Systematic Review/Meta-analysis

INTERNATIONAL JOURNAL OF SURGERY: GLOBAL HEALTH

OPEN

Efficacy and safety of Seladelpar in the treatment of primary biliary cholangitis: a systematic review and meta-analysis

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Background: Primary biliary cholangitis (PBC) is a progressive autoimmune liver disease marked by destruction of intrahepatic bile ducts, leading to fibrosis, cirrhosis, and liver failure. Current treatments, including ursodeoxycholic acid and obeticholic acid, are often inadequate or associated with adverse effects, highlighting the unmet need for effective, well-tolerated therapies. Seladelpar, a selective peroxisome proliferator-activated receptor delta agonist, has shown promise in improving biochemical markers and clinical outcomes in PBC. This systematic review and meta-analysis evaluates the efficacy and safety of Seladelpar in PBC management.

Methods: This review adhered to PRISMA guidelines and was registered with PROSPERO. A systematic search of PubMed, EMBASE, Cochrane Library, and ClinicalTrials.gov was conducted up to October 2024, focusing on studies evaluating Seladelpar in adult PBC patients. Randomized controlled trials, observational studies, and open-label extensions reporting efficacy (e.g., alkaline phosphatase [ALP] reduction) or safety outcomes were included. Meta-analysis was performed using RevMan, with pooled estimates presented as weighted mean differences or risk ratios.

Results: From 611 studies, seven met inclusion criteria, comprising 1019 participants across Phase 2 and Phase 3 trials and open-label extensions. Seladelpar significantly reduced ALP levels, with a dose-response relationship observed. The 10 mg dose showed the most pronounced efficacy, with a 53–63% ALP reduction compared to placebo. Clinical improvements, including reduced pruritus and enhanced quality of life, were consistent across studies. Long-term follow-up demonstrated sustained biochemical and clinical benefits. Adverse effects were dose-dependent, with pruritus, nausea, and dyspepsia most common. The 5 mg dose had the lowest incidence of adverse events.

Conclusions: Seladelpar demonstrates robust efficacy in improving biochemical markers and alleviating symptoms in PBC, with a favorable safety profile. Its potential for long-term clinical benefit underscores its role as a promising therapeutic option for patients with PBC. Further studies are warranted to confirm its long-term safety and efficacy in diverse patient populations.

Keywords: PPAR- δ agonist, primary biliary cholangitis, Seladelpar

Introduction

Primary biliary cholangitis (PBC) is a chronic, progressive autoimmune cholestatic liver disease characterized by the destruction of intrahepatic bile ducts[1]. The pathophysiology of PBC involves immune-mediated damage to biliary epithelial cells, leading to bile acid retention, chronic inflammation, and subsequent fibrosis[2]. Over time, this process may culminate in cirrhosis, liver failure, or hepatocellular carcinoma, contributing significantly to morbidity and mortality[2]. While the etiology of PBC remains unclear, genetic susceptibility and environmental triggers are thought to play pivotal roles in its pathogenesis[1]. The disease disproportionately affects middle-aged women, with a global prevalence ranging from 1.91 to 40.2 per 100 000 people, making it a substantial public health concern[3].

The clinical manifestations of PBC vary widely, from asymptomatic cases identified incidentally to symptomatic patients presenting with fatigue, pruritus, and complications of cirrhosis[4]. Fatigue and pruritus, in particular, substantially impair the quality of life. Biochemically, the hallmark of PBC is elevated alkaline phosphatase (ALP) levels, which correlate with disease progression and serve as a surrogate marker for therapeutic response.

The current standard of care for PBC includes ursodeoxycholic acid (UDCA), a bile acid derivative that improves bile flow and delays disease progression[5]. However, up to 40% of patients demonstrate an inadequate biochemical response to UDCA, necessitating alternative treatments. Obeticholic acid, a farnesoid X receptor agonist, is an approved second-line therapy but is limited by its adverse effect profile, particularly pruritus, and its

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Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

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International Journal of Surgery: Global Health (2025) 8:e00572

Received 23 April 2025; Accepted 21 May 2025

Published online 20 June 2025

http://dx.doi.org/10.1097/GH9.0000000000000572

associated cardiovascular risks[6]. Other investigational agents, such as fibrates, have shown promise in improving biochemical markers but lack robust long-term safety data. Thus, there remains a significant unmet need for novel, effective, and well-tolerated therapies for patients with PBC[7].

Seladelpar, a selective peroxisome proliferator-activated receptor delta (PPAR-δ) agonist, has emerged as a promising therapeutic option for PBC[8]. By modulating lipid metabolism, anti-inflammatory pathways, and bile acid synthesis, Seladelpar targets key mechanisms implicated in PBC pathogenesis. Preclinical studies have demonstrated its potential to reduce hepatobiliary inflammation and fibrosis. Moreover, early-phase clinical trials have reported substantial reductions in ALP levels and improvements in other liver function parameters, with a favorable safety profile[9]. These findings underscore Seladelpar's potential to address the therapeutic gaps in PBC management and improve clinical outcomes. The objective of this systematic review and meta-analysis is to evaluate the efficacy and safety of Seladelpar in the treatment of PBC.

