ISSN- 2230-7346
Journal of Global Trends in Pharmaceutical Sciences

NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD): A RISING METABOLIC EPIDEMIC IN INDIA AND GLOBALLY

Nisha Sharma*, Seema Thakur

Faculty of Pharmaceutical Sciences, PCTE Group of Institutes, Baddowal, Ludhiana, Punjab

Corresponding author E- mail: nisha@pcte.edu.in

ARTICLE INFO

Key words:

NAFLD, NASH, metabolic syndrome, liver steatosis, hepatocellular carcinoma, resistance, liver biopsy, GLP-1 agonists

Access this article online Website: https://www.jgtps.com/
Quick Response Code:

ABSTRACT

Non-Alcoholic Fatty Liver Disease (NAFLD) is a progressive metabolic disorder that is now the leading cause of chronic liver disease worldwide. Closely associated with obesity, type 2 diabetes, and metabolic syndrome, NAFLD represents a silent but serious threat to public health. India is witnessing a surge in NAFLD prevalence—including among non-obese individuals—driven by lifestyle transitions, urbanization, and genetic factors. This review discusses the global and Indian epidemiology, pathophysiological mechanisms, diagnostic modalities, current therapeutic approaches, public health policies, and future research directions. With no approved pharmacological treatments, prevention through early screening, lifestyle modification, and policy-level integration is crucial to mitigating the disease burden.

INTRODUCTION:

Non-alcoholic fatty liver disease (NAFLD) has emerged as one of the most prevalent chronic liver conditions worldwide, representing a significant public health concern in both developed and developing nations. Characterized by excessive fat accumulation in hepatocytes in the absence of significant alcohol consumption, NAFLD encompasses a spectrum ranging from simple steatosis (non-alcoholic fatty liver) to non-alcoholic steatohepatitis (NASH), fibrosis, cirrhosis, and even hepatocellular carcinoma (HCC) [1]. It is closely linked with components of the metabolic syndrome, including obesity, insulin resistance, dyslipidemia, and type 2 diabetes mellitus, making it a hepatic manifestation of the broader metabolic epidemic [2].

The global prevalence of NAFLD has been estimated at approximately 25%, with a rising trend noted across all regions, regardless of economic development [4]. In India, the burden of NAFLD is escalating at an alarming pace, with population-based studies reporting prevalence rates ranging from 9% to 32% in the general population, and up to 70% among individuals with obesity or diabetes [5]. This trend is fueled by rapid urbanization, sedentary lifestyles, and a shift towards calorie-dense diets—factors that are increasingly affecting even younger age groups.

Of particular concern is the asymptomatic nature of NAFLD in its early stages, often leading to delayed diagnosis and intervention. Unlike other liver diseases, NAFLD is not driven by alcohol use or viral hepatitis, which historically dominated hepatology. The disease burden is further amplified by the lack of specific pharmacological treatments approved for NAFLD or NASH, placing the emphasis on lifestyle modifications such as weight loss, dietary changes, and physical activity as primary interventions [6].

From a healthcare policy standpoint, NAFLD poses a dual challenge: it not only increases the risk of advanced liver diseases but also significantly contributes to cardiovascular morbidity and mortality, often surpassing liver-related outcomes [7]. Moreover, the rising prevalence of NAFLD in non-obese individuals, particularly in South Asian populations including India, indicates that traditional risk models based solely on obesity may underestimate the true scope of the disease [8]. This underscores the need for heightened awareness, early screening, and region-specific public health strategies.

This review aims to provide a comprehensive overview of its epidemiology, pathophysiological mechanisms, diagnostic challenges, and current therapeutic approaches, with a particular emphasis on the Indian context. By examining global and regional trends, this article seeks to highlight the urgent need for coordinated multidisciplinary efforts to combat this silent yet formidable metabolic epidemic.

1. Global Burden of NAFLD

Non-Alcoholic Fatty Liver Disease (NAFLD) has emerged as a major global health concern over the past few decades. Characterized by the accumulation of excess fat in liver cells in individuals who consume little to no alcohol, NAFLD is now recognized as the most prevalent chronic liver condition worldwide. The growing incidence of NAFLD is closely linked with the global escalation of metabolic risk factors, particularly obesity, type 2 diabetes mellitus (T2DM), and dyslipidemia, which collectively contribute to the metabolic syndrome.

