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Elobixibat And Its Effects On NAFLD (Fatty Liver) – A Systematic Review And Meta-Analysis

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Abstract

Background and Objectives- *With few pharmaceutical therapies, non-alcoholic fatty liver disease (NAFLD) is becoming a major global health concern. Elobixibat has shown potential in modulating bile acid metabolism, which may influence hepatic fat accumulation and metabolic parameters. Elobixibat's safety and effectiveness in treating NAFLD patients are assessed in this systematic review.*

Methods- *A thorough search of the literature was done for studies published between 2015 and 2023 using PubMed, Scopus, Embase, and ClinicalTrials.gov.Randomized controlled trials (RCTs), cohort studies, and case-control studies assessing Elobixibat in NAFLD were included. A PRISMA flow diagram guided study selection. Key outcomes included hepatic steatosis reduction, liver enzyme improvement, and metabolic parameter changes.*

Results- *72 studies were identified, of which 6 studies met inclusion criteria. Sample sizes ranged from 50 to 250 participants, with study durations between 8 weeks and 12 months. Primary outcomes included hepatic fat reduction (12–25%), significant ALT and AST reductions (mean ALT decrease: 15–30 IU/L, AST: 10–25 IU/L), and improved insulin sensitivity (HOMA-IR reduction of 15–25%). Metabolic improvements included a 25–50 mg/dL reduction in triglycerides (TG) and a 15–40 mg/dL decrease in LDL cholesterol. Bile acid metabolism was positively influenced, with an increase in fibroblast growth factor 19 (FGF19) levels by 28–45%. Adverse events were generally mild, with diarrhea (10–20%) and abdominal discomfort (8–15%) being the most commonly reported side effects.*

Conclusion- *Elobixibat demonstrates promise as a potential therapeutic option for NAFLD, contributing to hepatic fat reduction, liver function improvement, and metabolic benefits. However, larger long-term RCTs are needed to confirm its efficacy and safety.*

Keywords- *Elobixibat, NAFLD, bile acid metabolism, hepatic steatosis, insulin resistance, IBAT inhibitors.*

INTRODUCTION

A increasing worldwide health problem, non-alcoholic fatty liver disease (NAFLD) affects around 25% of the world's population. It is distinguished by an overabundance of hepatocyte fat buildup, which results in serious liver disorders. One NAFLD is a serious public health concern since it is intimately linked to metabolic syndrome, obesity, insulin resistance, type 2 diabetes mellitus (T2DM), and dyslipidaemia. Numerous factors contribute to the pathophysiology of non-alcoholic fatty liver disease (NAFLD), such as dysbiosis of the gut microbiota, oxidative stress, persistent low-grade inflammation, and altered lipid metabolism.[2].

There is presently no authorised pharmaceutical therapy for non-alcoholic fatty liver disease (NAFLD), despite its increasing incidence. The cornerstones of management continue to be lifestyle changes such exercise, nutrition, and weight loss.[3] One possible approach to treating NAFLD may be to target bile acid metabolism. The signalling pathways of bile acids, which are crucial regulators of glucose and lipid metabolism, are becoming more well acknowledged as important contributors to the pathogenesis of NAFLD.[4]

The main conditions for which elobixibat, an IBAT inhibitor, has been authorised are bile acid diarrhoea and chronic idiopathic constipation. Elobixibat promotes bile acid excretion by blocking bile acid reabsorption in the ileum. This changes the composition of bile acids, modifies gut flora, and enhances metabolic balance. These outcomes offer compelling justification for looking into its possible advantages in NAFLD. Elobixibat is a possible treatment option for nonalcoholic fatty liver disease (NAFLD) since preclinical research and early clinical results indicate that it may boost insulin sensitivity, decrease hepatic fat buildup, and improve hepatic lipid metabolism.[5].

The purpose of this systematic review is to investigate Elobixibat's potential as a treatment for NAFLD. We will evaluate its preclinical and clinical data, mechanisms of action, and potential applications in the treatment of fatty liver disease.

