

Pathophysiology, Clinical Manifestations, and Pharmacological Management of Pruritus in Primary Biliary Cholangitis: A Systematic Review

Retno Dwi Utami¹, Wibisono Hasanul Muhtaram², Mira Nupila Rahma³, Ashila Sallama Nur Fadlila⁴, Indri Tiffani⁵, Lalu Abdul Mubarak⁶, Baiq Mayada Isqie⁷, Florentcia Davina Gunawan⁸, Made Prajnana Adhi Parasikan Susana⁹, Nensy Dwi Astika¹⁰, Pande Komang Inten Widya Iswara Oka¹¹, Kurniati¹², Nurhidayati¹³

¹Faculty of Medicine and Health Sciences, Universitas Mataram, Mataram, West Nusa Tenggara, Indonesia

²Division of Digestive Pharmacology, Faculty of Medicine and Health Sciences, Universitas Mataram, Mataram, West Nusa Tenggara, Indonesia

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Abstract

Primary Biliary Cholangitis (PBC) is a chronic autoimmune cholestatic liver disease marked by the progressive destruction of small intrahepatic bile ducts. Chronic pruritus affects about 70-80% of patients, can greatly diminish quality of life, and does not present with primary skin lesions. Its pathogenesis is complicated, and the lack of primary lesion signs continues to make management a clinical challenge. This review aims to discuss the pathophysiology and the effectiveness of current pharmacological therapies for pruritus associated with PBC. Literature searches were carried out using PubMed and ScienceDirect, with keywords relating to PBC, pruritus, and treatment. Only original research articles in English published from 2016 to 2026 were included. In total, 29 studies met the inclusion criteria and were analyzed narratively. Pruritus in PBC involves several mediators, such as bile acids, autotaxin (ATX), lysophosphatidic acid (LPA), interleukin-31 (IL-31), and changes in gut microbiota. Clinically, cholestatic pruritus is usually worse at night, especially on the palms and soles, and occurs without primary skin lesions. Several pharmacological therapies have shown promising results, particularly seladelpar, bezafibrate, cholestyramine, rifampicin, nalfurafine, and inhibitors of the ileal bile acid transporter (IBAT). On the other hand, farnesoid X receptor agonists like obeticholic acid may worsen pruritus for some patients. Pruritus in PBC is a complex and multifactorial clinical problem. Treatments that target bile acid metabolism, the ATX-LPA pathway, pruritogenic cytokines, and the opioid system have shown potential to reduce pruritus intensity and improve quality of life for patients.

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Corresponding Author:

Retno Dwi Utami

Faculty of Medicine and Health Sciences, Universitas Mataram

Email: retnodwiiu@gmail.com

1. INTRODUCTION

Primary Biliary Cholangitis (PBC) is one of the chronic autoimmune liver diseases that deserves attention because it can lead to a decline in quality of life and progression of liver disease. PBC is defined by the progressive destruction of small intrahepatic bile ducts due to autoimmune processes. Chronic pruritus is a main clinical manifestation, reportedly

affecting about 70-80% of patients. Pruritus in PBC can disrupt daily activities and sleep, significantly lowering quality of life, and often appears before cirrhosis or liver failure develops [1].

The pathogenesis of pruritus in PBC is complex; it is not fully mediated by histamine as in common pruritus, nor does it present with primary skin lesions as seen in dermatitis. Various pruritogenic mediators resulting from cholestasis, such as bile acids, lysophosphatidic acid (LPA), and autotaxin (ATX), are thought to induce the sensation of itch without causing inflammation. The complexity of these mechanisms, along with the absence of primary lesion markers for PBC pruritus, makes its management a persistent clinical challenge [2], [3].

Currently, management of pruritus in PBC remains suboptimal, as patients respond differently to available therapies. While Ursodeoxycholic Acid (UDCA) is effective as a first-line therapy for improving liver biochemical parameters and slowing disease progression, it often fails to relieve pruritus adequately [1]. As a result, ongoing therapeutic developments aim to improve treatment effectiveness and patients' quality of life.

Given these issues, a thorough review of the pathophysiology and the effectiveness of newer pharmacological therapies for PBC pruritus is needed. This review is intended to provide a clearer understanding to optimize pruritus management and support better quality of life for PBC patients.

2. MATERIALS AND METHODS

2.1. Research Question based on PICO

The research question was developed using the PICO (Population, Intervention, Comparison, and Outcome) framework to ensure a systematic and organized approach. This framework helps in clearly identifying the main elements of the research question, making it easier to search for, select, and systematically explore relevant evidence-based articles.

Table 1. Research Question based on PICO

Component	Content
Population	Patients with Primary Biliary Cholangitis experiencing pruritus
Intervention	Pharmacological antipruritic therapy
Comparison	Placebo, standard therapy, or other pharmacological agents
Outcome	Changes in pruritus intensity, changes in pruritogenic marker and cholestasis marker levels before and after intervention, as well as changes in mediators involved in the mechanism of pruritus in PBC

2.2. Search Strategy

Literature was gathered by searching scientific databases, specifically PubMed and ScienceDirect, with the following Boolean keywords: ("primary biliary cholangitis" OR PBC) AND (pruritus OR "cholestatic pruritus" OR itching) AND (treatment OR therapy OR management OR therapeutics). The selected articles were original research focused on the treatment of pruritus in PBC patients, published between 2016 and 2026, written in English, and available in full-text.

The collected data were reviewed by extracting and comparing study details, such as authors and publication year, the type of intervention or therapy used, study design, method for assessing pruritus, sample size, dosage and length of treatment, and the main outcomes related to therapy effectiveness in PBC patients. In addition, the results from each study were summarized in a narrative form to describe how effective different therapies are for managing pruritus in PBC.

