The Developments of Drugs Based on Non-Alcoholic Fatty Liver

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Abstract. Non-Alcoholic Fatty Live (NAFL), a serious hepatopathy with a rising global prevalence, characterized through the simple excessive proliferation of triglyceride (TG) in the liver . It is triggered by an imbalance in fat metabolism by the reason of adiposity, fat-rich diet and insulin resistance (IR). The targets of treatment are to improve liver fat and function, focusing on the regulation of fat synthesis, metabolism and IR. This article mainly introduces the pathogenesis, therapeutic effect and development prospect of SGLT2 inhibitors, GLP-1/GIP analogues, ACC inhibitors, DGAT2 inhibitors and PPAR agonists which related to the above pathways in the therapies of NAFL diseases. Fortunately, these drugs corresponding to the targets have offered new strategies for the cure of NAFL.

Keywords: NAFL, ACC, DGAT2, SGLT2, GLP-1/GIP, PPAR

1 Introduction

Non-Alcoholic Fatty Liver Disease (NAFLD) is showed by the presence of diffuse macrovesicular steatosis in hepatocytes, which occurs without significant alcohol or other known liver-damaging factors. According to a large analysis published in 2023, the global morbidity of this disease has increased from 25.3% to 38.0% between the years 1990 and 2006,marking a 50.1% ($p<0.001$) increase in prevalence over the past three decadesand is expected to continue to climb over the next decade[1]. As the initial manifestation of NAFLD, NAFL is defined as the lipid content in hepatocytes can reach 5% or above without significant cell damage, with or without lobular inflammation[2]. However, poor dietary habit, obesity and IR have been shown to be the main factors causing hepatic steatosis [3].

When energy intake exceeds the body's consumption, the surplus energy is converted into TG and stored, leading to the proliferation of adipose tissue. In this process, lipids are decomposed into free fatty acids (FFAs) by lipid dissolution. Glucose from carbohydrate activates ChREBP after oxidation and transport. And insulin regulates SREBP in multiple dimensions, which together induce the expression of the target genes of FAS and ACC. Promote the transformation of glucose to fatty acids (FAs)[4]. At the same time, the amount of glucose in the body is influenced by the reabsorption pathway

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regulated by the SGLT2 located in renal tubules and the insulin secretion of pancreatic belta cells stimulated by GLP-1/GIP. In addition, the homeostasis of FFAs in hepatocytes is also regulated by their oxidation. The oxidation pathways of fatty acids mainly include peroxisome and mitochondrial belta oxidation, among which PPARs plays important role in fatty acid oxidation. PPARs promote the oxidation and breakdown of FFAs by activating belta oxidase enzymes such as CPT1A and CPT2. At the same time, PPARs can induce the expression of apolipoprotein genes to regulate lipid transport too[5]. A high-fat diet can also impair insulin receptor signaling pathways and make an imbalance of adiponectin and leptin, leading to IR. IR promotes the decomposition of lipids, inhibits the oxidation of fatty acid and the formation and release of VLDL, resulting in abnormal proliferation of TG in hepatocytes and the occurrence of NAFL ultimately (Figure1). These mechanisms together maintain the homeostasis of fatty acids, which is of great importance for the etiopathogenesis and therapy of NAFLD.

The primary endpoints of NAFL treatment are reduction of liver fat accumulation and improvement of liver function. At present, the intermediate processes and molecular targets involved in fat synthesis and metabolism and insulin resistance are regarded as the main directions of drug research. Existing studies have shown that SGLT2 inhibitors, GLP-1R/GIPR agonists GLP-1/GIP analogues, ACC and DGAT2 inhibitors can notably decrease the proliferation of TG in the liver. At the same time, PPAR agonists act as important regulatory factors to promote the oxidation and transport process of FFA. The above targeted therapeutic drugs have shown good clinical effects, providing a new strategy for NAFL treatment.

