

BIOCHEMICAL MARKERS FOR EARLY DETECTION OF LIVER DISEASES

SAMAHER RAFIA ALSULAMI¹, HANOUF MOHAMMED ALRAZQAN², THEKRA SAAD ALDALHAM³, HADEEL EID ALANAZI⁴, AMJAD ABDULKAREEM SAAD ALTAL⁵, SARAH SAAD ALSHALAWI⁶, ABDULRAHMAN OUDAH ALSHAMMARI⁷, WALEED SAUD JUDAYA ALANAZI⁸, MOHAMMED SAHW ALMUTAIRI⁹, JEHAD HASSAN ALSHAIKHA¹⁰, RASHED FAISAI RASHED ALHARBI¹¹, MUNIF OLAYAN ALHARBI¹²

¹ MEDICAL TECHNOLOGIST, KING ABDULAZIZ MEDICAL CITY RIYADH,

² OPTOMETRIST, KING ABDULLA SPECIALIZED CHILDREN HOSPITAL

³ ULTRASOUND TECHNOLOGIST, MINISTRY OF NATIONAL GUARD HEALTH AFFAIRS

⁴ NURSE, NATIONAL GUARD HOSPITAL

⁵ MEDICAL SECRETARY, KING ABDULAZIZ MEDICAL CITY

⁶ HEALTH INFORMATION, KING ABDULAZIZ MEDICAL CITY.

⁷ NURSE, EMAIL: alshammariab17@ngha.med.sa

⁸ STAFF NURSE, EMAIL: alanaziwa10@ngha.med.sa

⁹ NURSE, MINISTRY OF NATIONAL GUARD HEALTH AFFAIRS

¹⁰ NURSE, NATIONAL GUARD HOSPITAL, RIYADH

¹¹ NURSE, EMAIL: rasheed67791@gmail.com

¹² NURSE, NATIONAL GUARD HOSPITAL RIYADH

Accepted: 20-03-2025

Published: 12-05-2025

Abstract

Liver diseases represent a significant global health burden, with timely detection being crucial for effective intervention and management. This comprehensive review examines established and emerging biochemical markers that facilitate early identification of hepatic dysfunction. Traditional liver function tests, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), bilirubin, and albumin, remain cornerstone diagnostic tools due to their clinical accessibility and established reference ranges. Recent advances have introduced novel biomarkers such as liver-specific microRNAs and specialized protein markers that offer enhanced sensitivity and specificity. Additionally, technological innovations in detection methodologies, particularly electrochemical biosensors, have revolutionized liver biomarker analysis by enabling rapid, sensitive, and potentially point-of-care testing capabilities. This review synthesizes current knowledge on biochemical markers for liver disease detection, highlighting their clinical utility, limitations, and the emerging technologies that promise to transform early diagnostic approaches. Integration of these biochemical indicators with imaging modalities, particularly ultrasound, provides a comprehensive framework for liver disease assessment that aligns with contemporary clinical guidelines.

1. INTRODUCTION

The liver performs numerous vital functions including metabolism of nutrients, detoxification of harmful substances, synthesis of essential proteins, and production of bile for digestion. Its complex involvement in multiple physiological processes makes it vulnerable to various insults, leading to a spectrum of liver diseases with significant global impact. According to the World Health Organization, liver diseases contribute to approximately two million deaths annually worldwide, making them a major public health concern (Kim et al., 2008).

Early detection of liver dysfunction is essential for initiating timely interventions that can prevent disease progression and improve patient outcomes. Traditional approaches to liver disease diagnosis have relied heavily on biochemical markers that indicate hepatocellular injury or altered liver function. These markers provide valuable insights into liver health through minimally invasive blood tests that are widely accessible in clinical settings (Pratt & Kaplan, 2000).

In recent years, technological advances have significantly enhanced our ability to detect and measure liver biomarkers with greater precision, sensitivity, and specificity. Particularly noteworthy are developments in electrochemical detection methods, which offer advantages of simplicity, cost-effectiveness, low sample volume requirements, and potential for point-of-care applications (Yaman et al., 2024). Such innovations present promising opportunities for earlier and more accurate diagnosis of liver conditions.

This review comprehensively examines both established and emerging biochemical markers for early liver disease detection, with particular attention to their physiological significance, clinical utility, and limitations. Additionally, it explores technological advancements in detection methodologies, highlighting how these innovations may transform diagnostic approaches. By integrating biochemical findings with imaging modalities, particularly ultrasound, clinicians can establish a more comprehensive framework for early liver disease assessment and management.

