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Review Article

Non-alcoholic fatty liver disease: Insights into pathogenesis, molecular mechanisms, and therapy

Nourhan M. Kamar[a*], Haidy E. Michel[b], Sayed H. Seif el-Din[a], Naglaa M. El-Lakkany[a], Doaa A. Elsherbiny[b]

[a]*Department of Pharmacology, Theodor Bilharz Research Institute, 12411, Giza, Egypt*
[b]*Department of Pharmacology and Toxicology, Faculty of Pharmacy, Ain Shams University, Cairo, 11566, Egypt*

ABSTRACT

Nonalcoholic fatty liver disease (NAFLD) is a chronic liver disease prevalent worldwide, which affects patients' quality of life, and has become a significant health and economic issue. NAFLD has been classified into nonalcoholic fatty liver (NAFL) and nonalcoholic steatohepatitis (NASH). Understanding how biochemical pathways affect illness development and progression on an individual level is critical for effective care. In this review, the current understandings of the risk factors affecting the progression of NAFLD are summarized. Moreover, the review highlights the multifaceted pathogenesis of NAFLD, in addition to the molecular mechanisms that promote the advancement and progression of NAFLD for example lipotoxicity, insulin resistance, proinflammatory cytokines and inflammation, oxidative damage, and mitochondrial malfunction, additionally, gut microbiota and bacterial dysbiosis. In addition, this review highlights lifestyle adjustments and therapeutics with favorable prospects used for the management of NAFLD. Medicinal treatments used for their potential benefits, such as drugs targeting gut microbiota, as well as lipid-lowering drugs are discussed.

Keywords: *Non-alcoholic Steatohepatitis; High-Fat Diet; Fibrosis; Pathogenesis; Management.*

***Correspondence** | Nourhan M. Kamar Atef; Department of Pharmacology, Theodor Bilharz Research Institute, 12411, Giza, Egypt, Egypt. Email: nourhan.kamar20@pharma.asu.edu.eg

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1. Introduction

Nonalcoholic fatty liver disease (NAFLD), originally described in 1980 by Ludwig and colleagues **[1]**, is a chronic metabolic disorder with hepatic lipid accumulation that is similar to alcohol-induced liver injury but in patients with no alcohol consumption **[2]**. It is the utmost widespread chronic hepatic ailment in the world, accounting for approximately a quarter of the populace in 2016 **[3]**.

NAFLD is classified into two types: nonalcoholic fatty liver (NAFL) with steatosis but no hepatocyte injury or fibrosis, and nonalcoholic steatohepatitis (NASH) with liver steatosis, inflammation, and injury to hepatocytes with or without fibrosis. NASH is linked to a higher risk of cirrhosis, hepatocellular carcinoma (HCC), and liver-related mortality, particularly when fibrosis is present **[4]**. NAFLD is associated with extra-hepatic metabolic co-morbidities, including heart and kidney diseases, elevated blood pressure, metabolic syndrome (MS), excessive body weight, and type 2 diabetes mellitus (T2DM), leading to higher rates of mortality **[5]**. The pathogenesis of

NAFLD is multifaceted involving two major events: lipid buildup inside hepatocytes, particularly free fatty acids (FFAs), as well as immunological reactions linked to the liver **[6]**. However, before steatosis, inflammation may occur causing fat buildup **[7]**. As a result, several variables influence the beginning and course of NAFLD, encompassing lifestyle, genetic background, metabolic status, microbiota, and environmental exposure **[8]**. These factors can all result in inflammation or steatosis, which can then trigger the release of cytokine that promotes inflammation, insulin resistance, oxidative and endoplasmic reticulum stress, as well as cell death **[6]**. The intricate interplay of all these systems supports the presence of various phenotypes within NAFLD, each with its own set of altered molecular mechanisms, which might lead to different disease courses, natural histories, and clinical assessments **[9]**. Even though lifestyle changes such as diet and exercise have been found to ameliorate NAFLD, they are difficult to sustain and require pharmacological intervention. The treatment for NAFLD focuses on addressing underlying metabolic issues using insulin-sensitizing and lipid-lowering medicines while avoiding hepatotoxic medications **[10]**.