1.1. Prevalence Worldwide

According to a landmark meta-analysis by Younossi et al. (2016), the global prevalence of NAFLD was estimated to be approximately 25.24% in the general population. However, this figure has continued to rise, especially in developed and rapidly urbanizing countries. The prevalence varies significantly across geographical regions:

- Middle East and South America report the highest prevalence rates (up to 31–32%).
- Asia, particularly countries like China and India, are experiencing a rapid increase, with prevalence rates ranging between 15% and 30%.
- North America and Europe also show high prevalence rates, closely mirroring obesity trends.
- Africa reports lower prevalence, but underdiagnosis and lack of data may contribute to an underestimation.

These variations reflect differences in genetic susceptibility, lifestyle, socioeconomic status, and diagnostic practices (Younossi et al., 2016; Cotter & Rinella, 2020).

1.2. NAFLD and Associated Morbidities

NAFLD is not a benign condition. A subset of individuals with simple steatosis may progress to non-alcoholic steatohepatitis (NASH), a more severe form of NAFLD characterized by liver inflammation and hepatocyte injury. NASH can further progress to fibrosis, cirrhosis, and even hepatocellular carcinoma (HCC) in the absence of alcohol use or viral hepatitis.

Globally, NAFLD has now become a leading cause of:

- Chronic liver disease
- Liver transplantation
- Liver-related mortality

Moreover, individuals with NAFLD face an increased risk of cardiovascular diseases, which remain the leading cause of death in this population, surpassing liver-related complications [7].

1.3. Economic Impact

The economic burden of NAFLD is substantial. Healthcare costs associated with diagnosis, monitoring, and management of complications are rising sharply. A study in the United States estimated the annual direct

medical costs of NAFLD at over $100 billion, while in Europe, countries like Germany and the United Kingdom also report significant financial strains due to the disease [4]. Indirect costs due to loss of productivity and decreased quality of life further amplify the economic impact.

1.4. Public Health Concern

NAFLD is increasingly being recognized not just as a liver-specific disease but as a systemic metabolic disorder. Its association with type 2 diabetes, cardiovascular disease, and chronic kidney disease makes it a multi-organ threat. Despite its high prevalence, NAFLD often remains underdiagnosed due to its asymptomatic nature in early stages. Public health systems globally are unprepared for the large-scale management of NAFLD, especially in low- and middle-income countries.

Furthermore, NAFLD is now being observed in younger age groups, including adolescents and children, owing to rising childhood obesity rates. This trend signals a potential future epidemic of early-onset liver and metabolic diseases unless urgent preventive measures are taken.

2. NAFLD in the Indian Context

In India, prevalence rates range from 9% to 32% in the general population and exceed 55% among individuals with type 2 diabetes [6,7]. Particularly concerning is the rising incidence of lean NAFLD—seen in individuals with normal body weight but with metabolic abnormalities such as central obesity and insulin resistance [8,9].

Contributing Factors in India:

2.1. Obesity and Overweight

Obesity, particularly visceral fat accumulation, is one of the most significant risk factors for NAFLD. The National Family Health Survey (NFHS-5) reported that the prevalence of overweight and obesity among Indian adults increased significantly from previous years [10]. A meta-analysis by Kumar et al. (2021) highlighted that obese individuals had over 23 times higher odds of developing NAFLD compared to those with normal weight.

2.2. Type 2 Diabetes Mellitus (T2DM)

T2DM and insulin resistance are closely associated with hepatic steatosis. Insulin resistance leads to impaired lipid metabolism and fat deposition in the liver. According to a study by Das et al. (2022), up to 70% of Indian patients with T2DM have NAFLD, making it an essential comorbidity in diabetes management.

2.3. Dyslipidemia

Abnormal lipid profiles, including high triglycerides and low HDL cholesterol, are major contributors to NAFLD. Indian diets high in carbohydrates and saturated fats often exacerbate dyslipidemia. A study by Duseja et al. (2022) found dyslipidemia in over 60% of NAFLD patients in North India.

