RESEARCH PAPER

An Integrative Omics Approach for Hepatic Diseases

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Abstract

Hepatic liver disease is associated with multi-liver dysfunctions ranging from Acute Liver Disease (ALD) to Chronic Liver Disease (CLD). The infections and inflammations in liver covers histological, clinical and pathophysiological developments ranging from hepatic viral infection to liver cirrhosis which potentially grows towards liver failure. The existing study shows ALD associated with viral infections, intense inflammations immune-metabolism disorders which develops to metabolic dysfunctions and leading to the disease development. CLD develops from the existing liver disease like fatty liver disease to liver fibrosis then grow towards liver cirrhosis. The diagnosis methods including clinical tests and radio imaging methods are standard process to detect the disease where as its early symptoms are very mild to identify the disease at its primary stages. Now the increasing number of high-throughput Omics research on the molecular pathobiology of hepatic liver disease can be generated through analytical biochemical process. Omics is an integral approach which develops a comprehensive analysis of the disease ranging from its genetic level to the development of treatment level. Additionally, omics are developing a complete diagnostic technique for various stages of hepatic liver disease and the development of advance treatment methods. A comprehensive study of types, diagnosis and treatment of hepatic liver disease integrated with progressing omics study, starting from genomics to proteomics, metabolomics and bioinformatics are outlined here.

Key Words: Hepatic Disease, Acute Liver Disease, Chronic Liver disease, non-alcoholic liver diseases, alcoholic liver diseases, Omics approach.

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1. Introduction

The liver is a key organ in the human body with a complex physiology and a properly functioning regulatory system. Liver consists of around 2% of healthy adult's body weight. It is unique due to its dual blood supply from the portal vein (which is approximately 75%) and the hepatic artery (is also approximately about 25%) [1]. Liver is responsible for variety of physiological functions which including metabolism and digestion, which interacts with the gastrointestinal and endocrine systems of the body. Liver is consisting of different types of cells among which hepatocytes are the largest cell made up about 60-80% of the cytoplasmic mass in human liver tissue. Endothelial cells, Kupffer cells, stellate cells the bile duct epithelial cells are another four different cell types that make up the liver. Every type of cell has particular roles that work together to improve the organ's overall function [2]. Protein synthesis and clotting factors are two ways it contributes to haematology. In additionally, the liver also contributes to its breakdown into unconjugated bilirubin. It involves the metabolism of sex hormones and generates carrier proteins that are critical for development and reproduction [3]. There are certain conditions like hepatic viral infection, consume of excess alcohol, deposition of fat in liver and due to the adverse effect of some drugs liver fails to perform its normal function which leads to hepatic abnormalities [4]. Current study shows liver dysfunction associated with many kinds of symptoms like metabolic abnormalities, poor immune functions, infections, chronic inflammation and deposition of excess fat in the liver and abnormal drug metabolism. Chronic Liver Disease (CLD) is mostly occurred by chronic hepatitis C virus (CHC), chronic hepatitis B virus (CHB), alcohol related liver disease and non-alcohol fatty liver disease (NAFLD) which is rising its number day by day like a pandemic [5].

Currently, millions of individuals worldwide are suffering from liver diseases. The prevalence of viral hepatitis is decreasing in the majority of industrialized and developing

