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Therapeutics for Metabolic Dysfunction-Associated Fatty Liver Disease (MAFLD)

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Abstract: Metabolic dysfunction associated fatty liver disease (MAFLD) has been recently recognized as a new global chronic liver disease entity with non-alcoholic fatty liver disease (NAFLD) associated with overweight/obesity or type 2 diabetes mellitus (T2DM) and evidence of metabolic dysregulation. Due to the rising rates of obesity and diabetes, MAFLD is considered a rapidly emerging chronic liver disease globally. Nearly 25–30% of the global population poses health issues due to MAFLD with a substantial economic burden to societies. Disease progression depends on the persistence of risk factors and etiological agents, from simple steatosis, hepatitis, fibrosis, to cirrhosis, and if untreated, leads to hepatocellular carcinoma. In this review article we summarize various risk and etiological factors, diagnostic techniques, and therapeutic evaluation of pharmacological agents developed for MAFLD. Effective pharmaceutical agents for the treatment of MAFLD (and NAFLD) are lacking, and research is ongoing to search for effective medications in this direction. Currently, pioglitazone is advised for MAFLD patients, whereas Vitamin E is advised for non-diabetic MAFLD patients with ≥F2 non-cirrhosis. Current approaches to disease management emphasize diet control, lifestyle changes, and weight loss. In this review, we summarized the pharmacological agents currently being developed and their current status to treat patients with MAFLD.

Keywords: non-alcoholic fatty liver disease (NAFLD); metabolic dysfunction-associated fatty liver disease(MAFLD); metabolic disorder; metabolic dysfunction; therapeutics; pharmacological agents

1. Introduction

The term 'metabolic dysfunction-associated fatty liver disease' (MAFLD) refers to the most common form of chronic liver disease recognized previously as non-alcoholic fatty liver disease (NAFLD) and has been now linked to evidence of metabolic dysregulation, such as obesity and/or diabetes. Non-alcoholic fatty liver disease (NAFLD), which is characterized by the accumulation of fat in more than 5% of hepatocytes (detected by imaging techniques or histology), occurs in the absence of excessive alcohol consumption and other secondary causes, such as viral hepatitis. A persistent NAFLD may further progress to non-alcoholic steatohepatitis (NASH), liver fibrosis, liver cirrhosis, or hepatocellular carcinoma (HCC) [1]. This term "non-alcoholic fatty liver disease" was first used by Schaffner and Thaler in 1986 to describe the liver condition of excessive fat accumulation in the patient's liver without a secondary cause of steatosis [2]. NAFLD is intimately correlated with metabolic syndrome, which comprises abdominal obesity, hyperglycemia, hypertension, and dyslipidemia [3]. NAFLD by definition has limitations or is confined to only steatosis. The diagnostic criteria define hepatic steatosis of ≥5% without concurrent liver disease. With the advancement in understanding of disease and close association of NAFLD with obesity, metabolic syndrome, and type 2 diabetes mellitus (2DM), recently, a consensus international specialist advocated changing the term of NAFLD to metabolic dysfunction-associated fatty liver disease (MAFLD), on the criterion evidence of hepatic steatosis and one of the following three conditions: overweight/obesity, type 2 diabetes mellitus (T2DM),

or signs of metabolic dysregulation [4,5]. The term "MAFLD," was originally proposed in 2020 [5], to identify fatty liver disease conditions linked to metabolic abnormalities. The updates of NAFLD to new definition of MAFLD is considered most appropriate nomenclature and of great value to clinicians in the diagnosis of high-risk patients who are benefited with target management and medical treatment. Moreover, increased understanding in the healthcare community and wider general public awareness have been found to be of great value. Therefore, prevalence of MAFLD may significantly increase when obesity, diabetes, dyslipidemia, and hypertension are taken combinedly into the consideration [6,7]. MAFLD has an enhanced risk of mortality and a similar risk of cause-specific mortality in NAFLD [8]. MAFLD is also associated with hepatic cardiovascular and oncological sequences, resulting in an economic burden on society [9]. A considerable proportion of MAFLD patients are non-obese, and the spectrum of MAFLD varies from steatosis to concomitant inflammation, which can lead to fibrosis, cirrhosis, and hepatocellular carcinoma (HCC), with only a few patients progressing to more advanced disease stages [10,11] Research work in search of new molecules to effectively treat NAFLD/MAFLD is ongoing.

MAFLD is rapidly emerging as a major contributor to chronic liver disease in the United States because of the rising prevalence of type 2 diabetes and obesity. Nearly 25% of the world's population is affected by MAFLD, which has a serious fiscal impact in many countries.

MAFLD has become a global health issue, accounting for 25–30% in Asia Pacific region and 25% in Western countries [12]. The estimated global prevalence of MAFLD in overweight or obese adults as reported by Liu et al. (2022) from around the general population was reported in North America as around 34.0%, Central America 56.3%, South America 70.9%, Northern Europe 31.4%, Western Europe 49.9%, Eastern Europe 81.5%, Southern Europe 52.3%, Eastern Asia 52.1% Southeastern Asia 42.3%, and Southern Asia 47.0% [13]. Such an astonishingly high prevalence rate invites attention from the medical community health policy makers and the general public. MAFLD puts a huge economic burden on society. The national economic burden of NAFLD in terms of direct annual medical costs has been estimated at USD 103 billion in the US and in the UK GBP 5.24 billion/year, France, Italy, and Germany combined EUR 27.7 billion/year spent in the management of MAFLD and related conditions. The economic burden of MAFLD and related conditions in the 10 years time is predicted to increase USD 908 billion in the US and to EUR 302 billion in Europe [12–15].

Most people between the age group of 40 and 60 years are generally affected by MAFLD although it can also occur in children above the age of 10 years. The prevalence of disease is more in males than in females in the younger age group, whereas in the older age group above 65 years, it is reversed.

An unhealthy, high-carbohydrate, and high-fat diet leads to NAFLD and metabolic diseases such as diabetes. Gut microbial dysbiosis and choline deficiency also play key roles in disease development. The disease mostly goes unnoticed in the initial stages. Medical history, abdominal ultrasonography, and blood/serum biomarkers are recommended as primary diagnostic tools for detecting hepatic steatosis in MAFLD. Although liver biopsy is considered the standard for the diagnosis of fatty liver disease, its invasiveness and unavoidable complications limit its clinical application.