2. Prevalence of NASH

The worldwide prevalence of NASH/NAFLD has elevated from 19.34 million in the year 1990 to 29.49 million in 2017 among young adolescents and children, with a 1.35% annual increase.

Moreover, the incidence of NASH/NAFLD in adolescents has been extensively augmented within this period, irrespective of region and sex. The highest record for NAFLD/NASH incidence was detected in the Middle East and North Africa. An accelerating trend has been witnessed from 1990 to 2017 in almost all nations. The increasing prevalence of NAFLD/NASH may trigger a predictable rise in the burden of chronic hepatic diseases shortly **[11]**.

This review provides an overview of the risk variables as they are currently considered and the pathophysiology of NAFLD, in addition to efforts exerted to find effective therapeutics that target the molecular mechanisms implicated in its genesis and progression.

3. Risk factors affecting the progression of NAFLD

Patients with NAFLD frequently exhibit MS symptoms **[12]**, such as hypertension (40%), dyslipidemia (69%), obesity (51%), and diabetes (22.5%), which are regarded to be important risk factors for NAFLD. The increase in NAFLD incidence and prevalence is mostly attributed to all these risk factors **[13]**. Prediabetes and T2DM are also believed to be related to NAFLD, which has also been linked to hepatic inflammation and fibrosis **[14]**. Unfortunately, diabetes is linked to higher death rates in NAFLD patients. However, the link between NAFLD and insulin resistance is reciprocal, as NAFLD might lead to hyperglycemia and worsen metabolic decompensation in diabetic individuals **[15]**.

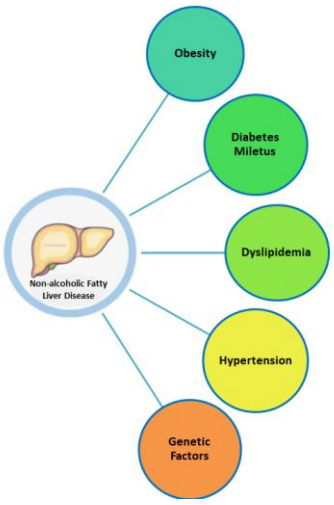

Fig. 1. Factors contributing to the development of non-alcoholic fatty liver disease.

Around 70% of NAFLD and NASH patients have dyslipidemia, which is characterized by

elevated total or low-density lipoprotein cholesterol levels **[3]**. Atherogenic dyslipidemia may contribute to increased cardiovascular risk in these patients. Mutations in genes related to lipid metabolism have been linked to the development and severity of NAFLD **[16]**. Factors contributing to NAFLD development are illustrated in **Fig. 1.**

4. Role of genetic factors in the development of NAFLD

Genetic predisposition can contribute to the development of NAFLD in certain circumstances, where it could amplify the effects of other variables on gene expression, leading to excessive inflammation, improper lipid metabolism, oxidation, and apoptosis which are associated with the advancement of liver disease, insulin resistance, T2DM, and an increased risk of fibrosis and hepatocellular cancer **[17]**. Polymorphism in certain genes, notably the patatin-like phospholipase domain containing 3 (PNPLA3), has been associated with NAFLD progression. It is the most well-known gene related to NAFLD. A genome-wide association study (GWAS) found people with the PNPLA3 I148M allele to have twice as much fat in their liver cells as non-carriers **[18]**. Adiponutrin, an enzyme having triglycerides (TG) hydrolase activity, is encoded by PNPLA3. It appears to be involved in the remodeling of TG and phospholipids in response to eating and is highly expressed in hepatocytes and adipocytes.

Moreover, apolipoprotein C3 (APOC3) polymorphism has been associated with NAFLD. APOC3 inhibits lipoprotein lipase activity and reduces TG elimination. In NAFLD, plasma concentrations of apolipoprotein C3 rise in APOC3 variations, resulting in poorer fat clearance. As TG clearance decreases, leftover chylomicron particles grow. This causes an increase in circulating chylomicron remnants, which are then removed by a receptor-mediated mechanism in the liver **[19]**.