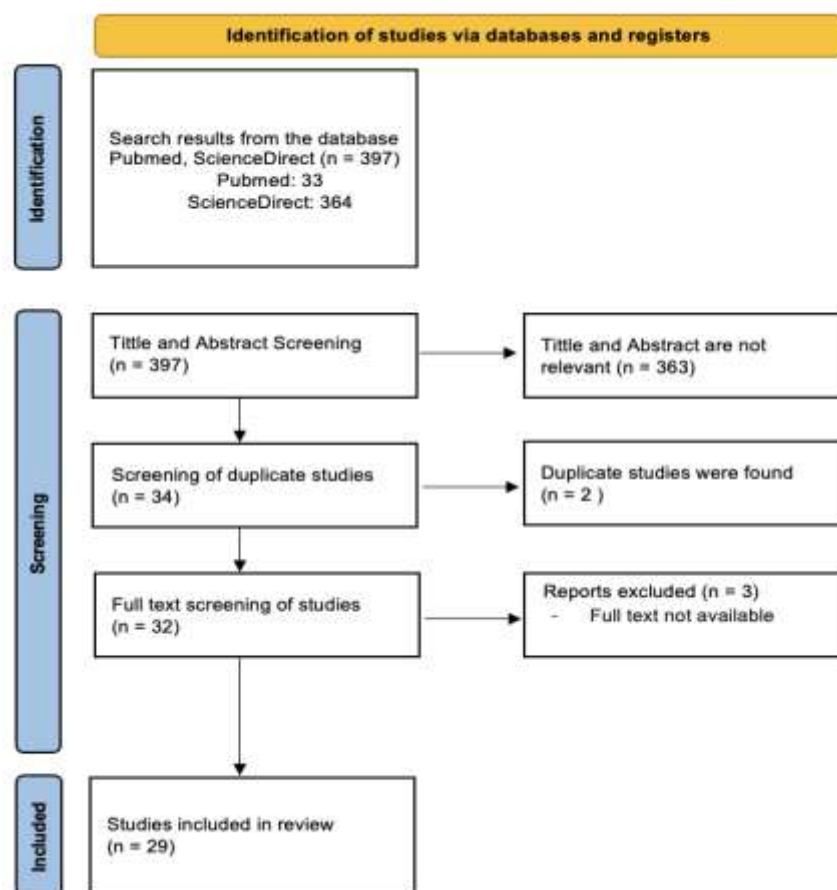


Figure 1. PRISMA flowchart

3. RESULTS AND DISCUSSION

3.1. Pathophysiology of Pruritus in Primary Biliary Cholangitis

The pathogenesis of cholestatic pruritus is complex and involves multiple factors, and even now, it is not completely understood. Several mediators are believed to contribute to pruritus, including increased levels of bile acids, lysophosphatidic acid (LPA), autotaxin, interleukin-31 (IL-31), and changes in the gut microbiota, particularly dysregulation under cholestatic conditions. These mediators are thought to activate pruritus pathways in both the peripheral and central nervous systems, which leads to the typical itching experienced by patients with cholestasis [3].

3.1.1. Alkaline Phosphatase (ALP)

The rise in alkaline phosphatase (ALP) during cholestasis is due to impaired bile flow, resulting in bile acid retention within hepatocytes. The build-up of bile acids, especially hydrophobic ones, has a detergent effect on the membranes of hepatocytes and canaliculi, which then stimulates greater synthesis and release of ALP into the bloodstream. Because of this, elevated serum ALP is used as a key biochemical marker in cholestatic conditions [4].

Although ALP levels are increased in cholestasis, this enzyme itself does not directly cause pruritus. The itching experienced in cholestasis is more closely linked to the accumulation of pruritogenic mediators that result from impaired bile flow, which happens alongside increased ALP; thus, the rise in ALP mirrors the underlying cholestatic process that contributes to

pruritus. This connection is supported by a study from Reig *et al.* (2018), which found that patients who had a complete ALP response showed a much lower prevalence of pruritus than those with incomplete responses (42% vs. 79%; $p < 0.01$). These results suggest that better biochemical responses, especially normalization of ALP, are associated with a lower incidence of pruritus in Primary Biliary Cholangitis (PBC) patients [5].

3.1.2. Bile Acids

Cholestatic pruritus is thought to result from the excessive accumulation of bile acids in cholestatic states. This process starts in hepatocytes when cholesterol is converted to bile acids through a pathway regulated by the CYP7A1 enzyme and an alternative pathway controlled by CYP27A1, with the latter being more active in chronic cholestatic diseases.

The bile acids produced are then secreted into the intestine, where they are metabolized by gut flora into secondary bile acids, and most are reabsorbed back to the liver via the enterohepatic circulation. Under normal circumstances, bile acid synthesis is regulated by negative feedback through the activation of the farnesoid X receptor (FXR) and Small Heterodimer Partner (SHP), which suppress CYP7A1 activity via liver receptor homolog-1 (LRH-1). In cholestasis, however, this inhibition can be bypassed due to increased CYP27A1 pathway activity, leading to higher bile acid levels in the blood.

The surplus bile acids are believed to deposit in tissues and activate the transmembrane G-protein coupled receptor (TGR5) on pruritus sensory neurons, which then triggers the itching. The involvement of bile acids in pruritus in PBC was highlighted in a study by Hegade *et al.* (2017), which observed that a 50% reduction in total serum bile acids was accompanied by a 57% decrease in pruritus intensity, as measured by the Numeric Rating Scale (NRS), in PBC patients. These results suggest there may be a link between bile acid levels and pruritus severity in cholestatic patients [6].

However, the relationship between lowering bile acid levels and improvement in pruritus was not specifically analyzed statistically in that study, so further research is needed to clarify the role of bile acids in the development of pruritus in PBC patients.

3.1.3. Autotaxin (ATX)

Autotaxin (ATX) is an important enzyme involved in making lysophosphatidic acid (LPA), a mediator that contributes to cholestatic pruritus. Higher ATX levels can increase LPA production, which can worsen itch intensity. Because of this, ATX is considered a possible target for treating cholestatic pruritus [7]. According to Kremer *et al.* (2019), serum ATX levels and ATX activity are positively correlated with baseline pruritus intensity (ATX level: $p = 0.33260$, $p = 0.0009$; ATX activity: $p = 0.21035$, $p = 0.0397$). These findings show that higher ATX is involved in the pathomechanism of pruritus in PBC [8].

3.1.4. Interleukin-31 (IL-31)

In cholestatic pruritus, higher bile acid levels can cause excessive activation of FXR. This activation of FXR leads to increased production of interleukin-31 (IL-31), a cytokine made by T cells that is involved in the development of itching by stimulating sensory neurons in the skin. This mechanism is often seen in cholestatic diseases like Primary Sclerosing Cholangitis (PSC) and PBC, where bile acid build-up causes excessive FXR

stimulation, raising IL-31 levels [7]. The role of IL-31 in pruritus in PBC is also supported by a study by Kremer *et al.* (2024), which found that baseline serum IL-31 levels were significantly correlated with pruritus severity based on the NRS ($r = 0.54$; $p < 0.0001$). These results suggest a direct link between higher IL-31 activity and pruritus intensity in PBC patients [8].

