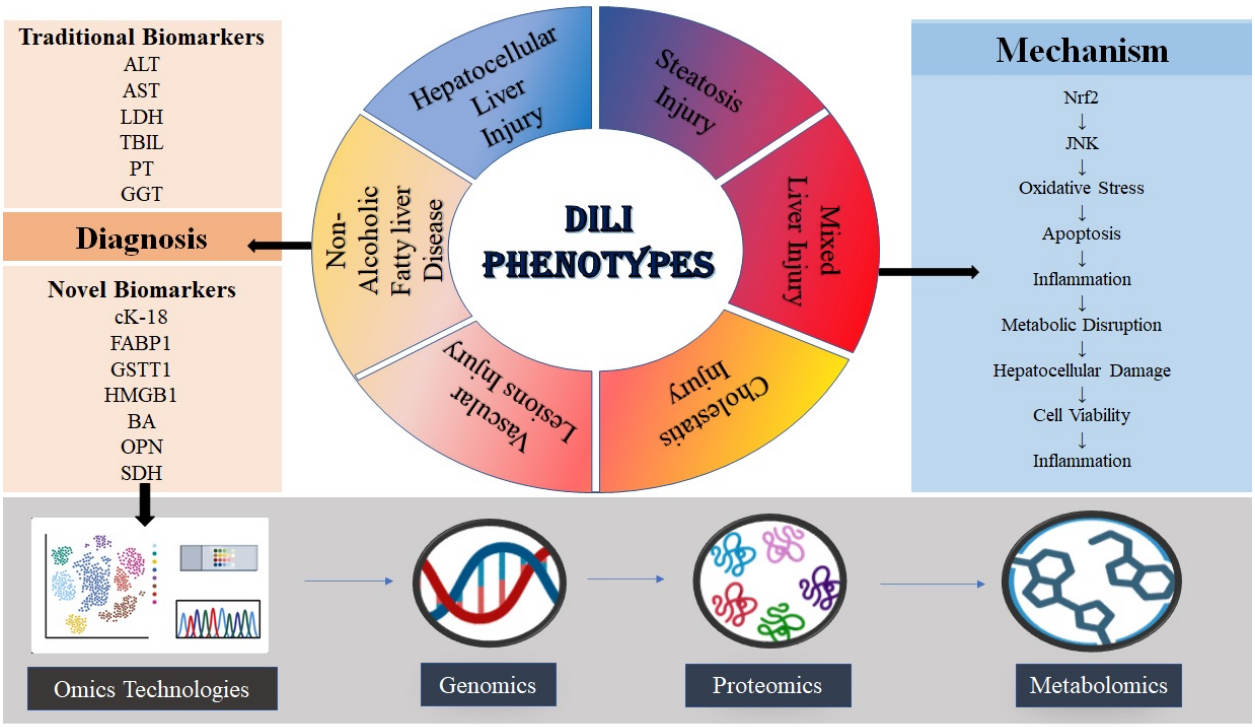
ABSTRACT

Drug-induced liver injury (DILI), a critical and complex undesirable effect of various therapeutic agents, manifesting diverse clinical phenotypes comprising hepatocellular injury, cholestasis, mixed injury, steatosis and vascular lesions. Additionally, non-alcoholic fatty liver disease (NAFLD) represents a significant comorbidity influencing hepatic gland susceptibility to toxicity. The diagnosis and monitoring of DILI rely heavily on traditional biochemical biomarkers such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin, lactate dehydrogenase (LDH), prothrombin time (PT), gamma-glutamyl transferase (GGT), and alkaline phosphate (ALP). While these makers provide essential clinical information, their limitations in specificity and sensitivity have led to exploration of novel biomarkers to enhance early detection and mechanistic understanding. Emerging biomarkers including sorbitol dehydrogenase (SDH), cytokeratin-18 (K-18), osteopontin (OPN), bile acids (BA's), fatty acid binding protein (FABP1), high-motility group box1 (HMGB1), microRNA-122 (miR-122), and glutathione S-transferase theta 1 (GSTT1) have shown promise in capturing distinct aspects of hepatocellular damage, oxidative stress, inflammation, and metabolic disruption. Additionally, omics-based technologies encompassing genomics, proteomics, metabolomics etc. offer comprehensive platforms to elucidate molecular signatures and predict individual susceptibility to DILI. This review consolidates current knowledge on DILI types, traditional and novel biomarkers and the advancing role of omics technologies, highlights their clinical and translational applications and identifies research gaps that must be needed for integrated biomarker panels to improve diagnosis, prognosis and personalized therapeutic management of drug-induced hepatotoxicity.

GRAPHICAL ABSTRACT

Drug-Induced Liver Injury: A Comparative Evaluation of Conventional Biomarkers and Omics-Based Diagnostic Signatures



KEYWORDS: Drug Induced Liver Injury (DILI), Traditional Biomarkers, ALT, AST, Total Bilirubin, Emerging Biomarkers, FABP1, HMGB1, miR-122, LDH, GGT, K-18, CYP450, Omics Technologies

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1. INTRODUCTION

Adult liver weight ranges from 1.2 to 1.5 kg, making it largest internal organ and gland in human body. It is situated just behind the diaphragm in the right upper abdomen. Drugs undergo active biotransformation and bioactivation activities in this organ, which may be harmful to the liver. The main parenchymal cells of the largest organ, hepatocytes, are widely dispersed and important for metabolic functions. In addition to eliminating xenobiotics and releasing necessary chemicals, hepatocytes oversee breaking down proteins, carbs, and lipids. They often accumulate in this organ or even reach their maximum concentration after being administered orally [1]. One of the primary organs involved in metabolism is the liver. In addition to materials from tissues that are either stored or utilized to produce new products, it receives nutrients from the colon [2]. Numerous widely used drugs have the potential to harm the liver. Indirect damage has appeared as a third kind of DILI, formerly classified as either idiosyncratic or direct dose dependent [3]. Medication-induced hepatotoxicity can cause inflammation, structural damage, and the generation of toxic substances, as well as worsen pre-existing damage and hinder medication processing. Careful observation, dose adjustments, or stopping the medication are common management strategies [4][5]. It is extremely challenging to anticipate unfavorable medication reactions since liver damage is linked to one or several biochemical reaction pathways to xenobiotic chemical consumption & varies from person to person depending on host factors [6]. Determined by the pattern of liver damage and the underlying cause, drug-induced liver injury (DILI) is separated into several kinds, including hepatocellular liver injury, cholestatic injury, mixed injury, steatosis, and others [7].

