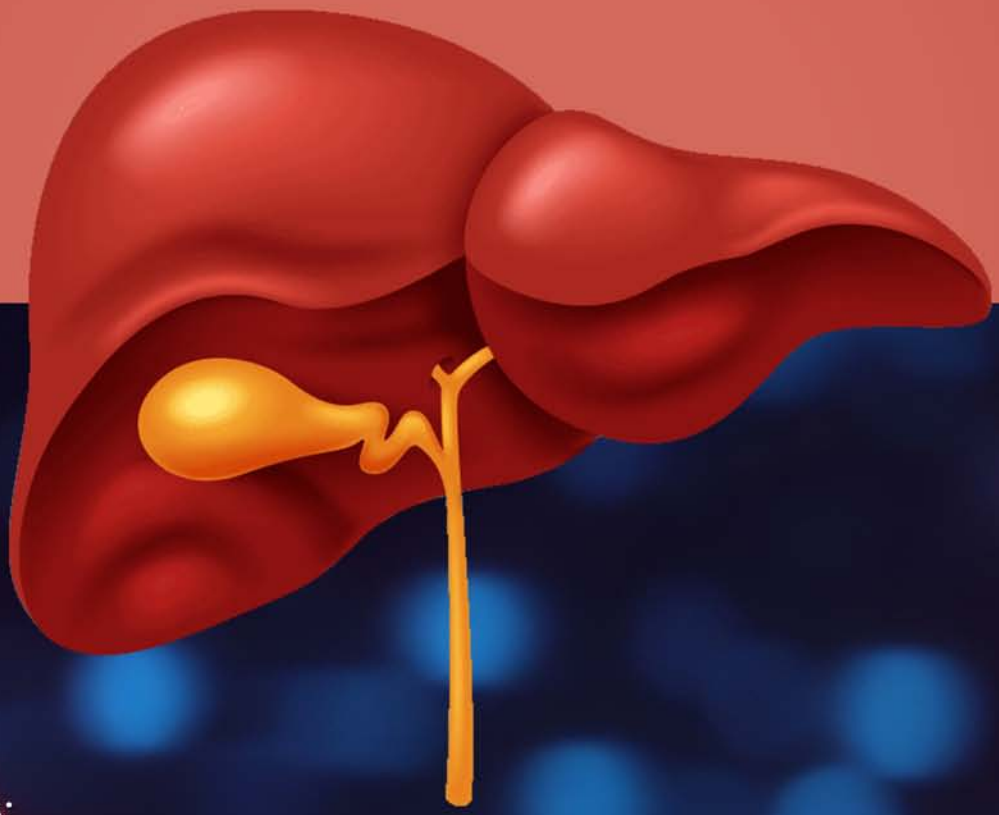
NANOCARRIER-BASED DRUG DELIVERY FOR THE MANAGEMENT OF FATTY LIVER DISEASE



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FOREWORD

The field of nanomedicine has revolutionized modern therapeutics by enabling precise, targeted, and efficient delivery systems for drugs. Among the many diseases that demand innovative treatment strategies, **Fatty Liver Disease (FLD)**—both alcoholic and non-alcoholic—stands out as a global health challenge, affecting millions worldwide. The complexity of its pathophysiology necessitates advanced approaches that transcend conventional pharmacotherapy.

This book, "*Nanocarrier-based Drug Delivery for the Management of Fatty Liver Disease*," provides a comprehensive and insightful exploration of the potential of nanotechnology to address this pressing medical concern. From the fundamentals of fatty liver disease to sophisticated nanocarrier-based therapeutic and diagnostic approaches, the book integrates scientific innovation with clinical relevance.

Each chapter, authored by distinguished experts in the field, delves into critical aspects such as liver-targeting nanocarriers, lipid- and polymer-based systems, pharmacokinetic considerations, safety profiles, and translational perspectives. This book is expected to serve as a valuable resource for researchers, academicians, clinicians, and pharmaceutical scientists seeking to leverage nanotechnology for the management of liver diseases. It is a commendable initiative that bridges the gap between nanoscience and hepatology, paving the way for future advancements in precision medicine.

I extend my heartfelt congratulations to the authors for their dedicated efforts in bringing this comprehensive and insightful book to fruition.

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Preface

Fatty liver disease has become a serious public health problem due to the rise in instances of obesity, diabetes, and associated metabolic diseases worldwide. Effective therapy remains difficult to achieve, even as advances in medical science have improved diagnosis and management. Numerous current treatments have drawbacks, including low medication absorption, insufficient liver tissue targeting, and unfavorable side effects. These difficulties highlight the need for creative therapeutic approaches.

With benefits, such as improved drug absorption, site-specific distribution, and reduced systemic toxicity, nanocarrier-based drug delivery systems have become a viable alternative. These technologies offer the opportunity to improve treatment outcomes for individuals with fatty liver disease by addressing the drawbacks of traditional approaches.

This book offers a thorough analysis of nanocarrier technologies and their potential for treating fatty liver disease. It provides readers with a comprehensive understanding of the potential impact of nanotechnology in this field by examining key concepts, therapeutic applications, and current research. The material bridges the gap between theoretical understanding and real-world application, covering everything from fundamental scientific concepts to the latest developments.

The book is intended as a useful resource for medical researchers, healthcare practitioners, and those in the pharmaceutical sector. It supports upcoming research projects in the field of drug delivery systems, fosters multidisciplinary collaboration, and stimulates new ideas.

We express our heartfelt gratitude to all of the writers and specialists who gave their time and expertise to this collection. In addition to offering clarification and direction, we hope that our work encourages further research and development in the management of fatty liver disease.

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CHAPTER 1

Introduction to Fatty Liver Disease

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Abstract: Fatty liver disease, encompassing non-alcoholic fatty liver disease and alcoholic fatty liver disease, is a growing global health concern characterized by excessive fat accumulation in liver cells. It is associated with metabolic disorders, obesity, and lifestyle factors, often progressing to severe conditions like non-alcoholic steatohepatitis, fibrosis, cirrhosis, or hepatocellular carcinoma. The objective of this chapter is to provide an overview of fatty liver disease, its pathophysiology, risk factors, and current therapeutic challenges, while introducing the potential of nanocarrier-based drug delivery systems for its management. This chapter reviews the current literature on the etiology, progression, and treatment strategies for fatty liver disease. The chapter also explores various nanocarrier systems, including liposomes, solid lipid nanoparticles, and polymeric nanoparticles, highlighting their advantages in enhancing drug solubility, targeting, and therapeutic efficacy. Nanocarrier-based drug delivery systems have demonstrated significant potential in improving the bioavailability and liver-specific delivery of therapeutic agents. Studies indicate that these systems can reduce hepatic fat accumulation, modulate inflammatory pathways, and prevent disease progression, with fewer side effects than conventional therapies. The integration of nanotechnology into the management of fatty liver disease represents a promising frontier in hepatology. By addressing the limitations of traditional treatments, nanocarriers offer a targeted, efficient, and safer approach to treating this prevalent condition.

Keywords: Disease, Fatty liver, Metabolism, Nanotechnology, Non-alcoholic, Targeting, Therapeutic efficacy.

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INTRODUCTION

Fatty liver and non-alcoholic fatty liver diseases are characterized by alterations in the macrovesicular fat accumulation that are not caused by excessive alcohol use and do not include lobular inflammation or inflammation (steatosis) [1]. The two primary forms are Non-Alcoholic Steatohepatitis (NASH) and Non-Alcoholic Fatty Liver (NAFL), sometimes referred to as steatosis. NAFL is hepatic steatosis without hepatocyte edema or other indications of liver injury [2 - 4]. High cholesterol, diabetes, obesity, and metabolic syndrome are often linked to non-alcoholic fatty liver disease (NAFLD). Approximately 80% of people with metabolic syndrome have NAFLD. Moreover, several reasons have been proposed for why fat might build up in the liver [5, 6].

Overview of Fatty Liver Disease

In 1986, Schaffner coined the phrase “non-alcoholic fatty liver disease” (NAFLD) [7]. It is characterized by abnormal buildup of liver fat, insulin resistance, and histological evidence of steatosis in more than 5% of hepatocytes. NAFLD is diagnosed after excluding other clear-cut factors, such as excessive alcohol use, viral hepatitis, and drugs that change fat that might cause steatosis or change the liver profile [8]. Non-invasive techniques, such as computed tomography [CT], ultrasonography [US], and magnetic resonance imaging (MRI), are used to detect hepatic fat accumulation in the liver [9]. Fatty liver is the term used to describe an excess of fat in the liver. It is common, especially in those with diabetes and obesity. Even without symptoms, it may cause serious health problems [10]. There are two kinds:

- **Simple fatty liver**, characterized by liver fat with little to no inflammation or damage to liver cells.
- **Nonalcoholic steatohepatitis (NASH)**, which is characterized by inflammation, loss of liver cells, and liver fat [11].

The development of fatty liver disease is associated with reduced beta-oxidation of mitochondrial fatty acids, increased endogenous fatty acid production or increased supply of fatty acids to the liver, and inadequate absorption or release of triglycerides as very low-density lipoprotein (VLDL) [12 - 14].

Epidemiology and Global Burden

The frequency of NAFLD varies significantly across cohorts. In the general population, the prevalence of NAFLD is estimated to be between 11.5% and 46%,

whereas in the US, it is 20%. NASH, on the other hand, accounts for 2% to 3% of the cases [15]. The average age at diagnosis is 50, with a range of 16–80. It is more common in white people than in black people, and it is more common in Hispanic individuals than in white people [16].

Nonalcoholic fatty liver disease (NAFLD) is one of the main causes of liver disease worldwide. With an estimated 47 cases per 1,000 people globally, NAFLD occurs more frequently in men than in women [17]. It is estimated that 32% of people globally are expected to have NAFLD, with males more likely to be affected by it (40%) than females (26%). The worldwide incidence of NAFLD has increased over time, from 26% in studies conducted before 2005 to 38% in studies conducted after 2016 [18].

CLASSIFICATION OF FATTY LIVER DISEASE

Fatty liver disease is primarily classified into two major types:

Non-Alcoholic Fatty Liver Disease (NAFLD)

Nonalcoholic fatty liver disease (NAFLD) is characterized by an excessive buildup of fat in the liver (≥5% of cells) in individuals who drink little or no alcohol. It is the most common chronic liver disease in the world [19]. NAFLD may be further divided into the following categories:

- A benign condition with a low risk of progressing to fibrosis, non-alcoholic fatty liver (NAFL) is characterized by hepatic fat accumulation without significant inflammation or damage to liver cells [20].
- Its prevalence is estimated at 25-30% of the world's population.
- Hepatocellular carcinoma (HCC), liver failure, and cirrhosis are possible outcomes.
- Globally, the prevalence ranges from 2 to 6%.

Risk Factors for NAFLD

- **Obesity:** Present in 60-90% of NAFLD cases.
- **Type 2 Diabetes Mellitus:** 70% of people with diabetes develop NAFLD.
- **Dyslipidemia:** High triglycerides and low HDL cholesterol.
- **Hypertension:** Common in NAFLD patients.
- **Genetic Predisposition:** PNPLA3 and TM6SF2 gene variants.
- **Sedentary Lifestyle and Poor Diet:** High fructose and fat intake.

CHAPTER 2

Non-Alcoholic Fatty Liver Disease: A Metabolic Threat

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Abstract: Non-alcoholic fatty liver disease (NAFLD) has emerged as the typical long-term liver disease disorder worldwide, affecting a significant portion of people. This condition includes various hepatic abnormalities, starting with basic steatosis, which can progress to more severe liver disease. NASH may result in fibrosis, cirrhosis, or hepatocellular cancer. NAFLD's pathophysiology is complex, with an intricate interplay among genetic factors, physiological dysregulation, and environmental factors. Central to its development is insulin resistance, which drives lipid accumulation in hepatocytes and triggers inflammatory and fibrotic pathways. In recent years, NAFLD has gained recognition not only as a hepatic condition but also as a systemic disorder intricately linked to being obese, type 2 diabetes, hyperlipidaemia, or heart disease, collectively referred to as metabolic syndrome. Despite its increasing prevalence, NAFLD remains underdiagnosed and undertreated, highlighting the urgent need for non-invasive diagnostic tools and effective therapeutic strategies.

Keywords: Nonalcoholic fatty liver disease, Nanocarriers, Liver targeting strategies, NASH, NAFLD.

INTRODUCTION

NAFLD has been recognized as an extremely chronic ongoing liver condition during the past four decades, impacting approximately 25 percent of the older generation globally [1], and is recognized as having a two-way relationship that includes the elements of metabolic syndrome [2]. While fewer than ten percent of those with NAFLD suffer issues with their livers, determining which patients are particularly at risk within the large number of patients suffering from NAFLD is hard. Due to its growing incidence, NAFLD is currently the most significant contributing factor to liver-related disease globally [3] and is becoming a key

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reason for advanced hepatic disorders [4]. Furthermore, liver transplantation places a substantial financial burden on the healthcare system [5]. Despite growing concern, NAFLD is not widely recognized as a severe chronic condition [6]. Few governmental programs or policies address NAFLD. It represents a group of disorders that induce metabolic abnormalities. Severe fatty hepatitis resulting in fibrosis was described more than twenty years ago [7]. Ludwig and colleagues coined the term "non-alcoholic steatohepatitis" (NASH) in 1980 [8]. NAFLD is diagnosed by the presence of steatosis in more than five percent of the liver in conjunction with biochemical risk factors (especially overweight or type 2 diabetes), along with the absence of significant alcohol consumption (≥30 g per day in men or ≥20 g per day in women) and other ongoing liver diseases [9]. Conventional terminology defines NAFLD as a diagnosis made by excluding other causes of liver disease rather than as a distinct pathological entity; nevertheless, there is ongoing debate regarding the adequacy and clarity of the current terminology and diagnostic criteria [10]. In 2020, a global panel of experts proposed the concept of MAFLD to emphasize the role of cardiovascular risk factors in the development and progression of liver disease, including among patients with other hepatic disorders [11]. Nevertheless, neither the American Association for the Study of Liver Diseases (AASLD) nor the European Association for the Study of the Liver (EASL) has officially adopted the term MAFLD in their clinical guidelines or research publications. The comparison between a healthy and a fatty liver is shown in Fig. (**1**).