countries due to advances in sickness prevention, detection, and treatment. Expanded hepatitis B vaccination programs have also greatly reduced the number of new cases in many nations, including India [6]. The frequency of metabolic liver illnesses, such as alcohol-related liver disease and non-alcoholic fatty liver disease, is expected to increase in parallel with rising living standards, which will ultimately result in an increase in end-stage liver diseases, such as liver failure, fibrosis, cirrhosis, and liver cancer. Over the last three decades, the progressive and developing governments of major countries have offered significant support for hepatology related scientific and clinical research, immunization programs, drug development and new drug discovery [7]. Because of advances in treatment and disease-related technology, liver physiology can now be viewed as an integrated system with numerous regulating systems acting at various stages. Proteins, RNAs, cellular organelles, metabolites, and biological networks serve as an intermediary scale for connecting liver disease and all relevant data [8]. This information about the disease mainly related to gene expression, disease pathway, protein networking and multi directional relation between the organ's clinical out come and its function at molecular level [9]. In more recent times hepatology research has been emerging of new omics technologies like genomics, proteomics, metabolomics and bioinformatics can easily analyse a vast data of genes, proteins, metabolites and predicted drug or disease related data [10]. The interaction of whole biological system represented through a single interdisciplinary advance scientific subject known as omics. Omics is an interdisciplinary scientific subject that examines the interactions of biological systems as a whole, rather than individual components [11]. This subject focuses on high-throughput technologies and large-scale molecular data. Computational tools are used to combine and evaluate data, providing insight into biological processes. The term "omics" encompasses various subfields, including genomics [12], transcriptomic [13], proteomics [14], metabolomics and bioinformatics [15], which provide a comprehensive examination of biomolecules. Omics has greatly improved our understanding of cellular and molecular processes, including human health, development, diagnosis, prognosis, and aging [16]. Omics technology provides a detailed knowledge about the disease occurrence, disease types, progression level and pathway mechanism [17]. In biological process omics act as an essential tool for monitoring and showing particular molecules and their potential role in metabolic pathways [18,19]. Multi omics is a key component of system biology which allowing researchers to analyze the biological system as an interconnected network [20,21]. Since the clinical history of liver disease is difficult to figure out because of its frequently changing characteristics so it is very challenging to find out its pathophysiological mechanism. The growing trend of omics study provides new insights into the essential information about the pathophysiological process of liver disease [22]. Despite the fact that omics data advance in a remarkable state but due to there is a struggle to identify the disease at early stages so it's being difficult to find the pattern of illness correlation and useful information from the massive amount of data about the disease. The pathophysiological mechanism behind the liver infection and inflammation may be adequately analyzed and explained by the help of comprehensive analysis of omics-based technology which provide more information about the etiology of the disease [23]. Along with the proper understanding of the mechanism of the disease the system biology opens its door for data integration, functional analysis and prediction of drug. It builds the biological networks-mostly molecular networks like gene regulatory networks, protein-protein interaction networks and signal networks are common step in the systems biology approach [24]. These networks are used to record molecular and signaling interactions which take specific measurements like gene, protein and metabolite expression.

2. Types of liver disease

Earlier study and the analysis of liver epidemiology indicates that liver disease mainly classifies into two major types including acute liver disease and chronic liver disease [25]. Acute liver disease shows no previous history of liver disease. It occurs by viral infections, toxicity, drug over doses or deposition of unusual fats which further grows to fatty liver disease. During pregnancy sometimes this happens to the mother [26]. One of the major global liver health issues is viral hepatitis, which encompasses hepatitis B and C. This can affect millions of individuals which mainly transmitted through contaminated blood and some body fluids [27]. Despite the fact that vaccinations have been effectively reduce the number of incidences of the disease but it is still challenging for nations to fight with these issues [28]. Hepatic C is also known as silent epidemic because the symptoms and presence of virus is difficult to detect at its early stages [27].

The chronic liver disease is the indication of pre-existing liver disease like chronic hepatitis and cirrhosis which further grows to deadly