3.1.5. Gut Microbiota

In PBC, there are changes in the gut microbiota (dysbiosis) that are believed to play a part in the disease's development. PBC is an autoimmune disease marked by damage to the intrahepatic bile ducts due to an immune response driven by T lymphocytes, and it is more common in women. Several studies have shown a reduction in protective intestinal bacteria, such as *Bacteroides*, and an increase in opportunistic bacteria like *Enterobacteriaceae*, *Veillonella*, *Lactobacillus*, *Haemophilus*, *Streptococcus*, and *Klebsiella*. These changes in the gut microbiota are thought to influence immune regulation, metabolism, and bile acid composition in PBC patients [9].

Alterations in the overall composition and diversity of the gut microbiota, without focusing on specific bacteria, were also shown in a study by Zhou *et al.* (2026). The study found that PBC patients with pruritus had a significant reduction in the alpha diversity of their gut microbiota compared to those without pruritus, as shown by lower Shannon and Simpson indices (both $p < 0.01$). Beta diversity analysis using Principal Coordinate Analysis (PCoA) and Non-metric Multidimensional Scaling (NMDS) also revealed significant differences in microbial community composition between the two groups. Additionally, after cholestyramine therapy, there was a notable increase in gut microbiota diversity (Shannon $p < 0.01$; Simpson $p < 0.01$), which matched the improvement in pruritus symptoms [10].

3.2. Clinical Manifestations of Pruritus in PBC

Pruritus linked to cholestasis often follows a circadian pattern, with patients reporting more severe itching in the early evening. This itching is usually most noticeable on the palms and soles, but it can be generalized and ranges from mild to severe. Unlike pruritus in skin diseases, primary skin lesions are not seen in patients with cholestatic pruritus. However, intense scratching can cause secondary skin changes like excoriation, folliculitis, lichenification, and prurigo nodularis, which can sometimes be mistaken for primary skin diseases [2].

3.3. Pharmacological Management of Pruritus in Primary Biliary Cholangitis

3.3.1. Seladelpar

Seladelpar is an anti-pruritic medication that helps reduce IL-31 and bile acids, which is linked to relief from itching in PBC patients. IL-31 is a key factor in pruritus in PBC and is a target for treatment. IL-31 influences itching by acting directly on sensory neurons or nearby keratinocytes, both of which have high-affinity IL-31 receptors. IL-31 can also cause these neurons to branch and persist [11]. The efficacy of seladelpar was tested in three recent Phase 2 Randomized Controlled Trials (RCTs), which found that VAS pruritus scores dropped in all treatment groups after 12 and 52 weeks, showing that higher doses led to greater and longer-lasting improvement in pruritus [12]. Kremer *et al.* (2022) also found that patients

with moderate-to-severe baseline itching (NRS ≥ 4) had a large reduction in NRS itch scores at week 52: a 2 mg dose reduced scores by -3.2; a 5 mg dose by -3.7; and a 10 mg dose by -3.8 ($p < 0.005$) [13].

In addition to being tested in Phase 2 trials, Hirschfield *et al.* (2023) have also tested seladelpar in two Phase 3 trials, which showed that in patients with active baseline pruritus (NRS ≥ 4), seladelpar at 10 mg/day for 3 months significantly lowered the mean itch severity score by -3.14 points; this reduction was much more effective ($p = 0.02$) than in the placebo group, which had a smaller reduction of -1.55 points [14]. Kremer *et al.* (2024) also found a significant drop in IL-31 after seladelpar use. At a 10 mg dose, IL-31 levels fell by -52% ($p < 0.0001$), and at 5 mg by -30% ($p = 0.0003$). In contrast, placebo increased IL-31 by +31%. The decrease in IL-31 matched clinical improvement in itching (a reduction in NRS score of more than 2) [11].

3.3.2. Obeticholic Acid (OCA)

Obeticholic Acid (OCA) is a medication that works by reducing bile acid production, increasing bile acid secretion, and lowering bile acid reabsorption. OCA also helps regulate anti-inflammatory and antifibrotic pathways. In some patients, OCA treatment is linked to increased pruritus, which can be managed with lifestyle adjustments and various therapies. Dose management and titration of OCA can also influence pruritus severity [15].

Several studies have examined this drug. Nevens *et al.* (2016), in a randomized double-blind placebo-controlled Phase 3 clinical trial, reported that pruritus was the most common side effect in patients receiving OCA, with higher rates in the 5-10 mg (56%) and 10 mg (68%) groups compared to placebo (38%). VAS scores and the 5-D Itch Questionnaire showed greater worsening of pruritus in the 10 mg group compared to placebo up to month 6, indicating that OCA can trigger or worsen pruritus, especially at higher doses [16].

In a double-blind placebo-controlled trial, Kowdley *et al.* (2018) found that pruritus was the most frequent and dose-dependent side effect; 35% (placebo), 70% (OCA 10 mg), 94% (OCA 50 mg). Most cases could be managed with antipruritics or temporary discontinuation. OCA 50 mg did not provide added benefit over 10 mg but led to more therapy discontinuations due to pruritus [17]. Terracciani *et al.* (2025), in a multicenter ambispective observational cohort study, confirmed that skin symptoms like pruritus were the most dominant side effect from FXR activation. This itching became a major clinical challenge and the leading cause (36.9%) of early treatment discontinuation, especially in the initial phase [18]. In an open-label extension study, Trauner *et al.* (2019) found that long-term OCA therapy (up to 48 months) resulted in stable reductions in ALP (-95.6 U/L from baseline), as well as bilirubin, ALT, and AST within normal ranges. Pruritus occurred in 77% of patients (149 of 193) [19]. D'Amato *et al.* (2021) in a multicenter retrospective real-world cohort study, also found that pruritus was the main side effect of OCA. From 52 patients with pruritus, 40 patients had occurred new pruritus and 12 had worsening condition of pruritus that already exist. Pruritus became the reason most patients (64%) discontinued OCA treatment [20].

3.3.3. Bezafibrate

Bezafibrate is a Peroxisome Proliferator-Activated Receptor (PPAR) agonist anti-pruritic drug with anti-inflammatory, anti-cholestatic, and antifibrotic effects [21]. This drug works by activating PPARs and has been shown to normalize ALP in 67% of PBC patients with incomplete biochemical responses or intolerance to UDCA [7].