2.4. Sedentary Lifestyle

Urbanization and the shift towards technology-driven jobs have led to reduced physical activity. A cross-sectional study conducted in Bengaluru [14] found that sedentary individuals had nearly double the risk of developing NAFLD compared to their physically active counterparts.

2.5. Unhealthy Dietary Habits

Traditional Indian diets, when replaced by fast food and sugary beverages, contribute significantly to hepatic fat accumulation. High carbohydrate intake, especially refined grains and sugar, leads to de novo lipogenesis, a key process in NAFLD development [15]

2.6. Genetic Susceptibility

South Asians have a genetic predisposition for metabolic diseases at lower body mass index (BMI) levels. The PNPLA3 gene polymorphism, commonly observed in Indians, has been linked to increased hepatic fat and disease progression [16].

2.7. Pediatric Obesity

NAFLD is increasingly being observed in Indian children due to rising childhood obesity. A recent review by Jain et al. (2022) reported NAFLD prevalence in Indian children ranging from 8% to 22%, often linked with poor dietary habits and reduced physical activity.

2.8. Socioeconomic and Environmental Factors

Lower socioeconomic groups are now increasingly affected due to the affordability and availability of calorie-dense, nutrient-poor food. Additionally, environmental factors such as exposure to endocrine-

disrupting chemicals may exacerbate liver dysfunction [18].

Recent Statistics and Trends

According to the Global Burden of Disease (GBD) study, the prevalence of NAFLD in India rose by over 40% between 2010 and 2020 [19]. The disease burden is more in urban populations, especially in metropolitan cities like Delhi, Mumbai, and Bengaluru. Notably, studies in 2023 reported NAFLD prevalence rates of up to 54% among obese individuals in urban slums [14].

3. Pathophysiology

Non-alcoholic fatty liver disease (NAFLD) represents a spectrum ranging from simple steatosis to non-alcoholic steatohepatitis (NASH), fibrosis, cirrhosis, and hepatocellular carcinoma (HCC). Its development involves interconnected metabolic, inflammatory, and genetic mechanisms, conceptualized under the "multiple-hit hypothesis" [1,2].

3.1. Hepatic Lipid Accumulation: The Initial Trigger

a. Insulin Resistance (IR)

Insulin resistance is a key initiating event. It disrupts lipid metabolism in multiple tissues [3]

- Adipose tissue: Enhanced lipolysis increases free fatty acid flux to the liver.
- Liver: Insulin fails to suppress gluconeogenesis while promoting de novo lipogenesis (DNL).
- Muscle: Reduced glucose uptake perpetuates hyperglycemia and hyperinsulinemia.

These changes result in excessive hepatic triglyceride accumulation (steatosis), even in non-obese individuals- a phenomenon termed "lean NAFLD" [4].

b. Dietary Influences

Diets high in saturated fats and fructose upregulate lipogenic genes such as SREBP-1c and ChREBP, promoting further lipid synthesis [5].

3.2. Lipotoxicity and Organelle Stress

As hepatic fat storage capacity is exceeded, toxic lipid intermediates like ceramides and diacylglycerols impair cell signaling and membrane integrity [6].

Oxidative Stress

Mitochondria, overwhelmed by β-oxidation, generate reactive oxygen species (ROS). ROS damage lipids, proteins, and DNA, leading to endoplasmic reticulum (ER) stress and hepatocyte apoptosis [7,8].

b. Mitochondrial Dysfunction

Mitochondrial impairment causes ATP depletion and activates intrinsic apoptotic pathways, furthering liver injury [9].