liver dysfunction. There are many types of Chronic Liver Disease (CLD) which are causing due to genetics causes, autoimmune disorder, due to fat accumulation and consumption of excess amount of alcohol. There are some genetic problems also responsible for causing chronic liver disease [29]. In children Alpha-1 antitrypsin deficiency is most prominent type of CLD. Another type of CLD is Wilson disease in which copper accumulation occurs which is an autosomal recessive disorder. Autoimmune hepatitis causes liver tissue destruction from autoantibodies, and patients who suffer from this condition are more likely to develop liver cirrhosis in the near future [30]. These two types of fatty liver diseases are more common and most dangerous due to its gradual progression of scar tissues in liver and again it moves towards liver fibrosis and cirrhosis [31]. The alcoholic fatty liver disease initially known as steatosis where fat accumulation in liver tissue occurs. After that inflammation in liver cells takes place which leads to injury in liver and then the end stage of liver damage happens which leads to cirrhosis. Major complications arise at this stage
because of its irreversible nature [32,33]. NAFLD is a chronic liver disease with very few symptoms at it early stages and it silently grow in patient's body. NAFLD having very certain health condition including metabolic disorders, obesity and type 2 diabetes in adults [34]. Here the accumulation of lipid in the liver of the people without any significant history of consumption of alcohol. Adopting modern lifestyle and unhealthy eating habits with very poor physical activity could rise the risk of metabolic syndrome which further leads to NAFLD. Now the growing NAFLD epidemic has been a great challenge in hepatics liver disease and the rate of liver cirrhosis grows globally [35]. NAFLD became dangerous when the deposited lipids and fats in the liver damage the liver tissues and affect to the cellular fibrous bands due to which scar occur in the liver. This chronic liver injury at its end stage known as cirrhosis [36]. Recent development in health care sector the pathophysiology and natural history of cirrhosis and the management of this deadly disease have been improved, this changes the life expectancy of a patient. Though pharmaceutical treatments can make major changes in patient's life but still it is an irreversible process which ends with liver transplant at end stage curative option [37].

3. Risk factors of Liver disease

Liver illness is most common in all over the world, and it is expected to increase in coming future according to its growing numbers where variations in liver disease epidemiology arise due to risk factors like obesity, viral hepatitis, hazardous alcohol consumption and adverse effect of some drug or chemical molecules. There is a significant increase in obesity leads to NAFLD, now a day which became a common liver disease and growing rapidly in all over the world. The major risk factor associated with NAFLD's development towards liver cirrhosis is irreversible [38]. Nonalcoholic steatohepatitis (NASH) and nonalcoholic fatty liver (NAFL) are two primary historical sub types of NAFLD [39]. The progression of NASH is higher as compared to NAFL [40]. Liver steatosis and its progression to nonalcoholic steatohepatitis (NASH) can be made more likely by obesity-induced lipotoxicity and glucotoxicity [41]. Current study indicates 25% of people with NAFLD develop NASH. Although disease prevalence and incidence estimates vary significantly due to different patient populations, geographical area and disease criteria, its estimated prevalence in the general population ranges from 1.50 to 6.45%. NASH is linked to extrahepatic diseases like cancer and cardiovascular disease (CVD), hepatic consequences like cirrhosis and hepatocellular carcinoma (HCC), and obesity and type 2 diabetes (T2D). Between 2020 and 2025, NASH cirrhosis is expected to overtake all other causes of liver transplantation (LT)
[42]. It appears that an intra-hepatic inflammatory process can be triggered by the accumulation of adipose tissue in the liver of obese people [43]. Obesity and physical inactivity are known to increase the chance of getting diabetes, and they are also directly linked to an individual's risk of developing NAFLD [44]. According to certain research, there is a direct link between growing older and the incidence of NASH, NASH-induced fibrosis [45]. However, a significant determinant of the association is the length of the illness, not just age. between age and the onset and/or severity of NASH that needs to be taken into account [46]. Nonetheless, epidemiological research has shown that fibrosis and NASH are linked to aging, especially beyond the fifth decade of life [41]. It is important to remember that children have been shown to proceed from NAFLD more aggressively and quickly than adults [47].
There is currently substantial evidence linking the pathophysiology and progression of NASH
to genetic and epigenetic variables as well as the disease's epidemiology [48]. The Isoleucine 148 Methionine (I148M) variation, a mutation in the patatin-like phospholipase domain-containing 3 (PNPLA3) gene, is the primary common genetic regulator of NAFLD [49]. The amount of hepatic fat that accumulates and the histological severity of hepatic damage can both be significantly impacted by this gene.