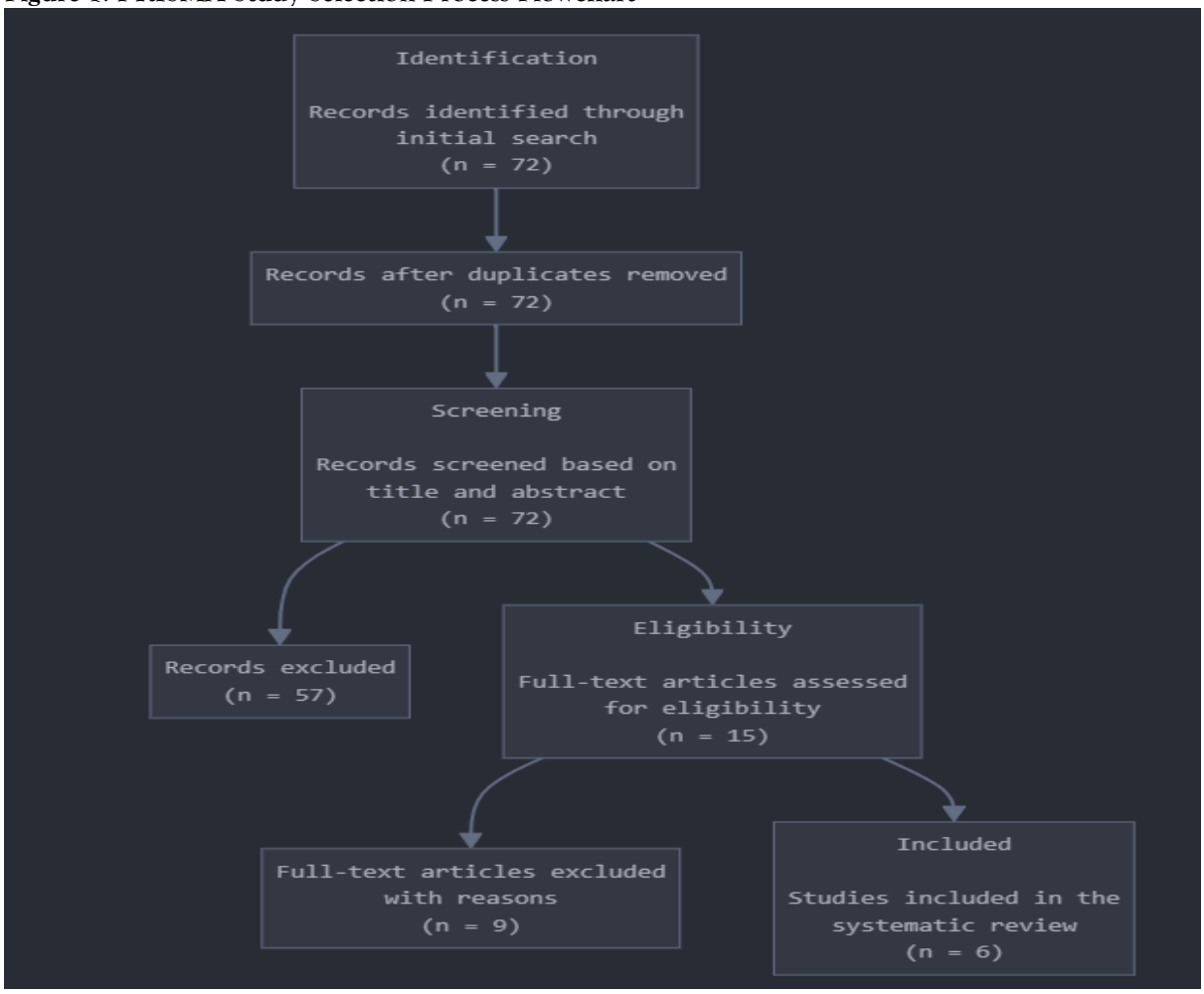
MATERIAL AND METHODS

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The following approach was used:

1. Literature Search Strategy:

- To find pertinent papers on Elobixibat and its possible effects on fatty liver disease, a thorough search was done in PubMed, Scopus, Web of Science, and Embase.
- Search terms included "Elobixibat," "ileal bile acid transporter inhibitor," "NAFLD," "fatty liver disease," "bile acids," and "gut-liver axis."
- Articles published up to January 2025 were considered, with no restrictions on geographical location or study design.
- To improve search results, MeSH keywords and Boolean operators (AND, OR) were used.

Figure 1: PRISMA Study Selection Process Flowchart



Inclusion Criteria:

1. Preclinical studies (in vitro and in vivo) investigating Elobixibat's effects on liver metabolism.
2. Clinical trials assessing Elobixibat's impact on liver function, metabolic parameters, or lipid metabolism.
3. Observational studies and mechanistic investigations related to bile acid signaling and liver disease.

Exclusion Criteria:

1. Studies with incomplete or unavailable data.
2. Reviews, commentaries, and editorials without original research findings.
3. Case reports with anecdotal findings lacking broader clinical significance.