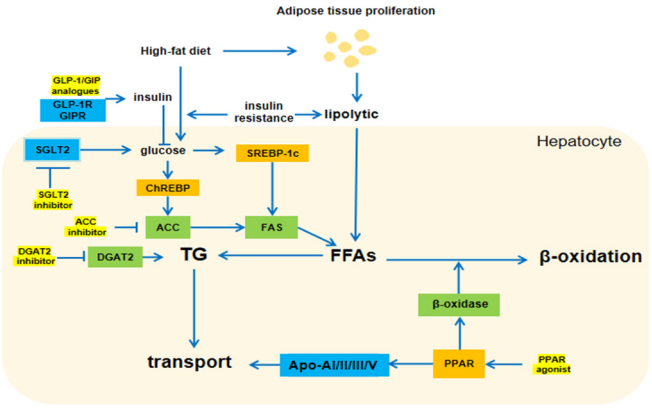


Fig. 1. Pathogenesis of NAFL .Abbreviations: FFAs: Free Fatty Acids; TG: Triglyceride; FAS: Fatty Acid Synthase; ACC: Acetyl-CoA Carboxylase; ChREBP: Carbohydrate Reaction Element Binding Protein; SREBP-1c:Sterol Regulatory Element-binding Protein-1c; DGAT2: Diacylglycerol Acyltransferase 2; SGLT2: Sodium-glucose Cotransporter 2; GLP-1: Glucagon-like Peptide-1; GIP: Glucose-dependent Insulinotropic Ploypeptide; GLP-1R: Glucagon-like Peptide-1 Receptor; GIPR: Glucose-dependent Insulinotropic Ploypeptide Receptor; PPAR: Peroxide Proliferation-activated Receptors; Apo-AI/II/III/V: Apolipoprotein A-I/II/III/V.
: enzyme :nuclear receptor :protein : drug : promote
: inhibit

2 ACC Inhibitors (ACCi)

As a key rate-limiting enzyme in lipid synthesis, ACC takes a significant part in the synthesis of FAs. Dietary carbohydrates produce acetyl-CoA via ACLY, which in turn is converted to malonyl-CoA. ACC1 is expressed in adipocytes and hepatocytes, catalyzes the production of malonyl-CoA, and participates in fatty acid synthesis[4]. ACC expression is upregulated in NAFLD patients, leading to FA accumulation. Therefore, ACC inhibitors show potential in the treatment of NAFLD, especially in combination with other drugs, and expanding the clinical indication of ACCi will be one of the hot areas[6]. ACC is a biotin-dependent carboxylase, and its BC domain has superior physical and chemical properties, making it an ideal target for drug targeting. The exploration of safe and effective BC domain inhibitors is a current research hotspot, which is expected to bring new breakthroughs in the treatment of NAFLD[7].

2.1 PF-05221304

PF-05221304 is a highly efficient and selective inhibitor of ACC1/2 developed by Pfizer Inc[8], with a half-life of about 14-18 hours in human body and good oral bioavailability. The IC50s for human ACC1 and ACC2 are 12.4nm and 8.7nm. Ross TT et al found that PF-05221304 significantly inhibited DNL and reduced the accumulation of TG in primary human hepatocytes in human in vitro studies. In addition, this medication blocked the polarization of human T cells to pro-inflammatory phenotypes and inhibited the activation of myofibroblasts by primary human astrocytes in vitro, suggesting its potential to decrease TG accumulation and potential lipid toxicity in the liver[9]. In clinical studies, high-dose PF-05221304 effectively inhibited DNL, and repeated administration could inhibit hepatic DNL in a dose-dependent manner. Although well tolerated, a high DNL inhibition rate (>90%) may lead to elevated serum TG level[10]. The latest study found that this drug combined with DGLT2 inhibitors (PF-06865571) may overcome the limitations of ACC inhibitors and offer a new strategy for NAFLD cure. But these findings also need to focus on drug interactions and safety[11].

