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Review

Targeting key players in lipid biosynthesis for NAFLD and NASH treatment

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Abstract

Undoubtedly, nonalcoholic fatty liver disease (NAFLD) is widely recognized as one of the most prevalent liver diseases worldwide, encompassing a broad spectrum from simple steatosis to the most advanced stage of nonalcoholic steatohepatitis (NASH). However, effective treatments for NAFLD and NASH have not yet been clearly defined. Using appropriate terms such as "Nonalcoholic Fatty Liver Disease", "NAFLD treatment", “Lipid metabolism”, “lipid biosynthesis”, autophagy “bFGF” and TFG-b” apoptosis, we searched for relevant articles in the PubMed and Scopus databases. This review will discuss the role of the most important players in controlling lipid biosynthesis and lipid metabolism imperfection, which leads to NASH and NAFLD. Furthermore, potential pharmacological agents for targeting molecules and signaling pathways involved in liver inflammation, fibrosis, and cell death are also discussed.

Keywords: NASH, NAFLD, Fibrosis, Signaling pathways, Treatment.

1. Introduction

Nonalcoholic fatty liver disease (NAFLD) refers to various conditions resulting from the accumulation of fat in the liver [1]. In fact, this kind of fatty liver [2] causes insulin resistance, which is presented as the presence of steatotic tissue in more than 5% of liver cells [3]. Fatty liver disease consists of nonalcoholic steatohepatitis (NAFLD) and nonalcoholic steatohepatitis (NASH). They can be recognized when they are involved in inflammatory activity and damage to liver cells in steatotic liver tissue [4]. A global increase in factors such as extra weight due to increasing caloric intake accompanies the widespread prevalence of NAFLD.. It causes a rise in body mass index (BMI) [5]. Finally, NAFLD results in hepatocellular carcinoma (HCC), liver dysfunction, and decompensated liver disease and makes patients prone to liver transplantation [6].

NAFLD includes various liver lesions and the occurrence of extrahepatic consequences. On the other hand, NASH, that is, steatosis along with prolonged inflammation with cellular damage histologically, along with lobular inflammation and blebbing of liver cells, it is clear that the second factor is the driving force of fibrosis, which in turn may turn into cirrhosis and decompensated cirrhosis [7, 8]. It has been reported that the disease progression is often slow in noncirrhotic NAFLD, and more than twenty percent of target patients with NAFLD expand a progressive form of NASH within 3 to 7 years [9]. In 10 to 20 years, more than 9-25% of people with NASH spread cirrhosis [10]. Of course, it is complicated to distinguish NASH from cirrhosis in patients because NASH is a complex multifactorial cause defined by genetic, lifestyle, epigenetic, and nutritional factors [10, 11]. Therefore, liver fibrosis is one of the major causes of liver-related mortality as well as morbidity [12] by increasing factor fibrosis (F) up to ≥ 2 based on the rank of 0-4, as suggested

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by the NASH Clinical Research Network Scoring System (NASH CRN) [13].

Despite the increasing incidence of NAFLD and NASH, effective therapeutic strategies remain limited. Understanding the underlying mechanisms of lipid accumulation in the liver and identifying key molecular targets in lipid biosynthesis are critical for developing new treatments. This review aims to provide a comprehensive overview of the multifactorial causes of hepatic lipid accumulation and the pivotal roles of different cell types and metabolic pathways involved in the progression from NAFLD to NASH. By highlighting key players in lipid biosynthesis and exploring common therapeutic approaches, this review seeks to inform future research directions and potential therapeutic interventions.

2. Causes of lipid accumulation inside of the liver (hepatic infection, alcohol abuse, diet, microbiome)

In the human intestine, there is a population of many bacteria, viruses, fungi, and archaea, and the microbiome differs with environmental factors such as diet, drugs, and age [14]. Any disturbance in the microbiome (dysbiosis) causes diseases such as obesity, inflammatory bowel disease, diabetes, cardiovascular disease, and liver cirrhosis. Of course, its cause-or-effect relationship is still not clear and needs a wider investigation [15]. Several studies related in animal and human models concluded that consumption of alcohol is connected to dysbiosis development [16]. In fact, alcohol increases the population of proteobacteria, Enterobacteriaceae, and Streptococcus and decreases bactericides, Acinetobacter, and Fecal coliform bacteria [16]. The presence of the mucous barrier in the intestine causes the immune function of the intestine, and the occurrence of any disorder in it causes disease. In fact, this mucosal barrier prevents pathogenic contents like Pathogen-associated molecular patterns (PAMPs) and bacterial endotoxins from entering portal circulation by connecting to neighboring enterocytes by claudin, occludin and apical obstruction zona proteins [17]. One of these causes of disruption in the intestinal mucosa is dysbiosis caused by alcohol consumption, which disrupts these tight connections. Therefore, immune system malfunction as well as increased circulation of inflammatory cytokines such as (TNF-α)and interleukin (IL)-1β disrupt the intestinal barrier [18].

3. The role of various types of cells in liver steatosis

A group of liver cells are involved in several vital functions in a healthy liver; for example, the response to damage is divided into two subtypes according to their functional status: resident Hepatic stellate cells (HSCs) and active HSCs [19]. The activation of hepatic stellate cells (HSCs) leads to liver damage, exemplified by Non-Alcoholic Steatohepatitis (NASH). This process involves a transition from a biogenic to a fibroblast phenotype, characterized by the loss of fat droplets and the development of contractile fibers. This transition results in increased cell proliferation and enhanced HSC chemotaxis, optimizing leukocyte recruitment through improved signaling mechanisms. Additionally, the maturation of the endoplasmic reticulum in HSCs supports the maintenance of extracellular matrix fibers and the production of matrix remodeling enzymes. (Figure 1) [20]. HSCs during the liver fibrosis progression can be activated by many intra- and extrahepatic factors that stimulate the immune system through a natural reaction called the inflammatory response.. HSCs reside in Disse, which means a perisinusoidal atmosphere between hepatocytes and liver sinusoidal endothelial cells, and store vitamin A in lipid drops, depicting the main storage site of that vitamin in humans [21]. PPARγ, C/EBPS, C/EBPB and SREBP-1c are crystallized by HSCs, adiponectin receptor 1, perilipin 2 (PLIN2/ADFP), adiponectin receptor 1, and perilipin 2 (PLIN2/ADFP) [22]. Consequently, activated HSCs are able to engage in inflammation of the liver by secreting cytokines (Figure 1) [23]. NAFLD proceeds with RAS activation, not only in the circulation but also locally in the liver [24]. RAS is composed of two routes: the classical route consists of Angiotensin-converting enzyme (ACE), angiotensin II (Ang II), Angiotensin II receptor type 1 (AT1R), and ACE/AngII/AT1R. ACE plays an important role in the classical RAS pathway that transforms AngI to AngII, and AngII exerts its biological impacts primarily via the type 1 receptor (AT1). According to the evidence, it has been shown that activating this factor can increase the levels of Tumor necrosis factor (TNF) α and Transforming growth factor beta (TGF β), activate HSCs by using paracrine signaling and further develop NAFLD [25]. Based on these studies, the balance between ACE1 and ACE2 is very important for homeostasis in organs and NAFLD development. Angiotensin-converting enzyme 2 (ACE2), angiotensin 1-7, and Mas Receptor (MasR) form the ACE2/Ang-1-7/MasR axis. Evidence suggests that Ang (1-7), which further attenuates HSC activation, is related to decreased TGF-β [26].