Other genetic variations linked to NAFLD include single nucleotide polymorphisms in the genes for lysophospholipase-like 1, neurocan, glucokinase regulator, and Transmembrane 6 Superfamily Member 2 [50]. These gene polymorphisms have a major effect on the liver's cellular metabolism of lipids, increased hepatic fat accumulation, and hepatic glucose absorption [51]. The pathophysiology and development of both ALD and NAFLD are significantly influenced by the epigenetics, which is the combination of genetic and environmental variables [52,53]. Histone protein modifications, chromatin remodeling, DNA methylation changes, and RNA-based processes like non-coding RNAs can all result in epigenetic changes that can explain the impact of environmental elements that affect phenotypic conditions. Accordingly, epigenetics may help to explain the missing heritability in liver disease and its previous history [52]. Obesity and diabetes in mothers, as well as the environment, food, lifestyle, and behavior of the parents, can all have an impact on the development of the embryo and cause significant changes in the offspring's chromatin structure and epigenome. They are associated with the development of liver dysfunction. According to recent research, NAFLD and its development to NASH can be directly impacted by gut microbiota. The gut microbiota balances the liver's pro- and anti-inflammatory effects by influencing how lipids and carbohydrates are metabolized by the liver [54]. Obesity and poor eating habits are common among NASH
patients. Consequently, the impact of nutrition and that related metabolic alterations on patients mostly seen in NASH disease. Under the same circumstances, it is challenging to differentiate the symptoms of NASH from those associated with the changed microbiota because of its mild symptoms [55]. Some studies have shown that giving the antibiotic rifaximin to NASH patients enhanced liver function by reducing the growth of bacteria in the small intestine [56].

The possible impact of certain environmental factors on the emergence of liver illnesses has recently come to light. Prior research indicated that lifestyle choices and nutritional composition, particularly in affluent nations, may make people more susceptible to NAFLD/NASH [57]. Previously mostly hepatic viral infections occur due to the toxicity added to the environmental factors like water pollutants and unhygienic food products which can accelerates the growth of hepatic virus in human body. Natural environment is a best provider of healthy food, water and medicinal products but due to many hazardous conditions it enhance the toxicity in natural environment which further leads to a poor hepatic health condition. According to a number of studies, food composition has a significant impact on the onset of liver disease. Eating a diet high in fat and sugar raises the risk of steatosis and interferes with portal circulation, which affects liver function [57]. Additionally, the least healthy eating practices, such as consuming fresh fruits and foods with lesser nutrients and excessive sodium, were more common among NAFLD/NASH patients [58]. Obesity and liver illnesses are on the rise in developed countries as a result of the increase in knowledge-based employment and the decline in physical exercise [59]. The major risk factors including obesity, consumption of alcohol, genetics factors and gut microbial health are affecting the liver and enhance the chance of liver disease. The early diagnosis and detection of the stage of disease is the most challenging task for the health care professionals. **Figure 1** describe this risk factors associated with liver diseases and after disease occur from the initial stage to the liver cirrhosis stage then the major diagnosis methods which are used to detect the disease.

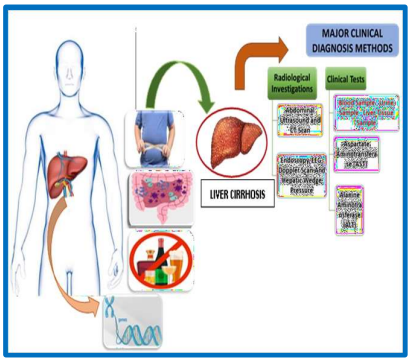

Figure 1. The risk factors involve in liver disease occurrence and methods of diagnosis after the disease occur.

4. Epidemiology

Liver diseases are being recognized as public health priorities in India since last few decades. Worldwide India has a heavy burden of liver disease as compared to other populous countries. The contribution of cirrhosis and its complications collectively known as chronic liver disease, or CLDs as it causes of death in India has been steadily rising science 1980. India has a heavy burden of liver disease, accounting for 18.3% of the liver disease related deaths worldwide in 2015 [60]. Now this number grows up to 38.6% within a decade in India which showing an alarming condition in the growth of liver disease in Indian population [61].

Previous study shows cirrhosis and various CLD were responsible for 2.1% of all the

hepatic disease related deaths in India till 2016. The most common causes of hepatic infection occur in India due to alcohol consumption, hepatic B virus and drug-induced liver damage. The increasing per capita alcohol consumption and co-existence of diabetic also adding fuel to increase Alcoholic Liver Disease. NAFLD raise in between the general population ranges from 8% to 20%; certain urban population groups and research indicate high prevalence, while studies in rural areas report lower prevalence [62].

