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Review Article: Targeting Peroxisome Proliferator-Activated Receptors in Primary Biliary Cholangitis

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ABSTRACT

Background: Primary biliary cholangitis (PBC) is a chronic, immune-mediated liver disease characterised by cholestasis, progressive fibrosis and symptoms of pruritus and fatigue. Ursodeoxycholic acid (UDCA) is first-line therapy; however, many patients respond inadequately or are intolerant. Peroxisome proliferator-activated receptor (PPAR) agonists have emerged as second-line options.

Aims: This review examines PPAR isoform (PPAR-α, PPAR-δ and PPAR-γ) mediated pathways relevant to PBC, and structural, biochemical and clinical efficacy and safety features of PPAR agonists for PBC.

Methods: Preclinical studies on therapeutic PPAR agonism and clinical literature on PPAR agonists in PBC were identified through targeted PubMed searches and manual reference screening.

Results: PPAR-α and PPAR-δ agonism improve cholestasis by reducing bile acid synthesis and inflammation. PPAR-α agonism also enhances bile acid detoxification and transport, while PPAR-δ agonism improves cholestatic pruritus by reducing pruritogenic signals. Individual PPAR isoforms are also associated with different safety profiles, with PPAR-α agonism linked to hepatic and muscle signals, and PPAR-γ agonism associated with fluid retention/weight gain. PPAR agonists differ in isoform selectivity. Although all agonists used in PBC reduce alkaline phosphatase levels, their impact on pruritus varies; PPAR-α predominant agonists (off-label fibrates, elafibranor) have a potential anti-pruritic effect, while selective PPAR-δ agonist, seladelpar, has demonstrated statistically significant improvements in pruritus. Fatigue is likely multifactorial, mediated through central nervous system effects and sleep disturbance; PPAR-α and PPAR-δ agents offer possible benefit.

Conclusions: Isoform selectivity contributes to the efficacy and safety profiles of PPAR agonists. Future research should investigate isoform-specific mechanisms, particularly regarding symptom relief and agent- and class-related toxicities.

Daria B. Crittenden and Grant Budas contributed equally as last authors.

1 | Introduction

Primary biliary cholangitis (PBC) is a chronic immune-mediated cholestatic liver disease, characterised by the destruction of small and medium intrahepatic bile ducts, resulting in cholestasis and bile duct inflammation [1–3]. PBC primarily affects middle-aged women [3], and if left untreated, may progress to hepatic fibrosis, cirrhosis and eventually end-stage liver disease [2]. Alkaline phosphatase (ALP) and bilirubin are well-established biochemical markers of PBC disease activity that are strong predictors of mortality risk and the need for liver transplantation [4].

Pruritus is one of the most common PBC symptoms, with a lifetime prevalence of around 70%, and a significant impact on health-related quality of life (HRQoL) [3, 5–7]. Fatigue is another frequent symptom that contributes to disease burden, and its pathophysiology remains poorly understood and understudied [6, 7].

Ursodeoxycholic acid (UDCA), a non-cytotoxic bile acid, is first-line treatment for PBC [3, 8]. UDCA is incorporated into the bile acid pool, replacing more toxic bile acids and reducing inflammation, cholestasis and apoptosis [8]. However, in some cohorts, up to 40% of patients have shown an inadequate response, typically defined as persistent disease activity reflected by elevated ALP, bilirubin and transaminases after 12 months of treatment, based on validated models such as the Globe Score and UK-PBC Risk Score [2, 3, 9, 10]. UDCA also does not improve extrahepatic symptoms including pruritus [3].

The bile acid analogue and farnesoid X receptor (FXR) agonist, obeticholic acid (OCA), was approved as second-line treatment for PBC in 2016 [11]. FXR activation reduces bile acid toxicity by suppressing bile acid synthesis and stimulating choleresis via transporter upregulation, while also exerting anti-inflammatory and anti-fibrotic effects [11]. In the initial OCA study in PBC, around half of patients achieved the primary endpoint of composite biochemical response (ALP $< 1.67 \times$ upper limit of normal [ULN] with $\geq 15\%$ reduction from baseline, and total bilirubin $\leq$ ULN at 12 months) [12]. Moreover, OCA has been shown to exacerbate pruritus [12], and there has been concern about the risk of hepatotoxicity in patients with more advanced disease and evidence of portal hypertension [11]. In 2024, the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) recommended revoking the conditional marketing authorisation of OCA after a phase 4, post-marketing approval trial (NCT02308111) failed to meet the primary endpoint, which was potentially related to its failure to recruit sufficient participants and retain participants once the drug was available in routine clinical practice. In September 2025, it was announced that OCA would be withdrawn in the USA following a request by the FDA [13].

Peroxisome proliferator-activated receptors (PPARs) are nuclear receptors that regulate the transcription of genes involved in inflammation, metabolism and tissue homeostasis [14, 15], thereby positioning them as therapeutic targets in several diseases. One PPAR agonist therapeutic class is the fibrates, approved for the treatment of dyslipidaemia since the 1960s, due to lipid-lowering effects [16]. Other classes of therapeutic PPAR agonists include the glitazones and glitazars. Glitazones have been used for the treatment of type 2 diabetes since the 1990s, owing to their insulin-sensitising effects [16]. Glitazars were developed with both anti-dyslipidaemic and anti-hyperglycaemic effects [16].

PPAR agonists have also proved to be effective in reducing ALP levels in patients with PBC [17–20]. The fibrates fenofibrate and bezafibrate have been used off-label as second-line treatments for PBC [1, 3], and in 2024, elafibranor was approved as a first-in-class second-line therapy [21]. Seladelpar, a first-in-class delpar, was also approved as second-line treatment for PBC in 2024 [22]. Beyond currently available agents, two PPAR agonists are in clinical development for PBC; saroglitazar (a glitazar) is in phase 3 development [23, 24], while pemafibrate (a fibrate) is in phase 2 development. The impact of PPAR agonists on pruritus in PBC, as well as their safety profiles, varies among agents.

This review examines PPAR isoform-mediated pathways relevant to PBC, describes the structural and biochemical distinctions (including selectivity) of PPAR agonists that are used or in development for PBC and discusses potential implications of these features on efficacy and safety in this indication.

2 | Mechanistic Insights Into Therapeutic PPAR Agonism From Pre-Clinical Models

Three PPAR isoforms (α, δ, γ) have been identified in mammals (Table 1) [25]. Each isoform forms a heterodimer with its retinoid X receptor, and binding of ligands to these complexes determines which genes they regulate [26]. Various fatty acids and fatty acid derivatives are endogenous agonist ligands for the PPARs [25]. The functions of the different isoforms can be inferred from their tissue-specific expression and the roles of their target genes.

2.1 | PPAR-α Isoform

In humans, PPAR-α is highly expressed in tissues with high fatty acid oxidation rates such as the liver, heart, kidney, brown adipose tissue and skeletal muscle [25]. This receptor is the predominant isoform in the liver, where it is highly expressed in hepatocytes and to a lesser extent in non-parenchymal cells (Figure 1). PPAR-α regulates bile acid metabolism and inflammation (Table 1), making it a therapeutic target for PBC [27]. PPAR-α also regulates lipid and lipoprotein metabolism in humans and is the primary target of fibrates used to treat dyslipidaemia [28].

2.1.1 | Regulation of Bile Acid Metabolism and Inflammation

Experiments in mice have shown that PPAR-α agonism reduces bile acid synthesis by attenuating transcription of the rate-limiting enzyme in the classic bile acid synthesis pathway (CYP7A1) and post-transcriptionally downregulating mRNA levels of the first enzyme in the acidic pathway of bile acid synthesis (CYP27A1) [29]. Human PPAR-α also downregulates expression of these enzymes [30–32].

TABLE 1 | Summary of hepatic and metabolic effects of activation of different PPAR isoforms.

	PPAR-α[a]	PPAR-δ[b]	PPAR-γ[c]
Anti-cholestatic activity	• Reduces bile acid synthesis • Stimulates bile acid detoxification and output	• Reduces bile acid synthesis by decreasing hepatocyte CYP7A1 expression	• Potential role in bile acid metabolism
Anti-inflammatory activity	• Inhibits inflammatory pathways	• Inhibits inflammatory pathways. • May promote the M2 phenotype in Kupffer cells • Reduces serum levels of the pruritogenic cytokine IL-31	• Inhibits inflammatory pathways • May promote the M2 phenotype in Kupffer cells
Effects on steatosis, fibrosis and liver injury	• Reduces steatosis, hepatic inflammation and fibrosis in rodent models of MASH	• Reduces steatosis, hepatic inflammation and fibrosis in rodent models of MASH	• Steatogenic role in hepatocytes • Reduces HSC activation and liver fibrosis
Metabolic activity	• Promotes fatty acid transport and oxidation and ketogenesis (fasting). • Modulates lipogenesis in response to nutritional conditions • Increases HDL levels in certain indications	• Reduces cholesterol absorption • Induces oxidation of fatty acids and attenuates fatty acid synthesis • May increase HDL levels	• Promotes lipogenesis • Drives adipogenesis. • Improves insulin sensitivity

Abbreviations: HDL, high-density lipoprotein; HSC, hepatic stellate cell; IL-31, interleukin-31; MASH, metabolic dysfunction-associated steatohepatitis; NR, not reported; PPAR, peroxisome proliferator-activated receptor.
[a][29–47, 146].
[b][18, 48, 49, 65–69, 73, 77, 79, 81–84, 134].
[c][25, 86–91, 147].