Fig. (1). Healthy liver and fatty liver.

TYPES OF NAFLD

- NAFLD (simple steatosis)
- Non-alcoholic steatohepatitis without fibrosis
- Non-alcoholic steatohepatitis with fibrosis

Non-alcoholic Fatty Liver (Simple Steatosis)

Hepatocellular steatosis is a key feature of NAFLD, with a diagnostic threshold of over 5% fat accumulation [12 - 14]. It is classified into macrovesicular and microvesicular forms. Although macrovesicular steatosis is more common in NAFLD, approximately 10% of cases may present with microvesicular steatosis [15, 16]. Initial studies portrayed NAFLD as a relatively harmless condition, with

a slower progression to cirrhosis compared to NASH [17, 18]. However, recent evidence challenges this view, revealing that about 25% of NAFLD patients may experience fibrosis development [19]. Longitudinal studies involving repeated biopsies of NAFLD patients found that 64% of individuals with simple steatosis progressed to NASH within 3.7 years [20]. Furthermore, the extent of steatosis is linked to lobular inflammation, fibrosis in zone 3, and the presence of steatohepatitis [21]. A meta-analysis highlighted comparable rates of liver fibrosis progression in both NAFLD and NASH patients (39.1% *vs*. 34.5%) [22]. In summary, 30-40% of NAFLD patients show fibrosis progression over time, underscoring the importance of monitoring even in the absence of inflammation.

Non-alcoholic Steatohepatitis without Fibrosis

Non-alcoholic steatohepatitis (NASH) without fibrosis is a form of non-alcoholic fatty liver disease (NAFLD) characterized by liver inflammation and fat accumulation without the presence of significant fibrosis (scarring). NASH represents a stage within a spectrum of liver damage, ranging from simple steatosis (fatty liver) to more severe forms, including cirrhosis. In NASH, liver inflammation can damage hepatocytes, leading to potential progression to fibrosis and cirrhosis if not managed. However, in the absence of fibrosis, NASH may not cause significant long-term liver damage but requires close monitoring to prevent progression [23]. The primary risk factors for NASH without fibrosis include obesity, insulin resistance, type 2 diabetes, and dyslipidemia. The condition is often asymptomatic, and individuals may not be aware of their liver abnormalities until routine blood tests reveal elevated liver enzymes or imaging studies, such as ultrasound, detect fatty liver changes. Symptoms, when present, may include mild fatigue or discomfort in the upper abdomen [24]. Management focuses on lifestyle modifications, including weight loss through a healthy diet and regular exercise. These changes can help reduce liver fat, improve insulin sensitivity, and reduce inflammation. While no specific pharmacological treatments have been approved for NASH without fibrosis, managing underlying conditions like diabetes and hyperlipidemia is crucial to prevent disease progression [25].

Non-alcoholic Steatohepatitis with Fibrosis

Non-alcoholic steatohepatitis (NASH) with fibrosis is a more advanced stage of NAFLD, characterized by liver inflammation and accumulation of fat, or the development of fibrosis, or scarring, within the liver tissue. NASH is a progressive condition, and when fibrosis develops, it signifies that liver damage has occurred over time. The severity of fibrosis can range from mild to severe, with advanced fibrosis potentially leading to cirrhosis and increasing the risk of

CHAPTER 3

Overview of Nanocarrier-based Drug Delivery Systems

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Abstract: Up to 25% of adults worldwide may suffer from noncommunicable chronic liver disorders, which is a serious and expanding public health concern. These illnesses currently have no known cure or effective treatment. With billions of doses safely administered worldwide, nanomedicines are transforming healthcare. However, there is significant interest in developing new translational techniques to address unmet diagnostic and treatment needs. As a step towards precision medicine, nanoparticle-based techniques present new possibilities for targeted and effective medication delivery to liver cells. Nanocarrier delivery systems offer a tool to address the urgent and unmet clinical needs of metabolic chronic liver diseases, including non-alcoholic fatty liver disease. This chapter emphasizes recent developments in nanomedicine to develop innovative diagnostic and therapeutic tools for non-alcoholic fatty liver disease and associated liver disorders.

Keywords: Chronic liver disease, Nanomedicine, Nanoparticle, Non-alcoholic fatty liver disease.

INTRODUCTION

With an estimated global prevalence of 24% and higher incidence rates in South America and the Middle East, followed by Asia, the United States, and Europe, nonalcoholic fatty liver disease (NAFLD) is the most prevalent noncommunicable

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chronic liver disease [1]. As NAFLD poses a major medical and economic burden, it is essential to develop evidence-based strategies for its diagnosis, treatment, and prevention, and to integrate these strategies into healthcare systems and globally accepted clinical guidelines [2]. It is widely acknowledged that underlying irregularities in metabolic health raise the risk of non-alcoholic fatty liver disease (NAFLD) and that it can coexist with other chronic disorders like diabetes and obesity. NAFLD is characterized by significant clinical heterogeneity [3].

The clinical spectrum of NAFLD begins with simple steatosis and can lead to liver cirrhosis, nonalcoholic steatohepatitis (NASH), and ultimately hepatocellular carcinoma (HCC). In the coming years, NASH, a complicated and multifactorial metabolic illness, is predicted to overtake the most common cause of liver transplants in the United States [4, 5]. It is also becoming a global health concern. As the fibrosis stage advances, especially with the prevalence of cirrhosis, the risk of all-cause mortality and the morbidity of NAFLD/NASH increase dramatically [6, 7]. According to estimates, 7–30% of individuals with NAFLD will develop NASH at some point in their lives [8]. Addressing the development of NASH can significantly aid in preventing the progression of NAFLD to more severe stages because liver damage is still reversible at this stage [9]. However, the presence of other comorbidities, such as metabolic syndrome, obesity, hyperglycemia, dyslipidemia, hypertension, insulin resistance, or dysbiosis, as well as lifestyle factors, such as diet, can alter this course [10].

Although age is acknowledged as a significant risk factor for non-alcoholic fatty liver disease (NAFLD), the rising incidence of juvenile obesity is raising concerns for kids and teenagers [11]. Individuals with a childhood onset of NASH may be more susceptible to an early or worse outcome [12]. Insulin sensitization, antioxidant medication, lifestyle changes (weight loss), and bariatric surgery are common therapeutic modalities for chronic metabolic liver disorders [13].

Effective cell-specific drug delivery offers a means to address the challenges and constraints in developing innovative treatments and may improve the efficacy of therapeutic drugs targeting the liver [14]. In this regard, the ability of nanomedicines to target specific cells offers unique opportunities for pharmacological control of the intricate interactions between proinflammatory and pro-resolution signals in chronic metabolic liver diseases. This chapter describes recent developments in nanomedicines and how the characteristics of nanoparticles (NPs) can be leveraged to enhance drug delivery and liver cell targeting, enabling new precision treatments and diagnostics for chronic liver diseases.

NPS AS DRUG-DELIVERY SYSTEMS

The field of nanomedicine is expanding rapidly and has the potential to deliver highly specific and effective treatments [15]. NPs, which are defined as entities up to 100 nm in a single dimension but can also encompass structures up to several hundred nanometers in diameter, are the building blocks of nanomedicines [16]. They can be created via bottom-up or self-assembly techniques, or a top-down process that uses mechanical force to create smaller particles from bigger compartments [17]. The administration of macromolecules and poorly water-soluble medications, combination therapy, tissue- or cell-specific drug delivery, and drug uptake across a variety of epithelial and endothelial barriers can all be facilitated by nanotechnology. By minimizing renal excretion and hepatic degradation, enabling “site-specific” drug delivery, raising the therapeutic index, and consequently lowering toxicity, nanomedicines' superiority over traditional medications enables them to extend the payload's circulation period [18]. The idea of nanomedicine is not limited to a straightforward drug delivery system; under the term “theranostics,” a combination of therapeutic and diagnostic entities has been envisioned, establishing a framework for next-generation NPs that will facilitate drug transport, release, and noninvasive diagnostics [19]. Currently, the FDA or EMA has approved over 27 nanomedicines for clinical use [20]. Targeting/surface components, the encapsulated payload, and a core material make up organic, inorganic, or hybrid nanocarrier units employed in nanomedicine applications [21]. Small molecules, proteins, peptides, nucleic acids, and RNA oligonucleotides are just a few of the payloads that may be loaded into these NPs to enable either targeted or nontargeted distribution [22]. Therapeutic and diagnostic agents for a variety of disorders have been delivered using a wide range of nanostructures [23].

The advantages of nanocarriers are depicted in Fig. (**1**). Moreover, various types of nanosystems employed for therapeutic or diagnostic delivery to the liver, along with some of their fundamental characteristics, are briefly discussed in the following discussion.

Lipid Nanosystems

Nanostructured lipid carriers, liposomes, and solid lipid nanoparticles (SLNs) are the three categories of lipid nanosystems [24]. As liposomes can encapsulate medications regardless of their chemical properties and mimic the shape of the cell membrane, they appear to be a near-perfect drug-delivery method. Increased bioavailability, biodistribution, and degradability, together with decreased toxicity and antigenicity, are key benefits for their usage in clinical settings [25]. Lipid-based NPs are the most commonly used NPs in the clinic, ranging from Doxil and

CHAPTER 4

Liver Targeting Strategies with Nanocarriers

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Abstract: Fatty liver diseases, including nonalcoholic fatty liver disease (NAFLD) and alcoholic fatty liver disease (AFLD), have emerged as some of the most prevalent causes of chronic liver disorders worldwide. Treatment options remain limited due to poor drug bioavailability and nonspecific targeting, resulting in suboptimal therapeutic outcomes. In this context, nanocarriers have shown significant promise by improving drug delivery, enabling precise targeting, and thereby enhancing therapeutic efficacy in the management of fatty liver diseases. This chapter offers a comprehensive review of liver-targeting strategies using nanocarriers, with particular attention to the complexity of fatty liver disease. It examines various nanocarrier systems, such as liposomes, polymeric nanoparticles, dendrimers, and lipid-based carriers, focusing on their structural features and potential for targeted drug delivery. Emerging strategies, including receptor-mediated and stimulus-responsive delivery systems, are critically analyzed. Furthermore, this chapter explores the integration of nanocarriers with cutting-edge technologies, such as RNA-based therapeutics and CRISPR-Cas9 gene editing. Issues related to scalability, safety, and regulatory challenges are also discussed, alongside the latest advancements in preclinical and clinical research. Overall, this chapter serves as a valuable resource, outlining current knowledge and future directions for researchers, clinicians, and pharmaceutical developers working to advance liver-targeted therapies for fatty liver diseases.

Keywords: Fatty liver disease, Liver-targeted drug delivery, Liposomes and nanoparticles, Nanocarriers, RNA-based and gene-editing therapeutics, Stimuli-responsive systems.

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INTRODUCTION

Fatty Liver Disease

Fatty liver disease refers to a condition characterized by excessive fat accumulation in liver cells not attributable to significant alcohol intake. It is broadly classified into two types: alcoholic fatty liver disease (AFLD) and nonalcoholic fatty liver disease (NAFLD). Of these, NAFLD, recently redefined as metabolic dysfunction-associated fatty liver disease (MAFLD), has gained prominence as a global health challenge owing to its increasing prevalence and close association with metabolic syndrome [1]. The reclassification of NAFLD to MAFLD in 2020 marks a paradigm shift, moving from exclusion-based diagnostic criteria to inclusion-based ones that center on metabolic dysfunction, including obesity, type 2 diabetes, and related risk factors [2, 3].

MAFLD is now the most common chronic liver condition worldwide. In Western countries, its prevalence ranges from 20–30%, while in China, it affects approximately 23.3% of the population, underscoring its global reach [4]. Its rising incidence parallels lifestyle transitions marked by increased caloric and fructose consumption, reduced physical activity, and the growing burden of obesity and metabolic syndrome. Notably, MAFLD is no longer restricted to adults; the escalating rates of childhood obesity have led to a concerning increase in pediatric cases, which could predispose affected individuals to lifelong complications. The condition is more common in men and postmenopausal women, suggesting a possible protective role of female sex hormones [5].

The burden of MAFLD extends far beyond liver-specific complications, such as cirrhosis, liver failure, and hepatocellular carcinoma. It is closely linked with systemic diseases like cardiovascular disease and type 2 diabetes, significantly contributing to increased morbidity and mortality [4, 5]. MAFLD arises from a complex interplay of genetic, environmental, and metabolic factors, with insulin resistance playing a central role in hepatic fat accumulation by enhancing lipogenesis and impairing lipid oxidation. Other key contributors include chronic inflammation, mitochondrial dysfunction, dyslipidemia, and oxidative stress. Central obesity, characterized by visceral fat accumulation, is a major driver of these metabolic disturbances [6].