2.2 Firsocostat (GS-0976)

Firsocostat is a dual ACC inhibitor targeting the liver that effectively inhibits ACC1 and ACC2 activity by binding to the BC domain. It is designed as a liver OATP substrate to achieve liver-specific distribution and ensure targeted therapy for NAFLD[12]. Animal studies have shown that Firsocostat treated diseased mice for 9 weeks, lowered the contents of malonyl-coA and liquid in their liver, and improved steatosis[13]. Diarrhea and headache are common adverse events, and their efficacy and safety need to be further evaluated. Future studies need to focus on drug dosing and medication strategies to optimize treatment and reduce side effects.In the future, adverse reactions of Firsocostat need to be carefully monitored[12]. A recent study (NCTO2781584) found that the combination of Firsocostat with FXR agonist(Cilofexor) and PPAR agonist (Fenofibrate) effectively reduced the increase of TG associated with ACC inhibition[14].

3 DGAT2 Inhibitors (DGAT2i)

DGAT has an important role in lipid synthesis by catalyzing the esterification of DAG to generate TG. DGAT2 is sunbtantially expressed in liver and adipose tissue .It has unique subcellular localization characteristics, making it a potential target for metabolic disease treatment[15]. DGATi can not only block the synthesis of triacylglycerol, but also increase the content of phosphatidylethanolamine in the endoplasmic reticulum(ER), thereby preventing the movement of SREBP-1 from ER to the Golgi apparatus for lysis and ultimately improving hepatic steatosis[16].

3.1 Ervogastat (PF-06427878)

Ervogastat is a potent and well-tolerated DGAT2 inhibitor. After treatment with it, the concentration of TG in the liver and circulating plasma of rats decreased, and the expression of lipid synthesis genes decreased. These non-clinical studies were extended to two Phase I human studies, and PF-06478878 was observed to be well tolerated[17]. The combination of DGAT2 inhibitors and ACC inhibitors (ACCi) can enhance therapeutic efficacy while mitigating adverse reactions caused by ACC inhibitors. This finding provides a new strategy for NAFLD treatment[18].

3.2 PF-07202954

PF-07202954 is a weakly alkaline DGAT2 inhibitor. In order to further optimize the pharmacological properties of DGAT2 inhibitors, the researchers successfully developed PF-07202954 on the basis of known DGAT inhibitors by introducing an alkaline group and fine-tuning its alkalinity and lipophilicity. This molecule has a long half-life, shows better pharmacokinetic properties, and has entered the research stage[19]. These research advances bring new hope for the treatment of metabolic diseases.

4 SGLT2 Inhibitors (SGLT2i)

SGLT2, as the main glucose transporter at the proximal end of renal tubules, is characterized by low affinity and high volume. By blocking SGLT2-mediated glucose and sodium reabsorption, SGLT2i increases sodium delivery in distal renal tubules, thereby increasing tube-bulb feedback and reducing glomerular pressure[20]. It not only improves insulin resistance and hyperinsulinemia, but also regulates blood sugar levels by protecting islet beta cell function and enhancing glucose sensitivity. Since 2012, SGLT2 inhibitors such as dagaglizin, Caglizin and Englizin have been approved for marketing in Europe and the U.S., and have also been applied in clinical practice in China since 2017, providing a new treatment option for diabetes patients. The pathogenesis and clinical application of these drugs reflect the multifaceted regulation of glucose metabolism and islet cell function, bringing new strategies for diabetes treatment[21].

4.1 Empagliflozin

Empagliflozin, a highly selective SGLT-2 inhibitor with inhibitory activity against human SGLT2 (IC50 of 3.1nM), has shown potential to improve IR in animal models. In a animal model of NAFL induced using a Western diet[22], Empagliflozin not only improved insulin sensitivity, but also reversed fatty liver lesions and had a positive effect on muscle mitochondrial morphology, suggesting that it may have metabolic benefits beyond glycemic control. Several Phase IV clinical trials (such as NCT04639414) for Empagliflozin in the cure of NAFLD are currently underway to estimate its efficacy and safety in human patients. These studies will provide a higher level of evidence for Empagliflozin in the treatment of NAFLD.