Studies in cultured human cells also indicate that PPAR-α decreases total bile acid toxicity by upregulating the genes encoding CYP3A4 (hydroxylates bile acids, decreasing their toxicity) [31, 32], SULT2A1 (facilitates elimination of the toxic secondary bile acid, lithocolic acid) [33] and UGT2B4 (catalyses glucuronidation of bilirubin and bile acids) [34], and downregulating the gene for basolateral transporter NTCP (responsible for bile acid uptake from plasma) [31]. Activation of mouse and human PPAR-α also increases bile acid transport by downregulating and upregulating expression of the bile acid transporters BSEP and MRP2, respectively [31, 35], and enhances the formation of phospholipid- and cholesterol-rich micelles that dilute and buffer against bile acid toxicity by inducing genes for hepatic cholesterol transporter ABCG5/G8 and lipid translocator MDR3 [31, 36, 37].

PPAR-α also has anti-inflammatory effects, with studies in mice and human cells identifying multiple mechanisms through which PPAR-α negatively modulates NF-kB and AP-1 pathways, thereby inhibiting the expression and duration of action of pro-inflammatory cytokines and chemokines [38–40]. The anti-inflammatory effects of hepatic PPAR-α may also stem from its ability to upregulate anti-inflammatory genes such as IL-1 receptor antagonist and IkB (NF-kB inhibitor), as shown in mice and human cell lines, suggesting that PPAR-α may act via both transactivation and transrepression mechanisms to induce anti-inflammatory pathways [41, 42].

2.1.2 | Regulation of Lipid Metabolism

The role of PPAR-α as a regulator of hepatic lipid metabolism is well conserved between mice and humans, although the genes it controls differ somewhat within each lipid metabolic pathway [43]. PPAR-α promotes fatty acid transport and oxidation (upregulates ACSL1, CPT1A, CPT2 and FABP1 in mice and humans) and ketogenesis (upregulates HMGCS2 in mice and humans) during fasting, as well as modulating lipogenesis in response to nutritional conditions as an activator of the SREBP1c promoter [43–45]. PPAR-α activation was also shown to regulate expression of apolipoproteins A in primary human hepatocytes [43], which likely accounts for the increased high-density lipoprotein (HDL) levels seen with fibrates [46]. It is of note, however, that no clear increases in HDL levels have been observed with therapeutic agonism of PPAR-α in PBC.

2.1.3 | Roles in Other Liver-Related Disease Processes

In rodent models of metabolic dysfunction-associated steatohepatitis (MASH), activation of PPAR-α has been shown to reduce steatosis, hepatic inflammation and fibrosis by stimulating lipid turnover and upregulating UCP3 expression in the liver [47].

Elafibranor, a PPAR-α and PPAR-δ agonist that has also been shown to activate PPAR-γ in in vitro studies, has demonstrated

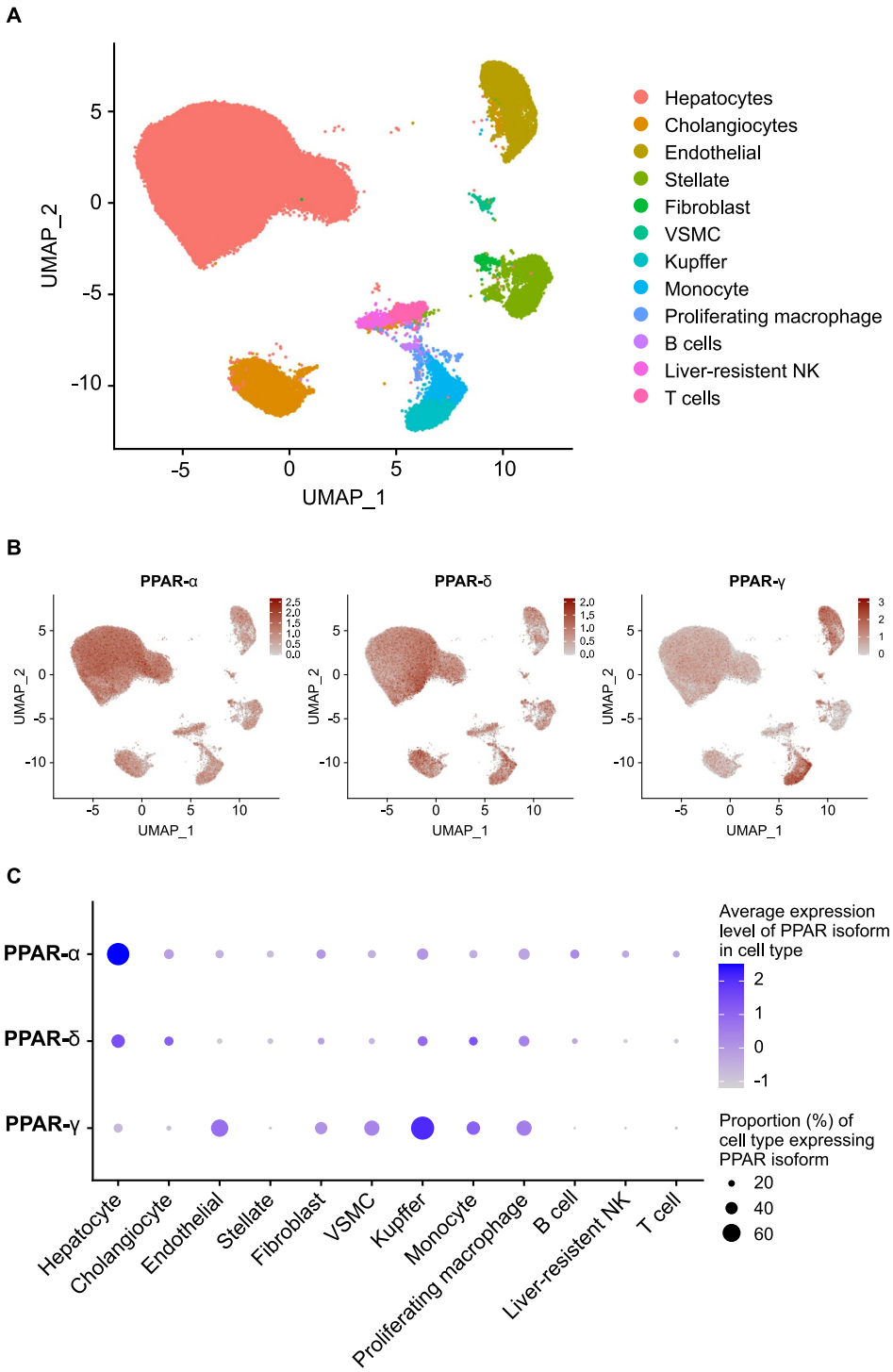

FIGURE 1 | PPAR isoform expression in human liver. We utilised nuclear-RNA sequencing data from Andrews et al. 2024 [148] to assess PPAR isoform distribution in human liver. (A) Single-cell atlas of human liver. (B) Expression of individual PPAR isoforms across hepatic cell lineages. (C) Dot plot demonstrating PPAR isoform expression per cell type. PPAR isoforms are expressed ubiquitously; however, the level of expression is cell-type dependent. PPAR-α is highly expressed in hepatocytes with lower expression observed in other cell types. PPAR-δ is also most highly expressed in hepatocytes, although at reduced levels compared to PPAR-α. In contrast, PPAR-γ is expressed at low levels in parenchymal cells, with the highest expression in hepatic immune cells (i.e., Kupffer cells and monocytes), endothelial cells and vascular smooth muscle cells. NK, natural killer; PPAR, peroxisome proliferator-activated receptor; UMAP, uniform manifold approximation and projection; VSMC, vascular smooth muscle cells.

potent activity in preclinical models of metabolic dysfunction-associated steatotic liver disease (MASLD) to reduce hepatic lipid accumulation and decrease expression of pro-inflammatory and profibrotic genes [48]. In a phase 2 study, elafibranor was also shown to resolve MASH without fibrosis worsening [49]; however, in a subsequent phase 3 study (RESOLVE-IT), elafibranor failed to meet the primary endpoint of MASH resolution without worsening of fibrosis versus placebo [50].