4. Lipid metabolism imperfection leads to NASH

Perhaps in physiological/pathological conditions in the liver, lipid absorption progression is also mediated by liver FA binding protein (FABP1) and CD36. Suppose the protein in question is not adequately regulated. In that case, it will increase the excessive accumulation of Nonesterified FAs (NEFAs) and TG in the liver, and finally, the incidence of cytotoxicity and NAFLD will occur.

CD36 is one of the main receptors that exists in Fatty acids (FA) transportation as well as Triglyceride (TG) storage, which is produced in macrophages, monocytes, and liver, heart, and adipose tissues [27]. CD36, considered a

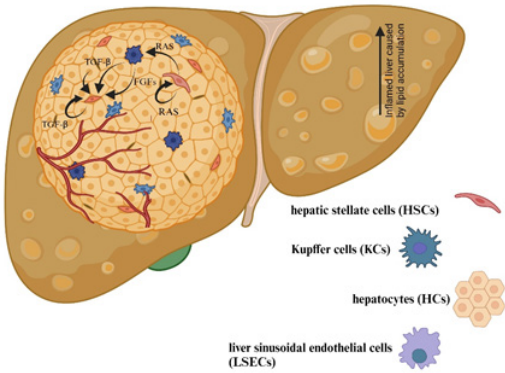

Fig. 1. The role of various types of cells accompanied in the progression of liver injury after lipid accumulation. TGF-β which is secreted from Hepatocyte cells affects stellate cells to change cells from quiescent to activated form. Another source of TGF-β is Kupffer cells which contributed to liver injury also by sending FGFs. Other players during liver injury are sinusoidal cells located near liver veins.

fatty acid protein, can promote the transport of such long-chain fatty acids (LCFAs) [28]. In other words, it can identify modified lipoproteins such as ox-LDL and improve the formation process of fat-filled foam cells. It also modulates events related to lipid utilization. Recent studies have shown that CD36 has an essential role in the organ, which can act by engaging in the absorption process of FA and TG saving and parting [29, 30]. CD36 acts as an agent of Free fatty acids (FFA) absorption in different tissues, and accordingly, the process of FA absorption has an essential role in liver steatosis. As a result, abnormalities in CD36 eventually cause liver steatosis [29].

FABP1 or L-FABP is considered one of the first family members of FABP, which has a higher concentration percentage in body organs such as the liver, kidney, and intestine [31]. The FABP group is a superfamily of low molecular weight (14-15 kDa) lipid-binding proteins that promote FA transport, storage, and utilization [31]. Therefore, FABP1 antisense ribonucleic acid (RNA) expression was significantly decreased [32]. The results of the laboratory studies clearly showed that the process of FA absorption increases with the excessive occurrence of FABP1. Therefore, the expression of FABP1 antisense ribonucleic acid (RNA) was significantly decreased [32]. Additionally, studies have shown that liver steatosis and liver damage caused by FFAs can be improved by better inhibiting FABP1 expression [33]. Therefore, the logical conclusion is that reducing the expression level of FABP1 can prevent liver steatosis and liver damage [33].

Additionally, defects in lipid metabolism lead to NASH [30], in which the following factors can play a prominent role:

The presence of fatty acids (FA) causes severe damage to the mitochondria, leading to their accumulation within these organelles. This accumulation contributes to insulin resistance and eventually results in liver inflammation and fibrosis. The damage disrupts membrane polarization, impairing the mitochondria's ability to complete β-oxidation and energy metabolism effectively. Consequently, this exacerbates the accumulation of FA in the liver [11].

Arachidonic acid metabolism and inflammation: Increased liver FFA levels have been introduced as the major causes of cell injury and death in NASH [34]. In contrast, the content of FFAs inside the liver in NAFLD patients remained unchanged [35]. This acid is considered one of the long-chain Omega-6 unsaturated fatty acids that are solid pro-inflammatory eicosanoid precursors. The two categories of increasing arachidonic acid levels in addition to decreasing n-3 FA levels can increase the rate of n-6:n-3 FAs [36].

Hepatic ceramide overload caused liver damage: Ceramide is made from one amino group in the sphingoid, which in turn can be saturated or monounsaturated fatty acid chains, the complete hydrophobic core of complex sphingolipids such as sphingomyelin and brain gangliosides, and form brain gangliosides [37]. Hepatic ceramide accumulation occurs from increased sphingomyelin hydrolysis via acid sphingomyelinase (ASM). ASM can be linked to NASH by a simple steatosis process. Therefore, ASM activity in NASH is increased by proinflammatory substances such as TNF-α, reactive oxygen species (ROS), and death receptor ligands, [38] which are critical areas for de novo synthesis in ceramides. The number of ceramide lipotoxicity process mechanisms in NASH can be as follows: 1) the presence of a kind of homeostasis imbalance in the calcium element in the Endoplasmic reticulum (ER), which results in apoptosis caused by endoplasmic reticulum stress; 2) NLRP3 inflammasome activation causes autophagy damage; and finally, 3) increasing the expression of hepcidin, which causes iron overload in the liver [39]. Therefore, the presence of ceramide ultimately causes liver damage, disturbances in sensitivity to insulin and mitochondrial metabolism, and an imbalance of calcium homeostasis in the ER.

5. The most important players in controlling lipid biosynthesis

5.1. TGF-β determination process

TGF-β signaling is engaged in physiological and pathological processes that play an important role in immunity, cancer, fibrosis, skeletal and cardiac diseases, and wound healing [40]. TGF-β members regulate and control many cellular activities, such as differentiation, cell proliferation, apoptosis, migration, and adhesion [41]. Cellular reactions to the TGF β signaling pathway may be further determined by the regulation of gene transcription. Accordingly, other tools for TGF-type β signaling to form cell behaviors, such as miRNA expression, epigenetic modification, and mRNA splicing, have been identified and offered [42]. Additionally, this procedure has been reported in cell metabolism regeneration [43]. Activated TGF-β ligands bind to a set of tetrameric receptors, including Type I and II TGF β receptors (TGF-βR), to better transmit the conventional TGF-β signal. On the other hand, TGF-βRII promotes TGF-βRI phosphorylation and propagates signals through SMAD2/SMAD3 phosphorylation to activate the cascade response. These proteins, together with SMAD4, are translocated to the basis in which the combination relates to the specific DNA region, SMAD limiting elements to accurately transcript genes [44]. If this technique is obstructed, the process of fatty acid oxidation increases, so the TGF β signaling pathway is undoubtedly capable of activating fatty acid synthesis. In other words, the three types of TGF-type β ligands were shown to increase the expression of stearoyl-CoA desaturase in a Smad-dependent way in various cell lines in the human body [45]. In addition, it can be said that other studies have also shown that the effect of TGF β on the oxidation and/or synthesis of fatty acids depends on the context (Table 1). Hep3B causes reduced absorption of carnitine-conjugated fatty acids that occurs concomitantly with fatty acid transporter gene regulation. This process means increasing the entry of carnitine-modified fatty acids into the mitochondria activated for β oxidation [46]. TGF-β2 or TGF-β3 can enhance the oxidation of fatty acids in myotubules and fat cells [47]. Liver ketone fractions are derived from acetyl-CoA made by oxidation of fatty acids, in which the further effects of TGF β signaling are still unclear and require further study. The lipid drop (LD) is a kind of organelle that has a primary role in processes such as fat and energy homeostasis [48]. The results showed that TGF-β induces various components in many cell types, which not only cause fatty acid storage but also the formation of LDs in acidosis-compacted cancer cells to meet cellular energy requirements for epithelial–mesenchymal transition (EMT) and cell invasion [49]. Zeynep and colleagues examined alterations in gene expressions related to lipid metabolism during TGF-ß-induced EMT, highlighting 180 genes linked to various aspects such as ß-

Table 1. The role of TGF-β and FGF in controlling lipid biosynthesis.