4.2 Dapagliflozin

Dapagliflozin, a newly approved oral hypoglycemic drug, is derived from the natural product phlorizin. By inhibiting SGLT2, excess glucose is eliminated from the body through urine. The use of this drug requires that patients with moderate to serious kidney inadequacy should condone the drug. An animal trial of Dapagliflozin showed that it reduced total cholesterol, triglycerides, insulin levels and blood sugar levels. Dapagliflozin may be a promising new therapy for the cure of T2DM-related NAFLD and dyslipidemia, which has antioxidant, anti-and anti-dyslipidemia effects[23]. Dapagliflozin also reduces liver lipid accumulation by promoting phosphorylation of ACC1 and upregulating the lipid balta ase CoA oxidase 1(ACOX1). In addition, daglipzin improves steatosis by making autophagy through the AMPK-mTOR pathway[24].

4.3 Canagliflozin

Canagliflozin, as the first SGLT2 inhibitor approved in the U.S., has demonstrated superior pharmacological potency and higher bioavailability compared to T-1095, a phlorizin analog, establishing its leading role in therapeutic medications. In human pharmacokinetic studies, Canagliflozin exhibited an oral bioavailability of 65%, with peak plasma drug concentrations achieved within 1 to 2 hours post-dosing. Further pharmacokinetic analysis revealed that in healthy subjects, 100 mg and 300 mg doses of Canagliflozin had mean half-lives of 10.6 and 13.1 hours, respectively, supporting its suitability for once-daily dosing regimens[25]. The clinical trial by Shaohan Huang et al. (NCT03136484) provided compelling evidence[26] that a daily 300 mg dose of Canagliflozin significantly improved visceral fat mass, offering recent wish for the treatment of adiposity and related metabolic syndromes. Moreover, the application of Canagliflozin in ob/ob mice and diabetic mouse models not only significantly improved glucose and insulin tolerance but also had a positive impact on hepatic steatosis and lipid accumulation in AML12 cells treated with FFAs[27], further highlighting its potential in metabolic regulation and liver protection.

5 GLP-1/GIP Agonists and GLP-1R/GIPR analogues

GLP-1, a peptide hormone consisting of 30 amino acids, exerts its biological effects through the GLP-1R. These receptors are widely distributed across various parts of the human body, including the distal ileum of the small intestine, the distal colon of the large intestine, alpha and beta cells in the pancreas. The central function of GLP-1 lies in its ability to enhance the response of beta cells to elevated blood glucose levels, thereby increasing insulin secretion[28]. GLP-1 can also regulate gastrointestinal motility and appetite, as well as increase glucose uptake by muscle cells and lipolysis, exerting a range of metabolic regulatory effects. Additionally, GLP-1 may have direct hepatoprotective effects. GIP, secreted by L and K cells in the intestine, increases insulin secretion through the GIPR. Meanwhile, activation of AMPK signaling pathway inhibits gluconeogenesis and promotes glycogen synthesis in liver.In two studies involving about a dozen Chinese and Japanese people， single nucleotide polymorphisms at the GIPR are associated with increased body fat distribution and visceral fat accumulation[29].

5.1 Tirzepatide

Tirzepatide, as a novel dual GIPR/GLP-1R agonist, has shown in Phase II clinical trials in patients with T2DM, effects of lowering liver enzyme levels and NASH biomarkers, while increasing adiponectin levels. Compared to basal insulin, Tirzepatide has showcased dose-dependent advantages in glycemic control and weight management. It is worth mentioning that, while Tirzepatide demonstrates remarkable clinical efficacy in glycemic management and weight control without increasing the risk of hypoglycemia, clinical trials have observed an association with an rised incidence of gastrointestinal harmful events[30] .