Corpechot *et al.* (2018) in a randomized, double-blind, placebo-controlled trial found that pruritus improvement in the bezafibrate group was consistent with the study's primary outcomes, suggesting that bezafibrate was considered effective for pruritus symptom improvement compared to placebo in PBC patients [22]. A prospective study by Reig *et al.* (2017) found a significant drop in VAS scores from a median of 3.7 to 0 ($p < 0.001$). Sixteen patients had complete resolution and seven had partial resolution of itching. Symptoms returned a median of 10 weeks after stopping the drug [5]. Two recent Phase 3 RCTs by de Vries *et al.* (2021) found that the main outcome of a $\geq 50\%$ reduction in itch intensity on the VAS scale was achieved by 45% of patients in the bezafibrate group, compared to only 11% in the placebo group ($p = 0.003$). Bezafibrate also significantly outperformed placebo in lowering absolute itch scores on the VAS ($p = 0.002$) and reducing the total 5-D Itch Scale score ($p = 0.002$). Along with these skin improvements, patient quality of life (ItchQoL) also improved significantly in the bezafibrate group ($p = 0.02$) [23]. Kremer *et al.* (2019) found that pruritus VAS scores improved significantly in the bezafibrate group compared to placebo. The median percentage change in itch intensity from baseline to 24 months was -100% (95% CI -100 to -71) in the bezafibrate group compared to 4% (95% CI -40 to 47) in the placebo group ($p = 0.0027$) [8].

3.3.4. Linerixibat

Linerixibat is a drug for pruritus that works by lowering the systemic load of pruritogenic bile acids. This is done by inhibiting the ileal bile acid transporter (IBAT), also called the apical sodium-dependent bile acid transporter (ASBT or SLC10A2). IBAT is a protein on terminal ileal epithelial cells that reabsorbs about 95% of bile acids, allowing them to return to the liver via the portal vein. This is known as enterohepatic circulation. By competitively blocking IBAT, linerixibat disrupts this reabsorption. This leads to more bile acid being excreted in feces. The resulting drop in total serum bile acid pool reduces MRGPRX4 activation on sensory neurons, which leads to less pruritus [24].

The effectiveness of this drug was tested in a Phase 2b, randomized, parallel-group, multicenter, placebo-controlled study with a prospective adaptive design for dose adjustment. It found that all linerixibat dose groups showed clear clinical improvement with a decrease in mean worst daily itch (MWDI) score of ≥ 2 points from baseline; however, this difference was not statistically significant compared to placebo ($p = 0.1106$) due to a strong placebo response for this subjective symptom. Nevertheless, longitudinal post hoc analysis in the per-protocol (PP) population demonstrated a significant linear relationship between dose increases and itch suppression, where the 180 mg once-daily ($p = 0.0424$), 40 mg twice-daily ($p = 0.0105$), and 90 mg twice-daily ($p = 0.037$) regimens significantly outperformed placebo [25].

3.3.5. GSK2330672 (IBAT Inhibitor)

Bile Acid Transporter (IBAT) inhibitor class. IBAT inhibitors target the reabsorption of bile acids in the ileum, stopping the enterohepatic circulation of bile acids, and reducing the total bile acid pool and liver exposure [26].

A study from Hegade *et al.* (2017) on the effectiveness of this drug was conducted by using a double-blind, randomized, placebo-controlled, crossover, phase 2a study. They found that after GSK2330672 therapy, there was a significant reduction in pruritus scores compared to baseline and placebo: NRS -57% ($p < 0.0001$), PBC-40 itch domain -30% ($p < 0.0001$), and 5-D itch scale -35% ($p < 0.0001$). Compared to placebo, GSK2330672 consistently showed significant improvement across all pruritus scales [6].

3.3.6. A4250 (IBAT Inhibitor)

A4250 is an anti-pruritic drug in the Ileal Bile Acid Transporter (IBAT) inhibitor class. IBAT inhibitors target the reabsorption of bile acids in the ileum, stopping the enterohepatic circulation of bile acids, and reducing the total bile acid pool and liver exposure [26]. A study on the effectiveness of this drug was conducted by Al-Dury *et al.* (2018) using a phase 2, open-label, exploratory study on oral A425 for cholestatic pruritus in PBC resistant to standard therapy. They found that out of 4 patients who finished A4250 treatment, pruritus in 2 patients completely resolved (100% recovered) with scores reaching, while the other 2 had a reduction in itching of 60% and 80%, respectively [27].

3.3.7. Nalfurafine

Nalfurafine is an anti-pruritic drug that acts as a highly selective κ -opioid receptor agonist, believed to work by activating central κ receptors, counteracting μ -receptor-mediated pruritus signals, and possibly modulating itch pathways linked to bile acids [28]. The effectiveness of this drug was tested in a prospective, multicenter, single-arm, post-marketing study by Yagi *et al.* (2018) which found that nalfurafine significantly improved clinical skin outcomes. The mean VAS itch score dropped from 42.9 at the start to 29.3 at week 12 ($p < 0.001$). This significant improvement in itching was seen as early as week 2 and stayed stable until the end of the study [29].

3.3.8. Tauroursodeoxycholic acid (TUDCA)

TUDCA is the taurine-conjugated form of UDCA and is more hydrophilic than its parent molecule. Pharmacologically, TUDCA works similarly to UDCA but is more potent in shifting the bile acid pool toward a more hydrophilic composition, reducing the harmful effects of endogenous hydrophobic bile acids like chenodeoxycholic acid and lithocholic acid. Experimental studies in mice showed that oral UDCA led to a unique bile acid profile with high TUDCA accumulation, which then sped up enterohepatic circulation by inhibiting FXR signaling in the ileum and lowering FGF15/19 levels, which in turn increased bile acid transporter expression in the liver [30].

Beyond its effects on FXR, TUDCA is also known as a chemical chaperone that reduces endoplasmic reticulum (ER) stress and stabilizes the unfolded protein response (UPR), and also inhibits apoptosis by preventing Bax translocation from the cytosol to mitochondria, blocking cytochrome c release, and activating survival pathways such as PI3K/Akt and MAPK [31]. TUDCA's strong ability to boost bicarbonate secretion by

cholangiocytes and its protective effects on mitochondria make it a promising treatment in chronic cholestasis [32].