5. Pathogenesis and molecular mechanisms of NAFLD

Numerous hypotheses suggest that NAFLD is caused by dietary variables, obesity, adipokines, insulin resistance, both epigenetic and genetic factors, and intestinal dysbiosis, and results in hepatocyte damage and steatohepatitis (NASH), which is caused by an overabundance of fatty acids (FAs) in the liver, which overwhelms physiologically adaptive mechanisms and results in cell death, local inflammation, and fibrogenesis **[20]**. Insulin resistance may play a key role in this notion as it disrupts lipolysis in adipose tissue, leading to increased FFA flow to the liver. Obesity can cause adipose tissue malfunction, leading to increased FFA liver absorption, lipid synthesis, and gluconeogenesis, further enhancing hepatic insulin resistance **[21]**. The "Multi-hit" concept may help to understand the pathogenesis of NAFLD. First, the "first hit" of NAFLD occurs when fat buildup in the liver cells rises, resulting in hepatic steatosis. Both hepatic lipid buildup and widespread insulin resistance distinguish this stage. The "second hit" occurs when inflammatory cytokines, adipokines, mitochondrial dysfunction, and oxidative stress all increase. Because a more comprehensive metabolic dysfunction occurs owing to both environmental and genetic variables, as well as alterations in the crosstalk between different tissues and organs, a more recognized view of NAFLD development is the "multiple hit model" **[22]**.

The pathogenic process of NAFLD development and progression to NASH is highly complicated, and scientific study has not fully comprehended it during the last decade. When the two-factor theory is replaced with the multifactorial hypothesis, it becomes clear that more than one or two pathways can account for

the pathophysiology of NAFLD and the development of NASH. It is conceivable that numerous and simultaneous processes play a role in NAFLD etiology at the same time, including fatty acid and triglyceride buildup, followed by the development of insulin resistance in the liver, adipose tissue, and skeletal muscle **[20]**. Hepatic steatosis is distinguished by excessive fat accumulation in liver cells, which results from a breakdown in the liver's equilibrium between lipid acquisition and breakdown. Mild steatosis is defined as the accumulation of fat droplets in 30% of hepatocytes, whereas severe steatosis is defined as the accumulation of lipid droplets in 60% of the cells **[23]**.

5.1. Accumulation of fats in the liver (Lipotoxicity)

The first and most recognized "hit" that results in the onset and progression of NAFLD is lipid accumulation in the liver **[13]**. An imbalance between FAs transported to the liver, lipid synthesis and oxidation, and TG transferred from the liver as very low-density lipoproteins (VLDL) causes this direct accumulation of fats inside the liver. Furthermore, excessive carbohydrates might be converted to TGs in addition to FFAs **[24]**. Dietary FAs enter the circulation after being absorbed through the small intestine, where they congregate as chylomicrons. Eventually, the majority of chylomicrons are delivered to adipose tissue where they are stored. The remaining chylomicrons are then absorbed by the liver **[25]**. The development of hepatic lipotoxicity is after the massive influx of lipids and lipid derivatives from adipose tissue, gastric and intestinal absorption, or raised levels of *de novo* lipogenesis in the liver; overwhelming the liver's capacity to absorb, store, and export these molecules. According to research, after lipolysis, adipose tissue TGs provide 60% of the hepatic FFAs, *de novo* lipogenesis provides 25%, and dietary FFAs contribute 15% **[26]**. Hepatotoxic lipids for example ceramides, free cholesterol, bile acids, and lysophosphatidylcholine can be biotransformed from FFAs and TGs **[24]**.

Reactive oxygen species (ROS) excessive production causes inflammation, lipid peroxidation, and injury to DNA. The inhibition of the microsomal triglyceride transfer protein, which facilitates the transit and export of hepatic TGs to VLDL-C, might increase TG accumulation in the liver **[27]**. This is the initial stage of the transition from primary steatosis to NASH **[7]**.