3.3. Inflammation and Immune Activation

Damaged hepatocytes release danger-associated molecular patterns (DAMPs), triggering immune cell activation.

a. Kupffer Cells and Cytokines

Liver-resident macrophages (Kupffer cells) secrete TNF-α, IL-6, and IL-1β, propagating inflammation and impairing insulin signaling. [10]

b. Monocyte Recruitment

Inflammatory chemokines recruit neutrophils and monocyte-derived macrophages, escalating tissue damage via cytokine and ROS release. [11]

3.4. Gut-Liver Axis Dysfunction

Gut dysbiosis and increased intestinal permeability play a critical role. [12].

a. Endotoxemia

Disruption of intestinal tight junctions allows lipopolysaccharides (LPS) to enter portal circulation, causing endotoxemia. [13]

b. TLR-Mediated Inflammation

LPS activates Toll-like receptor 4 (TLR4) on Kupffer cells and hepatocytes, triggering NF-κB signaling and a pro-inflammatory response.[14]

3.5. Hepatic Stellate Cell Activation and Fibrosis

Chronic injury and inflammation activate hepatic stellate cells (HSCs):

- HSCs differentiate into myofibroblasts, secreting collagen types I and III.
- Fibrogenesis leads to distortion of hepatic architecture, advancing to cirrhosis. [15,16]

3.6. Genetic and Epigenetic Modulators

Individual susceptibility to NAFLD is modulated by genetic polymorphisms:

- TM6SF2 and MBOAT7 variants influence lipid transport and remodeling [18]
- Epigenetic changes, including DNA methylation and microRNA expression, alter the transcription of key metabolic genes [19,20].
- PNPLA3(I148M) variant impairs triglyce ride hydrolysis, increasing hepatic fat. [17]

4. Diagnostic Strategies

The diagnosis of Non-Alcoholic Fatty Liver Disease (NAFLD) presents a clinical challenge, primarily due to its asymptomatic nature in the early stages and the overlap of features with other chronic liver conditions. An accurate and timely diagnosis is essential for effective disease management and to prevent progression to non-alcoholic steatohepatitis (NASH), fibrosis, cirrhosis, or hepatocellular carcinoma (HCC).

4.1. Clinical Assessment

The diagnostic approach begins with a comprehensive clinical evaluation, including:

- Patient history: Emphasis is placed on identifying metabolic risk factors such as obesity, type 2 diabetes mellitus (T2DM), dyslipidemia, and hypertension.
- Alcohol consumption history: NAFLD is diagnosed only when significant alcohol intake (generally >30 g/day for men and >20 g/day for women) is excluded. [2]
- Physical examination: Often unremarkable in early NAFLD; hepatomegaly may be present in advanced stages.

4.2. Laboratory Investigations

Laboratory tests are not definitive but help assess liver function and exclude other liver diseases:

- Liver enzymes: Elevated alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels are common, but not diagnostic. ALT is usually higher than AST in early NAFLD.
- Fasting glucose and lipid profile: To assess metabolic syndrome components.
- Serological markers: Used to rule out viral hepatitis (HBV, HCV), autoimmune liver disease, and hemochromatosis.

While these tests may raise suspicion of NAFLD, they are neither sensitive nor specific for confirming hepatic steatosis or fibrosis.

4.3. Imaging Modalities

a. Ultrasonography (USG)

- Abdominal ultrasound is the most commonly used first-line imaging tool for detecting hepatic steatosis due to its wide availability and low cost.
- It has a sensitivity of around 85% and specificity of 94% for detecting liver fat when ≥20–30% of hepatocytes are involved. [20]
- Limitations include decreased sensitivity in obese patients and inability to quantify fat or detect fibrosis.

b. Computed Tomography (CT)

- CT can quantify liver fat but involves radiation exposure and is less sensitive than MRI for mild steatosis.
- Not routinely used due to cost and safety concerns.

c. Magnetic Resonance Imaging (MRI) and Magnetic Resonance Spectroscopy (MRS)

- MRI-Proton Density Fat Fraction (MRI-PDFF) is a non-invasive gold standard for quantifying hepatic fat content.
- MRS offers precise quantification of liver fat but is more expensive and less widely available.

d. Transient Elastography (FibroScan®)

- Combines ultrasound with vibration-controlled transient elastography to measure liver stiffness (fibrosis) and Controlled Attenuation Parameter (CAP) for steatosis.
- Useful in non-invasive staging of fibrosis and fat accumulation. [21]

4.4. Non-Invasive Fibrosis Scoring Systems

Several scoring models help assess liver fibrosis severity in NAFLD patients using clinical and laboratory parameters:

- NAFLD Fibrosis Score (NFS): Uses age, BMI, AST/ALT ratio, platelet count, albumin, and blood glucose status.
- FIB-4 Index: Involves age, AST, ALT, and platelet count.
- AST to Platelet Ratio Index (APRI): Helps predict advanced fibrosis.