High-fructose diets, sedentary behavior, and genetic mutations, particularly in the PNPLA3 gene, further exacerbate susceptibility. Disease progression spans a broad spectrum, beginning with simple steatosis and potentially advancing to nonalcoholic steatohepatitis (NASH), fibrosis, cirrhosis, and ultimately liver failure. Fibrosis, in particular, is associated with a markedly increased risk of liver-related mortality [7].

Early detection is essential to prevent disease progression. Non-invasive diagnostic tools, such as ultrasound and elastography, are widely used to assess hepatic steatosis and fibrosis, offering safer alternatives to liver biopsy [8]. Biomarkers and scoring systems, including the Fibrosis-4 (FIB-4) index, are gaining attention for their utility in disease staging and risk stratification. Management primarily revolves around correcting metabolic dysfunction, with lifestyle changes, especially weight loss through diet and exercise, as the cornerstone of treatment. While pharmacological therapies targeting insulin resistance, lipid metabolism, and inflammation are under development, their clinical effectiveness remains limited, reflecting the need for novel therapeutic approaches [9].

In this context, nanotechnology has emerged as a promising strategy, enabling the development of targeted drug-delivery systems that enhance therapeutic efficacy while minimizing off-target effects. Nanocarriers, such as liposomes, polymeric nanoparticles, and lipid-based nanoparticles, offer new avenues for delivering therapeutic agents directly to hepatocytes, thereby addressing the underlying mechanisms of MAFLD with greater precision.

Limitations of Conventional Therapies

Despite numerous advances, current treatments for fatty liver disease (NAFLD) face significant challenges due to the complexity of its pathophysiology. Pharmacological intervention remains limited by the lack of drugs that specifically target the disease or its advanced stage, NASH. Most therapies address associated metabolic conditions, such as obesity, type 2 diabetes, and dyslipidemia [10, 11], but not the underlying mechanisms, such as hepatic inflammation, lipid accumulation, and fibrosis. This creates a gap in treatment options, depriving patients of therapies capable of halting disease progression or reversing damage.

Diagnostic challenges further compound this gap. Accurate diagnosis is essential for timely treatment, but faces barriers. While liver biopsy is the gold standard for diagnosing and staging NAFLD, it is invasive, costly, and carries risks, such as bleeding and infection. Non-invasive imaging methods like ultrasound and transient elastography offer safer alternatives but often lack sensitivity, particularly in early or mild cases [12]. These limitations delay treatment initiation and complicate disease management. In addition to diagnostic and therapeutic challenges, implementing lifestyle interventions is also difficult. Changes in diet and physical activity are poorly adhered to due to a lack of motivation, time, and support [13, 14]. Few structured programs exist, and long-term adherence remains a challenge, especially in patients with advanced disease

CHAPTER 5

Lipid-based Nanocarriers for Fatty Liver Disease

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Abstract: Lipid-based nanocarriers (LBCs) have emerged as a promising strategy for the targeted treatment of fatty liver diseases, including non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH). These nanocarriers offer several advantages, including enhanced bioavailability, controlled release, and targeted delivery of therapeutic agents, all of which are crucial for improving treatment outcomes in hepatic disorders. Solid lipid nanoparticles (SLNs), liposomes, and nanostructured lipid carriers (NLCs) are lipid nanoparticles that have been extensively studied for their ability to encapsulate lipophilic drugs, antioxidants, and gene therapies, offering efficient liver-specific drug-delivery solutions. This chapter explains the different ways LBC can deliver drugs to the liver, the formulation techniques used, and how they may help reduce the pathophysiology of fatty liver diseases. Additionally, it examines the challenges, potential applications, and clinical implications of developing lipid-based nanocarrier systems for liver-targeted therapies.

Keywords: Lipid-based nanocarriers, Liposomes, Non-alcoholic fatty liver disease, Nanostructured lipid carriers.

INTRODUCTION TO FATTY LIVER DISEASES

Non-alcoholic fatty liver disease (NAFLD) is a common disorder characterized by an excessive buildup of fat in the liver in people, especially those who consume little to no alcohol. NAFLD, which includes a range from simple steatosis to non-alcoholic steatohepatitis (NASH), is characterized by liver inflammation, cell injury, and fibrosis, significantly raising the risk of cirrhosis, liver failure, and carcinomas, which are closely associated with obesity, type 2 diabetes, and high cholesterol. Up to 25% of people worldwide suffer from NAFLD, with a higher prevalence in Western nations as a result of the growing frequency of metabolic diseases. Even though it is less frequent, NASH is predicted to rise as more instances of NAFLD develop into this severe type. Imaging techniques, such as

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ultrasound or MRI, are usually used for diagnosis, with biopsy employed in more advanced stages [1, 2].

CURRENT THERAPEUTIC APPROACHES AND THEIR LIMITATIONS

For the treatment of NAFLD and NASH, current strategies primarily focus on reducing liver fat content and improving liver function tests. Other therapeutic interventions are as follows:

- Lifestyle Modifications
- Weight Loss
- Dietary Adjustments
- Physical Activity

However, they are not sufficient to reverse the more severe forms of liver damage seen in NASH, such as fibrosis and cirrhosis [3]. For targeting the underlying pathophysiological mechanisms of NAFLD and NASH, pharmacological therapies have been explored, but are associated with side effects. For example

- Thiazolidinediones improve insulin sensitivity and have shown promise, but weight gain and edema side effects limit their use [4].
- Statins and lipid-lowering medications possess the potential to reduce liver inflammation and fibrosis, but their effectiveness specifically for NASH remains uncertain [5].

Moreover, the antioxidant vitamin E has demonstrated some benefit in reducing liver inflammation in non-diabetic individuals with NASH; however, its long-term safety and efficacy are still awaited [6].

ROLE OF NANOTECHNOLOGY IN THE TREATMENT OF LIVER DISEASE

Liver diseases like NAFLD and NASH could be managed using nanotechnology due to its site-specific drug delivery and lower systemic toxicity. API can be delivered directly to the liver using nanoparticle engineering. Enhanced bioavailability and improved treatment with reduced side effects are the primary objectives of nanotechnology. It allows for precise delivery at the cellular or molecular level. Furthermore, nanoparticles can be used as sophisticated imaging agents that enable non-invasive monitoring and detection of liver fibrosis and inflammation using techniques, such as CT and MRI [7 - 10].

Role of Nanocarriers in the Management of NASH and NAFLD

Nanocarriers are compact particles in the size range of 1-1000 nanometers that are used to deliver drugs, genes, or other agents to specific hepatic sites. Due to their small size, nanocarriers can easily navigate biological barriers, such as cell membranes, making them highly effective for targeted drug delivery to hepatic cells.

Lipid-based Nano Carriers (LBCs) in the Management of NASH and NAFLD

LBCs are an emerging class of drug delivery systems that use lipids as the primary material for encapsulating therapeutic agents for liver delivery. The various types of LBCs, along with their properties, are shown in Table **1**. These nanocarriers are designed to enhance the solubility, stability, and bioavailability of hydrophobic drugs. Additionally, their biocompatibility, biodegradability, and enhanced targeting capabilities have made them attractive platforms for pharmaceutical and biomedical applications. The most common LBCs include:

Table 1. Types of LBCs with their properties.

Feature	SLNs	NLCs	Liposomes
Structure	Solid lipid core with surfactant shell	Blend of solid and liquid lipids forming a hybrid matrix	One or more phospholipid bilayers forming spherical vesicles
Size Range	50–1000 nm	50–300 nm	Variable 50–500 nm
Drug Encapsulation	Mainly lipophilic drugs	Enhanced loading for hydrophobic drugs	Both hydrophilic (core) and hydrophobic (bilayer) drugs
Targeting Ability	Passive targeting, potential for nucleic acid delivery	Passive targeting, improved cellular uptake	Naturally targets liver (RES uptake); can be surface-modified
Stability	Good thermal stability (up to 37 °C)	Long-Term stability due to lipid matrix flexibility	Structurally similar to cell membranes but prone to physical instability
Formulation Methods	- High-pressure homogenization - Solvent evaporation -Microemulsion method	- Hot/cold homogenization -Ultrasonication - Solvent diffusion	- Thin film hydration - Reverse-phase evaporation
Applications	-Vaccine delivery (Hepatitis B) -siRNA & DNA delivery	-Delivery of hydrophobic drugs -Controlled release systems	-Gene therapy - Liver-targeted drug delivery - Antioxidant delivery
References	[11 - 15]	[16 - 18]	[19, 20]

CHAPTER 6

Polymeric Nanocarriers for Fatty Liver Disease

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Abstract: An essential organ in our body, the liver performs a wide range of functions, including detoxification, metabolism, digestion, immune responses, and the storage of minerals and vitamins. As a result, liver function abnormalities caused by a variety of hepatic conditions, including transplant rejection, non-alcoholic steatohepatitis, hepatitis B virus infection, hepatic fibrosis, and hepatocellular cancer, represent a serious threat to human health worldwide. Compared with traditional therapeutic agents, polymer-based nanomedicines, which are readily customisable and possess ideal physicochemical properties and functions, offer significant advantages in the treatment of liver diseases, including improved therapeutic outcomes and reduced side effects. This chapter discusses the structure and function of the liver, treatment approaches for hepatic diseases, liver-targeting strategies, and the intrahepatic effects of polymeric nanomedicines, while also highlighting the challenges and opportunities associated with their use in managing hepatic disorders.

Keywords: Nanotechnology, polymeric nanoparticles, liver disease, drug delivery, liver fibrosis.

INTRODUCTION

Overview of Fatty Liver Disease (NAFLD and NASH)

Fatty liver disease, or hepatic steatosis, refers to the accumulation of excess fat in liver cells, affecting about one in three adults in many Western countries. It can

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result from heavy alcohol use (alcoholic fatty liver disease) or metabolic factors, such as obesity and diabetes (nonalcoholic hepatic steatosis (NASH), nonalcoholic fatty liver disease (NAFLD), or metabolic-associated fatty liver disease, MAFLD). In most cases, fatty liver is asymptomatic but may occasionally cause fatigue or discomfort in the upper right abdomen. Over time, persistent fat accumulation can lead to inflammation and scarring, escalating to steatohepatitis and progressing to fibrosis and cirrhosis, potentially resulting in irreversible liver damage or even liver cancer. Diagnosis often depends on medical history, laboratory tests, and imaging studies, and management includes addressing risk factors like alcohol intake, diet, and body weight, with early intervention offering a favorable prognosis [1].

Fatty liver disease can result from a range of factors, predominantly obesity, type 2 diabetes, metabolic syndrome, and high triglycerides, with alcohol abuse being the primary cause of alcoholic fatty liver. Less common causes include certain medications (such as methotrexate and tamoxifen), rapid weight loss, malnutrition, viral hepatitis, and genetic conditions affecting fat metabolism. The initial stage, simple steatosis, may remain stable for years. However, with additional triggers like infection or hormonal imbalance, it can progress to inflammation (steatohepatitis), fibrosis, and eventually cirrhosis or liver cancer. Diagnosis typically relies on blood tests for liver enzymes and metabolic markers, viral hepatitis screening, and imaging studies, such as abdominal ultrasound, CT, or MRI, to detect and quantify liver fat. Definitive staging of steatohepatitis and fibrosis may require a liver biopsy. Management centers on lifestyle interventions, weight loss via healthy diet and exercise, controlling diabetes and lipid levels, and abstinence from alcohol, while drugs affecting the liver should be discontinued, and patients at risk should be monitored for complications and comorbidities [2].

Current Therapeutic Challenges

Current therapeutic challenges in the treatment of fatty liver disease include a lack of approved pharmacological therapies, the heterogeneous pathogenesis of the disease, and difficulties in identifying patients who will benefit most from specific interventions. Lifestyle modification, including dietary changes and increased physical activity, remains the cornerstone of management, but many patients struggle with adherence and sustainable weight loss, limiting overall effectiveness. Pharmacologic agents like pioglitazone and GLP-1 receptor agonists show benefit in nonalcoholic steatohepatitis (NASH). Yet, concerns about side effects, limited efficacy in reversing fibrosis, and a lack of long-term data limit widespread use. Furthermore, the biological complexity of fatty liver disease, encompassing metabolic, inflammatory, and fibrotic pathways, hampers

therapeutic development, with most novel drugs still in clinical trials, underscoring an urgent need for personalized, combination, or multi-targeted strategies [3].

Furthermore, therapeutic management is complicated by the need for coordinated care across specialties, insufficient awareness and education for both patients and healthcare providers, and socioeconomic barriers, such as healthcare access and medication availability. Effective management requires the creation of multidisciplinary strategies, digital health monitoring, and policy-level interventions to address the underlying metabolic risk factors and promote early detection, sustained weight management, and patient empowerment. As novel therapies are developed, long-term studies and better personalized approaches, including combination and multi-targeted regimens, will be crucial to overcome the current limitations and achieve successful outcomes in fatty liver disease [4].