Biomarkers are measurable indicators of various types of cholestasis, hepatocellular damage, or liver disease. The National Institutes of Health defines a biomarker as "a biological molecule found in blood, other body fluids, or

tissues that is a sign of a normal or abnormal process, or of a condition or disease" [8]. FABP1, HMGB1, BAs, and other biomarkers are examples of classic and innovative biomarkers. The conventional biomarkers for DILI include bilirubin, PT, GGT, LDH, AST, and ALT, among others. Novel biomarkers are recently identified indications that indicate usual or aberrant metabolic processes or pharmacologic reactions to remedial interventions.

Despite extensive biomarker research, regulatory and clinical decision making in DILI still relies predominantly on ALT and AST. Multiple emerging biomarkers have been proposed; however, their comparative diagnostic performance, temporal kinetics and clinical readiness remain poorly integrated. Current review focuses on individual markers rather than data-driven prioritization.

2. HETEROGENICITY OF DRUG-INDUCED LIVER INJURY (DILI)

The liver functions as the major organ engaged in metabolism. It gets nourishment from the colon other than components from surrounding tissues that are either saved or used to create novel products [2]. Many commonly used medications can cause liver damage. Once categorized as either idiosyncratic or direct dose-dependent, indirect damage has become a third kind of DILI [3]. Drug-induced hepatotoxicity can exacerbate pre-existing damage, impair drug processing, and result in inflammation, structural damage, and the production of toxic chemicals. Common treatment techniques include careful monitoring, dosage modifications, or drug discontinuation [4][5]. Because liver damage relates to one or many biochemical pathways due to xenobiotic chemical ingestion & varies from person to person depending on host variables, it is very difficult to predict adverse pharmaceutical responses [6].

2.1 Phenotypic classification of Drug-Induced Liver Injury

DILI is categorized into many types, such as hepatocellular liver injury, cholestatic injury, mixed injury, steatosis, and others, regulated by pattern of liver damage and the fundamental cause as described in **Fig.1** [7].

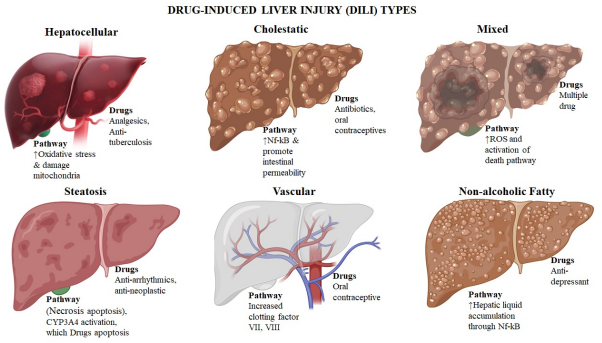

Fig (1). This figure illustrates major DILI phenotypes defined by distinct pathogenic mechanisms including oxidative stress, mitochondrial dysfunction, inflammatory signaling, lipid dysregulation and vascular injury. This underscores the mechanistic heterogeneity of DILI and supports drugs causing the injury.

2.1.1 Hepatocellular Liver Injury

Hepatocellular liver injury is due to virus known as Hepatitis B. HBV infection as well as its follow-ups are vital global health problems and belongs to the family Hepadnaviridae [9]. HBV, the archetypal element of the Hepadnaviridae family, is a non-damaging DNA virus which is transferred by contact via contaminated blood and bodily fluids, including immune-mediated hepatic diseases of varying severity and duration [10]. Hepatitis B virus is primarily transferred via percutaneous (across blood), sexual, and vertical (mother-to-child) routes. Transmission often occurs through direct exposure with infected blood, sexual fluids and perinatal exposure [11]. Upon entry of HBV specifically infects hepato-cells by attaching to the NTCP receptor on their surface. In hepato-cells, the virus forms covalently closed circular DNA (cDNA), which serves as a blue-print for viral replication. HBV produces viral proteins, including surface antigen (HBsAg), core antigen (HBcAg), and e antigen (HBeAg), which circulates in the blood. Acute infection triggers non-specific and acquired immune responses that often clear the virus, but immune dysfunction, especially functional impairment of CD8+ T cells and B cells, leads to chronic infection [12]. HBV employs multiple immune evasion mechanisms such as inhibiting interferon signaling, causing T-cell exhaustion, and expanding regulatory T-cells. Liver damage results mainly from immune-mediated cytotoxicity leading to inflammation, fibrosis, and potentially hepatocellular carcinoma (HCC) [13]. Chronic HBV infection can progress to cirrhosis, HCC, or fulminant hepatic failure. Updated guidelines

emphasize rapid post-exposure vaccination, maternal screening, and immune prophylaxis to prevent vertical transmission. Innovative therapies targeting viral DNA and immune exhaustion pathways are being developed to improve outcomes. [14] [15] [16].

2.1.2 Cholestasis Liver Disease

CLD is described as the reduction of normal synthesis of bile by hepato-cells and cholangiocytes or its diminished capacity to reach the anterior intestine, which occurs as the result of joining flow via the biliary tract and the gallbladder-connecting ducts. CLD is defined as interruption of bile flow, resulting in intraparenchymal buildup of poisonous bile acids. BA control acts as complex process, managed by various hepatocellular processes, particularly sinusoidal absorption, discharge of canalicular secretion & intra-cellular metabolism [17]. It began by the extra-hepatic blockage of biliary system or intrahepatic impairment of bile secretion that eventually leads to collenchyma damage in the hepatic gland, producing cholestatic [18]. Therefore, on the fourth week of CLD, ALP and total bilirubin were considerably high [19]. Several variables may condition biliary flow derangements. Though the exact environmental triggers remain largely unidentified, factors such as antigenic stimulation, exotoxins, endotoxins, xenobiotics, and microbial agents can activate cholangiocytes, potentially leading to cholestatic liver conditions. Obstruction of bile flow further contributes to the risk. Both intrahepatic and extrahepatic bile duct blockages may occur due to external benign compressions like cystic disorders, malignant growths such as cholangiocarcinomas, or the formation and migration of gallstones within the biliary system. These obstructive conditions hinder bile transport, resulting in cholestasis categorized by increased bile acid levels. Additional influences like sepsis, elevated estrogen levels during pregnancy, congestive heart failure and genetic mutations affecting bile acid transporters can alter bile acid composition, increase its cytotoxicity and exacerbate the cholestatic condition [20].