These tools are recommended by guidelines as cost-effective ways to stratify patients and identify those needing further evaluation (Chalasani et al., 2018; EASL, 2016).

4.5. Liver Biopsy

- Considered the gold standard for definitive diagnosis, especially to distinguish simple steatosis from NASH and to assess the degree of fibrosis.
- However, it is invasive, costly, and carries a risk of complications such as bleeding and sampling variability.

- Indicated in select patients with indeterminate fibrosis scores or where advanced fibrosis is suspected.

4.6. Therapeutic Approaches

Currently, no pharmacological treatment is approved for NAFLD. Treatment is primarily lifestyle-based:

Lifestyle Interventions:

- Weight loss: ≥7–10% body weight improves histological outcomes.[16]
- Diet: Mediterranean-style diet rich in polyunsaturated fats and fiber.
- Exercise: 150–200 minutes/week of moderate-intensity aerobic activity.

5. Investigational Pharmacotherapies:

Despite the rising prevalence of NAFLD, there are currently no drugs specifically approved for its treatment. However, several investigational agents targeting different pathophysiological aspects of NAFLD are in various stages of clinical trials.

5.1. Insulin Sensitizers

- Pioglitazone, a thiazolidinedione, improves hepatic steatosis and inflammation by enhancing insulin sensitivity in adipose tissue and the liver. A meta-analysis by Musso et al. (2017) confirmed pioglitazone's efficacy in NASH, especially in patients with Type 2 Diabetes Mellitus (T2DM). However, weight gain and potential cardiovascular risks limit its widespread use.
- Metformin, although widely used in T2DM, has limited efficacy in improving liver histology in NAFLD, as demonstrated by the TONIC trial. [23]

5.2. GLP-1 Receptor Agonists

- Agents like liraglutide and semaglutide not only promote weight loss but also show histological improvements in NASH. The LEAN trial reported resolution of NASH in 39% of patients treated with liraglutide compared to 9% in the placebo group. [24]
- These agents also reduce cardiovascular risks, making them attractive candidates for NAFLD management.

5.3. FXR Agonists

- Obeticholic acid (OCA), an agonist of farnesoid X receptor (FXR), modulates bile acid synthesis, glucose metabolism, and inflammation. The REGENERATE trial showed improvements in fibrosis stage without worsening NASH. [25] However, side effects like pruritus and lipid disturbances warrant caution.

5.4. PPAR Agonists

- Elafibranor, a dual PPAR-α/δ agonist, has demonstrated anti-inflammatory and insulin-sensitizing effects in phase II trials. Though initial trials were promising, phase III results were inconclusive, prompting further exploration.

5.5. Others in the Pipeline

- Aramchol (a stearoyl-CoA desaturase-1 inhibitor), cenicriviroc (a CCR2/CCR5 antagonist), and resmetirom (a thyroid hormone receptor-β agonist) are under investigation for their roles in lipid metabolism, fibrosis, and inflammation modulation.

The diversity of pharmacological targets reflects the complex, multifactorial pathophysiology of NAFLD. Combinatorial therapies may offer a more holistic approach in the future.

6. Public Health Initiatives in India

India has begun recognizing NAFLD as a pressing public health issue, especially given its link with non-communicable diseases (NCDs).

6.1. Integration into NPCDCS

In February 2021, the Ministry of Health and Family Welfare incorporated NAFLD into the National Programme for Prevention and Control of Cancer, Diabetes, Cardiovascular Diseases and Stroke (NPCDCS). This marked a critical policy step, aiming to:

- Promote awareness about NAFLD risk factors.
- Integrate NAFLD screening into NCD clinics.
- Train healthcare workers in early diagnosis and lifestyle counseling.