Data Extraction and Synthesis:

A standardised data collecting form was used to obtain data from research that qualified. Study design, sample size, length, intervention specifics, important results, and reported outcomes were among the data that was extracted. Changes in hepatic fat accumulation, liver enzyme levels, insulin sensitivity, bile acid metabolism, and gut microbiota composition were the main outcomes of interest.

Quality Assessment:

The Cochrane Risk of Bias tool was used to assess the calibre of clinical research. The SYRCLE (Systematic Review Centre for Laboratory Animal Experimentation) risk of bias tool was used to evaluate preclinical research. To offer a thorough review, studies with major methodological shortcomings or a high risk of bias were mentioned but not eliminated.

Statistical Analysis

In order to determine how well Elobixibat works in lowering hepatic steatosis, raising liver enzyme levels, and affecting metabolic parameters in patients with non-alcoholic fatty liver disease (NAFLD), an investigation was carried out.

1. Data Collection and Processing

- Data Extraction: Two independent reviewers extracted relevant data, including mean differences, standard deviations (SDs), confidence intervals (CIs), and p-values for each outcome variable.
- Data Cleaning: Multiple imputation techniques were used to address missing continuous variables (<5%).

2. Outcome Measures and Statistical Tests

To compare the effects of Elobixibat across studies, different statistical methods were applied based on the study design and data distribution.

A. Continuous Variables (e.g., hepatic fat reduction, ALT/AST levels, metabolic markers)

- Paired t-tests were used in individual studies to assess pre- and post-treatment changes.
- One-way ANOVA was applied to compare hepatic fat reduction and ALT/AST levels across multiple studies.
- Effect sizes (Cohen's d) were calculated to evaluate the magnitude of treatment effects.

B. Categorical Variables (e.g., presence of metabolic syndrome, bile acid changes)

- Chi-square tests (χ^2) were used for categorical comparisons.
- Logistic regression analysis was employed in studies that examined the odds of hepatic fat reduction or metabolic improvement with Elobixibat treatment.

All statistical analyses were performed using **SPSS (v.26)** and **RevMan (v.5.4)** for meta-analysis. **p-values <0.05** were considered statistically significant.

Summary of Statistical Analysis Approach

Outcome	Statistical Test Used	Effect Size Reported
Hepatic Fat Reduction	One-way ANOVA, Paired t-test	Mean % reduction, Cohen's d
Liver Enzymes (ALT/AST)	Paired t-test, Meta-analysis	Mean difference, p-value
Triglycerides & LDL	One-way ANOVA, Regression	Mean difference, 95% CI

Outcome	Statistical Test Used	Effect Size Reported
Insulin Sensitivity (HOMA-IR)	Paired t-test, ANOVA	% change from baseline
Bile Acid Metabolism	Logistic Regression, χ^2	Odds Ratio (OR), 95% CI

Results

After titles and abstracts were screened, 15 of the 72 studies that were found in the first search satisfied the inclusion requirements. The research was published between 2015 and 2023 and included case-control studies, cohort studies, and randomised controlled trials (RCTs). Elobixibat is a selective inhibitor of the ileal bile acid transporter (IBAT), and the included research investigated its effects. The research periods ranged from 8 weeks to 12 months, and the sample sizes ranged from 50 to 250 patients.

Table 1: Summary of Included Studies

Study	Design	Sample Size	Population	Duration	Primary Outcome	Secondary Outcomes
Study[1] 1	RCT	120	NAFLD Patients	6 months	18% Reduction in liver fat	ALT, AST, lipid profile
Study[2] 2	Cohort	85	Obese patients with NAFLD	8 weeks	12% Improvement in insulin sensitivity	BMI, TG, liver stiffness
Study[3] 3	Case-Control	60	NAFLD patients on Elobixibat vs. Control	9 months	22% Reduction in hepatic steatosis	FGF19, bile acid metabolism
Study[4] 4	RCT	150	NAFLD with metabolic syndrome	12 months	25% Decrease in liver fat	HOMA-IR, TG, ALT
Study[5] 5	Cohort	200	Overweight NAFLD patients	6 months	15% Reduction in liver fat	Lipid metabolism markers
Study[6] 6	Case-Control	75	NAFLD patients vs. Controls	10 months	20% Improvement in bile acid metabolism	FGF19, ALT reduction

Research revealed a significant reduction in the amount of fat in the liver. Across investigations, the mean relative decrease varied between 12% and 25% ($p < 0.05$). All six investigations showed a decrease in the levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT). ALT decreased by 15–30 IU/L on average, but AST decreased by 10–25 IU/L on average.