2.1.4 | Safety

Therapeutic agonism of PPAR-α has been associated with increases in cholesterol excretion into the bile, possibly due to upregulation of biliary cholesterol transporters, leading to risk of cholelithiasis [51–54]. Liver effects include mild and transient serum aminotransferase elevations [55] and instances of acute liver injury at approved doses [17, 19, 20]. Myopathy and rhabdomyolysis have also been observed with marketed PPAR-α and mixed PPAR agonists used as monotherapies or in combination with statin regimens [19, 51, 56–58]. Experiments with mice have revealed a mechanism by which liver and muscle effects may occur, with activation of PPAR-α inducing significant peroxisome proliferation in skeletal muscle and liver, and concomitant increases in liver weights and clinical chemistry indicators of skeletal muscle damage, myopathy and/or liver injury [59]. It is thought that the prolonged elevation of peroxisomal fatty acid oxidation could lead to oxidative stress-induced toxicity [59]. PPAR-α and PPAR-α/δ agonists have also been associated with elevations in serum creatinine levels [17, 51, 60]. These elevations may not reflect a decline in renal function, but rather an increase in the metabolic production rate of creatinine, independent of muscle cell lysis, or a decrease in creatinine clearance without a change in glomerular filtration rate [61–63].

2.2 | PPAR-δ Isoform

In humans, PPAR-δ is ubiquitously expressed in the body [64]. In the liver, PPAR-δ is most highly expressed in hepatocytes, followed by cholangiocytes and immune cell subsets such as Kupffer cells and monocytes (Figure 1). PPAR-δ regulates bile acid metabolism and inflammation (Table 1) and is the therapeutic target of seladelpar used to treat PBC [64]. PPAR-δ has other important roles, including regulating lipid metabolism [25].

2.2.1 | Regulation of Bile Acid Metabolism, Inflammation and Pruritus

Experiments in mice have revealed that PPAR-δ activation reduces bile acid synthesis in hepatocytes via FGF21-dependent inhibition of CYP7A1 [65]. Reduced CYP7A1 expression by PPAR-δ agonism was confirmed in primary human hepatocytes [65]. In mouse liver, PPAR-δ agonism has also been shown to induce expression of the hepatic cholesterol transporter ABCG5/ABCG8 and increase bile flow and bile salt secretion rate [66, 67]; however, associated effects have not been reported in humans.

PPAR-δ exerts anti-inflammatory effects via downregulation of inflammatory mediators, such as TNF-α, IL-1 and IL-6, as demonstrated in mice, cultured mice macrophages, and human cholangiocytes [68, 69]. Knock-out studies in mice suggest that PPAR-δ also plays a role in promoting the anti-inflammatory M2 phenotype in Kupffer cells [70].

PPAR-δ agonism is also associated with anti-pruritic effects [18], including a reduction of bile acids, which are thought to contribute to cholestatic itch through G-protein coupled receptor signalling and activation of sensory neurons [71, 72]. In addition, PPAR-δ agonism in PBC reduces serum levels of IL-31 [18, 73, 74]. IL-31 promotes pruritus via stimulation of the IL-31RA/OSMRβ receptor, which subsequently results in activation of TRPV1 and TRPA1 ion channels and BNP signalling in sensory neurons [75]. In skin diseases (e.g., atopic dermatitis), elevated levels of IL-31 are driven by type 2 cytokines from T-helper 2 cells [75]. However, seladelpar does not affect serum levels of type 2 cytokines [73], and in cholestatic itch, IL-31 is thought to originate from the liver [76], suggesting a potentially distinct, liver-derived mechanism of IL-31-mediated pruritus in the setting of PBC. The bile acid analogue OCA also reduces bile acids, but via FXR agonism. OCA has been observed to induce expression and secretion of the pruritic inflammatory mediator IL-31 from human hepatocytes in a humanised liver murine model [76] and leads to increases in pruritus in patients with PBC [11].

2.2.2 | Roles in Other Liver-Related Disease Processes

PPAR-δ activation may be beneficial for both liver injury and fibrosis, as evidenced by reductions in plasma levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) and markers of liver injury, and reductions in steatosis and fibrosis in mouse models of MASH evaluating the effects of seladelpar [77]. As noted above, elafibranor has been suggested to resolve MASH in a phase 2 clinical study, with anti-inflammatory and anti-fibrotic effects observed in non-clinical studies. In PPAR-α knock-out mice, elafibranor also prevented Western diet-induced steatosis and inflammation and had a more pronounced protective effect on the expression of profibrotic genes, suggesting that the anti-fibrotic effect may be mediated through PPAR-δ activation [48]. In a phase 2 study of seladelpar in patients with MASH, the primary endpoint of change in hepatic fat fraction at week 12, assessed by imaging, was not met. Histology data were limited due to early termination of the study but the available findings suggest fibrosis improvement in both the seladelpar and placebo groups after 1 year [78].

2.2.3 | Regulation of Lipid Metabolism

Activation of PPAR-δ decreases cholesterol absorption by inhibiting intestinal expression of NPC1L1 [79, 80], and may also decrease cholesterol synthesis, as shown by decreased serum levels of the cholesterol synthesis precursor, lathosterol, in seladelpar-treated patients [66]. A reduced availability of cholesterol for bile acid synthesis enhances the effect of seladelpar on CYP7A1 in reducing total bile acid pools. PPAR-δ activation may also influence HDL cholesterol levels, with human PPAR-δ shown to increase expression of APOAII and phospholipid transfer protein in Huh7 cells and mouse PPAR-δ shown to raise plasma preβ-HDL formation, likely by increasing expression of phospholipid transfer protein in the liver [81, 82]. In addition, studies in mice with diet-induced hypertriglyceridemia and hepatic steatosis indicate another role for PPAR-δ in lipid metabolism, with its activation reducing triglyceride accumulation by inducing fatty acid oxidation and attenuating fatty acid synthesis [83, 84].

2.2.4 | Safety

Signals of muscle injury were observed with the PPAR-δ agonist GW0742 in a non-clinical study in mice [59]; however, the effect was attributed to PPAR-α-mediated mechanisms at exposures significantly exceeding clinically relevant levels. Notably, seladelpar demonstrates a significant species-specific difference in selectivity for PPAR-δ over PPAR-α, with its selectivity in humans nearly 50 times greater than in rats [80].

Elevated liver enzymes were observed with seladelpar in animal studies at exposures exceeding clinically relevant levels [80]. At 5–20 times the clinical dose of seladelpar (10 mg), increases in liver transaminases, muscle pain and/or elevations in creatine phosphokinase levels were observed in patients with PBC [22]. These effects resolved upon discontinuation and have not been observed at the clinical dose [22].

2.3 | PPAR-γ Isoform

In humans, PPAR-γ is mainly expressed in adipose tissue, the colon, immune cells, retina and kidney [25, 85]. PPAR-γ is expressed at low levels in parenchymal cells, with expression highest in Kupffer cells, monocytes, endothelial cells and vascular smooth muscle cells (Figure 1). PPAR-γ regulates adipogenesis, lipogenesis and insulin sensitivity (Table 1) and is the target for glitazones used to treat type 2 diabetes [25]. This receptor also regulates inflammation and may play a role in bile acid metabolism and is activated by some agents used or in development for PBC [86–89].

2.3.1 | Regulation of Insulin Sensitivity

Activation of PPAR-γ enhances whole body insulin sensitivity by several known mechanisms, including enhancing white adipose tissue expandability, which in turn redistributes lipids from the liver and skeletal muscle to white adipose tissue, and inducing adiponectin production in white adipose tissue [90].

2.3.2 | Regulation of Bile Acid Metabolism and Inflammation

There is some evidence that PPAR-γ may influence bile acid metabolism, as its activation in mice has been shown to increase the expression of proteins involved in this process (FXR, BSEP and ABCG5), reversing α-naphthylisothiocyanate-induced elevation of liver biochemical markers and reducing liver injury [88]. PPAR-γ agonism in mice was also shown to prevent cholesterol stone formation by upregulating genes involved in bile acid synthesis and enterohepatic circulation (ABCG5, ASBT, BSEP, CYP7A1, CYP27A1, NTCP and OSTα/β) [87, 88]. However, effects on cholestasis in humans have not been established.

Like PPAR-α and PPAR-δ, PPAR-γ also has anti-inflammatory activity, with experiments in cultured cholangiocytes, including a PBC liver-derived cell line, demonstrating that agonism of human PPAR-γ reduces LPS-induced NF-kB activation and TNF-α production [86]. Studies in mice have also shown that PPAR-γ may promote the anti-inflammatory M2 phenotype of macrophages (including Kupffer cells), while inhibiting activation of the M1 phenotype [89].

2.3.3 | Roles in Other Liver-Related Disease Processes

Activation of PPAR-γ has been shown to exert both beneficial and detrimental effects, depending on the cellular context. Studies in mice have shown that PPAR-γ activation is steatogenic, mediating the expression of adipogenic genes (e.g., Ap2 and CD36), inducing increased fatty acid uptake and stimulating the induction of lipogenic enzymes such as fatty acid synthase and acetyl-CoA carboxylase 1, promoting intracellular triglyceride accumulation [89]. Conversely, in human hepatic stellate cells (HSCs), PPAR-γ activation appears to have anti-fibrotic effects, suppressing HSC activation and thereby reducing liver fibrosis. This may occur via PPAR-γ-mediated suppression of transcription factor EB and a subsequent decrease in autophagy [91]. The relevance and implications of these effects in humans have not been directly investigated.