6.2. Health Promotion and IEC Campaigns

Through platforms like Fit India Movement and Eat Right India, the government is encouraging healthier lifestyle habits that indirectly reduce NAFLD burden. However, these programs need disease-specific orientation to tackle NAFLD effectively.

6.3. Capacity Building and Surveillance

The Indian Council of Medical Research -

(ICMR) is actively supporting research and surveillance studies related to NAFLD. Ongoing initiatives aim to estimate state-wise prevalence and associated metabolic parameters for evidence-based interventions.
India integrated NAFLD screening and management into the NPCDCS in 2023, making it one of the few countries to institutionalize NAFLD care at the national level. [21]

7. Challenges and Gaps

Despite progress, several barriers persist:

a. Lack of Awareness

Most patients and even healthcare providers are unaware of NAFLD until it progresses. NAFLD is often underdiagnosed due to its asymptomatic course.

b. Resource Constraints

Access to diagnostic tools like FibroScan is limited to tertiary centers. Many public health facilities lack liver specialists, leading to underreporting and misdiagnosis.

c. Absence of Standardized Guidelines

India lacks national consensus guidelines on NAFLD management adapted for diverse population subsets (urban/rural, adult/pediatric).

d. Limited Focus on Pediatric NAFLD

Rising childhood obesity in India demands early screening programs in schools. Currently, such initiatives are sporadic or nonexistent.

e. Cost and Accessibility of Investigational Drugs

Even if new drugs are approved, their high cost and limited insurance coverage may restrict access, particularly among low-income groups.

8. Future Directions

As the prevalence of Non-Alcoholic Fatty Liver Disease (NAFLD) continues to rise globally and in India, it becomes crucial to explore emerging frontiers that could lead to earlier diagnosis, better risk stratification, and personalized therapeutic interventions. Several promising research areas are being actively investigated to address current limitations in NAFLD management.

8.1. Identification of Novel Biomarkers (e.g., microRNAs, Metabolomics)

Current diagnostic approaches for NAFLD heavily rely on liver biopsies or indirect markers like liver enzymes, which are often nonspecific and invasive. There is growing interest in identifying novel biomarkers that offer both sensitivity and specificity for early detection and staging.

a. microRNAs (miRNAs)

MicroRNAs are small, non-coding RNAs that regulate gene expression post-transcriptionally. Studies have shown that circulating miRNAs such as miR-122, miR-34a, and miR-192 are upregulated in NAFLD and correlate with disease severity. [26]. These molecules may serve as non-invasive biomarkers for differentiating NAFLD from non-alcoholic steatohepatitis (NASH).

b. Metabolomics

Metabolomic profiling involves analyzing small molecule metabolites in biological samples. This technique can identify metabolic changes specific to NAFLD, such as alterations in lipidomics, bile acids, and amino acid metabolism. Such profiles could serve as a diagnostic "fingerprint" for disease stratification [27].

8.2. Gut Microbiome Modulation Through Probiotics

The gut-liver axis has emerged as a critical player in NAFLD pathogenesis. Dysbiosis, or the imbalance of gut microbiota, leads to increased intestinal permeability, endotoxemia, and hepatic inflammation.

a. Role of Probiotics

Probiotics such as Lactobacillus and Bifidobacterium species have shown promise in modulating the gut microbiome, reducing liver fat accumulation, and improving insulin sensitivity. Clinical trials have demonstrated that probiotic supplementation can lead to improvements in liver enzymes and inflammatory markers in NAFLD patients.[28].

b. Synbiotics and Postbiotics

Emerging research suggests that combining probiotics with prebiotics (synbiotics) or using bacterial metabolites (postbiotics) may have a synergistic effect in restoring gut microbial balance and reducing hepatic inflammation.

8.3. Personalized Medicine Based on Genetic Profiling

Inter-individual variability in NAFLD progression points to the need for

personalized therapeutic strategies. Genomic studies have identified specific genetic polymorphisms that influence disease susceptibility.