Methods

Study design and registration

This systematic review and meta-analysis was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and reported according to A MeaSurement Tool to Assess Systematic Reviews (AMSTAR) to ensure a transparent methodology. The study protocol was registered with PROSPERO to enhance methodological rigor and prevent duplication of research efforts.

Search strategy

A systematic literature search was performed across multiple electronic databases, including PubMed, Google Scholar, EMBASE, Scopus, Cochrane Library, and ClinicalTrials.gov, from inception to October 2024. The search strategy incorporated a combination of Medical Subject Headings terms and keywords related to PBC and Seladelpar. Examples of search terms included "Primary Biliary Cholangitis," "PBC," "Seladelpar," "PPAR-delta agonist," "efficacy," and "safety." Boolean operators (AND/OR) were used to refine the search, and filters were applied to include only human studies. Reference lists of included articles and relevant reviews were also screened for additional studies (Fig. 1).

Inclusion and exclusion criteria

Inclusion criteria:

1. Studies involving adult patients diagnosed with PBC based on established clinical and histological criteria.
2. Randomized controlled trials, observational studies, and open-label extensions evaluating Seladelpar for the treatment of PBC.
3. Studies reporting at least one efficacy outcome (e.g., alkaline phosphatase reduction, normalization of liver enzymes) or safety outcome (e.g., adverse events, drug tolerability).
4. Publications in English with full-text availability.

Exclusion criteria:

1. Studies focusing on non-PBC populations or unrelated interventions.
2. Case reports, editorials, and conference abstracts lacking sufficient data.
3. Non-English publications or those without full-text access.
4. Studies with incomplete outcome reporting or insufficient methodological details.

Data extraction

Two independent reviewers conducted data extraction using a predesigned data collection form to ensure consistency and reduce bias. Extracted data included study characteristics (e.g., author, year, design, sample size), baseline patient demographics, intervention details (Seladelpar dose, duration), efficacy outcomes (e.g., ALP reduction, changes in liver function tests), and safety outcomes (e.g., incidence of adverse events). Disagreements between reviewers were resolved through discussion or by consulting a third reviewer.

Outcome measures

Efficacy outcomes:

- Primary: reduction in ALP levels.
- Secondary: normalization of liver enzymes, bilirubin levels, and improvement in pruritus or quality of life.

Safety outcomes:

- Incidence of adverse events (e.g., gastrointestinal disturbances, pruritus).
- Drug tolerability and withdrawal rates due to adverse effects.

Risk of bias assessment

The quality of included clinical trials was evaluated using the Cochrane Risk of Bias 2.0 tool (Fig. 2).

Statistical analysis

Meta-analysis was conducted using RevMan. Pooled estimates of continuous outcomes (e.g., ALP reduction) were calculated as weighted mean differences with 95% confidence intervals (CI). Dichotomous outcomes (e.g., adverse events) were analyzed using risk ratios. Heterogeneity among studies was assessed using the I^2 statistic, with values of 25%, 50%, and 75% representing low, moderate, and high heterogeneity, respectively. A random-effects model was employed to account for variability among studies. Sensitivity analyses were performed to evaluate the robustness of the findings, and publication bias was assessed visually using funnel plots and quantitatively using Egger's test. This rigorous methodology ensures a comprehensive evaluation of the efficacy and safety of Seladelpar in the treatment of PBC.

Results

The initial search identified 611 studies. After screening titles and abstracts, many were excluded for failing to meet relevance criteria. A full-text assessment further eliminated studies lacking Seladelpar as a therapy for PBC, relevant outcome