2.3.4 | Safety

Therapeutic agonism of PPAR-γ with glitazones has been shown to cause fluid retention, resulting in weight gain [92, 93], with studies in mice revealing potential mechanisms by which this could occur. PPAR-γ was shown to increase amiloride-sensitive sodium absorption and upregulate the expression of *Scnn1g*, encoding the γ-subunit of the epithelial sodium channel (ENaC) [94]. However, in another study, conditional inactivation of *Scnn1a* (encoding ENaCα) did not prevent weight gain or fluid retention in mice caused by PPAR-γ-agonism, with increased expression of a 23-pS non-selective cation channel identified as an alternative mechanism [95, 96].

The glitazones rosiglitazone and pioglitazone also appear to be associated with an increased risk of bone fractures in female patients [92, 93, 97]. This effect may be mediated by a PPAR-γ-induced increase in adiposity in bone marrow, which reduces osteoblast and aromatase activity, decreasing oestrogen production and promoting bone resorption [97].

Rosiglitazone and pioglitazone have also been associated with rare instances of acute liver injury [98, 99], while troglitazone was withdrawn from the market due to the frequency of severe liver injury [100]. The mechanisms of liver injury with glitazones remain unknown [98, 99].

Development of the glitazars (dual PPAR-α/γ agonists) tesaglitazar and muraglitazar was discontinued after phase 3 trials showed an increased risk of cardiac dysfunction [101]. This may relate to dual PPAR-α/γ activation inhibiting the SIRT1-PGC1α axis, thereby impairing cardiac mitochondrial biology and energy homeostasis [101].

3 | Structure and Function of PPAR Agonists Relevant in PBC

PPAR agonists are a structurally diverse group of hydrophobic compounds that activate PPARs with varying isoform selectivity

(Table 2) [14]. Fibrates, also known as 'clofibrate derivates', are a distinct medicinal class of PPAR agonists, characterised by PPAR-α agonism and the presence of a fibric acid moiety in their chemical structure (Figure 2A) [102]. In addition to their lipid-lowering effects, fibrates and other fibric acid-based molecules have demonstrated efficacy in reducing ALP levels in PBC and may also improve pruritus [17, 19, 20, 103, 104]. The fibrates fenofibrate (Figure 2B) and bezafibrate (Figure 2C) are used off-label as second-line agents to treat PBC [1]. Elafibranor, recently approved for second-line PBC treatment [21], is a fibric acid-based molecule (Figure 2D) [105]. Pemafibrate, another fibrate (Figure 2E) with established lipid-lowering effects, is in phase 2 clinical development for PBC. Delpars represent a new medicinal class of selective PPAR-δ agonists. Seladelpar, the first approved agent in this class (Figure 2F), was recently approved as second-line therapy for PBC [22]. Glitazars, defined by dual PPAR-α/γ agonism, represent another distinct medicinal class of PPAR agonists. Saroglitazar (Figure 2G) exhibits lipid-lowering and insulin-sensitising properties and is in phase 3 clinical development for PBC.

3.1 | Fenofibrate

Fenofibrate and its pharmacologically active metabolite, fenofibric acid [106], are approved as lipid-lowering agents [51, 54]. Fenofibrate and fenofibric acid are contraindicated for use in active liver disease in the US [51, 54] and contraindicated in patients with PBC based on drug labels in several European countries [107–109]. However, they are used off-label as second-line PBC treatment in some geographies.

In vitro biochemical assays show that while fenofibric acid predominantly targets PPAR-α (EC_{50}: 9.47 μM), it also activates PPAR-γ (EC_{50}: 61.0 μM), albeit with a 6-fold lower potency [110]. Fenofibric acid shows negligible activation of PPAR-δ (> 500 μM) (Table 2) [110]. These findings are supported by coactivator recruitment assays, which show that fenofibric acid recruits coactivator peptides to both PPAR-α (EC_{50}: 3.41–11.1 μM) and PPAR-γ (EC_{50}: 121–238 μM), while recruitment to PPAR-δ is insignificant [111]. These biochemical profiles suggest the efficacy and safety of fenofibrate and fenofibric acid primarily stem from PPAR-α activation, with some effects likely related to PPAR-γ activation. Consistent with this, fenofibrate has been shown to significantly increase serum levels of high molecular weight adiponectin, a marker for PPAR-γ activation, in humans [112].

3.1.1 | Fenofibrate Efficacy and Safety in PBC

The efficacy of fenofibrate with regard to reducing ALP levels has been reported (Table 2) in three randomised trials (participant numbers ranging from 10 to 117) [20, 55, 113], two single-arm trials [114, 115] and two observational studies [116, 117]. In a randomised trial of patients with an incomplete response to UDCA (defined as ALP, γ-glutamyltransferase, or total bilirubin > ULN; $n = 48$), 54.2% of those receiving fenofibrate + UDCA achieved normal ALP levels at 12 months versus 4.2% with UDCA alone ($p < 0.001$) [20]. Notably, ALP levels required for study entry were lower than typically required for other PBC studies [20]. Improvements in ALT or AST levels (markers of liver injury) are not established for fenofibrate, nor are improvements in lipid profiles in patients with PBC [20, 55, 113, 114]. Although no randomised controlled trials have assessed the effect of fenofibrate on pruritus in PBC using validated measures, data from a 2021 systematic review and meta-analysis suggest a potential anti-pruritic effect [104].

In terms of safety, fenofibrate treatment has been associated with elevations in serum transaminase levels, reversible increases in serum creatinine levels, muscle injury including rhabdomyolysis (particularly in patients receiving concomitant statins) and fluid retention in PBC trials and real-world studies (Table 2) [51, 55, 116, 118]. Notably, the occurrence of fluid retention, a well-recognised side effect of PPAR-γ agonism, supports the notion that fenofibrate exhibits some PPAR-γ activity. A cohort study indicated that up to 22% of patients discontinued fenofibrate treatment, largely due to adverse effects, most of which were abdominal pain, myalgia and bilirubin doubling (2/46 patients each) [116].

3.2 | Bezafibrate

Bezafibrate is not approved or available in the USA. It is, however, approved in other regions of the world as a lipid-lowering agent, including in Europe, where it is indicated for the treatment of severe hypertriglyceridemia and mixed hyperlipidaemia when a statin is contraindicated or not tolerated [56, 119]. Like fenofibrate, bezafibrate is contraindicated in patients with any hepatic disease other than MASLD [119]. In regions where it is available, bezafibrate is also used off-label as a second-line treatment for PBC.

Bezafibrate is a pan-PPAR agonist. In vitro biochemical data indicate that its potency is greatest for PPAR-α (EC_{50}: 30.4 μM), with approximately 3-fold lower potency for PPAR-δ (EC_{50}: 86.7 μM) and 6-fold lower potency for PPAR-γ (EC_{50}: 178 μM) (Table 2) [110]. However, target activity can vary depending on assay conditions. This is illustrated by results from a different study showing EC_{50} values of 50 μM for PPAR-α, 20 μM for PPAR-δ and 60 μM for PPAR-γ [120]. Bezafibrate was also shown to recruit coactivator peptides to all three receptors: PPAR-α (EC_{50}: 4.16–14.8 μM), PPAR-δ (EC_{50}: 24.5–101 μM) and PPAR-γ (EC_{50}: 24.5–108 μM) [111]. In vitro data suggest that bezafibrate may also induce genes targeted by the pregnane X receptor (PXR), including those involved in bile acid detoxification, such as CYP3A4 [31]. Thus, based on the above biochemical and mechanistic data, bezafibrate may function as a dual PPAR/PXR agonist [121], with effects from PPAR agonism potentially related to all three isoforms.

3.2.1 | Bezafibrate Efficacy and Safety in PBC

Bezafibrate has shown efficacy for improving ALP levels and maintaining normal ALP levels in controlled clinical trials [17, 122, 123], with effectiveness supported by long-term real-world studies [124–126]. The phase 3 BEZURSO trial demonstrated that 24 months of bezafibrate treatment significantly

TABLE 2 | Biochemical properties, and clinical efficacy and safety data (based on key placebo-controlled trials), of PPAR agonists that are approved, used off-label, or in late phase development for PBC.