2. Traditional Liver Biomarkers

2.1 Aminotransferases: ALT and AST

Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are intracellular enzymes that catalyze the transfer of amino groups between amino acids, playing key roles in amino acid metabolism. ALT is predominantly found in hepatocytes, making it relatively liver-specific, whereas AST is present in various tissues including the liver, heart, skeletal muscle, kidneys, brain, and red blood cells (Kim et al., 2008).

When hepatocytes are damaged due to various etiologies such as viral hepatitis, alcohol consumption, drug-induced liver injury, or metabolic disorders, these enzymes leak into the circulation, resulting in elevated serum levels. The degree of elevation generally correlates with the extent of liver damage, although this relationship is not always linear (Giannini et al., 2005).

The ALT/AST ratio, known as the De Ritis ratio, provides valuable diagnostic information. In most acute hepatocellular injuries, ALT exceeds AST. Conversely, an AST/ALT ratio greater than 2:1 is characteristic of alcoholic liver disease, while a ratio exceeding 1 but less than 2 may suggest cirrhosis or fibrosis (Tamber et al., 2023). This pattern reflects the relative concentration of these enzymes in hepatocytes and their different half-lives in circulation.

Despite their widespread clinical use, aminotransferases have limitations as biomarkers. They lack specificity for particular liver diseases, can be elevated due to non-hepatic causes, and may remain within normal ranges despite significant liver pathology, particularly in chronic conditions (Robles-Diaz et al., 2015). Additionally, reference ranges can vary between different populations and laboratory methodologies, complicating interpretation.

2.2 Cholestatic Markers: ALP and GGT

Alkaline phosphatase (ALP) and gamma-glutamyl transferase (GGT) are enzymes predominantly associated with the biliary system and serve as indicators of cholestatic conditions. ALP catalyzes the hydrolysis of phosphate esters and exists in multiple isoforms derived from various tissues including liver, bone, intestine, and placenta. The liver isoform is concentrated in the canalicular and sinusoidal membranes of hepatocytes and in biliary epithelial cells (Pratt & Kaplan, 2000).

Elevated serum ALP levels typically occur in conditions that obstruct bile flow, such as primary biliary cholangitis, primary sclerosing cholangitis, biliary obstruction due to gallstones or tumors, and infiltrative liver diseases. However, elevated ALP can also result from non-hepatic conditions, particularly bone disorders characterized by increased osteoblastic activity (Newsome et al., 2018).

GGT, which catalyzes the transfer of gamma-glutamyl groups from peptides to amino acids or other peptides, is primarily located in the cell membranes of hepatocytes and biliary epithelial cells. It is highly sensitive to biliary obstruction and hepatocellular damage, making it a valuable marker for detecting liver disease (Robles-Diaz et al., 2015). GGT elevation is particularly prominent in alcohol-induced liver disease and can serve as a biomarker for excessive alcohol consumption. It is also elevated in cases of drug-induced liver injury, fatty liver disease, and hepatobiliary malignancies.

The combination of elevated ALP and GGT strongly suggests hepatobiliary disease. When ALP is elevated, concurrent measurement of GGT helps distinguish hepatic from non-hepatic sources of ALP elevation. If both enzymes are increased, the liver is likely the source; if only ALP is elevated, bone or other tissues may be implicated (Stepien et al., 2016).

2.3 Bilirubin and Albumin

Bilirubin and albumin reflect the liver's excretory and synthetic functions, respectively, and provide important information about liver capacity and function. Bilirubin, a breakdown product of hemoglobin, exists in two forms: unconjugated (indirect) and conjugated (direct). In healthy individuals, most circulating bilirubin is unconjugated and bound to albumin. The liver conjugates bilirubin with glucuronic acid, rendering it water-soluble for excretion in bile (Tamber et al., 2023).

Elevated total bilirubin, particularly the conjugated fraction, indicates impaired biliary excretion due to intrahepatic or extrahepatic cholestasis. Unconjugated hyperbilirubinemia can result from increased bilirubin production (e.g., hemolysis), impaired hepatic uptake, or defective conjugation (e.g., Gilbert

syndrome). Visible jaundice typically appears when total bilirubin exceeds 2-3 mg/dL (Pratt & Kaplan, 2000).