5. Diagnosis of Liver Disease

The causes and effect of illness determine the diagnosis of chronic liver disease. There are several types of diagnosis methods used to determine the different stages of liver disease. CT
scan, endoscopy, EEG, Doppler scan, abdominal ultrasound and hepatic wedge pressure are the most common diagnostic method to detect liver disease [63]. Abdominal ultrasound is an imaging test with reasonable price to diagnosis chronic liver disease. Liver size and can be measure through ultrasound which indicates the stage of fatty liver and presence of nodules which shows the stages of liver cirrhosis. The advantages of ultrasound in CLD also measure the diameter of the portal vain and hepatic vain which evaluating clots in that vein [64]. Computed tomography scan can more accurately and reveal a liver lesion or biliary channel blockage. Another diagnosis method which can identify liver cirrhosis at early stage is transient elastography [65]. Wedge hepatic venous pressure uses to measure portal venous pressure in chronic liver disease. Liver biopsy is the mostly used diagnosis method which includes various techniques such as percutaneously, laparoscope or trans jugular to detect the liver cirrhosis. EEG visualized delta waves in hepatic encephalopathy.

Apart from these radiological investigations there are some clinical tests also indicates the liver abnormalities. In chronic liver disease due to inflammation and hepatocyte loss, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) level elevated due to its release into blood. AST and ALT may be two to three times higher than normal during cirrhosis. These markers cannot be at normal level if there is any stage of liver cirrhosis occurs [66]. Due to jaundice bilirubin levels also increase. In cirrhosis related hepatocellular deficiencies, the level of albumin falls whereas the ammonia rise which results hepatic liver damage [67]. The mechanism of liver dysfunction happens due to increase level of ammonia, short-chain fatty acids, octopamine, mercaptans and improved oxidative stress [68,69].

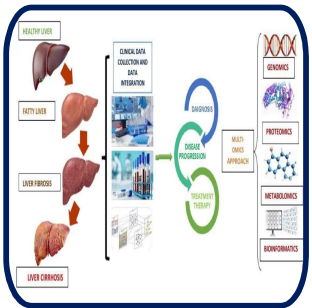

Figure 2. The methods of diagnosis after the liver disease occur.

6. Omics Approach in Liver Disease

The pathophysiological mechanism of hepatic liver disease is still challenging to identify in clinical process as well as it is time consuming and cost effective. In recent years Omics based methods including genomics, proteomics, transcriptomic and bioinformatics have been developed which can provide an extensive range of data and information regarding pathophysiology, diagnosis and clinical study of the hepatic liver disease. The **Figure 3** shows the progression of liver disease at different stages from which the clinical data and sample could collected and it further used for the advance research in the field of genomics, proteomics, metabolomics as well as bioinformatics to know the origin, evolution, disease mechanism and disease growth. This information provides the insides to future research in the field of Omics like drug designing, structural and sequential bioinformatics

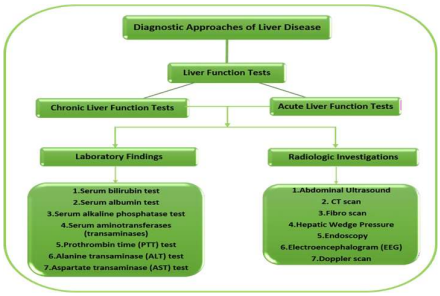

Figure 3. Studies shows stages and development of Liver disease, collection of clinical data from patient and integration of Omics data using system biology.