The heterogeneous presentation of NAFLD across populations suggests a significant genetic component. Polymorphisms in genes such as PNPLA3, TM6SF2, and MBOAT7 are strongly associated with increased hepatic fat accumulation, fibrosis risk, and variability in treatment response. [17,19]

- PNPLA3 I148M variant, prevalent in South Asian populations, is linked to increased liver fat content and higher fibrosis scores, independent of BMI and insulin resistance.
- Pharmacogenomics can help predict which patients may respond better to certain treatments such as GLP-1 receptor agonists or FXR agonists.

Research Implication: Future research should explore integrating genomic data with clinical algorithms to stratify patients by risk and tailor therapeutic strategies accordingly—ushering in an era of personalized hepatology.

8.4. Development of Cost-Effective Non-Invasive Tests

Liver biopsy, while diagnostic, is invasive, costly, and carries procedural risks. Hence, there is a pressing demand for non-invasive, affordable, and scalable diagnostic modalities—particularly in resource-limited settings like India.

Tools such as transient elastography (FibroScan) and magnetic resonance elastography (MRE) are effective but financially inaccessible to most patients.

Serum-based composite indices like NAFLD Fibrosis Score (NFS) and FIB-4 require further validation across ethnicities and comorbidities.

Research Implication: Development and validation of low-cost imaging tools or point-of-care diagnostic kits—possibly integrating artificial intelligence (AI) and machine learning—can transform community-level screening and monitoring of NAFLD.

8.5. Exploration of Natural Products and Phytochemicals

Traditional medicinal systems such as Ayurveda and Traditional Chinese Medicine offer a rich repository of plant-based compounds with hepatoprotective, antioxidant, and anti-inflammatory properties.

- Curcumin (from turmeric), silymarin (milk thistle), and berberine (from Berberis aristata) have demonstrated beneficial effects on liver enzymes, lipid profiles, and insulin resistance in preclinical and limited clinical studies. [27]
- Green tea catechins and resveratrol show potential in reducing hepatic steatosis and oxidative stress.

Research Implication: Systematic exploration and standardization of herbal compounds through phytochemical screening, mechanism elucidation, and clinical validation can provide accessible adjunct therapies for NAFLD, particularly in regions with rich ethnobotanical traditions.

CONCLUSION

NAFLD is not merely a hepatic condition but a systemic metabolic disorder that poses a substantial threat to India's public health system. While lifestyle interventions remain the cornerstone of management, there is a growing role for pharmacological treatments, many of which are currently under investigation. Government efforts like integrating NAFLD into national NCD programs are commendable, but much remains to be done in terms of awareness, early diagnosis, and equitable access to care. Addressing NAFLD effectively requires a coordinated effort across clinical, policy, and community domains. The time to act is now, to curb the silent spread of this metabolic epidemic before it becomes unmanageable.

REFERENCES

1. Tilg H, Moschen AR. Evolution of inflammation in nonalcoholic fatty liver disease: The multiple parallel hits hypothesis. Hepatology. 2010;52(5):1836-1846.
2. Buzzetti E, Pinzani M, Tsochatzis EA. The multiple-hit pathogenesis of non-alcoholic fatty liver disease (NAFLD). Metabolism. 2016 Aug;65(8):1038-1048.
3. Samuel VT, Shulman GI. Mechanisms for insulin resistance: Common threads and missing links.