Pathophysiology of MAFLD is not well understood. Accumulation of aberrant lipid metabolism, sedentary life style and unhealthy dietary patterns, insulin resistance, and diabetes are several interlinked pathological factors involved in the pathogenesis of the disease. Hepatic steatosis is a characteristic feature of NAFLD and MAFLD, based on serum biomarkers, imaging methods, or histology, coupled with no alcohol consumption and no other liver disease or causes of hepatic steatosis. In addition, at least one of the criteria, such as being overweight or having type 2 diabetes, is linked with MAFLD. Evidence of metabolic dysregulation, as seen in the form of increased waist circumference, hypertension low serum HDL-cholesterol levels, hypertriglyceridemia, impaired fasting plasma glucose, elevated HOMA-IR (approximates insulin resistance), increased C-Reactive

protein (chronic), is also strongly associated with MAFLD. The differential features of NAFLD and MAFLD are presented in Figure 1.
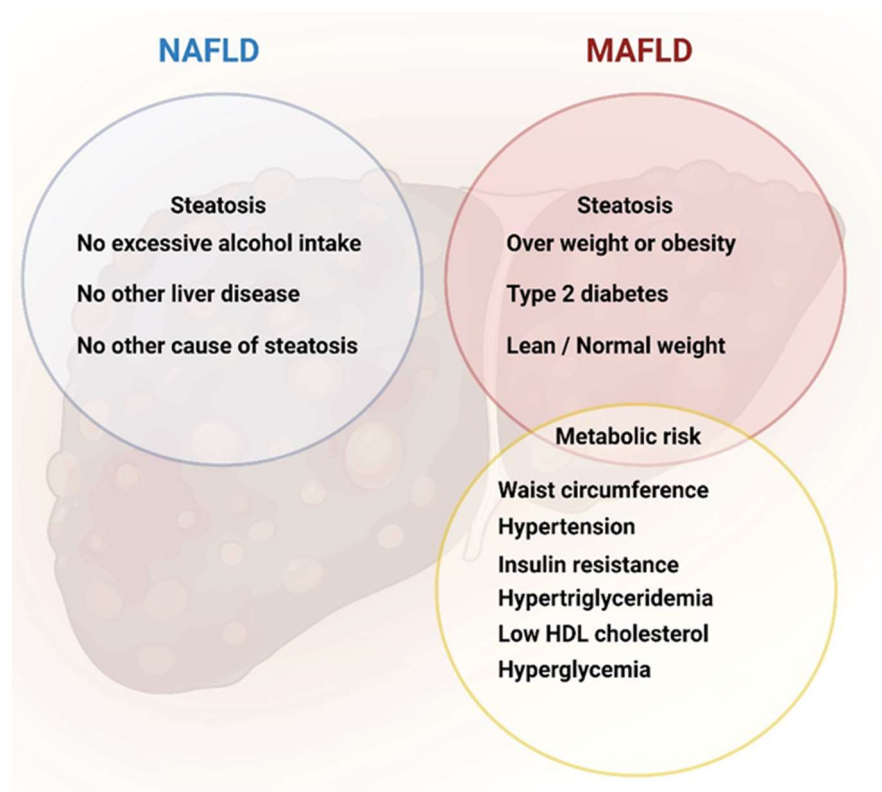
Figure 1. Differential features of NAFLD and MAFLD. Steatosis is a common feature in both NAFLD and MAFLD. A strong association of overweight, obesity, type 2 diabetes, and metabolic risk factors such as hypertension, insulin resistance, high triglycerides level, low LDL cholesterol, and high blood glucose level differentiate MAFLD from NAFLD.

Research work in search of new molecules to effectively treat NAFLD/MAFLD is ongoing [7] since no suitable, safe, and effective pharmaceutical agent is available for the treatment covering the entire spectrum of the disease.

In this review, we describe the different pharmacological agents or targets developed recently for MAFLD as effective medications that can be recommended as per clinical practice guidelines (CPGs) issued by the Liver International Society in the US, which may help to improve the health of MAFLD patients since at present no suitable and potent treatment is available.

2. Materials and Methods

A systematic literature search was conducted to source articles from the following databases: PubMed Central, Ovid-Medline search, and Google scholar. Specific keywords included "Non-Alcoholic Fatty Liver Disease", "NAFLD" or "Metabolic dysfunction-associated fatty liver disease", "MAFLD", combined with any of the terms: "therapeutic agents", "pharmacological agents", metabolic disorder, metabolic dysfunction, etiology, diagnosis. Boolean operators, specifically "AND" and "OR", were also taken into consideration when searching for articles. The articles published within 19 years, i.e., from January 2004 to June 2023 were included and those articles published more than 19 years ago, i.e., before January 2004 were excluded. Thereafter, descriptive characteristics of the only relevant studies were extracted as follows: first author with the year of publication, journal title, the aim of the study, study design, and conclusion of the study.

3. Aetiology

The infiltration of lipids in the liver and their deposition involves various genetic and acquired factors [16]. The primary underlying cause of hepatic steatosis cannot be explained, and alcohol is not a real etiological cause; the disease is defined as non-alcoholic fatty liver disease. Secondary factors such as viral hepatitis are not considered etiological factors for NAFLD.

Metabolic diseases and conditions such as type 2 diabetes, insulin resistance, abdominal obesity, blood pressure, hyperglycemia, and hyperlipidemia are strongly associated with NAFLD. Furthermore, NAFLD is associated with hormonal disorders, persistently elevated transaminase levels, increasing age, and hypoxia.

3.1. Dietary Factors

Dietary factors such as unhealthy diet composition, quantity, and habits leading to obesity are major factors in NAFLD/MAFLD. Further, overnutrition in lean NAFLD and NASH is a major factor of disease according to the Asia-Pacific Working Group (APWG) [17]. Lipid deposition in hepatocytes, oxidative stress, mitochondrial malfunction, and dysregulation of several cytokines are predicted to cause cellular injury, apoptosis, and the onset of NASH [18–20]. De novo lipogenesis and inflammation are relevant mechanisms involved in the pathogenesis of NAFLD and NASH [21,22].

The progression of NAFLD to NASH and fibrosis is significantly influenced by diet quality and quantity, particularly omega 6 fatty acids [23,24]. NAFLD onset can be attributed to choline insufficiency [25]. Diets containing high sugar levels, such as fructose or sucrose, increase the risk of NAFLD [26]. The term "glucotoxicity" refers to the harmful effects of high blood glucose levels on cells. T2DM and the evolution of NAFLD are caused by a persistent glucotoxicity with hyperglycemia [27]. Insulin resistance (IR) is caused by low-grade grade glucotoxicity [28]. In addition, glucotoxicity-related inflammation can be explained by increased oxidative stress in hepatocytes [29]. The progression of hepatic steatosis and T2DM is collectively influenced by overall glucotoxicity, insulin resistance, and chronic inflammation, which supports the newly defined terminology MAFLD.