	Fenofibrate	Bezafibrate	Elafibranor	Seladelpar	Saroglitazar	Pemafibrate
Medicinal class	Fibrates and other fibric acid-based molecules	Fibrates and other fibric acid-based molecules	Fibrates and other fibric acid-based molecules	Delpar	Glitazar	Fibrates and other fibric acid-based molecules
PPAR isoform(s) contributing to PBC clinical pharmacological effects	PPAR-α/γ	PPAR-α/δ/γ	PPAR-α/δ (and possibly PPAR-γ)	PPAR-δ	PPAR-α/γ	PPAR-α
Predominant target isoform based on EC_{50} values in in vitro studies[110, 127, 128]	PPAR-α	PPAR-α	PPAR-α	PPAR-δ	PPAR-α	PPAR-α
Fold-reduction in potency for other isoforms based on EC_{50} values in in vitro studies[110, 127, 128]						
PPAR-α	Reference	Reference	Reference	81	Reference	Reference
PPAR-δ	> 53	3	4 (5)[b]	Reference	> 53	993
PPAR-γ	6	6	3 (8)[b]	175	2	> 3571
Key RCT[a]	**ChiCTR1800020160, phase NR** [20]	**BEZURSO, phase 3** [17]	**ELATIVE, phase 3** [19]	**RESPONSE, phase 3** [18]	**EPICS, phase 2** [23]	**NCT06247735, phase 2**
Country	China (single centre)	France (multicentre)	Global (multicentre)	Global (multicentre)	USA (multicentre)	Global (multicentre)
Design (*n*)	Open-label RCT (48)	Blinded RCT (100)	Blinded RCT (161)	Blinded RCT (193)	Blinded RCT (37)	Blinded RCT
Treatment	Fenofibrate 200 mg	Bezafibrate 400 mg[c]	Elafibranor 80 mg[d]	Seladelpar 10 mg[d]	Saroglitazar 4 mg or 2 mg[c]	Pemafibrate dose A or B[d]

(Continues)

TABLE 2 | (Continued)

	Fenofibrate	Bezafibrate	Elafibranor	Seladelpar	Saroglitazar	Pemafibrate
Comparator	None (UDCA alone)	Placebo[c]	Placebo[d]		Placebo[c]	Placebo[d]
Key inclusion criteria	≥6 months of UDCA treatment ALP, GGT or total bilirubin > ULN	≥6 months of UDCA treatment ALP or AST >1.5×ULN, or total bilirubin > ULN	≥12 months of UDCA treatment (or UDCA intolerance with no treatment for >3 months) ALP ≥1.67×ULN and total bilirubin ≤2×ULN			Inadequate response to UDCA/OCA treatment ALP>ULN for ≥6 months ALP ≥1.5×ULN
Biochemical efficacy with ALP reduction: study drug vs. comparator (yes/no)[e]	Yes (see text)	Yes (see text)	Yes ALP change from BL to month 12: −117.0 vs. −5.3 U/L	Yes ALP change from BL to month 12: −133.9 vs. −16.9 U/L	Yes (see text)	—
Other effects: study drug vs. comparator (yes/no/trend)[f]						
Total bilirubin ↓	Yes	Trend	No	No	No	—
Bile acids ↓	NR	Yes: % toxic bile acids within bile acid pool	NR	Trend	Trend	—
C4 ↓	NR	Trend	Trend	Trend	Trend	—
Transaminases ↓	No	Trend: ALT, AST; ALT change from BL to month 24: −36% vs. 0% (treatment difference [95% CI]: −35 [−56 to −14] %)	No; ALT change from BL to month 12: −9.3 U/L vs. −5.4 U/L (treatment difference [95% CI]: −3.8 [−11.0 to 3.4] U/L)	Yes: ALT No: AST; ALT change from BL to month 12: −23.5% vs. −6.5% (treatment difference [95% CI]: −17.0 [−28.1 to −5.9] %)	Trend: ALT, AST; ALT change from BL to week 16: −11.1 (4 mg) and −10.8 (2 mg) U/L vs. 1.7 U/L (treatment difference [95% CI] at 4 mg and 2 mg: −12.8 [−29.2 to 3.6] and −12.5 [−28.5 to 3.5] U/L)	—

(Continues)

TABLE 2 | (Continued)

	Fenofibrate	Bezafibrate	Elafibranor	Seladelpar	Saroglitazar	Pemafibrate
Lipids improved (TG, TC, LDL and VLDL ↓; HDL ↑)	No	Trend: TC, LDL No: HDL	Yes: TG, TC, LDL, VLDL No: HDL	Yes: TG, TC, LDL Trend: HDL	Yes: TG, VLDL No: TC, HDL, LDL	—
Confirmed pruritus ↓	NR Note: Systematic review and meta-analysis suggested possible anti-pruritic effect (less effective than bezafibrate) [104]	No: Significant improvement in VAS not observed Note: • Trend towards improvement by VAS in BEZURSO. • FITCH study showed significant effect over 21 days [103].	No: Significant improvement in NRS not observed Note: PBC-40 itch domain and 5D itch score at month 12 suggest possible benefit	Yes: Significant improvement in NRS observed Note: PBC-40 itch domain and 5D itch score showed benefit consistent with NRS	No: significant improvement in PBC-40 itch domain not observed	—
Safety findings (more AEs with treatment than with placebo)						
Liver AEs	Yes: 2 cases receiving fenofibrate required dose reduction or discontinuation owing to transaminase elevations	Yes: 3 serious events of transaminase elevations with bezafibrate, resulting in 2 drug discontinuations	Not observed in phase 3 study (risk observed at 1.5-times the recommended dose of elafibranor [21])	Not observed in phase 3 study (risk observed at 5- and 20-times the recommended dose of seladelpar [22])	Yes: 4 cases of drug discontinuation in the saroglitazar arm owing to transaminase elevations	—
Muscle AEs	Not observed in randomised study (risk observed in other studies [51])	Yes: myalgia and serious CK elevation; 1 case of rhabdomyolysis in patient who received bezafibrate and a concomitant statin	Some increases in CK and myalgia/muscle pain; 1 case of rhabdomyolysis in patient with advanced cirrhosis who received elafibranor and concomitant atorvastatin [21]	Not observed in phase 3 study (risk observed at 5- and 20-times the recommended dose of seladelpar [22])	—	—

(Continues)

TABLE 2 | (Continued)

	Fenofibrate	Bezafibrate	Elafibranor	Seladelpar	Saroglitazar	Pemafibrate
Notable renal AEs	Yes: 1 event of dose reduction of fenofibrate owing to elevated creatinine (risk also shown in other studies [55, 116])	Yes: 1 event of stage 3 CKD with bezafibrate; overall mild increases in creatinine	Not observed in phase 3 study	Not observed in phase 3 study	—	—
Weight gain/fluid retention	Not observed in randomised trial (potential risk shown in other studies [116])	Not observed in phase 3 study	Events were more frequent in the treatment than placebo arm (23% vs. 21%) but a causal relationship has not been established [21]; most common AE in the ELATIVE OLE [131]	Not observed in phase 3 study	Limited data; SAEs with saroglitazar reported in 2 patients included peripheral oedema	—
Fractures	Not observed in randomised study	Not observed in phase 3 study	Events were more frequent in the treatment than placebo arm (6% vs. 0%) but a causal relationship has not been established [21]	Events were more frequent in the treatment than placebo arm (4% vs. 0%) but a causal relationship has not been established [22]	Not observed in phase 2 study	—
Regulatory status in PBC	**Not approved (used off-label)** Note: contraindicated in active liver disease and severe renal impairment in the US	**Not approved (used off-label)** Note: not available in the US, and in regions where it is available, it is contraindicated in liver disease other than MASLD	**Approved** [21]	**Approved** [22]	**In phase 3 clinical development**	**In phase 2 clinical development**
Indication (label)	N/A	N/A	Treatment of PBC in combination with UDCA in adults who have an inadequate response to UDCA, or as monotherapy in patients unable to tolerate UDCA		N/A	N/A

Note: Dash indicates no data are available.

Abbreviations: AE, adverse event; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BL, baseline; C4, 7α-hydroxy-4-cholesten-3-one; CK, creatine kinase; CKD, chronic kidney disease; EC_{50}, half maximal effective concentration; GGT, γ-glutamyltransferase; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MASLD, metabolic dysfunction-associated steatotic liver disease; N/A, not applicable; NR, not reported; NRS, numerical rating scale; OCA, obeticholic acid; OLE, open-label extension; PBC, primary biliary cholangitis; PBC-40, primary biliary cholangitis-40; PPAR, peroxisome proliferator-activated receptor; RCT, randomised clinical trial; SAE, serious adverse event; TC, total cholesterol; TG, triglycerides; UDCA, ursodeoxycholic acid; ULN, upper limit of the normal range; VAS, visual analogue scale; VLDL, very low-density lipoprotein.

[a]The most advanced RCT in patients with PBC and inadequate response or intolerance to UDCA was selected for each drug for the most relevant comparison.

[b]Data shown in brackets pertain to the active metabolite, GFT1007.

[c]Active drug and placebo were administered with standard-of-care UDCA.

[d]Active drug and placebo were administered with standard-of-care UDCA unless patients had a history of unacceptable side effects.

[e]'Yes' indicates a statistically significant difference. 'No' indicates no statistically significant difference.

[f,c]'Yes' indicates a statistically significant difference (non-overlapping confidence intervals were considered to indicate a significant difference). 'No' indicates no statistically significant difference or trend difference. 'Trend' indicates an observed difference that was either not statistically significant or was not tested for statistical significance.