5.2 Liraglutide

Liraglutide, a GLP-1 analogue with 97% amino acid homology to native glucagon-like peptide-1, is widely utilized in the management of T2DM, administered via a once-daily subcutaneous injection. The pharmacokinetic profile of this drug ensures 24-hour exposure coverage[31]. An animal study demonstrated that both exercise alone and Liraglutide independently improved muscle insulin sensitivity. However, the combination of both fully restored the rate of insulin-mediated glucose disposal[32]. Moreover, Liraglutide may ameliorate NAFLD associated with T2DM through activating the AMPK/ACC pathway and inhibiting hepatocyte apoptosis[33].

5.3 Semaglutide

Semaglutide, developed upon the extensive research foundation established for Liraglutide[34], exhibits a prolonged half-life compared to daily Liraglutide injections, enabling once-weekly administration[35]. While the injectable route may pose an

impediment to certain potential users, particularly when contrasted with daily or twice-daily subcutaneous injections, the identification of an absorption enhancer, N-[8-(2-hydroxybenzoyl)amino] caprylic acid sodium salt (SNAC), has been instrumental. SNAC facilitates protection of Semaglutide against degradation by gastric proteases and enhances its transmucosal absorption across the gastric epithelium through transient modulation of the transcellular pathway[36].In a pivotal clinical investigation led by Weghuber D et al. (NCT04102189)[37], adolescents (12-18 years old) with adiposity were received hypodermic injection with Semaglutide (2.4 mg/W) or placebo randomly. After 68 weeks, the adolescents treated with Semaglutide experienced a significant reduction in BMI (-16.1%) compared to a negligible change in the placebo cohort (+0.6%). Notably, the incidence of gastrointestinal adverse events was higher in the Semaglutide group (62%) relative to the placebo group (42%).

6 PPAR Agonists

PPAR, as a type of the nuclear receptor and a member of the superfamily of transcription factors, comprises PPARα, PPARβ/δ, and PPARγ, which have been particularly showcased a significant promise in the treatment of NAFLD. These PPAR subtypes, in concert with RXRs, recruit multi-protein coactivator complexes to specific genomic regulatory sites, synergistically activating gene transcription. The differential effects on PPRE gene expression elicited by agonists of distinct PPAR subtypes are partly attributed to variations in coactivator recruitment[38].PPARα modulates the expression of genes involved in lipoprotein lipase, FA catabolism, transportation, and oxidation (FABP1, FABP3, and ACS et al).This regulation leads to a substantial clearance of triglycerides and an elevation in plasma high-density lipoprotein levels. Conversely, PPARβ/δ and PPARγ are expressed in Kupffer cells, hepatic stellate cells and hepatocytes. PPARγ selectively promotes lipid absorption and lipid synthesis, leading to a reduction in circulating TG and FFAs, and contributing to IR. Activation of PPARβ/δ has been shown to conduct oxidation in skeletal muscle, thereby significantly enhancing muscle endurance to physiological exercise[39].

6.1 Saroglitazar

Saroglitazar, a PPARα/γ agonist with unique pharmacokinetic properties, exhibits minimal food effect upon oral administration, with a median time to plasma peak concentration of 0.63-1 hour and a terminal half-life averaging 5.6 hours, demonstrating favorable bioavailability[40]. It has been authorized by the U.S. Food and Drug Administration (FDA) for the cure of diabetic dyslipidemia and hypertriglyceridemia. Preclinical mouse studies have demonstrated that Saroglitazar can significantly enhance weight management, optimize blood biochemical parameters, and reduce dyslipidemic lipid accumulation[41].A Phase II clinical trial (NCT03061721) confirmed that Saroglitazar (4mg) can substantially decrease hepatic fat content (19.7%) and insulin resistance (6.3%), while improving lipoprotein particle composition and lipotoxic lipid species[42]. Recent results from a combination therapy with vitamin E have shown

positive outcomes, with co-administration further reducing the degree of liver stiffness (LSM) and CAP values, while improving biochemical markers and glycemic and lipid parameters, as compared to monotherapy . However, monotherapy with Saroglitazar may lead to weight gain, necessitating attention to its effects on weight management[43].