Study	Player	Lipid mediators	Metabolic changes	In vitro or In vivo evaluation	Results	Ref
Samuel et al., 2002	TGF-β	SCD	Unsaturated fatty acid synthesis ↑	Epithelial cells and fibroblasts	SCD Expression ↓	[70]
L Jiang et al., 2015	TGF-β	FASN	Fatty acid synthesis ↓	lung cancer cells	EMT induction	[71]
Li Yang et al., 2016	TGF-β	FASN	fatty acid synthesis ↑	A549CisR	EMT induction	[72]
Liu et al., 2020	TGF-β	FASN	Fatty acid synthesis ↓	lung cancer cells	EMT induction	[73]
Yamanaka et al.2004	TGF-β	SPHK1	Sphingosine-1P ↑	Fibroblasts	TIMP-1 upregulation	[74]
Valderrama-Carvajal et al., 2002	TGF-β	SHIP	PI(3, 4, 5)P3 ↓	hematopoietic cells	Induction of apoptosis	[75]
Schrumpf et al., 2020	TGF-β	CYP24A1	1,25(OH)2D3 ↓	Airway epithelial cells	Impaired host defense	[76]
Sato et al., 2003	TGF-β	Ceramide	Ceramide ↑	Fibroblasts	ECM production	[77]
Chen et al.,2003	TGF-β	Ceramide	Ceramide ↓	Fibroblasts	Cell survival	[78]
Corbet et al., 2020	TGF-β	Lipid droplet	Fatty acids storage ↑	Acidosis-adapted cancer cells	EMT, invasion	[48]
Trempolec et al., 2020	TGF-β	Lipid droplet	Fatty acids storage ↑	Dendritic cells	Impaired tumor immunity	[49]
Chauvin et al. 2015	TGF-β	ASAH1	Sphingosine ↑	Choriocarcinoma cells	Dysfunctional placentae	[75]
LUO et al., 2014	FGF19	Cyp7a1	C4 ↓	Mice model of cholestasis	Decreased hepatic bile acid accumulation	[79]
Gälman et al., 2003	FGF19	Cyp7a1	C4 ↓	healthy volunteers	Decreased hepatic bile acid accumulation	[80]
Harrison SA et al., 2018	FGF19	Cyp7a1	↓Liver fats, C4↓	NASH patients (II)	↓Liver fat content, ALT, AST	[81]
Mayo et al., 2018	FGF19	Cyp7a1	C4↓	PBC patients	↓ALP, GGT, ALT, AST, LDL	[82]
Oduyebo et al., 2018	FGF19	Cyp7a1	C4↓	Functional constipation	↓GE T1/2, fecal Bas ↑Colonic transit	[83]
Hirschfield GM., 2019	FGF19	Cyp7a1	C4↓	PSC patients	↓ C4, serum BAs, ALT, AST, GGT, pro-C3,	[84]
Talukdar S., 2016	FGF21	Cyp7a1	adiponectin↓	T2D	↓Triglycerides ↑ HDL	[85]
Sanyal A., 2018	FGF21	Cyp7a1	↓pro-C3 ↑adiponectin	NASH	↓ Body fat, hepatic lipids, Triglycerides, AST, ALT	[86]

SCD, stearoyl-CoA desaturase; FASN, fatty acid synthase; SPHK1, sphingosine kinase 1; ASAH1, N-acyphingosine amidohydrolase 1; SHIP, SH2 domain-containing 5′ inositol phosphatase; CYP24A1, cytochrome P450 family 24 subfamily A member 1; P4HA3, prolyl 4-hydroxylase subunit alpha 3, Cyp7a1: cholesterol 7α-hydroxylase, C4: 7α-hydroxy-4-cholesten-3-one, PBC: PBC, primary biliary cholangitis, EMT: epithelial-mesenchymal transition, ECM: extracellular matrix, NASH: nonalcoholic fatty liver disease.

oxidation, adipogenesis, and lipogenesis. Out of these, 29 genes showed notable changes in expression levels, including key ones like Egr1, Fasn, and Cebp. These findings underscore the intricate nature of lipid metabolism gene expressions during TGF-ß-induced EMT and emphasize the importance of cellular phenotypes in this context [50]. In addition, it increases the amount of LD substances in dendritic cells under different acidic bindings [51]. Serum deprivation protein response (SDPR), part of the caveolin family, is a likely target affected by TGF-β. Studies have shown that SDPR is notably reduced in gastric cancer and contributes to TGF-β-driven tumor metastasis. Functionally, SDPR interacts with extracellular signal-regulated kinase (ERK), suppressing the ERK/PPAR pathway to inhibit the transcription of a crucial fatty acid metabolism gene, Carnitine palmitoyl transferase 1A (CPT1A) [52]. (Table 1).

5.2. Basic fibroblast growth factor (FGF2/FGF-β)

Fibroblast growth factors (FGFs) can be a subset of a large family of 22 signaling proteins whose purpose is to regulate reproduction, growth, repair, and metabolism . Human FGF is grouped into 7 major subclassifications on the basis of phylogenetic divergence and sequence homology. Most FGFs are members of the classic FGF subgroups that act as paracrine factors and are connected with FGF receptors to activate them. It should be said that the three main endocrine members in the FGF are FGF19,

FGF21, and FGF23. All of them are involved in endocrine processes such as the metabolism of lipids, bile acids, and carbohydrates in the body, covering the extracellular matrix as well as free blood flow [53]. Endocrine FGFs act by activating their fibroblast growth factor receptors (FGFRs), which are considered nuclear receptors, along with associated glycoproteins; thus, FGF19 and FGF21 are recognized as important regulators of accurate metabolism of glycolipid content and bile acid by limiting FGFRs/β-Klotho. FGFR/α-Klotho stimulation in different glands, for example, the kidney and parathyroid glands, causes FGF23 to have a main role in regulating the amount of vitamin D and phosphate in processes such as homeostasis. In addition, it has been shown that the number of FGF members in other preclinical investigations maintains energy homeostasis better and regulates glucose and lipid metabolism more accurately [51]. The regulation and presence of FGF analogs greatly reduce the pathological conditions of liver steatosis, liver fibrosis, and steatohepatitis [54]. Both FGF19 and FGF21 are mainly useful medicines for NAFLD and are particularly effective in relieving liver fibrosis, steatohepatitis, and hepatic steatosis [55] (Table 1).