High-fat diet feeding in both humans and rodents develops hepatic steatosis within a few days, as well as a diet enriched in saturated fat or elevated intrahepatic triglyceride content in overweight males [30–32]. These results confirm that lipotoxicity plays a significant role in NAFLD. In obese individuals, nearly 60% of hepatic triglycerides are derived from free fatty acids (FFAs) [33]. Increasing visceral adipose tissue in obese people may lead to insulin resistance and hyperinsulinemia, which promotes lipolysis of adipose tissue [33]. Two classes of lipids, diacylglycerol (DAG) and ceramide, play essential roles in causing hepatic IR [34]. Lipid metabolites function as intermediates in the causal link between lipotoxicity and IR and both contribute to the development of NAFLD/MAFLD.

3.2. Metabolic Conditions

The risk factors for developing NAFLD and NASH are metabolic disorders such as diabetes and obesity, in addition to age, sex, and race/ethnicity [35]. Diabetic patients with insulin resistance and obesity have enhanced lipolysis and increased free fatty acid transport to hepatocytes [36]. The majority of NAFLD patients with normal weights, referred to as "Lean NAFLD," are sedentary and have poor insulin sensitivity, making them more prone to cardiovascular disease. These are the result of an increase in hepatic de novo lipogenesis and a decrease in the ability of adipose tissue to store fat [10,17]. Secondary causes of NAFLD include inborn errors of metabolism, iatrogenic causes (diseases caused by medical treatment or examination), viral hepatitis, and nutritional disorders. These factors are less well recognized but are nevertheless significant. Many etiological factors, including alcohol abuse, obesity, and diabetes mellitus, contribute to fatty liver changes.

3.3. Gut Microbes

Furthermore, gut microorganisms contribute to the development of NAFLD [37]. Dysbiosis of the gut microbiota affects the risk of NAFLD in various ways [38]. Owing to the increased permeability of the intestine, the liver may be exposed to harmful substances, such as translocated bacterial toxins and inflammatory chemical signals that promote hepatic inflammation. These alterations enhance nutrient and calorie absorption and alter metabolism [39–41]. Excessive consumption of micronutrients disturbs gut homeostasis and causes gut inflammation [42]. The various etiological factors responsible for the development of NAFLD and MAFLD are depicted in Figure 2.
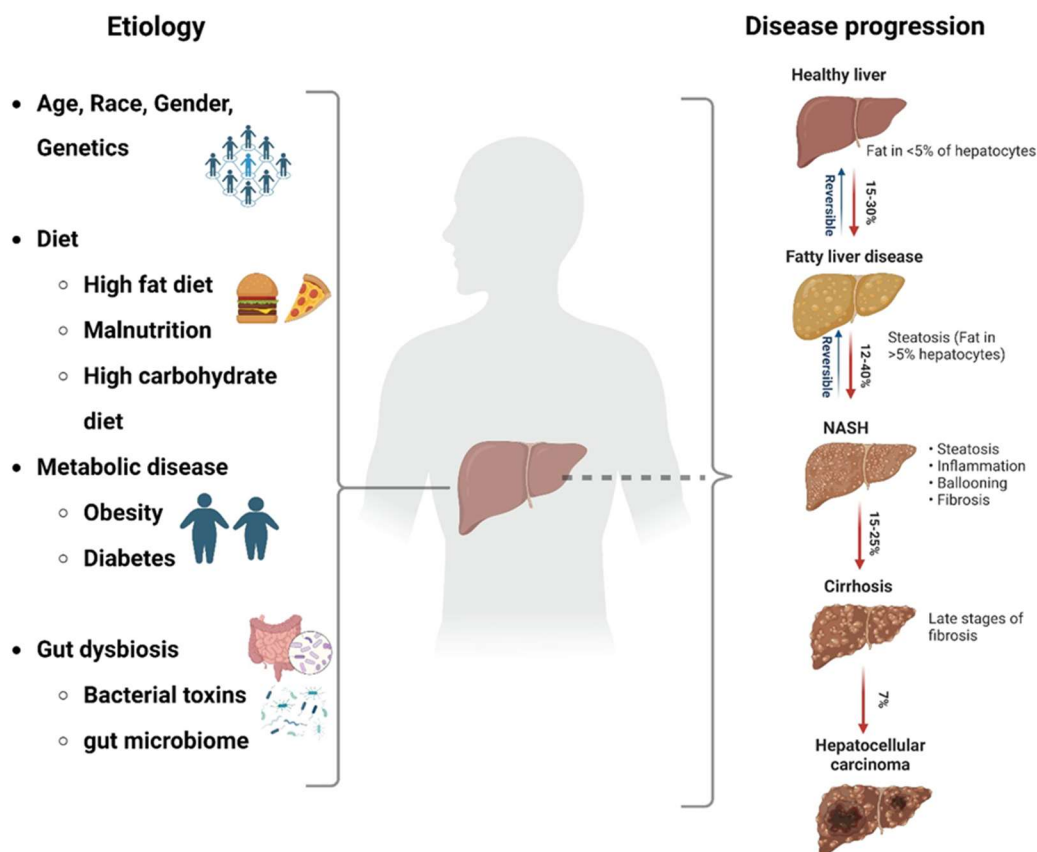
Figure 2. Various etiological agents responsible for the initiation and progression of NAFLD/MAFLD. Various etiological agents such as unhealthy diet, high fat diet, malnutrition, high carbohydrate diet are responsible for the development of metabolic disease such as obesity and or diabetes. Bacterial toxins and gut microbiome disbalance are also associated with the development of disease. As a result, exposure of these agents to subjects develops fatty liver and leads to disease progression as inflammation may lead to fibrosis, cirrhosis, and hepatocellular carcinoma depending on persistence of etiological agents. Age, race, gender, and genetics of persons show variations in disease pattern.

4. Diagnosis

The diagnosis of the disease is based on the medical history of the patient, including dietary habits. The selection of a diagnostic test depends on cost and sensitivity. The suggested MAFLD diagnostic criteria are predicated on the presence of hepatic steatosis, which can be identified using imaging methods, blood biomarkers, or liver histology [43].

4.1. Imaging Techniques

NAFLD is an asymptomatic disease that is frequently detected using abdominal ultrasound, CT scans, or magnetic resonance imaging (MRI) and can show hepatic fatty

infiltration [44]. The limitation of this technique is that its sensitivity decreases when the steatosis level is lower than 30% [45,46].

Owing to its accessibility and low cost, ultrasound is favored as the first-line examination [47]. The limitations of the test are as follows: (1) it is unable to distinguish between steatosis and fibrosis, and (2) it is not sensitive if the liver's fat content is less than 20%. Alternatively, the controlled attenuation parameter (CAP) is more sensitive, and 1H-MRS is also an acceptable quantitative marker of steatosis. Laboratory biochemical testing is also appropriate for high-risk populations [47]. For all patients with metabolic risk factors, the EASL and AASLD recommend performing an ultrasound examination and measuring liver enzymes.

In clinical practice, ultrasonography is widely used because of its convenience, cost-effectiveness, and sensitivity when the fat content is >30% in the liver [48,49].