2.1.3 Mixed Liver Injury

Drugs may result in cholestatic damage, primarily hepatocellular injury, or mixed injury, an intermediate phenotype [21]. Clinical signs of DILI include cholestasis, hepatocellular damage, or a combination of the two [22]. A common antibiotic (amoxicillin) and anti-tuberculosis medications (isoniazid and rifampicin) cause toxic metabolites to damage the bile ducts, causing mixed-pattern hepatitis that may proceed to cirrhosis and chronic cholestatic syndrome [23]. Three sequential phases are necessary for drug-induced hepatotoxicity: an initial cellular insult, a mitochondrial permeability change, and finally the commencement of cell death. As a crucial mediator, TNF-α triggers intracellular processes that control hepatocyte growth and death, such as IKK, JNK, and ROS signaling [24]. Clinically, hepatitis, cholestasis, steatosis, and fibrosis are among the acute and chronic diseases that can show signs of medication induced hepatic damage [25]. The major methods for identifying DILI are still traditional indicators for hepatic injury, such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin (TBIL), Lactate Dehydrogenase (LDH) etc. [26]. DILI can be classified as mixed liver damage, cholestatic (predominantly elevated alkaline phosphatase), or hepatocellular (predominantly elevated alanine transaminase). Severe DILI is indicated in individuals with hepatocellular liver damage if their increased bilirubin concentration exceedingly twice the normal upper limit [28]. The effectiveness of osteopontin, K-18, macrophage colony-stimulating 1 factor receptor (CSF1R), and several of these novel biomarkers for DILI prognosis have been confirmed by recent clinical trials [27].

2.1.4 Steatosis Injury

The abnormal buildup of fat within liver cells is known as steatosis; generally speaking, this is defined as fat that makes up more than 5% to 10% liver mass. The hallmark of steatosis hepatic illness linked to metabolic inefficiency is hepatic steatosis, which is frequently seen in liver histology [29]. Hepatic steatosis occurs when the liver's lipid accumulation outpaces its lipid disposal [34]. The liver undergoes metabolic-related alterations due to a variety of circumstances. Imbalances in the gut microbiota, known as dysbiosis, can arise from excessive nutrition. The disruption may allow microbial molecules to pass through the intestinal barrier more easily, travelling via the portal vein leading to the liver and further into the bloodstream, which can provoke inflammatory responses in the liver. Additionally, certain dietary components have the capacity to directly induce disease related changes within hepatic tissues [30]. Steatosis liver disease (SLD), another major CLD with steadily rising frequency, affects between 25% and 40% of patients with CHB infection. 7–9 liver-related problems including cirrhosis, liver cancer, and death, may result from hepatic steatosis (HS) [31]. Excessive

triglyceride (TG) synthesis in hepatocytes causes hepatic steatosis in NAFLD; white adipose tissue (WAT) provides 60% of the substrate for this synthesis, de novo lipogenesis (DNL) provides 26%, and eating a high-fat or high-sugar diet contributes 15% [32]. Although they make up a small portion of the liver's cell population, HSCs play essential role in both normal hepatic function & damage response. The two main functions of HSCs are the synthesis of collagen-dense extracellular matrix during liver fibrosis and their activation during liver damage [33]. This kind is distinguished by a preponderance of fat accumulation, which raises the weight of the liver. Jaundice, nausea, and weariness are typical symptoms. Examples include methotrexate and amiodarone. Hepatic lipid accumulation is promoted by the uptake of fatty acids by hepatocytes, which are released from the breakdown of triglycerides stored in adipose tissue [35].

2.1.5 Vascular Lesions Liver Injury

The four main anatomical systems affected by these lesions are the liver venous motor system (including obstruction associated with the large and small liver veins), the sinusoids (including peliosis, perisinusoidal fibrosis, and sinusoidal dilatation), the portal venous system and its tributaries, along with the hepatic arterial network. The process of creating, expanding, and reshaping new blood vessels from an existing vascular system is known as angiogenesis. This process is necessary for the movement of blood to tissues and organs across the body to supply oxygen and other nutrients required for bodily functions, as well as for the movement of metabolic waste products to excretory organs [41]. Furthermore, drug-related vascular tumors and changes within hepatic tumors that are not primarily vascular in nature represent possible complications [36]. Early detection and prevention of these lesions depend on an understanding of the pathophysiologic mechanisms behind them. Vascular lesions are one subset of DILI, which affects approximately 20 individuals per 100,000 people annually and is accountable for about 11% of all sudden hepatic decompensation in the US. These statistics highlight its significant impact on liver health and emphasize the importance or early diagnosis and management to reduce morbidity and mortality associated with acute liver failure. Clinical practice in DILI is essential because it helps healthcare professionals recognize, diagnose and manage liver damage caused by medications [37]. In many illness situations, vascular lesions are a significant pathophysiological mechanism. Recurrent hypoxia associated with obstructive sleep apnea-hypopnea syndrome (OSAHS) leads to vascular damage that impacts various organ systems including the heart, brain, eyes, kidneys and reproductive organs. This vascular injury is characterized by endothelial barrier disruption, metabolic imbalance, oxidative stress and inflammation of blood vessels. Together, these pathological changes drive the systemic complications associated with OSAHS, highlighting its far-reaching effects beyond the respiratory system [38]. A lack of VWF-dependent antigenic control causes vascular anomalies in individuals with von Willebrand disease; in all forms of VWD, the gastrointestinal tract accounts for more than 80% of lesions. Within the group of common signs of systemic lupus erythematosus (SLE) is vascular damage, which may be crucial in determining the best course of therapy and predicting prognosis [40].