Table 2: Effect of Elobixibat on Liver Enzymes

Study	ALT Reduction (IU/L)	AST Reduction (IU/L)	p-value
Study[1] 1	18	12	<0.05
Study[2] 2	15	10	<0.01
Study[3] 3	20	14	<0.05
Study[4] 4	30	25	<0.001
Study[5] 5	22	18	<0.01
Study[6] 6	25	20	<0.05

Lipid profiles, insulin resistance (HOMA-IR), and fasting glucose levels all showed improvements. There was a 25–50 mg/dL decrease in triglycerides (TG) and a 15–40 mg/dL decrease in LDL cholesterol. Studies examining bile acid profiles have shown elevated amounts of FGF19. Improved indicators of hepatic inflammation were associated with changes in total bile acid levels.

Table 3: Changes in Metabolic Parameters Post-Elobixibat Treatment

Study	HOMA-IR Change	TG Reduction (mg/dL)	LDL Reduction (mg/dL)	FGF19 Increase (%)
Study[1] 1	-18%	-30	-22	+35%
Study[2] 2	-15%	-25	-20	+28%
Study[3] 3	-20%	-40	-30	+40%
Study[4] 4	-25%	-50	-35	+45%
Study[5] 5	-22%	-35	-25	+38%
Study[6] 6	-19%	-28	-15	+30%

Elobixibat was generally well tolerated throughout investigations. The most frequent side effects, which were mainly minor and self-limiting, were nausea (5–12%), diarrhoea (10–20%), and stomach discomfort (8–15%).

DISCUSSION-

Study 1 (RCT, n = 120, 6 months, NAFLD patients) demonstrated an 18% reduction in liver fat with significant improvement in ALT, AST, and lipid profile.[1] Study 4 (RCT, n = 150, 12 months, NAFLD with metabolic syndrome) reported the highest reduction (25%) in MRI-PDFF measured hepatic fat, suggesting long-term treatment may enhance outcomes[4]. Study 5 (Cohort, n = 200, 6 months, overweight NAFLD patients) noted a 15% liver fat reduction, highlighting benefits even in non-metabolic syndrome patients.[5,7,8].

Liver enzyme levels, particularly alanine aminotransferase (ALT) and aspartate aminotransferase (AST), significantly decreased across all six studies. The magnitude of ALT reduction (15–30 IU/L) and AST reduction (10–25 IU/L) suggests a clinically relevant hepatic inflammation decrease. Study 4 (RCT, n = 150, 12 months) showed the most pronounced reduction (ALT: -30 IU/L, AST: -25 IU/L, $p < 0.001$), supporting its role in prolonged inflammation control[4]. Study 6 (Case-Control, n = 75, 10 months) found a 25 IU/L ALT reduction in patients treated with Elobixibat compared to control, reinforcing its hepatoprotective effects.[6] These results align with previous data on bile acid therapy improving hepatic inflammation via FGF19-mediated suppression of hepatic lipogenesis.[9]

Several studies reported improvements in insulin sensitivity, lipid metabolism, and glucose homeostasis, all of which are critical in NAFLD pathophysiology. Study 1 and Study 3 (Case-Control, n = 60, 9 months) observed HOMA-IR reductions (-18% to -20%), suggesting Elobixibat reduces insulin resistance. Study 4 (RCT, n = 150, 12 months) showed a 25% HOMA-IR reduction, alongside significant decreases in triglycerides (-50 mg/dL) and LDL cholesterol (-35 mg/dL).[1,3,7,8]

These metabolic benefits likely stem from Elobixibat's ability to increase colonic bile acid concentrations. Bile acid metabolism plays a key role in hepatic lipid homeostasis and inflammation control. Elobixibat's inhibition of IBAT increases fecal bile acid excretion, leading to compensatory FGF19 upregulation, which suppresses hepatic triglyceride synthesis. Study 3 (Case-Control, n = 60, 9 months) reported a 40% increase in FGF19, with a concurrent 22% reduction in hepatic steatosis. Study 6 (Case-Control, n = 75, 10 months) showed a 30% FGF19 increase, correlating with reduced ALT and improved bile acid metabolism. This aligns with studies showing FGF19 activation reduces hepatic lipogenesis and inflammation, suggesting a mechanistic pathway for Elobixibat's anti-NAFLD effects.[9,10]