Role of Nanotechnology in Liver-targeted Therapy

The liver, one of the most vital organs in the human body, performs a wide array of essential functions, including protein synthesis, nutrient metabolism, immune regulation, hormonal balance, and detoxification. Consequently, any impairment of liver function, whether caused by viral hepatitis, fatty liver disease, fibrosis, cirrhosis, or hepatocellular carcinoma (HCC), poses a serious threat to human health, contributing to nearly two million deaths worldwide each year [5]. A variety of therapeutic approaches have been employed in the clinical management of liver diseases, including interventional procedures, surgical resection, immunotherapy, antiviral therapy, chemotherapy, radiotherapy, and liver transplantation [6, 7]. Despite notable progress, several challenges continue to limit the effectiveness of these treatments. For instance, incomplete tumor removal often results in recurrence, while conventional drug therapies may lead to drug resistance, systemic toxicity, and reduced efficacy due to their lack of specificity. Furthermore, following liver transplantation (LT), patients must take lifelong immunosuppressants to prevent graft rejection, which can cause severe adverse effects and compromise quality of life [8, 9]. Complex conditions, such as non-alcoholic steatohepatitis (NASH) and hepatic fibrosis, still lack standardized therapies, despite some agents showing promise in clinical trials [10, 11]. Recent advances in nanomedicine (NMs) offer new opportunities to address these limitations. By facilitating targeted drug delivery to the liver, nanomedicines can improve therapeutic efficacy while minimizing systemic side effects. This approach has been applied to a wide range of therapeutics, including natural extracts, chemotherapeutic agents, and nucleic acid–based therapies, demonstrating considerable potential in overcoming the shortcomings of conventional treatments.

CHAPTER 7

Dendrimers and Hybrid Nanocarriers for Fatty Liver Disease

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Abstract: Liver problems continue to be a major worldwide health concern despite advances in medical understanding, and pharmacological therapy is usually complicated by drug toxicity. Fatty liver disease, which comprises both alcoholic and non-alcoholic forms, is defined by an excessive buildup of hepatic fat. Nanotechnology may be employed to deliver drugs to the liver. Dendrimers and hybrid nanocarriers are two unique approaches for effective drug delivery. Dendrimers are artificial polymers. They have a central core, branches, and functional groups at their ends. The specific qualities of dendrimers, such as their high water solubility, well-defined structure, biocompatibility, and high encapsulation efficiency, make them excellent for a range of nanomedicine research. Conjugates of organic and inorganic materials produced by different techniques that combine the benefits of the materials in a synergistic manner are known as hybrid nanocarriers. In drug transport, hybrid nanocarriers combine the benefits of two or more nanocarrier systems, overcoming their flaws to build a new, perhaps safer, and more effective nanocarrier structure. This chapter discusses the chemistry and structure of dendrimers and hybrid nanocarriers, with a focus on their potential value in the treatment of fatty liver disease. It also covers the most recent advances in preliminary studies on these nanotechnologies for the treatment of fatty liver disease. This chapter also covers the challenges and opportunities for developing a framework for better fatty liver disease treatment.

Keywords: Dendrimers, Drug delivery, Fatty liver disease, Hybrid nanocarriers, Nanotechnology.

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INTRODUCTION

Triglyceride accumulation in hepatocytes, known as "fatty liver," can lead to steatohepatitis [1]. Alcohol usage is the major cause of alcoholic fatty liver disease, whereas insulin resistance and metabolic syndrome are the main reasons for NAFLD [2]. Regardless of other traits of the metabolic syndrome, NAFLD is a risk factor in and of itself, and there is growing evidence associating it with an increased risk of atherosclerosis and cardiovascular disease [3]. Studies demonstrated that between 9% and 53% of Indians suffer from NAFLD, and that fatty liver is a major worldwide pandemic [4, 5]. The initial stage of NAFLD is marked by simple hepatic steatosis, which may develop into cirrhosis, fibrosis, hepatocellular cancer, or NASH [6]. Given India's enormous population, fatty liver disease can have a detrimental effect on the nation's limited resources and impose a significant strain on the healthcare system.

CONVENTIONAL THERAPEUTIC APPROACHES FOR FATTY LIVER DISEASE

Lifestyle Modifications

Lifestyle modification aimed at weight loss and increased physical activity is vital in managing all patients with NAFLD, irrespective of their underlying liver histology. An appropriate diet, such as the Mediterranean diet (whole grains, vegetables, fruits, lean protein, and healthy fats), is beneficial for reducing liver fat and inflammation [7]. Patients should be encouraged to avoid a sedentary lifestyle by increasing daily activities, undertaking regular exercise, and eating a healthy diet. Overall, lifestyle interventions, including behavioral, dietary, and exercise changes, can be very effective in reducing body weight.

Pharmacological Interventions

- ***Insulin Sensitizers***

Insulin resistance is a hallmark of NAFLD; therefore, targeting this pathway has been a significant focus of many studies. Insulin sensitizers, such as metformin and TZDs, have been relatively well studied. Newer agents in this class include GLP-1 agonists and DPP-4 inhibitors (*i.e.*, incretins) [8].

• ***Metformin***

Metformin has been evaluated in several small studies on nondiabetic NAFLD patients. It has been shown to improve transaminase levels and hepatic steatosis [9]. However, its effect on inflammation was less robust, and improvement in fibrosis was demonstrated in only one study. Most of these were small, short-duration trials, and, unfortunately, histological follow-up was incomplete. The results of the most extensive study on metformin, the treatment of NAFLD in children (TONIC) trial, which evaluated metformin, vitamin E, and placebo in a pediatric population, were recently published [10].

LIMITATIONS OF CONVENTIONAL TREATMENTS

Conventional treatment for FLD, in particular, faces many limitations. Firstly, managing NAFLD involves lifestyle changes, such as weight loss through regular exercise, which can improve liver health by reducing inflammation and fat accumulation [11]. However, these changes are often challenging to maintain over a long time, and there are no standard pharmacological treatments explicitly approved for NAFLD. In improving insulin resistance, liver fat-reducing pharmacological interventions have shown some benefit, for example, metformin and TZDs. However, their effects are dependent on weight loss and may not persist after discontinuation of the medicine. Additionally, TZDs are associated with their side effects, i.e., weight gain and edema, which can limit their use. The anti-diabetic drugs, including GLP-1 receptor agonists, such as liraglutide, show promising results in reducing liver fat and enhancing insulin sensitivity, but they can cause side effects in the GIT [12].

For morbidly obese patients with NAFLD, bariatric surgery is another way to improve the metabolic syndrome and liver histology. However, bariatric surgery is not suitable for all patients, particularly those who have cirrhosis and fibrosis, because of the increased surgical risks [13]. Moreover, the direct liver benefit is not demonstrated in anti-obesity drugs, and some have been withdrawn from the market due to safety issues. In summary, the cornerstone of NAFLD management is lifestyle changes. They require sustained effort and may not be sufficient for all patients. Current pharmacological options have limitations in safety and efficacy, and they need more targeted management and more effective [14]. Continued research into novel therapies, such as lipase inhibitors and FGF21 analogues, offers hope for future advances in the management of fatty liver disease [15].

CHAPTER 8

Novel Therapeutics for Fatty Liver Disease

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Abstract: Fatty liver disorders encompass both alcoholic fatty liver disorder (AFLD) and non-alcoholic fatty liver disorder (NAFLD) and have arisen as a substantial universal problem owing to their escalating occurrence and linkage with metabolic diseases. At advanced stages, fatty liver disease becomes more precarious as it can be converted into liver cirrhosis, fibrosis, steatohepatitis, and carcinoma in hepatic cells. The conventional pharmacotherapy for various liver diseases mainly focuses on lifestyle modifications to manage associated health concerns, but these approaches have limitations and side effects, prompting scientists to explore more modern approaches via novel therapeutics. This chapter provides insights into pioneering innovations in the management of fatty liver disease, accentuating novel drug delivery systems, molecular targets, and bioactive combinations. Advancements in new-era technologies, including lipid nanoparticles and novel polymeric formulations with enhanced bioavailability profiles, have emerged as cutting-edge approaches for delivering therapeutic agents to specific sites in the liver. Moreover, other evolving treatment strategies, including the roles of biomarkers, such as fibroblast growth factor analogues, peroxisome proliferator-activated receptor agonists, and gut microbiota modulators, are reviewed for their significant roles in modulating metabolic pathways, thereby decreasing hepatic lipid accretion and, in turn, improving patient safety. This chapter offers an inclusive overview of novel therapeutic strategies and other non-pharmacological strategies available, aiming to promote further investigation to address the medical needs in the management of fatty liver disorders.

Keywords: AFLD, Biomarkers, Fatty liver, NAFLD, Novel therapeutics.

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INTRODUCTION

Fatty liver disease (FLD) is a public health problem worldwide, characterized by excess hepatic fat. The disease, which affects about a quarter of the world population, is linked to metabolic disorders, including obesity, type 2 diabetes, and dyslipidaemia. FLD, when not treated, can progress to severe liver diseases, such as cirrhosis and hepatocellular carcinoma (HCC), leading to a significant burden on health care [1]. Sedentary lifestyles, poor dietary habits, and increases in the prevalence of obesity have led to the rising rate of FLD. Although awareness of the disease has increased, early diagnosis remains challenging because it is typically asymptomatic in its initial stages. As a result, a large cohort of patients receives a diagnosis only after progression to more advanced stages, creating an urgent need for improvements in both therapeutic and diagnostic approaches [2]. This disease is of two broad types: a) Alcoholic Fatty Liver Disease (AFLD), resulting from excess alcohol consumption, causing liver inflammation and fibrosis. b) Non-Alcoholic Fatty Liver Disease (NAFLD), which occurs in individuals who consume little or no alcohol and is mainly associated with metabolic disorders. NAFLD encompasses a spectrum of disease ranging from simple steatosis to non-alcoholic steatohepatitis (NASH), involving inflammation and fibrosis. Despite advancements in therapies, the treatment of FLD remains difficult due to the lack of Food and Drug Administration (FDA)-approved pharmacological therapies. The only available strategies are designed to modify lifestyle or to use existing medications off-label, which have limited efficacy for slowing disease progression [3].

PATHOPHYSIOLOGY AND DISEASE PROGRESSION

Severe liver damage is caused by the pathophysiology that comprises multiple molecular mechanisms associated with disease progression from simple steatosis. Increased de novo lipogenesis (DNL) mediated by SREBP-1c and ChREBP, combined with impaired fatty acid β-oxidation, leads to hepatic lipid accumulation. Insulin resistance also contributes to this phenomenon by stimulating lipogenesis and inhibiting fatty acid oxidation, thereby enhancing hepatic fat deposition. Impaired very-low-density lipoprotein secretion also leads to sterol build-up in the liver [4]. The mechanisms and risk factors are graphically represented in Fig. (**1**) and summarized in Table **1**.

The progression from a healthy liver to cirrhosis involves lipid accumulation, oxidative stress, glucose impairment, insulin resistance, and systemic chronic inflammation, ultimately leading to hepatocellular injury and fibrosis. Significant underlying molecular mechanisms, such as hepatic stellate cell activation, mitochondrial dysfunction, and cytokine release, further aggravate the disorder

and result in irreversible cirrhosis and liver failure. HSC-Hepatic Stellate Cells, NAFLD - Non-Alcoholic Fatty Liver Disease, NASH- Non-Alcoholic Steatohepatitis, ECM-Extracellular Matrix Deposition [10, 11].

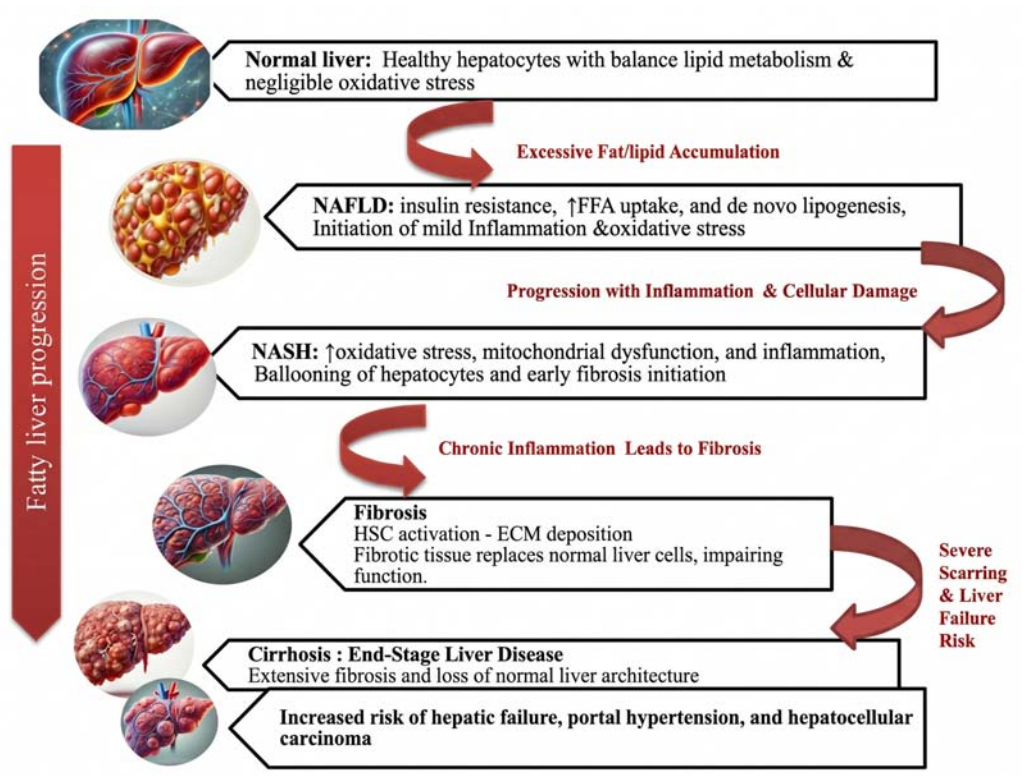

Fig. (1). Schematic overview of the pathophysiology and progression of NAFLD/NASH.

Table 1. Molecular mechanisms, risk factors, and progression of fatty liver disease.

