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].