2.1.6 Non-Alcoholic Fatty Liver Disease

NAFLD is thought to be a widespread outbreak that impacts approximately one-fourth of the global population. Metabolic interactions between the host and gut bacteria have recently been identified as unique molecular mechanisms involved in the onset of NAFLD [42]. Triglyceride accumulation within hepatocytes is a crucial characteristic of NAFLD, reflecting clinical and pathological changes frequently linked to disorders like obesity, type 2 diabetes, high cholesterol and impaired insulin resistance This buildup results and imbalance between lipid uptake, synthesis, and disposal in the liver which plays a role in disease progression and metabolic complications. One important element in the progression of hepatic steatosis may be the movement of CD36 to the hepatocytes' cell membrane alterations in NAFLD [27]. Hepatic steatosis is caused by the liver's absorption of FAs, which can also lead to lipid toxicity and the advancement of NAFLD [47]. Furthermore, it appears that intestinal microbiota has an involvement in encouraging the development of NAFLD by other processes. This latter in particular seems to have the ability to modify bile acid metabolism, which impacts VLDL export and de novo lipogenesis [43]. In NAFLD, there is a disruption in the balance of triglyceride export from the liver as very low-density lipoproteins (VLDLs), lipid synthesis and breakdown, and the delivery of fatty acids affecting the liver originating from the diet, new fat production (de novo lipogenesis) and fat breakdown in lipid tissue. This imbalance contributes to the accumulation of fat within hepatic cells, which drives the progression of the disease. Additionally, these metabolic

disturbances promote inflammation, oxidative stress and insulin resistance further promoting risk of liver injury [44][45][46].

3. OVERVIEW OF BIOMARKERS IN LIVER INJURY:

A biomarker refers to a quantifiable characteristic that reflects normal biological activity, a specific physiological condition, or an underlying pathological process in a living system. A biomarker is described by both The National Cancer Institute (NCI) and The National Institutes of Health (NIH) as a biological element present in blood, bodily fluids or tissues that serve as evidence of standard pathological processes or a particular condition or a disease syndrome. Additionally, as defined by European regulators, such molecules can be used to observe and monitor various biological activities and disease development in both people and animals [48]. Biomarkers and physiology of DILI as described in **Fig.2** serve as essential tools for mechanistic understanding and early diagnosis.

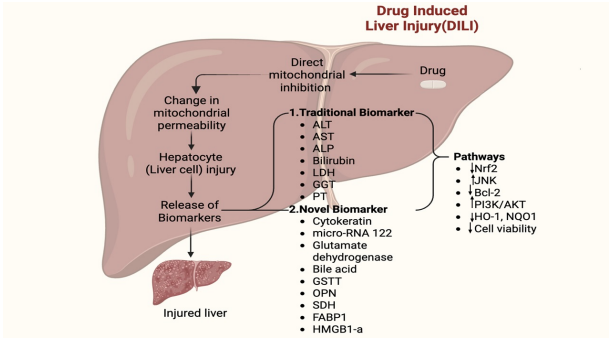

Fig (2). The schematic illustrates drug mediated mitochondrial dysfunction leading to hepatocyte injury and subsequent release of traditional and emerging biomarkers, alongside activation of stress, apoptosis and survival signaling pathways. The integrated framework highlights the limitations of conventional enzymes and emphasizes the mechanistic value of novel biomarkers in DILI stratification.

3.1 Traditional Liver Enzymes: Diagnostic Utility and Constraints

Hepatotoxicity was assessed by evaluating conventional serum biochemical markers alongside microscopic examination of hepatic tissue [49]. Traditional biomarkers in DILI are the conventionally used liver enzymes and related biochemical parameters (such as ALT, AST, Alkaline Phosphate, total bilirubin, Prothrombin time, GGT, LDH) that serve as indicators of hepatocellular damage, cholestasis, NAFLD, or overall liver dysfunction.

3.1.1 Aspartate Aminotransferase (AST)

Aspartate aminotransferase (AST) levels are primarily aid for diagnosing hepatic disease [50], and it is also named serum glutamic oxaloacetic transaminase (GOT), is an enzyme predominantly present in liver and found in red blood cells, heart, muscle, pancreas and kidneys. It plays a important role in amino acid metabolism by catalyzing the transfer of an amino group from amino acids like L-aspartate to α-ketoglutarate, resulting in-formation of oxaloacetate and L-glutamate [53]. Clinically, AST levels are important for diagnosing liver diseases and detecting abnormalities related to liver function, including active alcoholic liver disease, where elevated, AST activity is often seen [51]. Analytical techniques for detecting AST include chromatography, chemiluminescence, radiochemical methods, and electrochemical assays. Statistically, AST data can be analyzed using tests like one-way ANOVA, Kruskal-Wallis, chi-square, or Fisher's precise test depending on the variable type [50,52]. Elevated AST levels commonly indicate hepatocellular injury from drugs such as acetaminophen and isoniazid.

3.1.2 Alanine Aminotransferase (ALT)

Enhanced blood extents of the enzyme alanine transaminase (ALT), which is used in liver function tests, can be a sign of liver illness or damage, such as cirrhosis or hepatitis. It is also known as serum glutamic pyruvic transaminase (SGPT). With intracellular activity there are almost 3000-fold greater than that of serum. ALT is mostly accumulated in the cytoplasm of hepatocytes [52]. ALT levels only rise to a high level in cases of severe liver damage because they are not very sensitive. For example, about one-fifth of patients receiving INH therapy had a small, symptom-free rise in SGPT. However, in majority of situations, hepatic function tends to recover to normal levels if medication is sustained for a long time [54]. Viral hepatitis and nonalcoholic fatty liver disease can also cause substantial increases in ALT levels. Following an acute illness, a prolonged rise of ALT may indicate chronic liver disease [55]. Hepatocellular damage raises ALT levels. The drugs that cause it are anti-tuberculosis and analgesics.

3.1.3 Alkaline Phosphate (ALP)

Alkaline phosphate (ALP) is an enzyme that catalyzes the removal of phosphate groups from various compounds, typically functioning optimally in an alkaline (basic) pH environment. It is commonly utilized as an indicator to

evaluate liver function and linked to biliary tract disease. Elevated ALP levels have been identified as a prognostic indicator in HCC, accompanied by patients showing ALP levels above 81 U/dL experiencing mor extensive liver surgery, vascular invasion, and cancer recurrence [56]. Factors such as gender, extent of liver resection, existence of satellite lesions, elevated tumor grades and changes in perioperative hepatic function tests are associated with patient outcomes. ALP consists of four isoenzymes categorized by expression in tissues such as intestinal, placental, germ cells and other non-specific isozyme found in liver, bone and kidney [57]. Its level tends to rise in cholestasis and certain drugs including-antibiotics and oral contraceptives can influence ALP activity.