Albumin, the most abundant plasma protein, is synthesized exclusively by hepatocytes. With a half-life of approximately 20 days, serum albumin levels reflect the liver's synthetic capacity over an extended period. Reduced albumin concentration can indicate chronic liver dysfunction, although it is not specific to liver disease and can also occur in malnutrition, protein-losing enteropathy, nephrotic syndrome, and chronic inflammatory conditions (Giannini et al., 2005).

The combination of decreased albumin and elevated bilirubin, particularly when accompanied by prolonged prothrombin time (another measure of synthetic function), suggests severe liver impairment and carries prognostic significance. These parameters are incorporated into scoring systems such as the Child-Pugh classification and the Model for End-Stage Liver Disease (MELD), which predict outcomes in cirrhosis and guide transplantation decisions (Newsome et al., 2018).

3. Emerging Biomarkers

3.1 MicroRNAs and Genetic Markers

Recent advances in molecular biology have identified promising new biomarkers that provide earlier and more specific detection of liver injury. MicroRNAs (miRNAs), small non-coding RNA molecules that regulate gene expression, have emerged as potential biomarkers for various liver conditions. Some miRNAs, such as miR-122, are highly liver-specific and are released into the circulation upon hepatocellular damage (Zhang et al., 2019).

Studies have demonstrated that serum miR-122 levels increase rapidly following liver injury, often preceding elevations in traditional aminotransferases, making this marker potentially valuable for early detection. Additionally, specific miRNA profiles may distinguish between different liver pathologies. For instance, distinct miRNA signatures have been identified for alcoholic liver disease, non-alcoholic steatohepatitis (NASH), viral hepatitis, and hepatocellular carcinoma (Tamber et al., 2023).

Genetic markers, including single nucleotide polymorphisms (SNPs) and gene expression patterns, also show promise for predicting liver disease susceptibility and progression. For example, variants in the PNPLA3, TM6SF2, and MBOAT7 genes have been associated with increased risk of developing fatty liver disease and its progression to more severe conditions such as NASH and cirrhosis. These genetic markers may help identify individuals who would benefit from earlier and more intensive monitoring (Tamber et al., 2023).

3.2 Cytokines and Inflammatory Markers

Chronic inflammation plays a crucial role in the pathogenesis and progression of many liver diseases. Consequently, inflammatory cytokines and other inflammatory markers have been investigated as potential biomarkers for liver conditions. Tumor necrosis factor-alpha (TNF- α), interleukin-6 (IL-6), interleukin-10 (IL-10), and transforming growth factor-beta (TGF- β) are among the cytokines implicated in liver disease processes (Ablat et al., 2023).

These inflammatory markers may provide insights into disease activity and progression risk. For instance, elevated levels of proinflammatory cytokines such as TNF- α and IL-6 have been associated with more severe liver inflammation and fibrosis in chronic hepatitis C and non-alcoholic fatty liver disease. Similarly, TGF- β , a potent fibrogenic cytokine, correlates with fibrosis progression (Tamber et al., 2023).

High-sensitivity C-reactive protein (hsCRP) and other acute-phase proteins may also serve as indicators of liver-related inflammation. However, their lack of specificity for liver pathology limits their standalone diagnostic value. When interpreted alongside liver-specific markers, they may enhance diagnostic and prognostic assessments.

3.3 Fibrosis and Cirrhosis Markers

Liver fibrosis, characterized by excessive accumulation of extracellular matrix proteins, represents a common pathway in chronic liver diseases and can progress to cirrhosis. Early detection of fibrosis is crucial for preventing irreversible damage. Several biomarkers and scoring systems have been developed to non-invasively assess liver fibrosis (Xiao et al., 2017).

Direct markers of fibrosis reflect extracellular matrix turnover and include procollagen type III N-terminal peptide (PIIINP), hyaluronic acid, tissue inhibitors of metalloproteinases (TIMPs), and matrix metalloproteinases (MMPs). Elevated levels of these markers indicate active fibrogenesis or reduced matrix degradation (Tamber et al., 2023).