6.2 Lanifibranor

Lanifibranor, an oral pan-PPAR agonist, is capable of recruiting four distinct activators that act upon the PPARα/β/γ-LBD with varying potencies and efficacies (PGC-1α, CBP, SRC1, and TRAP220), enabling balanced activation of all three PPAR subtypes[44]. In rats treated with, hepatic sinusoidal endothelial cell (LSEC) and hepatic stellate cell (HSC) phenotypes are improved, hepatic microvascular function is restored, hepatic inflammation is reduced, and liver fibrosis is significantly ameliorated[45]. A clinical study by Francque SM et al. demonstrated that patients treated with 1200mg and 800mg doses of Lanifibranor showed decreased levels of liver enzymes and improved levels of most lipids, biomarkers of inflammation and fibrosis, with adverse event rates below 5%, primarily consisting of diarrhea, nausea, and peripheral edema[45] .Patients with NAFLD)often have poor cardiac metabolic health (CMH) and cardiovascular events are the leading cause of mortality. The histological effects of Lanifibranor on the liver are accompanied by improvements in CMH, suggesting potential clinical cardiovascular benefits[46]. Currently, a Phase III clinical trial (NCT03459079) is underway, evaluating the potency and safety of Lanifibranor in patients with type 2 diabetes and NAFLD, aiming to further assess its benefits in this patient population.

6.3 Elafibranor

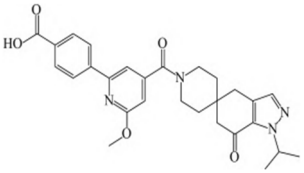
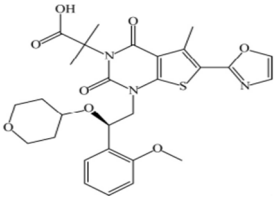
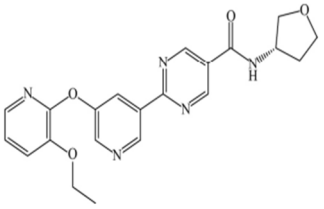
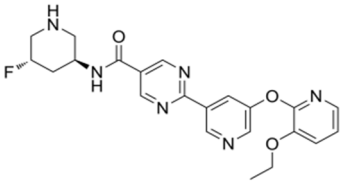
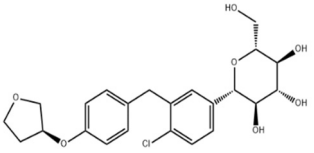
Elafibranor, a PPARα/δdouble agonist with EC50 values of 45 nM and 175 nM, has been the subject of considerable research for its potential in a treatment. In a large, 52-week study, the proportion of patients in the 120mg daily Elafibranor group with NASH remission and no fibrosis progression was higher than in the placebo group[47]. However, the outcomes of its Phase III clinical trials were less promising, with a higher than expected response rate in the placebo group and less pronounced improvements in NASH histological features and hepatic fibrosis. These findings underscore the ongoing challenges in late-stage clinical trials for Elafibranor and highlight the need for further investigation to ascertain its role in the therapeutic arsenal for NASH.

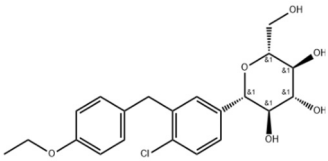
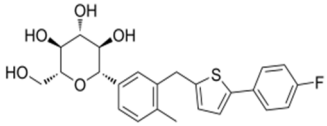
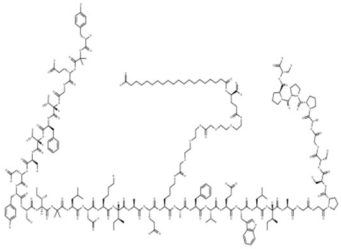
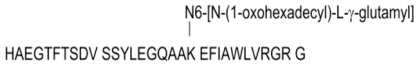
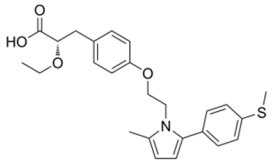
6.4 Pemafibrate