5.3. Autophagy

Autophagy is a cellular defense mechanism that aims to cope with external and internal cell threats [56]. One of its main roles is increasing the circulation of macromolecules and intracellular organelles to prohibit injury to cells, destroy pathogens, and increase their rejuvenation [56]. Macroautophagy, Chaperone-mediated mediated autophagy (CMA), and microautophagy are different types [56]. The most common mechanistic autophagy is macroautophagy, which contains the receptor of a bimembrane cell load not only that contains injured organelle protein collection but also other macromolecules and sends them to different intracellular organelles named a lysosome [56]. Such a fully fused structure, known as an "autolysosome," can degrade the contents of autophagosomes and target several pH-sensitive lysosomal hydrolases through efflux [56]. Some proteins are present in autophagosome structures, the identification of certain loads, autophagosome integration with lysosomes, and finally lysosome processes [56]. Therefore, the first set of proteins capable of contributing greatly to autophagosome formation consists of autophagy-activating kinases such as autophagy-related proteins1 (ATG1), Unc-51, and FIP200. The number of ATG subfamily genes, for example, the PI3K complex, such as ATG14L, BECN1, VPS34, and VPS15; the ATG9 vesicle, such as ATG2, ATG9A, and WIPI1/2; the ATG12 conjugation system, for example, ATG7, ATG10, ATG12, ATG5, and ATG16L; and the LC3 conjugation system, such as ATG4, ATG7, ATG12, ATG3APTG1, ATG12, ATG12, ATG12, ATG12, ATG12, ATG12, ATG12, ATG12, ATG12, ATG12, ATG12, ATG12, ATG12, ATG10, can be named [57]. Determining and controlling the volume of the cell load also includes other groups of proteins, such as SQSTM1, that are very effective in reaching the target inside autophagosomes [56]. Autophagosome combination with cell load with lysosomes can be attributed to protein movements such as Rubicon, VAMP8, Rab7, and STX17. Several proteins, such as LAMP1, LAMP2, and V-ATPases, which are associated with the lysosomal membrane, regulate lysosomal activity [56, 57]. The sensitivity of autophagy increases when autophagy is regulated by nutrient levels, intracellular energy, and extracellular hormones [58]. In the anabolic state and with the availability of sufficient nutrients for the organism to function, insulin production through activating mammalian of rapamycin group 1 (MTORC1) inhibits autophagy [58]. When energy is limited, AMP protein kinase (AMPK) is activated and induces that activity by exposing MTORC1 [58]. It is noteworthy that the process of autophagy transcription and lysosomal genes is made possible by using some core hormone receptors and is performed by Transcription factor EB (TFEB) [54]. Lipids alter cellular autophagy and play a prominent role in justifying damage from lipotoxicity in NAFLD [59]. Therefore, in NASH and NAFLD in both animal and human models, the autophagy process is impaired [60]. Since lipid metabolism affects the balance of energy during liver functions, autophagy has a vital role in NASH development. For this reason, autophagy assessment and cytokines which play roles in controlling it look very effective. Although we must take into account that studies evaluating autophagy during the progression of different liver diseases are widespread, it seems that more examination are still needed. The point is that autophagy plays the role of a double-edged sword in controlling liver disease. Moreover, the number of cytokines and molecules included in autophagy pathways is very variable. [61, 62].

5.4. Apoptosis

On the one hand, apoptosis (programmed cell death) is a conserved method under the control of genes, which is used for purposes such as the elimination of unwanted or unnecessary cells of living organisms, as well as in many mechanisms related to the system. Immunity or diseases are also involved, and on the other hand, they are also involved in forming exogenous apoptotic pathways that start with limiting other ligands within the cell surfaces, such as TNF, FasL, and TRAIL receptors [63]. Accordingly, the caspase superfamily can be one of the members of a large family of mature-kept cysteine, which is dependent upon endonucleases and mainly plays critical roles in actions such as cell death and inflammatory responses. Therefore, it can be stated that the caspases engaged in apoptosis are split into two general and significant classifications: 1) initiator caspases means 2, 8, 9, and 10; 2) and effector caspases means 3, 6, and 7 [64]. Current studies have shown that caspases 3, 6, 7, 8, and 9 cause further and faster progression of NASH [65]. Caspase-8 is generally involved in exogenous apoptosis. Caspase-9 may be involved in an endogenous way. The results show a positive increase in dUTP nick end labeling (TUNEL) with deoxynucleotidyl transferase in NASH patient liver tissue, which can show apoptosis engagement in that progression. The rate of endoplasmic reticulum stress has a significant relationship with lipotoxicity and NASH [66]. The Suppressor of cytokine signaling (SOCS) family is a group of proteins with negative feedback regulation in cytokine signaling pathways, which includes eight members of SOCS1-SOCS7 and cytokine-containing SH2 protein (CIS) [67]. Limited investigations have been conducted regarding the consequence of SOCS2 on local lipid metabolism, which can effectively prevent the action of hepatic steatosis stimulated by a high-fat diet [68]. Several studies have indicated that it does not increase Fatty Acid Oxidation (FAO)

in the liver [69]. Therefore, it is recommended to investigate the effects of SOCS family members by showing FAO via the JAK and STAT pathways in regulating macrophage polarization and apoptosis.

6. Common therapeutic approaches related to liver diseases

6.1. Origin based

One of the world's major health problems is chronic liver disease, which accounts for more than 2 million people annually. Liver cirrhosis is considered the 11th most common cause of death among liver diseases worldwide [87]. Liver cirrhosis in the early stages causes fibrosis in the liver, which is a reversible and complex pathological process. Organ fibrosis is considered one of the characteristics of the spread of prolonged inflammatory diseases. The logical evaluation shows that liver fibrosis treatment should be prioritized. Similarly, discussing etiological treatment means eliminating the primary pathogens and taking countermeasures against the category of liver fibrosis. Persistent liver damage is reduced on condition that the involved factors are suppressed or eliminated.. CHB nucleotide analogs of interferon can be mentioned among the effective therapeutic drugs in this disease. Entecavir can be considered a leading antiviral drug in treating 120 patients (CHB) with liver fibrosis, indicating that 54 patients, almost 45% of the patients, showed regression of fibrosis after passing 78 weeks of antiviral cure. undoubtedly, it reduces organ stiffness and liver fibrosis [88]. Sofosbuvir is indeed a nucleoside inhibitor of HCV-NS5B polymerase; Among the studies investigated, it is clear that the results showed significant improvement in liver fibrosis in 32 Community Health Center (CHC) patients with the problem after passing twelve weeks of tiny treatment. [89]. The results of various studies indicated that an immunosuppressive treatment is a vital way to reverse the process of Autoimmune Hepatitis (AIH) liver fibrosis. Patients with Drug-induced liver injury (DILI) and liver fibrosis must reduce or pause taking associated medications that cause liver damage and fibrosis. On the other hand, patients with liver fibrosis derived from NASH must balance their diet, exercise, and control their weight regularly. Also, patients with NASH should refrain from drinking alcohol [90] (Table 2).