5.2. Insulin resistance

NAFLD and insulin resistance (IR) have a bidirectional interaction, with insulin resistance promoting the advancement of NAFLD, while NAFLD triggers insulin resistance progression. The adipose tissue, liver, and skeletal muscle lose their sensitivity to insulin and its metabolic effects in case of insulin resistance **[28]**. Insulin resistance is also associated with MS, hypertension, obesity, and hyperglycemia. Although elevated IR is often indicative of NAFLD, not all patients suffer from it. In a meal high in carbohydrates, superfluous glucose is converted via lipogenesis, which uses acetyl-CoA generated from pyruvate driven by glycolysis, into fatty acids. After being incorporated into VLDL, these fatty acids are then sent to white adipose tissue for storage **[29]**. Serine phosphorylation of insulin receptor substrate-1 (IRS-1) is a crucial factor in disrupting insulin signaling through inflammatory signal transducers like c-jun N-terminal protein kinase 1 (JNK1) or nuclear factor-κB kinase-β (IKK-β) inhibition. Lipid accumulation in adipocytes activates downstream signaling pathways such as c-Jun N-terminal kinase (JNK) and nuclear factor-kappa B (NF-κB), leading to the synthesis of cytokines that promote inflammation such as TNF-α and IL-6 **[30]**. According to previous research, activating JNK speeds up lipid buildup,

increasing liver damage. Insulin resistance, liver damage, and enhanced autophagy were all seen in a high-fat diet (HFD) NAFLD model where JNK inhibition lowered autophagy and insulin resistance **[31]**.

Moreover, macrophages as well as the inflammasome pathway are believed to be involved in the progression of insulin resistance. The inflammasome pathway regulates the production of interleukin IL-1β and IL-18 via complexes such as nucleotide-binding oligomerization domain (NOD)-leucine-rich repeats-and pyrin domain-containing protein 3 (NLRP3) and stimulation of caspase-1 **[32]**. Many stressors might result in the formation of inflammasomes in NAFLD, these include damage-associated molecular patterns (DAMPS), and pathogen-associated molecular patterns (PAMPS) such as lipopolysaccharide (LPS) derived from the gut-liver axis (GLA), endoplasmic reticulum stress, in addition to ROS originating from mitochondria **[32]**. The NLPR3 inflammasome activation has been related to the development of the illness from steatosis to NASH **[32]**, as a result, targeting the inflammasome will enhance insulin signaling and mitochondrial function.

5.3. Oxidative stress and mitochondrial dysfunction

Oxidative stress occurs when the body's antioxidant defense mechanism is insufficient and reactive species synthesis is excessive, such as reactive nitrogen species (RNS) or ROS. Mitochondria are primarily responsible for generating ROS in cells **[33]**. NASH occurs when excessive TG overloads the liver's adaptive systems, causing lipotoxicity, inflammation, ROS production, and hepatocellular damage **[34]**. When FA enters the hepatocyte, mitochondria use it by β-oxidation and oxidative phosphorylation. Peroxisomes and endoplasmic reticulum also contribute to FA oxidation. Excessive ROS generation can deplete the cell's antioxidants, causing protein and lipid peroxidation, DNA damage, and inflammation **[35]**. Mitochondrial activity decreases in the advanced stages of NASH, creating a vicious cycle. One of the main causes of tissue damage in NASH patients is oxidative stress-triggered hepatocyte destruction and cell death **[36]**. It has been demonstrated that NAFLD and NASH patients have a markedly elevated rate of FA removal via mitochondrial ß-oxidation as a response to ameliorating hepatic steatosis **[37]**. Nevertheless, research comparing the function of mitochondria in NAFLD and NASH patients has reported that the degree of adaptability is lost in NASH patients in the final stages because of a higher level of ROS-provoked mitochondrial dysfunction **[38]**.