3.1.4 Bilirubin

Bilirubin is a yellow pigment that results from the metabolic breakdown of aged or damaged erythrocytes, primarily originating from the heme fraction of hemoglobin [58]. Most of the bilirubin circulating in the blood arises from the degradation of hemoglobin in older red blood cells, and this molecule is widely utilized as a biochemical marker in detecting hepatobiliary and metabolic system abnormalities. As a principal by-product of heme-containing proteins, especially hemoglobin, bilirubin serves crucial roles in clinical evaluation, prognosis and ongoing monitoring of hepatic conditions [59]. Accumulation of bilirubin in the body leads to jaundice, characterized by the yellow discoloration of skin and eyes. Hepatic tissue is central to the processing of bilirubin and any disruption in liver functionality can substantially elevate circulating bilirubin concentrations [60]. Gamma-glutamyl transferase (GGT) levels have been found to correlate inversely with other hepatic biomarkers such as ALT, AST and total bilirubin. Given its antioxidative, anti-inflammatory and protective characteristics, bilirubin is regarded as a valuable biomarker for early detection [61]. Raised bilirubin levels are typical in cases of cholestasis and mixed hepatic injury and have multiple pharmacological agents have been implicated in liver toxicity. Bilirubin also imparts notable anti-inflammatory and antioxidant effects [62].

3.1.5 LDH (Lactate Dehydrogenase)

Lactate dehydrogenase (LDH) acts as an indicator for liver injury because its levels inside the blood grow following liver cell destruction. When hepatocytes are harmed, LDH is discharged into circulation because of loss of cell membrane integrity, making increased LDH an increased non-specific indication of hepatic injury. Lactate dehydrogenase (LDH) found in many types of human tissues is an oxidoreductase enzyme [63]. LDH activity was determined using a standard kinetic assay that monitors the dropping in NADH absorbance within the reaction mixture [64]. Elevated levels of LDH in the bloodstream are associated with poorer outcomes and un-favorable treatment responses, particularly in cancer patients like those with melanoma [65]. LDHB carries out an essential role by catalyzing the reversible conversion of lactate to pyruvate, thereby maintaining cellular metabolic balance [66].

3.1.6 Prothrombin Time (PT)

PT along with prothrombin itself serves as a frequently used biomarker to assess liver injury and overall liver function, particularly in cases involving acute and chronic hepatic diseases. PT is involved in activating hepatic stellate cells and shows variable expression across different liver conditions [67]. PT caused by deficiency of vitamin K, antagonist-II or alpha-fetoprotein are recognized markers for HCC. The effectiveness of these markers or patients with HCV related cirrhosis undergoing therapy with direct acting viral agents have yet to be clearly established [68]. For statistical analysis comparison between independent groups were performed using ANOVA one way and when ANOVA testing was not met then Kruskal Wallis Test is done [69].

3.1.7 Gama Glutamyl Transferase (GGT)

GGT functions as a biochemical catalyst typically present on the outer surface of cell membranes in various organs, although it is notably prevalent in the liver. High serum GGT levels signify injury to liver cells or bile ducts, as the enzyme is released into the bloodstream when these tissues are harmed. GGT is an indicator for hepatocellular and cholestatic damage [70]. GGT plays a vital role in glutathione metabolism and synthesis across various tissues. The typical GGT range is between 0 and 30IU/L, although newborns typically exhibit levels 6 to 8 times higher than adults [71,72]. While chemotherapy can elevate GGT levels due to liver damage, but it does not affect glutathione reductase. Elevated GGT and AST levels are commonly observed in cases of biliary obstruction [73].

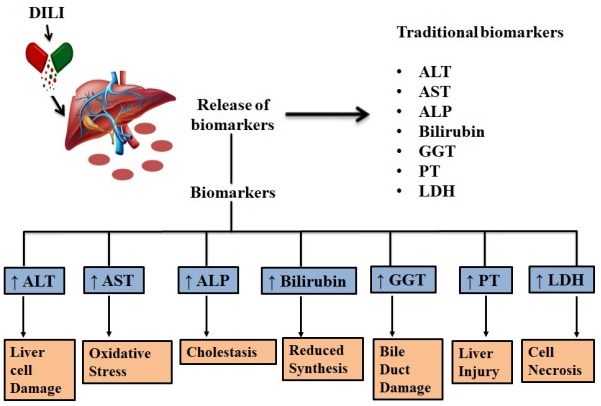

Fig (3). This figure demonstrates drug-induced hepatic injury leading to the release of traditional serum biomarkers including ALT, AST, ALP, Total bilirubin, GGT, PT and LDH each reflecting distinct patterns. This framework highlights the diagnostic utility and inherent limitations of enzyme-based biomarkers in capturing the complexity of DILI.

3.2 Limitations of traditional biomarkers

There are significant restrictions on the traditional hepatotoxicity markers' ability to be used therapeutically. The choices made during the pharmaceutical development process may be impacted by the low liver specificity and potential for false positive results from non-hepatic sources of the current gold standard, alanine aminotransferase (ALT) [74][75]. ALT levels may provide little information about patient outcomes and may not be a reliable indicator of the extent of damage [76][27]. Other enzymatic indicators like Lactate Dehydrogenase and Prothrombin indicate potential, but they require a more thorough qualifying analysis. Although emerging biomarkers, particularly microRNAs, show remarkable organ selectivity and stability in biofluids, there is still a lack of research on clinically suitable evaluation techniques [75]. To get around these limitations, more accurate and predictive biomarkers have to be generated.

3.3 Emerging Mechanism-Based Biomarkers

Novel biomarkers refer to recently identified indicators such as molecules, proteins or genetic alterations that reflect normal or abnormal biological activities. These emerging biomarkers hold significant potential to enhance the diagnostic precision of DILI, overcoming the limitations posed by traditional markers like ALT, AST and TBIL. Leading candidate biomarkers include cytokeratin-18, glutamate dehydrogenase, microRNA-122, high-mobility group box 1 proteins, osteopontin etc. [77]. Among emerging biomarkers, miR-122, HMGB-1 and FABP-1 demonstrate the highest translational readiness due to early release kinetics, liver specificity and availability of standardized assays whereas GST polymorphisms remain risk modifiers rather than diagnostic tools.