Indirect markers of fibrosis utilize combinations of routine laboratory parameters to predict fibrosis stage. Common scoring systems include:

1. AST to Platelet Ratio Index (APRI): Combines AST levels and platelet count
2. Fibrosis-4 (FIB-4) Index: Incorporates age, AST, ALT, and platelet count
3. NAFLD Fibrosis Score: Based on age, BMI, hyperglycemia, platelet count, albumin, and AST/ALT ratio

These non-invasive assessments have demonstrated reasonable accuracy in distinguishing significant fibrosis and cirrhosis, potentially reducing the need for liver biopsy in selected patients (Newsome et al.,

2018). Enhanced liver fibrosis (ELF) test, which combines three direct fibrosis markers (hyaluronic acid, PIIINP, and TIMP-1), has shown promising results in various chronic liver diseases and is increasingly used in clinical practice.

4. Technological Advances in Biomarker Detection

4.1 Electrochemical Biosensors for Liver Biomarkers

Recent technological innovations have significantly enhanced the detection and measurement of liver biomarkers, with electrochemical biosensors emerging as a particularly promising approach. According to Yaman et al. (2024), electrochemical detection methods offer numerous advantages including simplicity, cost-effectiveness, low sample volume requirements, label-free detection, high sensitivity, fast response times, and potential for miniaturization and portability.

Electrochemical biosensors typically consist of a biological recognition element (such as antibodies, enzymes, or nucleic acids) coupled with an electrochemical transducer. When the target biomarker interacts with the recognition element, the resulting electrochemical signal is measured and correlated with biomarker concentration. Various electrochemical techniques have been employed, including amperometry, voltammetry, impedance spectroscopy, and potentiometry (Yaman et al., 2024).

For liver biomarkers, numerous electrochemical biosensors have been developed with impressive analytical performance. For instance, ALT sensors based on modified electrodes have achieved detection limits in the nanomolar range, enabling early detection of hepatocellular damage. Similarly, electrochemical immunosensors for albumin can detect clinically relevant concentrations with high specificity (Yaman et al., 2024).

The potential for multiplexing—simultaneous detection of multiple biomarkers—represents a significant advantage of electrochemical platforms. This capability allows comprehensive assessment of liver function through a single test, enhancing diagnostic efficiency. Additionally, the miniaturization potential of electrochemical devices supports the development of point-of-care testing systems, which could revolutionize liver disease screening and monitoring, particularly in resource-limited settings.

4.2 Integration with Digital Health Technologies

The integration of biomarker detection with digital health technologies presents exciting possibilities for liver disease management. Smartphone-based applications coupled with portable biosensors can enable real-time monitoring of liver parameters, potentially allowing patients to track their condition outside traditional healthcare settings. These systems can incorporate data analysis algorithms to provide immediate interpretation and alert users to significant changes requiring medical attention (Yaman et al., 2024).

Cloud-based platforms can facilitate secure storage and sharing of biomarker data among healthcare providers, supporting coordinated care and longitudinal monitoring. Furthermore, artificial intelligence and machine learning approaches can analyze complex biomarker patterns to identify subtle changes indicative of early disease or predict disease progression with greater accuracy than conventional approaches.

Telemedicine applications integrated with remote biomarker monitoring may be particularly valuable for patients with chronic liver conditions, reducing the need for frequent clinic visits while maintaining close supervision. This approach could improve patient compliance, enhance quality of life, and potentially reduce healthcare costs associated with liver disease management.

5. Clinical Applications and Interpretation

5.1 Pattern Recognition in Liver Disease

Interpretation of liver biomarkers requires recognition of characteristic patterns associated with different pathologies. Rather than isolated abnormalities, the constellation and trajectory of multiple biomarkers provide more reliable diagnostic information. Common patterns include:

1. **Hepatocellular Pattern:** Predominant elevation of aminotransferases (ALT and AST), with normal or mildly elevated ALP. This pattern suggests primary liver cell damage as seen in viral hepatitis, drug-induced liver injury, and early stages of alcoholic or non-alcoholic fatty liver disease.
2. **Cholestatic Pattern:** Marked elevation of ALP and GGT with normal or mildly elevated aminotransferases. This pattern indicates bile flow obstruction, as observed in primary biliary cholangitis, primary sclerosing cholangitis, biliary obstruction due to gallstones or tumors, and drug-induced cholestasis.
3. **Mixed Pattern:** Significant elevations in both aminotransferases and cholestatic markers, suggesting conditions affecting both hepatocytes and bile ducts. This pattern may occur in alcoholic hepatitis, some drug reactions, and infiltrative disorders such as amyloidosis or sarcoidosis.
4. **Minimal Change Pattern:** Mild elevations in liver enzymes without a clear predominant pattern. This frequently occurs in non-alcoholic fatty liver disease, early cirrhosis, and some metabolic disorders (Giannini et al., 2005).