5.4. Proinflammatory cytokines

Inflammation is a critical feature of NASH, which can develop from both extrahepatic factors and from inside the liver as a response to lipotoxic stimuli **[39]**. The immunological reaction starts by triggering the inflammasomes, intracellular protein complexes that activate caspase-1. This enzyme converts proinflammatory cytokines like IL-1 and IL-18 into their active forms **[40]**. These complexes' sensor proteins are pattern recognition receptors (PPRs) that respond to DAMPs. There are several varieties of PPRs, including NOD-like receptor proteins (NLRP) **[41]**, and toll-like receptors (TLRs) **[42]**. Furthermore, it has been shown that in hepatocytes, FFAs, and cholesterol, which are two molecules linked to metabolism, initiate inflammatory cell death, induced via the inflammasome **[43]**. DAMPs produced by inflammatory cell death can activate Kupffer cells and liver-resident macrophages. Activated Kupffer cells release TNF-α, a pro-inflammatory cytokine that causes insulin resistance and regulates NF-κB activation, among other effects

[44], suggesting that they may play a role in worsening liver inflammation.

5.5. Gut microbiota

The gut-liver axis (GLA) stands for the relationship between the gut, microbiota, and liver [45]. The portal vein delivers gut-derived molecules to the liver, enabling crosstalk. An extensive study on GLA dysfunction, including bacterial overgrowth, intestinal dysbiosis, and alterations in mucosal permeability, was recently done to find possible therapy agents for NAFLD. Dysbiosis can lead to increased mucosal permeability and translocation of bacteria, including PAMPs like LPS, and fermentative metabolites such as short-chain fatty acids (SCFAs), alcohols, and trimethylamine **[46]**. Bacterial dysbiosis or changes in the intestinal barrier, leads to the development and initiation of NAFLD by disrupting the GLA at several levels, including epithelial layer malfunction. Consequently, the gut becomes more permeable to bacteria and substances originating from bacteria, which can penetrate the portal circulation of the liver.

This might trigger the immune system and worsen inflammation. This increase in the number of bacteria entering the liver causes inflammation by activating TLRs and other pattern recognition receptors in kupffer cells (KCs) **[47]**. Research suggests that the gut microbiota may play a role in NAFLD pathogenesis through various mechanisms, including enhanced production and absorption of SCFA and delivery of microbiota-derived ethanol to the liver, as well as changes in bile acid pools in dietary choline metabolism and gut permeability and endotoxin leakage **[48]**. Dysbiosis is commonly accompanied by a rise in bacterial endotoxins. Endotoxin levels were dramatically increased in NAFLD patients, with a notable rise observed in the early phases of fibrosis **[49]**. Lipopolysaccharide (LPS) activates NF-κB by binding to TLR4. Activation of TLRs by bacterial LPS, particularly TLR-4, on Kupffer cells causes a pro-inflammatory response, and stellate cells lead to hepatic fibrogenesis **[50]**. Intestinal dysbiosis and its associated effects leading to metabolic derangement and NAFLD are illustrated in **Fig. 2.**

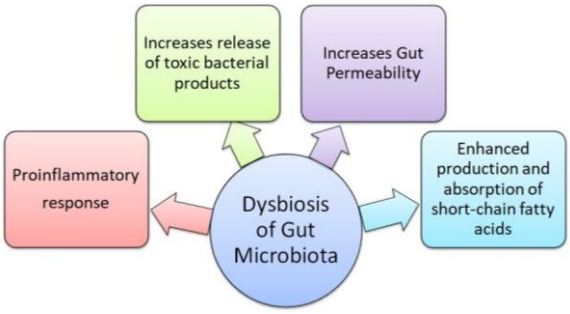

Fig. 2. The complex actions accompanying gut dysbiosis, which in turn, leads to metabolic derangement and non-alcoholic fatty liver disease.