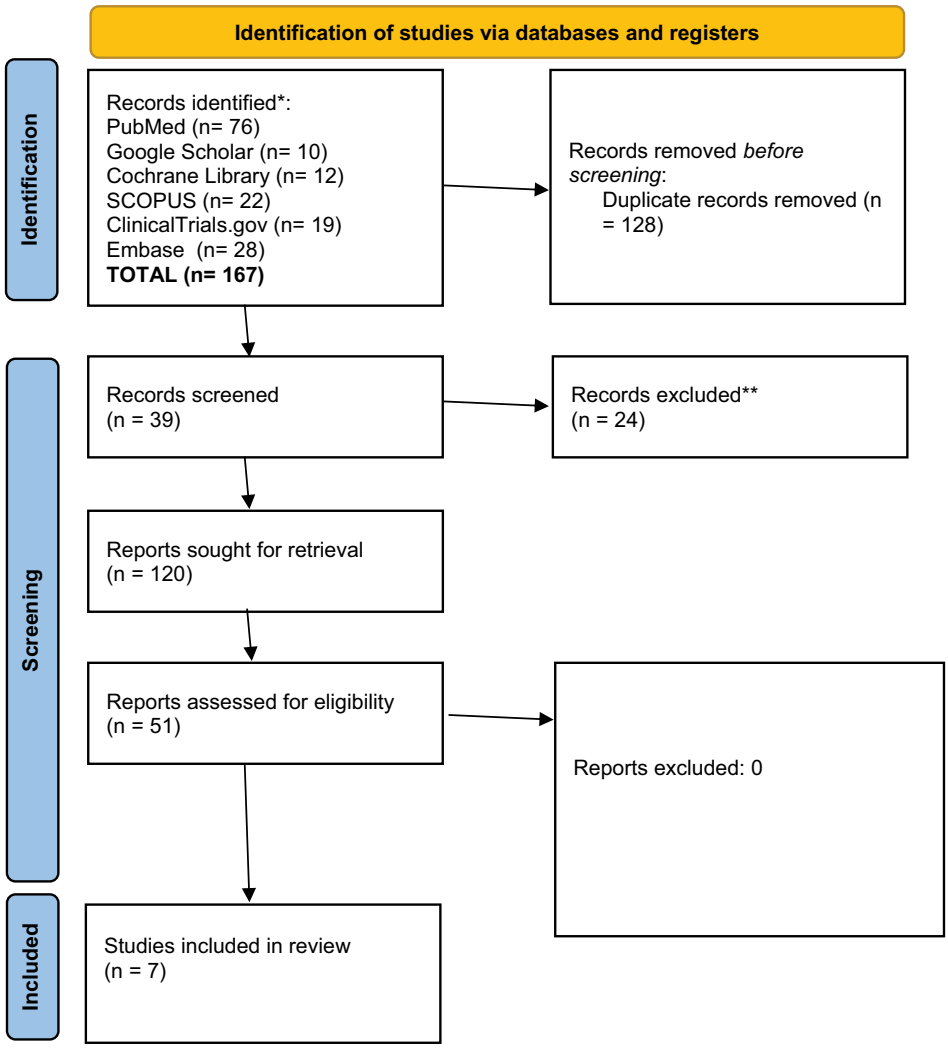

Figure 1. PRISMA selection of the included studies.

measures, or sufficient data. Ultimately, seven studies[7-13] met the inclusion criteria, allowing for a qualitative synthesis of the evidence on Seladelpar's efficacy and safety in treating PBC (Table 1).

The review studies included 1019 participants. The studies included four Phase 2 randomized, double-blind, placebo-controlled trials and three Phase 3 randomized, double-blind, placebo-controlled trials, alongside two open-label extension studies. The average doses of Seladelpar administered across these studies varied, with the most common doses being 5 mg, 10 mg, and 50 mg per day.

Efficacy

A network meta-analysis was conducted using data from three studies, encompassing seven pairwise comparisons and 466 patients. The analysis revealed that 10 mg Seladelpar demonstrated superior efficacy compared to 5 mg Seladelpar, 2 mg Seladelpar, and placebo, as illustrated in Fig. 3. Among these comparisons, the most pronounced effect was observed between 10 mg Seladelpar and placebo, with an odds ratio (OR) of 10.24 (95% CI: 3.41–30.76), indicating a nearly 9-fold greater effectiveness compared to placebo. Comparisons between different Seladelpar doses suggested a dose-response relationship, where higher doses consistently exhibited greater efficacy. However, the analysis showed a high degree of heterogeneity (I^2 = 70.7%), suggesting variability across studies. Figure 4 provides a network plot illustrating the relationships between the included treatments and comparisons.

Biochemical improvement

Seladelpar demonstrated significant efficacy in improving biochemical markers associated with PBC. Multiple studies[7,8,11–13] reported a notable reduction in ALP levels. For instance, Jones *et al*[7] observed a reduction of 53% in the 50 mg group and 63% in the 200 mg group compared to placebo. Similarly, the Phase 3 RESPONSE study by Hirschfield *et al*[9] showed that 42% of patients on Seladelpar achieved the primary endpoint compared to 26% on placebo. Normalization of ALP levels was achieved in a substantial proportion of patients receiving Seladelpar across various trials.