4.2. Computerized Tomography (CT)

This diagnostic technique is more precise than ultrasonography (US), but it is limited to patients with mild steatosis and radiation exposure [50]. CT is more sensitive than US in assessing hepatic fat content, but substances such as iron may act as confounders and affect the diagnosis [51]. The CAP Technique is an ultrasound-based method for the quantification of steatosis (>10% steatosis). Although the test does not seem to be very dependable [52], the Asia-Pacific guidelines still recommend CAP as a useful tool in NAFLD patients.

Although magnetic resonance imaging (MRI) and magnetic resonance spectroscopy (MRS) can detect hepatic steatosis and fibrosis, their use in clinical practice is constrained by high cost [53,54]. Because of the test's operational complexity and complex algorithm, MRS use in routine clinical practice is limited despite its ability to identify 5.56% of the liver fat content, which makes it the gold standard for steatosis [54].

More recently, transient elastography (TE FibroScan), performed using an ultrasound procedure, has gained popularity because it provides quick and convenient measurements of liver stiffness, which are closely linked to the stage of liver fibrosis [55]. The sensitivity and specificity of CK18-based NAFLD diagnosis are 66% and 82%, respectively [14].

4.3. Blood and Serum Biomarkers

Biochemical parameters of NAFLD in patients with metabolic syndrome including alanine aminotransferase (ALT), aspartate aminotransferase (AST), hemoglobin A1C, homeostatic model assessment (HOMA)-IR, triglycerides, BMI, and gamma-glutamyl transferase (GGT) could provide good prediction of disease condition [56–58].

The insulin-like growth factor1 (GF-1) and cytokeratin18 fragment (CK18F) have also demonstrated encouraging results in routine NAFLD screening [59]. Another diagnostic blood miRNA test is highly effective in detecting NASH in obese individuals [60]. It is crucial to identify the disease at an early stage using non-invasive diagnostic methods so that the proper course of action can be taken to prevent the disease from progressing from an early stage of simple steatosis to steatohepatitis.

4.4. Histological Biopsy

Liver biopsy remains the gold standard for determining the presence of NAFLD and, more specifically, for determining the presence of NASH at an advanced stage [61]. Liver biopsy is an invasive procedure that carries a 0.05% risk of mortality due to test-related complications [43]. Additionally, the test is expensive and requires trained pathologists and skilled operators [62]. Furthermore, this technique has limitations for mass screening (European Assoc 2015). The sampling error that occurs during biopsy can result in an erroneous prognosis. Non-invasive methods may be preferred as the first strategy to identify NAFLD/MAFLD because inter-observer variability can result in over- or underestimation of the hepatic fibrosis stage [63]. If NASH and liver fibrosis cannot be determined using non-invasive methods, additional liver biopsy is only performed on individuals in whom the etiology of the liver needs to be clarified [64].

5. Pharmacological Therapeutics Evaluation

Pharmacological therapeutics have been developed for MAFLD based on the mechanisms of action and adverse events. The Liver International Society in the Americas (AASLD) [9,14,15] made recommendations according to the clinical practice guidelines used by these agents.

Medications based on potential benefits include vitamin E, which is recommended for non-diabetic, non-cirrhotic patients, and pioglitazone with or without diabetes, while no clear benefit was observed using statins for cardiovascular disease; similarly, metformin, n-3polyunsaturated fatty acids, ursodeoxycholic acid, and pentoxifylline showed no clear benefit in MAFLD.

Currently, drugs with potential benefits include thiazolidinediones (pioglitazone) and Vitamin E′ in MAFLD. Pioglitazone has been proven to be effective in diabetic and MAFLD patients with substantial fibrosis (>F2), while vitamin E is advised for nondiabetic MAFLD patients with >F2 non-cirrhosis [65]. There have been studies on new pharmacological agents targeting various MAFLD patients [66]. Eight new drug classes with different targets are described here, owing to the disputed pathophysiology of MAFLD. They are first- and second-generation farnesoid X receptors, peroxisome proliferator activated receptor (PPAR), C-c chemokine receptor), the GLP-1 (glucagon-like peptide-1) receptor, and thyroid hormone receptor (TSH).

5.1. Farnesoid X Receptor Agonist

The first generation include obeticholic acid (OCA)(INT-747), whereas the second generation included Cilofexor (GS-9674) and Tropifexor. New pharmacological therapeutics, such as FXR, are targets for metabolic dysregulation caused by obesity, including type 2 diabetes, NAFLD, and atherosclerosis. The nuclear receptor family, which includes the farnesoid X receptor (FXR), is activated by bile acids and expressed in the liver. The effective absorption of fat and fat-soluble vitamins is facilitated by bile acids, which also aid in digestion and play a significant role in controlling inflammation and the cholesterol and triglyceride homeostasis. Bile acids regulate hepatic lipid and glucose metabolism [67]. Inhibiting lipogenesis, gluconeogenesis, and the regulation of insulin sensitivity are inhibited by the FXR receptor, which is activated by bile acids [68,69].

OCA is a semi-synthetic bile acid analogue. The chemical structure of OCA is 6-alpha-ethyl-chenodeoxycholin acid, which has been developed and commercialized under the brand name Ocaliva, in combination with ursodeoxycholic acid used to treat primary biliary cholangitis. Intercept Pharmaceuticals Inc. holds the right to develop this drug outside of Japan and China. OCA was the first FXR agonist used in human drug studies. USFDA approved it in October 2016 for the treatment of primary biliary cholangitis. OCA was proposed to treat NASH [70] and reduced markers of liver inflammation, fibrosis, and increased insulin sensitivity [71]. The long-term safety issues of increased cholesterol and adverse cardiovascular events may warrant the concomitant use of statins in OCA treatment. Furthermore, the Intercept Pharma Govt Scientist FDA label updated in 2018 warns of liver injury from improper Ocaliva dosing.

The most frequent adverse effect, mild to moderate pruritus, was recorded, which led to discontinuation of OCA. Currently, OCA is not approved by the US Food and Drug Administration for the treatment of MAFLD.

5.2. Second Generation: Cilofexor (GS-9674), Tropifexor (LJN 452)

Cilofexor, a non-steroid FXR agonist, primarily activates intestinal FXR without affecting enterohepatic circulation. Cilofexor decreased portal hypertension and reduced liver fibrosis in NASH rats [72]. In a recent study, hepatic steatosis, as determined by magnetic resonance imaging, protein density fat fraction, and blood gamma-glutamyltransferase levels were significantly reduced in NASH patients. However, there were no discernible alterations in the lipid profiles. Side effects such as mild-to-severe pruritus have also been observed [73]. Cilofexor is being developed by Gilead Sciences and showed improvement

in NAFLD and NASH as seen by reduction in fibrosis and steatosis, improved cholestasis, and reduced markers of liver injury [73,74].