Sr.no	Key Factors	Description	Reference
	Molecular Mechanisms		
1.	**Hepatic Lipid Accumulation (Steatosis)**	Activation of de novo lipogenesis (DNL) via SREBP-1c and ChREBP, β-oxidation impaired, poor very-lo--density lipoprotein oozing, and excess free fatty acid influx from adipose tissue.	[12, 13]
2.	**Insulin Resistance and Metabolic Dysfunction**	Enhanced lipogenesis as a result of the hyperinsulinemic conditions. Diminished AMPK activation limits fatty acid oxidation and increases hepatic glucose output, exacerbating metabolic stress.	[14]

CHAPTER 9

Nanocarrier-based Imaging Agents for Fatty Liver Disease Diagnosis

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Abstract: Given the disadvantages of liver transplantation, including chronic immunosuppression, invasiveness, and a lack of donor livers, prompt diagnosis of fatty liver diseases is crucial. Nanocarriers have emerged as a transformative technology in the diagnosis and management of fatty liver diseases, which encompass a range of metabolic disorders characterized by abnormal fatty acid metabolism. This chapter explores the innovative applications of biocompatible nanocarriers to enhance diagnostic accuracy and efficiency in fatty acid diseases. By encapsulating diagnostic agents, including contrast agents and biomarkers, nanocarriers facilitate delivery to affected tissues through active and passive targeting, thereby improving the sensitivity and specificity of detection methods. Furthermore, their unique physicochemical properties enable real-time monitoring of metabolic processes, providing invaluable insights into disease progression and treatment responses. This chapter also discusses the integration of nanocarrier-based diagnostics with advanced imaging techniques, such as magnetic resonance imaging (MRI) and computed tomography (CT), to visualize fatty acid metabolism *in vivo*. Additionally, we address the challenges and future perspectives in the development of nanocarriers for clinical application, including biocompatibility, regulatory hurdles, and scalability. By harnessing the potential of nanocarriers, researchers and clinicians can pave the way for more effective diagnostic tools, ultimately leading to improved patient outcomes in fatty acid diseases.

Keywords: Fatty liver disease, Imaging agents, Nanocarriers, Real-time monitoring, Targeting.

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INTRODUCTION

Fatty liver disease is characterized by excessive fat accumulation in liver cells. It is categorized into two main types: alcoholic fatty liver disease (AFLD) and non-alcoholic fatty liver disease (NAFLD). NAFLD is a generic term that encompasses the spectrum of non-alcoholic fatty liver (NAFL), non-alcoholic steatohepatitis (NASH), and NASH-related cirrhosis [1]. Simple steatosis is generally benign, while NASH can lead to significant liver damage and complications. The pathophysiology of NAFLD involves insulin resistance, oxidative stress, inflammation, and dysregulation of hepatic lipid metabolism. Accurate and early diagnosis is crucial for effective management and treatment of the disease. Traditional imaging techniques such as ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI) have limitations in sensitivity and specificity for diagnosing fatty liver disease. Recent advancements in nanotechnology have opened new avenues for developing novel imaging agents that enhance diagnostic accuracy (Fig. **1**).

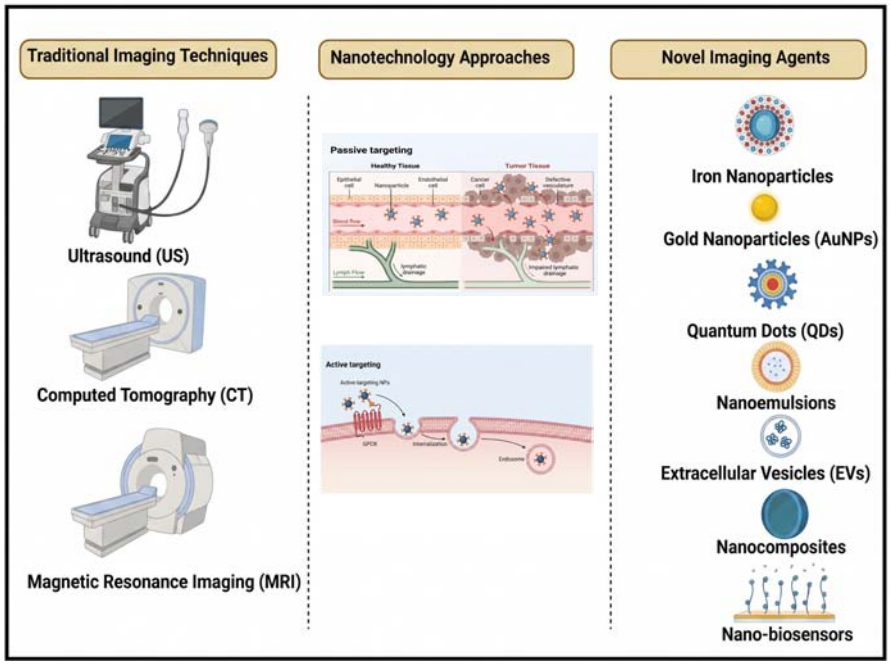

Fig. (1). Comparison of traditional imaging techniques and nanotechnology-based approaches in medical imaging. The figure illustrates the transition from conventional methods such as Ultrasound (US), Computed Tomography (CT), and Magnetic Resonance Imaging (MRI) to advanced nanotechnology-driven imaging agents, including Iron Nanoparticles, Gold Nanoparticles (AuNPs), Quantum Dots (QDs), Nanoemulsions, Extracellular Vesicles (EVs), Nanocomposites, and Nano-biosensors. These novel imaging agents offer enhanced precision and functionality in diagnostic applications.

Numerous methods have been employed to diagnose fatty liver disease, each with its own advantages and limitations. Ultrasound is commonly the first-line imaging technique used for detecting fatty liver due to its safety, widespread availability, and cost-effectiveness. However, its sensitivity in detecting and grading steatosis can be compromised, particularly in patients with larger body habitus. In such cases, steatosis may be overestimated due to beam attenuation caused by surrounding adipose tissue rather than liver fat itself. Additionally, ultrasound provides relatively imprecise qualitative classifications of steatosis, ranging from mild to severe, and can struggle to differentiate between steatosis and fibrosis in patients with chronic liver disease. Factors such as shadowing from ribs or gas can obscure portions of the liver, further complicating assessment, as ultrasound measurements serve as indirect indices of fat content [2]. Machine learning-based ultrasound imaging is increasingly recognized for its effectiveness in detecting and quantifying non-alcoholic fatty liver disease (NAFLD). Techniques such as transient elastography, acoustic radiation force impulse, and magnetic resonance elastography provide accurate measurements of liver stiffness, a key indicator of fibrosis. However, these methods often entail high costs, limited availability, and a need for skilled operators, hindering widespread adoption [3]. Computed tomography (CT) scans offer rapid acquisition, straightforward analysis, and quantitative results; however, they are limited in accurately diagnosing mild steatosis and expose patients to ionizing radiation. CT scan calibration can vary significantly across scanners, manufacturers, and reconstruction algorithms, leading to variability in results. Moreover, the attenuation of X-ray beams is not specific to steatosis [4]. Magnetic Resonance Imaging (MRI) is superior in distinguishing fat from water and quantifying fat content more accurately than ultrasound or CT. MRI assesses the proton density fat fraction (PDFF), a fundamental tissue property that does not require internal calibration or reference standards. This allows for volumetric assessments of steatosis. Nonetheless, MRI is often more expensive and less accessible than other imaging modalities. Additionally, motion artifacts and parallel imaging can negatively affect measurement accuracy, and magnitude data-based MRI struggles to differentiate fat fractions above and below 50%. Current MRI techniques also face challenges with R2* correction [5]. While liver biopsy remains the gold standard for diagnosing non-alcoholic fatty liver disease (NAFLD) and evaluating its severity, it is an invasive procedure prone to observer bias and lacks standardization. Non-invasive testing methods can be categorized into blood-based biomarker tests and imaging techniques. Blood-based tests, particularly multi-biomarker panels, can effectively measure biological processes within the liver and are often more accessible and cost-effective than imaging methods. For instance, the Fibrosis-4 index and enhanced liver fibrosis panel show promise in detecting advanced fibrosis and predicting disease progression. However, these tests may be

CHAPTER 10

Clinical Translation of Nanocarrier-based Drug Delivery Systems for the Treatment of Fatty Liver Disease

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Abstract: Fatty Liver Diseases (FLDs), including basic steatosis to Non-Alcoholic Steatohepatitis (NASH), are an increasing global health issue. Current therapeutic options for FLD are limited, highlighting the need for innovative approaches. Nano-medicines are revolutionising healthcare, with vaccines such as those from Pfizer/BioNTech and Moderna COVID-19 delivering billions of doses safely. This chapter highlights recent advances in nano-medicines for developing diagnostic and therapeutic tools for fatty liver disease without alcohol use, a growing global health challenge, paving the way for precision medicines. Nano carrier-based drug delivery systems (NDDS) offer a promising avenue for enhancing drug delivery to the liver, improving therapeutic efficacy, and minimising side effects. This chapter explores the potential of NDDS in FLD management, focusing on recent advancements in nanomaterial design, targeting strategies, and clinical translation, and discusses the challenges and opportunities associated with the development and clinical application of NDDS for FLD, including safety considerations, regulatory hurdles, and the need for well-designed clinical trials. Despite these challenges, NDDS has significant potential to improve the treatment of FLD and patient outcomes. The clinical trials investigating the efficacy of NDDS in FLD have shown promising results. Additionally, silibinin-loaded nanoparticles enhance mucosal penetration and oral absorption compared with conventional silibinin. Nanoparticulate approaches have shown promise in overcoming lipid metabolism disorders in preclinical trials, indicating potential effectiveness in humans.

Keywords: Non-alcoholic steatohepatitis, Novel drug delivery system, Nano-medicines, Nanocarrier, Nanomaterial design.

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INTRODUCTION

The excessive accumulation of fat in the liver, known as fatty liver disease (FLD), is the leading cause of chronic liver disease, the main reason for liver transplants, and a significant contributor to the clinical and financial burdens worldwide. Clinically, the diagnosis is verified in patients without substantial alcohol use or other known causes of chronic liver disease using non-invasive imaging techniques or invasive procedures, such as a biopsy that shows 5% or more macro vesicular steatosis in hepatocytes [1]. The illness presents with several phenotypes, ranging from Non-Alcoholic Steatohepatitis (NASH) to mild steatosis or Non-Alcoholic Fatty Liver Disease (NAFLD). Hepatocellular carcinoma (HCC), cirrhosis, or liver fibrosis are more likely to develop in people with NASH. According to available data, there are several reversible cycles in the early phases before the disease progresses to fibrosis, indicating that the transition from NAFLD to NASH is a dynamic process. Both hepatocellular carcinoma (HCC) and NASH-related cirrhosis may occur as consequences of rapid fibrosis developing in approximately 10-20% of these cycles [2]. Besides the increased incidence of cardiovascular morbidity and mortality, NAFLD patients suffer from a significantly greater prevalence of atherosclerosis and other cardiovascular risk factors [3]. Fig. (**1**) illustrates the progression of Non-Alcoholic Fatty Liver Disease (NAFLD) from a healthy liver to cirrhosis, along with its underlying aetiology.

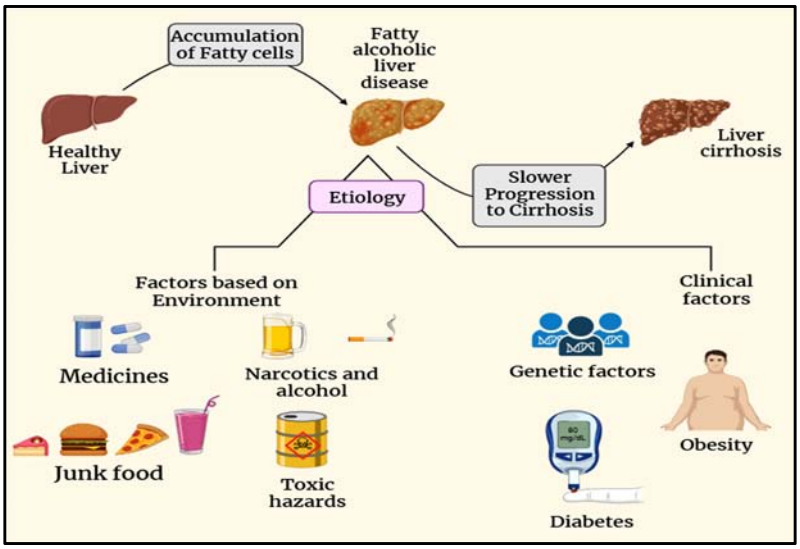

Fig. (1). Schematic diagram of Non-alcoholic Fatty Liver Disease (NAFLD) development from healthy liver to cirrhosis and its aetiology.

Patients with FLD often present with associated metabolic disorders, including insulin resistance, type 2 diabetes (T2D), hypertension, abdominal obesity, and dyslipidemia. Irrespective of other comorbidities, cardiovascular diseases are, by far, the commonest cause of death among FLD patients [4]. However, it is important to note that FLD can also develop in patients without metabolic syndrome. As highlighted in this chapter, FLD is a complex condition resulting from multiple interacting mechanisms and patient-specific pathways [5]. A diagnosis of FLD confirms the presence of hepatocellular steatosis, defined as an excess fat accumulation exceeding five percent of liver weight [6]. Steatosis has two types: macrovesicular and microvesicular. While macrovesicular steatosis is the most common type in patients with FLD, microvesicular steatosis is observed in roughly 10% of patients [7]. Prior studies have suggested FLD to be a benign condition. Compared to NASH, studies using paired or repeated liver biopsies suggested FLD has a much better overall prognosis, along with a lower risk of cirrhosis development. However, this idea was contested when more data became available, and FLD is now acknowledged as a progressive illness [8, 9]. The worldwide obesity and diabetes epidemics are the main causes of the rise in NAFLD as a health concern [10]. On the other hand, greater than 5% hepatic steatosis is a characteristic of metabolic-associated fatty liver disease (MAFLD), which does not rule out other liver disorders, including alcoholic liver disease [11]. Hepatic and systemic insulin resistance, gut dysbiosis, lipotoxicity, and hepatic immune dysfunction are all part of the pathogenesis, making this ailment a classic example of a systemic metabolic disease [12].