6.1. Genomics

During the initial stage of omics analysis introduced, the area of genomics came first. It can use as a successful tool for examining the genetic code of living things and may be looking at the structure of genomes, evolutionary relationships, and the significance of gene sequences
in system biology. Two important methods for genomics research are whole-genome sequencing (WGS) and whole-exome

sequencing (WES). Though WES is designed to analyze the exon portion of the genome, WGS includes nearly the entire genome, including the gene regulatory sections. WES often has a lower cost and more thorough coverage in target locations than WGS [70]. Though scientists used to study individual genes a few decades ago but now due to technical advancements whole genomes can be sequenced quickly with affordable cost [71]. The first human genome, which was created in the midst of this enormous shift in sequencing experiment, was created by a global collaboration at a cost of billions of dollars but currently individual genome sequencing may be finish quickly [72]. This advancement in technology promotes investigations that focused on whole genomes rather of individual genes. The field of genomics includes number of methods for examining and comprehending the DNA of organisms. This covers the study of the structure and composition of the genome (genes and non-coding sections), as well as variation, function, evolution, and the interactions of the various components. This covers a variety of topics, including as variation, evolution, functions and the structure of the genome (genes and non-coding sections), as well as their roles and interactions with one another. The discovery of new coding and regulatory regions [73] and our comprehension of the spatial arrangement of DNA within a cell nucleus [74] have both been significantly impacted by the overall sequencing capabilities. By making it possible to identify protein targets and speeding up to drug discovery, genomics has also completely transformed the pharmaceutical sector and playing a great role in these fields [75-78]. The subject has grown quickly, with models and techniques created for examining gene duplication, phylogenetic networks, gene clustering, and genomic rearrangements [78,79]. Due to higher cost of Next Generation Sequencing (NGS) genotyping of individuals for genome wide association studies (GWSA) is used and it perform by using microarrays to quantify the common variants of liver cells [80]. Integrating the results of liver biopsies, elastography, liver enzymes and electronic health records can signify GWAS and meta-analysis have defined the genetic causes of steatosis, steatohepatitis and fibrosis from NAFLD and ALD [81]. Current research focused on finding the genes and its variation that could causes and enhance the liver disease. Single-nucleotide variations may alter the activity of signalling receptors, including Toll-like receptors, or regulate the release of inflammatory cytokines by innate immune cells. The genetic variants in genes encoding the receptor associated with the innate immune system which includes mannan-binding lectin (MBL), MBL-associated serine proteases, or nucleotide-binding oligomerization domain 2 (NOD2), after genotyping 21 innate immunity single nucleotide polymorphisms (SNPs) with known functional implications in association with the risk of causing early death in patients [82].

6.2. Proteomics

The term "proteomics" describes the study of the proteome, which is technical uses for identifying and measuring the proteins found in a cell, tissue or organism [83]. Proteomic analysis is preferable over genome or transcriptome analyses when looking for biomarkers to diagnosis and further experiment on non-alcoholic fatty liver disease [84]. Proteomics research is still limited, nevertheless, by the inability of existing technologies to detect and precisely quantify candidate proteins. Furthermore, a number of post-translational modifications and splicing make the proteome more dynamic and complex than the transcriptome or genome [85]. However, the development of proteomics technologies and applications, mass spectrometry (MS), and protein microarrays have allowed for advancements in research on the discovery of some proteins that are differently communicated between people with and without NAFLD, and could be potential proteomic biomarkers [86]. Due to methodological and technical issues, proteomics-based research on the identification of potential biomarkers in NAFLD has been limited [87]. However, using next-generation microarrays, which provide the benefits of high throughput and low cost. The identification of NAFLD protein biomarkers is undoubtedly anticipated in the future due to biomarker studies, the application of nanotechnology, and advancements in bioinformatics software acceleration [88]. Recently certain technology developed for single-molecule protein sequencing (SMPS) that transformed the proteomics research with high sensitivity to identify smaller length proteins [89]. The mostly used technique to identifying clinically useful biomarkers is plasma proteomics because circulating proteins that contains both proteins that drain from injured organs and plasma proteins that sustains the physiological homeostasis and also protein that bleed form damaged tissues [90]. This causes may lead to scar in liver tissue which further became liver steatosis. Hepatocytes release proteins that called hepatokinase are associated with the development of metabolic dysfunction. Protein such as retinol-binding protein 4 (RBP4), selenoprotein P, fetuin A, and fetuin B connected to the development of metabolic dysfunction which further cause the development of hepatic steatosis, show the

hepatic steatosis and insulin resistance are strongly correlated in non-hepatic tissues, then steatosis further modifies hepatokine secretion to affect metabolic phenotypes through inter-organ communication [91]. The current research found several blood biomarkers for HBV-ACLF that might be utilized to forecast the severity of the disease, including MIP-3α, PGBM, and N RP1 by using single-run quantitative proteomic analysis and cytokine antibody array detection methods [91]. In omics study the application and analysis of proteomics is still limited.