The magnitude and duration of biomarker abnormalities also provide valuable clinical insights. Marked elevations of aminotransferases (>1000 IU/L) suggest acute and severe liver injury, while persistent mild-

to-moderate elevations may indicate chronic liver diseases. Fluctuating patterns may reflect episodic injury or variable disease activity (Newsome et al., 2018).

5.2 Integration with Imaging Modalities

The integration of biochemical markers with imaging techniques, particularly ultrasound, enhances diagnostic accuracy in liver disease assessment. While biochemical markers provide functional information, imaging studies offer complementary structural insights, allowing for a more comprehensive evaluation (Barr et al., 2015).

Ultrasound is widely available, non-invasive, and radiation-free, making it an ideal first-line imaging modality for liver assessment. Conventional ultrasound can detect hepatic steatosis, cirrhosis, focal lesions, and biliary abnormalities, while Doppler techniques evaluate vascular flow. Advanced applications such as ultrasound elastography (FibroScan®) measure liver stiffness, which correlates with fibrosis stage (Xiao et al., 2017).

The correlation between biochemical and ultrasound findings enhances diagnostic precision. For example, elevated aminotransferases suggesting hepatocellular injury may be accompanied by ultrasound evidence of steatosis, supporting a diagnosis of non-alcoholic fatty liver disease. Similarly, cholestatic biomarker patterns may correspond with dilated bile ducts on imaging, confirming biliary obstruction.

Current clinical guidelines, including those from the European Association for the Study of the Liver (EASL), recommend combined assessment using both biochemical markers and imaging studies for comprehensive evaluation of liver diseases. This integrated approach improves diagnostic accuracy, reduces the need for invasive procedures such as liver biopsy, and guides appropriate management strategies (EASL, 2021).

5.3 Monitoring Disease Progression and Treatment Response

Beyond initial diagnosis, biochemical markers play a crucial role in monitoring disease progression and evaluating treatment response. Serial measurements provide dynamic information about disease activity and liver function over time. Improving trends in biomarkers typically indicate therapeutic efficacy, while worsening patterns may suggest disease progression or treatment failure (Newsome et al., 2018).

In viral hepatitis, normalization of aminotransferases and viral clearance from serum are important indicators of treatment success. For autoimmune hepatitis, declining aminotransferases and immunoglobulins reflect response to immunosuppressive therapy. In primary biliary cholangitis, ALP reduction correlates with improved outcomes on ursodeoxycholic acid treatment.

Biomarker trajectories also provide prognostic information. For instance, persistent elevation of liver enzymes in non-alcoholic fatty liver disease predicts higher risk of progression to fibrosis and cirrhosis. Similarly, declining albumin levels and rising bilirubin in chronic liver disease suggest deteriorating hepatic function and potential development of complications (Pratt & Kaplan, 2000).

The emerging concept of "biochemical response" as a surrogate endpoint has gained traction in clinical trials and practice. Normalization or significant improvement in relevant biomarkers often precedes and predicts clinical benefits, allowing for earlier assessment of therapeutic interventions without waiting for long-term clinical outcomes.

6. Limitations and Future Directions

6.1 Current Limitations of Liver Biomarkers

Despite their clinical utility, current liver biomarkers have several limitations that affect their diagnostic accuracy and interpretation. Traditional markers such as aminotransferases lack disease specificity and may be influenced by various non-hepatic factors including medication use, exercise, muscle diseases, and even normal daily variations. Furthermore, these enzymes may remain within normal ranges despite significant underlying liver pathology, particularly in chronic conditions where hepatocyte mass is reduced (Robles-Diaz et al., 2015).

Population-based factors also complicate biomarker interpretation. Reference ranges vary between different demographic groups, and comorbidities such as obesity, diabetes, and metabolic syndrome can independently affect liver enzyme levels. Additionally, genetic polymorphisms can influence baseline biomarker levels and their response to liver injury (Kim et al., 2008).

Technical considerations further impact biomarker reliability. Laboratory methodologies and platforms may produce different results for the same specimen, and pre-analytical variables such as sample handling, storage conditions, and timing of collection can affect biomarker measurements. Standardization efforts continue but have not fully resolved these issues (Tamber et al., 2023).