EPIDEMIOLOGY OF NAFLD

Non-Alcoholic Fatty Liver Disease (NAFLD), which presently affects an estimated 38% of the world's residents, has rapidly become the most common liver disease globally. Although only a small percentage of NAFLD patients progress to cirrhosis or hepatocellular carcinoma, the large overall prevalence of the disease means that a significant number of individuals remain at risk for these serious complications [13]. The global increase in metabolic syndrome, obesity, and diabetes has led to a considerable rise in the prevalence of NAFLD, which currently affects around 25% of the world's population [14]. Due to the increasing prevalence of non-communicable illnesses, major lifestyle changes over the past century have changed health priorities worldwide. The rising burden of NAFLD, which coincides with the global rise in obesity, is directly associated with the developing epidemic of chronic liver disease. It is now believed that 24% of people worldwide have NAFLD. While studies based on elevated liver enzymes have consistently overestimated the true prevalence, community surveys using proton NMR spectroscopy or ultrasonography have assessed the prevalence of

CHAPTER 11

Pharmacokinetics and Pharmacodynamics of Nanocarrier-based Therapeutics

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Abstract: Fatty liver disease, comprising non-alcoholic fatty liver disease (NAFLD) and its more acute form, non-alcoholic steatohepatitis (NASH), has emerged as a significant health challenge because of its intricate relationship with metabolic disorders worldwide. Despite several therapeutic developments, the effectiveness of traditional drug delivery methods is restricted due to their low bioavailability, fast degradation, and inadequate hepatic targeting. In contrast, nanocarrier-based therapeutics have emerged as viable strategies for enhancing the pharmacokinetics and pharmacodynamics of drugs. Pharmacokinetic studies revealed that nanocarrier delivery systems, including polymeric nanoparticles, liposomes, and lipid nanoparticles, can substantially enhance drug biodistribution and liver accumulation while reducing enzymatic degradation and premature clearance. In addition, they enable liver-targeted delivery via active targeting with surface ligands or passive accumulation via the increased permeability and retention effect, thereby minimizing systemic toxicity and improving therapeutic efficiency. Pharmacodynamic investigations demonstrated that nanocarrier-based systems effectively modulate key pathways, including inflammatory pathways, lipid metabolism, oxidative stress, and fibrosis inhibition, in the management of fatty liver disease. Furthermore, preclinical data reveal promising results with surface ligand nanocarriers, such as peptides and antibodies, which enhance cellular targeting via receptor-mediated drug uptake by hepatocytes and stellate cells. This chapter highlights the pharmacokinetics and pharmacodynamics of nanocarrier-based therapeutics for the management of fatty liver disease, discussing recent advancements, challenges, and potential future directions. By understanding these dynamics, highly effective, targeted treatments can be developed for the management of fatty liver disease, thereby addressing a significant, overlooked clinical need.

Keywords: Fatty liver disease, Liver-targeted drug delivery, Nanocarrier, Pharmacokinetics, Pharmacodynamics.

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INTRODUCTION

Overview of Fatty Liver Disease (FLD)

Among liver pathologies, fatty liver disease (FLD) is the leading and most prevalent histological abnormality among liver disorders, which involves a pathological sequence starting from steatosis (simple fat accumulation in the liver), potentially evolving into steatohepatitis (inflammation), with or without perisinusoidal fibrosis, culminating in cirrhosis and liver cancer. Most recent data revealed that the mortality rate related to cirrhosis has increased by 65% annually, and a rising trend in liver cancer-related death has approximately doubled in the United States over the past three decades [1]. Furthermore, steatosis arises primarily from dysfunction of the lipid metabolic pathway, along with alterations in the body's energy regulation [2]. The FLDs are classified based on the underlying cause or etiological exposure involved in their progression. Initially, fatty liver disease (FLD) was classified as alcoholic liver disease (ALD) based on high alcohol intake, followed by non-alcoholic fatty liver disease (NAFLD), which is now also referred to as metabolic dysfunction–associated steatotic liver disease (MASLD) [3, 4]. Although NAFLD/MASLD is usually linked with metabolic disorders, such as diabetes and obesity, it is not restricted to individuals with these conditions [5]. Moreover, it is increasingly recognized that long-term exposure to workplace chemicals and environmental toxins may be associated with the development of FLD, which is termed toxicant-associated steatohepatitis (TASH) [6]. All these conditions could progress into more serious NAFLD/MASLD complications, like cirrhosis or hepatocellular carcinoma (HCC), liver fibrosis, metabolic dysfunction-associated steatohepatitis (MASH), or non-alcoholic steatohepatitis (NASH), which could be the reason for early morbidity and death in FLD patients globally. Therefore, the implementation of targeted treatment strategies and the adoption of healthier lifestyle changes are necessary to manage FLD [7, 8].

Non-Alcoholic Fatty Liver Disease (NAFLD)

MASH, an advanced form of NAFLD, is currently the leading cause of liver transplants in the U.S. and a critical reason for the development of HCC [9]. NAFLD, a term introduced by Schaffner in 1986, is characterized by steatosis (fat accumulation) in more than 5% of hepatocytes and is often associated with metabolic disorders, such as insulin resistance, primarily affecting individuals with type 2 diabetes (T2D), who consume little or no alcohol [10, 11]. It is estimated that NAFLD potentially affects up to one billion people globally and

accounts for around 25% of the world's total population. A dynamic modeling study assessing the health burden of NAFLD and NASH in the US population projected that by 2030, NAFLD and NASH cases will increase by 21% and 63%, respectively, with liver-related deaths expected to rise substantially by 178%, reaching approximately 78,300 deaths [12]. In those affected by NAFLD, the leading cause of death is cardiovascular complications, trailed by cancer and then liver failure, representing the second cause of mortality worldwide [11]. Necroinflammation and hepatocellular damage, including hepatocyte ballooning, are characteristics of non-alcoholic steatohepatitis (NASH), which raises the risk for cirrhosis, fibrosis, and other liver-related issues [13, 14]. However, NAFLD may arise as a result of an interaction between the metabolism of lipids and the immune system-driven inflammatory response. The term metabolic dysfunction-associated fatty liver disease (MAFLD) was suggested in 2020 by a global panel of experts to highlight the role of cardiometabolic risk factors in both the onset and worsening of hepatic disorder, including patients with additional hepatic diseases [13].

Non-alcoholic Steatohepatitis *(NASH)*

The progressive form of NAFLD, called non-alcoholic steatohepatitis (NASH), is marked by liver inflammation and steatosis (accumulation of fat in the liver), primarily affecting obese women over 50 years of age, especially those suffering from type 2 diabetes mellitus [15]. Furthermore, the PNPLA3 gene, which is highly expressed in the liver, is recognized as a key genetic factor linked to the progression of NASH, cirrhosis, as well as HCC risk, especially in individuals who have metabolic issues like insulin resistance, obesity, hypertriglyceridemia, high blood pressure, and metabolic syndrome, along with additional environmental factors, particularly alcohol intake and smoking. However, the majority of studies confirmed that the actual contributing factor promoting NAFLD progression to NASH remains unknown and requires further study. It may be driven by a complex interaction of genetic and environmental factors [16]. Overall, the prevalence of NASH-associated comorbidities is high (approximately 15 to 94%) with the rise in cases of obese and NAFLD populations, indicating a wider NASH population burden, as one-third of patients with NAFLD progress to NASH. Although the prevalence of NASH is increasing, reliable non-invasive diagnostic methods remain unavailable [17]. Therefore, the primary objective is to understand the epidemiological profile and prevalence of NASH in the healthcare sector and highlight critical gaps in existing knowledge to provide accurate recommendations for early detection and successful interventions [18].

CHAPTER 12

Safety and Toxicity Considerations of Nanocarrier-based Therapeutics

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Abstract: A novel strategy in pharmaceuticals, nano-formulations increase therapeutic effectiveness, decrease side effects, and enhance medication dispersion. In this study, the laws, safety, and ethics related to nano-formulations are covered in great detail. Regulatory obstacles, such as the need for particular legislation designed for medications using nanotechnology, are a significant issue. A thorough analysis of characterisation methods, stability evaluations, and the development of standardised production and quality control procedures are all necessary to address these issues. To ensure effectiveness and safety while accelerating the transition of research into clinical applications, regulatory authorities worldwide must create flexible frameworks to streamline approval processes. Risk-benefit analyses, informed consent, and fair access to technical innovations are the main ethical factors in nano-formulations. Making moral decisions requires weighing potential advantages against potential disadvantages and maintaining open communication with all stakeholders. Furthermore, healthcare systems worldwide face moral conundrums about the fair distribution and cost of these cutting-edge treatments. Important safety issues include knowing how nanoparticles interact with the biological environment, their potential toxicity, and their long-term impacts. Thorough safety evaluations, including in vitro and in vivo studies, are necessary to assess biocompatibility and mitigate unanticipated risks associated with nanocarriers. Ongoing safety evaluations are also conducted through post-marketing surveillance and continuous monitoring. Regulatory authorities, researchers, physicians, and ethicists must work together to fully use these formulations while maintaining patient safety, moral behaviour, and legal obligations.

Keywords: Bio-compatibility, Nanocarrier, Safety, Therapeutics, Toxicity.

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INTRODUCTION

Although still in its infancy, nanomedicine, the application of nanotechnology in medicine, has the potential to drastically transform the healthcare industry [1]. The rapidly expanding area of nanomedical research is being actively supported by government funding and legislation. As nanomedicines advance, they might provide many advantages over traditional therapies, including improved targeting, safety, effectiveness, bioavailability, dose response, and personalization [2]. Perhaps the most exciting concept in nanomedical research is the creation and manufacture of multifunctional nanoparticle (NP) complexes that simultaneously deliver therapeutic and diagnostic drugs to specific sites. These abilities might greatly enhance the monitoring, diagnosis, and treatment of patients. Despite these possible advantages, little is known about the pharmacokinetics, pharmacodynamics, and toxicity of certain nanomaterials.

Rising Interest Due to Enhanced Drug Delivery, Targeting, and Bioavailability

Nanotechnology has applications across the pharmaceutical, cosmetic, electronic, food, and numerous other industries. According to the Woodrow Wilson International Center for Scholars' Project on Emerging Nanotechnologies, approximately 800 products currently incorporate nanotechnology [3]. It has been employed in digital cameras, cell phones, computers, water filtration systems, and cosmetics. Research is also underway to enhance the solubility of food ingredients and develop packaging that can detect and prevent spoilage. In the medical field, nanotechnology has advanced various products and procedures, including medications, antimicrobial materials, medical imaging, sunscreens, burn and wound dressings, dental bonding agents, protective coatings for eyeglasses, and skin care products. Moreover, nanotechnology has improved drug targeting and absorption, increased the sensitivity of biomarker detection, enhanced therapeutic delivery, and advanced diagnostic imaging [4].

Importance of Safety and Toxicity Evaluation in Clinical Translation

The merging of nanotechnology with medicine gives rise to the interdisciplinary domain of nanomedicine [5]. Advances in genetics, proteomics, molecular and cellular biology, materials science, and bioengineering have supported this growing discipline, which focuses on physiological processes at the nanoscale. Most cellular internal operations naturally occur at the nanoscale, since various physiologically significant components, such as water, glucose, proteins, enzymes, receptors, haemoglobin, and antibodies, already have sizes within the nanoscale range. Many researchers are currently employing nanotechnology to enhance medical processes, equipment, and gadgets in terms of sensitivity, safety,

efficacy, and customisation. Nanotherapeutics may deliver benefits, including enhanced solubility, greater dose responsiveness, reduced toxicity, and improved absorption, compared with standard drugs [6]. Another major area of scientific interest is the production of magnetic nanoparticles (NPs) for the targeted delivery of diverse pharmacological or diagnostic chemicals.

The potential for detecting magnetic nanoparticles (NPs) via MRI and correlating the results with post-therapy histology has generated significant interest in magnetic NP targeting applications. Polymer/SPIO composites are the most commonly employed NPs for theranostics (diagnostics). The backbone of a polymer/IO conjugate may incorporate a number of anticancer drugs. The drugs may combine to perhaps boost efficacy by releasing at the tumour location. As SPIO NPs emit heat when exposed to an alternating magnetic field, external electromagnetic fields can also be used to remotely activate them for thermal ablation therapy [7].

TYPES OF NANOCARRIERS

Liposomes

In recent years, a lot of studies have focused on liposomes for the controlled delivery of medications. Liposomes are frequently stable owing to their biodegradable nature [8]. The inner core of the liposome holds the medicines. Liposomes may be used in a range of therapeutic applications due to their low toxicity, biodegradability, biocompatibility, and ability to encapsulate both hydrophilic and hydrophobic drugs. Liposomes were engineered to carry CD147 antibodies, a polyclonal antibody highly expressed in liver cancer cell lines and HCC tissues. Using CD147 as the target, a novel liposome-based carrier was developed to deliver doxorubicin. The results demonstrated that this nanocarrier exhibited enhanced cytotoxic effects in the HCC3736 model, as well as in Huh-7 and HepG2 cells [9].