6.3. Metabolomics

Study on the molecular biomarkers is made possible by the study of chemicals or metabolites inside cells and the biochemical processes that are linked to them. This field is known as metabolomics. The term "metabolomics" describes an extensive investigation of the metabolome found in an organism's cells, tissues, and bodily fluids [92]. Amino acids, fatty acids, and carbohydrates are examples of metabolic products and tiny molecules that are included in it [93]. Due to their dynamic nature, metabolomics only offers a clear picture of the metabolic profile during a given period of time and under particular circumstances [94]. In order to find biomarkers for NAFLD and other liver illnesses, metabolomics research have increased in number thanks to the adoption of high-throughput analytical methods like mass spectrometry and nuclear magnetic resonance spectroscopy [95]. The major sub types of metabolomics research are targeted metabolomics and untargeted metabolomics. Targeted and untargeted shows the systematic examination of every metabolite in a sample and absolute quantification of the metabolites, respectively [96]. On the other hand, the poor sensitivity and need for a large enough high-purity sample limit its use in evaluating the fine structure of toxins or hazardous chemicals. Integration of new technology like gas chromatography mass spectroscopy (GCMS) or liquid chromatography mass spectroscopy (LCMS), which enhances the analytical resolution by increasing the specificity and sensitivity. This technology is essential tool for the identification and quantification of metabolites [97]. Research developing high-throughput Liquid Chromatography-High Resolution Mass Spectrometry (LC-HRMS) which demonstrated a substantial change in metabolic pathways, specifically a significant reduction in mitochondrial fatty acid β-oxidation, which lowers oxidative phosphorylation and ATP synthesis. In addition to glucose, blood amino acids during this process drive the creation of proteins and nucleotides in the activated innate immune system, thereby increasing the illness [98]. The study of metabolomics research has indicated differences in the metabolism of glucose, amino acids, lipids, and bioenergy and has mostly examined the correlation between prognosis and etiology. The metabolic pathways and biomarkers linked to the development of hepatic liver disease should be further validated for future research and investigation which could help in linking between identification and treatment of disease.

6.4. Bioinformatics

In the post-genomics era, bioinformatics is transforming the design of molecular experiments, favoring comprehensive perspectives on various levels of biological functionalities and making significant contributions to the advancement of scientific knowledge while introducing fresh viewpoints [99]. Bioinformatics tools and databases are providing data such as genes and protein sequences as well as structure related data [100]. In liver disease research work The Gene Expression Omnibus database was used to download the gene expression chip data for NAFLD and other hepatic infection in order to find the differentially expressed genes (DEGs) between NAFLD and normal controls. The Kyoto Encyclopaedia of Genes and Genomes (KEGG) and gene ontology (GO) pathway enrichment analyses were then used to examine the possible roles of DEGs for NAFLD as well as for other hepatic liver disease. To create a protein–protein interaction network (PPI), the STRING database was utilized which also used in the study of pharmaconutrient methods [101]. Over the past decade the number of three-dimensional (3D) structures of pharmacological targets and macromolecules discover by experimental approach has increased. The development and refinement of bioinformatics techniques have become an essential tool to predicting high-quality 3D compounds. This kind of growth is a regulator which allows drug discovery programs in the field of computational biology. The goal of structure-based drug design (SBDD) is to develop a therapeutic candidate drug molecule that is appropriate for clinical study by designing and optimizing phytochemical and synthetic chemical structures. The method of lead identification is simpler and less expensive than the traditional way of research, and by using bioinformatics it can speeds up the drug discovery process [102].