6. Challenges and opportunities of current pharmacological management of NASH

Despite the advancement in comprehending the clinical problem of NASH and the endless efforts to establish innovative approaches to pharmaceutical management, many questions remain unanswered. No sufficient evidence is available to prove that various genetic polymorphisms may alter the response to therapy **[51]**. Nevertheless, it has been recently suggested that patients with genetic and metabolic NAFLD exhibit remarkably diverse pathogenic mechanisms, with only metabolic NAFLD being related to insulin resistance **[18]**. Another influential obstacle in the management of NAFLD/NASH is the uncertainty of whether patients will exhibit remarkable clinical progress. Clinical trials with comparable inclusion and exclusion criteria and with analogous follow-up reported markedly different rates of clinical progression **[52]**. Taken together, no current criteria are available to optimally classify the patients liable to disease worsening relying on semiquantitative histological staging systems.

7. Therapeutic strategies

NAFLD therapy is challenging owing to its complex origin, difficult diagnosis, diverse phases, and potential concomitant disorders. Treatments for NAFLD/NASH prioritize addressing hepatic steatosis, inflammation, and fibrosis due to its complicated pathophysiology.

7.1. Lifestyle modification

Lifestyle adjustments, notably weight loss, form the basis for NAFLD management. This might be accomplished by eating less and participating in more physical activity. A low-calorie diet reduced overall body weight while also lowering visceral fat and hepatic lipid content **[53]**. The Mediterranean diet may treat NAFLD by reducing visceral obesity, insulin resistance, dyslipidemia, and chronic inflammation, which are all linked to metabolic syndrome. The diet contains macronutrients that improve glycemic and lipidic metabolism, potentially reducing the risk of fatty liver disease. Moreover, this diet is rich in mono-unsaturated fatty acids, poly-unsaturated fatty acids, and fiber, but minimal in processed carbohydrates and fructose **[54]**. Sedentary lifestyles are linked to obesity, T2DM, NAFLD, and MS. A total of at least 150 minutes per week of moderate-intensity physical activity, or 75-150 minutes per week of more strenuous aerobic exercise is recommended **[53]**.

7.2. Pharmacological therapy

Clinical studies have tested various pharmacological strategies for treating NAFLD, including antidiabetic, antioxidant, probiotic, bile acid system, and lipid-lowering therapies, based on the physiopathology of the disease.

7.2.1. Lipid-lowering drugs

Dyslipidemia contributes to the progression of NAFLD and is characterized by TG level elevation and the accumulation of cholesterol **[55]**.

Statins such as atorvastatin, pravastatin, and rosuvastatin, are well-known clinical lipid-lowering drugs and are the basis of hyperlipidemia treatment, statins, can stop the synthesis of cholesterol by blocking 3-hydroxy-3-methyl glutaryl coenzyme A (HMG-CoA) reductase Moreover, they are anti-inflammatory and antifibrotic thus are beneficial in NASH **[56]**. Ezetimibe, a cholesterol absorption inhibitor may affect NAFLD/NASH **[57]**. Moreover, ezetimibe in combination with fish oil could notably enhance the recovery from fatty liver disease in rats by raising cholesterol efflux transporter **[58]**.

Fibrates are agonists of the PPARα transcription factor and are clinically used for the treatment of dyslipidemia. Also, they have been shown to up-regulate TG lipase enzyme leading to a decrease in the hepatic triacylglycerol content **[59]**. Though preclinical studies support fibrates' contribution to the prevention and management of NAFLD, no beneficial effects were shown in clinical studies **[60]**.

PPARγ ligands: Both rosiglitazone and pioglitazone are activators of the PPARγ pathway. A 48-week treatment with rosiglitazone improved NASH markers including steatosis, numbers of Kupffer cells, hepatocellular ballooning, and zone 3 fibrosis **[61]**. Moreover, rosiglitazone therapy has revealed improvement in steatosis and transaminase levels in patients **[62]**. A meta-analysis has revealed that treatment of NASH patients with pioglitazone improved hepatic histopathology and enzymes (AST and ALT), besides, it decreased blood lipids **[63]**.