6.2. Anti-inflammatory treatment

Other groups of treatment are the ones that target the pathways that help the progression of liver fibrosis. For instance, inflammation is part of the fibrotic process due to the activation of immune cells. As a result, anti-inflammatory drugs showed significant effectiveness in the rehabilitation of liver fibrosis. Moreover, during the development of liver diseases, mostly when lipid metabolism defection occurs, oxidative stress accompanies the liver injury. For these reasons, therapeutic approaches that targeted lipid degradation compartment showed significant potency. In continuing, a list of drugs that revealed the impact on liver dysfunctions was evaluated. In Table 2, the summary of the drugs and the origin of their function is presented. Cenicriviroc (CVC), simply play role as CCR2/5 chemokine receptor antagonist with an antifibrotic act in young patients with NASH. Studies related to the phase 2b CENTAUR showed the improvement of liver fibrosis without affecting steatohepatitis, providing a complex of CVCs with several molecular combinations that have many effects on the metabolism of NASH [91]. Puengel et al. showed a potential therapeutic approach by combining two pharmacological agents in a mouse model of NASH [92]. CCR2 and CCR5 antagonists were applied as antifibrotic agents, and an analog of Fibroblast growth factor (FGF21) was used to compare the impact of drug material treatment by applying compound treatment. The results of the combined treatment showed better healing effects in inflammation and fibrosis of the liver [92]. Further studies in the human NASH model should be performed to investigate this issue more precisely.

Thus, laboratory tests of the number of patients with NASH identified that a Gal-3 inhibitor called blepectin (GR-MD-02) was safe and highly effective at a dose of 8 in progressive fibrosis [93]. Conducting phase 2b multicenter placebo-controlled clinical tests (NCT02462967) regarding bleeding in patients with these conditions, such as liver fibrosis, NASH, and cirrhosis, revealed that the drug was tolerable and safe at a dose of 2 mg/kg for 52 weeks. It did not have a notable impact on reducing scores related to fibrosis or NASH. Related research has shown that a relatively high percentage of target patients in both the placebo and blepectin groups had wide ranges of side effects such as various infections and gastrointestinal diseases of level 1 (mild) or 2 (moderate) severity. A study conducted by Chalasani showed that 2 mg/kg blepectin reduces the gradient of venous pressure in the liver and further growth of varicose veins in NASH patients without the appearance of varicose veins in the esophagus [94]. Therefore, aspirin is a classic anti-fever and pain-killer drug that can quickly produce tremendous anti-inflammatory consequences by depicting IL-6 and TNF-α and reducing the number of inflammatory cells. It is also able to prevent generation, proliferation, and activation. of HSCs throug inhibit Toll-Like Receptor 4 (TLR4) or Nuclear Factor Kappa Beta (NF-κB) signaling. According to these results, aspirin is used as a potentially effective drug to cure liver fibrosis [95].

According to findings from gut microbiota analysis using shotgun metagenomics, patients with liver diseases like NAFLD exhibit a depletion of Adlercreutzia equolifaciens compared to healthy individuals. The abundance of A. equolifaciens decreases progressively with disease advancement, eventually disappearing in the advanced stages, indicating a strong correlation with disease severity. Additionally, research by Onate and colleagues has demonstrated that A. equolifaciens possesses anti-inflammatory properties, both in vitro and in a humanized mouse model of NAFLD. Thus, there appears to be an association between NAFLD progression, the presence of A. equolifaciens, and its anti-inflammatory effects [96].

Genistein, an isoflavone initially derived from the Dyer's Genista tinctoria plant found in the Fabaceae family, has notable effects on liver health [97]. Administering genistein at a dose of 0.3 mmol/kg body weight has shown to improve liver fibrosis and apoptosis in mice by reducing the expression of proinflammatory cytokines like TNF-α and IL-6, as well as profibrotic cytokines like TGF-β1, and cell caspase [98]. Additionally, in a rat model of NAFLD, genistein demonstrated significant enhancements in lipid profiles, lowered AST and ALT levels, and mitigated key NASH features such as hepatocyte balloon degeneration, macrovascular steatosis, and lobular inflammation. Moreover, genistein has been observed to suppress the

Table 2. Various categories of pharmacological agents target liver fibrosis by different mechanisms.

Study	Year	Agent	category	Dose	Research state	Target	Results
Bernuth S et al., [88]	2016	sofosbuvir	Origin based	400 mg daily	I	HCV NS5B polymerase	↓ELF ↓FibroScan
Wu S et al., [107]	2018	Entecavir	Origin based	0.5 mg	I	HBV reverse transcriptase	fibrosis regression
Berres M et al., [108]	2010	Met-CCL5	Anti-inflammatory	100 ng/ml	Preclinical study (mice)	CCR5	liver fibrosis↓
Friedman S et al., [109]	2016	Cenicriviroc	Anti-inflammatory	150 mg	IIb	CCR2/5	Complete resolution of NASH
Chalasani N et al., [93]	2020	Belapectin	Anti-inflammatory	2 mg/kg	Phase 3	Gal-3	No significant reduction in fibrosis
Liu Y et al., [94]	2020	Aspirin	Anti-inflammatory	40 mmol/L	Cell culture	TLR/NF-kB	α-SMA , TGF-β1↓
Loomba R et al., [110]	2018	GS-0976	Anti-inflammatory	20 mg	Phase 3	ACC	MRI-PDFF↓ TIM1↓ acylcarnitine↓
Gao Y., et al. [111]	2020	WZ66	Anti-inflammatory	50 mg/kg	Preclinical study (mice)	ACC1/2	TG, DG, PC, SM↓
Armstrong M et al. [112]	2016	Liraglutide	Anti-inflammatory	1.8 mg	Phase 3	GLP-1	Improvement of liver histology
Harrison S et al. [113]	2019	Resmetirom	Anti-inflammatory	80 mg	Phase 2	THR-β	Hepatic fat↓
Shen M et al. [114]	2020	Oroxylin A	Inhibition of oxidative stress	20-40 mg/kg	Preclinical study	ROS	PI3K/Akt/mTOR signaling↓ Fibrosis↓
Cheng Q et al. [115]	2019	Methyl ferulic acid	Inhibition of oxidative stress	5 mg/kg	Preclinical study (rat)	NOX4/ ROS	HA, PC-III, CIV, LN↓
Aoyama T et al., [116]	2012	GKT137831	Inhibition of oxidative stress	60 mg/kg	Phase 2	NOX1/4	ROS, NOX, ↓ Fibritic Genes↓
Colmenero J et al. [117]	2009	Losartan	Inhibition of oxidative stress	50 mg/day	Phase 4	AngII	NOXA-1, PC-I, MMP-2, uPA↓
Witek R et al. [118]	2009	VX-166	Inhibition of hepatocyte apoptosis	6 mg/kg	Preclinical study (mice)	Pancaspase	collagen 1α1, α-SMA↓ NAFLD activity score↓
Frenette C et al. [119]	2019	Emricasan	Inhibition of hepatocyte apoptosis	25 mg	Phase 2	Pancaspase	MELD, Child-Pugh scores, ↓NASH↓
Harrison S et al. [120]	2020	Emricasan	Inhibition of hepatocyte apoptosis	5 mg or 50 mg	Phase 2	Pancaspase	fibrosis improvement ALT, AST↓
Toda K et al. [121]	2009	Pentoxifylline	Inhibition of hepatocyte apoptosis	20 mg/kg	Preclinical study (rat)	TNF-α	HSC proliferation IL-6↓
Liu J et al. [122]	2011	β-elemene	Inhibition of hepatocyte apoptosis	-	Preclinical study (rat)	TNF-α	hepatic CD14↓ TNF-α↓ plasma endotoxin↓
Harrison S et al. [123]	2020	Selonsertib	Inhibition of hepatocyte apoptosis	6 mg or 18 mg	Phase 3	ASK1	hepatic phospho-p38↓ no antifibrotic effect
Yoon Y et al. [124]	2020	Selonsertib	Inhibition of hepatocyte apoptosis	50 mg/kg	Preclinical study (rat)	ASK1	Collagen↓ α-SMA↓ fibronectin↓