Another second-generation potent oral FXR agonist, tropifexor, which is structurally unrelated to bile acids, has shown significant efficacy in reducing hepatic steatosis. This investigational drug was discovered by researchers from Novartis and the Genomix Institute of the Novartis Research Foundation. The interim analysis of Phase 2-part C revealed a drop in ALT as well as a decrease in body weight and hepatic fat. Significant side effects of pruritus and elevated blood LDL-cholesterol are still the most frequent adverse events leading to tropifexor discontinuation [75]. A combination therapy of tropifexor and cenicriviroc (an antiretroviral agent) showed improvement in liver fibrosis in NASH patients [76,77].

5.3. Peroxisome Proliferator-Activated Receptor (PPAR) Agonists

PPAR agonists act on peroxisome proliferator-activated receptors. PPAR agonists are classified into three groups: (1) PPAR alpha/or gamma elafibranor (GET 505), (2) Pan-PPAR agonist (PPAR-alpha, PPAR-beta/gamma, and PPAR-gamma) lanifibranor (IVA 337), and (3) dual agonist of PPAR-alpha/gamma saroglitazar. PPAR transcription factors, particularly those that control lipid and glucose metabolism are involved in controlling energy balance as well [78]. PPAR-gamma activation enhances insulin sensitivity and plays a role in fat storage, whereas PPAR-alpha activation lowers plasma triglyceride levels. By suppressing the inflammatory macrophage phenotype, the activation of PPAR-beta/gamma improves fatty acid metabolism and exhibits anti-inflammatory effects [79].

Elafibranor (GFT505) is a dual PPAR alpha-PPAR delta agonist investigational drug developed by Genfit for the treatment of cardiometabolic diseases such as diabetes, insulin resistance, dyslipidemia, and non-alcoholic fatty liver disease [80]. Elafibranor (GFT 505) showed lower plasma triglyceride levels and increased HDL cholesterol in prediabetic individuals. Currently, there are no indications of PPARy-related adverse effects, which is a comforting safety profile. Elafibranor is a top contender for the treatment of NAFLD because of its effects on insulin sensitization and hepatoprotection. Elafibranor failed to sufficiently enhance histological NASH endpoints in a phase 3 trial (NCT 02704403). However, several individuals exhibited renal impairment and elevated serum creatinine levels during treatment, raising concerns about its safety.

Lanifibranor (IVA 337) is a pan-PPAR agonist of PPAR-alpha, PPAR-beta/delta, and PPAR-gamma that has both antifibrotic and positive metabolic effects [81]. In terms of lowering liver fibrosis and inflammatory gene expression, the pan-PPAR agonist lanifibranor is more effective than single or dual PPAR agonists [81]. In NASH patients, lanifibranor was well tolerated and reduced steatosis and fibrosis by at least two points without worsening fibrosis. Based on these encouraging findings, the FDA designated lanifibranor as a "breakthrough treatment" for a phase 3 trial targeting NASH patients. Lanifibranor is the first drug candidate to achieve statistically significant results at the main endpoints, and the USA FDA and European Medicine Agency (EMA) authorized lanifibranor for a phase III trial in the future.

Another PPAR alpha/gamma dual agonist compound, saroglitazar, is marketed under the trade name Lipaglyn for the treatment of type 2 diabetes mellitus, dyslipidemia, and hypertriglyceridemia associated with type 2 diabetes mellitus, which is not controlled by statin therapy. In clinical research, saroglitazar has been demonstrated to decrease triglycerides, LDL, VLDL, non-HDL, and increase HDL cholesterol. Additionally, it has demonstrated anti-diabetic effects by lowering fasting blood sugar and HB A1c in diabetic patients and might be useful in diabetic nephropathy [82]. Saroglitazar exhibits positive effects by reducing hepatic steatosis in NASH patients and by enhancing lipid and glycemic profiles in diabetic people with dyslipidemia [83]. However, no significant difference in liver stiffness measurements was reported [84,85]. No major serious adverse events have been reported; however, long-term cardiovascular safety has not been established [82]. Saroglitazar (Lipaglyn), a dual PPAR alpha/gamma agonist, has been approved for the treatment of NASH. This is the first medication used to treat NASH worldwide and has

received approval from the Drug Controller General of India (DCGI). Saroglitazar lowers the hepatic fat content and ALT levels in obese patients with NASH [85].

Thiazolidinedione (TZD) is a peroxisome proliferator-activated receptor gamma agonist. Insulin sensitizers are also known in the management of type 2 diabetes mellitus (T2DM). Thiazolidinediones mostly promote adipocyte differentiation, lower plasma FFA, decrease hepatic fat deposition, and improve insulin resistance [86]. Pioglitazone significantly reduced hepatic fat content in T2DM patients with NASH; however, vitamin E was effective in NASH patients without diabetes [87].

5.4. Glucagaon-Like Peptide-I (GLP-1) Agonists

Current diabetes and obesity treatments include GLP-1 analogs because of their beneficial metabolic effects, particularly on glucose metabolism. MAFLD development is intimately correlated with the GLP-1 signaling pathway [88]. GLP-1 receptor agonist (GLP-1-RA) is effective in improving cardiovascular and T2DM outcomes [89].

This class contained three subclasses: (1) Liraglutide and semaglutide, which function as GLP1 receptor agonists; (2) Tirazapatide, a dual agnostic GLP-1 receptor and glucose-dependent insulinotropic polypeptide (GIP) receptor (LY3298176); (3) dual glucagon and GLP-1 receptor agonist Cotadutide (MEDI0382). The incretin hormone glucagon-like peptide (GLP-1) is released after food intake and stimulates insulin secretion along with hyperglycemia affecting weight loss [90].

Liraglutide (a-GLP-1 agonist), is marketed under the trade name Victoza and is used to treat type 2 diabetes, obesity, and chronic weight management. Victoza is recommended for type 2 diabetes, in addition to diet and exercise, to enhance glycemic control and lower the risk of serious adverse cardiovascular events. Long-term use involves the risk of thyroid C-cell tumors, pancreatitis, hypoglycemia, renal impairment, hypersensitivity reactions, and acute gallbladder disease. Common side effects include low blood sugar, nausea, dizziness, abdominal pain, pain at the site of injection, gastrointestinal side effects, medullary thyroid cancer, angioedema, pancreatitis, gallbladder disease, and kidney problem. This drug was approved in the United Sates in 2010 with issued warning of adverse effects that include thyroid cancer and pancreatitis.

Liraglutide in patients with NASH was assessed for safety and efficacy and was found to be effective considering histological resolution, safe, well tolerated, and warranting extensive long-term studies [91]. Liraglutide treatment helps in reducing weight loss, and decreased serum cholesterol and triglyceride levels, and hepatic fat content in T2DM patients with MAFLD; in a pilot 48-week treatment, it was able to stop the progression of liver fibrosis [91–93].