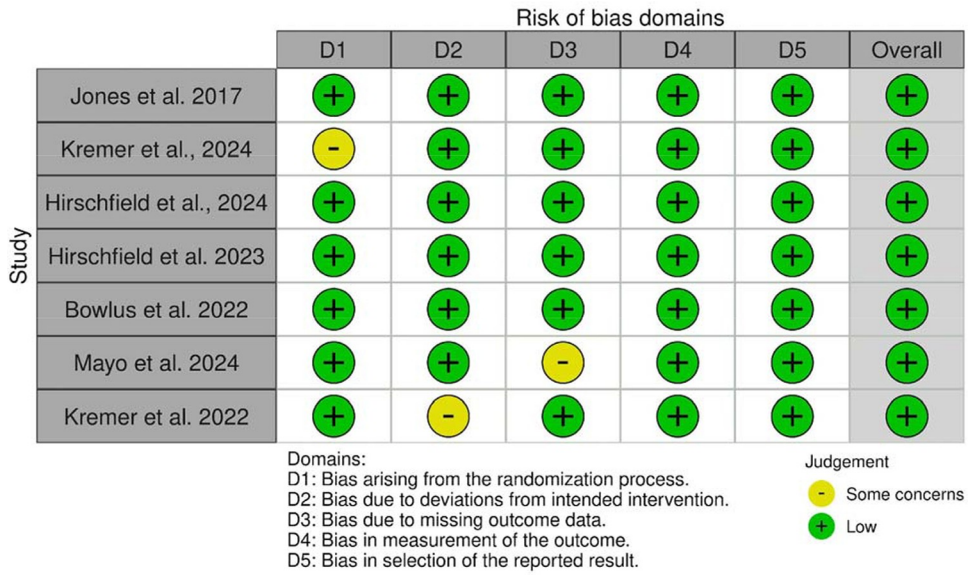

Figure 2. Network meta analysis of efficacy.

Clinical outcomes

A notable and consistent theme across the reviewed studies was the significant reduction in pruritus. The ENHANCE study[10] reported substantial improvements in pruritus scores. Patients receiving Seladelpar demonstrated a statistically significant decrease in pruritus Numerical Rating Scale (NRS) scores, which correlated with enhanced sleep quality and overall quality of life. The relationship between reduced pruritus and improved quality of life was further supported by findings from the RESPONSE study[11], where patients noted marked relief from pruritus, enhancing their daily functioning and well-being.

In the trial led by Hirschfield *et al*[9], 61.7% of patients on the 10 mg dose met the primary composite endpoint, which included criteria for ALP reduction and bilirubin normalization, compared to only 20% in the placebo group. Further reinforcing this trend, other studies demonstrated similar success rates in meeting composite endpoints. The Phase 3 RESPONSE study[11] reported significant biochemical improvements in alkaline phosphatase levels and total bilirubin among patients receiving Seladelpar. In this study, a striking 42% of patients treated with Seladelpar achieved the primary endpoint, showcasing its robust efficacy compared to the 26% of patients on placebo.

In long-term follow-up studies, such as the Mayo *et al*[12] open-label extension, patients who completed prior Seladelpar trials continued to show sustained improvements. A composite endpoint at 2 years indicated that 79% of patients achieved clinically significant responses, with ALP normalization observed in 42% of participants. This long-term data further emphasizes Seladelpar's potential for prolonged efficacy in managing PBC. Statistical analyses across these studies consistently revealed that the improvements associated with Seladelpar treatment were not only clinically relevant but also statistically significant, with *P* values typically less than 0.0001. This rigorous statistical validation enhances the credibility of the findings, supporting Seladelpar's role as an effective therapeutic option for patients suffering from PBC.

Safety profile

The prevalence of adverse effects varied across the Seladelpar treatment groups, as summarized in Table 2. The 5 mg Seladelpar group exhibited the lowest incidence of adverse effects, including Pruritus: 13.99% (95% CI: 2.88–30.83), Nausea: 12.74% (95% CI: 4.82–23.44), Dyspepsia: 3.7% (95% CI: 0.06–10.84). Other reported adverse effects across different doses included muscle spasms, arthralgia, fatigue, headache, and abdominal pain. Adverse effect prevalence for other doses: Pruritus: Highest in the 2 mg group (52.39%; 95% CI: 30.07–74.28), Nausea: Most prevalent in the 2 mg group (42.79%; 95% CI: 21.50–65.35), Dyspepsia: Most prevalent in the 2 mg group (27.27%; 95% CI: 4.39–57.92). The data demonstrated substantial variability in adverse effects across dose levels, with heterogeneity measures (I^2) particularly high for the 5 mg and 10 mg groups across pruritus and nausea outcomes, indicating inconsistent results across studies.

Seladelpar has demonstrated a favorable safety profile among patients with PBC. Across various studies, the incidence of adverse events was comparable between the Seladelpar and placebo groups, indicating that the treatment is generally well-tolerated. For instance, the Phase 3 RESPONSE study[9] revealed that none of the patients in the Seladelpar group experienced serious treatment-related adverse events, reinforcing the drug's acceptability in clinical practice.

The most frequently reported treatment-emergent adverse events (TEAEs) included mild to moderate pruritus, headaches, nausea, and abdominal pain. In the ENHANCE study[8], while adverse events were noted in both the Seladelpar and placebo groups, a notable 56% of patients receiving Seladelpar reported TEAEs compared to 50% in the placebo group. Among these, pruritus emerged as the most common side effect, affecting 30% of patients on Seladelpar compared to 20% in the placebo group.