3.3.1 Cytokeratin-18

CK-18 is an indicator of apoptosis and overall cell death which is also regarded as a valuable biomarker for NAFLD [78]. This intermediate filament protein, predominant found in epithelial cells has gained attention for its potential to predict liver disease outcomes [79]. During hepatocyte damage, intact keratin-18 and its caspase cleaved fragments form are discharged from the cytoskeleton and can be recognized using serum antibodies M30 and M65. While M30 specifically identifies cK18 released during apoptosis, M65 detects both K-18 and cK-18 reflecting total cell death [80,81]. Analytical methods such as Mann-Whitney U test, Kruskal Wallis and chi-square test have been applied in studies assessing these biomarkers [82]. It correlates with hepatocyte death extent and has been proposed as independent predictors for non-alcoholic steatohepatitis (NASH) [83]. In the hepatic gland, various protein including vimentin, desmin, nestin, and glial fibrillary acidic protein are expressed in HSC, while hepatocytes express cK-8 and cK-18 heterodimers [84]. Fat accumulation in NAFLD triggers caspase activation, increasing cK-18cleavage and its release into circulation. Hepatocyte apoptosis activates HSC playing an essential involvement in fibrosis advancement in NAFLD [85]. This study focused on evaluating plasma cK-18 fragment stages as a non-invasive marker for liver fibrosis detection in pediatric NAFLD. CK18 as a part of the cytokeratin family is produced by various epithelial cells and its fragments in peripheral blood represent epithelial cell death with M30 and M65 antigens indicating apoptosis and necrosis respectively [86].

3.3.2 Fatty Acid Binding Protein (FABP 1)

FABP1 is a new emerging biomarker in Liver disorders. FABP1, commonly called as Liver Fatty Acid-Binding Protein (L-FABP), is a protein found inside cells and abundantly produced in hepatocytes. It increases the intracellular absorption, transport and metabolism of long-chain fatty acids and different lipophilic substances, serving a vital role in liver cell lipid-homeostasis. Advances in research over the last five years have clearly established FABP1 as a significant biomarker for a spectrum of liver illnesses including NAFLD, NASH, fibrosis, cirrhosis, and acute liver damage. Demonstrated

that FABP1 is elevated in patients diagnosed with type 2 diabetes and NAFLD, correlating with steatosis liver index and BMI highlighting its utility for non-invasive diagnosis and monitoring [87]. Further emphasized FABP1 has great ability to detect early liver injury with both true positive and true negative rates and its potential to differentiate fibrosis stages non-invasively. FABP1's relevance extends into inflammation and fibrotic processes crucial to liver disease progression [88]. [89] Utilized transcriptome approaches to find FABP1-associated gene profiles predictive of progression from NAFLD to NASH, revealing its prognostic importance. It is found that FABP1 is linked to signs of liver inflammation and fibrosis, which helps to understand what causes the disease [90]. Recent advancements in therapy are innovative therapeutic avenues by modulating fatty metabolism and oxidative stress in hepatic disorders [90] [91]. Urinary FABP1 serves as an early detection marker for acute liver and renal injury, particularly in hepatosplenic patients, with point-of-care assays developed and validated. [92]. It was found that urinary FABP1 is a novel biomarker for diabetic nephropathy, further attesting to its multi-organ disease association [93]. Other significant findings include establishing FABP1's basic function in hepatic fatty acid substrate transport [94], Future clinical standardization and validation of FABP1 measurement are necessary for greater inclusion into liver disease management regimens [95].

3.3.3 Glutathione S-Transferase Theta 1 (GSTT1)

GSTT1 is an essential enzyme engaged in the detoxification of ROS and toxic electrophilic chemicals by conjugation with glutathione. This enzyme is coded by the GSTT1 gene, which is known to display a deletion polymorphism resulting in the so-called "null" genotype, where the enzyme is totally missing. This polymorphism has been associated to susceptibility to several illnesses, including liver disorders such as NAFLD, HCC, and DILI. An increasing amount of data proves that the GSTT1 null genotype is linked with higher risk for NAFLD [96]. Furthermore, a meta-analysis showed GSTT1 null genotype carriers had a considerably greater risk of developing HCC, especially among Asian populations, suggesting that GSTT1 status might be a key factor in liver cancer. (97). Drug-induced liver damage is another area where GSTT1's significance has been emphasized. GSTT1's importance in liver disease severity has also been studied [98]. It was revealed that differences in GSTT1 gene copy counts are related with liver cirrhosis, notably in Ethiopian communities, underlining its genetic effect on disease development (98). GSTM1 and GSTT1 null genotypes are connected to moderate hepatotoxicity in individuals treated with valproic acid, which is essential for customized therapy methods. antioxidant enzyme alterations in metabolic associated steatosis hepatic disease and studied therapeutic benefits of vitamin E, emphasizing the impact of oxidative stress pathways in liver disorder treatment. GSTT1's genetic variation plays an important role in liver disease susceptibility, progression and response to remedy. As a biomarker, it has promise for early diagnosis, tailored therapy, and risk assessment in liver illnesses. Further investigations are required to sponsor these findings into clinical practice and create GSTT1-based therapies for liver health [99].

3.3.4 High-Mobility Group Box 1 (HMGB1)

HMGB1 is a strongly conserved nuclear protein involved in chromatin remodeling, DNA repair, and gene transcription. Under standard physiological conditions, HMGB1 is predominantly identified inside the nucleus. However, when cells undergo stress, damage or inflammation, HMGB1 can be actively produced and secreted by immune cells or released passively from necrotic or injured cells. In these extracellular locations the HMGB1 functions as a damage associated molecular patten (DAMP) molecule which plays an essential role in initiating inflammatory responses and promoting tissue repair processes. This dual function makes HMGB1 a significant factor in different liver illnesses, from inflammation to fibrosis and cancer. Recent studies have increasingly pointed to HMGB1's function in liver fibrosis (100). Oxidative stress-induced HMGB1 plays a significant role in the evolution of liver fibrosis, suggesting that targeting HMGB1 pathways might have therapeutic promise. Simvastatin decreases liver damage in alcohol-induced hepatotoxicity in rats via regulating HMGB1 expression [101]. It also plays a important role in identifying liver cancer. Its involvement in HCC is that HMGB1 released by myeloid cells increases tumor growth, presenting it as a possible biomarker for early detection and prognosis [102]. Biomarker discovery in gastrointestinal cancers, where HMGB1 was commonly linked in cancer development and immune evasion mechanisms. Its function in schistosomiasis-induced liver fibrosis, demonstrating that larger levels of HMGB1 associated with poorer clinical outcomes [103]. Additional investigations have validated the mechanistic significance of HMGB1 in liver damage and healing.

molecular variants of HMGB1 are utilized as mechanistic biomarkers in acetaminophen-induced liver failure, indicating that HMGB1 levels correlate with mechanisms of cell death and patient prognosis [104]. Furthermore, systemic inflammatory responses connected to liver disorders have been examined in the context of HMGB1 [105]. Liver-derived inflammatory mediators, including HMGB1, might impact brain inflammation through the liver-brain axis in nonalcoholic fatty liver disease, bringing novel insights into multi-organ crosstalk and possible treatment targets [106]. Future research should focus on verifying HMGB1's significance across varied populations and illness stages, as well as finding therapies that might control its activity to enhance patient outcomes.