In a multicenter, double-blind, controlled, non-inferiority phase III clinical trial in 199 Chinese PBC patients, Ma *et al.* (2016) compared TUDCA 750 mg/day (250 mg three times daily) with an equivalent dose of UDCA for 24 weeks. The results showed that TUDCA was not inferior to UDCA, with 75.97% of patients in the TUDCA group and 80.88% in the UDCA group reaching the primary endpoint of a reduction in serum ALP of more than 25% from baseline ($p = 0.453$). Similarly, the percentage of patients achieving an ALP reduction of more than 40% was 55.81% in the TUDCA group and 53% in the UDCA group ($p = 0.699$). Serum levels of total bilirubin, AST, and ALP improved similarly in both groups ($p > 0.05$). Interestingly, in the UDCA group, the percentage of patients with pruritus raised from 1.43% to 10.00% whereas in the TUDCA group there was no change ($p = 0.023$), showing TUDCA's advantage in symptom improvement. The two groups' adverse event rates were similar, and both medication was well-tolerated [32].

3.3.9. SAME

In chronic liver diseases, including PBC, there is an acquired deficiency of S-Adenosyl-L-Methionine (SAME) due to reduced activity of methionine adenosyltransferase, which is responsible for making SAME from methionine. SAME is a major donor of methyl and sulfate groups and a precursor to cysteine and glutathione; its deficiency can impair liver detoxification and increase oxidative stress. Previous experimental studies in rat hepatocyte models found that combining SAME with UDCA had an added hepatoprotective effect in overcoming cholestasis caused by both lithocholate and 17β -estradiol glucuronide, likely due to SAME's role as a sulfate donor, increasing the solubility of cholestatic compounds [33].

A deeper molecular mechanism was revealed by Kilanczyk *et al.* (2020), showing that in human cholangiocytes, SAME protects against mitochondrial oxidative stress by raising nuclear factor erythroid 2-related factor 2 (Nrf2) and heme oxygenase-1 (HO-1) levels, and by suppressing apoptosis and the expression of the PDC-E2 antigen (a component of the pyruvate dehydrogenase enzyme, which is the main target of anti-mitochondrial antibodies) induced by glycochenodeoxycholic acid (GCDC). Furthermore, in 9 of 17 PBC patients who responded to SAME, there was an increase in serum protein S-glutathionylation, which matched a decrease in AMA-M2 antibody titers and biochemical improvement of the liver [34].

Wunsch *et al.* (2018) designed a study as a proof-of-principle trial to assess the effect of adding 120 mg/day of SAME for 6 months in PBC patients already on standard dose UDCA. The result showed that adding SAME 1200 mg/day for 24 weeks in non-cirrhotic PBC patients on UDCA led to significant improvements in several liver biochemical parameters. ALP dropped from 204 ± 104.8 IU/L to 170 ± 97.0 IU/L ($p < 0.05$), gamma-glutamyl transferase (GGT) from 189 ± 210.6 IU/L to 113 ± 147.6 IU/L ($p < 0.01$), and total cholesterol also decreased significantly. In cirrhotic patients, only total bilirubin dropped significantly (from 2.3 ± 1.2 mg/dL to 2.0 ± 1.0 mg/dL; $p < 0.05$), while other parameters did not change much. The control group on UDCA alone showed no significant changes in liver

function. However, the idea that SAME's liver-protective effect is due to increased liver sulfation capacity was not statistically confirmed; the lithocholate/lithocholate sulfate (LCA/LCA-S) ratio dropped from 4.8 ± 8.1 to 2.8 ± 3.4 ($p = 0.55$), and fibroblast growth factor-19 (FGF-19) levels, as a marker of cholestatic response, also did not change significantly. These findings suggest that SAME's effect in PBC may not depend on the sulfation pathway or FGF-19 modulation, and its benefits seem more pronounced in earlier stages of the disease [33].

Besides improving liver biochemistry, SAME therapy also had a significant positive effect on the health-related quality of life (HRQoL) of PBC patients, especially in symptom areas that are often hard to treat. Based on the PBC-40 questionnaire, there was a significant improvement in the pruritus domain (from 6.9 ± 3.5 to 5.2 ± 2.3 ; $p = 0.006$) and fatigue (from 30.2 ± 7.8 to 26.9 ± 7.4 ; $p = 0.04$) after 24 weeks of SAME therapy. In anxiety assessment using the State-Trait Anxiety Inventory (STAI) 2, there was a highly significant reduction in score from 47.8 ± 5.8 to 44.6 ± 6.0 ($p = 0.003$), while STAI 1, HADS (Depression and Anxiety), and Modified Fatigue Impact Scale (MFIS) scores showed a trend toward improvement but did not reach statistical significance. This improvement is likely related to the known antidepressant and anti-anxiety effects of SAME, even though Selective Serotonin Reuptake Inhibitors (SSRIs) were previously not proven effective for fatigue in PBC. Still, these results should be interpreted carefully since six patients (25%) dropped out of the study, including two with severe pruritus that did not get better and four with nonspecific symptoms like abdominal cramps. Overall, this pilot study showed that adding SAME to UDCA benefits liver biochemistry (especially in non-cirrhosis) as well as pruritus, fatigue, and anxiety symptoms, and further validation in larger groups is needed [33].

3.3.10. Elafibranor

Elafibranor is a dual agonist of the peroxisome proliferator-activated receptor (PPAR) subtypes α and δ , which are widely present in liver tissues [35]. PPAR α activation is known to suppress the expression of the CYP7A1 gene, which encodes the cholesterol 7 α -hydroxylase enzyme, the rate-limiting step in classic bile acid synthesis [36]. Meanwhile, PPAR α and PPAR δ activation helps with anti-inflammatory effects by inhibiting NF- κ B and AP-1 signaling pathways, as well as modulating the BCL6 pathway. The combination of activating these two PPAR subtypes produces a synergistic effect in controlling bile acid homeostasis, improving liver detoxification, and lowering systemic inflammatory responses. Unlike FXR agonists (such as obeticholic acid) which raise FGF19 levels and may be linked to long-term tumor risk, elafibranor suppresses bile acid synthesis via an FGF19-independent mechanism, offering a different safety profile for long-term PBC therapy. Elafibranor 80 mg once daily showed good efficacy in PBC patients [35].