Discontinuation rates due to adverse events varied across studies, highlighting the treatment's tolerability. In the trial

Table 1

Study characteristics

Author & year	Study design	Study size	Treatment regimen	Efficacy	Safety outcomes	Other key outcomes
Jones *et al* 2017	Double-blind, randomized, placebo-controlled, phase 2, proof-of-concept study	41 patients	Seladelpar (50 mg/day and 200 mg/day) vs placebo in patients continuing on ursodeoxycholic acid (UDCA) for 12 weeks	Significant reduction in alkaline phosphatase: −53% in the 50 mg group, −63% in the 200 mg group ($P < 0.0001$ vs placebo); no significant difference between doses	Three patients experienced reversible grade 3 alanine aminotransferase (ALT) increases, leading to early study termination. Other adverse events included pruritus, nausea, diarrhea, and muscle spasms.	Normalization of alkaline phosphatase levels was achieved in all patients completing 12 weeks of treatment. The study was terminated early due to safety concerns related to ALT increases. Further studies at lower doses were recommended.
Kremer *et al*, 2024	Randomized, double-blind, placebo-controlled (Phase 3, ENHANCE study)	161 patients	Seladelpar (5 mg (n = 53) and 10 mg (n = 53)daily) vs placebo(n = 55) for 3 months	Seladelpar significantly reduced pruritus and IL-31 levels. Greater dose-dependent reductions were seen in IL-31 and bile acid levels.	No significant differences in adverse events compared to placebo. A few instances of increased ALT were noted.	Correlations were found between IL-31 and pruritus severity as well as between IL-31 and bile acid levels. The treatment improved sleep and quality of life.
Hirschfield *et al*, 2024	Randomized, double-blind, placebo-controlled (Phase 3, RESPONSE study)	245 patients	Seladelpar (daily doses) vs placebo (standard-of-care UDCA)	Significant improvement in biochemical markers (alkaline phosphatase and total bilirubin). 42% of patients on Seladelpar achieved the primary endpoint compared to 26% on placebo.	Similar incidence of adverse events in both groups. Most common side effects included mild pruritus and headache.	Reduction in pruritus Numerical Rating Scale (NRS) scores among patients with moderate-to-severe pruritus. Improvements in quality of life were observed.
Hirschfield *et al* 2023	Phase 3, randomized, placebo-controlled study	265 patients with PBC	Seladelpar 5 mg (n = 89), 10 mg (n = 89), or placebo (n = 87) daily for 3 months	At month 3, significantly more patients receiving Seladelpar met the primary composite endpoint (5 mg: 57.1%, 10 mg: 78.2%) vs placebo (12.5%) ($P < 0.0001$). ALP normalization occurred in 5.4% (5 mg) and 27.3% (10 mg) vs 0% for placebo.	No serious treatment-related adverse events. Most common TEAEs (treatment emergent adverse events) were pruritus, upper abdominal pain, and nausea. 6 patients discontinued due to TEAEs.	Seladelpar 10 mg significantly reduced mean pruritus NRS(numerical rating scale) vs placebo. ALT decreased significantly with Seladelpar vs placebo.
Bowlus *et al* 2022	Phase 2, randomized, open-label study	121 patients with PBC	Seladelpar 2 mg (n = 11), 5 mg (n = 53), or 10 mg (n = 55) daily for 52 weeks After 12 weeks, patients in 2 mg and 5 mg groups could uptitrate to 10 mg/day based on inadequate response	At week 52, composite response rates were 64%, 53%, and 67% in the 2 mg, 5 mg, and 10 mg groups. ALP normalization rates were 9%, 13%, and 33%.	No treatment-related serious adverse events or deaths. 4 patients discontinued due to adverse events. Most common TEAEs were pruritus, diarrhea, and nausea.	Pruritus visual analog scale score decreased in 5 mg and 10 mg groups. ALP was dose-dependently reduced by 23% to 43% at Week 12.
Mayo *et al* 2024	Open-label extension study of phase 2 and 3 trials	106 patients with PBC who completed previous Seladelpar trials	Seladelpar 2 mg (n = 1), 5 mg (n = 18), or 10 mg (n = 87) orally once daily for up to 2 years	Composite endpoint at year 2: 79% (95% CI not provided). ALP normalization at year 2: 42% (95% CI not provided). Mean ALP decrease from baseline to year 2: 49.8%	No serious treatment-related adverse events. 4 discontinuations for safety reasons. Most common adverse events: pruritus (24.5%), nausea (21.7%), fatigue (18.9%)	Pruritus improvement (VAS ≥20-point decrease): 58% (5/10 mg) and 93% (10 mg) in patients with moderate-to-severe baseline pruritus. Significant reductions in serum bile acid precursor C4: −46% (5/10 mg, $P = 0.0044$) and −31% (10 mg, $P = 0.0005$)
Kremer *et al* 2022	Open-label, uncontrolled phase 2 study	101 patients with PBC and inadequate response to or intolerance to UDCA	Seladelpar 5/10 mg (n = 49) or 10 mg (n = 52) orally once daily for 1 year	Pruritus improvement (VAS ≥20-point decrease): 58% (5/10 mg) and 93% (10 mg) in patients with moderate-to-severe baseline pruritus	There were no reports of serious liver-related treatment-emergent adverse events (TEAEs). This study refers to safety data from the parent studies (phase 2 and ENHANCE trials)	Improvements in sleep disturbance: 81% (5/10 mg) and 78% (10 mg) of patients with baseline sleep disturbance. Fatigue improvement: 55% (5/10 mg) and 64% (10 mg) of patients. C4 reduction: −46% ($P = 0.0044$) in 5/10 mg group, −31% ($P = 0.0005$) in 10 mg group