3.3.5 Bile Acids (BA's)

BAs are produced from cholesterol in the liver and are crucial not only for fat digestion and nutritional absorption but also for maintaining metabolic homeostasis and immunological control. In patients with NAFLD, altered serum bile acid concentration are correlated with disease progression with increased levels of chenodeoxycholic acid (CDCA) and reduced levels of taurocholic acid (TCA) correlating with more advanced stages of the disease, suggesting their utility for early diagnosis and disease monitoring [107, 108]. Such alterations represent disturbances in bile acid production and metabolism, which may worsen hepatic inflammation and fibrosis. In cholestatic liver disorders diseases such as primary biliary cholangitis and primary sclerosing cholangitis and impaired bile flow restriction leads to accumulation of toxic BAs in the liver, leading to hepatocellular damage and triggering immune system activation [109]. BAs exert their actions through nuclear receptors such farnesoid-X receptor (FXR) and G-protein coupled receptors, which affect gene expression associated with lipid metabolism and bile acid pathways. Dysregulation of these pathways has been associated with liver fibrosis and inflammation, making them intriguing therapeutic targets for modifying bile acid signaling in chronic liver diseases [110]. Additionally, merging BA profiles with lipid and inflammatory markers has increased diagnostic accuracy, particularly in separating NAFL from alcoholic fatty liver (AFL), which display unique metabolic signatures [111]. Bile acid metabolism has been examined as a marker in different hepatic and systemic diseases. Furthermore, changes in BA pathways have been related with metabolic dysfunction-associated steatohepatitis (MASH), with non-invasive biomarkers implicated in the urea and tricarboxylic acid (TCA) cycles being studied as prospective diagnostic tools [112]. Recent studies have also established the utility of integrating bile acid and lipid indicators in metabolic liver disorders, giving more sophisticated methods to diagnosis and treatment [113].

3.3.6 Osteopontin

Osteopontin (OPN) was a combination name consisting of "osteo" and "pontin", which was often termed to define its connecting role of bone cells to the bone extracellular [114]. It is a versatile protein present among human tissues and body fluids including bone, skin, urine, milk and blood [115]. OPN acts as a highly modified integrin-binding extracellular matrix glycol phosphor-protein synthesized by immune cells, epithelial tissue cells, smooth muscle cells, osteoblasts, and cancer cells [116]. It plays an essential role in pro-inflammatory responses mediated by macrophages and promotes the production of interleukin (IL-12) while suppressing the anti-inflammatory cytokine IL-10 in macrophages, which ultimately leads to activation of T helper cells [117]. OPN expression reflects raise in response to strain or tissue damage demonstrating a significant role specifically in the control of inflammation. It is identified regarding the involvement of OPN during the development of liver fibrosis [118]. Further investigation should focus on verifying OPN's relevance across varied populations and disease stages, as well as creating drugs that could control its activity to maximize patient outcomes.

3.3.7 miR-122

MicroRNAs are small non-coding RNAs participating in control of gene expression. It may be found in tissues along with in physiological fluids such as plasma/serum, where they are unusually stable due to their nature and structure [123]. Some microRNAs such as miR-122 seem to have great features as biomarkers because of strong stability, high tissue selectivity and easily detection of hepatic disorders across many species. Current findings have demonstrated that miR-122 is a very specific marker for liver and detectable in blood after hepatic damage [119]. Circulating miR-122 levels was analyzed in plasma & compared to standard markers such as ALT, histopathology, and additional markers like AST, GLDH, SDH, α-GST, L-FABP, ALP, TBIL and γ-glutamyl transferase [120]. Capillary microRNA-122 is a predictive biomarker of liver damage in the medical treatment of individuals with overdosing of paracetamol [121]. These miRNAs were substantially related with

steatosis, liver rigidity and hepatic fat accumulation [122]. It has a part in modulating the stimulation of HSC which is essential for the development of liver fibrosis. In the adult liver miR-122 is critical for development, differentiation, homeostasis, metabolism of fatty acids and cholesterol. It is also a signal of liver damage such as chronic hepatitis B or C and NAFLD [124] [125].

3.3.8 Sorbitol Dehydrogenase

SDH is an enzyme complex located in inner mitochondrial membrane that facilitates electron transfer in the respiratory chain and supports the Kreb's cycle metabolism [126]. It is a mitochondrial holoenzyme made up of four subunits that is SDHC/SDHD, which anchor the hydrophobic segment which is embedded within the inner membrane of the mitochondria and in moving electrons across the electron transport chain while SDHA and SDHB form the catalytic domain that permits the conversion of succinate to fumarate via oxidation [127,128]. ALT, AST and MODS all showed favorable correlations with SDH [129]. SDH act as potential prognostic indicators for HCC in patients with diabetes mellitus and hepatitis C virus [130]. It is more accurate indicator for liver damage associated with INH [131].

4. Comparative Diagnostic Performance of conventional and emerging biomarkers in Drug Induced Liver Injury

Table-1 presents an author derived comparative framework based on evaluation of published studies assessing the diagnostic sensitivity, specificity and temporal profiles of established and emerging biomarkers in DILI.