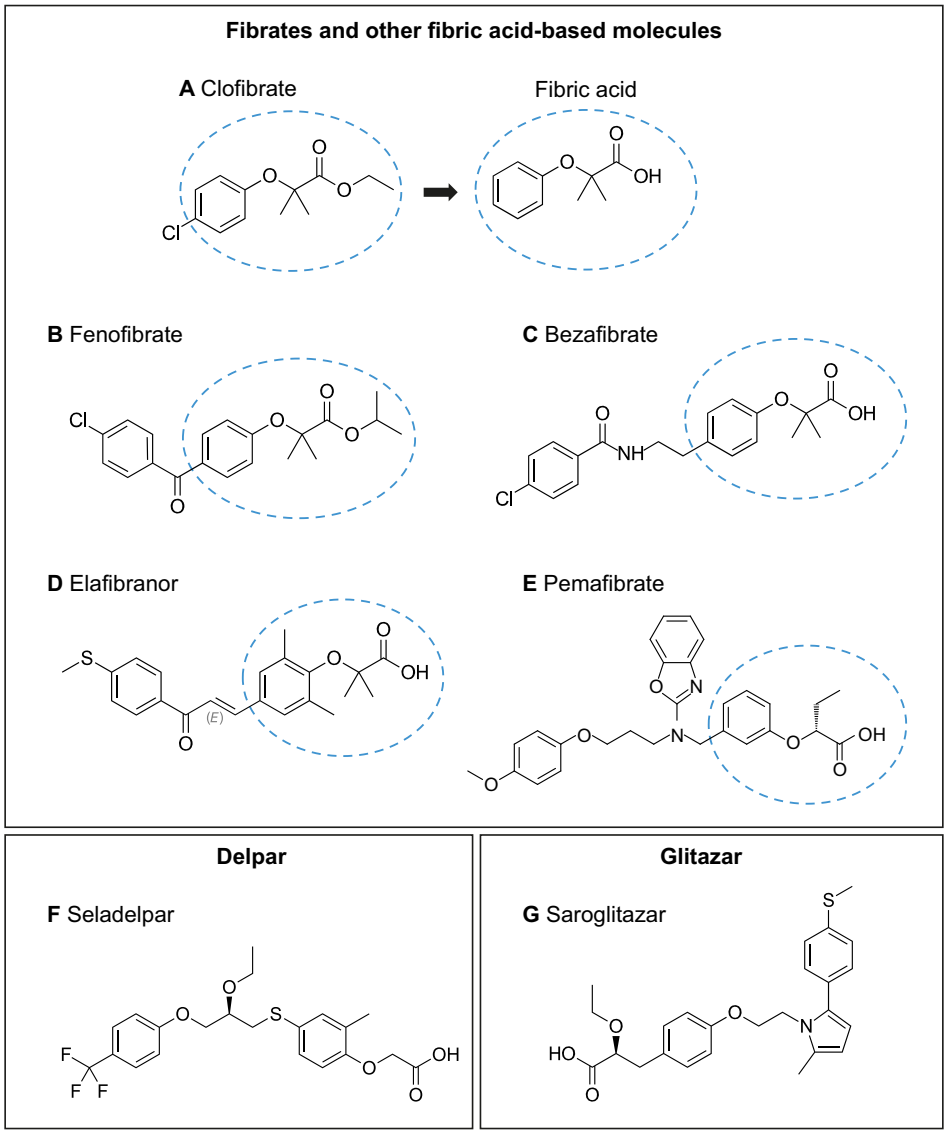

FIGURE 2 | Chemical structures of PPAR agonists that are approved, used off-label, or in late phase development for PBC [14, 105, 110]. (A) Clofibrate and the fibric acid element. (B) Fenofibrate. (C) Bezafibrate. (D) Elafibranor. (E) Pemafibrate. (F) Seladelpar. (G) Saroglitazar. The blue ovals in A–E show the fibric acid element. PBC, primary biliary cholangitis; PPAR, peroxisome proliferator-activated receptor.

improved rates of biochemical response based on the primary endpoint (normalisation of ALP, aminotransferase, albumin and total bilirubin levels, as well as normalisation of prothrombin index [the patient's prothrombin time expressed as a percentage of the normal value]) compared with placebo in patients who had a previous inadequate response to UDCA (defined as ALP $>1.5\times$ULN) (Table 2) [17]. At 24 months, 67% of bezafibrate-treated patients achieved normal ALP levels versus 2% with placebo [17]. A median 60% reduction in ALP levels from baseline was observed at 3 months [17].

In BEZURSO, bezafibrate treatment led to a trend of improvement in ALT and AST levels, and total cholesterol and low-density lipoprotein (LDL) cholesterol levels; HDL cholesterol levels were similar in both groups [17]. Real-world evidence suggests that bezafibrate + UDCA treatment decreases all-cause and liver-related mortality/need for liver transplantation compared with UDCA alone [125].

Pruritus was assessed in BEZURSO as a secondary endpoint without adjustment for multiple comparisons and demonstrated a non-significant trend towards reduction [17]. However, most patients had mild pruritus at baseline, potentially limiting the ability to detect a treatment effect. In the FITCH trial, which assessed bezafibrate for pruritus reduction in patients with fibrosing cholangiopathies, a post hoc analysis showed that 55% (6/11) of bezafibrate-treated patients with PBC achieved a reduction of at least 50% in pruritus intensity on the visual analogue scale after 21 days of treatment compared with 13% (2/15) in the placebo group [103]. These findings are supported by data from the 2021 systematic review and meta-analysis suggesting a potential anti-pruritic benefit [104].

Fatigue was also assessed in BEZURSO by patient report as being absent, intermittent or continuous; after 24 months, fatigue improved (i.e., transition to a less severe category) in 30% of bezafibrate-treated patients versus 19% with placebo [17].

In the BEZURSO trial, bezafibrate was associated with higher rates (vs placebo) of myalgia (20% vs. 10%) and abdominal pain (14% vs. 12%), as well as serious adverse events (SAEs) of elevated (> 5 × ULN) aminotransferase levels (6% vs. 2%), elevated (> 5 × ULN) creatine kinase levels (2% vs. 0%) and creatinine increase with worsening stage of chronic kidney disease (2% vs. 0%). One case of rhabdomyolysis occurred with concurrent statin use and resolved after discontinuation of bezafibrate. Additionally, patients' creatinine levels rose by 5% with bezafibrate and declined by 3% with placebo, a difference that mostly persisted over the 24-month trial [17]. Real-world data from a UK cohort study conducted between 2017 and 2021 investigating second-line therapy for PBC found that 21% of patients receiving bezafibrate ($n = 48$) or fenofibrate ($n = 60$) discontinued treatment by month 12, mainly owing to adverse effects [118]. The most common of these were miscellaneous intolerances (13/108 patients), deterioration in liver biochemistry (3/108 patients) and myalgia (2/108 patients) [118]. Of note, within the study, the proportion of patients receiving fibrates who required escalation in anti-pruritic therapy over the 1-year study period was similar to those receiving OCA treatment (14% vs. 12%, respectively) [118].

3.3 | Elafibranor

Elafibranor is approved for the treatment of PBC in combination with UDCA in adults who have an inadequate response to UDCA, or as a monotherapy in patients intolerant to UDCA [21]. Elafibranor is metabolised to form GFT1007, the main active metabolite [21].

Although elafibranor is generally referred to in the literature as a dual PPAR-α/δ agonist, it has been shown, along with GFT1007, to also activate PPAR-γ (Table 2) [21]. In vitro biochemical experiments show the highest potency for PPAR-α (EC_{50}: 0.046 μM), with potency approximately 3-fold lower for PPAR-γ (EC_{50}: 0.143 μM) and 4-fold lower for PPAR-δ (EC_{50}: 0.177 μM) [127]. Another study observed the same rank order of EC_{50} values across the isoforms; however, values were approximately an order of magnitude lower for each isoform, and the fold-reductions in potency relative to PPAR-α were more pronounced [128]. Consistent with these findings, elafibranor was also shown to recruit coactivator peptides to all three isoforms: PPAR-α (EC_{50}: 2.77–6.44 μM), PPAR-δ (EC_{50}: 9.56–11.8 μM) and PPAR-γ (EC_{50}: > 10 – > 30 μM) [111]. Based on its biochemical profile, the efficacy and safety of elafibranor could be predominantly mediated through PPAR-α activation, with comparatively lower contributions from PPAR-δ and potentially some PPAR-γ activation.

3.3.1 | Elafibranor Efficacy and Safety in PBC

Elafibranor has demonstrated improvements in ALP levels in phase 2 and phase 3 PBC clinical trials [19, 129]. The pivotal phase 3 ELATIVE trial found that 12 months of elafibranor treatment significantly improved the rate of biochemical response based on its primary endpoint (ALP level < 1.67 × ULN, with a decrease in ALP of ≥ 15% from baseline, and normalisation of total bilirubin levels) compared with placebo in patients who had an inadequate response (defined as ALP ≥ 1.67 × ULN), or were intolerant, to UDCA (Table 2) [19]. At 12 months, 15% of elafibranor-treated patients achieved normal ALP levels versus 0% with placebo ($p = 0.002$); the least-squares mean change in ALP from baseline was −117.0 U/L in the elafibranor group and −5.3 U/L in the placebo group (treatment difference [95% CI]: −40.6 [−47.8 to −33.5] U/L) [19]. No difference in ALT levels was seen between the groups (treatment difference [95% CI]: −3.8 [−11.0 to 3.4] U/L) [19], which was consistent with findings from the phase 2 study, in which treatment with elafibranor 80 mg or 120 mg did not improve ALT levels compared with placebo at 12 weeks [129]. Elafibranor treatment led to significantly reduced triglyceride, total cholesterol, LDL cholesterol and very low-density lipoprotein (VLDL) cholesterol levels at month 12 [19]; HDL cholesterol levels remained stable [19].