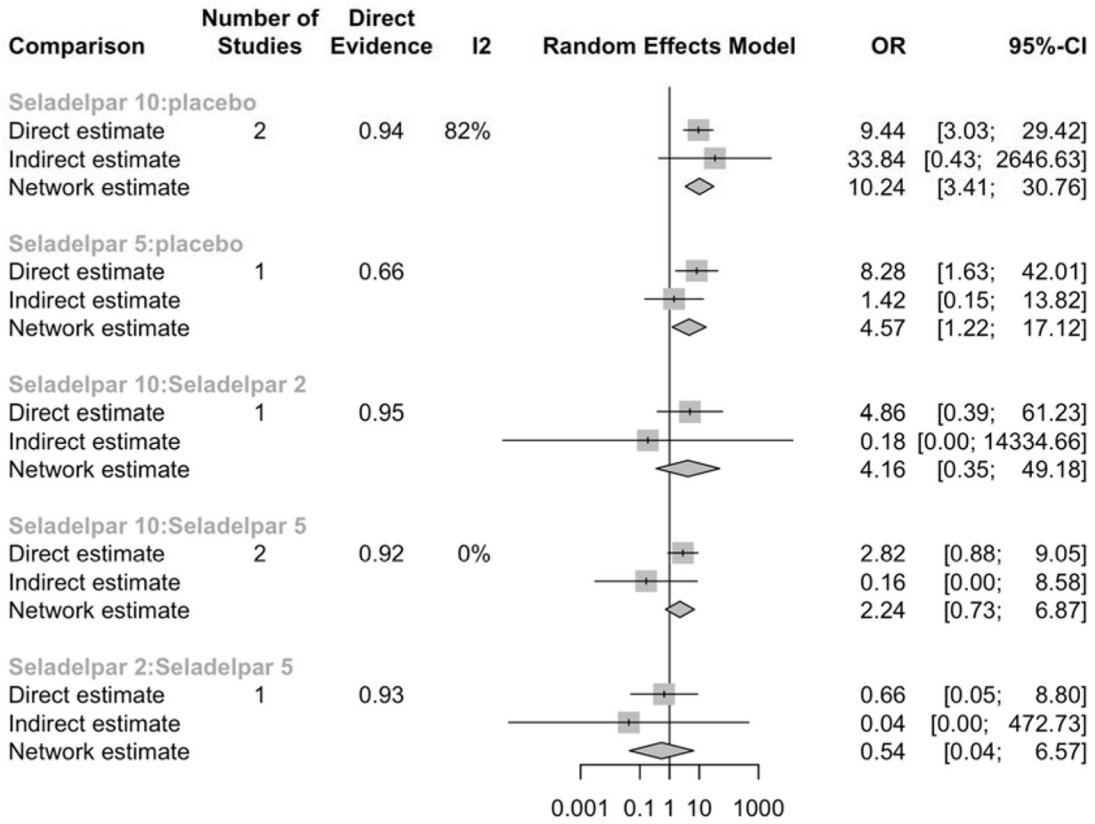

Figure 3. Analysis.

conducted by Hirschfield *et al*[8], six patients – approximately 2.3% of the total 265 participants – discontinued treatment due to TEAEs. This suggests that while most patients tolerated Seladelpar well, a minority experienced intolerable side effects. The safety profile also indicated a dose-dependent relationship, where higher doses of Seladelpar were associated with increased reports of mild adverse effects. For example, in the study by Bowlus *et al*[11], among patients receiving Seladelpar at a 10 mg dose, 36% experienced adverse events compared to 30% in the 5 mg group and 10% in the 2 mg group. This underscores the importance of individualized treatment approaches, as higher doses may enhance efficacy while potentially increasing the likelihood of mild adverse effects.

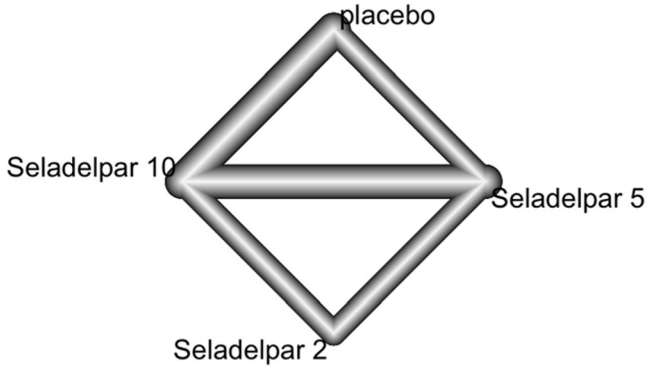

Figure 4. Network analysis.