A population pharmacokinetic and pharmacokinetic-pharmacodynamic (PKPD) analysis from 17 clinical trials confirmed that the 80 mg/day dose improves ALP and total bilirubin compared to placebo. This analysis also found that the effect on ALP reached saturation at exposures above 30 μ mol-h/L, which was reached by about 60% of patients, further supporting that the 80 mg/day dose is an effective choice for PBC [37].

In a 12-week multicenter, double-blind, placebo-controlled phase II clinical trial in 45 PBC patients with incomplete responses to UDCA (ALP ≥ 1.67 times the upper limit of normal), elafibranor at 80 mg and 120 mg once daily led to significant reductions in ALP of $-48.3 \pm 14.8\%$ ($p < 0.001$) and $-40.6 \pm 17.4\%$ ($p < 0.001$), respectively, compared to placebo which actually increased by $+3.2 \pm 14.8\%$. A composite endpoint of ALP $\leq 1.67 \times \text{ULN}$, an ALP reduction $> 15\%$, and total bilirubin below ULN was achieved in 66.7% of the 80 mg group and 78.6% of the 120 mg group, compared to only 6.7% in the placebo group. GGT levels dropped by 37.1% and 40.0%, respectively, while IgM and hsCRP, as disease activity markers, also fell significantly. Importantly, elafibranor did not cause or worsen pruritus; in fact, patients with baseline pruritus reported symptom improvement on the VAS scale (median change -24% to -49%). Drug-related side effects were mostly mild to moderate, mainly digestive issues. One patient in the 120 mg group had a stroke deemed unrelated to treatment, and another had transaminase elevation suggesting autoimmune hepatitis in a patient with myasthenia gravis. Overall, elafibranor showed promising efficacy and safety as second-line therapy in PBC, supporting further phase III trials [35].

3.3.11. Maralixibat

Maralixibat (SHP625; previously known as LUM001) is a selective competitive inhibitor of the apical sodium-dependent bile acid transporter (ASBT), also called the ileal bile acid transporter (IBAT), with minimal systemic absorption [38]. This drug works locally in the terminal ileum by blocking the reabsorption of bile acids from the gut back into the enterohepatic circulation [39]. This inhibition leads to more bile acid being excreted in feces, followed by a compensatory increase in new bile acid production in the liver through a negative feedback mechanism involving fibroblast growth factor 19 (FGF-19). Maralixibat has been approved for treating hereditary cholestatic diseases such as Alagille syndrome and progressive familial intrahepatic cholestasis (PFIC) [38]. By reducing the build-up of toxic and pruritogenic bile acids, maralixibat is expected to improve cholestasis symptoms, especially pruritus, in cholestatic liver diseases like PBC [39].

In a randomized, double-blind, placebo-controlled phase 2 clinical trial on 66 adult PBC patients with pruritus who had received UDCA for at least 6 months or were intolerant to UDCA, maralixibat did not show statistically significant pruritus improvement compared to placebo. Patients were randomized 2:1 to maralixibat (10 or 20 mg/day) or placebo for 13 weeks. The main results showed that the weekly Adult Itch Reported Outcome (ItchROTM) score reduction from baseline in the maralixibat group (LS mean change -26.5; 95% CI -31.8 to -21.2) was not significantly different from placebo (-23.4; 95% CI -30.3 to -16.4), with an inter-group difference of only -3.1 ($p = 0.48$). Still, maralixibat did lower serum bile acid levels and raised C4 levels (a marker of bile acid synthesis) while lowering autotaxin, a biomarker linked to cholestatic pruritus severity, showing that the pharmacological target was hit. Side effects were more common in the maralixibat group (97.6%) than placebo (70.8%), mainly diarrhea (61.9% vs. 25.0%) and abdominal pain (23.8% vs. 4.2%). The study concluded that a large placebo effect (up to 47%) likely hid the active effect; thus, future

clinical trials for pruritus need to consider ways to reduce the placebo effect and optimize dosing with a slower dose increase [40].

3.3.12. Dupilumab

Dupilumab is a recombinant monoclonal antibody that binds specifically to the alpha subunit of the interleukin-4 receptor (IL-4R α), blocking downstream signaling of interleukin-4 (IL-4) and interleukin-13 (IL-13), two important cytokines in type 2 inflammatory pathways [41]. Although hepatogenic pruritus is not histopathologically marked by obvious skin inflammation, recent research shows that skin sensory neurons express IL-4R α , and activating this pathway can increase neuronal sensitivity to various pruritogens, including substance P, serotonin, and bile acids [42]. By blocking the IL-4/IL-13 pathway, dupilumab is expected to reduce the overactivity of sensory neurons even without skin inflammation, offering a new approach different from standard therapies for chronic cholestatic pruritus.

Evans *et al.* (2026) reported results from an open-label, single-arm, exploratory pilot study assessing dupilumab's efficacy and safety in nine patients with moderate to severe chronic hepatogenic pruritus from various liver diseases, including alcoholic cirrhosis, PBC, and primary sclerosing cholangitis (PSC). All subjects received an initial 600 mg dose of dupilumab subcutaneously, followed by 300 mg every two weeks for 18 weeks. At week 18, the Peak Pruritus Numerical Rating Scale (PPNRS) score dropped significantly from a baseline of 8.2 ± 1.7 to $4. \pm 3.5$ ($p = 0.023$), with a difference of -4.1 that exceeded the clinically meaningful threshold of 3 points. A similar drop was seen in the 5-D itch scale score (19.8 ± 3.5 to 11.4 ± 5.3 ; $p = 0.006$), especially in itch duration ($p = 0.02$) and intensity ($p = 0.034$) domains. Also, the percentage of patients reporting mild or no itching on the VAS increased from 0% at baseline to 75% at week 18 ($p = 0.021$). No side effects related to liver function or therapy discontinuation due to side effects were found. The researchers concluded that dupilumab showed good efficacy and tolerability in reducing hepatogenic pruritus, but the small sample size means larger studies are needed [43].

3.3.13. Tropifexor

Tropifexor (LJN452) is a non-bile acid farnesoid X receptor (FXR) agonist with subnanomolar potency, optimized with a unique benzothiazole carboxylic acid moiety structure to improve affinity for the FXR ligand-binding domain [44]. FXR activation by tropifexor in the gut and liver increases FGF19 secretion, which then suppresses new bile acid synthesis through negative feedback by lowering CYP7A1 expression, as shown by a drop in C4 (7-alpha-hydroxy-4-cholesten-3-one) levels [45]. Through this mechanism, tropifexor reduces the build-up of toxic bile acids in intrahepatic cholestasis, which may help reduce bile duct injury and improve cholestatic biochemical markers in liver diseases like PBC.