Cell. 2012 Mar 16;148(5):852-871.
4. Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease—Meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology. 2016 Jul;64(1):73-84.
5. Softic S, Cohen DE, Kahn CR. Role of dietary fructose and hepatic de novo lipogenesis in fatty liver disease. Dig Dis Sci. 2016 May;61(5):1282-1293.
6. Malhi H, Gores GJ. Cellular and molecular mechanisms of liver injury. Gastroenterology. 2008 May;134(6):1641-1654.
7. Begriche K, Igoudjil A, Pessayre D, Fromenty B. Mitochondrial dysfunction in NASH: causes, consequences and possible means to prevent it. Mitochondrion. 2006 Apr;6(1):1-28.
8. Zhang D, Du J, Yang Z, et al. Oxidative stress and mitochondrial dysfunction in NAFLD: New insights and therapeutic strategies. Redox Biol. 2020 Dec;37:101689.
9. Sunny NE, Parks EJ, Browning JD, Burgess SC. Excessive hepatic mitochondrial TCA cycle and gluconeogenesis in humans with nonalcoholic fatty liver disease. Cell Metab. 2011 Nov 2;14(6):804-810.
10. Seki E, Schwabe RF. Hepatic inflammation and fibrosis: functional links and key pathways. Hepatology. 2015 Jan;61(3):1066-1079.
11. Miura K, Ohnishi H. Role of gut microbiota and Toll-like receptors in nonalcoholic fatty liver disease. World J Gastroenterol. 2014 Sep 28;20(23):7381-7391.
12. Leung C, Rivera L, Furness JB, Angus PW. The role of the gut microbiota in NAFLD. Nat Rev Gastroenterol Hepatol. 2016 Jul;13(7):412-425.
13. Nagpal R, Yadav H. Bacterial lipopolysaccharide and its inflammatory effects on the liver. World J Hepatol. 2014 Sep 27;6(9):653-661.
14. Csak T, Ganz M, Pespisa J, et al. Fatty acid and endotoxin activate inflammasomes in mouse hepatocytes that release danger signals to stimulate immune cells. Hepatology. 2011 Sep;54(1):133-144.
15. Friedman SL. Hepatic stellate cells: protean, multifunctional, and enigmatic cells of the liver. Physiol Rev. 2008 Jan;88(1):125-172.
16. Anstee QM, Targher G, Day CP. Progression of NAFLD to diabetes mellitus, cardiovascular disease or cirrhosis. Nat Rev Gastroenterol Hepatol. 2013 Jun;10(6):330-344.
17. Romeo S, Kozlitina J, Xing C, et al. Genetic variation in PNPLA3 confers susceptibility to nonalcoholic fatty liver disease. Nat Genet. 2008 Dec;40(12):1461-1465.
18. Mancina RM, Dongiovanni P, Petta S, et al. The MBOAT7-TMC4 variant rs641738 increases risk of nonalcoholic fatty liver disease in individuals of European descent. Gastroenterology. 2016 Apr;150(5):1219-1230.e6.
19. Pirola CJ, Sookoian S. Epigenetics in NAFLD: A new frontier. Hepatology. 2018 Feb;67(2):761-771.
20. Nakagawa H, Vallee D, Hsieh W, et al. microRNA-122 and non-alcoholic fatty liver disease. J Hepatol. 2013 Aug;59(2):475-482.
21. Ministry of Health and Family Welfare, Government of India. National Programme for Prevention and Control of Cancer, Diabetes, Cardiovascular Diseases and Stroke (NPCDCS). Operational guidelines. 2023.
22. Musso G, Cassader M, Paschetta E, Gambino R. Thiazolidinediones and advanced liver fibrosis in nonalcoholic steatohepatitis: a meta-analysis. JAMA Intern Med. 2017 Apr 1;177(4):633-640.
23. NIDDK. Trial of metformin in nonalcoholic fatty liver disease in children (TONIC). N Engl J Med. 2011 Apr 14;364(14):1317-1326.
24. Armstrong MJ, Gaunt P, Aithal GP, et al. Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis (LEAN): a multicentre, double-blind, randomized, placebo-controlled phase 2 study. Lancet. 2016 Jul 2;387(10019):679-690.

25. Younossi ZM, Ratziu V, Loomba R, et al. Obeticholic acid for the treatment of non-alcoholic steatohepatitis: interim analysis from a multicentre, randomized, placebo-controlled phase 3 trial. Lancet. 2019 May 11;394(10215):2184-2196.
26. Eslam M, Newsome PN, Sarin SK, et al. A new definition for metabolic dysfunction-associated fatty liver disease: An international expert consensus statement. J Hepatol. 2020 Nov;73(1):202-209.
27. Rahmani AH, Al Shabrmi FM, Aly SM. Active ingredients of medicinal plants for the management of diabetes mellitus and its complications. Evid Based Complement Alternat Med. 2014;2014:378657.
28. Eslamparast T, Poustchi H, Sharafkhah M, et al. Synbiotic supplementation in nonalcoholic fatty liver disease: a randomized, double-blind, placebo-controlled pilot study. Eur J Clin Invest. 2014 Feb;44(2):109-117.