Discussion

This review evaluated the efficacy and safety of Seladelpar, a selective PPARδ agonist, in treating PBC. The findings indicate that Seladelpar significantly reduces alkaline phosphatase levels, bilirubin levels, and pruritus severity among patients with PBC. Additionally, the review included seven studies, demonstrating that Seladelpar's administration leads to notable improvements in patient-reported outcomes such as sleep quality and overall quality of life. The significant biochemical response observed with Seladelpar aligns with previous research indicating the need for alternative therapeutic options in PBC, particularly for patients who have suboptimal responses to UDCA. With up to 40% of patients failing to achieve adequate biochemical control with UDCA, Seladelpar's ability to normalize alkaline phosphatase levels in 61.7% of patients in the trial by Hirschfield *et al*[10] presents a compelling argument for its incorporation into treatment regimens. Furthermore, the observed reductions in pruritus not only enhance patient comfort but also positively affect sleep and quality of life, underscoring Seladelpar's multifaceted benefits.

The findings of this review show Seladelpar's potential as a valuable second-line therapy for patients with PBC, particularly for those who demonstrate inadequate responses to UDCA. Seladelpar has shown the ability to achieve meaningful

Table 2

Adverse effect

	2 mg	5 mg	10 mg	50 mg	200 mg
Pruritus					
%(CI)	52.39 (30.07–74.28)	13.99 (2.88–30.83)	19.20 (3.97–41.58)	33.33 (8.96–62.86)	7.69 (0–30.13)
No. of studies	2	3	4	1	1
I^2	0	86.82	94.72	0	0
Nausea					
%(CI)	42.79 (21.50–65.35)	12.74 (4.82–23.44)	8.89 (3.93–15.42)	25 (3.93–53.92)	7.65 (0–30.13)
No. of studies	2	3	4	1	1
I^2	0	71.55	66.87	0	0
Dyspepsia					
%(CI)	27.27 (4.39–57.92)	3.7 (0.06–10.84)	1.79 (0–7.51)	16.67 (0.41–43.95)	7.69 (0-30.13)
No. of studies	1	1	1	1	1
I^2	0	0	0	0	0

biochemical responses, as demonstrated by the studies reviewed, where it led to a normalization of ALP levels in a considerable percentage of patients. Seladelpar's favorable safety profile is particularly noteworthy, especially in light of the adverse effects often associated with other therapeutic agents. In the reviewed studies, Seladelpar was generally well-tolerated, with a similar incidence of TEAEs compared to placebo groups. This safety aspect is crucial for a patient population that may already be dealing with the burdens of chronic illness. The absence of serious treatment-related adverse events in the Phase 3 RESPONSE study reinforces the acceptability of Seladelpar in clinical practice. Furthermore, the significant reductions in pruritus – a debilitating symptom of PBC – can have profound implications for patients' quality of life. The relationship between pruritus severity, sleep quality, and overall well-being highlights the importance of addressing this symptom in therapeutic strategies. Improved pruritus control not only enhances patient comfort but also positively impacts psychosocial aspects, such as mental health and social interactions, which are often compromised in chronic illness contexts. Clinicians should therefore prioritize symptom management, utilizing Seladelpar to alleviate pruritus alongside its role in normalizing liver function tests.

The evidence from this review suggests that Seladelpar may also have broader implications for the management of PBC. As treatment algorithms evolve, the incorporation of Seladelpar as a second-line option provides clinicians with a novel tool to tailor therapy to individual patient needs. This is particularly relevant in cases where patients may have specific contraindications to UDCA or exhibit intolerable side effects. Moreover, as research progresses and our understanding of PBC pathophysiology deepens, Seladelpar's role may extend beyond simply serving as an alternative to UDCA. Its dual mechanism of action – anti-cholestatic and anti-inflammatory – positions it as a potential disease-modifying therapy that could not only improve symptomatic relief but also impact disease progression. Future studies are warranted to explore these aspects further, particularly the long-term effects of Seladelpar on liver histology and fibrosis progression, which are crucial for comprehensive PBC management.

While the review highlights promising results, several limitations must be acknowledged. Many studies included were of relatively short duration, and the long-term efficacy and safety of Seladelpar remain uncertain. Additionally, variations in study design and patient populations may affect the generalizability of the findings. The reliance on patient-reported outcomes also introduces subjectivity, which could bias the results. Furthermore, the absence of long-term follow-up data prevents a comprehensive understanding of the sustainability of Seladelpar's benefits. Future studies should focus on longer-term outcomes associated with Seladelpar treatment, including its impact on disease progression and liver-related morbidity and mortality. Direct comparisons with emerging therapies for PBC will be vital in determining Seladelpar's relative efficacy. Additionally, exploring the drug's effects in diverse patient populations, including those with advanced disease, will enhance our understanding of its therapeutic potential. Investigating the mechanisms underlying Seladelpar's hepatoprotective effects and its role in modulating liver fibrosis could provide insights into its application in other chronic liver diseases, such as nonalcoholic steatohepatitis.