ELF: enhanced liver fibrosis, ACC: acetyl-CoA carboxylase, TGs: triglycerides, DGs: diglycerides, PC: phosphatidylcholine, SM: sphingomyelin, HA: hyaluronic acid, PC-III: procollagen type III, CIV: type IV collagen, LN: laminin, uPA: urokinase-type plasminogen activator, MELD: model for end-stage liver disease, ASK1: apoptosis signal-regulating kinase 1, GLP-1: glucagon-like peptide 1, Gal-3: galectin 3, THR- β: thyroid hormone receptor β, ROS: reactive oxygen species, NOX4: NADPH oxidase,

activation of the PERK-eIF2α-CHOP signaling pathway induced by a high-fat high-sucrose diet group [99]. It has also been reported that sleeve gastrectomy but not calorie restriction could induce higher plasma genistein levels by altering the gut microbiota. This change could promote NAFLD remission [100].

Emricasan is also a pancaspase inhibitor that can be useful in reducing liver apoptosis and inflammation by reducing the levels of aminotransferases and inflammatory markers in NAFLD patients [101]. Thus, a randomized placebo-controlled trial of 217 patients with cirrhosis of NASH, which were treated with 2 doses of 5 or 25 mg of placebo, indicated that emericasan was safe and well endured but was ineffective clinically [101] (Table 2).

Empagliflozin (EMPA) is, in fact, a sodium-glucose transporter marker that decreases the activation of HSCs and the expression of profibrogenic genes, such as α-SMA, TGF-β cytokine, and collagen 1α1. It also prevents fibrosis by reducing the Yes Associated Protein (YAP) level and its stimulation, which is done by phosphorylation. This can easily suppress the activated HSC proliferation process in vivo and in vitro by activating Hippo/YAP signaling [102].

6.3. Clinical Trials in NAFLD and NASH

A comprehensive evaluation of various clinical trials in NASH highlights the challenges and progress in developing effective treatments. The diversity of therapeutic approaches being tested, including metabolic modulators, anti-inflammatory agents, and anti-fibrotic therapies. The landscape of NASH clinical trials illustrates the multifaceted nature of the disease and the ongoing efforts to find safe and effective treatments.

A Phase 3, Randomized, Controlled Trial of Resmetirom in NASH with Fibrosis evaluated the efficacy of resmetirom, a thyroid hormone receptor beta-selective agonist, in patients with biopsy-confirmed NASH and varying stages of fibrosis (F1B, F2, F3). The study found that 25.9% of patients on the 80 mg dose and 29.9% on the 100 mg dose achieved NASH resolution without worsening fibrosis, compared to 9.7% in the placebo group. Improvements in fibrosis were also noted, indicating the potential of resmetirom as a therapeutic option for NASH with fibrosis [103]. The Farnesoid X Receptor Ligand Obeticholic Acid in NASH Treatment Trial (FLINT) investigated the effects of obeticholic acid (OCA), a farnesoid X receptor agonist, on liver function in patients with NASH. OCA treatment was associated with improved liver function. However, it also led to increased itching (pruritus) and higher total cholesterol levels. These findings have prompted further large-scale studies to assess the long-term safety and efficacy of OCA, making it a subject of continued research interest in NASH therapy [104] .In another trial, The Pioglitazone or Vitamin E for NASH Study (PIVENS) assessed the effectiveness of vitamin E and pioglitazone in improving NASH symptoms in adults. Vitamin E showed significant improvement in NASH symptoms, making it a viable treatment option. Pioglitazone had mixed results; while some participants experienced improvement in liver histology, others faced adverse effects such as weight gain. This highlights the need for careful patient selection and monitoring in the use of pioglitazone [105]. The Treatment of NAFLD in Children (TONIC) trial focused on the treatment of NAFLD in children, particularly evaluating the effects of vitamin E. The study indicated that vitamin E improved severe forms of fatty liver disease in some children. However, further research is needed to assess the long-term risks and benefits of vitamin E in pediatric populations. This trial underscores the importance of early intervention and tailored treatment strategies for children with NAFLD [106].

7. Future direction of NASH/NAFLD prevention

7.1. Study of key molecules

7.1.1. miRNA

The critical role of miRNAs as one of the most important genetic factors and the regulation of lipid and cholesterol biosynthesis in liver cells is remarkable. Recently, it has been shown that such molecules are also regarded as strong biomarkers in diagnosing liver diseases. The discussion of miRNA involvement in this field should also be highly evaluated as a follow-up and treatment tool for discovering different noninvasive solutions that can replace a valid method for distinct liver biopsy conditions [125]. Therefore, miRNAs in patients with NAFLD and NASH are very important because miRNAs can target oligonucleotides effectively in a specific disease and check its changes [125]. Additionally, miRNAs can circulate in the blood current in which their manifestation level is highly fixed and can be simply measured. They can also be introduced as appropriate clinical biomarkers [126]. Based on these findings, the authors suggested miRNA panels to increase the accuracy of NAFLD diagnosis. In their works, Tan et al. & Pirola et al. presented miR-122-5p, 1290, 27b-3p, and 192-5p for better identification of NAFLD. Therefore, they uncovered that miR-192-5p, miR-122, miR-192, miR-19a, miR-125, and miR-375 could serve as a backup panel [127]. Other authors have suggested combining RNA panels with classical biomarkers to predict NASH more accurately, especially miR-122, 192, and 21, along with Alanine transaminase (ALT) and cytokeratin-18-Asp396 [128].

miRNAs can be beneficial tools in assessing NAFLD progression. Therefore, miR-192 and miR-375 are related to NAFLD and classical biomarker activity [8, 127]. Based on the aforementioned findings, miRNAs have become a hopeful opportunity to progress the trend and cover other classical biomarkers in identifying and managing NAFLD.

Numerous studies have explored the link between pathogenesis and miRNAs in NASH/NAFLD [129]. For instance, serum miRNA-34a shows promise in NAFLD diagnosis by potentially downregulating the PPARα signaling pathway, leading to lipid buildup in liver cells [130]. On the other hand, miR-223, particularly in neutrophils, is elevated in hepatocytes and hinders NASH progression in obese mice [131]. This miRNA targets genes like CXCL10, NLRP3, and TAZ, known for fueling liver inflammation and fibrosis, thereby advancing NAFLD [131]. Interestingly, miR-223 derived from extracellular vesicles suppresses hepatic inflammation and fibrosis genes upon uptake by hepatocytes.

Additionally, miR-372-3p and miR-373-3p, by targeting Adipocyte enhancer binding protein 1 (AEBP1), are reduced in patients with advanced NASH and fibrosis [132]. miR-21 contributes to NASH through the STAT3 pathway and triggers liver fibrosis via HSC activation and collagen deposition through the TGF-β/Smad3/Smad7 pathway [133]. Meanwhile, miR-27 overexpression boosts hepatic insulin receptor expression, potentially influencing

early hepatic insulin resistance development [134].