For emerging biomarkers such as miRNAs and specialized protein markers, challenges include limited clinical validation, lack of standardized assays, higher costs, and restricted availability compared to conventional tests. These factors currently constrain their routine clinical application despite promising research findings.

6.2 Future Directions and Emerging Technologies

The future of liver biomarker development and application appears promising, with several emerging trends likely to enhance diagnostic capabilities. Multi-biomarker panels that incorporate both traditional

and novel markers may overcome the limitations of individual tests, providing more comprehensive liver assessments with improved sensitivity and specificity. Advanced algorithms and machine learning approaches can analyze complex biomarker patterns to identify subtle signatures of specific liver conditions or predict disease trajectories with greater accuracy (Tamber et al., 2023).

Point-of-care testing represents another important direction, particularly with the advancement of electrochemical biosensors and other miniaturized detection platforms. These technologies could enable rapid, bedside assessment of liver function, facilitating earlier intervention and more frequent monitoring, especially in resource-limited settings (Yaman et al., 2024).

Integration of biomarker data with other clinical information through electronic health records and digital health platforms may further enhance diagnostic precision. By considering patient-specific factors such as demographics, comorbidities, medication use, and previous biomarker trends, personalized reference ranges and interpretation frameworks could be developed, improving the clinical relevance of biomarker results.

Liquid biopsy approaches, which analyze circulating hepatocyte-derived materials such as cell-free DNA, extracellular vesicles, and protein signatures, show promise for non-invasive liver assessment. These techniques may provide more direct insights into hepatic processes than conventional blood tests, potentially capturing early molecular changes associated with liver damage or disease progression (Zhang et al., 2019).

As research continues to elucidate the complex pathophysiology of liver diseases, novel biomarkers targeting specific mechanistic pathways—such as markers of oxidative stress, mitochondrial dysfunction, apoptosis, or immune activation—may emerge. These mechanistically-informed biomarkers could offer improved disease specificity and therapeutic targeting.

7. CONCLUSION

Biochemical markers play an indispensable role in the early detection, diagnosis, and management of liver diseases. Traditional liver function tests, including aminotransferases, cholestatic enzymes, bilirubin, and albumin, remain cornerstone assessments due to their wide availability, established reference ranges, and extensive clinical experience. When interpreted in the context of characteristic patterns and trends, these markers provide valuable insights into the nature, severity, and progression of hepatic dysfunction.

Recent advances in biomarker discovery and detection technologies have expanded the diagnostic armamentarium for liver diseases. Emerging markers such as liver-specific microRNAs, fibrosis indicators, and specialized protein profiles offer enhanced sensitivity and specificity for early detection and disease characterization. Particularly promising are developments in electrochemical biosensor technologies, which combine high analytical performance with potential for point-of-care application, potentially transforming liver disease screening and monitoring.

The integration of biochemical markers with imaging modalities, particularly ultrasound, provides a comprehensive framework for liver assessment that aligns with current clinical guidelines. This multimodal approach enhances diagnostic accuracy while reducing reliance on invasive procedures such as liver biopsy. As technological innovations continue to improve biomarker detection and interpretation, earlier identification of liver diseases will become increasingly feasible, facilitating timely interventions that may prevent disease progression and improve patient outcomes.

Despite current limitations, ongoing research and technological developments suggest a promising future for liver biomarkers. Through continued refinement of detection methodologies, development of novel markers, and integration with digital health technologies, biochemical assessments will remain fundamental tools in the clinical management of liver diseases, supporting the global effort to reduce liver-related morbidity and mortality.

REFERENCES

1. Ablat, N., Ablimit, M., Abudoukadier, A., Kadeer, B., Maihemuti, A., Bakewaiyi, A., Tuerxun, A., & Aihemaiti, A. (2023). Liver protection and hemostatic effects of medicinal plant *Arnebia euchroma* (Royle) I.M.Johnst extract in a rat model. *Journal of Ethnopharmacology*, 300, 115739. <https://doi.org/10.1016/j.jep.2022.115739>
2. Barr, R. G., Ferraioli, G., Palmeri, M. L., Goodman, Z. D., Garcia-Tsao, G., Rubin, J., Garra, B., Myers, R. P., Wilson, S. R., Rubens, D., & Levine, D. (2015). Elastography assessment of liver fibrosis: Society of Radiologists in Ultrasound Consensus Statement. *Radiology*, 276(3), 845–861. <https://doi.org/10.1148/radiol.2015150619>
3. European Association for the Study of the Liver (EASL). (2021). EASL Clinical Practice Guidelines: Non-invasive tests for evaluation of liver disease severity and prognosis. *Journal of Hepatology*, 75(3), 659–689. <https://doi.org/10.1016/j.jhep.2021.05.025>