Conclusion

This systematic review and meta-analysis highlights the therapeutic potential of Seladelpar as a promising treatment option for PBC. The findings demonstrate that Seladelpar, particularly at a 10 mg dose, significantly reduces ALP levels and offers superior efficacy compared to placebo and lower doses. The observed dose-response relationship shows its potential to optimize treatment outcomes, while the lower incidence of adverse effects at 5 mg highlights the importance of tailoring doses to individual patient needs. Seladelpar's efficacy in improving surrogate markers of disease progression, such as ALP, provides a strong foundation for its role as a second-line therapy, particularly in patients with an inadequate response to first-line treatments like UDCA. However, the safety profile at higher doses, coupled with variability in adverse event reporting and high study heterogeneity, necessitates further investigation. Future research should prioritize long-term outcomes, including liver histology and survival benefits, as well as the evaluation of Seladelpar in diverse patient populations and real-world settings. As evidence continues to emerge, Seladelpar has the potential to reshape the treatment landscape for PBC, offering hope to patients who struggle with this chronic and progressive disease.

Ethical approval

Not applicable.

Consent

Not applicable.

Sources of funding

None.

Author contributions

I.A.C. conceptualized the study. I.A.C. and C.E. extracted the data from the reviewed studies. All authors wrote the final and first drafts and were involved in the literature review. All authors read and approved the final manuscript..

Conflicts of interest disclosure

The authors declare that they have no competing interests.

Research registration unique identifying number (UIN)

PROSPERO (CRD42024618877).

Guarantor

Chimezirim Ezeano.

Provenance and peer review

Not commissioned, externally peer-reviewed.

Data availability statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

References

[1] Trivella J, John BV, Levy C. Primary biliary cholangitis: epidemiology, prognosis, and treatment. Hepatol Commun 2023;7:e0179.
[2] Shaker M, Mansour N, John BV. Primary biliary cholangitis in males: pathogenesis, clinical presentation, and prognosis. Clin Liver Dis 2022;26:643–55.
[3] Tababi R, Mrabet S, Akkari I, *et al*. Prognostic scores in primary biliary cholangitis. Future Sci OA 2024;10:FSO975.
[4] Feng J, Xu J-M, Fu H-Y, *et al*. Prognostic scores in primary biliary cholangitis patients with advanced disease. World J Gastrointest Surg 2023;15:1774–83.
[5] Küçükyurt AK, Atakul N, Solak Y. Pregnancy cholestasis typically occurs in the third trimester of pregnancy and is a significant clinical condition. Arch Gynecol Obstet 2024;310:2531–39.
[6] Kouno T, Liu X, Zhao H, *et al*. Selective PPARδ agonist Seladelpar suppresses bile acid synthesis by reducing hepatocyte CYP7A1 via the fibroblast growth factor 21 signaling pathway. J Biol Chem. 2022;298:102056.
[7] Jones D, Boudes PF, Swain MG, *et al*. Seladelpar (MBX-8025), a selective PPAR-δ agonist, in patients with primary biliary cholangitis with an inadequate response to ursodeoxycholic acid: a double-blind, randomised, placebo-controlled, phase 2, proof-of-concept study. Lancet Gastroenterol Hepatol 2017;2:716–26. Epub 2017 Aug 14.
[8] Hirschfield GM, Shiffman ML, Gulamhusein A, *et al*. ENHANCE study group*. Seladelpar efficacy and safety at 3 months in patients with primary biliary cholangitis: ENHANCE, a phase 3, randomized, placebo-controlled study, Hepatology 2023;78:397–415.
[9] Kremer AE, Mayo MJ, Hirschfield GM, *et al*. Seladelpar treatment reduces IL-31 and pruritus in patients with primary biliary cholangitis, Hepatology 2024;80:27–37.
[10] Hirschfield GM, Bowlus CL, Mayo MJ, *et al*. RESPONSE Study Group. A phase 3 trial of Seladelpar in primary biliary cholangitis. N Engl J Med 2024;390:783–94.
[11] Bowlus CL, Galambos MR, Aspinall RJ, *et al*. A phase II, randomized, open-label, 52-week study of Seladelpar in patients with primary biliary cholangitis. J Hepatol 2022;77:353–64.
[12] Mayo MJ, Vierling JM, Bowlus CL, *et al*. Open-label, clinical trial extension: two-year safety and efficacy results of Seladelpar in patients with primary biliary cholangitis. Aliment Pharmacol Ther 2024;59:186–200.
[13] Kremer AE, Mayo MJ, Hirschfield G, *et al*. Seladelpar improved measures of pruritus, sleep, and fatigue and decreased serum bile acids in patients with primary biliary cholangitis. Liver Int 2022;42:112–23.