Studies also highlight miR-29a's potential in mitigating NASH and NAFLD by suppressing CD36, thus reducing fat deposition and total liver triglyceride content [134]. Conversely, reducing miR-122 increases liver fat deposition and decreases beta-oxidation and energy expenditure, leading to weight gain [135]. Furthermore, miR-129-5p negatively modulates HSC activation linked to paternally expressed gene 3 (PEG3) [136], while inhibiting miR-188-5p shows promise in alleviating liver fibrosis by suppressing HSC activation through the PTEN/PI3K/Akt pathway [137]. As the prevalence of NAFLD/NASH is projected to rise, there is an imminent requirement to devise prompt diagnostic and therapeutic strategies utilizing miRNAs.

7.1.2. Glucagon-like peptide 1 (GLP-1)

Many of the advantages of GLP-1RAs on NASH are due to several effects they have on, for example, insulin resistance, weight loss, and direct effects on liver organs. As a result, it considers different aspects of metabolic syndrome [138]. Preclinical evidence indicates that GLP-1RAs reduce de novo lipogenesis, motivate fatty acid oxidation, and enhance multiple components of insulin signaling pathways [138]. GLP-1RAs are part of a group that may reduce liver inflammation through mechanisms relatively independent of weight loss factors [112]. GLP-1 receptor agonists and dual GLP-1/GIP receptor agonists stand out as highly effective medications for addressing multiple health concerns simultaneously. They not only aid in weight reduction and diabetes management but also play a crucial role in alleviating oxidative stress and inflammation linked to diabetic NASH [139]. Hartman et al. conducted a study to investigate the impact of tirzepatide, a dual agonist targeting glucose-dependent insulinotropic polypeptide and GLP1 receptors, on NASH and fibrosis biomarkers among Type 2 diabetes mellitus (T2DM) patients. The findings revealed notable reductions in baseline ALT (across all groups), AST (except in the tirzepatide 10 mg group), K-18 (observed in tirzepatide 5, 10, 15 mg groups), and Pro-C3 (specifically in the tirzepatide 15 mg group) levels after 26 weeks. Significant decreases were noted with tirzepatide compared to placebo for K-18 (at 10 mg) and Pro-C3 (at 15 mg), and compared to dulaglutide for ALT (at 10, 15 mg). Moreover, adiponectin levels notably increased with tirzepatide compared to placebo (at 10, 15 mg) from baseline [140].

The author has investigated the potential role of GLP-1RAs in treating NAFLD and NASH in several phase II trials and sponsored studies. The investigator's study, LEAN, provided a mechanistic approach [141], suggesting that there are liver-specific benefits of GLP-1RA that go beyond losing net extra weight [142]. The LEAN study accurately evaluated the efficiency and safety of 1.8 mg compared to placebo after passing 48 weeks in 52 overweight patients with clinical evidence of NASH [80]. Another related study determined the effect of liraglutide versus placebo on organ-specific insulin sensitivity, lipid dysfunction, and hepatic lipid management in 14 patients participating in that investigation [142]. A recently published phase II trial of semaglutide showed a significant improvement in outcomes reported for liraglutide [143]. Newsome et al [143] attempted to compare once-daily subcutaneous semaglutide at doses of 0.1, 0.2, or 0.4 mg and placebo in 320 patients with NASH and biopsy-proven liver fibrosis in stages F1, F2, or F3 [143]. Different researchers believe that if the type of GLP-1 receptor is not identified in the liver, GLP-1RAs in NASH achieve beneficial side effects on weight and better insulin resistance and reduce metabolic disturbances, inflammation, and lipotoxic impacts [143].

7.1.3. PPARs

Undoubtedly, a healthy liver does not accumulate lipids. Nevertheless, the liver can manage lipid anabolism by releasing fatty acids for peripheral organs, for example, white adipose tissue, store energy, and fat catabolism due to their movement from adipose tissue in the rapid mode. Accordingly, PPARα engagement in lipid metabolism gene activation is well-defined [144]. The proper process of activation of PPARα results in increased expression of a broad scope of genes that exist in whole steps of lipid metabolism, including storage, lipoprotein metabolism, transferring, synthesis, fasting ketogenesis, mitochondrial and peroxisomal degradation, binding, and uptake [145]. PPARα is expressed at similar high levels in human and mouse livers [146]. A short, inactive, and less expressed isoform has also been found in the human liver due to the introduction of a premature stop codon, i.e., the absence of exon 6 [146]. In their work, Thomas and colleagues indicated that the shortened isoform can easily prohibit inflammation in human liver cells [146]. The results obtained from the studies finally led to more research on the relationship between the abundance of PPARα in NAFLD and NASH. The results from studies conducted on patients with near NAFLD generally showed no distinctions in PPARα between healthy and NAFLD subjects [145].

In the phase IIb GOLDEN 505 study with 274 non-cirrhotic patients having biopsy-proven NASH and a baseline NAFLD activity score ≥4, the dual PPARα/δ agonist elafibranor (120 mg daily) demonstrated a reduction in histological NASH (20% with elafibranor vs. 11% with placebo; $p = 0.018$) [147]. A secondary post hoc analysis revealed that elafibranor achieved a revised endpoint of NASH resolution (disappearance of ballooning and lobular inflammation or persistence of mild lobular inflammation without worsening liver fibrosis) in 19% of patients compared to 12% with placebo ($p = 0.045$) [147]. Patients experiencing improved NASH also showed enhanced fibrosis. Additionally, elafibranor improved insulin sensitivity in the liver and muscles [148]. However, the phase III RESOLVE-IT trial (NCT02704403) did not confirm a significant advantage of elafibranor over placebo in inducing NASH resolution [149]. Kamata et al. delved into understanding the effectiveness, strength, and specificity against PPARα/δ/γ of three prior and current investigational drugs for treating NASH. They acquired seven detailed cocrystal structures via X-ray diffraction analyses, specifically focusing on the PPARα/δ/γ-ligand-binding domain (LBD) interactions with lanifibranor, seladelpar, and elafibranor. Their findings revealed distinct binding patterns and activation potentials across the PPAR subtypes. Lanifibranor and seladelpar interacted with varied regions within the PPARα/δ/γ-ligand-binding pockets, activating all PPAR subtypes with diverse strengths and efficacies across the assays. Conversely, elafibranor prompted transactivation and coactivator recruitment across all PPAR subtypes but did not influence thermal stability, although cocrystals with PPARδ/γ-LBD were not obtained. These

results underscore the diverse activation profiles and binding mechanisms of these PPAR ligands, crucial factors defining their pharmacological effects [150].

Another study conducted on people with suspected NAFLD with relatively lower levels of PPARα was demonstrated in the livers of NASH patients [151]. Hepatic PPARα expression was negatively correlated with NASH, hepatocyte ballooning, fibrosis, NASH activity score, and steatosis severity [151]. Lim et al. demonstrated that TNF-α suppresses PPARα mRNA modification in 2 factors in a dose- and time-dependent manner at the transcription level by increasing the activity of conventional NF-κB signaling pathways [152]. All the data obtained indicate a strong correlation between the three inflammatory factors, PPARα, and the onset of NASH.