The ELATIVE study assessed change in pruritus intensity based on the Worst Itch Numeric Rating Scale (WI-NRS) at weeks 24 and 52 in patients with moderate-to-severe pruritus at baseline (WI-NRS ≥ 4), as a statistically powered key secondary endpoint [19]. Elafibranor did not show a statistically significant improvement in pruritus at either time point; at week 52, the least-squares mean change in WI-NRS was −1.9 in the elafibranor group and −1.2 in the placebo group (difference: −0.78; 95% CI: −1.99 to 0.42; $p = 0.20$) (Table 2) [19]. However, there were favourable trends in changes from baseline at week 52 in other pruritus scales (i.e., the itch domain of the PBC-40 quality-of-life questionnaire and total score on the 5-D itch scale).

Using the fatigue-specific instrument Patient-Reported Outcome Measurement Information System (PROMIS) Fatigue Short Form 7a (PFSF 7a), numerically greater proportions of patients with moderate-to-severe fatigue at baseline in ELATIVE reported a clinically meaningful improvement in fatigue with elafibranor versus placebo through 104 weeks [130]. No clear effect on fatigue was observed based on the subdomains for fatigue in the patient-reported PBC-40 questionnaire [130].

In the ELATIVE trial, treatment discontinuation due to adverse events (AEs) occurred at similar rates in the elafibranor (10%) and placebo (9%) groups. One case of drug-induced liver injury was observed in the elafibranor group [21] and two probable cases were observed in the placebo group [19]. Drug-induced liver injury has also been observed in two patients who received 1.5 times the recommended dose of elafibranor, per product labelling [21]. Elevated creatine phosphokinase levels occurred in 4% of elafibranor-treated patients, leading to treatment discontinuation; two of these patients were also receiving a statin [19, 21]. Myalgia was reported in 4% of elafibranor-treated patients compared with 2% of placebo-treated patients [21]. One case of rhabdomyolysis occurred in a patient with advanced cirrhosis who received elafibranor and concomitant atorvastatin [19]. No clinically meaningful changes in renal function were observed [19]. Preliminary data from the ELATIVE open-label extension study indicate that there were no treatment-related AEs of creatine phosphokinase elevation, myalgia or rhabdomyolysis with up to 4.5 years of exposure [131].

In the primary analysis of the ELATIVE study, fractures occurred in 6% of patients receiving elafibranor compared with no

patients receiving placebo [21]. Bone mineral density was, however, stable or slightly improved with elafibranor (vs. placebo) in ELATIVE, and bone turnover markers were similar between treatment groups at 52 weeks [132]. The biochemical profile of elafibranor indicates potential for PPAR-γ-mediated effects. In the ELATIVE trial, weight gain was marginally higher with elafibranor 80 mg (23% [24/108]) than with placebo (21% [11/53]) [21]. In the open-label extension of ELATIVE, abnormal weight gain was the most common AE, reported in 16.7% (23/138) of patients with up to 4.5 years of elafibranor exposure [131]. The phase 2 ELMWOOD trial in PSC reported weight gain in 17% (4/23) of patients receiving elafibranor 120 mg, 9% (2/22) of patients receiving elafibranor 80 mg and 4% (1/23) of patients receiving placebo [133]. No imbalance in weight gain between treatment and placebo groups was observed in a phase 2 study of elafibranor in MASH [49]. Taken together, these data suggest that elafibranor may have the potential to cause PPAR-γ-related weight gain in PBC due to fluid retention. However, larger real-world studies are needed to confirm this.

3.4 | Seladelpar

Seladelpar is approved for use in combination with UDCA in adults who have an inadequate response to UDCA, or as a monotherapy in patients intolerant to UDCA [22]. Seladelpar is a selective PPAR-δ agonist that exhibits high potency (EC_{50}: 0.0202 μM) for PPAR-δ in in vitro biochemical assays [128]. Its potency is 81-fold less for PPAR-α (EC_{50}: 1.64 μM) and 175-fold less for PPAR-γ (EC_{50}: 3.53 μM) [128]. Consistent with these findings, seladelpar exhibited potent recruitment of coactivator proteins to PPAR-δ (EC_{50}: 0.0317–0.0748 μM), while recruitment to PPAR-α (EC_{50}: 1.19–2.05 μM) and PPAR-γ (EC_{50}: 4.98–22.4 μM) occurred with substantially lower potency [111]. Based on its biochemical profile, the efficacy and safety of seladelpar are attributable to activation of PPAR-δ.

3.4.1 | Seladelpar Efficacy and Safety in PBC

Seladelpar has demonstrated improvements in ALP levels in several PBC clinical trials [18, 66, 134, 135] and two long-term extension studies [136, 137]. The pivotal phase 3 RESPONSE trial found that 12 months of seladelpar treatment significantly improved rates of biochemical response based on its primary endpoint (ALP level $<1.67\times$ULN, with a decrease in ALP of $\geq 15\%$ from baseline, and normalisation of total bilirubin levels) compared with placebo in patients who had an inadequate response (defined as ALP $\geq 1.67\times$ULN) or were intolerant to UDCA (Table 2) [18]. At 12 months, 25% of seladelpar-treated patients achieved normal ALP levels versus 0% with placebo ($p<0.001$); ALP levels were reduced by 42.4% from baseline in the seladelpar group compared with 4.3% in the placebo group (least-squares mean difference [95% CI]: −38.2 [−46.3 to −30.1]) [18].

Seladelpar treatment also led to significant reductions (vs. placebo) in ALT levels beginning at month 3, with sustained effects through month 12 (least-squares mean difference [95% CI] at month 12: −17.0 [−28.1 to −5.9]%) [18]. Similar findings were seen for seladelpar versus placebo in the phase 3 ENHANCE study [134]. No differences in AST levels were observed between the groups [18]. Favourable changes in lipid parameters were also observed, including significant reductions in total cholesterol (based on non-overlapping confidence intervals), triglycerides and LDL cholesterol levels, and a trend towards improvement in HDL cholesterol levels [18, 74].

In the RESPONSE study, pruritus was assessed using the numerical rating scale (NRS) at month 6 in patients with moderate-to-severe pruritus (NRS ≥ 4) at baseline, as a statistically powered key secondary endpoint [18]. Seladelpar significantly reduced pruritus with a least-squares mean change in the NRS from baseline of −3.2 points in the seladelpar group versus −1.7 points in the placebo group (difference [95% CI]: −1.5 [−2.5 to −0.5]; $p=0.005$) [18]. Based on quantitative and qualitative assessments, a 3-point reduction in the NRS is considered clinically meaningful [138]. PBC-40 itch domain and 5-D itch scores also indicated a benefit with seladelpar treatment consistent with the NRS results, further supporting its pharmacological efficacy for PBC-related pruritus (Table 2) [18]. These findings are consistent with results from the earlier phase 3, placebo-controlled ENHANCE study, in which seladelpar significantly reduced mean pruritus NRS (vs. placebo) at month 3 (−3.14 points vs. −1.55 points; $p=0.02$) [134]. Seladelpar has been shown to reduce serum IL-31 and bile acid levels in several studies, including RESPONSE [18, 73, 139]. Changes in these biomarkers have been shown to correlate with each other and with pruritus improvement [73], providing a potential a mechanism for the antipruritic effect of seladelpar in patients with PBC.

In an open-label, single-arm study of seladelpar, fatigue improvement based on the fatigue subdomain of the PBC-40 questionnaire was observed, with the number reporting a decrease (improvement) being 3 times higher than the number reporting an increase at month 12 [139]. Preliminary analyses from RESPONSE also demonstrated reductions in fatigue with seladelpar compared with placebo over 12 months in patients with severe pruritus at baseline, based on the PBC-40 [140].

Safety profiles for seladelpar and placebo were similar in the RESPONSE trial [18]. AEs leading to treatment discontinuation occurred in 5% of patients in the placebo group and 3% of those in the seladelpar group [18]. No SAEs were deemed by the investigators to be related to seladelpar [18]. Overall, the liver safety profile was similar between both groups and no concerning AEs affecting the muscles were observed, including among those who received statins [18]. Post-baseline creatine kinase levels exceeding 3 times the ULN were reported in one patient in the placebo group and two in the seladelpar group [18]. No clinically meaningful changes in serum creatinine levels were observed [18, 22].