Semaglutide, another GLP-1 receptor agonist, boosts insulin secretion, controls blood sugar, is effective for weight loss, and reduces liver enzymes [94]. This GLP-1RAS shared common transient adverse effects with gastrointestinal symptoms, including nausea, vomiting, and abdominal pain. The probability of long-term injection may increase the risk of pancreatitis, pancreatic cancer, thyroid cancer, biliary disease, kidney injury, and retinopathy; however, no definite conclusion has been drawn [95]. Semaglutide improves insulin sensitivity and results in long-lasting weight loss in diabetic patients, whereas individuals with NASH in Phase 2 had considerable resolution but no improvement in the fibrosis stage [96].

Semaglutide is clinically effective in overweight or obese people for weight loss, to be used together with diet and exercise for weight loss at 3 and 6 months [97]. It is also effective in type 2 diabetes and lowers the risk of heart attack, stroke, or death in patients. Semaglutide treatment of overweight and obesity at a dose of 2.4 mg subcutaneously once a week consistently reduced the mean weight loss by 14.9%–17.4% in participants without diabetes and showed improvement in cardiometabolic risk factors, physical function, and quality of life [98]. Nova Nordisk Pharmaceutical Company developed semaglutide in both injectable formulations (Ozempic and Wegovy approved in 2017 in the US) and oral formulations (Rybelsus, approved in 2019 in the US).

Tirzapatide (Ly3298176, Eli Lilly and Company) is a dual GIP and GIP-1 agonist and a new therapeutic option for the treatment of type 2 diabetes. Side effects include tiredness, loss of appetite, nausea, vomiting, diarrhea, and abdominal pain. In comparison with dulaglutide, another GLP-1 agonist, a phase II RCT demonstrated improved glycemic control and weight loss with a favorable tolerability and safety profile [99]. In a phase IIb study, the efficacy and safety of tirzapatide in patients with NASH are still being evaluated (NCT04166773). Tirzapatide is prescribed subcutaneously once per week to treat type 2 diabetes and is sold under the brand name Mounjiaro. Swelling/redness/itching were also observed at the injection site. This drug was manufactured by Eli Lilly and was approved in 2022.

Cotadutide (MED 10382) is a dual glucagon and GLP-1 agonist that is effective against overweight T2DM in reducing weight and serum transaminase compared to placebo (NCT 03235050) in a phase IIb RCT [100]. By imitating the human hormones, glucagon-like peptide 1 and glucagon, which participate in blood sugar regulation, reduce blood glucose levels. This medication is a peptide injected under the skin. As of February 2021, this medication began phase II clinical trials. This investigational drug is under development for NASH and chronic kidney disease with type 2 diabetes.

5.5. Thyroid Hormone Receptor Beta Agonist: Resmetirom (MGL-3196)

The thyroid hormone receptor beta (THR-beta) agonist resmetirom (MGL-3196) is very selective. It is a liver-targeted drug with strong affinity for thyroid hormone receptor-beta, which is intended to reduce lipotoxicity and ameliorate NASH by accelerating hepatic fat metabolism. The drug was developed by Madrigal Pharmaceuticals (West Conshohocken, PA, USA). Resmetirom is a prospective lipid-lowering medication that also shows promise in the treatment of non-alcoholic fatty liver disease and hepatic insulin resistance. It is a liver-specific agonist of thyroid hormone receptor beta (TRBeta). TRBeta controls the metabolic pathway, which lowers triglyceride and cholesterol levels, improves insulin sensitivity, promotes liver fat metabolism, and decreases cell apoptosis. Resmetirom demonstrated efficacy in phase IIb NASH by reducing hepatic steatosis [101], and its efficacy and safety have been studied in phase III RCT (MAESTRO NASH) in stage 2–3 fibrosis NASH patients (NCT 03900429). Resmetirom was well tolerated, but had the most common gastrointestinal adverse events, such as diarrhea and nausea.

5.6. C-C Chemokine Receptor Type 2 (CCR2) and Type 5 (CCR5) Antagonist

Cenicriviroc is a dual CCR2/CCR5 antagonist. Although CCR5 promotes the proliferation of collagen-producing activated hepatic stellate cells/myofibroblasts and is linked to the advancement of fibrosis, CCR2 is crucial for the recruitment and activation of monocytes and macrophages at sites of hepatic damage. Cenicriviroc, however, was not very effective in treating NASH and required further validation in a phase3 trial [102], while in the phase III RCT of cenicriviroc in patients with NASH it lacked efficacy to treat liver fibrosis; further development was stopped due to lack of benefit [103]. Hence, at present, there are no approved drugs for patients with NASH from this family. Cenicriviroc was developed by Takeda and Tobira Therapeutics, with code numbers TAK-652 and TBR-652, respectively.

5.7. Antifibrotic Drugs

Selonsertib (GS-4997) is a selective inhibitor of apoptosis signal-regulating kinase1(ASK1). The treatment of NASH patients with this compound increases the risk of fibrosis, scarring, cirrhosis, liver failure, and cancer. In conclusion, selonsertib does not reduce fibrosis in NASH patients [104].

Simtuzumab (GS-6624) is a humanized monoclonal antibody designed to treat fibrosis. It acts as an immunomodulator by binding to enzyme lysyl oxidase-like2 (LOXL2). This product was developed by Gilead Sciences; however, in the phase 2 clinical study, it was terminated in January 2016 due to idiopathic pulmonary fibrosis and lack of efficacy.

(Gilead Press release 5 January 2016). In the phase IIb trial of NASH patients, simtuzumab was ineffective in decreasing hepatic collagen content or hepatic venous pressure gradients (Clinical trial Govt NCT 01672866 and NCTO 1672879) [105].

5.8. Pancaspase Inhibitor

Caspase inhibitors are hepatoprotective drugs, and Idun Pharmaceuticals developed the prospective medication emricasan in 1998 for the treatment of human hepatic disease [106]. Emricasan (IDN-6556, PF-03491390) is an oral irreversible pan-caspase inhibitor and was found to be well tolerated in a phase II RCT but ineffective in reducing fibrosis in NASH patients with fibrosis stages 1–3 [107,108].

5.9. Natural Plant Drugs or Food Products

Natural plant medicine curcumin has anti-inflammatory, antioxidant, and lipid-modifying characteristics that may be helpful for MAFLD. Although a meta-analysis of RCTs demonstrated that curcumin improved the pathology of the liver and had a positive effect on lipid profiles, it failed to achieve statistical significance [109]. Functional foods or natural health products could be useful in the direction of decrease of obesity metabolic consequences and weight management [110]. However, scientific evidence is needed to support with clinical studies. Curcumin, silymarin, an extract from milk thistle seeds, resveratrol may benefit metabolic health [111,112] but natural plant drugs are inferior to metabolic targeted drugs for NAFLD [109].