Farnesoid X receptor agonists: among its many beneficial effects on metabolism, the nuclear transcription factor farnesoid X receptor also lowers hepatic triglyceride levels and

promotes the excretion of bile acid, therefore farnesoid X receptor agonists appear to be promising treatments for NAFLD. The farnesoid X receptor agonists tropifexor, vonafexor, and cilofexor have been demonstrated in recent clinical studies to lower the amount of fat in the liver in NASH patients **[64]**.

7.2.2. Drugs targeting gut microbiome

The pathogenesis of NASH could be exacerbated by the gut microbiota via releasing (LPS), increasing production of SCFA and ethanol, and activating inflammatory cytokines in hepatic cells **[65]**. For instance, *Proteobacteria* seem to be increased in NAFLD **[66]**, whereas *Ruminococcaceae* or *Bifidobacteriaceae* were described to be decreased in NAFLD **[67]**. Probiotics are "living microorganisms which when administered in adequate amounts confer a health benefit to the host" **[68]**. The most frequently used probiotics are known as *Lactobacillus* and *Bifidobacterium.* They are known to inhibit the expansion of pathogenic gram-negative bacteria, ameliorate liver steatosis, and lower the levels of inflammatory cytokines, fatty acids, and serum transaminases **[69]**.

7.2.3. Anti-diabetic drugs

Glucagon-like peptide 1 receptor agonists (GLP1-RAs): The foregut secretes the intestinal hormone GLP-1 in response to food ingestion. It can both raise insulin synthesis and lower glucagon release. GLP-1 receptor agonist, include liraglutide, semaglutide, dulaglutide and exenatide. They appear to have the most encouraging positive effects on NAFLD or NASH. By increasing satiety, GLP1-RAs decrease food intake by imitating the actions of physiological GLP1, such as stimulating insulin secretion, and inhibiting glucagon and gastrointestinal motility **[70]**. In addition to their anti-hyperglycemic action, GLP-1 RAs have a noteworthy influence on body weight as well as clinical, biochemical, and histological indicators of fatty liver in NAFLD patients **[71]**. Semaglutide has been shown to improve liver steatosis and reduce mitochondrial damage, lipogenesis, and lipid deposition, besides, it increases beta-oxidation and exhibits antioxidative effects; which can improve NAFLD **[72]**. Furthermore, NASH patients receiving liraglutide showed improvement in their lipid profile, according to a recent meta-analysis **[73]**.

Sodium–glucose transporter 2 (SGLT2) inhibitors: facilitate the excretion of glucose through the urine by blocking the SGLT2 transporter. In turn, this lowers levels of glucose in the blood and enhances and improves insulin sensitivity in patients suffering from T2DM **[74]**. These drugs may have favorable effects on NAFLD by decreasing hepatic steatosis, fibrosis, and enzyme levels, as well as reducing insulin resistance and body weight **[75]**. The impact of empagliflozin on the amount of liver fat in people with T2D and NAFLD was examined by Kuchay *et al*. When compared to controls, empagliflozin dramatically decreased liver fat **[76]**. Similarly, T2DM individuals with NAFLD, given an oral dosage of ipragliflozin for 24 weeks, at a dose of 50 mg each day showed improvement in levels of fasting blood glucose and liver enzyme values, as well as lowered body weight and visceral fat area **[77]**.

Glibenclamide (GLB) is a sulfonylurea medication commonly referred to as glyburide widely used to treat T2DM. Effects of GLB were mediated by decreasing the levels of glucose, triglycerides, cholesterol, DNA damage, apoptosis, and inflammatory markers, and by improving the anti-oxidant status and insulin signaling pathway in high-fat diet-fed rats **[78]**.

7.2.4. Natural products

Natural products such as vitamin E, vitamin C, and coffee have been used to prevent the

progression of NAFLD. For example, vitamin E can lower hepatic lipid peroxidation while increasing endogenous hepatic antioxidant activity and concentrations **[79]**.