In a phase II, randomized, double-blind, placebo-controlled clinical trial by Schramm *et al.* (2022) evaluating the safety, tolerability, and efficacy of tropifexor in 61 PBC patients with inadequate biochemical responses to UDCA, patients were randomized (2:1) to receive tropifexor at 30, 60, 90, or 150 μ g or placebo once daily for 28 days. The main results showed that tropifexor led to a decrease in gamma-glutamyl transferase (GGT) by 26-

72% from baseline on day 28, with statistically significant differences at the 60, 90, and 150 µg doses compared to placebo ($p < 0.001$). Normalization of GGT (< 65 U/L) was achieved in 18.2%, 33.3%, 66.7%, and 12.5% of patients in the tropifexor 30, 60, 90, and 150 µg groups, respectively. Moderate reductions in ALP were also seen, though only a few patients reached the target ALP $< 1.67\times$ the upper limit of normal. Pruritus was the most common side effect (52.5% on tropifexor vs. 28.6% on placebo), with the highest rate at the 150 µg dose (87.5%), and most cases were mild to moderate. Three patients (37.5%) in the 150 µg group stopped treatment due to side effects, including raised ALT and pruritus. Significant drops in LDL, HDL, and total cholesterol were seen at 60-150 µg doses, which returned to baseline after stopping therapy. The researchers concluded that tropifexor showed dose-dependent improvement in cholestasis markers with an acceptable safety profile at doses of 30-90 µg, supporting further clinical development for PBC therapy [46].

3.3.14. Baricitinib

Baricitinib is an orally administered small molecule from the Janus kinase (JAK) 1 and 2 inhibitor group, approved for treating moderate to severe rheumatoid arthritis [47]. Pharmacologically, baricitinib blocks the phosphorylation and activation of signal transducer and activator of transcription (STAT) proteins, thereby interfering with the intracellular signaling of several proinflammatory cytokines involved in the pathogenesis of PBC, including type I interferon (via JAK1/TYK2), interleukin-12, and interleukin-23 (via JAK1/TYK2) [48]. By modulating this cytokine network, baricitinib is thought to reduce the autoimmune response that causes bile duct injury in PBC, and may also improve cholestatic biochemical markers and systemic symptoms like pruritus and fatigue.

A randomized, double-blind, placebo-controlled phase II proof-of-concept study evaluated baricitinib at a dose of 2 mg per day for 12 weeks in PBC patients who had an inadequate response or intolerance to UDCA. Due to a low participation rate, the study was stopped early, so only two subjects were successfully randomized (one to baricitinib, one to placebo). Still, the available data revealed very different response patterns. The patient who received baricitinib had a 30% drop in ALP (from 224 U/L to 157 U/L) at week 12, meeting the criteria for therapeutic response ($< 1.67\times$ ULN). Notably, ALP returned to pre-treatment levels within four weeks after stopping therapy. The Itch Numerical Rating Scale score also dropped from 9 to 2 points, showing a marked improvement in pruritus. On the other hand, the placebo subject did not show any meaningful improvement in ALP or itch score. Baricitinib was also linked to improvements in inflammatory markers (hs-CRP) and liver fibrosis score (ELF), with side effects limited to a single episode of non-serious moderate sinusitis. Gordon *et al.* (2021) stated that these findings provide an initial basis for baricitinib's potential as a new therapy in PBC, but emphasized the need for larger studies to confirm these results [49].

3.3.15. Rifampicin

Rifampicin is a semisynthetic ansamycin antibacterial agent that works by inhibiting DNA-dependent RNA polymerase in bacteria; however, its use in cholestatic pruritus is based on its role as a PXR agonist, which

induces the transcription of bile acid transporter and metabolism genes and lowers serum bile acid levels [50]. Rifampicin also affects the central opioid system and reduces autotaxin, an enzyme that produces LPA, a known pruritus mediator in cholestatic diseases [51]. Through this dual action, reducing bile acid burden and direct neuromodulation, rifampicin can relieve itching in some patients with intrahepatic cholestasis, though the precise mechanism is not fully understood.

A retrospective cohort study by Webb *et al.* (2018) included 105 patients with cholestatic liver disease (mainly primary biliary cholangitis and primary sclerosing cholangitis) who were given rifampicin for pruritus. In this largest real-world study to date, the median treatment duration was 131 days. Five out of 105 patients (4.8%) developed rifampicin-induced hepatitis, as determined by the Roussel-Uclaf Causality Assessment Method (RUCAM) with a score of ≥ 6 (probable or highly probable). The median time to hepatitis onset was 70 days (range 27-130 days) after starting the drug. All hepatitis cases resolved after stopping rifampicin, though one patient needed hospitalization and corticosteroids. Interestingly, 44 patients (41.9%) had a baseline bilirubin level ≥ 2 times the upper limit of normal and 28 patients (26.7%) had a baseline ALT ≥ 3 times the upper limit of normal, but no baseline characteristics (including the degree of jaundice, elevated transaminases, or liver disease diagnosis) were significantly linked to the risk of hepatitis. In total, 95% of patients did not develop clinically significant hepatotoxicity. The authors concluded that rifampicin is relatively safe for cholestatic pruritus in adults, even in those with advanced liver disease or jaundice, and in rare cases (about 5%), the hepatitis it causes is reversible after stopping the drug [52].

3.3.16. NGM282 (aldafermin)

NGM282 is a recombinant analog of FGF19 that has been genetically modified to remove tumorigenic potential while keeping its metabolic activity. Normally, FGF19 is an endocrine hormone released by the ileum in response to FXR activation by bile acids. NGM282 acts directly on hepatocytes by binding to the FGFR4/ β -Klotho receptor complex, which strongly suppresses CYP7A1 gene expression. This gene encodes the cholesterol 7 α -hydroxylase enzyme, the first and rate-limiting step in bile acid synthesis through the classical liver pathway [53].

The liver-protective effects of NGM282 are not limited to bile acid metabolism but also include direct improvements in liver histology. This was shown in a phase 2 clinical trial in patients with nonalcoholic steatohepatitis (NASH), where NGM282 given for 12 weeks led to significant improvements in the disease activity score (NAS) and fibrosis stage, without worsening the safety profile [54]. These results add to the evidence that NGM282's structural changes preserved FGF19's metabolic activity while providing a better safety profile for treating chronic liver disease.