Combination therapy of novel monotherapies targeting different mechanistic approaches is an attractive approach for investigation. Currently, FXR agonists are the most favorable agents and may be worth trying in combination, which will need additional clinical data in the evaluation of benefits in NASH as well as safety profiles.

5.10. Anti-Obesity Drugs Evaluated for MAFLD

Anti-obesity medications have also been evaluated for MAFLD. The following medications are currently licensed for the treatment of obesity in the United States and Europe: orlistat, naltrexone/bupropion, liraglutide, and semaglutide [113]. Orlistat did not alter liver histology in MAFLD patients, and further research is needed to determine its precise efficacy [114]. Similarly, the effectiveness of naltrexone may be associated with weight loss and may improve the liver health whereas other anti-obesity drugs for MAFLD are unknown and further research is required [115].

5.11. Anti-Hyperglycemic Agents for MAFLD

Two diseases, T2DM and MAFLD, frequently coexist and increase the risk of disease worsening [116,117]. Metformin and dipeptidyl peptide 4 (DPP4) inhibitors failed to demonstrate substantial efficacy in hepatic steatosis and fibrosis, whereas glucagon-like peptide-1 receptor agonists (GLP-1, RA), thiazolidinediones, and sodium-dependent glucose transporter 2 (SGLT2) inhibitors showed some improvement in the histological features of steatohepatitis.

5.12. Sodium–Glucose Cotransporter-2 (2SGLT-2) inhibitors

The use of sodium–glucose cotransporter-2 (2SGLT-2) inhibitors in T2DM patients at risk of cardiovascular disease is currently common [118]. For T2DM patients with MAFLD, other inhibitors in this group, including luseogliflozin, canagliflozin, ipragliflozin, and empagliflozin, all demonstrated improvements in liver fat content, ranging from 3.9% to 6.9% and reduced body fat and abdominal fat area and fibrosis regression [119–122].

Canagliflozin belongs to a class of SGLT2 inhibitors used in type 2 diabetes along with diet and exercise, or sometimes with other medications, to lower blood sugar levels. Canagliflozin reduces the risk of stroke and heart attack in patients with diabetes, as well as the risk of severe kidney disease. This medication is not used for the treatment of type 1 diabetes. Canagliflozin was developed for NASH in NASH activity for commercial

preparation under the brand name Ivokana. Side effects include dizziness, lightheadedness, fainting when getting up, several urinary-related problems, and sometimes very serious ketoacidosis. The FDA is concerned about the cardiovascular safety of this drug.

Empagliflozin is also an SGLT2 inhibitor developed under the brand name Jardiance for type 2 diabetes that lowers the risk of cardiovascular death and hospitalization for heart failure. Jardiance reduces the hepatic fat content. This drug is not recommended for people with type1 diabetes and those with severe kidney problems. This medication can cause serious side effects such as ketoacidosis and urinary tract infection.

5.13. Metformin and Dipeptidyl Peptidase 4 Inhibitors

Metformin is well established drug for T2DM and helps in reducing obesity and improving liver dysfunctions [123]. Evidence for the use of metformin in reducing liver fat accumulation in MAFLD patients is needed to support clinical studies [124].

5.14. Fibroblast Growth Factors

Aldafermin is an engineered analog of fibroblast growth factor 19 (FGF 19 analog) (formerly NGM 282), and in a phase 2 trial, aldafermin therapy decreased the amount of liver fat in NASH patients as determined by MRI-PDFF and indicated a trend toward fibrosis improvement [125]. Aldafermin was well tolerated but had uncertainty over the efficacy of treatment and risk-benefit profile; hence, it could not be approved. The development of aldafermin was funded by NGM Biopharmaceuticals.

Efruxifermin (EFX) was developed to reverse fibrosis, reduce hepatic fat and inflammation, increase insulin sensitivity, and improve lipoprotein levels. It has been shown to dramatically decrease liver fat in patients with NASH and F1–F3 fibrosis, while being safe and well tolerated. After 16 weeks of treatment, the medication was successful in lowering the hepatic fat fraction liver injury marker level and improving the histology and metabolic criteria, indicating that efruxifermin may have the ability to alter the progression of NASH. Efruxifermin should be further examined in long-term studies with larger patient populations to be developed as a first-line therapy for NASH [126]. EFX was designed for convenient subcutaneous dosing once per week. This product is being developed by Akero Therapeutics and US FDA has recognized the potential of this medication and approved it for clinical research studies.

Both efruxifermin and pegbelfermin (formerly BMS* -986036*Bristol-Myers-squib) are both FGF21 analogues developed as injectable preparations for subcutaneous administration once per week for 16 weeks. Pegbelfermin is an investigational PEGylated fibroblast growth factor 21 analog that has been developed for the treatment of NASH. It has also been shown to improve liver damage and cardiometabolic parameters. Pegbelfermin treatment was well tolerated and significantly reduced the hepatic fat fraction in patients with non-alcoholic steatohepatitis. Further studies should be conducted in a larger number of patients with NASH using liver biopsies and their effects on liver histology to demonstrate reduced progression to cirrhosis. Most adverse events, observed such as nausea and diarrhea, are mild [127,128].

While efruxifermin showed benefits in serum lipid metabolism and glycemic management, as well as weight loss, pegbelfermin exhibited improvements in liver damage indicators and cardiometabolic parameters. To evaluate the effectiveness of histological endpoints, additional studies with efruxifermin in patients with NASH (NCT 04767529) and NASH-related compensated cirrhosis (NCT 05039450) are currently underway. Further studies with pegbelfermin should be carried out to demonstrate reduced progression to cirrhosis.

The pharmacological agents developed for MAFLD treatment, and their current status are summarized in Table 1.

Table 1. Therapeutic profile of pharmacological agents developed for MAFLD/NAFLD.