Silymarin is composed of several compounds. The major active compound of Silymarin is Silybin, which acts by reducing lipid peroxidation and the production of collagen, resulting in decreased liver fibrosis **[80]**. Silybin can help NAFLD patients by improving their liver steatosis, insulin resistance, and plasma indicators of liver fibrosis **[80]**. Resveratrol (RSV): The natural polyphenol_resveratrol also has a potent antioxidant activity, it showed liver-protective effects in NAFLD in preclinical studies **[81]**. Curcumin is the most prevalent curcuminoid in turmeric curcumin inhibits the pathological progression of NAFLD to fibrosis and hepatocellular carcinoma by its ability to regulate inflammation, oxidative stress, and apoptosis **[82]**.

7.2.5. Innovative therapeutic candidates for NAFLD

Pirfenidone is an orally accessible derivative of pyridone that has been applied in clinical settings to treat idiopathic pulmonary fibrosis **[83]**. Pirfenidone had promising antifibrotic effects as it has been shown to reduce fibrosis, inflammation, oxidative stress, and insulin resistance, in models of NAFLD and NASH in mice **[84]**.

Glucosamine is an amino monosaccharide derivative of glucose considered a useful treatment option for osteoarthritis **[85]**. In mice models of NAFLD glucosamine reduces hepatic lipid buildup insulin resistance, systemic oxidative stress, and the inflammatory response and generally improves liver function. Enhancing the function of the intestinal barrier, controlling the LPS/TLR4/NF-κB inflammatory pathway, and enhancing hepatic metabolism of lipids, are further activities that are assigned to the drug effect on NAFLD **[86]**.

Lubiprostone is a laxative medication that enhances intestinal permeability and is used to treat persistent constipation and irritable bowel syndrome. In a mouse model of NAFLD, lubiprostone enhanced the permeability of intestine permeability, caused by a diet rich in fat, via colonic mucus development, moreover, it reduced plasma ALT and AST and hepatic steatosis **[87]**. In NAFLD patients, Lubiprostone may prevent fibrosis and enhanced inflammation caused by endotoxins obtained from the gut by decreasing intestinal permeability. Phase IIa trial results indicate that lubiprostone decreased liver enzyme levels and was well tolerated in NAFLD and constipation patients **[88]**.

Pentoxifylline is a hemorheologic agent with primary actions that include increasing erythrocyte flexibility, reducing blood viscosity, and increasing microcirculatory flow and tissue perfusion **[89]**. Pentoxifylline can interfere with various stages in the cytokine/chemokine pathway implicated in the pathophysiology of NAFLD. One of its many physiological effects is the reduction in TNF-α gene transcription and the reduction of oxidative stress. As a result, it has been studied in many clinical trials, the majority of which have demonstrated positive benefits on weight reduction, liver function, and histological alterations in NAFLD/NASH patients as concluded by two meta-analyses studies **[90]**.

Conclusion

NAFLD is becoming increasingly prevalent, most likely as a result of obesity and type 2 diabetes. NAFLD is a high-priority healthcare condition with a significant financial impact resulting from its widespread occurrence. The primary targets of therapeutic interventions for NAFLD/NASH are hepatic steatosis, inflammation, and fibrosis. Since obesity, type 2

diabetes, dyslipidemia, hypertension, and NAFLD are closely related conditions, seeking individualized treatment that addresses all pertinent comorbidities is advised.

Declarations

Ethics Approval and Consent to Participate

Not applicable.

Consent to Publish

All authors have read and agreed to the published version of the manuscript.

Availability of Data and Materials

All data generated or analyzed during this study are included in this published article in the main manuscript.

Competing Interests

The authors declare that no competing interests exist.

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Authors' Contributions

All authors contributed to the study of the literature collection and writing of the first draft of the manuscript was done by Nourhan M. Kamar. Organizing, editing, and reviewing the manuscript were done by: Haidy E. Michel, Sayed H. Seif el-Din, Naglaa M. El-Lakkany, and Doaa A. Elsherbiny. All authors read and approved the final manuscript.

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