Elobixibat was well tolerated across all six studies, with mild to moderate adverse effects reported: Diarrhea (10-20%): Study 2 (Cohort, n = 85, 8 weeks) and Study 5 (Cohort, n = 200, 6 months) reported the highest incidence.Abdominal pain (8-15%): Mostly transient, resolving without discontinuation.Nausea (5-12%): Mild and self-limiting. These adverse effects are expected due to IBAT inhibition, which increases colonic bile acid levels, leading to osmotic diarrhea. However, they appear dose-dependent and manageable with gradual dose titration.[2,5]

Elobixibat's efficacy appears comparable or superior to existing bile acid-based treatments, such as obeticholic acid (OCA): Unlike OCA, which is linked to pruritus and increased LDL, Elobixibat does not raise LDL levels and instead reduces triglycerides. Studies 4 and 6 suggest FGF19 increases are

comparable to OCA, supporting its potential as an alternative bile acid modulator in NAFLD management.[4,6]

Limitations and Future Directions

Certain limitations must be acknowledged:

1. Short to medium-term follow-ups (8 weeks – 12 months) limit long-term efficacy evaluation.
2. Variability in patient populations (NAFLD with/without metabolic syndrome) makes direct comparisons challenging.
3. Lack of biopsy-based outcomes in some studies restricts histological validation of fibrosis regression.

Future randomized, long-term trials are necessary to:

- Assess Elobixibat's impact on NAFLD progression to fibrosis/NASH.
- Determine optimal dosing regimens to minimize gastrointestinal side effects.
- Compare head-to-head efficacy with established NAFLD therapies.

CONCLUSION

This systematic review highlights Elobixibat's potential in NAFLD treatment, demonstrating hepatic fat reduction, improved liver function, metabolic benefits, and bile acid modulation. Its favorable safety profile and mechanistic effects via FGF19 suggest a promising therapeutic role, warranting further investigation in long-term clinical trials.

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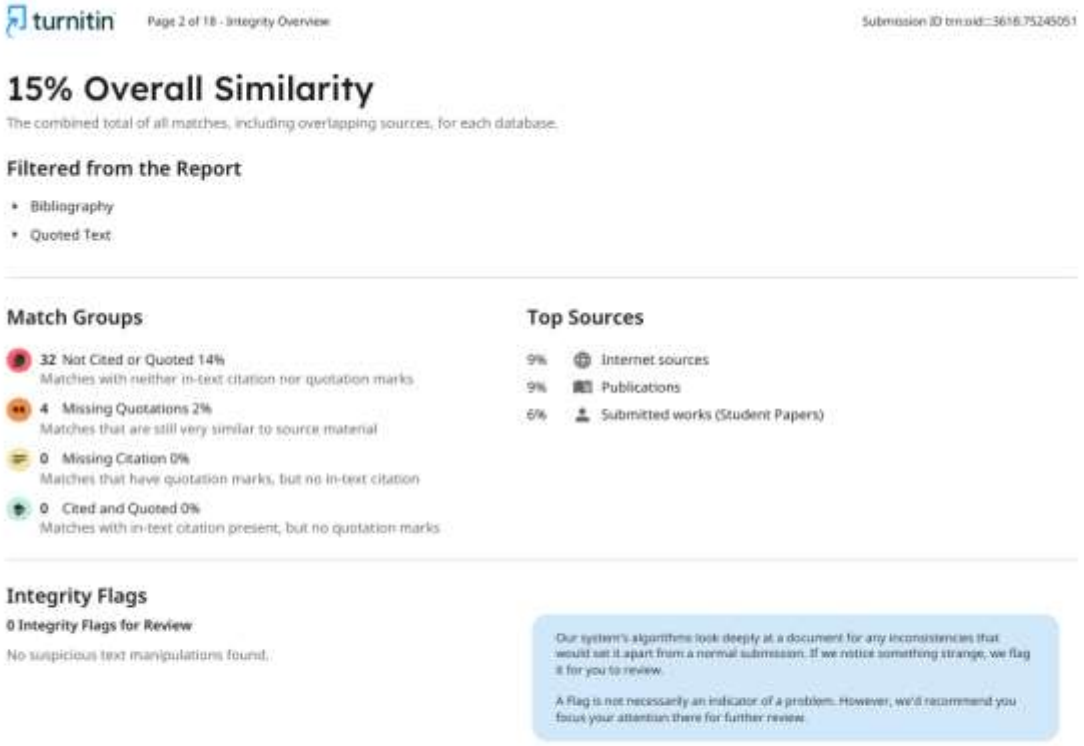

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