Fractures occurred in five (4%) seladelpar-treated patients compared with no patients in the placebo group [22]. Three of these patients were considered to have likely or possibly osteoporotic fractures based on the location and nature of the event; all three had a medical history of osteoporosis, osteopenia or a recent fracture (itself a risk factor for future fractures) at the start of the study [141]. The overall safety profile of seladelpar in RESPONSE was consistent with data from an earlier phase 2 [135] and phase 3 trial [134]. In addition, longer-term treatment with seladelpar in the open-label ASSURE study indicated no

new safety concerns with up to 3 years of exposure [137]. Recent preliminary data from up to 4 years of exposure suggest a safety profile consistent with previous, shorter-duration clinical trials [142].

3.5 | Saroglitazar

Saroglitazar is a dual PPAR-α/γ agonist in phase 3 development in PBC (Figure 1). In vitro biochemical data show that saroglitazar activates both PPAR-α (EC_{50}: 0.19 μM) and PPAR-γ (EC_{50}: 0.31 μM), while activation of PPAR-δ is negligible (EC_{50}: > 10 μM) (Table 2) [128], with potency > 53 times lower than for PPAR-α, and efficacy limited to just 6% [128]. Consistent with these results, saroglitazar was shown to recruit coactivator peptides to PPAR-α (EC_{50}: 0.280–0.814 μM) and PPAR-γ (EC_{50}: 1.87–8.43 μM), while only faint recruitment to PPAR-δ was observed [111]. Based on its biochemical profile, the efficacy and safety of saroglitazar are driven by dual PPAR-α and PPAR-γ activation.

3.5.1 | Saroglitazar Efficacy and Safety in PBC

The placebo-controlled phase 2 EPICS trial found that 16 weeks of treatment with saroglitazar 4 mg or 2 mg significantly improved ALP levels (least-squares mean change: −163.3 and −155.8 U/L, respectively) compared with placebo (least-squares mean change: −21.1 U/L; $p < 0.001$ with both doses) in patients who had a previous inadequate response (defined as ALP ≥ 1.67 × ULN) or were intolerant to UDCA (Table 2) [23]. Saroglitazar did not significantly reduce ALT and AST at either dose level [23]. Triglycerides and VLDL levels were significantly reduced in the 2 mg group, but not in the 4 mg group; no changes in other lipid parameters were observed compared with placebo [23].

An improvement in pruritus or fatigue, based on the itch domain of the PBC-40 questionnaire, was not seen with either dose of saroglitazar in EPICS [23].

In EPICS, saroglitazar was discontinued in four patients (three patients in the 4 mg group and one patient in the 2 mg group) due to increases in aminotransferases [23]. SAEs were reported in two patients (in the 2 mg group) and included appendicitis, dyspnoea and peripheral oedema [23]. A placebo-controlled, phase 2b/3 trial (EPICS-III, NCT05133336) evaluated the effects of 1 mg and 2 mg doses of saroglitazar; after a dose selection period, the 1 mg dose was selected as the optimal regimen. At the time of writing this manuscript, the full trial results are pending.

3.6 | Pemafibrate

Pemafibrate is approved in Japan for the treatment of hyperlipidaemia. This agent is known as a 'selective PPAR α modulator' and is in phase 2 development in PBC (Figure 1). In vitro biochemical data show that pemafibrate activates PPAR-α (EC_{50}: 0.0014 μM) at concentrations that are three orders of magnitude lower than those at which it activates PPAR-δ (EC_{50}: 1.39 μM) and PPAR-γ (EC_{50}: > 5 μM) (Table 2) [110]. Consistent with this, pemafibrate exhibits potent recruitment of coactivator proteins to PPAR-α (EC_{50}: 0.0476–0.131 μM), while recruitment to PPAR-δ (EC_{50}: 4.75–14.9 μM) and PPAR-γ (EC_{50}: 5.58–13.8 μM) occurs at substantially lower potency [111]. Based on its biochemical profile, the efficacy and safety of pemafibrate are attributable to activation of PPAR-α. A placebo-controlled, phase 2 trial (NCT06247735) is ongoing at the time of writing to assess the safety and efficacy of two dosing regimens of pemafibrate in patients with PBC.

4 | Conclusions, Clinical Implications and Future Directions

PPARs have served a valuable role in the treatment of hyperlipaemia and other indications. They have also provided an off-label option for treating PBC in some geographies in the absence of approved second-line therapies. More recently, however, approved second-line PBC treatments, specifically seladelpar and elafibranor, have emerged.

The predominant target isoform for most of the PPAR agonists is PPAR-α, and most of the agonists have been shown to have clinically relevant activity against at least one other isoform. An exception is seladelpar, which belongs to the novel delpar class and shows high selectivity for PPAR-δ. Although head-to-head trials are lacking, differences in the efficacy and safety profiles of PPAR agonists used as second-line PBC treatments are emerging (and becoming evident in dosing recommendations), likely reflecting their distinct pharmacological properties.

The efficacy of PPAR agonists in reducing ALP levels has been clearly demonstrated in patients with PBC, and appears generally similar across agents, with the caveat that cross-study comparisons are inherently limited and enrolled patients at baseline are not identical. Fibrates have shown a potential anti-pruritic effect, but seladelpar is unique in demonstrating significant and robust reductions in pruritus in two placebo-controlled trials. Saroglitazar, a dual PPAR-α/γ agonist, showed no effect on pruritus in phase 2; however, the sample size was small. The precise mechanism of cholestatic pruritus is uncertain, but pruritogenic mediators including bile acids and IL-31 are thought to play a role, and seladelpar has been shown to reduce both of these markers.

Fatigue in PBC is not well understood and is likely multifactorial, involving signals in the central nervous system and potentially sleep disturbance; both central and peripheral factors may play a role [143]. There is increasing interest to gain a better understanding of the effect of second-line PBC therapies on fatigue, and initial data suggest favourable effects for bezafibrate, elafibranor and seladelpar. These observations underscore the need for further research to elucidate the mechanisms and natural history of fatigue, optimise measurement tools and quantify the impact of current and emerging therapies on this burdensome symptom.

The ability to reduce ALT levels may also differentiate PPAR agonists. It is important to recognise that the baseline levels of ALT and AST are different across studies and therefore direct

comparisons are not possible. In BEZURSO, bezafibrate showed trends towards reduced ALT and AST levels. Seladelpar significantly reduced ALT levels from month 3 in RESPONSE, while elafibranor did not significantly reduce ALT levels in ELATIVE. While these findings may suggest favourable hepatic effects mediated via distinct PPAR-regulated pathways, it is important to note that ALT and AST, like ALP, are surrogate markers rather than direct measures of clinical benefit in PBC. The clinical relevance of changes in these markers in PBC will ultimately depend on whether they translate into meaningful outcomes, such as slowing fibrosis progression and improving transplant-free survival.

Most PPAR agonists have shown at least a trend towards improving triglyceride and LDL/VLDL cholesterol levels. The clinical significance of these effects in PBC remains unclear; however, these data underscore the role of PPARs in modulating lipid metabolism. Although fibrates are known to increase HDL cholesterol levels in individuals with hyperlipidaemia, and seladelpar has shown similar effects in this patient population (data on file, Gilead Sciences Inc.), neither the fibrates, fibric acid-based molecules nor seladelpar have demonstrated clear increases in HDL cholesterol levels in patients with PBC, suggesting variability in their lipid-modifying efficacy across different disease states. Importantly, while elevated cholesterol levels in patients with PBC may not confer increased cardiovascular risk [144], traditional risk factors such as features of metabolic syndrome do [145].

In terms of safety, PPAR agonists have been linked to liver and muscle injury, and may affect creatinine levels and possibly renal function and bone health, with varying degrees of risk. Elafibranor and seladelpar are supported by more robust safety data than the fibrates used off-label in PBC, given the rigorousness of data collection in registrational trials. To date, these data suggest that elafibranor and seladelpar have a more favourable safety and tolerability profile than fenofibrate and bezafibrate.

The safety profile of elafibranor is consistent with PPAR-α agonism and potentially some PPAR-γ effects, with cases of ALT and creatine kinase elevations observed. Seladelpar has not shown an increase in liver or muscle biomarkers at the approved dose, including among patients receiving statins, possibly consistent with its selective PPAR-δ activity. Open-label data from the long-term extension of ELATIVE and from the ASSURE study suggest favourable safety profiles for elafibranor for up to 4.5 years and seladelpar for up to 4 years. Phase 4 studies will further delineate the safety and efficacy profiles of these agents in real-world settings where comorbidities and comedications in patients with PBC will dictate the most appropriate second-line treatment. The safety of saroglitazar in PBC remains to be presented in a placebo-controlled study of adequate size and duration.

The development of novel PPAR agonists as second-line treatment in PBC represents a significant advancement for patients. However, the absence of head-to-head studies and inherent limitations of cross-trial comparisons constrain our ability to fully distinguish the clinical profiles of the agents. Further studies are needed to clarify the mechanistic roles of PPAR isoforms, especially for symptom relief and agent- and class-related toxicities, to further our understanding of the clinical profiles of these agents and our ability to refine and enhance treatment strategies.

Author Contributions

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Data Availability Statement

The data that support the findings of this study are openly available in NCBI Gene Expression Omnibus (GEO) at https://www.ncbi.nlm.nih.gov/geo/, reference number GSE243977 and GSE247128.

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