7.2. Krüppel-like factors (KLFs)

Krüppel-like factors (KLFs) constitute a family of DNA-binding transcriptional regulators pivotal in numerous cellular processes, spanning proliferation, migration, inflammation, and angiogenesis. Currently, 18 distinct members, denoted as KLF1-18, have been characterized based on their order of discovery. Notably, KLFs exert significant control over glucose, lipid, and amino acid metabolism within the liver [153].

Lipid metabolism regulation is one of the essential functions of young livers, and KLF15 is a vital factor in lipid metabolism in the liver. Mutating or targeting Klf15 ameliorates a High-fat diet (HFD), which induces hepatic insulin resistance without impacting endoplasmic reticulum (ER) stress or hepatic inflammatory reactions. This action is usually closely related to insulin resistance [154]. KLF6 has a significant role in fetal liver growth and plays an important role in the pathogenesis of liver steatosis and fibrosis [155]. According to the studies, the increase in the expression level of KLF6 was well observed in the process of primary liver fibrosis in response to liver damage caused by the administration of Carbon tetrachloride 4 (CCl4) in rats [156]. KLF6 can be defined as a transcriptional form of transforming growth factor β1 (TGF-β1) and TGF-β receptors in hepatic stellate cells at the onset of injury. It is worth noting that with the activation of the TGF-β signaling pathway in stellate cells, different genes that are engaged in making fibrosis are positively regulated, such as the genes that encode the extracellular matrix. They also regulate plasminogen activator inhibitors and platelet-derived growth factor receptors [89]. It is better to say that there is a direct relationship between TGF-β1 and liver fibrosis, with increased expression of collagen I in hepatic stellate cells. Accordingly, in the study of laboratory mouse models, it was shown that Klf6 and Tgfb1 are properly regulated during the progression of NASH, and the deletion of Klf6 in liver cells preserves not only HFD-induced hepatic but also increases insulin resistance. This shows that KLF6 is helpful in the development of NASH [156].

KLF10, a member of the KLF family, is known for its involvement in TGF-β-mediated processes such as cell growth, apoptosis, and differentiation. Recent research has also linked it to glucose regulation and insulin sensitivity. Lee et al [157] explored the impact of KLF10 on liver disease progression in mice fed a High-sucrose diet (HSD). They compared wild-type (WT) mice with those lacking Klf10 (KO), feeding them either a regular diet or HSD for eight weeks. The Klf10 KO mice showed significant hepatic steatosis, inflammation, and liver damage when on the HSD, whereas WT mice only displayed mild steatosis without apparent liver damage [157]. The livers of HSD-fed Klf10 KO mice exhibited increased endoplasmic reticulum stress, oxidative stress, and proinflammatory cytokines. These findings suggest that KLF10 may protect against the progression of hepatic steatosis to liver fibrosis under conditions of increased lipogenesis [157].

Chen et al, found that KLF14 expression decreased in individuals with NASH and in mice fed a choline-deficient, L-amino acid-defined, high-fat diet (CDAHFD). Treating hepatocytes with oleic acid and palmitic acid also reduced KLF14 levels. Knocking down KLF14 led to a decrease in genes related to fatty acid oxidation, thereby promoting hepatic steatosis progression [158]. Conversely, increasing KLF14 expression in the liver alleviated lipid accumulation and oxidative stress in CDAHFD mice. Notably, inhibiting PPARα weakened the protective effects of KLF14 overexpression against steatosis in mice treated with oleic acid and palmitic acid. These findings suggest that hepatic KLF14 modulates lipid accumulation and oxidative stress via the KLF14-PPARα pathway during the development of NASH. Targeting KLF14 may offer a promising therapeutic approach for hepatic steatosis [158].

7.3. Acetyl-CoA Carboxylase 1 (ACC1)

Acetyl-CoA carboxylase 1 (ACC1) is a key enzyme in this pathway, converting acetyl-CoA to malonyl-CoA, which serves as a substrate for fatty acid synthesis. Given its pivotal role in lipid metabolism, targeting ACC1 has emerged as a promising therapeutic strategy for NAFLD. ncreased expression and activity of ACC1 have been observed in the livers of patients with NAFLD, contributing to the excessive accumulation of hepatic lipids [159]. Inhibition of ACC1 can effectively reduce malonyl-CoA levels, thereby decreasing the substrate availability for fatty acid synthesis and promoting fatty acid oxidation [160]. This dual effect can mitigate hepatic steatosis and improve overall liver health. Recent studies have demonstrated the efficacy of selective ACC1 inhibitors in preclinical models. For instance, a novel selective ACC1 inhibitor, Compound-1, was shown to significantly reduce hepatic malonyl-CoA levels and inhibit DNL in both in vitro and in vivo models [161]. In a study involving melanocortin 4 receptor knockout mice, which serve as a model for NAFLD, treatment with Compound-1 for eight weeks led to a marked reduction in liver hypertrophy and hepatic triglyceride content [161]. These findings suggest that selective inhibition of ACC1 can ameliorate the pathological features of NAFLD, including steatosis and fibrosis.

7.4. Fatty Acid Synthase (FAS)

Fatty Acid Synthase (FAS) is a crucial enzyme in the de novo lipogenesis (DNL) pathway, responsible for converting acetyl-CoA and malonyl-CoA into palmitate, a saturated fatty acid. In patients with NAFLD, the expression of FAS is often significantly elevated, contributing to increased hepatic lipid accumulation and the progression of liver disease [162]. The overactivity of FAS is linked to the development of steatosis, inflammation, and fibrosis, which are hallmarks of Non-Alcoholic Steatohepatitis (NASH), a more severe form of NAFLD [163]. Inhibition of FAS not only reduces lipid synthesis but also mitigates

the inflammatory and fibrogenic signals that exacerbate liver damage.Studies have demonstrated that pharmacological inhibition of FAS can lead to substantial improvements in liver histology and function [163]. For instance, the use of FAS inhibitors such as TVB-3664, TVB-3166, and TVB-2640 (denifanstat) has shown promise in preclinical models [164]. These inhibitors effectively reduced triglyceride accumulation in hepatocytes and decreased markers of fibrosis in hepatic stellate cells, which are critical mediators of liver fibrosis. Furthermore, FAS inhibition has been associated with a reduction in pro-inflammatory cytokines, thereby addressing multiple drivers of NASH.

8. Conclusion

Based on these evaluations, no confirmed cure for NAFLD and NASH has been reported thus far. Of course, novel noninvasive recognition markers such as miRNA can take a special place in the future to diagnose NAFLD and NASH. On the other hand, if NAFLD is diagnosed early, the patient is less exposed to fibrosis in the liver, HCC liver disease, and cirrhosis. Therefore, a more detailed investigation of the molecules and signaling pathways involved in liver inflammation, fibrosis, and cell death are among the factors that can suggest more effective biomarkers for prognosis, diagnosis, and curing goals connected to NASH and NAFLD. PPARs, including the effective key molecules of the miRNAs GLP-1 and KLFs, are considered potential targets in treating the metabolic diseases NAFLD and NASH. A better understanding of the primary mechanism of NASH/NAFLD pathogenesis is crucial and valuable for choosing the essential treatment.

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SS and MM. Wrote the main manuscript text, NZ and AE: literature search, and prepared Tables 1 and 2. RR: Supervisor and manuscript final edition.MR: Critically reviewed the manuscript.

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