The overall applicability of web-based bioinformatics tools to organize and interpret the vast amounts of biological data that are made available by existing-omics techniques is closely related to the accuracy, consistency, quality, and updating of the data. This has an

impact on the potential for integrating with other resources, the user-friendly accessibility, and the value-added information that may be provided. Apart from a number of factors, such as the diversity of scientific disciplines, the various experimental approaches' performances, the technical and methodological peculiarities, and the limitations of the bioinformatics data processing discussed in this review, the availability of vast amounts of diverse, multifaceted data also presents a significant challenge in terms of distribution, maintenance, and coherent
versioning. Initiating from the collection of data to how they can be useful for the future research with the use of omics is describing in **Figure 4**.

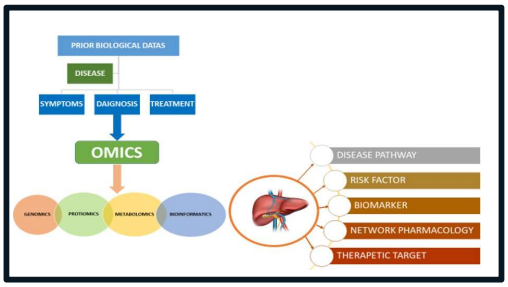

Figure 4. Collection of clinical data and future application omics showing in the above figure.

Future Prospective:

Hepatic liver disease is a very challenging task to detect and study on its pathophysiology at early stages due to its asymptomatic nature at initial stage and irreversible nature at end stage of this disease it becomes more difficult to detect as well as to treatment which is also very cost effective. Now it became a major reason among the deadly disease which starts with very mild symptoms but grows towards its end stage very rapidly. However, the advance ongoing study may overcome these challenges to fight against hepatic liver disease and slow down its mortality rate in near future. Now the pathophysiology process is at its advance era due to integration omics and AI based diagnosis methods which have possibility to reveal interesting biological insights about the disease starting from the disease mechanism stage to disease cure stage including highly efficient diagnostic methods up to discovery to effective drug molecules. In this study, we tried to evaluate how omics studies aid in finding the disease mechanism, development of disease from its genetic level to advance level then it also includes the development of new drugs by clarifying and integrating knowledge about protein ligand interactions with the data about disease and protein found at the different stages of liver disease.

However, the advance technology and AI application having great capacity to collect, store and regenerate data. The rapid spreading omics technologies, coordination in data provision and maintenance are still crucial for organizing valuable data collections and comparable datasets that are helpful for appropriate computational bench works for relevant investigations. There are many opportunities to respond various scientific goals based on different experimental specificities, numbers of result collections, storage of huge amount of information are making it difficult to support the useful integration of these data and information need an appropriate comparative effort. This follows multilevel analyses, proper data organization, annotation and integration in web-accessible resources, data curation, and user-friendly accessibility which are still highly demanded, exposing the field to the new challenge of integrative biological study. In the field of Omics, extensive comparison analyses are preferred by covering cogent multilevel research in the same systems and under similar input, ranging from genomes to metabolomics and taking bioinformatics into accounts.

Here in this review, we put together which provides understanding about the advancement about the identification of protein, RNA, and metabolic profiles of liver disease and significantly improvement of disease at every stages. This study also aids in the development of new drugs by clarifying and integrating knowledge about host-pathogen interactions with the data about proteins found at different stages of liver disease. Omics- based approaches and analysis of omics data is still a very challenging task is still a difficult for researchers. Currently OMICS having significantly developed which provides a lot of data but future approaches to this could leads to provide a clear knowledge of disease mechanism, prospective therapeutic targets, novel drug designing and potential treatment of hepatic liver disease but the moment towards its vaccination, disease mechanism study, diagnosis process, treatment and cure process still need a potential therapeutic approach based on system biology. In near future omics approach can make it possible to develop precision treatment methods for hepatic liver disease with minimum cost effect which leads to an affordable treatment may process for patient in developed as well as developing countries. It is expected that in near future omics study will focus on real issues and challenges like collecting and integrating data and finding data gap in omics field applied on liver disease. It is expected that future of disease related data and its application in omics will focus on current and real issues and challenges such as identification,

characterization, toxicity check and development of new marker and drugs related to hepatic disease. These innovative approaches and assays in omics will inform about testing and prediction, health risk monitoring and assessment, and advance way to utilization of natural resource in the ways that helps to maintain human hepatic health.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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