NGM282's effectiveness in altering the course of cholestatic disease was shown in a multicenter, double-blind, placebo-controlled phase 2 clinical trial in PBC patients who did not respond to ursodiol. The study found that subcutaneous NGM282 for 28 days significantly reduced ALP levels, a key marker of cholestasis. In the 3 mg dose group, there was an average ALP drop of 66. IU/L ($p = 0.003$) compared to placebo, with 46% of patients

achieving at least a 15% reduction from baseline. Additionally, NGM282-mediated suppression of bile acid synthesis was shown by a marked decrease in serum C4 (7 α -hydroxy-4-cholesten-3-one) levels, especially in the high-dose group ($p < 0.0001$), which was linked to improvements in transaminase enzymes (ALT/AST) and IgM immunoglobulins, suggesting anti-inflammatory and immunomodulatory effects [53].

Another important finding from this study is the favorable tolerability profile of NGM282, particularly regarding pruritus, which is often a challenge in PBC therapy. Unlike FXR agonists such as obeticholic acid, which often worsen itching, NGM282 did not cause or aggravate pruritus. No significant relationship was found between changes in pruritus scores and the reduction in total serum bile acids, although a positive correlation was seen with changes in conjugated glycocholic acid (GCA) levels. The most common side effects were mild to moderate gastrointestinal symptoms like diarrhea, which are thought to be related to faster colonic transit due to FGF19 signaling. Overall, these results support NGM282 as a possible alternative therapy for PBC patients who do not respond well to first-line ursodiol [53].

3.3.17. Cholestyramine

Cholestyramine, an anion-exchange resin, is mainly known as a bile acid sequestrant that lowers the systemic cholestatic load by binding bile acids and increasing their excretion in feces. However, a prospective multi-omics study by Zhou *et al.* (2026) showed that the therapeutic effect of cholestyramine in PBC patients with pruritus depends not just on its chelating action but also on its influence on the host metabolite-gut microbiota axis [55].

This study found that PBC patients with pruritus have marked microbiota dysbiosis, with lower Shannon and Simpson diversity indices, higher levels of pro-inflammatory genera like *Romboutsia*, and fewer beneficial taxa such as *Lachnospiraceae* and *Bacteroidaceae*. On a metabolic level, this is accompanied by reduced indole derivatives (e.g., norharman) and medium-chain fatty acids (MCFAs), which have gut barrier and anti-inflammatory properties. Giving cholestyramine 4 g twice daily for 4 weeks restored microbiota diversity, reduced *Romboutsia* abundance, and normalized norharman and MCFA levels, suggesting that this resin acts through microbiota remodeling and restoring metabolic balance [55]. Clinically, a 4-week cholestyramine course led to measurable multisystem improvements in PBC patients with moderate to severe pruritus.

Zhou *et al.* (2026) reported a significant drop in the 5-D pruritus score from a median of 20 to 7 ($p < 0.01$), which matched the normalization of serum autotaxin (ATX) levels, an objective marker of cholestatic pruritus, from 54.08 ng/mL to 25.67 ng/mL ($p < 0.01$). At the same time, there was a significant decrease in cholestasis markers, including ALP, GGT, and total bilirubin (all $p < 0.01$). Further analysis showed that the *Romboutsia*-norharman-ATX/ALP axis is important in the development of pruritus in PBC, where higher *Romboutsia* is positively linked with ALP ($r = 0.36$) and GGT ($r = 0.31$), while lower norharman is negatively linked with ATX ($r = -0.42$) and ALP ($r = -0.42$). Also, the presence of *Enterobacteriaceae* and the buildup of long-chain fatty acids (LCFAs) like palmitic acid and eicosenoic acid were found to predict a weaker response to cholestyramine

[55]. These results show that cholestyramine not only relieves symptoms by binding bile acids but also by restoring the host metabolite-microbiota axis.

3.3.18. Intranasal Butorphanol

Butorphanol is a kappa-opioid receptor (KOR) agonist and at the same time a mu-opioid receptor (MOR) antagonist, acting centrally in the dorsal horn of the spinal cord to affect itch perception. Activating KORs with butorphanol is known to reduce scratching in animal models, while blocking MORs prevents the increase in pruritus usually caused by pure MOR agonists like morphine. In terms of pathophysiology, cholestatic pruritus is thought to result from an imbalance in the endogenous opioid system, specifically increased MOR and decreased KOR signaling in the central nervous system. With its dual action as a KOR agonist and MOR antagonist, butorphanol pharmacologically corrects this imbalance, making it effective for relieving itching without the side effects often seen with pure MOR antagonists like naltrexone, such as opioid withdrawal-like symptoms [56].

In a case series of eight adult patients with cholestatic diseases (PBC and PSC) and moderate to severe pruritus (VAS score 7-10) who did not respond to various first- and second-line therapies, it found that intranasal butorphanol at 1-3 mg/day led to meaningful clinical improvement in 62.5% of patients (5 out of 8), with a VAS score drop of 2-10 points. Two patients saw no change or only temporary improvement, and one patient had a paradoxical increase in itch intensity. Reported side effects included drowsiness (2 patients), sedation (1 patient), nausea (2 patients), vomiting (1 patient), and dizziness (1 patient). Importantly, no abnormal changes were seen in liver biochemistry (ALP, AST, ALT, total bilirubin) or kidney function (creatinine) during up to 33 months of treatment, and there were no episodes of cirrhotic decompensation or bacterial cholangitis linked to butorphanol use. The benefits of intranasal butorphanol include a quick onset of action (within 15 minutes), peak effect at 1-2 hours, and ease of use, making it a safe and effective off-label option for refractory cholestatic pruritus [56].

4. CONCLUSION

Pruritus in Primary Biliary Cholangitis (PBC) is a common clinical problem, typically presenting as a chronic itch that worsens at night, especially on the palms and soles, without primary skin lesions. Its pathogenesis is complex and involves bile acids, the autotaxin-lysophosphatidic acid (ATX-LPA) axis, interleukin-31, and changes in gut microbiota. Standard treatments like cholestyramine and rifampicin remain important, while newer therapies such as seladelpar, bezafibrate, and IBAT inhibitors have shown encouraging results in reducing pruritus and improving cholestasis markers. However, more research is needed to determine the long-term efficacy and safety of these treatments.

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