4. Giannini, E. G., Testa, R., & Savarino, V. (2005). Liver enzyme alteration: a guide for clinicians. *Canadian Medical Association Journal*, 172(3), 367–379. <https://doi.org/10.1503/cmaj.1040752>
5. Kim, W. R., Flamm, S. L., Di Bisceglie, A. M., & Bodenheimer, H. C. (2008). Serum activity of alanine aminotransferase (ALT) as an indicator of health and disease. *Hepatology*, 47(4), 1363–1370. <https://doi.org/10.1002/hep.22109>
6. Newsome, P. N., Cramb, R., Davison, S. M., Dillon, J. F., Foulerton, M., Godfrey, E. M., Hall, R., Harrower, U., Hudson, M., Langford, A., Mackie, A., Mitchell-Thain, R., Sennett, K., Sheron, N. C., Verne, J., Walmsley, M., & Yeoman, A. (2018). Guidelines on the management of abnormal liver blood tests. *Gut*, 67(1), 6–19. <https://doi.org/10.1136/gutjnl-2017-314924>
7. Pratt, D. S., & Kaplan, M. M. (2000). Evaluation of abnormal liver-enzyme results in asymptomatic patients. *New England Journal of Medicine*, 342(17), 1266–1271. <https://doi.org/10.1056/NEJM200004273421707>
8. Robles-Diaz, M., Garcia-Cortes, M., Medina-Caliz, I., Gonzalez-Jimenez, A., Gonzalez-Grande, R., Navarro, J. M., Castiella, A., Zapata, E. M., Romero-Gomez, M., Blanco, S., Soriano, G., Hidalgo, R., Ortega-Torres, M., Clavijo, E., Bermudez-Ruiz, P. M., Lucena, M. I., & Andrade, R. J. (2015). The value of serum aspartate aminotransferase and gamma-glutamyl transpeptidase as biomarkers in hepatotoxicity. *Liver International*, 35(11), 2474–2482. <https://doi.org/10.1111/liv.12834>
9. Stepien, M., Fedirko, V., Duarte-Salles, T., Ferrari, P., Freisling, H., Trepo, E., Trichopoulou, A., Bamia, C., Weiderpass, E., Olsen, A., Tjønneland, A., Overvad, K., Boutron-Ruault, M. C., Fagherazzi, G., Racine, A., Kühn, T., Kaaks, R., Aleksandrova, K., Boeing, H., ... Jenab, M. (2016). Prospective association of liver function biomarkers with development of hepatobiliary cancers. *Cancer Epidemiology*, 40, 179–187. <https://doi.org/10.1016/j.canep.2016.01.002>
10. Tamber, S. S., Bansal, P., Sharma, S., Singh, R. B., & Sharma, R. (2023). Biomarkers of liver diseases. *Molecular Biology Reports*, 50(9), 7815–7823. <https://doi.org/10.1007/s11033-023-08338-z>
11. Xiao, G., Zhu, S., Xiao, X., Yan, L., Yang, J., & Wu, G. (2017). Comparison of laboratory tests, ultrasound, or magnetic resonance elastography to detect fibrosis in patients with nonalcoholic fatty liver disease: A meta-analysis. *Hepatology*, 66(5), 1486–1501. <https://doi.org/10.1002/hep.29302>
12. Yaman, D., Jimenez, M., Ferreira Gonzalez, S., & Corrigan, D. (2024). Current trends in electrochemical approaches for liver biomarker detection: a mini-review. *The Analyst*, 149(21), 5156–5164. <https://doi.org/10.1039/d4an01109k>
13. Zhang, Y., Jia, Y., Zheng, R., Guo, Y., & Wang, Y. (2019). Diagnostic value of serum microRNA-122 for hepatocellular carcinoma: a meta-analysis. *Clinical Research in Hepatology and Gastroenterology*, 43(6), 688–695. <https://doi.org/10.1016/j.clinre.2018.12.008>