Table-1 Integrated diagnostic performance and translational limitations of traditional and emerging biomarkers in DILI

Biomarkers	Injury pattern detected	Time of elevation vs ALT	Sensitivity (%)	Specificity (%)	Major Limitations
Alanine aminotransferase (ALT)	Hepatocellular	Late	60-70	Low	Poor specificity. Delayed rise
Aspartate aminotransferase (AST)	Hepatocellular	Late	55-65	Low	Extra-hepatic origin
Alkaline Phosphate (ALP)	Cholestatic	Late	60-70	Moderate	Drug-independent elevation
Total Bilirubin	Severe/mixed injury	Very late	-	Moderate	Indicates advanced injury
miR-122	Hepatocellular	Early	85-95	High	Assay Standardization
High mobility group box-1 (HMGB1)	Necrosis	Early	75-85	Moderate	Influenced by NAFLD
Fatty acid binding protein-1 (FABP1)	Hepatocellular	Very Early	90+	High	Limited routine availability
Sorbitol Dehydrogenase (SDH)	Mitochondrial Injury	Early	70-80	Moderate	Limited human validation
Cytokeratin-18 (M30/M65)	Apoptosis	Early	75-85	Moderate	Influenced by NAFLD, obesity and metabolic syndrome

Bile acids (BA)	Mixed	Early	70-85	Moderate	Influenced b diet and microbiota
Osteopontin (OPN)	Fibrosis	Intermediate	70-80	High	Elevated in non-hepatic inflammation

5. Multi-Omics integration for risk stratification in DILI

Omics technologies include genomics, transcriptomics, proteomics, metabolomics and secret omics for transforming hepatotoxicity research by enabling comprehensive profiling of liver injury mechanisms, biomarker discovery, and stratification of risk in drug-induced liver injury (DILI) as shown in Table-2. These approaches facilitate early detection of hepatocellular stress prior to conventional enzyme elevation and provide mechanistic resolution of injury phenotypes including hepatocellular, cholestatic, mixed etc. patterns. Genomics analyses primarily inform susceptibility and interindividual variability whereas transcriptomic and proteomic signatures reflect dynamic cellular injury responses. Metabolomic profiling further captures functional disturbances in bile acid homeostasis and mitochondrial metabolism and enhancing phenotype differentiation. Integration of multi-omics data supports development of biomarker panels rather than reliance on single indicators, improving translational relevance for clinical monitoring, drug development and regulatory risk assessment.

Table 2. Translational landscape of Omics-based biomarkers platforms for risk stratification, early detection and mechanistic characterization of Drug induced Liver injury (DILI)

Omics Technologies	**Biomarkers**	**Added value over ALT/AST**	**Translational status**	**Application**	**Reference**
Genomics	GSTP1, GSTM1, GSTT-1	Predicts risk before biochemical injury	Translational	Risk Stratification, Profiling of cells	[132]
Transcriptomics	miR-122, EFNA1	Detects injury earlier	Clinical exploratory	DILI type differentiation, hepatocyte injury marker	[133]
Proteomics	Keratin-18, FABP1, HMGB1, Osteopontin	Provides mechanistic and prognostic information	Investigational Clinical	Marker for apoptosis, necrosis and mitochondrial damage	[132],[27]
Metabolomics	BA's, SDH, GLDH	Enables injury pattern discrimination	Translational	Fingerprinting for early detection of amino acids	[134], [135]
Secretomics	Secreted liver cell proteins	Detects toxicity before clinical enzyme elevation	Preclinical	Monitoring DILI *in-vitro,* drug safety evaluation	[136]
Micro RNA profiling	miR-122, miR-192	High liver specificity	Clinical exploratory	Early marker for hepato	[76]

		and bioflui d stabilit y		cellula r injury	

6. Research Gaps and challenges

Despite significant advances several gaps remain in the application of the omics technologies to DILI. Some are discussed below: -

- Most omics-derived biomarkers lack large scale prospective clinical validation, limiting their routine clinical adoption.
- Inter-study variability and absence of standardized analytical pipelines
- Integration of multi-omics data with clinical endpoints remains limited, restricting translational from mechanistic insights to decision-making tools.
- The influence of liver diseases and polypharmacy on omics-based signatures is insufficiently characterized.

CONCLUSION

Drug-induced liver injury remains a principal clinical and regulatory challenge due to its unpredictable onset, diverse presentations, and potential severity. Traditional biomarkers such as ALT, AST, LDH, TBIL and PT have served as the cornerstone for DILI detection; however, their limited specificity & delayed response often hinder early diagnosis and accurate prognostication. Recent advances have led to the identification of emerging biomarkers, including miRNAs, CK-18, glutamate dehydrogenase, BA, and genetic signatures, which offer greater sensitivity and mechanistic insights. Integrating these emerging markers with established diagnostic tools holds promise for improving risk assessment, patient monitoring, and therapeutic decision-making. Moving forward large-scale validation studies and the incorporation of multi-biomarker panels into clinical practice will be essential to connect the gap between research findings and practical implementation. Ultimately, the evolution from traditional to novel biomarkers marks a pivotal step toward more precise and personalized management of DILI.

AUTHORS' CONTRIBUTIONS

The authors confirm their contributions to the paper as follows: data collection: SJ; study conception and design: AM; analysis and interpretation: BP and MC; draft manuscript: all authors. All authors reviewed the findings and approved the final version of the manuscript.

LIST OF ABBREVIATIONS

AFL = Alcoholic Fatty Liver
ALP = Alkaline Phosphatase
ALT = Alanine Aminotransferase
AST = Aspartate Aminotransferase
BA(s) = Bile Acid(s)
cK-18 = Cleaved Cytokeratin-18
CLD = Cholestatic Liver Disease
CYP450 = Cytochrome P450
DNL = De Novo Lipogenesis
FABP1 = Fatty Acid Binding Protein 1
FXR = Farnesoid X Receptor
GGT = Gamma-Glutamyl Transferase
GLDH = Glutamate Dehydrogenase
GSTT1 = Glutathione S-Transferase Theta 1
HBV = Hepatitis B Virus
HBsAg = Hepatitis B Surface Antigen
HBcAg = Hepatitis B Core Antigen
HBeAg = Hepatitis B e Antigen
HCC = Hepatocellular Carcinoma
HMGB1 = High-Mobility Group Box 1
HSC(s) = Hepatic Stellate Cell(s)
INH = Isoniazid
K-18 = Cytokeratin-18
LDH = Lactate Dehydrogenase
L-FABP = Liver Fatty Acid Binding Protein
miRNA = MicroRNA
NAFLD = Non-Alcoholic Fatty Liver Disease
NASH = Non-Alcoholic Steatohepatitis
NCI = National Cancer Institute
NIH = National Institutes of Health
NTCP = Sodium Taurocholate Co-Transporting Polypeptide
ROS = Reactive Oxygen Species
SDH = Sorbitol Dehydrogenase
SGOT = Serum Glutamic Oxaloacetic Transaminase
SGPT = Serum Glutamic Pyruvic Transaminase
SLD = Steatotic Liver Diseases

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CONFLICT OF INTEREST

The author declares that there is no conflict of interest.

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