The anticancer potential of hepatoblastoma (HB) against HepG2 cells was investigated using butyric acid (BA)-loaded chitosan-coated and uncoated liposomes. It was observed that the cytotoxic impact of chitosan-coated liposomes loaded with BA was greater than that of both free BA and uncoated liposomes. The experimental data indicated that sorafenib-loaded liposomes enhanced biocompatibility, reduced biotoxicity, and increased anti-tumour activity compared with free sorafenib. The study suggests that liposomes offer a novel, acceptable therapeutic approach as nanocarriers to extend the duration of HCC therapy.

CHAPTER 13

Case Studies: Nanocarriers Based Drug Delivery in Fatty Liver Disease

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Abstract: Non-alcoholic fatty liver disease (NAFLD) has become a global health concern due to its rising prevalence and its correlation with metabolic syndrome, diabetes, and cardiovascular disorders. Efficient drug delivery to the liver is a considerable challenge in managing fatty liver diseases due to the modified microenvironment and compromised liver function. Nanotechnology offers a viable approach for targeted medication delivery to the liver, which possesses distinct anatomical and physiological characteristics that make it an optimal target for nanomedicine. Various categories of nanomaterials, including inorganic nanomaterials, polymer nanomaterials, and multifunctional nanoparticles (NPs), have been investigated as potential agents for targeting this organ in the context of liver illnesses. Nanomedicine enhances internalization and penetration, thereby facilitating targeted drug delivery, combination therapy, and theranostics. Recent advancements in nanomedicine have led to efforts to integrate nanomaterials, including liposomes, polymer nanoparticles, micelles, and cocrystals, into pharmacotherapy for liver diseases. This integration significantly enhances drug solubility and targeting, thereby improving therapeutic efficacy and minimizing toxic side effects. This chapter explores a wide range of nanotechnology-based systems as potential innovative approaches for treating liver diseases, focusing on the different categories of nanocarriers, their advantages, and the challenges they pose.

Keywords: Non-alcoholic fatty liver, Nanocarriers, Nano-formulations, Nanotechnology.

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is more common than alcoholic fatty liver disease. It is characterized by deposition of excessive fat in the liver without

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or with little consumption of alcohol by patients [1]. It is a multi-factorial progressive liver disease encompassing a range of multiple liver disease conditions, ranging from benign simple hepatic steatosis (grade 1) to non-alcoholic steatohepatitis with lobular inflammation (grade 2), having substantial potential to progress to liver fibrosis (grade 3) to liver cirrhosis, followed by liver carcinoma and finally liver failure [2]. Epidemiological studies have documented a 38% prevalence of NAFLD globally in 2019, which has been increasing rapidly [3, 4]. NAFLD is also referred to as metabolic dysfunction-associated steatosis liver disease (MDASLD), as it has been found to be associated with several metabolic disorders, including type-2 diabetes, insulin resistance, obesity, dyslipidemia, hypertension, and cardiovascular disorders [5 - 7]. The growing prevalence of NAFLD has led to a rise in hepatic-related mortality and the need for hepatic transplantation; therefore, there is an urgent demand for an effective and therapeutic strategy to manage this disease or prevent disease progression. Currently, management of NAFLD primarily involves liver modifications, insulin-sensitizing agents, lipid-lowering medications, and dietary interventions. However, many promising drugs have failed to demonstrate therapeutic efficacy in late-stage clinical trials due to limited liver concentrations [8]. In this chapter, we review recent case studies on nanocarrier-based drug delivery systems aimed at hepatocytes, Kupffer cells, hepatic stellate cells, and liver sinusoidal endothelial cells for the treatment of NAFLD. The development of several novel drug carriers, such as liposomes, nanoparticles, nanoemulsions, and micelles, for poorly water-soluble pharmaceuticals, intended to improve bioavailability and reduce adverse effects, has been enabled by the magnificent growth in the field of biomedical biotechnology [9, 10]. Fig. (**1**) provides a comprehensive overview of recent research investigating nanotechnology-based approaches for diagnosing and treating NAFLD. A wide range of nanotechnology-based formulations, including liposomes, nanogels, polymeric nanoparticles, niosomes, dendrimers, and nanosuspensions, as well as quantum dots, have been examined to explore their therapeutic role in NAFLD treatment [11, 12]. However, many ongoing clinical trials for NAFLD/NASH are still focused on small drug molecules, lifestyle interventions, or non-nanoparticle-based biologics [13], with only a limited number of clinical trials directly involving nanocarrier-based systems. For instance, a double-blind, randomized, placebo-controlled trial in overweight/obese NAFLD patients showed that nanocurcumin supplementation (40 mg twice daily for 3 months) significantly improved serum lipids, glucose indices, inflammatory markers, liver transaminases, nystatin levels, and the degree of liver steatosis compared to placebo [15]. Similarly, BMS-986263, a lipid nanoparticle formulation encapsulating siRNA targeting HSP47 (a collagen chaperone), has been assessed in a phase 2 clinical trial in patients with advanced hepatic fibrosis due to NAFLD and shows promise for ameliorating fibrosis [16]. Beyond these

clinical studies, several preclinical studies employing *ex vivo*, *in vitro,* and *in vivo* disease models have provided invaluable insights into the development of nanocarrier systems for NAFLD treatment, which are discussed below.

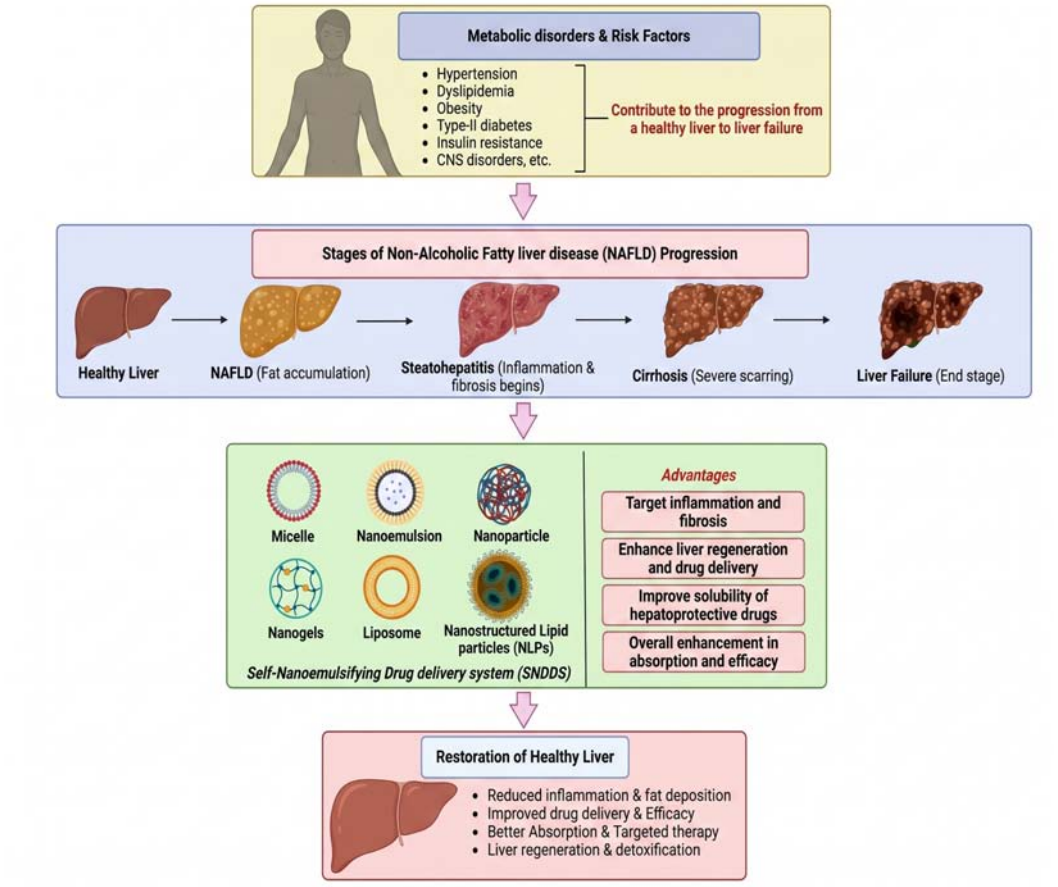

Fig. (1). Summary of various conditions of NAFLD and uses of nanocarriers for NAFLD treatment and diagnosis.

CASE STUDIES ON NANOCARRIER-BASED APPROACHES TO FATTY LIVER DISEASE

The section highlights various case studies on the application of nanocarriers for the management of fatty liver. These studies demonstrate the potential of nanocarrier systems in improving drug delivery, efficacy, and targeting in fatty liver disease.

CHAPTER 14

Challenges and Opportunities in Nanocarrier-based Drug Delivery for Fatty Liver Disease

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Abstract: Fatty liver disease (FLD), ranging from benign hepatic steatosis to non-alcoholic steatohepatitis (NASH), is becoming the most common chronic liver disease globally, largely propelled by the global epidemic of obesity, type 2 diabetes, and metabolic syndrome. Although it has a growing burden and potential for progression to cirrhosis and hepatocellular carcinoma, no pharmacotherapy is universally agreed upon, and lifestyle changes alone are frequently insufficient to prevent further disease progression. Successful treatment is hindered by the multifactorial etiology of FLD and by the limitations of systemic drug administration, such as low solubility, fast degradation, and off-target toxicity. Targeted drug delivery systems, especially nanocarrier-based platforms, have emerged as a promising solution to overcome these limitations. Nanocarriers enhance drug stability and solubility, and facilitate liver-specific uptake via passive and active targeting mechanisms. In addition, they facilitate the controlled release of drugs, the simultaneous co-delivery of dual therapeutic agents, and the minimization of systemic side effects, all of which are vital for the treatment of chronic liver diseases. In this chapter, the therapeutic application, existing limitations, and novel approaches of nanocarrier-mediated drug delivery in FLD are discussed with emphasis on its revolutionary role in the formulation of more efficient and safer long-term treatment protocols.

Keywords: Controlled release, Fatty liver disease, Liver fibrosis, Metabolic syndrome, Non-alcoholic steatohepatitis, Nanocarriers.

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INTRODUCTION

Fatty liver disease (FLD) is arguably the most common chronic liver condition globally, fueled by the rising incidence of obesity, type 2 diabetes mellitus, and metabolic syndrome. FLD represents a heterogeneous group of liver disorders, ranging from simple hepatic steatosis (fatty infiltration of hepatocytes) to non-alcoholic steatohepatitis (NASH), which is characterized by inflammation, hepatocellular injury, and varying degrees of fibrosis. Untreated NASH will progress to cirrhosis, liver failure, and finally hepatocellular carcinoma [1, 2]. Unlike alcohol-induced liver disease, FLD occurs in patients regardless of alcohol consumption, and its occult, insidious progression often results in delayed presentation at an advanced stage. Despite increasing FLD global load, no universally accepted pharmacotherapy exists for this entity; the cornerstone of management remains lifestyle modifications. However, lifestyle modification is itself typically not sufficient to stop disease progression in patients with NASH and fibrosis. This underscores the need for practical therapeutic measures that can influence the multifactorial pathological processes underlying FLD, such as hepatic steatosis, insulin resistance, inflammation, and fibrogenesis [1]. Drug delivery to the liver, specifically to cell types, such as hepatocytes, hepatic stellate cells, or Kupffer cells, without inducing side effects in other organs, remains one of the greatest challenges in developing effective treatments for FLD. Most candidate therapeutic compounds, including antioxidants, anti-inflammatory drugs, and anti-fibrotic agents, are plagued by low water solubility, rapid degradation, short circulation half-lives, and off-target toxicity following systemic administration. In addition, the complex architecture of the liver and the altered microenvironment in FLD, *i.e*., steatosis and fibrosis, may interfere with drug penetration and action. These constraints emphasize the value of targeted drug-delivery systems that can improve the bioavailability of the therapeutic agent, selectively target diseased liver tissues, and reduce systemic side effects [2]. Targeted delivery systems would not only improve the therapeutic index of drugs but also enable low-dose therapy and less treatment-related toxicity, an important factor in chronic diseases like FLD that need to be treated for many years. Nanocarrier-based drug delivery systems present a promising solution to these problems. Taking advantage of the desirable properties of nanoscale materials, *i.e*., their size-controllable dimensions, surface properties, and drug-loading ability, nanocarriers are able to deliver drugs in a stabilized state, increase their solubility and stability, and allow them to accumulate in the liver through passive or active targeting mechanisms [3]. Passive targeting leverages the liver's natural filtering capacity and fenestrated vasculature to increase nanoparticle uptake, whereas active targeting entails surface modification of the nanocarrier with ligands that bind receptors overexpressed on liver cells, *i.e.*, the glycoprotein receptor of hepatocytes or the mannose receptor of Kupffer cells [4]. In addition,

nanocarriers can be designed to release drugs in a sustained, controlled manner, prolonging therapeutic action with fewer doses. Nanocarrier systems are also highly versatile for the co-delivery of two or more drugs, which can treat the multifactorial pathogenesis of FLD more effectively. With future advancements in materials science and nanotechnology, nanocarrier-based therapy is poised to revolutionize the therapeutic paradigm for FLD, offering new hope of halting or even reversing the disease process [5]. This chapter presents the potential, challenges, and novel applications of nanocarrier-based drug delivery methods for the treatment of fatty liver disease.