Pharmacological Agents	Therapeutic Class	Activity Profile	Adverse/ Side Effect	Current Status	Commercialized Trade Name	Remarks
Obeticholic acid (OCA) [70,71]	FXR	For primary biliary cholangitis, possibly may have beneficial role in NASH, reduced inflammation, fibrosis, insulin sensitivity, supports further clinical studies.	Lipid increased abnormality, cardiovascular abnormality, mild to moderate pruritus. May cause liver damage.	Medication for PBC primary biliary cholangitis.	Ocaliva	Ocaliva may cause serious side effects including liver failure
Cilofexor [72,73]	FXR agonist 2nd generation	NAFLD, NASH (Non-cirrhotic), PSC (primary sclerosis cholangitis), reduction in steatosis	Generally well tolerated, most frequently headache, with combination of Firsocostat caused pruritis or skin itching, headache, diarrhea and nausea	Phase II		Not approved by US FDA no NASH resolution, no decreased fibrosis
Tropifexor [75–77]	FXR, 2nd generation	Cholestatic liver disease, NASH, reduction in steatosis, improvement in liver fibrosis in combination with cenicriviroc	Significant pruritus, increased LDL cholesterol	Phase II in progress		Discontinued because of side effects
Elafibranor [80,129]	Dual PPAR alpha/delta agonist	Diabetes2, IR, dyslepidemia, NAFLD, NASH resolution, no fibrosis decreased	Generally, well tolerated, renal impairment, elevated serum creatinine level	Phase IIb Phase III in clinical pathway, FDA grants approval for PBC		Investigational. not approved for any particular hepatic condition. elevated serum creatinine concern about its safety.
Lanifibranor [81,130]	Pan-PPAR Agonist of PPAR alpha, PPAR beta and delta, PPAR gamma.	Reduction in NASH, lipid profile, glycemic control	Highest risk of diarrhea, constipation, nausea, abdominal pain	Approved for Phase III and other studies are in progress		Research is in progress
Saroglitazar [82–85]	Dual PPAR, alpha/ delta agonist	Type 2 diabetes, dislipidemia. potential therapeutic option for NAFLD, approved for NASH diabetic nephropathy, hypertriglyceridemia	No major but increased serum creatin may cause concern. May cause nausea, vomiting, diarrhea, headache	Phase II	Lipaglyn	Longterm cardiovascular safety not established, qualified for NASH treatment In India
Liraglutide [91–93,131]	GLP-1R receptor agonist	Type 2 diabetes, chronic obesity atherosclerotic cardiovascular disease NASH resolution, no decreased fibrosis	GI side effect low blood glucose thyroid cancer, pancreatitis	Phase II	Victoza, Saxenda	
Semaglutide [94–98]	GLP-1R	Diabetic Type 2, obesity, plus diet & exercise NASH resolution but no decrease in fibrosis.	GI side effect. GERD		Ozempic	Contraindication in people with thyroid carcinoma
Tirzapatde [99,132,133]	Dual GIP and GLP1 agonist	Type 2 diabetes	GI side effects, abdominal pain, nausea, vomiting. Diarrhea, loss of appetite, tiredness.	Phase IIb	Mounjiaro	Efficacy in NASH is under evaluation

Table 1. *Cont.*

Pharmacological Agents	Therapeutic Class	Activity Profile	Adverse/ Side Effect	Current Status	Commercialized Trade Name	Remarks
Cotadutide [100,134,135]	Glucagon and GLP1agonist	Type 2 diabetes Reducing weight, supports for further evaluation after NASH and CKD with type 2 diabetes.	Increased incidence of gastrointestinal disorders	PhaseII, Phase III		Investigational drug
Resmetirom [101]	THR-B	NAFLD NASH resolution	GI side effect, nausea, diarrhea, otherwise well tolerated.	Phase III		Investigational drug
Cenicriviroc [102,103]	CCR2/CCR5 antagonist	No NASH resolution decreased Fibrosis		Phase IIb No benefit in NASH, hence stopped.		Not approved.
Selonsertib [104]	Antifibrotic inhibitor of ASK1	treatment of NASH	Increases risk of cirrhosis fibrosis, scarring cirrhosis, liver failure and cancer			Does not reduce fibrosis. Not developed
Simtuzumab [105]	Antifibrotic drug humanised monoclonal antibody	Fibrosis	Caused IPF (idiopathic pulmonary fibrosis	Phase II terminated		Lack of efficacy
Emericasan [106]	Pancaspase inhibitor	Liver disease, NASH and cirrhosis, developed for decreased fibrosis	Well tolerated	Phase II		Investigational drug
Canagliflozin [136,137]	SGL2 inhibitor	Type2 diabetes, reduces risk of heart attack ESKD (End Stage kidney disease), improvement in liver fat content	Low blood sugar, G.I. problem, kidney problem, UTI, increased risk of diabetic ketoacidosis	Phase II trial For treatment of obesity in US and Europe	Invokana, Sulisent, Prominand	FDA Concern about cardiovascular safety. Increased risk of leg and foot amputation
Empagliflozin [138]	SGL2 inhibitor	Type2 diabetes, proven lower risk of cardiovascular death and hospitalization for heart failure. Improvement in liver fat content.	Hyperventilation, diabetes ketoacidosis, urinary tract infection, female genital mycotic infection	US FDA approved	Jardiance	
Aldafermin [125]	Analogue of fibroblast growth factor 19	Decreases amount of liver fat in NASH and F1–F3, liver fat	Generally mild to moderate diarrhea, headache, nausea and joint pain	Phase II		Not developed due to uncertainty of efficacy
Efruxifermin [126]	FGF21 Fibroblast growth factors	Decreases hepatic fat in NASH and F1–F3 fibrosis, improves insulin sensitivity, lipoprotein	Well tolerated	Phase IIa Progress in longterm studies for NASH underway		
Pegbelfermin [127,128]	PEGylated fibroblast growth factor 21 analogue	For the treatment of NASH, improvement in liver damage and cardiometabolic diseases.		Under phase II trial		Investigational drug

Currently, there are no FDA-approved drugs for the treatment of fatty liver disease. The two best options affirmed by the American Association for the Study of Liver Diseases for biopsy-proven NASH are vitamin E (an antioxidant) and pioglitazone (used to treat diabetics). Amongst several pharmaceuticals researched, only a few molecules such as obeticholic acid, saroglitazar, liraglultide, semaglutide, tirzapatde, canagliflozin, and empagliflozin have been developed and are commercially available for the treatment at phases of NAFLD and or its associated disease MAFLD. The serious adverse effects of these drugs are taken into consideration during treatment.

In conclusion, regardless of the current or future progress in pharmacotherapy, a healthy lifestyle, good food habits, and weight loss remain the primary goal of MAFLD treatment. Second, (2) CPGs suggest utilizing pioglitazone and vitamin E in patients with considerable fibrosis ($\geq$F2 fibrosis), whether they have T2DM or not, as an alternative strategy. Third, (3) many innovative therapeutics that target various pathogenetic pathways and the admixture of several types of targeted pharmacotherapies are now being researched to develop effective disease-treating drugs for individuals with MAFLD, NAFLD, and NASH.

6. Future Research Directions

1. Search for safe and effective novel therapeutic agents for MAFLD remain a priority for biomedical research in the near future.

2. New strategies combining multitarget drugs need to be studied.

3. Simple and reliable noninvasive diagnostic tools for disease identification are required.

4. The pathogenesis of the disease is not very well understood; therefore, research work is needed to explore the role of glucotoxicity, lipotoxicity, and antioxidant defense through diet.

5. Development of suitable animal models to explore the various aspects of the disease process and the evaluation of new therapeutic agents.

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