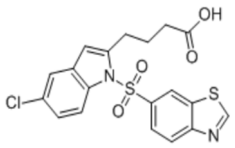
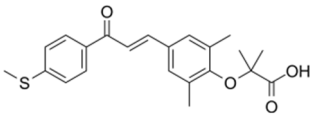
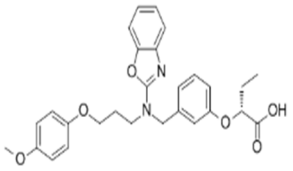
Pemafibrate, a PPARα agonist developed by Kowa Company , has been the subject of significant research regarding its impact on lipid profiles and liver health[48]. A large-scale meta-analysis in 2022 demonstrated that a three-month course of Pemafibrate therapy led to a reduction in the TG/HDL-C ratio. However, a lower TG/HDL-C ratio has also been associated with the incidence of cardiovascular disease[49].In a double-blind Phase II clinical trial, liver rigidity measured by magnetic resonance elastography

(MRE) was significantly reduced at 48 weeks (-5.7%, P=0.036) and maintained at 72 weeks (-6.2%, P=0.024) in the Pemafibrate group compared to placebo, followed by noticeable reductions in alanine aminotransferase and LDL-C levels. Simultaneously, the two groups indicate good tolerability of the treatment[50] .

Table 1. Drugs based on non-alcoholic fatty liver

Target for drugs	Name of drug	Chemical Structure	Clinical progression
ACC	PF-05221304		Phrase II clinical trial
	Firsocosta（GS-0976）		Phrase II clinical trial
DGAT2	Ervogastat (PF-06427878)		Phrase II clinical trial
	PF-07202954		Preclinical study
SGLT2	Empagliflozin		Phrase IV clinical trial

	Dapagliflozin		Phrase IV clinical trial
	Canagliflozin		Phrase IV clinical trial
GLP-1/GIP	Tirzepatide		Phrase IV clinical trial
GLP-1	Liraglutide		Phrase IV clinical trial
	Semaglutide	H-His-Aib-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys (AEEAc-AEEAc-γ-Glu-17-carboxyheptadecanoyl)-Glu-Phe-Ile-Ala-Trp-Leu-Val-Arg-Gly-Arg-Gly-OH	Phrase IV clinical trial
PPAR	Saroglitazar		Phrase II clinical trial

Lanifibranor		Phrase III clinical trial
Elafibranor		Phrase III clinical trial
Pemafibrate		Phrase II clinical trial

7 Conclusions

The escalating incidence of NAFLD has galvanized an accelerated pursuit of pharmacological interventions aimed at its management. At the vanguard of NAFLD treatment lies the emphasis on dietary modifications and lifestyle adjustments, foundational strategies that address the metabolic underpinnings of the disease.

Concomitantly, recognizing the intricate interplay between NAFLD pathogenesis and extrahepatic organ dysfunctions, particularly those associated with diabetic conditions, has steered research efforts towards molecular targets such as PPARs, SGLT2, and GLP-1 and GIP. This targeted approach facilitates a holistic treatment paradigm that not only tackles hepatic manifestations but also mitigates associated metabolic disorders.

However, the clinical application of these medications has unveiled adverse effects, prompting the exploration of synergistic therapies. For instance, the use of ACC inhibitors in conjunction with DAGT2 nhibitors has shown to significantly enhance therapeutic efficacy while mitigating adverse reactions. This synergy has positioned combination therapy as a focal point of current research endeavors.

As the pipeline of NAFLD therapeutics matures, several candidates are advancing into late-stage trials. Their potential approval by the U.S FDA hinges on stringent evaluations of safety, tolerability, and their efficacy in improving histological markers of steatohepatitis and fibrosis. The quest for efficacious and safe treatment regimens remains paramount, with the ultimate goal of arresting disease progression and preventing liver-related morbidities.

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