PATHOPHYSIOLOGY OF FATTY LIVER DISEASE

Fatty liver disease (FLD) is generally classified into two categories based on its etiology: alcoholic fatty liver disease (AFLD) and non-alcoholic fatty liver disease (NAFLD). Even though they share histological features, such as hepatic steatosis, inflammation, and fibrosis, their etiologies are quite distinct [6]. AFLD is a consequence of long-standing and excessive alcohol use, and the subsequent hepatic accumulation of fat is a result of dysfunctional oxidation of fatty acids, augmented lipogenesis, and oxidative damage induced by ethanol. NAFLD, by contrast, affects patients with little or no alcohol use and is very much related to metabolic risk factors, including obesity, type 2 diabetes, dyslipidemia, and insulin resistance. NAFLD has emerged as the world's leading liver disease after the increasing epidemic of metabolic syndrome. Both types of FLD tend to progress through similar pathological phases: simple steatosis (steatosis and inflammatory liver) to steatohepatitis (hepatocytic injury and inflammation), followed by fibrosis, cirrhosis, and, finally, hepatocellular carcinoma [7]. The non-alcoholic form, however, is more insidious in its course and would remain undetected until late because it is usually asymptomatic. At the molecular level, the pathogenesis of FLD is multifactorial and further exacerbated by a cascade of fibrotic remodeling, inflammatory reactions, and metabolic derangements. In NAFLD, insulin resistance is the primary driver of excess lipid deposition in the liver by enhancing rapid free fatty acid flux from adipose tissue, promoting de novo lipogenesis, and inhibiting fatty acid oxidation [8]. This excess lipid triggers lipotoxicity and hepatocyte injury and activates stress signaling pathways, including oxidative stress, ER stress, and mitochondrial dysfunction. Cellular stresses induce the release of pro-inflammatory cytokines (*e.g.*, TNF-α, IL-6) and chemokines, leading to recruitment of immune cells and sustenance of hepatic inflammation. In addition, the gut-liver axis plays a role; dysbiosis and elevated gut permeability facilitate endotoxin (*e.g.*, lipopolysaccharide) translocation to the liver and contribute to enhanced inflammation [9]. In AFLD and in NAFLD, ongoing hepatocellular tissue damage induces hepatic stellate cells to undergo

CHAPTER 15

Emerging Trends and Future Perspectives for Fatty Liver Disease Management

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Abstract: The term "fatty liver" describes the buildup of triglycerides in the hepatocytes, which can result in steatohepatitis and is linked to a number of illnesses, including type 2 diabetes, elevated oxidative stress, inflammation, obesity, heart disease, and liver disease, especially metabolic dysfunction associated with fatty liver disease. This may then develop into cirrhosis and ultimately a higher chance of hepatocellular carcinoma (HCC) development. Fatty liver disease appears in two main types: alcoholic liver disease and non alcoholic liver disease, which may develop into cirrhosis, fibrosis, and hepatocellular cancer. Although liver biopsies are the gold standard for assessing fat and determining the extent of fibrosis, they are invasive and cannot be used in large patient groups. Traditional methods, such as ultrasound, are more subjective and yield qualitative evaluations of fat. Furthermore, its medical significance needs to be re-evaluated, as it may be challenging to detect inflated hepatocytes with limited biopsied specimens. Body fluid indicators and less invasive imaging techniques are required because repeated liver biopsies to evaluate histological NAFLD activity for therapy response are also unfeasible. The significance of advanced fibrosis as a factor influencing the outcome of non-alcoholic fatty liver disease has been highlighted by recent longitudinal observational studies. A number of clinical trials are underway to develop a first-in-class medication, despite the significant heterogeneity of NAFLD with respect to underlying disease, patient age, and fibrosis stage. To address unmet medical needs, this chapter provides an overview of the current state and future prospects of fatty liver disease research.

Keywords: Fatty liver, Fibrosis, Hepatocytes, Hepatocellular cancer.

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INTRODUCTION

Overview of Fatty Liver Disease

The term “fatty liver” refers to the accumulation of triglycerides in hepatocytes, which can lead to steatohepatitis [1]. Subsequent development of liver cirrhosis and hepatocellular carcinoma (HCC) may occur. Fatty liver disease appears in two main types: non-alcoholic fatty liver disease (NAFLD), which is primarily associated with insulin resistance and metabolic syndrome, and alcoholic fatty liver disease, which is induced by chronic alcohol consumption. The frequency of NAFLD in India has been shown to range from 9 to 53%, making fatty liver a major global epidemic. Given India's enormous population, fatty liver can have a detrimental effect on the country's limited resources and place a significant strain on the healthcare system [2]. The frequency of NAFLD in India has been shown to range from 9 to 53%, making fatty liver a major global epidemic. Given India's enormous population, fatty liver can have a detrimental effect on the country's limited resources and place a significant strain on the healthcare system [3]. The liver can store fat for several reasons, as shown in Fig. (**1**).

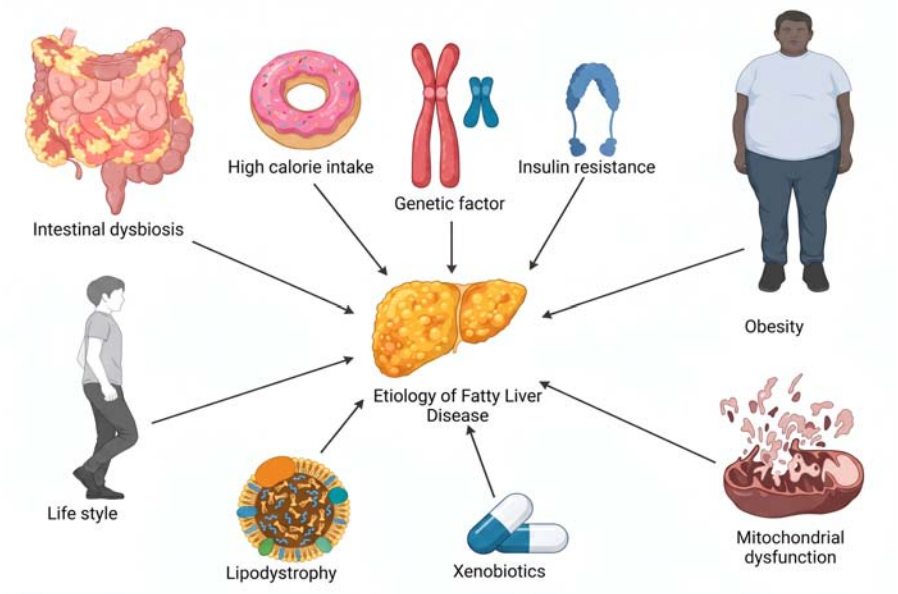

Fig. (1). Etiology of fatty liver disease.

Stellate cells can be activated by oxidative stress in hepatocytes, leading to inflammation and collagen synthesis. In the 19th century, pathologists began to understand the importance of higher fat deposition in the liver. Numerous

extensive studies conducted by American and European pathologists over the 20th century have shown links between cirrhosis and hepatic steatosis and alcohol, diabetes, and obesity [4]. The 1980s Mayo Clinic study is credited with introducing the term "NASH" into the fatty liver disease nomenclature, even though it was not the first to use the term. In the study on 20 individuals with liver biopsies, Ludwig *et al*. found that 90% of them were obese, 65% were female, 25% had diabetes and/or hyperlipidemia, and 15% had hypertension. Over the next ten years, the concept of NAFLD gained acceptance, in large part due to pathologists' contributions to clinico-pathologic studies [5]. According to these studies, 2.8% of the U.S. population had "unexplained" elevations in liver tests. In the latter study, an elevated body mass index (BMI) accounted for 68% of these instances [6]. These findings highlight the usefulness of tissue evaluation in identifying non-fatty entities, such as diabetic hepatosclerosis. Significant steatosis is not observed in either of these conditions [7]. This chapter covers the types, pathophysiology, and treatment of fatty liver disease.

Types of Fatty Liver Diseases

There are various types of fatty liver disease [8]. Some of them are mentioned in Fig. (**2**), and their detailed introduction is discussed as follows:

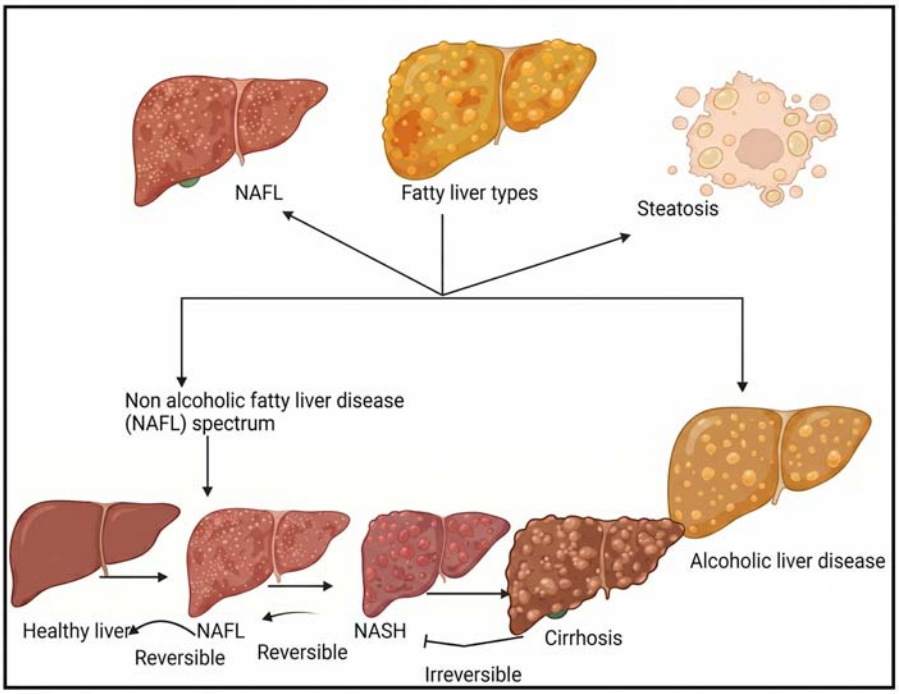

Fig. (2). Types of fatty liver disease.

SUBJECT INDEX

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Dr. Anjali Sharma is an academician and researcher, currently serving as Associate Professor (Pharmaceutics) at Guru Gobind Singh College of Pharmacy, Yamuna Nagar, Haryana, India. With over 12 years of teaching experience, including extensive postgraduate teaching, she has made significant contributions to pharmaceutical education and research. Her expertise lies in nanotechnology-based drug-delivery systems, with a focus on improving therapeutic efficacy and patient compliance. She has an impressive academic portfolio comprising 50 research/review publications, 45 book chapters, seven books, 12 design patents, and 5 copyrights. A life member of APTI and IPGA, she has received several prestigious awards for her contributions.

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Dr. Devkant Sharma is an academician currently serving as an Associate Professor at Ch. Devi Lal College of Pharmacy, Jagadhri, Yamuna Nagar, Haryana, India. He holds a B.Pharm from Pt. B.D. Sharma University of Health Sciences, Rohtak; an M.Pharm (Pharmaceutics) from Punjab Technical University, Jalandhar; and a Ph.D. in Pharmaceutical Sciences from Shobhit University, Gangoh. With over 13 years of teaching experience, his research expertise centers on lipid-based drug delivery systems. He has a strong academic record, including 30 research and review publications, 40 book chapters, three authored books, 10 design patents, and 5 copyrights. He was honored with the Pharma Excellence Award (2024) by IPGA Uttarakhand State Branch.

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Ajmer Singh Grewal, Ph.D. (Pharmaceutical Sciences), is a Professor of Pharmaceutical Chemistry with over 14 years of experience in pharmaceutical education and research. His expertise lies in computational drug design and medicinal chemistry, focusing on anticancer, anti-diabetic, anti-Alzheimer's, and anti-inflammatory agents. He has authored 130+ research articles, 25 books, and holds multiple patents. Dr. Grewal has supervised postgraduate and doctoral research scholars and is actively guiding Ph.D. candidates. He has received several prestigious recognitions, including inclusion in Stanford University's World Top 2% Scientists list and the Best Innovative Teacher Award, reflecting his excellence in research and academic leadership.

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Geeta Deswal, Ph.D. (Pharmaceutical Sciences), is a Professor and Head of Pharmacognosy with over 14 years of experience in pharmaceutical education and research. Her expertise includes phytochemical analysis, herbal drug standardization, and plant tissue culture. She has published 32 research papers and holds multiple patents, design registrations, and copyrights, along with several books and book chapters. Dr. Deswal has secured research grants from DBT and MSME and actively contributes to academic quality assurance through IQAC and NBA coordination. A dedicated mentor and researcher, she has supervised numerous undergraduate and postgraduate students and organized various academic and professional development programs.

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Dr. Ganga Reddy Velma is a Scientist III at the University of Arizona, USA, in the R. Ken Coit College of Pharmacy, where he is engaged in drug discovery programs focused on triple-negative breast cancer (TNBC), Alzheimer's disease, and SARS-CoV-2. He previously worked as a Visiting Research Fellow at RMIT University, Australia. He received his B.Sc. (2009) and M.Sc. (2011) degrees in Chemistry from Osmania University, Hyderabad, and earned his Ph.D. in Medicinal Chemistry from CSIR-Indian Institute of Chemical Technology (IICT), Hyderabad. His research focuses on the rational design and development of small-molecule therapeutics for drug discovery, with expertise in lead optimization.